28 April 2016
EMA/373867/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Imbruvica

International non-proprietary name: ibrutinib

Procedure No. EMEA/H/C/003791/II/0016

Marketing authorisation holder (MAH): Janssen-Cilag International NV

Note

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

Table of contents

List of abbreviations

AR – assessment report

AUC – area under the curve

BCR - B cell antigen receptor

BTK - Bruton's tyrosine kinase

CHMP – committee for Medicinal Products for Human Use

CLL - chronic lymphocytic leukaemia

CNS – central nervous system

CR – complete response

DLBCL - diffuse large B cell lymphoma

ECOG – Eastern Cooperative Oncology Group

EFS – event-free survival

EPAR – European public assessment report

ERA - environmental risk assessment

ESMO - European Society of Medical Oncology

FACIT - functional assessment of chronic illness therapy

FC - fludarabine-cyclophosphamide

FCR - fludarabine-cyclophosphamide-rituximab

GCP – good clinical practice

GLP – good laboratory practice

HED - human equivalent Dose

HR – hazard ratio

ICH - international conference on harmonisation

IRC – independent review committee

ITT - intent-to-treat

iwCLL – international workshop on CLL

MAA - marketing authorisation application

MAH - marketing authorisation holder

MCL – mantle cell lymphoma

MedDRA - Medical Dictionary for Drug Regulatory Affairs

MRD – minimal residual disease

NOAEL – no-observed-adverse-effect-level

ORR – overall response rate

OS – overall survival

PAM – post-authorisation measure

PBRER – periodic benefit-risk evaluation report

PD - progressive disease

PFS – progression-free survival

PR – partial response

PRAC – pharmacovigilance risk-assessment committee

PRL – PR with lymphocytosis

PSUR – periodic safety update report

RMP – risk management plan

SAE – serious adverse events

SLL - small lymphocytic lymphoma

SmPC – summary of product characteristics

SOC – system organ class

TEAE – treatment-emergent adverse events

WM – Waldenström'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 13 October 2015 an application for a variation.

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, II and IIIB

Extension of indication to all previously untreated chronic lymphocytic leukaemia (CLL) patients including those with 17p deletion or TP53 mutation, based on the results from the final CSR of study PCYC-1115-CA (MEA 021) for Imbruvica. As a consequence, sections 4.1, 4.6, 4.8, 5.1 and 5.3 of the SmPC are being updated. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial changes to the SmPC and to bring Annex II in line with the latest QRD template version 9.1. Moreover, the updated RMP version 5.0 has been submitted.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Imbruvica was designated as an orphan medicinal product EU/3/12/984 on 23/10/2014. Imbruvica was designated as an orphan medicinal product in the following indication: Treatment of chronic lymphocytic leukaemia.

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

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

Protocol assistance

The applicant did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Filip Josephson

Timetable	Actual dates
Submission date	13 October 2015
Start of procedure:	31 October 2015
CHMP Rapporteur Assessment Report	22 December 2015
PRAC Rapporteur Assessment Report	8 January 2016
PRAC members comments	6 January 2016
Updated PRAC Rapporteur Assessment Report	13 January 2016
PRAC Outcome	14 January 2016
CHMP members comments	18 January 2016
Request for supplementary information (RSI)	28 January 2016
MAHs responses	2 March 2016
Restart of the procedure	3 March 2016
PRAC Rapporteur Assessment Report	15 March 2016
PRAC members comments	N/A
Updated PRAC Rapporteur Assessment Report	N/A
CHMP Rapporteur Assessment Report	22 March 2016
PRAC Outcome	17 March 2016
CHMP members comments	23 March 2016
Updated CHMP Rapporteur Assessment Report	24 March 2016
Request for supplementary information (RSI)	1 April 2016
MAHs responses	5 April 2016
Restart of the procedure	6 April 2016
PRAC Rapporteur Assessment Report	14 April 2016
PRAC members comments	N/A
Updated PRAC Rapporteur Assessment Report	N/A
PRAC Outcome	14 April 2016
CHMP Rapporteur Assessment Report	14 April 2016
CHMP members comments	18 April 2016
Updated CHMP Rapporteur Assessment Report	22 April 2016
Opinion	28 April 2016
The CHMP adopted a report on similarity of Arzerra and Gazyvaro on date (Appendix 1)	17 December 2015

2. Scientific discussion

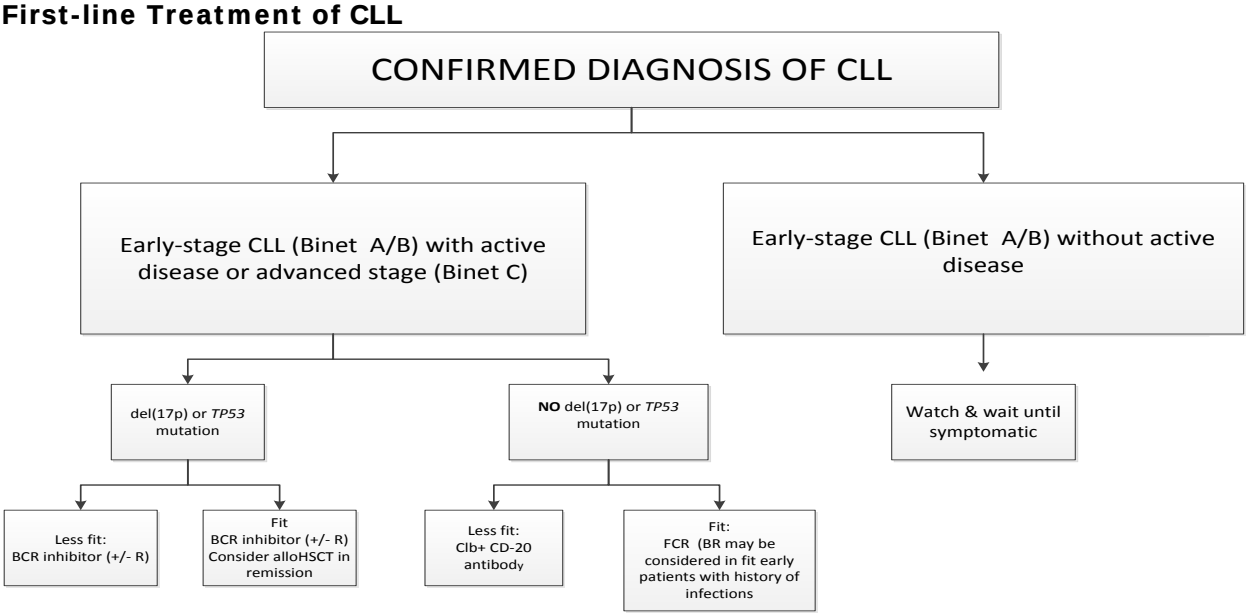
2.1. Introduction

Chronic lymphocytic leukaemia (CLL) is a progressive hematologic disease characterized by an accumulation of monoclonal mature B cells (CD5+CD23+) in the blood, bone marrow, and secondary lymph organs; diagnosis requires the presence of ≥5000 B-lymphocytes/µL in the peripheral blood (Hallek 2013). It is the most common form of adult leukaemia in the Western world, with an overall age-adjusted annual incidence of 4.65 per 100,000 persons and the number of deaths per year of 1.4 per 100,000 persons. An exponential increase in the incidence of CLL with age is observed; the median age at diagnosis is 72 years of age (Molica 2013).

The clinical course for CLL is associated with diminished bone marrow function, which is a hallmark of leukaemia. Recent guidelines on the management of CLL state that the biological parameters guiding treatment of CLL are genetic aberrations including deletions in the short arm of chromosome 17p13.1 (del17p), deletions/mutations in TP53 and deletions in the long arm of chromosome 11 (del11q), which confer a poor prognosis (Ghielmini 2013). In particular, patients with the del17p abnormality have an increased risk of relapse and death; the median life expectancy is 2 to 3 years from first-line treatment (Stilgenbauer 2010; Eichhorst 2011; Ghielmini 2013).

Current treatment guidelines from the European Society of Medical Oncology (ESMO) indicate the choice of treatment for previously untreated patients with CLL is based on stage of disease, whether a patient is considered "fit" and presence or absence of del17p or *TP53* mutation (Figure 1).

Figure 1: European Society for Medical Oncology Clinical Practice Guidelines for First-line Treatment of CLL



Source: Eichorst 2015

A representative summary of first-line treatments approved for patients with CLL in the European Union (EU) is shown in Table 1.

Monotherapy with alkylating agents has traditionally been used for the initial treatment of CLL. For several decades, single-agent chlorambucil has been a standard first-line therapy for CLL due to its moderate toxicity profile, which is of particular advantage for frail and/or older patients (Hallek 2013). Chlorambucil has been used as comparator in a large number of studies conducted in patients with

previously untreated CLL, across a range of ages and baseline characteristics. These studies have used various criteria to define patient fitness, including age, presence of comorbidities (eg, cumulative illness ratings score [CIRS] >6), and creatinine clearance. Bendamustine was approved in the EU as a single agent for patients with CLL based on a randomized controlled study in patients <75 years showing an improvement in PFS compared with chlorambucil without demonstration of overall survival (OS) benefit (Table 1; Knauf 2009). In addition to bendamustine, alemtuzumab therapy has resulted in better PFS than chlorambucil, also without improvement in OS (Hillmen 2007). Of note, marketing authorization for alemtuzumab, which had been indicated for the treatment of CLL in patients for whom fludarabine combination chemotherapy is not appropriate, was withdrawn in the EU in August 2012. In a Phase 3 study of CLL patients 65 years and older, the purine analogue fludarabine improved the response rate without improving PFS or OS (Eichhorst 2009). Additionally, purine analogs and bendamustine are associated with increased toxicity over chlorambucil.

In fit patients without significant comorbidities, the standard first-line therapy for patients without TP53 deletion/mutations is the CIT combination fludarabine-cyclophosphamide-rituximab (FCR) (Figure 1; Eichorst 2015). The addition of rituximab to fludarabine-cyclophosphamide (FC) demonstrated a significant improvement in PFS compared with FC (hazard ratio [HR] = 0.51, 95% confidence interval [CI] 0.39, 0.67; Hallek 2010). However, no efficacy benefit was evident for the FCR regimen in the subset of subjects (N=81) ⩾70 years (HR=1.17, 95% CI 0.51, 2.66; Casak 2011) and the CIT regimen was associated with an increase in toxicity. Furthermore, in a more recent Phase 3 study, fit patients ⩾65 years treated with FCR did not derive a benefit in efficacy compared with bendamustine plus rituximab (BR) and experienced a higher rate of ⩾Grade 3 toxicity including infections (Eichhorst 2014). Therefore, in this group of patients, treatment with BR may be considered, although it produces fewer complete remissions than FCR (Eichorst 2015).

In patients who are “less fit”, but without TP53 deletion/mutation, the combination of chlorambucil plus an anti-CD20 antibody (rituximab, ofatumumab or obinutuzumab) has recently become a recommended approach (Figure 1; Eichhorst 2015). Data from randomized clinical studies have shown that the addition of anti-CD20 antibodies such as ofatumumab, obinutuzumab, or rituximab to chlorambucil provides incremental improvement in median PFS (median PFS range: 15.4 to 29.2 months) compared to chlorambucil alone (median PFS: 13.1 months; Goede 2015; Hillmen 2015). With the increase in treatment intensity, there is also an increase in toxicity including infusion reactions, as well as an increased rate of cytopenias, a common complication of all available first-line treatment regimens (Grade 3/4: 7% to 21%; MabThera Product Information 2015; Arzerra® Product Information 2015; Gazyvaro Product Information 2015).

Despite improvement in PFS, none of the anti-CD20-based CITs demonstrated improved outcomes in patients with del17p or TP53 alterations (Goede 2014; Hallek 2010). Patients with TP53 deletion/mutation have a poor prognosis even after FCR therapy (Hallek 2010). Therefore, it is recommended that these patients are treated with novel inhibitors such as ibrutinib or idelalisib plus rituximab, in the first-line setting (Eichhorst 2015).

In summary, chlorambucil has remained a mainstay of treatment for CLL. Current treatment options include combination CIT, however older patients and those with comorbidities are less likely to tolerate combination CIT due to its association with more severe toxicities. In addition, patients with poor performance or functional status may not tolerate long infusions. Grade 3 or 4 cytopenias are often dose-limiting and are frequent causes of morbidity in patients of any age with CLL. Moreover, treatment with traditional cytotoxic chemotherapy early on in the course of the disease may select for the development of more aggressive forms of CLL by introducing mutations (eg, TP53), which confer a poor prognosis or lead to treatment-related myelodysplasia or AML(Benjamini 2015). Patients become increasingly resistant to the currently available therapeutic agents, with decreased response rates and

PFS with each subsequent regimen (Brown 2015; Hillmen 2011; Maddocks and Lin 2009). Therefore, there is a need for alternative treatment options that can be safely administered to all patients regardless of age or comorbidities and that provide enhanced clinical outcomes (including improvement in hematologic function), which would be considered a substantial improvement over currently available therapies.

Table 1: Summary of Approved Treatments for First-line Treatment of CLL in the European Union

Treatment /Approval Year	Indication	Monotherapy or combination	Approval based on /comparator	No. of Subjects	Efficacy Endpoints
Ibrutinib 2014	CLL with 17p deletion or *TP53* mutation in patients unsuitable for CIT	Monotherapy	Phase 3/ ofatumumab	391	PFS, OS, ORR
Idelalisib + rituximab 2014	In combination with rituximab for CLL with 17p deletion or *TP53* mutation in patients unsuitable for CIT	Combination	Phase 3/rituximab	220	PFS, OS
Ofatumumab with chlorambucil or bendamustine 2014	In combination with chlorambucil for the treatment of patients with CLL who have not received prior therapy and who are not eligible for fludarabine-based therapy	Combination	Phase 3/ chlorambucil	444	PFS, ORR, DOR
Obinutuzumab with chlorambucil 2014	In combination with chlorambucil, for the treatment of patients with previously untreated chronic lymphocytic leukemia and with comorbidities making them unsuitable for full-dose fludarabine based therapy.	Combination	Phase 3/ chlorambucil	356	PFS, DOR, OS
Rituximab[a] 2010	CLL (in combination with chemotherapy is indicated for the treatment of patients with previously untreated and relapsed/refractory chronic lymphocytic leukaemia)	Combination	Phase 3/FC	817	PFS
Bendamustine[a, b] 2008	CLL in patients for whom fludarabine combination chemotherapy is not appropriate).	Monotherapy	Phase/ chlorambucil	301	ORR, PFS
Cyclophosphamide[a] 1959	CLL (unspecified)	Monotherapy	Unknown	Unknown	Unknown
Chlorambucil[a] 1957	CLL (unspecified)	Monotherapy	Unknown	Unknown	Unknown
Fludarabine[c] 1994	CLL (unspecified)	Monotherapy	Phase 3/ chlorambucil	394	ORR, DOR, TTP

CLL: chronic lymphocytic leukemia; DOR: duration of response; EU: European Union; FC: fludarabine + cyclophosphamide; N/A: not available; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; TTP: time to progression

[a] Efficacy in CLL relative to first-line therapies other than chlorambucil has not been established. [b] Used for first- and second-line treatment of CLL. [c] Information from approved FLUDARA UK SmPC, revision date 14 October 2015

Ibrutinib is a potent, small molecule inhibitor of Bruton's tyrosine kinase (BTK). Ibrutinib forms a covalent bond with a cysteine residue (Cys 481) in the BTK active site, leading to sustained inhibition of BTK enzymatic activity. BTK, a member of the Tec kinase family, is an important signalling molecule of the B cell antigen receptor (BCR) and cytokine receptor pathways. The BCR pathway is implicated in the pathogenesis of several B cell malignancies, including MCL, diffuse large B cell lymphoma (DLBCL), follicular lymphoma, and CLL. BTK's pivotal role in signalling through the B cell surface receptors results in activation of pathways necessary for B cell trafficking, chemotaxis and adhesion. Preclinical studies have shown that ibrutinib effectively inhibits malignant B cell proliferation and survival in vivo as well as cell migration and substrate adhesion *in vitro* (SmPC section 5.1).

The current indication for CLL for Imbruvica is as follows:

IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy, or in first line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo immunotherapy.

The marketing authorisation holder (MAH) applied for the following indication: IMBRUVICA is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL), including those with 17p deletion or TP53 mutation.

IMBRUVICA is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.

The recommended indication for approval is: Imbruvica as a single agent is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) (see section 5.1).

Imbruvica is indicated for the treatment of adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy.

The recommended dose for the treatment of CLL and is 420 mg (three capsules) once daily (SmPC section 4.2).

2.2. Non-clinical aspects

2.2.1. Introduction

Chronic general toxicology studies in rats and dogs, fertility and early embryonic development in rats and the definitive embryo/fetal development studies in rabbits were performed in compliance with GLP regulations. Toxicokinetic evaluations of ibrutinib and PCI-45227 (M37) were also conducted in accordance with GLP regulations.

Nonclinical general toxicology studies of up to 6 months (rats) and 9 months (dogs) duration were conducted. In accordance with International Conference on Harmonisation (ICH) guidance S5(R2), the rat was used for evaluation of effects on male and female fertility and early embryonic development and the rat and rabbit were used for the definitive assessment of embryo/fetal development toxicity.

In addition, reference was made to the 4-week GLP study (14-239-M-PO-TX (TOX10814), in CByB6F1 hybrid mice (Tg.rasH2 non-transgenic littermates) submitted in procedure EMEA/H/C/003791/II/0018 and toxicokinetic results were submitted as part of the extension of indication.

2.2.2. Pharmacology

N/A

2.2.3. Pharmacokinetics

N/A

2.2.4. Toxicology

Repeat dose toxicity

Six-Month Toxicity Study in Rats Dosed Orally (TOX 10827)

Table 2. Design of study TOX 10827

Species/Number/Sex/Group	Dose (mg/kg/day)/ Route/Formulation	Duration	NOAEL (mg/kg/day)	Study, GLP
Rat/20M,20F	0, 25, 50, 100M/80F/oral/0.5% MC, 0.1%SLS	6-mo + 1-mo recovery	100M/50F	14-057-R-PO-TX, GLP

No adverse effects were seen in males at any ibrutinib dose. In females, the 80 mg/kg/day ibrutinib dose was considered adverse due to moderate effects on mean body weight and mean body weight gain and a single pre-term death of uncertain aetiology (with no prodromal signs). The effects on female body weight parameters showed partial recovery during the 1-month dosing-free recovery phase. Lower spleen weights were observed in males across all ibrutinib dose groups and in females in the 80 mg/kg/day group at terminal necropsy. Decreases in liver, pituitary, and adrenal gland weights were seen in females across all dose groups at terminal necropsy. Ibrutinib-related changes in clinical pathology parameters were limited to minimal, non-adverse, dose-related, shortened coagulation times (prothrombin times and activated partial thromboplastin times) in ⩾25 mg/kg/day males at termination. The coagulation times were similar to controls following recovery. Test article-related non-adverse microscopic changes in the pancreas (minimal to mild acinar atrophy or haemorrhage) were observed in all dose groups, including controls, at terminal necropsy with a slightly greater incidence and severity in the treated males as compared to the treated females.

Table 3. *Comparison 13-weeks and 6-month study*

Affected Site or System	Study	
	13-Week	**6-Month**
Whole body		Mortality, undetermined etiology - 1 Female at 80 mg/kg/day ↓ Body weight/body weight gain - Females at 80 mg/kg/day
Lymphoid Nodes or Peyer's Patches	Lymphoid depletion in lymph nodes: - Females at 175 mg/kg/day	No adverse findings
Clinical correlates in lab animals	*↓ Mean B-cell counts (F=84%) in peripheral blood*	
Spleen	Lymphoid depletion in spleen: - Females at 175 mg/kg/day	No adverse findings
Clinical correlates in lab animals	*↓ Mean B-cell counts (F=84%) in peripheral blood*	
Gastrointestinal Tract	Edema, ulceration, and squamous epithelium atrophy of nonglandular stomach: - Females at 175 mg/kg/day Acute inflammation in intestine with	No treatment-related changes

	ulceration - Females at 175 mg/kg/day	
Clinical correlates in lab animals	*Soft feces with yellow or brown material on urogenital or anogenital areas*	
Pancreas	Moderate acinar atrophy: - Males at 100 and 300 mg/kg/day	No adverse findings
Clinical correlates in lab animals	*None*	
Bone	Thinning of cortical bone and fewer primary trabeculae: - Males at 300 mg/kg/day - Females at 100 and 175 mg/kg/day	No treatment-related changes
Clinical correlates in lab animals	*None*	
NOAEL:	30 mg/kg/d (HED = 4.8)	100 mg/kg/day (male; HED=16) 50 mg/kg/day (female, HED=8)

Nine-Month Toxicity Study in Dogs Dosed Orally (TOX10828)

Table 4. ***Design of study TOX 10828***

Species/Number/Sex/Group	**Dose (mg/kg/day)/ Route/Formulation**	**Duration**	**NOAEL (mg/kg/day)**	**Study, GLP**
Dog/4-6M,4-6F	0, 30, 50, 80/oral/0.5% MC, 0.1%SLS	9-mo + 1-mo recovery	80	14-060-D-PO-TX, GLP

No adverse effects were noted at 80 mg/kg/day in either males or females. Non-adverse treatment-related changes included lower mean body weights and body weight gains in treated males as well as minor alterations in hematologic and clinical chemistry parameters in both males and females. Decreased circulating lymphocytes and minimal to mild lymphoid depletion (Peyer' s patches) were considered non-adverse and attributed to the intended pharmacology of ibrutinib.

Table 5. ***Comparison 13-weeks and 9-month study***

Affected Site or System	**Study**	
	13-Week	**9-Month**
Lymphoid Nodes or Peyer's Patches	Lymphoid depletion in Peyer's patches: - Males and females at 80/60 and 220/120 mg/kg/day	No adverse findings
Clinical correlates in lab animals	↓ *Mean lymphocyte counts in peripheral blood at the 220/120 mg/kg dose level*	
Spleen	No treatment-related changes	No treatment-related changes
Clinical correlates in lab animals	-	
Gastrointestinal Tract	Smooth muscle degeneration in stomach: - Females at 220/120 mg/kg/day Acute inflammation in the intestines: - One female at 220/120 mg/kg/day	No treatment-related changes
Clinical correlates	-	

in lab animals		
Pancreas	No treatment-related changes	No treatment-related changes
Clinical correlates in lab animals	-	
Bone	No treatment-related changes	No treatment-related changes
Clinical correlates in lab animals	-	
NOAEL:	30 mg/kg/day (HED = 16)	80 mg/kg/day (HED=43)

Reproduction toxicity

Fertility and Early Embryonic Development (TOX11002)

Table 6. *Design of study TOX 11002*

Species/Number/Sex/Group	Dose (mg/kg/day)/ Route/Formulation	Duration	NOAEL (mg/kg/day)	Study, GLP
Rat/22M,22F	0, 25, 50, 100/0.5% MC, 0.1%SLS	M: 4 weeks pre-pairing, during pairing and until confirmation of fertility F: 2 weeks pre-pairing, during pairing until Day 7 of presumed pregnancy	F0 M; 100, F0 F; 100	14-205-R-PO-RP, GLP

There were no effects on fertility or reproductive capacities in males or females up to the maximum dose tested of 100 mg/kg/day [Human Equivalent Dose (HED) 16 mg/kg].

Definitive Embryo/Fetal Development Study in Rabbits

Table 7. Design of study TOX 10823

Species/Number/Sex/Group	Dose (mg/kg/day)/ Route/Formulation	Duration	NOAEL (mg/kg/day)	Study, GLP
Rabbit/20	0, 5, 15, 45/0.5% MC, 0.1%SLS	G6-G19	F0: 15 mg/kg, F1:5 mg/kg	13-133-B-PO-TT, GLP

Six of 20 dams in the 45 mg/kg/day group showed persistent body weight loss, reduced fecal output and severely decreased food consumption from the start of dosing onwards resulting in pre-terminal sacrifice (from day 14 to 23) for humane reasons. All other females survived to the scheduled necropsy on day 28 of pregnancy.

In the 45 mg/kg/day group, maternal toxicity was evidenced by a significant decrease in mean body weight gain and reduced food consumption during the dosing period. During the post-dosing period, mean body weight gain and food consumption partially recovered. In the 15 mg/kg/day group, slightly decreased food consumption was noted during the initial dosing phase but mean body weight and mean body weight gain remained similar to the vehicle group.

In the 5 and 15 mg/kg/day groups, there were no adverse effects on litter parameters. In the 45 mg/kg/day group, maternal toxicity resulted in an increased number of resorptions and, hence, increased post-implantation loss. Fetal weight and sex ratio in the ibrutinib administered groups were not affected

by treatment at any dose level. There were no adverse treatment-related external or visceral effects on fetuses. There was a statistically significant and dose-related increase in the incidence of litters with fetuses with fused sternebrae in the groups receiving 15 and 45 mg/kg/day, with 47.1% and 100% of litters affected, respectively. In conclusion, ibrutinib cases malformations in both rat (heart and major vessels) and rabbit (fused strebebra). In addition, an increase in skeletal variations was observed in rat.

Toxicokinetic data

Full exposure coverage data in preclinical species versus human for ibrutinib and the major human metabolites M21, M25, M34 and PCI-45227 (M37) is presented in Table 8.

Table 8. Stead-State animal-to-human toxicokentics

Species/ Study, GLP	Dose Level (mg/kg/d)	Study Day(a)	AUC (ng·h/mL)		AUC Animal/human (420 mg/d) Exposure Ratio		AUC Animal/human (560 mg/d) Exposure Ratio	
			M	F	M	F	M	F
Ibrutinib								
Human	5.3 7.0	8	680 953					
Rat, 13-week, GLP	30		2480	19712	3.6	29	2.6	21
	100		5506	20661	8.1	30	5.8	22
	175			51549		76		54
	300			21732		32		23
Rat, 6-mo, GLP	25	177	1640	2990	2.4	4.4	1.7	3.1
	50		2970	6820	4.4	10	3.1	7.2
	100M, 80F		4430	11200	6.5	16	4.6	12
Dog, 13-week, GLP	30		377	1683	0.6	2.5	0.4	1.9
	60		3414	2211	5.0	3.3	3.6	2.3
	120		12179	6628	18	9.7	13	7.0
Dog, 9-mo, GLP	30	271	343	221	0.5	0.3	0.4	0.2
	50		370	571	0.5	0.8	0.4	0.6
	80		2990	3590	4.4	5.3	3.1	3.8
Rabbit, embryo/fetal, GLP	5	19f		714		1.1		0.7
	15			1920		2.8		2.0
	45			4670		6.9		4.9
M37 (PCI-45227)								
Human	5.3b	8	1248					
Rat, 6-mo, GLP	25	177	1330	2350	1.1	1.9	1.1	1.9
	50		3210	5350	2.6	4.3	2.5	4.2
	100M, 80F		4400	8470	3.5	6.8	3.5	6.7
Dog, 9-mo, GLP	30	271	267	152	0.2	0.1	0.2	0.1
	50		257	324	0.2	0.3	0.2	0.3
	80		1140	1280	0.9	1.0	0.9	1.0
Rabbit, embryo/fetal, GLP	5	19f		553		0.4		0.4
	15			1760		1.4		1.4
	45			5760		4.6		4.6
M21								
Human	7.0b	22	3170					
Rat, 6-mo, GLP	25	42	411	461			0.1	0.1
	50		912	1100			0.3	0.3
	100M, 80F		1330	1450			0.4	0.5
Dog, 9-mo, GLP	30	42	620	582			0.2	0.2
	50		517	1390			0.2	0.4
	80		1600	2940			0.5	0.9
Rabbit, embryo/fetal, GLP	5	19f		24.6				0.01
	15			56.2				0.02
	45			102				0.03
M25								
Human	7.0b	22	1910					
Rat, 6-mo, GLP	25	42	57.2	37.1			0.03	0.02
	50		129	91.5			0.07	0.05
	100M, 80F		221	130			0.12	0.07
Dog, 9-mo, GLP	30	42	35.5	39.5			0.02	0.02
	50		19.4	75.4			0.01	0.04

	80		54.7	92.2			0.03	0.05
Rabbit, embryo/fetal, GLP	5	19f		667				0.3
	15			1630				0.9
	45			4210				0.05
M34								
Human	7.0b	22	1500					
Rat, 6-mo, GLP	25	42	47.2	42.2			0.03	0.03
	50		115	156			0.08	0.1
	100M, 80F		199	265			0.13	0.18
Dog, 9-mo, GLP	30	42	396	215			0.3	0.1
	50		232	982			0.2	0.7
	80		989	1620			0.6	1.1
Rabbit, embryo/fetal, GLP	5	19f		93.8				0.1
	15			335				0.7
	45			1350				1.1

As noted, in rat and rabbit, ibrutinib metabolites M21, M25, and M34 show subclinical exposures. However, in a subsequent 4-week GLP study (14-239-M-PO-TX (TOX10814), in CByB6F1 hybrid mice (Tg.rasH2 non-transgenic littermates) submitted in procedure EMEA/H/C/003791/II/0018, conducted as a dose range finding study for a 6 month Tg.rasH2 carcinogenicity study, maximum observed concentration (Cmax) and area under the concentration-time curve (AUC) exposures above those seen in humans were attained for each of these metabolites (Seq0049/M4.2.3.4.2/14-239-M-PO-TX [TOX10814]). The mouse no-observed-adverse-effect level (NOAEL) in this study was the highest dose administered (1000 mg/kg/day), therefore the Applicant considers that these metabolites M21, M25 and M34 are now adequately assessed for toxicity in accordance with ICH M3 (R2).

Table 1 to Table 4 summarize all available nonclinical exposure data from the initial MAA onwards including the recent study 14-239-M-PO-TX (TOX10814) and include references to the source data, including the eCTD sequence in which the data was originally submitted. Table 1 presents human reference exposure to ibrutinib and its important metabolites. Animal exposures and animal-to-human exposure ratios for metabolites M21 (Table 2), M25 (Table 3), and M34 (Table 4), include mouse, rat, rabbit, and dog data.

Table 9 Human Reference Exposures for Ibrutinib and Important Human Plasma Metabolites of Ibrutinib

Test Article	C_{max} (µg/mL)	(µM)	AUC (µg/mL·h)	(µM·h)	AUC (% of total)	Source
Ibrutinib	0.164	0.372	0.953	2.163	11.6	[Seq0000/M5.3.5.2/1104/TabPK3/p25]
M21	0.341	0.635	3.170	5.908	31.8	[Seq0043/M4.2.2.4/15-201-Hu-PO-PK (FK11020)]
M23	0.010	0.026	0.210	0.543	2.92	[Seq0043/M4.2.2.4/15-201-Hu-PO-PK (FK11020)]
M25	0.267	0.565	1.910	4.042	21.7	[Seq0043/M4.2.2.4/15-201-Hu-PO-PK (FK11020)]
M34	0.205	0.447	1.500	3.271	17.6	[Seq0043/M4.2.2.4/15-201-Hu-PO-PK (FK11020)]
PCI-45227 (M37)	0.122	0.257	1.263	2.662	14.3	[Seq0000/M5.3.5.2/1104/TabPK3/p31]

Table 10. Steady-State Animal-to-Human M21 Exposure Ratios for Animal Toxicology Doses Relative to Clinical Doses

Species/ Study	Dose Level (mg/kg/d)	Study Day[a]	C_{max} (ng/mL)		C_{max} Animal/human (560 mg/d) Exposure Ratio		AUC (ng·h/mL)		AUC Animal/human (560 mg) Exposure Ratio	
			M	F	M	F	M	F	M	F
Human										
Phase 1b/2	7.0[b]	22	341[c]		1		3170[c]		1	
Mouse	100	28	3490	1910	10	5.6	9110	6280	2.9	2.0
4-wk toxicity[d]	500		3090	9050	9.1	27	10,300	35,500	3.2	11
	1000		1460	8470	4.3	25	10,100	34,800	3.2	11
Rat	25	42	99.5	126	0.3	0.4	411	461	0.1	0.1
6-mo toxicity[e]	50		158	223	0.5	0.7	912	1100	0.3	0.3
	100M, 80F		185	244	0.5	0.7	1330	1450	0.4	0.5
Rabbit	5	19[g]	-	4.6	-	0.01	-	24.6	-	0.01
Embryo/fetal development toxicity[f]	15		-	8.9	-	0.03	-	56.2	-	0.02
	45		-	11.0	-	0.03	-	102	-	0.03
Dog	30	42	93.6	103	0.3	0.3	620	582	0.2	0.2
9-mo toxicity[h]	50		129	178	0.4	0.5	517	1390	0.2	0.4
	80		189	274	0.6	0.8	1600	2940	0.5	0.9

[a] Day of blood specimen collection. First day of dosing designated study day 0 for nonclinical studies and study day 1 for clinical studies.
[b] Clinical dose was fixed at 560 mg/day (maximum therapeutic dose). Weight-based dose assumes an 80 kg individual.
[c] Source: EMEA/H/C/003791/II/0016, Seq0043/M4.2.2.4/15-201-Hu-PO-PK (FK11020)
[d] Source: EMEA/H/C/003791/II/0018, Seq0049/M4.2.3.4.2/14-239-M-PO-TX (TOX10814)
[e] Source: EMEA/H/C/003791/II/0016, Seq0043/M4.2.3.2/14-057-R-PO-TX (TOX10827)
[f] Source: EMEA/H/C/003791/II/0016, Seq0043/M4.2.3.5.2/13-133-B-PO-TT (TOX10823)
[g] Animals were dosed on gestation days 6 through 19
[h] Source: EMEA/H/C/003791/II/0016, Seq0043/M4.2.3.2/14-060-D-PO-TX (TOX10828)

Table 11. Steady-State Animal-to-Human M25 Exposure Ratios for Animal Toxicology Doses Relative to Clinical Doses

Species/ Study	Dose Level (mg/kg/d)	Study Day[a]	C_{max} (ng/mL)		C_{max} Animal/human (560 mg/d) Exposure Ratio		AUC (ng·h/mL)		AUC Animal/human (560 mg) Exposure Ratio	
			M	F	M	F	M	F	M	F
Human										
Phase 1b/2	7.0[b]	22	267[c]		1		1910[c]		1	
Mouse	100	28	1060	649	4.0	2.4	2220	1710	1.2	0.9
4-wk toxicity [d]	500		1530	3920	5.7	15	3980	14,900	2.1	7.8
	1000		874	4930	3.3	18	4580	18,800	2.4	9.8
Rat	25	42	35.0	21.3	0.1	0.1	57.2	37.1	0.03	0.02
6-mo toxicity[e]	50		51.7	36.9	0.2	0.1	129	91.5	0.07	0.05
	100M, 80F		51.9	48.6	0.2	0.2	221	130	0.12	0.07
Rabbit	5	19[g]	-	171	-	0.6	-	667	-	0.3
Embryo/fetal development toxicity[f]	15		-	362	-	1.4	-	1630	-	0.9
	45		-	523	-	2.0	-	4210	-	2.2
Dog	30	42	11.3	10.9	0.04	0.04	35.5	39.5	0.02	0.02
9-mo toxicity[h]	50		10.8	16.3	0.04	0.06	19.4	75.4	0.01	0.04
	80		12.2	11.5	0.05	0.04	54.7	92.2	0.03	0.05

[a] Day of blood specimen collection. First day of dosing designated study day 0 for nonclinical studies and study day 1 for clinical studies.
[b] Clinical dose was fixed at 560 mg/day (maximum therapeutic dose).Weight-based dose assumes an 80 kg individual.
[c] Source: EMEA/H/C/003791/II/0016, Seq0043/M4.2.2.4/15-201-Hu-PO-PK (FK11020)
[d] Source: EMEA/H/C/003791/II/0018, Seq0049/M4.2.3.4.2/14-239-M-PO-TX (TOX10814)
[e] Source: EMEA/H/C/003791/II/0016, Seq0043/M4.2.3.2/14-057-R-PO-TX (TOX10827)
[f] Source: EMEA/H/C/003791/II/0016, Seq0043/M4.2.3.5.2/13-133-B-PO-TT (TOX10823)
[g] Animals were dosed on gestation days 6 through 19
[h] Source: EMEA/H/C/003791/II/0016, Seq0043/M4.2.3.2/14-060-D-PO-TX (TOX10828)

Table 12. Steady-State Animal-to-Human M34 Exposure Ratios for Animal Toxicology Doses Relative to Clinical Doses

Species/ Study	Dose Level (mg/kg/d)	Study Day[a]	C_{max} (ng/mL)		C_{max} Animal/human (560 mg/d) Exposure Ratio		AUC (ng·h/mL)		AUC Animal/human (560 mg) Exposure Ratio	
			M	F	M	F	M	F	M	F
Human										
Phase 1b/2	7.0[b]	22	205[c]		1		1500[c]		1	
Mouse	100	28	52.1	102	0.3	0.5	148	343	0.1	0.2
4-wk toxicity[d]	500		129	548	0.6	2.7	683	2430	0.5	1.6
	1000		278	614	1.4	3.0	1360	3950	0.9	2.6
Rat	25	42	23.2	22.0	0.1	0.1	47.2	42.2	0.03	0.03
6-mo toxicity[e]	50		35.3	51.5	0.2	0.3	115	156	0.08	0.10
	100M, 80F		41.8	85.9	0.2	0.4	199	265	0.13	0.18
Rabbit	5	19[g]	-	15.6	-	0.1	-	93.8	-	0.1
Embryo/fetal development toxicity[f]	15		-	47.9	-	0.2	-	335	-	0.2
	45		-	131	-	0.6	-	1350	-	0.9
Dog	30	42	63.5	61.6	0.3	0.3	396	215	0.3	0.1
9-mo toxicity[h]	50		95.1	128	0.5	0.6	232	982	0.2	0.7
	80		146	191	0.7	0.9	898	1620	0.6	1.1

[a] Day of blood specimen collection. First day of dosing designated study Day 0 for nonclinical studies and study day 1 for clinical studies.

[b] Clinical dose was fixed at 560 mg/day (maximum therapeutic dose).Weight-based dose assumes an 80 kg individual.

[c] Source: EMEA/H/C/003791/II/0016, Seq0043/M4.2.2.4/15-201-Hu-PO-PK (FK11020)

[d] Source: EMEA/H/C/003791/II/0018, Seq0049/M4.2.3.4.2/14-239-M-PO-TX (TOX10814)

[e] Source: EMEA/H/C/003791/II/0016, Seq0043/M4.2.3.2/14-057-R-PO-TX (TOX10827)

[f] Source: EMEA/H/C/003791/II/0016, Seq0043/M4.2.3.5.2/13-133-B-PO-TT (TOX10823)

[g] Animals were dosed on gestation days 6 through 19

[h] Source: EMEA/H/C/003791/II/0016, Seq0043/M4.2.3.2/14-060-D-PO-TX (TOX10828)

2.2.5. Ecotoxicity / environmental risk assessment

The MAH has submitted an updated ERA dated October 2015 in which an updated CONai, based on sales forecast, is set to 2700 kg/year in the EU by 2018.

Phase I

Using the 2700 kg/year CONai claimed by the MAH F_{pen} is set to 0.0026% giving a $PEC_{surfacewater}$ of 0.0073 µg/L.

The outcome of the Phase II Tier A fate and effects analysis using these figures and previously presented ERA data gives;

$PEC_{surfacewater}/PNEC_{water}$ = 0.0073 (υg/L)/1.55 (υg/L) = 0.0047 which is below 1, thus further testing in the aquatic compartment is not necessary.

$PEC_{surfacewater}/PNEC_{microorganisms}$ = 0.0073 (υg/L)/100 000 (υg/L) = $0.73x10^{-7}$ which is below 0.1, thus further evaluation of the fate and effects of ibrutinib on microorganisms is not required.

$PEC_{groundwater}/PNEC_{groundwater}$ = 0.0018 (υg/L) / 4.79 (υg/L) = 0.004 which is below 1, thus further testing in the aquatic compartment is not necessary.

Phase II

PEC_{soil} / $PNEC_{soil}$ = 0.004 which is below 1, thus further testing in the terrestrial compartment is not necessary.

$PEC_{sediment}$ / $PNEC_{sediment}$ = 0.005 which is below 1, thus further testing in the sediment compartment is not necessary.

The revised PEC/PNEC ratios recalculated to broaden the existing indication showed some variation compared to previously calculated values. However, this does not change the conclusions drawn from previous ERAs and ibrutinib is unlikely to represent a risk to the environment.

2.2.6. Discussion on non-clinical aspects

In the toxicity studies presented and assessed as part of the initial Marketing Authorisation Application (MAA) several target organs were identified in both rat and dog. In the studies submitted as part of this extension of indication, lymph nodes, spleen, decreased bone marrow lymphoid cells, thymus, nonglandular stomach, intestines, pancreas and cortical and trabecular bone were identified as target organs/tissues of toxicity. Additionally, atrophy of squamous epithelium was noted in some tissues (oesophagus, stomach, skin and vagina). The primary toxicologic target in dogs dosed for 4 or 13 weeks was the intestinal tract. Additional target tissues noted in dogs dosed for 13 weeks included the Peyer's patches and stomach. In studies of up to 13 weeks duration in rats and dogs, treatment-related soft faeces and/or diarrhoea was a consistent clinical finding. Also, rats dosed at 175 or 300 mg/kg/day for 13 weeks included minimal to mild acute inflammation in the cecum, colon, and/or rectum. Slight corneal dystrophy/opacity was noted during ophthalmic examinations for 3 of 10 high-dose group dogs (150 mg/kg/day) in the 4-week study and for 1 high-dose group dog (220/120 mg/kg/day) in the subsequent 13-week study. In the 13-week study preformed in dog for the initial MAA most findings were observed in the high dose group (220/120 mg/kg/day), however the NOAEL in that study were set to 30 mg/kg/day due to findings in Peyer's patches and stomach at the 80/60 mg/kg/day dose. In the 13-week rat study the NOEAL were set to 30 mg/kg/day due to multiple findings in the higher dose groups (100, 300M, 300/175F).

In general, many of these signals have not been re-identified in the new toxicity studies presented in this type II variation. For instance atypical bone marrow cells were not seen in either the rat 6-month study at overlapping dose levels or in the dog 9-month study. Also, the intestinal tract toxicity initially observed in dog was not re-identified in the 9-month study. It could be speculated that treated animals develops tolerance to ibrutinib over time. However, when comparing the exposure data from the previously assessed studies and the now submitted prolonged toxicity studies it is clear that the animals in the new longer studies are not exposed to the levels reached in the previous studies. Consequently, it can be questioned whether the decrease in toxicity is due to tolerance or if the lack of toxicity in the new studies is due to under exposure, especially since the major toxicities found in the previous studies were observed at higher exposure than what was tested in the new studies. Nevertheless, it can be concluded that no new relevant toxicity has been revealed in the new rat and dog studies.

There were no effects on fertility or reproductive capacities in males or females rats up to the maximum dose tested of 100 mg/kg/day [HED 16 mg/kg].

In pregnant rabbits, ibrutinib at a dose of 15 mg/kg/day or greater was associated with skeletal malformations (fused sternebrae) and ibrutinib at a dose of 45 mg/kg/day was associated with increased post implantation loss. Ibrutinib caused malformations in rabbits at a dose of 15 mg/kg/day (approximately 2.0 times the exposure (AUC) in patients with MCL administered ibrutinib 560 mg daily and 2.8 times the exposure in patients with CLL or WM receiving ibrutinib dose 420 mg per day).

Consequently the foetal NOAEL was 5 mg/kg/day (approximately 0.7 times the AUC of ibrutinib at a dose of 560 mg daily) (SmPC section 5.3).

No effects on fertility or reproductive capacities were observed in male or female rats up to the maximum dose tested, 100 mg/kg/day (Human Equivalent Dose [HED]16 mg/kg/day) (SmpC section 5.3).

Normally, non-clinical *in vivo* evaluation of major human metabolites (>10% of total) should be performed before entering phase III. In the case of ibrutinib, the initial indication falls under the ICH S9 guideline, in which it is noted that in some cases, metabolites that have been identified in humans have not been qualified in nonclinical studies. It is further commented in for these metabolites, a separate evaluation is generally not warranted for patients with advanced cancer. Since the first-line CLL indication applied for in the context of this application, includes patients with a longer life expectancy, the non-clinical evaluation of major human metabolites needs to be addressed, and more specifically M21, M25 and M34. The exposures to these metabolites in human correspond up to three times that of ibrutinib. The MAH presented data on exposure with the major human metabolites in the pivotal toxicity studies and in the dose-range finding study performed in a transgenic Tg.rasH2 mouse model. The data clearly showed that supra-clinical exposures where only reached in the transgenic Tg.rasH2 mouse model but not in the pivotal toxicity studies or in the embryo-foetal studies.

The study performed in transgenic Tg.rasH2 mice had the objective to determine the potential toxicity of ibrutinib and to support the dose selection for a 26-week oral carcinogenicity study in this strain of mice. In addition, the toxicokinetic characteristics of ibrutinib and 5 of its metabolites were determined. The study was performed over 28 days of daily dosing without recovery. The following parameters and end points were addressed; clinical signs, body weights, body weight changes, food consumption, clinical pathology parameters (hematology and clinical chemistry), gross necropsy findings, organ weights, and histopathologic examinations (assessed in relation to procedure EMEA/H/C/3791/II/18). The data showed that ibrutinb was well tolerated (with only minimal severity non-adverse findings at ≥ 500 mg/kg/day) also at the highest dose tested and NOEAL were subsequently set at this dose (1000 mg/kg/day).

The potential transformation of ibrutinib into genotoxic metabolites has not been addressed by the MAH. For the intended indication such transformation is regarded as a potential safety concern. Consequently, the MAH will perform, a (Q)SAR/DEREK analysis and AMES test for M21 and M34 but not for the M25 since it is form *in vitro* using rat S9 metabolic activation and consequently already evaluated for mutagenic potential and since M25 did not generate structural alerts when analyzed by DEREK-analysis (see discussion on clinical efficacy).

The revised PEC/PNEC ratios recalculated to broaden the existing indication showed some variation compared to previously calculated values. However, this does not change the conclusions drawn from previous ERAs and ibrutinib is unlikely to represent a risk to the environment.

2.2.7. Conclusion on the non-clinical aspects

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

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.

- Tabular overview of clinical studies

Study ID EudraCT Number First Patient First Visit / Completion date (day Month year) Study Status[a]	Country(ies)/ Number of Centers[b]	Phase Study Description/Design, Study Population, Primary Objective(s)	Total Number of Subjects	Study Drug(s): Formulation (Route of Administration) Dose Regimen Duration of Treatment	Number of Subjects Treated (by Treatment Group)[b]	Type of Study Report Issue Date Document ID Number CTD Location of Report or Publication
New Clinical Study						
PCYC-1115-CA 2012-003967-23 21 March 2013 28 May 2015 Completed Synopsis	AUS, BEL, CAN, CHN, CZE, UKR, IRL, ISR, ITA, NZL, RUS, TUR, USA 88	Phase: 3 Randomized, open-label Subjects ≥65 years with treatment-naive CLL/ SLL Assess efficacy of ibrutinib compared with chlorambucil based on PFS by IRC	Randomized: 273 Treated: 267	ibrutinib: capsule (Oral) Arm A: chlorambucil 0.5 mg/kg on Days 1 and 15 of each 28-day cycle Treatment Arm B: ibrutinib 420 mg/day Until PD or unacceptable toxicity	132 135	Full Report 04 Aug 2015 EDMS-ERI-11001940 5.3.5.1
Prior Clinical Studies Contributing Data for This Submission						
PCYC-1112-CA 2012-000694-23 22 Jun 2012 06 Nov 2013 Ongoing[c]	AUS, AUT, ESP, FRA, GBR, IRL, ITA, POL, USA 67	Phase: 3 Randomized, open-label Subjects with CLL/SLL who had relapsed or refractory disease following at least 1 line of prior systemic therapy Evaluate efficacy of ibrutinib compared to ofatumumab based on IRC assessment of PFS	Randomized: 391 Treated: 386	ibrutinib: capsule (Oral) ibrutinib 420 mg/day ofatumumab Week 1: 300 mg initial dose Weeks 2 to 8: 2,000 mg weekly Weeks 12 to 24: 2,000 mg every 4 weeks Until disease progression or unacceptable toxicity	195 191	Full Report 25 Mar 2014 EDMS-ERI-79413055 5.3.5.1
PCYC-1118E[d] N/A 18 May 2012 28 Feb 2014 Ongoing[c]	USA 3	Phase: 2 Simon 2-stage, open-label, single-arm Subjects with relapsed or refractory Waldenström's macroglobulinemia Assess ORR, major response rates, and VGPR/CR rates	Enrolled: 64 Treated: 63	ibrutinib: capsule (Oral) ibrutinib 420 mg/day Until progressive disease or unacceptable toxicity	63	Full Report 29 Sep 2014 EDMS-ERI-89280446 5.3.5.2

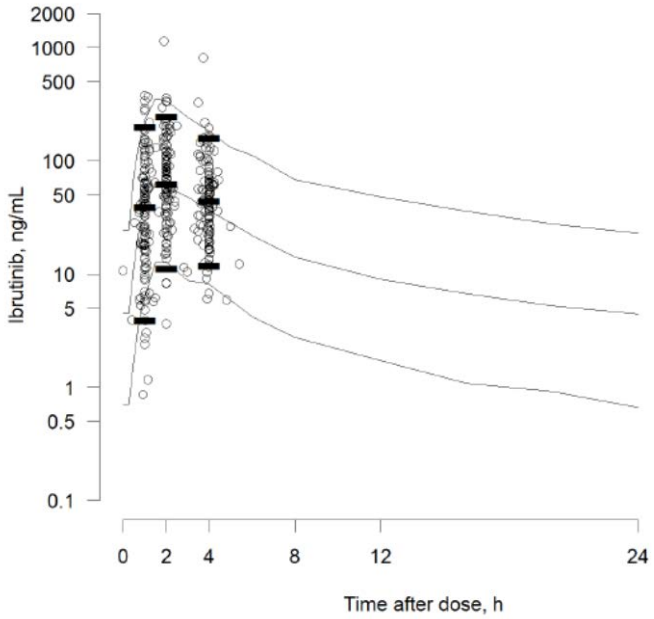
PCYC-1102-CA N/A 20 May 2010 18 Dec 2012 Completed	USA 8	Phase: 1b/2 Open-label, nonrandomized Subjects with treatment-naive CLL/SLL (≥65 years), relapsed/refractory CLL/SLL (≥18 years) or high-risk relapsed/refractory CLL/SLL (≥18 years) Determine safety of 2 fixed doses of ibrutinib	Enrolled: 133 Treated: 132	ibrutinib: capsule (Oral) ibrutinib: 420 mg/day ibrutinib: 840 mg/day Until PD or unacceptable toxicity	94 38	Full Report 26 Mar 2014 EDMS-ERI-81264430 5.3.5.2
PCYC-1104-CA 2010-022939-11 08 Feb 2011 17 Jan 2014 Completed	DEU, GBR, POL, USA 18	Phase: 2 Open-label, nonrandomized Subjects with histologically-documented MCL that has relapsed after 1 (but not >5) prior treatment regimens Evaluate ORR	Enrolled: 115 Treated: 111	ibrutinib: capsule (Oral) ibrutinib 560 mg/day PD or unacceptable toxicity	111	Full Report: 24 Jul 2014 EDMS-ERI-90891875 5.3.5.2

a. As of September 2015.
b. Information is provided only for completed studies and ongoing studies that have completed primary analysis.
c. Primary analysis completed.
d. Investigator-initiated study.

2.3.2. Pharmacokinetics

In the pivotal trial (Study 1115), the patients in the ibutinib arm (n=136) received 420 mg/day, which is the same dose as already approved for second line treatment of CLL. Sparse sampling for determination of ibrutinib and metabolite PCI-45227 concentrations was performed on day 1 in Cycles 2 (predose and around 1, 2 and 4 hours) and 3 (predose).

The plasma concentrations observed were in agreement with previous data in CLL and other patient populations. Below the observed concentrations are shown overlayed to the model based simulations derived from a previous popPK model.



2.3.3. Discussion and conclusions on clinical pharmacology

Pharmacokinetics in the new patient population appears to be similar to the pharmacokinetics in previously approved indications. This is expected. No changes in the SmPC regarding pharmacokinetics

(section 5.2) or drug interactions (section 4.5) are required. Information regarding drug interactions and special populations can be extrapolated from previous indications.

2.4. Clinical efficacy

2.4.1. Dose response study

N/A

2.4.2. Main study

PCYC-1115-CA (Study 1115)

Study 1115 was a randomized, multicenter, open-label, phase 3 study of the Bruton's Tyrosine Kinase Inhibitor ibrutinib versus chlorambucil in patients 65 years or older with treatment naive chronic lymphocytic leukemia or small lymphocytic lymphoma (SLL).

Methods

Study participants

Key inclusion criteria

1. Male or female ≥ 65 years of age. Subjects between 65 and 70 years of age were required to have at least 1 of the following additional comorbidities that could preclude the use of frontline chemo-immunotherapy with fludarabine, cyclophosphamide, and rituximab:
    - Creatinine clearance < 70 mL/min
    - Platelet count < 100,000 µL or hemoglobin < 10 g/dL
    - Clinically apparent autoimmune cytopenia (autoimmune hemolytic anemia or immune thrombocytopenia)
    - ECOG PS score of 1 or 2

2. Diagnosis of CLL or SLL per published diagnostic criteria (Hallek et al, 2008)

3. Active disease meeting at least 1 of the iwCLL 2008 criteria for requiring treatment (Hallek et al, 2008)

4. Measurable nodal disease by computed tomography (CT)

5. ECOG PS score of 0-2

6. Acceptable laboratory parameters (ie, absolute neutrophil count [ANC] ≥ 1,000/µL independent of growth factor support for at least 7 days prior to screening, platelets ≥ 50,000/µL independent of transfusion and growth factor support for at least 7 days prior to screening)

Key exclusion criteria

1. Any previous CLL/SLL treatment

2. Known lymphoma or leukaemia of the central nervous system (CNS)
3. History or current evidence of Richter's transformation or prolymphocytic leukaemia
4. del17p-positive disease
5. Requirement for anticoagulation with warfarin

Treatments

Treatment Arm A

Oral chlorambucil 0.5 mg/kg on Days 1 and 15 of each 28-day cycle; the dose could be increased, if well tolerated, in increments of 0.1 mg/kg on Day 1 of each cycle to a maximum of 0.8 mg/kg; patients received a minimum of 3 and a maximum of 12 cycles, in the absence of progressive disease or unacceptable toxicity.

Subjects in the chlorambucil group who had progressive disease confirmed by the IRC could subsequently receive ibrutinib in the follow-on study, PCYC-1116-CA.

Treatment Arm B

Oral ibrutinib 420 mg/day, until progressive disease (PD) or unacceptable toxicity.

Objectives

The primary objective of this study was to evaluate the efficacy of ibrutinib compared with chlorambucil based on the independent review committee (IRC) assessment of PFS in subjects 65 years of age or older with treatment-naive CLL or SLL.

Secondary objectives were to compare the treatment arms in terms of the following:

- Efficacy
    - Overall response rate (ORR) according to International Workshop on CLL (iwCLL) 2008 criteria, as assessed by the IRC
    - Rate of minimal residual disease (MRD)-negative complete responses (CRs)
    - Overall survival (OS)
    - Fatigue measured by Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)
    - Haematological improvement measured by haemoglobin and platelet counts
- Safety
    - Safety and tolerability of ibrutinib compared with chlorambucil

Outcomes/endpoints

The primary endpoint of this study was progression-free survival (PFS) as assessed by the IRC, defined as the time from the date of randomization to date of IRC-confirmed disease progression or date of death from any cause, whichever occurred first.

Secondary efficacy endpoints were:

- ORR as assessed by the IRC, defined as the proportion of subjects who achieved a best overall response of CR, CRi, nPR, or PR per IRC assessment.
- OS, defined as the time from the date of randomization to the date of death from any cause

- Event-free survival (EFS) as assessed by the IRC, defined as the time from the date of randomization to the date of first documentation of EFS event
- Hematologic improvement:
    - Rate of sustained platelet improvement, defined as the proportion of subjects with sustained improvement defined as platelet counts >100 $\times 10^9$/L if baseline ≤100 $\times 10^9$/L or increase ≥ 50% over baseline, sustained continuously for ≥ 56 days without blood transfusions or growth factors.
    - Rate of sustained haemoglobin improvement, defined as the proportion of subjects with sustained improvement defined as haemoglobin >11 g/dL if baseline ≤11 g/dL or increase ≥ 2 g/dL over baseline, sustained continuously for ≥ 56 days without blood transfusions or growth factors.
- Rate of MRD-negative response, defined as the proportion of subjects who achieved MRD-negative response defined as <1 CLL cell per 10,000 leukocytes, assessed by flow cytometry of a bone marrow aspirate or peripheral blood sample, per central laboratory.
- Rate of clinically meaningful improvement in FACIT-Fatigue score, defined as the proportion of subjects who achieved a clinically meaningful improvement defined as an improvement of ≥ 3 points at any post-baseline time point measured by FACIT-Fatigue scale prior to the initiation of anti-neoplastic therapy.

Sample size

This study was designed to evaluate the effect of treatment on PFS and was powered for this endpoint. A minimum of 272 subjects were to be enrolled. The sample size for the study was calculated based on the following considerations:

- A 1:1 randomization ratio between Arms A and B.
- A uniform accrual rate of approximately 40 subjects per month.
- A target HR of 0.5. Assuming the median PFS for Arm A is 15 months from randomization, a target HR of 0.5 corresponds to a 2-fold increase in median PFS for Arm B relative to Arm A (ie, 30 months vs. 15 months, respectively).
- Eighty-one progression events provide approximately 85% power to detect the target HR of 0.5 based on a log-rank test and a 1-sided overall significance level of 0.025.
- No interim analysis.

The sample size and power calculations were based on a 1-sided log-rank test for PFS. A total of 273 subjects were randomized to participate in the study. Four of the subjects were randomized at Site 381 which was closed due to GCP quality findings with respect to source data collection and improper handling of study drug. Therefore these 4 subjects were excluded from the clinical database.

As a result, only 269 subjects were considered as being randomized for the intent-to-treat (ITT) analyses performed.

Randomisation

Patients were randomised 1:1, with 136 subjects randomized to the ibrutinib arm and 133 subjects randomized to the chlorambucil arm.

The randomisation of treatment assignment was blocked by geographic region (US vs. non-US) and stratified by ECOG PS (0, 1 vs. 2) and presence of advanced-stage disease (Rai stage ≤ II vs. III-IV)

Blinding (masking)

This was an open-label study.

Statistical methods

Analyses of efficacy endpoints were conducted on the Intent-to-treat (ITT) Population, defined as all randomized subjects in the clinical database. The analysis for the study occurred 15 months after randomization of the last subject.

In general, all tests were to be performed at a 2-sided significance level of 0.05, unless otherwise specified.

If the primary endpoint achieved statistical significance, tests of secondary endpoints were to be performed at the 2-sided significance level of 0.05 in a sequential hierarchical manner based on a closed testing procedure. All key secondary endpoints were to be ranked in sequence according to the following hierarchical order: ORR; OS; EFS; Rate of sustained platelet improvement; Rate of sustained hemoglobin improvement; Rate of MRD-negative response; Rate of clinically meaningful improvement in FACIT-Fatigue score.

Results

Participant flow

A total of 269 subjects were randomized, with 136 subjects randomized to the ibrutinib arm and 133 subjects randomized to the chlorambucil arm (see table below). Four additional randomized subjects from a single site (Site 381) were excluded from the clinical database due to significant GCP issues and for-cause closure of this clinical site.

Table 13. Subject disposition (Study 1115)

	Ibrutinib N=136 n (%)	Chlorambucil N=133 n (%)	Total N=269 n (%)
Subjects who never received study drug	1 (0.7)	1 (0.8)	2 (0.7)
Reason never received study drug			
Withdrawal of consent	1 (0.7)	1 (0.8)	2 (0.7)
Subjects who received study drug	135 (99.3)	132 (99.2)	267 (99.3)
Still on treatment[a]	118 (86.8)	0	118 (43.9)
Completion of 12-cycles chlorambucil treatment	NA	53 (39.8)	53 (19.7)
Discontinued study drug	17 (12.5)	79 (59.4)	96 (35.7)
Primary reason for discontinuation of study drug			
Unacceptable toxicity/adverse event	12 (8.8)	30 (22.6)	42 (15.6)
IRC-confirmed PD	2 (1.5)	6 (4.5)	8 (3.0)
Death	2 (1.5)	0	2 (0.7)
Withdrawal from treatment by patient	1 (0.7)	6 (4.5)	7 (2.6)
Investigator decision	0	37 (27.8)	37 (13.8)
SCT	0	0	0
New anti-cancer therapy other than SCT	0	4 (3.0)	4 (1.5)
Other	0	33 (24.8)	33 (12.3)
Lack of efficacy	0	21 (15.8)	21 (7.8)
PD	0	11 (8.3)	11 (4.1)
Other	0	1 (0.8)	1 (0.4)

IRC: independent review committee; NA: not applicable; PD: progressive disease; SCT: stem cell transplant.
N= number of subjects in the specified population. n=number of subjects in each category. % = 100*n/N.
Sub-category for primary reason for study drug discontinuation is listed in descending order of frequency in the ibrutinib treatment arm.
[a] Subjects who were still on treatment when study closed for final analysis.

Recruitment

This study was conducted at a total of 88 study sites including 16 study sites in the United States (US) and 42 study sites in the European Union (EU) and 30 study sites in 6 additional countries worldwide: Australia, Canada, China, Israel, New Zealand and Turkey. The data lock for the final analysis was 28 May 2015.

Conduct of the study

Table 14. Protocol amendments (Study 1115)

Amendment Number and Date	Key Changes
1.1 03 Jan 2014	• Removed the 12-month time limit after last chlorambucil dose to receive second-line ibrutinib in Study 1116 • Updated guidance on missed dose, treatment-related lymphocytosis, use of anti-coagulant, anti-platelet and QT-prolonging agents • Added guidance on perioperative management of ibrutinib • Required that SAEs that occur >30 days after the last dose of study drug, if deemed ibrutinib-related, be reported to the Sponsor • Added that other malignancies were to be reported throughout the study • Updated the Summary of Safety section to align with the IB and the FDA approved product label
1.1 Version 2 05 Mar 2014	• Updated the guidance for the management of ibrutinib with concomitant CYP3A inhibitors or inducers • Required screening FISH analysis results to be available prior to randomization
2.1* 17 Feb 2015	• Clarified that in the event that a bone marrow sample for MRD assessment could not be obtained, a peripheral blood sample should be submitted • Clarified criteria for hematological improvement • Specified that PFS will not be censored at the start of new anti-cancer therapy • Clarified criteria defining PR and PRL based on updated response criteria (Hallek et al, 2013; Cheson et al, 2012; Hallek et al, 2012) • Updated safety information and concomitant medication administration sections to align with the IB and the FDA-approved product label • Revised assessment of EFS and revised the schedule for subjects confirmed as MRD negative in the marrow to be followed by peripheral blood MRD analyses, from every 3 months to every 4 months to be consistent with the 4-month visit schedule

CYP: cytochrome P450; EFS. event-free survival; EMA: European Medicines Agency; FDA: Food and Drug Administration; FISH: fluorescence *in situ* hybridization; IB: Investigator's Brochure; MRD: minimal residual disease; PFS: progression-free survival; PR: partial response; PRL: partial response with lymphocytosis; SAE: serious adverse event.

*Protocol Amendment 2 was submitted to FDA for review; not distributed to study sites. The summaries of change associated with Amendments 2 and 2.1 were both submitted to the study sites along with Protocol Amendment 2.1

An overview of protocol violations is provided in the table below:

Table 15. Protocol deviations (Study 1115)

Category	Ibrutinib N=136 n (%)	Chlorambucil N=133 n (%)	Total N=269 n (%)
Total	**9 (6.6)**	**7 (5.3)**	**16 (5.9)**
Eligibility	2 (1.5)	4 (3.0)	6 (2.2)
Informed Consent	4 (2.9)	1 (0.8)	5 (1.9)
Investigational Product	1 (0.7)	0	1 (0.4)
Prohibited Concomitant Medication	2 (1.5)	2 (1.5)	4 (1.5)

Baseline data

Table 16. Demographic characteristics (Study 1115)

	Ibrutinib N=136	Chlorambucil N=133	Total N=269
Age (years)			
n	136	133	269
Mean (SD)	73.1 (5.67)	73.4 (5.95)	73.3 (5.81)
Median	73.0	72.0	73.0
Min, Max	65, 89	65, 90	65, 90
Age groups - n (%)			
<70 years	40 (29.4)	40 (30.1)	80 (29.7)
≥70 years	96 (70.6)	93 (69.9)	189 (70.3)
Gender - n (%)			
Male	88 (64.7)	81 (60.9)	169 (62.8)
Female	48 (35.3)	52 (39.1)	100 (37.2)
Race - n (%)			
White	120 (88.2)	125 (94.0)	245 (91.1)
Asian	9 (6.6)	4 (3.0)	13 (4.8)
Black or African American	5 (3.7)	3 (2.3)	8 (3.0)
Native Hawaiian or Other Pacific Islander	0	1 (0.8)	1 (0.4)
Subject declined to answer/unknown	2 (1.5)	0	2 (0.7)
Ethnicity – n (%)			
Not Hispanic or Latino	132 (97.1)	129 (97.0)	261 (97.0)
Hispanic or Latino	3 (2.2)	2 (1.5)	5 (1.9)
Subject declined to answer/ unknown	1 (0.7)	2 (1.5)	3 (1.1)
Geographic Region - n (%)			
US	31 (22.8)	29 (21.8)	60 (22.3)
Non-US	105 (77.2)	104 (78.2)	209 (77.7)

SD: standard deviation; US: United States
N=number of subjects in the specified population; n=number of subjects in each category; %=100*n/N.
Sub-categories for "race" and "ethnicity" (except "Subject declined to answer/unknown") are listed in descending order of frequency in the ibrutinib treatment arm.

Table 17. Baseline disease characteristics (Study 1115)

	Ibrutinib N=136	Chlorambucil N=133	Total N=269
Months from initial diagnosis to randomization			
n	136	133	269
Mean (SD)	45.1 (45.33)	50.4 (57.50)	47.7 (51.68)
Median	30.5	31.0	31.0
Min, Max	1, 241	1, 294	1, 294
Histology at diagnosis – n (%)			
CLL	123 (90.4)	126 (94.7)	249 (92.6)
SLL	13 (9.6)	7 (5.3)	20 (7.4)
Rai stage as reported on IRT/IWRS – n (%)			
Stage 0	3 (2.2)	2 (1.5)	5 (1.9)
Stage I	32 (23.5)	28 (21.1)	60 (22.3)
Stage II	41 (30.1)	41 (30.8)	82 (30.5)
Stage III	28 (20.6)	29 (21.8)	57 (21.2)
Stage IV	32 (23.5)	33 (24.8)	65 (24.2)
ECOG PS score per IRT/IWRS – n (%)			
0	60 (44.1)	54 (40.6)	114 (42.4)
1	65 (47.8)	67 (50.4)	132 (49.1)
2	11 (8.1)	12 (9.0)	23 (8.6)
Bulky Disease[a] – n (%)			
Yes (≥5 cm)	54 (39.7)	40 (30.1)	94 (34.9)
No (<5 cm)	80 (58.8)	90 (67.7)	170 (63.2)
Missing	2 (1.5)	3 (2.3)	5 (1.9)
del11q22.3 (ATM) – n (%)			
Yes	29 (21.3)	25 (18.8)	54 (20.1)
No	101 (74.3)	96 (72.2)	197 (73.2)
Missing/not reported	6 (4.4)	12 (9.0)	18 (6.7)
Cytopenia – n (%)			
Hemoglobin ≤11 g/dL	51 (37.5)	55 (41.4)	106 (39.4)
Platelets ≤100 x 10^9/L	35 (25.7)	28 (21.1)	63 (23.4)
Absolute neutrophil count ≤1.5 x 10^9/L	10 (7.4)	7 (5.3)	17 (6.3)
Any of the above	72 (52.9)	73 (54.9)	145 (53.9)

ATM: ataxia telangiectasia mutated; CLL: chronic lymphocytic leukemia; del11q: deletion in the long arm of chromosome 11; ECOG PS: Eastern Cooperative Oncology Group performance status; IRT: interactive response technology; IWRS: interactive web response system; SD: standard deviation; SLL: small lymphocytic lymphoma.
N: number of subjects in the specified population. Percentages are calculated by 100*n/N.
[a] Based on the largest longest diameter of target lymph node at screening per the IRC assessment.

Numbers analysed

Table 18. Data sets analysed (Study 1115)

Population	Ibrutinib	Chlorambucil	Total
Intent-to-treat (ITT)	136	133	269
Safety	135	132	267

Outcomes and estimation

Primary endpoint - PFS per IRC assessment

Table 19. PFS (ITT population - Study 1115)

Progression Free Survival	Ibrutinib N=136	Chlorambucil N=133	Comparison/ Difference: Ibrutinib vs. Chlorambucil
Events - n (%)	15 (11.0)	64 (48.1)	
Disease progression- n	12	57	
Death - n	3	7	
Censored - n (%)	121 (89.0)	69 (51.9)	
PFS (Months)			
Median[a]	NE (NE, NE)	18.9 (14.1, 22.0)	
Min, Max	0.03+ , 24.71+	0.03+ , 23.98+	
P value[b]			<0.0001
Hazard ratio (95% CI)[c]			0.161 (0.091, 0.283)
PFS at landmark times (%)[a]			
6 Months	97.8	76.7	21.0
12 Months	93.2	61.7	31.5
15 Months	89.9	54.3	35.6
18 Months	89.9	51.5	38.4
24 Months	83.9	--	--

CI: confidence interval; PFS: progression-free survival
N = number of subjects in the specified population. + Indicates censored observation.
[a] Estimated by Kaplan-Meier method.
[b] P value is from stratified log-rank test.
[c] Hazard ratio is estimated using stratified Cox regression model with treatment as the only covariate.
The strata factors used in both stratified log-rank test and Cox regression model are ECOG (0-1 vs. 2) and Rai stage (≤II vs. III/IV) at baseline as reported in IWRS.

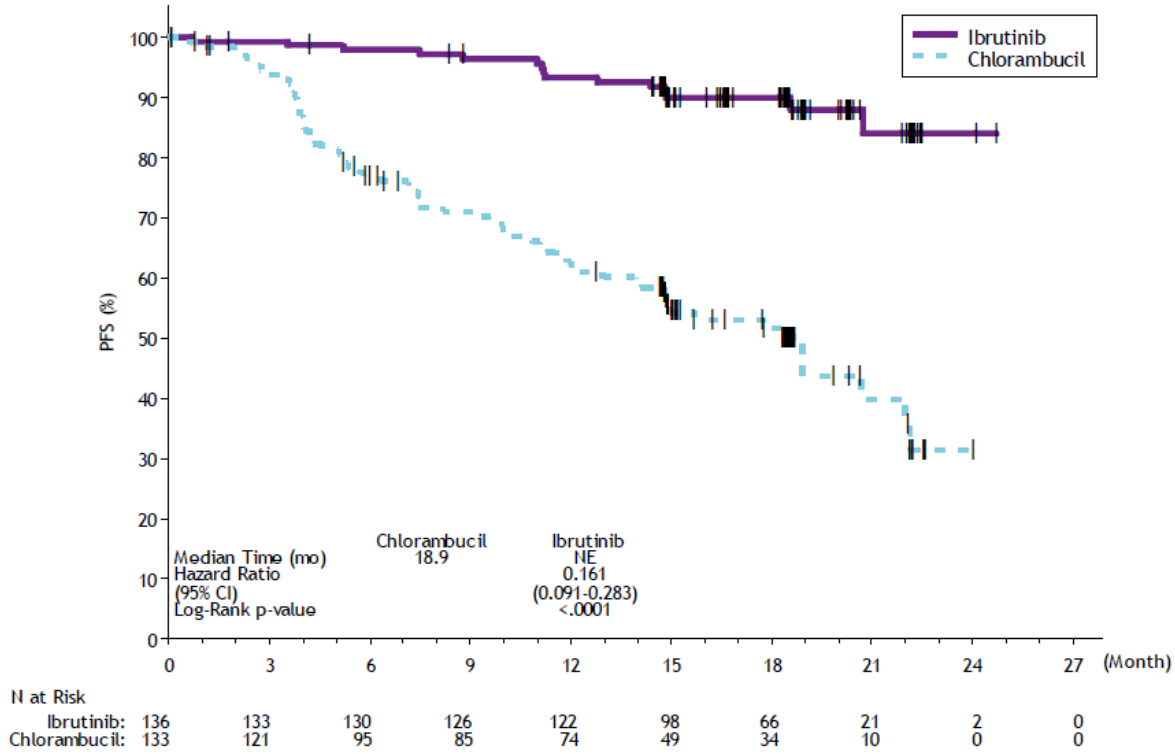
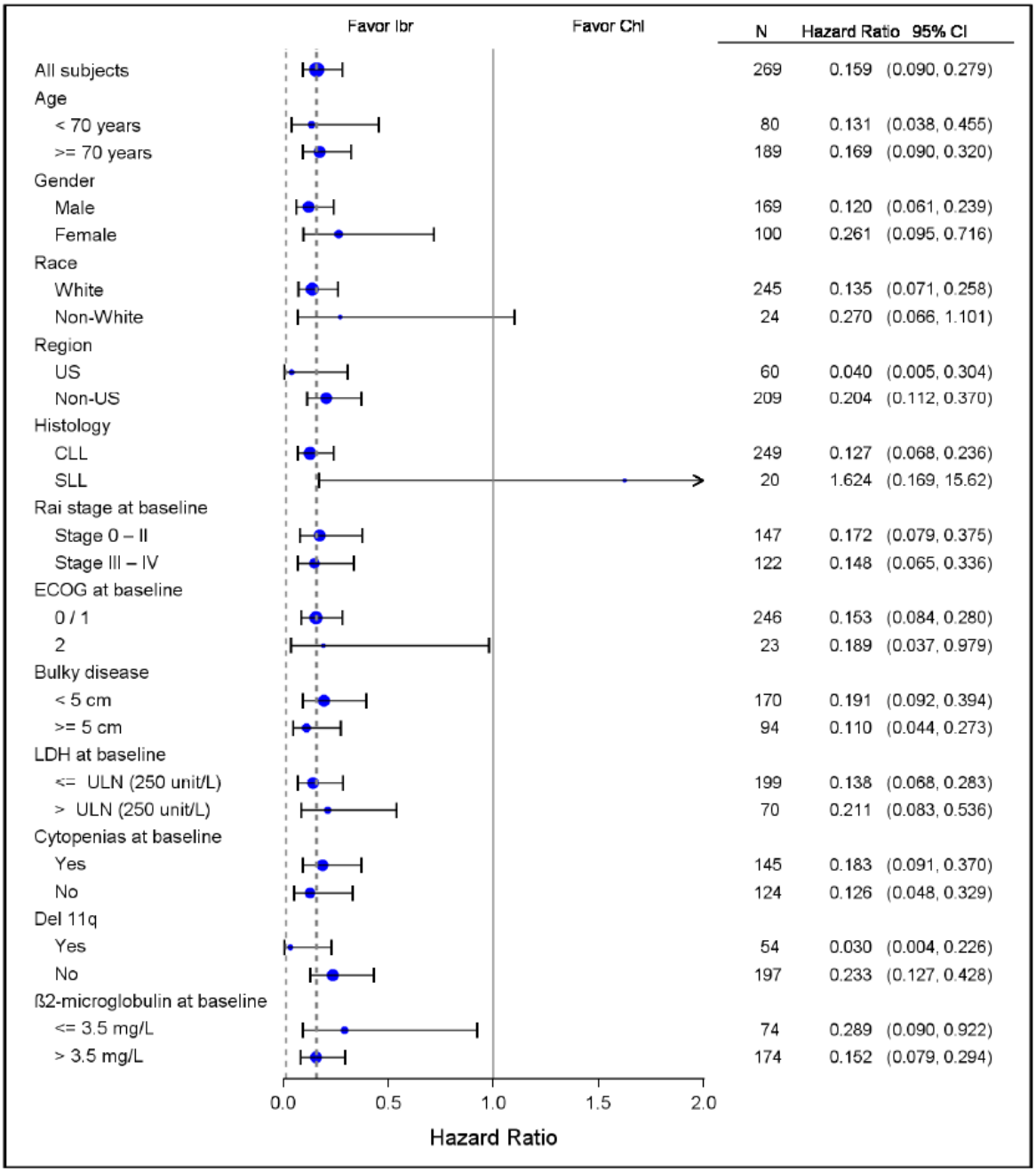


Figure 2. Kaplan-Meier curves of PFS per IRC assessment (ITT population - Study 1115)

Table 20. Sensitivity analyses for PFS (ITT population - Study 1115)

Sensitivity Analysis	Ibrutinib vs. Chlorambucil HR (95% CI)	P value
IRC-assessed PFS by unstratified log-rank test and unstratified Cox regression model	0.159 (0.090, 0.279)	<0.0001
IRC-assessed PFS: Subjects who received subsequent antineoplastic therapy were censored at the last disease assessment showing no evidence of progressive disease before the use of subsequent therapy	0.161 (0.091, 0.284)	<0.0001
Investigator-assessed PFS by stratified log-rank test and stratified Cox regression model	0.086 (0.043, 0.172)	<0.0001

IRC: independent review committee; PFS: progression-free survival.



Chl: chlorambucil; CI: confidence interval; CLL: chronic lymphocytic leukemia; del11q: deletion in the long arm of chromosome 11; ECOG PS: Eastern Cooperative Oncology Group performance status; Ibr: ibrutinib; LDH: lactic acid dehydrogenase; SLL: small lymphocytic lymphoma; ULN: upper limit of normal; US: United States

Figure 3. Forest plot of hazard ratios for PFS (ITT population - Study 1115)

Secondary endpoint - ORR per IRC assessment

Table 21. ORR by IRC assessment (ITT population - Study 1115)

	Ibrutinib N=136	Chlorambucil N=133	Ibrutinib vs. Chlorambucil
ORR (CR, CRi, nPR, or PR)	112 (82.4)	47 (35.3)	
Rate ratio (95% CI) [a]			2.32 (1.82, 2.95)
P-value [a]			<0.0001
ORR with PRL (CR, CRi, nPR, PR, or PRL)	117 (86.0)	47 (35.3)	
Rate ratio (95% CI) [a]			2.42 (1.91, 3.07)
P-value [a]			<0.0001
Best overall response, n(%)			
Complete response (CR)	5 (3.7)	2 (1.5)	
CR with incomplete blood count recovery (CRi)	1 (0.7)	0	
Nodular partial response (nPR)	1 (0.7)	0	
Partial response (PR)	105 (77.2)	45 (33.8)	
PR with lymphocytosis (PRL)	5 (3.7)	0	
Stable disease (SD)	13 (9.6)	61 (45.9)	
Progressive disease (PD)	0	17 (12.8)	
Not evaluable (NE)	6 (4.4)	8 (6.0)	

N=number of subjects in the specified population. n=number of subjects in each category. % = 100*n/N.

CI: confidence interval; ORR: overall response rate

CR, CRi, nPR, PR and PRL require confirmation with two consecutive assessments that are at least 56 days apart and no use of blood supportive product and/or growth factor during this period.

[a] Rate ratio and p-values for ORR and ORR with PRL are based on CMH chi-square test stratified by ECOG PS score (0-1 vs. 2) and Rai stage (≤II vs. III/IV) at baseline as reported in IWRS.

Secondary endpoint – OS

Table 22. OS (ITT population - Study 1115)

Overall Survival	Ibrutinib N=136	Chlorambucil N=133	Comparison/ Difference: Ibrutinib vs. Chlorambucil
Deaths - n (%)	3 (2.2)	17 (12.8)	
Censored - n (%)	133 (97.8)	116 (87.2)	
Overall survival (OS) (months)			
Median (95% CI)[a]	NE (NE, NE)	NE (NE, NE)	
Min, Max	0.10+ , 24.84+	0.10+ , 24.25+	
P value[b]			0.0010
Hazard ratio (95% CI)[c]			0.163 (0.048, 0.558)
OS at landmark times(%)[a]			
6 Months	97.8	96.2	1.6
12 Months	97.8	91.5	6.3
15 Months	97.8	89.2	8.6
18 Months	97.8	87.2	10.6
24 Months	97.8	85.3	12.4

CI: confidence interval; NE: not estimable; OS: overall survival

N = number of subjects in the specified population. + Indicates censored observation.

[a] Estimated by Kaplan-Meier method.

[b] P-value is from unstratified log-rank test. The corresponding unstratified Wilcoxon p-value is 0.0017.

[c] Hazard ratio is estimated using unstratified Cox regression model with treatment as the only covariate.

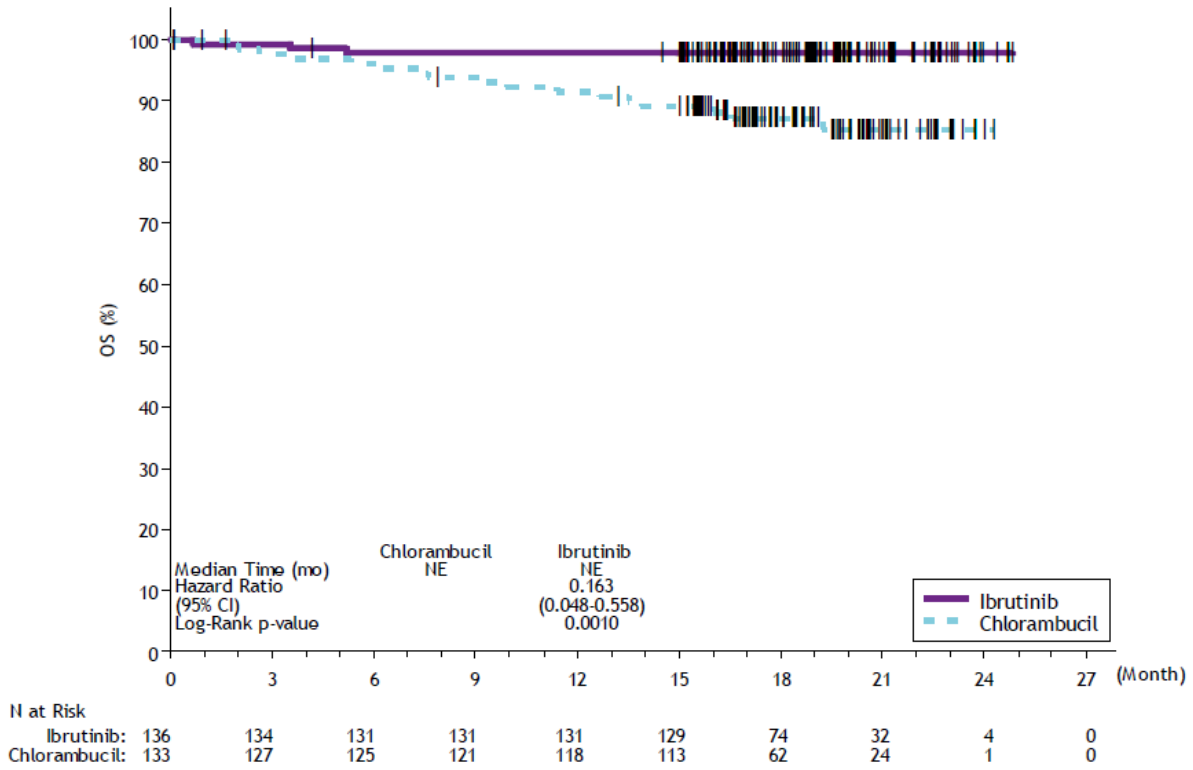


Figure 4. Kaplan-Meier curves for OS (ITT population - Study 1115)

Secondary endpoint – Sustained Hematologic improvement

Table 23. Proportion of subjects with sustained haematologic improvement (ITT Population - Study 1115)

	Ibrutinib N=136 n (%)	Chlorambucil N=133 n (%)	Ibrutinib vs. Chlorambucil P-value
Platelets	37 (27.2)	15 (11.3)	0.0009
Hemoglobin	62 (45.6)	27 (20.3)	<0.0001

N=Number of subjects in the specified population, n = number of subjects with sustained hematological improvement.
%=(n/N)*100.

Sustained hematologic improvement is defined as hematological improvement (platelet counts > 100 x 10^9/L if baseline ≤ 100 x 10^9/L or increase ≥50% over baseline; hemoglobin > 11 g/dL if baseline ≤ 11 g/dL or increase ≥ 2 g/dL over baseline) sustained continuously for ≥ 56 days without blood transfusions or growth factors.

Table 24. Proportion of subjects with sustained haematological improvement (ITT subjects with thrombocytopenia and anaemia at baseline - Study 1115)

	Ibrutinib N=136	Chlorambucil N=133	Ibrutinib vs. Chlorambucil P-value
Platelets ≤100 x 10^9/L at baseline - n	35	28	
Sustained improvement – n(%)	27 (77.1)	12 (42.9)	0.0054
Hemoglobin ≤11 g/dL at baseline - n	51	55	
Sustained improvement – n(%)	43 (84.3)	25 (45.5)	<0.0001

N = Number of subjects in the specified population, n = number of subjects with sustained hematological improvement.
%= (n/N)*100.

Sustained hematologic improvement is defined as hematological improvement that sustained continuously for ≥ 56 days without blood transfusion or growth factors which includes: platelet counts > 100 x 10^9/L if baseline ≤ 100 x 10^9/L or increase ≥ 50% over baseline; hemoglobin > 11 g/dL if baseline ≤ 11 g/dL or increase ≥ 2 g/dL over baseline.

Secondary endpoint – EFS

Table 25. EFS based on IRC assessment (ITT Population - Study 1115)

Event Free Survival (Months)	Ibrutinib (N=136)	Chlorambucil (N=133)	Comparison/Difference Ibrutinib vs. Chlorambucil
Events - n (%)	23 (16.9)	84 (63.2)	
Non-response within 12 months of randomization [1] - n	9	29	
Disease Progression - n	11	48	
Death - n	3	7	
Censored - n (%)	113 (83.1)	49 (36.8)	
Median (95% CI) [2]	NE (NE, NE)	12.0 (NE, NE)	
Min, Max	0.03+ , 24.71+	0.03+ , 23.98+	
P-value [3]			<.0001
Hazard Ratio (95% CI) [4]			0.165 (0.103, 0.262)
EFS at landmark times - % (95% CI) [2]			
6 months	97.8 (93.2, 99.3)	76.7 (68.4, 83.1)	21.0 (13.3, 28.7)
12 months	86.3 (79.2, 91.1)	37.5 (29.0, 46.1)	48.8 (38.4, 59.2)
15 months	83.8 (76.2, 89.1)	33.6 (25.2, 42.1)	50.3 (39.6, 60.9)
18 months	83.8 (76.2, 89.1)	32.2 (23.8, 40.9)	51.6 (40.9, 62.3)
24 months	78.2 (66.3, 86.3)		

N = number of subjects in the specified population. CI= confidence interval. + Indicates censored observation.
[1] Failure to achieve IRC confirmed CR, CRi, nPR, PR, or PR with lymphocytosis on or prior to study day 365 or initiation of subsequent antineoplastic therapy whichever earlier. The event date was set to study day 365 for this type of event.
[2] Estimated by Kaplan-Meier method.
[3] P value is from stratified log-rank test.
[4] Hazard ratio is estimated using stratified Cox regression model with treatment as the only covariate.
The strata factors used in both stratified log-rank test and Cox regression model are ECOG (0-1 vs 2) and Rai stage (0/I/II vs III/IV) at baseline as reported in IWRS.

Secondary endpoint – MRD negative response

Table 26. MRD negative response (ITT population - Study 1115)

	Ibrutinib (N=136) n (%)	Chlorambucil (N=133) n (%)	Ibrutinib vs. Chlorambucil P Value [1]
Subjects with MRD test performed	16 (11.8)	9 (6.8)	0.2078
MRD-Negative Response	0	0	NE

Secondary endpoint - FACIT-Fatigue

Table 27. Clinically meaningful improvement in FACIT-Fatigue scale (ITT population - Study 1115)

	Ibrutinib (N=136) n (%)	Chlorambucil (N=133) n (%)	Ibrutinib vs. Chlorambucil P value Chi-Square Test
Subjects with baseline and any post-baseline measurements	129 (94.9)	125 (94.0)	0.7564
Subjects with clinically meaningful improvement	84 (61.8)	71 (53.4)	0.1643

Table 28. Time to clinically meaningful improvement in FACIT-Fatigue scale (ITT population - Study 1115)

Ibrutinib			Chlorambucil			Ibrutinib vs. Chlorambucil	
N	Clinically Meaningful Improvement n (%)	Median (95% CI) [1] (Months)	N	Clinically Meaningful Improvement n (%)	Median (95% CI) [1] (Months)	Hazard Ratio (95% CI) [2]	P Value [3]
136	84 (61.8)	4.0 (2.8, 6.5)	133	71 (53.4)	4.7 (2.8, 18.2)	1.079 (0.786, 1.482)	0.6365

Ancillary analyses

Pharmacodynamic Analysis – Lymphocytosis

Table 29. Lymphocytosis (Safety population - Study 1115)

	Ibrutinib (N=135) n (%)	Chlorambucil (N=132) n (%)
Subjects with baseline and any post-baseline ALC measurements - N1	135	132
With lymphocytosis - n (%)	77 (57.0)	2 (1.5)
Without lymphocytosis - n (%)	58 (43.0)	130 (98.5)
Subjects with lymphocytosis		
Peak ALC during the first 9 months on study (x10^9/L) [1]		
N	77	2
Median	104.8	21.3
Min, Max	9.0, 432.9	8.6, 34.0
Time to peak ALC during the first 9 months on study (weeks) [1]		
N	77	2
Median	5.7	6.1
Min, Max	1.6, 26.1	2.1, 10.1
Time to lymphocytosis (weeks) [2]		
N	77	2
Median	2.1	6.1
Min, Max	1.6, 12.1	2.1, 10.1
Duration of lymphocytosis (weeks) [3]		
N	77	2
Resolved (event)	73 (94.8)	1 (50.0)
Not resolved (censored)	4 (5.2)	1 (50.0)
Median (95% CI)	12.4 (10.6, 17.1)	NE (2.3, NE)
Min, Max	0.1+ , 77.7	2.3 , 4.1+

N=number of subjects in the specified treatment arm in safety the population. N1= number of subjects with baseline and any post-baseline ALC measurements. n=number of subjects with lymphocytosis. %=100*n/N1. ALC=Absolute lymphocyte count, CI = Confidence Interval. '+' on Min or Max means subject was not recovered (censored) at the last ALC measurement.
Lymphocytosis was defined as ALC increasing >= 50% from baseline and achieving level >= 5x10^9 /L.
Resolution of Lymphocytosis occurred when ALC decreased to the baseline level or lower or achieving level of < 5x10^9 /L for subjects with lymphocytosis.
[1] Maximum ALC values within 274 days of first dose of study treatment. Descriptive statistics are presented.
[2] Number of weeks from first dose date of study treament to the first post-baseline ALC which met the lymphocytosis criteria Descriptive statistics are presented.
[3] Number of weeks from first post-baseline ALC which met the lymphocytosis criteria to the earliest date of the following ALC which met the resolution of lymphocytosis criteria or date of censoring (date of last non-missing ALC). The Kaplan-Meier method was used to estimate the median time.

ORR per IRC assessment in Small Lymphocytic Laeukemia (SLL) patients

Table 30. ORR based on IRC assessment in SLL subjects (ITT population - Study 1115)

	Ibrutinib (N=13) n (%)	Chlorambucil (N=7) n (%)	Ibrutinib vs. Chlorambucil
Overall Response Rate (CR, CRi, nPR, PR)	8 (61.5)	5 (71.4)	
Rate ratio (95% CI) [1]			1.0444 (0.4263, 2.5586)
P value [1]			0.9055
Overall Response Rate including PRL (CR, CRi, nPR, PR, PRL)	9 (69.2)	5 (71.4)	
Rate ratio (95% CI) [1]			1.1333 (0.4548, 2.8240)
P value [1]			0.7150
Best Overall Response			
Complete response (CR)	0 (0.0)	1 (14.3)	
CR with incomplete blood count recovery (CRi)	0 (0.0)	0 (0.0)	
Nodular partial response (nPR)	0 (0.0)	0 (0.0)	
Partial response (PR)	8 (61.5)	4 (57.1)	
PR with lymphocytosis (PRL)	1 (7.7)	0 (0.0)	
Stable disease (SD)	2 (15.4)	1 (14.3)	
Progressive disease (PD)	0 (0.0)	1 (14.3)	
NE/Unknown	2 (15.4)	0 (0.0)	

Summary of main study

The following table summarises the efficacy results from the main study 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 31. Summary of Efficacy for Study 1115

Title: A randomized, multicenter, open-label, phase 3 study of the Bruton's Tyrosine Kinase Inhibitor PCI-32765 versus chlorambucil in patients 65 years or older with treatment-naive chronic lymphocytic leukemia or small lymphocytic lymphoma (RESONATE-2)			
Study identifier	PCYC-1115-CA		
Design	Randomised, multicentre, open-label, phase 3 study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		21 March 2013 to 28 May 2015 not applicable not applicable
Hypothesis	Superiority		
Treatments groups	ibrutinib arm		420 mg/day, until confirmation of PD, unacceptable toxicity, or other criteria N=136
	chlorambucil arm		0.5 mg/kg on Days 1 and 15 of each 28-day cycle; if well-tolerated, increased in increments of 0.1 mg/kg on Day 1 of each cycle to a maximum of 0.8 mg/kg; given for up to 12 cycles N=133
Endpoints and definitions	Primary endpoint	Progression free survival (PFS)	time from the date of randomization to date of IRC-confirmed disease progression or date of death from any cause
	Secondary endpoint	Overall response rate (ORR)	proportion of subjects who achieved a best overall response of CR, CRi, nPR, or PR per IRC assessment
	Secondary endpoint	Overall survival (OS)	time from the date of randomization to the date of death from any cause
Database lock	28 May 2015		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat 28 May 2015		
Descriptive statistics	Treatment group	ibrutinib arm	chlorambucil arm

and estimate variability	Number of subjects	136	133
	Median PFS (months)	NE	18.9
	95% CI	NE, NE	14.1, 22.0
	ORR (%)	82.4	35.3
	95% CI		
	Median OS (months) 95% CI	NE NE, NE	NE NE, NE

Effect estimate per comparison	Primary endpoint: PFS	Comparison groups	ibrutinib vs. chlorambucil
		HR	0.161
		95% CI	0.091, 0.283
		P-value	<0.0001
	Secondary endpoint: ORR	Comparison groups	ibrutinib vs. chlorambucil
		Rate ratio	2.32
		95% CI	1.82, 2.95
		P-value	<0.0001
	Secondary endpoint: OS	Comparison groups	ibrutinib vs. chlorambucil
		HR	0.163
		95% CI	0.048, 0.558
		P-value	0.0010
Notes	Stratification factors: ECOG PS (0, 1 vs. 2) and presence of advanced-stage disease (Rai Stage ≤ II vs. III-IV).		

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

Not applicable

Clinical studies in special populations

Not applicable

Supportive study

Study 1102

This was an open-label, nonrandomized, multicentre, Phase 1b/2 study of ibrutinib in subjects with treatment-naïve or relapsed/refractory CLL/SLL conducted in the United States. Cohorts were defined by the disease population (treatment-naïve or relapsed/refractory) and by the ibrutinib dose level (420 mg or 840 mg). Subjects received study treatment once daily until disease progression, unacceptable drug-related toxicity, or other reason for treatment discontinuation. After a minimum of 12 cycles of treatment or at the closure of this study, in the absence of disease progression, subjects could continue treatment in a long-term extension study PCYC-1103-CA (Study 1103).

In total 132 subjects were enrolled in Study 1102 and 27 of these subjects were previously untreated and received 420 mg/day of ibrutinib. Efficacy was a secondary objective of this study; 19 of the 27 previously untreated subjects (70.4%) were considered responders (partial response or better) and 4 subjects (14.8%) achieved a complete response. Sustained hematological improvement was also observed for platelet counts (63.6%) and hemoglobin (70.0%) in previously untreated subjects who had baseline thrombocytopenia and anemia.

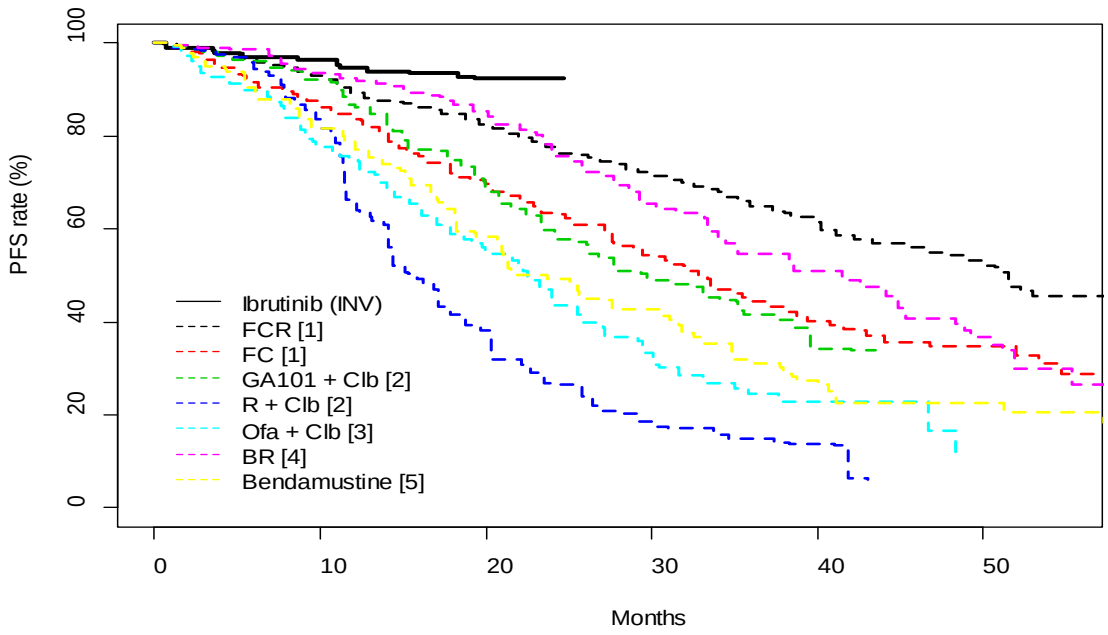
The study was completed after a median follow-up of 31 months. At the 24-month landmark, the estimated PFS rate was 95.8% and the estimated survival rate 96.2% in previously untreated subjects.

At the end of the study, 18 of 19 subjects who achieved a response of PR or better (94.7%) were alive without disease progression. After a median follow-up of 3 years, median PFS and OS were not reached in ibrutinib-treated subjects in Study 1102/extension Study 1103.

Efficacy in the context of historical data

The indication sought based on the 1115 study includes not only patients unfit for the standard first-line therapy FCR, or those for whom the comparator chlorambucil as monotherapy would be appropriate. To substantiate that ibrutinib would be an appropriate alternative also for patients eligible for chemo-immunotherapy, including FCR, cross-study comparisons with trials on which alternative therapies are based were presented. As such comparisons are not straightforward, exponential distribution modelling was utilised, generating the following graphs.

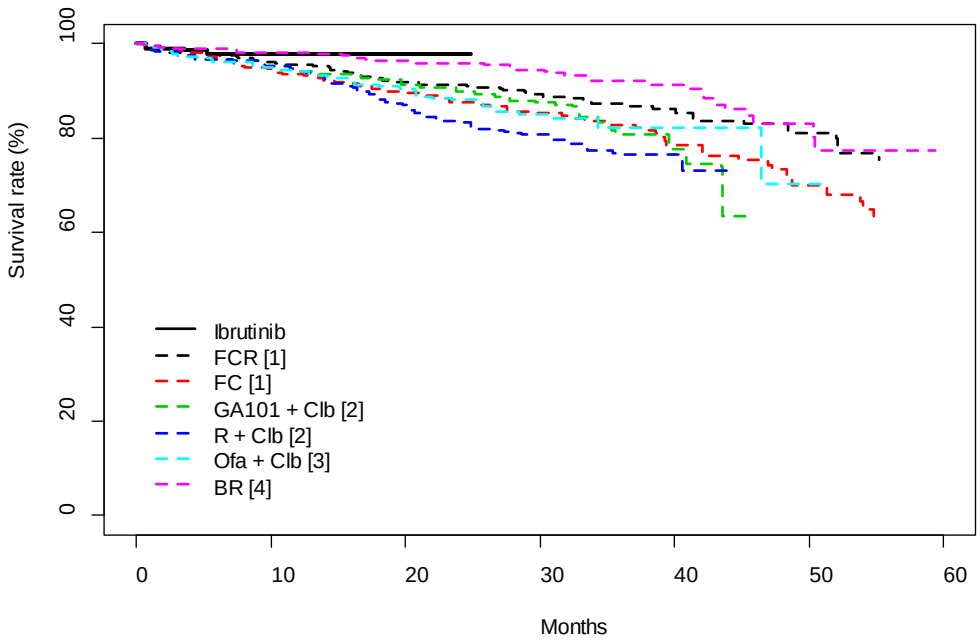
Figure 5. Historical Comparison of Progression-Free Survival in Patients with Treatment Naïve CLL vs. Progression-Free Survival for Study 1115 Based on Investigator Assessment



BR: bendamustine-rituximab; Clb: chlorambucil; FC: fludarabine-cyclophosphamide; FCR: fludarabine-cyclophosphamide-rituximab; GA101: obinutuzumab; INV: investigator; Ofa: ofatumumab; R: rituximab

14. Goede V, Fischer K, Engelke A, et al. Obinutuzumab as frontline treatment of chronic lymphocytic leukemia: updated results of the CLL11 study. Leukemia. 2015;29(7):1602-1604.
15. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukemia: A randomised, open-label, phase 3 trial. Lancet. 2010;376:1164-1174.
20. Hillmen P, Robak T, Janssens A, et al. Chlorambucil plus ofatumumab versus chlorambucil alone in previously untreated patients with chronic lymphocytic leukaemia (COMPLEMENT 1): a randomised, multicentre, open-label phase 3 trial. Lancet. 2015;385:1873-1883.
21. Knauf WU, Lissichkov T, Aldaoud A, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol. 2009;27(26):4378-4384.
Eichhorst et al, 2014 : Final Analysis of an International, Randomized Study of the German CLL Study Group (GCLLSG) (CLL10 Study). ASH abstract book 2014, abs # 19.

Figure 6. Historical Comparison of Overall Survival in Patients with Treatment-Naïve CLL vs. Overall Survival for Study 1115 Based on Investigator Assessment



BR: bendamustine-rituximab; Clb: chlorambucil; FC: fludarabine-cyclophosphamide; FCR: fludarabine-cyclophosphamide-rituximab; GA101: obinutuzumab; Ofa: ofatumumab; R: rituximab

14. Goede V, Fischer K, Engelke A, et al. Obinutuzumab as frontline treatment of chronic lymphocytic leukemia: updated results of the CLL11 study. Leukemia. 2015;29(7):1602-1604.
15. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukemia: A randomised, open-label, phase 3 trial. Lancet. 2010;376:1164-1174.
20. Hillmen P, Robak T, Janssens A, et al. Chlorambucil plus ofatumumab versus chlorambucil alone in previously untreated patients with chronic lymphocytic leukaemia (COMPLEMENT 1): a randomised, multicentre, open-label phase 3 trial. Lancet. 2015;385:1873-1883.
21. Knauf WU, Lissichkov T, Aldaoud A, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol. 2009;27(26):4378-4384.
Eichhorst et al, 2014 : Final Analysis of an International, Randomized Study of the German CLL Study Group (GCLLSG) (CLL10 Study). ASH abstract book 2014, abs # 19.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

In the open-label 1115 study patients with del 17-negative disease ≥70 years old, or ≥65-69 years old with at least one defined comorbidity, were randomised between continuous ibrutinib (n=136) or maximum 12 cycles of chlorambucil (n=133). The primary endpoint was PFS as assessed by an IRC and a sequential design was applied for the secondary outcomes. The clinical cut-off for the final analysis was 15 months after enrolment of the last subject. Demographics seem reasonably balanced between study arms. The median age was 73 years. Baseline characteristics were balanced between study arms. Approximately 50% had stage I-II disease, 7% had SLL and 20% had 11q del disease.

With regard to the population under investigation the current ESMO guideline (2015) recommends chlorambucil + anti- CD20 therapy in less fit patients without del 17/TP53 mutated disease. In two recent studies superior efficacy of chlorambucil plus anti-CD20 (obinutuzumab, rituximab or ofatumumab)

therapy over chlorambucil monotherapy has been shown (Goede et al, 2014; Hillmen at el, 2015), albeit at the cost of safety. In addition, bendamustin-based therapy may now be an option in some of these patients. Nevertheless, in the CHMP advice given 2012, it was considered that the proposed inclusion/exclusion criteria probably define a population where chlorambucil would be reasonably therapy. In this situation where new more efficacious treatment regimens have been reported since the initiation of the pivotal study, historical data may be of value. Here, the comparisons provided by the MAH are considered informative. Acknowledging the shortcomings of inter-study comparisons, ibrutinib data on PFS, and probably also OS, so far seem unlikely to be inferior of the chlorambucil plus anti-CD20 combinations. Taken together, the chlorambucil monotherapy control is considered acceptable.

Important protocol deviations were reported in relatively small but roughly similar fractions of subjects in both study arms and are deemed unlikely to affect the interpretation of the study results.

Efficacy data and additional analyses

The primary endpoint, PFS by IRC, showed a highly significant HR of 0.161 (0.091, 0.283) at an event rate of 11% in the ibrutinib arm and 48% in the chlorambucil arm, mainly due to disease progression. The median was 19 months in the chlorambucil arm while not reached in the ibrutinib arm. The KM PFS at 24 months was 84% for the ibrutinib arm. The KM curve showed an early separation that increases over time. The sensitivity analyses, including investigator-assessed PFS, support the primary analysis.

The subgroup analyses are consistent with the exception of SLL that shows a point estimate for HR of 1.6. However, given the small size of this subgroup (n=20), the positive outcome in bulky disease and the lack of a biological rationale for different activity in SLL vs CLL as these are considered to represent the same disease, the finding is considered likely to reflect chance. The effectiveness also in del 11q disease is noted.

Furthermore, it has been shown that the activity of ibrutinib is unaffected by poor prognostic factors such as del 17p. Cross study comparisons are indicative that ibrutinib as monotherapy does not yield lower efficacy than does various chemo-immunotherapy combinations in more fit patients, though such comparisons are necessarily fraught with uncertainty. Further, the tolerability of this single agent in more fit patients is highly unlikely to be worse than in less fit patients.

Significant activity of ibrutinib in terms of response rates was observed; ORR was 82% in the ibrutinib arm vs 35% in the chlorambucil arm. In line with previous experience few CRs were seen and no MRD-negativity was detected.

Regarding OS, based on 3 events in the ibrutinib arm and 17 events in the chlorambucil arm a HR of 0.163 (0.048, 0.558) was observed, p<0.001. Due to immaturity, outcome in patients with better prognosis remains to be described. In order to address it, the MAH will submit the final study report from study PCYC-1116-CA the open-label extension of Study PCYC-1115-CA (see Risk Management Plan).

There was a statistically significant sustained platelet or hemoglobin improvement in the ITT population in favor of ibrutinib versus chlorambucil. In patients with baseline cytopenias, sustained hematologic improvement was: platelets 77.1% versus 42.9%; hemoglobin 84.3% versus 45.5% for ibrutinib and chlorambucil respectively.

At 12 months, 9 patients (7%) in the ibrutinib arm and 29 patients (22%) in the chlorambucil arm were non-responders. The EFS difference between study arms was highly statistically significant, HR 0.165. The median EFS was 12 months in the chlorambucil arm while not reached in the ibrutinib arm.

2.4.4. Conclusions on the clinical efficacy

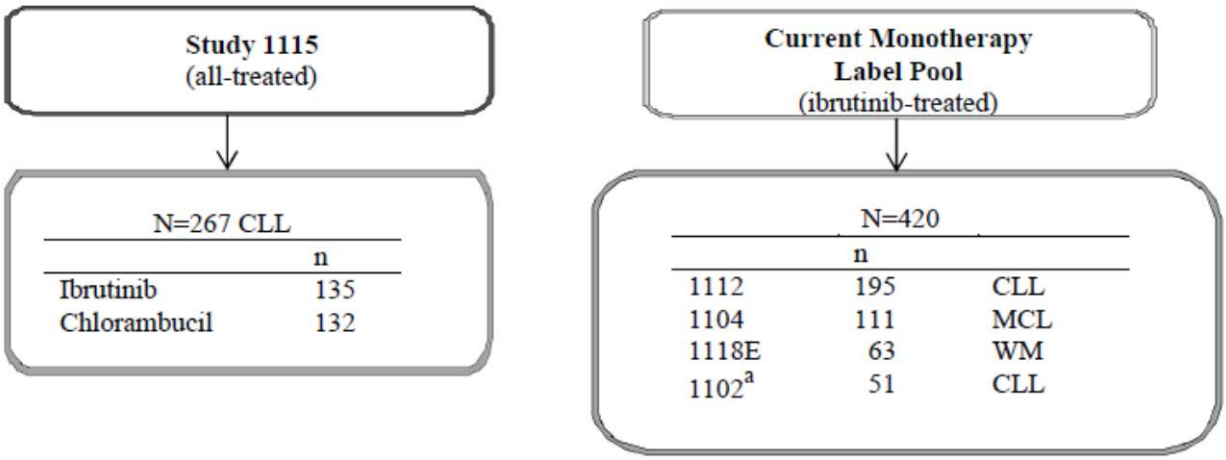
With a median time on study of 18.4 months at the cut- off, and a maturation level of 48% in the control arm for the PFS analysis, convincing and internally robust data across the major efficacy endpoints, and with strong statistical significance, clearly favour imbrutinib from an efficacy point of view.

2.5. Clinical safety

Introduction

In this Type II variation, the Applicant integrated the data from Study 1115 in previously-untreated CLL with the safety profile described for ibrutinib in CLL, MCL, and WM (from Studies 1112, 1102, 1104, 1118E) in the ibrutinib SmPC. These 5 studies thus form the basis for the safety profile of ibrutinib in Section 4.8 of the proposed SmPC.

Figure 7. Overview of safety studies



[a] Previously-treated subjects who received 420 mg/day ibrutinib

CLL = chronic lymphocytic leukemia; MCL = mantle cell lymphoma; WM = Waldenström's macroglobulinemia

Table 32. Data Cut-off Dates for Safety Analyses involving Current Monotherapy Label Pool

Study	Data Cutoff Dates for Safety Analyses			
	Primary CSR	Original MAA Filing	Current SmPC[a]	Current Type II variation
1102	28 Nov 2012	28 Nov 2012	28 Nov 2012	28 Nov 2012
1112	06 Nov 2013	06 Nov 2013	20 Jun 2014 (4-month update)	06 Nov 2013
1104	26 Dec 2012	15 May 2013 (4-month update)	03 Mar 2014 (final follow-up data)	26 Dec 2012
1118E	28 Feb 2014	28 Feb 2014	28 Feb 2014	28 Feb 2014

CSR = clinical study report; MAA = Marketing Authorisation Application; SmPC = Summary of Product Characteristics.

Note: Data cutoff dates reflect last date of data entry for a given study for a given reporting activity.

[a] Utilizing data submitted in Type II variation for WM (EMEA/H/C/003791/II/0001).

Patient exposure

The demographic and baseline disease characteristics are shown in the table below.

Table 33. Demographic and Baseline Disease Characteristics and Laboratory Results - PCYC-1115 and Current Monotherapy Label Pool; Safety Population

	PCYC-1115		
	Ibrutinib	Chlorambucil	Current Monotherapy Label Pool
Time from initial diagnosis to randomization/ first dose (months)			
N	135	132	420
Mean (SD)	45.3 (45.42)	50.6 (57.62)	87.4 (64.21)
Median	32.1	32.3	73.6
Range	(1; 241)	(1; 294)	(2; 334)
Histology			
N	135	132	420
CLL/SLL	135 (100.0%)	132 (100.0%)	246 (58.6%)
MCL	0	0	111 (26.4%)
WM	0	0	63 (15.0%)
Lines of prior therapy			
N	135	132	420
Mean (SD)	0.0 (0.00)	0.0 (0.00)	3.3 (2.12)
Median	0.0	0.0	3.0
Range	(0; 0)	(0; 0)	(1; 12)
Creatinine Clearance (mL/min)			
N	135	132	418
≥60 mL/min	75 (55.6%)	65 (49.2%)	305 (72.6%)
<60 - ≥30 mL/min	58 (43.0%)	65 (49.2%)	109 (26.0%)
<30 mL/min	2 (1.5%)	2 (1.5%)	4 (1.0%)
Missing	0	0	2 (0.5%)
Hepatic Function[a]			
N	135	132	420
Normal	119 (88.1%)	128 (97.0%)	347 (82.6%)
Abnormal	15 (11.1%)	4 (3.0%)	66 (15.7%)
Mild	15 (100.0%)	4 (100.0%)	62 (93.9%)
Moderate	0	0	4 (6.1%)
Severe	0	0	0
Missing	1 (0.7%)	0	7 (1.7%)

CLL = chronic lymphocytic leukemia; MCL = mantle cell lymphoma; N = number of subjects with data; ROW = rest of world; SD = standard deviation; SLL = small lymphocytic lymphoma; WM = Waldenström's Macroglobulinemia

[a] Using NCI Organ Dysfunction Working Group criteria.

Current Monotherapy Label Pool includes Studies 1112, 1102, 1104, and 1118E.

Table 34. Extent of Exposure - PCYC-1115 and Current Monotherapy Label Pool; Safety Population

	PCYC-1115		Current Monotherapy Label Pool
	Ibrutinib	Chlorambucil	
Analysis set: safety population	135	132	420
Treatment duration (months)			
N	135	132	420
Mean (SD)	17.07 (4.988)	7.30 (3.528)	10.47 (5.812)
Median	17.41	7.11	9.38
Range	(0.7; 24.7)	(0.5; 11.7)	(0.2; 28.7)
0 - <3 months	6 (4.4%)	17 (12.9%)	45 (10.7%)
3 - <6 months	3 (2.2%)	44 (33.3%)	37 (8.8%)
6 - <9 months	2 (1.5%)	14 (10.6%)	111 (26.4%)
9 - <12 months	3 (2.2%)	57 (43.2%)	95 (22.6%)
12 - <15 months	16 (11.9%)	0	50 (11.9%)
15 - <18 months	40 (29.6%)	0	28 (6.7%)
18 - <24 months	63 (46.7%)	0	40 (9.5%)
≥24 months	2 (1.5%)	0	14 (3.3%)
Average dose level per administration (mg/day for Ibrutinib, mg/kg for Chlorambucil)			
CLL/SLL			
N	135	132	246
Mean (SD)	397.0 (46.16)	0.6 (0.10)	397.6 (43.23)
Median	414.7	0.5	416.8
Range	(148; 420)	(0; 1)	(141; 430)
MCL			
N	0	0	111
Mean (SD)	-	-	522.5 (59.51)
Median	-	-	550.0
Range	-	-	(278; 567)
WM			
N	0	0	63
Mean (SD)	-	-	390.6 (60.68)
Median	-	-	416.0
Range	-	-	(158; 420)
Relative dose intensity (%)			
N	135	132	420
Mean (SD)	94.5 (10.99)	95.6 (8.10)	94.0 (11.09)
Median	98.7	100.0	99.1
Range	(35; 100)	(66; 111)	(33; 102)
<75 %	10 (7.4%)	6 (4.5%)	28 (6.7%)
75%-<90%	10 (7.4%)	18 (13.6%)	50 (11.9%)
≥ 90%	115 (85.2%)	108 (81.8%)	342 (81.4%)

[TSIEXP01A.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_CLL_MCL_EU_2015\tsiexp01a.sas] 02SEP2015, 09:30

CLL = chronic lymphocytic leukemia; MCL = mantle cell lymphoma; N = number of subjects with data; ROW = rest of world; SD = standard deviation; SLL = small lymphocytic lymphoma; WM = Waldenström's Macroglobulinemia
Current Monotherapy Label Pool includes Studies 1112, 1102, 1104, and 1118E.

Adverse events

Table 35. Overall Summary of Treatment-emergent Adverse Events - PCYC-1115 and Current Monotherapy Label Pool; Safety Population

	PCYC-1115		
	Ibrutinib	Chlorambucil	Current Monotherapy Label Pool
Analysis set: safety	135	132	420
Any TEAE	133 (98.5%)	124 (93.9%)	419 (99.8%)
Grade ≥ 3	89 (65.9%)	68 (51.5%)	263 (62.6%)
Drug related	114 (84.4%)	101 (76.5%)	351 (83.6%)
Grade≥ 3	48 (35.6%)	51 (38.6%)	148 (35.2%)
Any TESAE	55 (40.7%)	33 (25.0%)	194 (46.2%)
Grade ≥ 3	45 (33.3%)	27 (20.5%)	174 (41.4%)
Drug related	17 (12.6%)	13 (9.8%)	79 (18.8%)
TEAE leading to treatment discontinuation	14 (10.4%)	30 (22.7%)	39 (9.3%)
TEAE leading to treatment dose reduction	13 (9.6%)	25 (18.9%)	32 (7.6%)
TEAE with outcome death	3 (2.2%)	4 (3.0%)	32 (7.6%)
Death within 30 days after last dose of study treatment[a]	2 (1.5%)	1 (0.8%)	31 (7.4%)

TEAE = Treatment-emergent adverse event, TESAE = Treatment-emergent serious adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator.
[a] Includes any death that occurred post first dose of study treatment and within 30 days of the last dose of study treatment.
Current Monotherapy Label Pool includes Studies 1112, 1102, 1104, and 1118E.

Table 36. Treatment-emergent Adverse Events (Any Grade) by System Organ Class and Preferred Term with Subject Incidence ≥10% in Study 1115 or Current Monotherapy Label Pool; Safety Population

	PCYC-1115		
	Ibrutinib	Chlorambucil	Current Monotherapy Label Pool
Analysis set: safety	135	132	420
Subjects with Any TEAE	133 (98.5%)	124 (93.9%)	419 (99.8%)
System Organ Class			
Preferred Term			
Gastrointestinal disorders	97 (71.9%)	83 (62.9%)	338 (80.5%)
Diarrhoea	57 (42.2%)	22 (16.7%)	201 (47.9%)
Nausea	30 (22.2%)	52 (39.4%)	108 (25.7%)
Constipation	21 (15.6%)	21 (15.9%)	74 (17.6%)
Vomiting	18 (13.3%)	27 (20.5%)	68 (16.2%)
Stomatitis	11 (8.1%)	5 (3.8%)	51 (12.1%)
Abdominal pain	17 (12.6%)	14 (10.6%)	42 (10.0%)
Dyspepsia	15 (11.1%)	3 (2.3%)	35 (8.3%)
Infections and infestations	87 (64.4%)	67 (50.8%)	313 (74.5%)
Upper respiratory tract infection	23 (17.0%)	23 (17.4%)	89 (21.2%)
Sinusitis	7 (5.2%)	1 (0.8%)	55 (13.1%)
Urinary tract infection	14 (10.4%)	10 (7.6%)	46 (11.0%)
Pneumonia	9 (6.7%)	4 (3.0%)	43 (10.2%)
General disorders and administration site conditions	84 (62.2%)	74 (56.1%)	251 (59.8%)
Fatigue	41 (30.4%)	50 (37.9%)	129 (30.7%)
Pyrexia	23 (17.0%)	19 (14.4%)	82 (19.5%)
Oedema peripheral	25 (18.5%)	12 (9.1%)	64 (15.2%)
Skin and subcutaneous tissue disorders	74 (54.8%)	40 (30.3%)	236 (56.2%)
Petechiae	5 (3.7%)	1 (0.8%)	48 (11.4%)
Rash	5 (3.7%)	3 (2.3%)	44 (10.5%)
Respiratory, thoracic and mediastinal disorders	62 (45.9%)	51 (38.6%)	215 (51.2%)
Cough	30 (22.2%)	20 (15.2%)	76 (18.1%)
Dyspnoea	14 (10.4%)	13 (9.8%)	60 (14.3%)
Epistaxis	8 (5.9%)	5 (3.8%)	44 (10.5%)
Musculoskeletal and connective tissue disorders	72 (53.3%)	35 (26.5%)	213 (50.7%)
Muscle spasms	15 (11.1%)	7 (5.3%)	63 (15.0%)
Arthralgia	22 (16.3%)	9 (6.8%)	60 (14.3%)
Back pain	17 (12.6%)	9 (6.8%)	42 (10.0%)
Blood and lymphatic system disorders	58 (43.0%)	63 (47.7%)	200 (47.6%)
Neutropenia	21 (15.6%)	30 (22.7%)	85 (20.2%)
Anaemia	25 (18.5%)	27 (20.5%)	76 (18.1%)
Thrombocytopenia	11 (8.1%)	17 (12.9%)	71 (16.9%)
Nervous system disorders	47 (34.8%)	43 (32.6%)	164 (39.0%)
Dizziness	15 (11.1%)	16 (12.1%)	57 (13.6%)
Headache	16 (11.9%)	13 (9.8%)	56 (13.3%)
Metabolism and nutrition disorders	45 (33.3%)	31 (23.5%)	135 (32.1%)
Decreased appetite	13 (9.6%)	19 (14.4%)	47 (11.2%)
Eye disorders	74 (54.8%)	30 (22.7%)	124 (29.5%)
Vision blurred	18 (13.3%)	10 (7.6%)	28 (6.7%)
Dry eye	23 (17.0%)	6 (4.5%)	23 (5.5%)
Lacrimation increased	18 (13.3%)	8 (6.1%)	18 (4.3%)
Visual acuity reduced	15 (11.1%)	3 (2.3%)	11 (2.6%)
Injury, poisoning and procedural complications	46 (34.1%)	21 (15.9%)	117 (27.9%)
Contusion	11 (8.1%)	2 (1.5%)	60 (14.3%)
Investigations	42 (31.1%)	31 (23.5%)	81 (19.3%)
Weight decreased	14 (10.4%)	16 (12.1%)	18 (4.3%)
Vascular disorders	31 (23.0%)	17 (12.9%)	60 (14.3%)
Hypertension	19 (14.1%)	0	34 (8.1%)

[TSFAE03A.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_CLL_MCL_EU_2015\tsfae03.sas] 20AUG2015, 07:20

TEAE = Treatment-emergent adverse event.

Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.

Current Monotherapy Label Pool includes Studies 1112, 1102, 1104, and 1118E.

Table 37. Grade 3 or 4 Treatment-emergent Adverse Events by System Organ Class and Preferred Term with Subject Incidence ≥2% in Study 1115 or Current Monotherapy Label Pool; Safety Population

	PCYC-1115		
	Ibrutinib	Chlorambucil	Current Monotherapy Label Pool
Analysis set: safety	135	132	420
Subjects with Any Grade 3 or 4 TEAE	86 (63.7%)	64 (48.5%)	231 (55.0%)
System Organ Class			
Preferred Term			
Gastrointestinal disorders	13 (9.6%)	6 (4.5%)	33 (7.9%)
Diarrhoea	5 (3.7%)	0	16 (3.8%)
Abdominal pain	4 (3.0%)	1 (0.8%)	9 (2.1%)
Infections and infestations	24 (17.8%)	10 (7.6%)	93 (22.1%)
Upper respiratory tract infection	3 (2.2%)	2 (1.5%)	1 (0.2%)
Urinary tract infection	2 (1.5%)	1 (0.8%)	11 (2.6%)
Pneumonia	5 (3.7%)	2 (1.5%)	25 (6.0%)
Cellulitis	3 (2.2%)	0	10 (2.4%)
General disorders and administration site conditions	4 (3.0%)	11 (8.3%)	29 (6.9%)
Fatigue	1 (0.7%)	7 (5.3%)	12 (2.9%)
Skin and subcutaneous tissue disorders	9 (6.7%)	3 (2.3%)	12 (2.9%)
Rash maculo-papular	4 (3.0%)	2 (1.5%)	3 (0.7%)
Respiratory, thoracic and mediastinal disorders	8 (5.9%)	3 (2.3%)	15 (3.6%)
Pleural effusion	3 (2.2%)	1 (0.8%)	1 (0.2%)
Blood and lymphatic system disorders	24 (17.8%)	43 (32.6%)	114 (27.1%)
Neutropenia	14 (10.4%)	24 (18.2%)	68 (16.2%)
Anaemia	8 (5.9%)	11 (8.3%)	22 (5.2%)
Thrombocytopenia	3 (2.2%)	8 (6.1%)	36 (8.6%)
Febrile neutropenia	3 (2.2%)	3 (2.3%)	12 (2.9%)
Haemolytic anaemia	0	3 (2.3%)	0
Nervous system disorders	9 (6.7%)	6 (4.5%)	7 (1.7%)
Syncope	1 (0.7%)	3 (2.3%)	2 (0.5%)
Metabolism and nutrition disorders	10 (7.4%)	2 (1.5%)	39 (9.3%)
Hyperuricaemia	0	0	9 (2.1%)
Dehydration	1 (0.7%)	0	9 (2.1%)
Hyponatraemia	4 (3.0%)	0	7 (1.7%)
Investigations	10 (7.4%)	2 (1.5%)	16 (3.8%)
Platelet count decreased	4 (3.0%)	1 (0.8%)	0
Cardiac disorders	8 (5.9%)	2 (1.5%)	27 (6.4%)
Atrial fibrillation	2 (1.5%)	0	17 (4.0%)
Vascular disorders	6 (4.4%)	3 (2.3%)	15 (3.6%)
Hypertension	6 (4.4%)	0	13 (3.1%)

[TSFAE02AA.rtf] [JNJ-54179060\Z_SCS\DBR_ISS_CLL_MCL_2015\RE_ISS_CLL_MCL_EU_2015\tsfae02xx.sas] 04SEP2015, 10:31

TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Current Monotherapy Label Pool includes Studies 1112, 1102, 1104, and 1118E.

Specific adverse events of clinical interest

Haemorrhage

In Study 1115, 47.4% of the 135 ibrutinib-treated subjects experienced a haemorrhagic TEAE of any grade; the most common haemorrhagic events (≥5%) of any severity in the ibrutinib group of Study 1115 were contusion (8.1%), increased tendency to bruise (5.9%), epistaxis (5.9%), and haematuria (5.9%). In the current monotherapy label pool, 46.9% of ibrutinib-treated subjects experienced a haemorrhagic TEAE of any severity.

In the chlorambucil arm, haemorrhagic TEAEs (any grade) were reported for 20 (15.2%) subjects.

Approximately half of all subjects in the ibrutinib (53.3%) or chlorambucil (53.8%) groups in Study 1115, and 32.9% of subjects in the current monotherapy label pool, used concomitant anticoagulant and/or antiplatelet medication at any time during the study treatment period.

Leukostasis

No cases of leukostasis were reported in Study 1115. There were 2 reports of leukostasis in the current monotherapy label pool.

Tumour lysis syndrome

No cases of TLS were reported in Study 1115; one event was reported in the current monotherapy label pool.

Infections

Pneumonias were the most frequently reported type of Grade 3 or 4 infection among ibrutinib- treated subjects in Study 1115.

Atypical infections were uncommon in subjects treated with ibrutinib in Study 1115, and included single reports of pneumonia legionella and tuberculosis.

One subject in the experimental arm died from a Klebsiella infection and 1 patient in the control arm died from an acute Hepatitis B infection.

For 9 subjects (2.1%) in the current monotherapy label pool, the infection event was fatal. Pneumonia (6.9%) and urinary tract infection (2.1%) were also the most common serious infection TEAEs in this safety population.

Table 38. Summary of Infection-related Treatment-emergent Adverse Events - PCYC-1115 and Current Monotherapy Label Pool; Safety Population

	PCYC-1115		
	Ibrutinib	Chlorambucil	Current Monotherapy Label Pool
Analysis Set: Safety Population	135	132	420
Infection and Infestation MedDRA SOC			
Any grade TEAE	87 (64.4%)	67 (50.8%)	313 (74.5%)
Grade 3 or 4 TEAE	24 (17.8%)	10 (7.6%)	93 (22.1%)
Serious TEAE	20 (14.8%)	7 (5.3%)	96 (22.9%)
TEAE leading to dose reduction	1 (0.7%)	3 (2.3%)	5 (1.2%)
TEAE leading to treatment discontinuation	2 (1.5%)	4 (3.0%)	14 (3.3%)
TEAE leading to death (Grade 5)	1 (0.7%)	1 (0.8%)	9 (2.1%)

SOC = system organ class; TEAE = treatment-emergent adverse event
Note: Percentages calculated with the number of subjects in safety analysis set as denominator.
Current Monotherapy Label Pool includes Studies 1112, 1102, 1104, and 1118E

Cardiac arrhythmias

Cardiac arrhythmia TEAEs were reported in 14.8% of the 135 ibrutinib-treated subjects in Study 1115 as well as in the current monotherapy label pool vs. 4.5% in chlorambucil group. In both ibrutinib safety analysis sets, atrial fibrillation was the most frequent cardiac arrhythmia.

Most of the cardiac arrhythmia TEAEs were Grade 1 or 2 in severity and non-serious, and few (<2%) led
Most of the cardiac arrhythmia TEAEs were Grade 1 or 2 in severity and non-serious, and few (<2%) led
to ibrutinib discontinuation or dose reduction. None of these events were fatal in the ibrutinib group of Study 1115; 2 were fatal in the current monotherapy label pool (both were episodes of cardiac arrest).

Table 39. Overview of Atrial Fibrillation and Atrial Flutter Events - PCYC-1115 and Current Monotherapy Label Pool; Safety Population

	PCYC-1115		
	Ibrutinib Atrial Fibrillation/Flutter	Chlorambucil Atrial Fibrillation/Flutter	Current Monotherapy Label Pool Atrial Fibrillation/Flutter
Analysis Set: Safety Population	135	132	420
Any Treatment-emergent Atrial Fibrillation/Flutter Adverse Events	10 (7.4%)	1 (0.8%)	30 (7.1%)
Grade 3-4	3 (2.2%)	0	18 (4.3%)
Fatal	0	0	0
SAE	4 (3.0%)	1 (0.8%)	16 (3.8%)
Leading to treatment discontinuation	2 (1.5%)	0	2 (0.5%)
Leading to dose reduction	0	0	1 (0.2%)
Time to Onset of First Event (Days)[a]			
N	10	1	29
Mean (SD)	121.50 (77.949)	70 (-)	125.86 (108.573)
Median	99.00	70.00	91.00
Range	(28.0; 253.0)	(70.0; 70.0)	(17.0; 448.0)

SAE = serious adverse event; SD = standard deviation
Note: Percentages calculated with the number of subjects in safety analysis set as denominator.
[a] Days = Onset of the event – First dose date + 1.
Current Monotherapy Label Pool includes Studies 1112, 1102, 1104, and 1118E.

The median time to onset of the initial report of atrial fibrillation and/or atrial flutter was approximately 3 months after initiation of ibrutinib therapy (median, 99 days), with only 1 subject having an onset of the event within the first month of treatment.

Among the 10 ibrutinib-treated subjects in Study 1115 who experienced atrial fibrillation/flutter, 8 were using anticoagulant/antiplatelet therapies, independent of the indication for use. None of the 10 subjects with these events had a major haemorrhage, and none had a reported event of ischemic stroke. In the current monotherapy label pool, 22 of the 30 subjects (73.3%) with atrial fibrillation or atrial flutter were using anticoagulant/antiplatelet therapies. A major haemorrhage was reported for 3 of these 30 subjects at some time during the study period. A medical review of the 3 cases disclosed that the major haemorrhage occurred while on anticoagulant/antiplatelet therapy.

Other malignancies

Table 40. Incidence of Other Malignancies of Any Grade - PCYC-1115 and Current Monotherapy Label Pool; Safety Population

	PCYC-1115		
	Ibrutinib	Chlorambucil	Current Monotherapy Label Pool
Analysis Set: Safety Population	135	132	420
Subjects with Any Other Malignancy	23 (17.0%)	7 (5.3%)	35 (8.3%)
Type			
Preferred term			
Non-melanoma skin cancer	18 (13.3%)	5 (3.8%)	25 (6.0%)
Basal cell carcinoma	13 (9.6%)	3 (2.3%)	12 (2.9%)
Squamous cell carcinoma	6 (4.4%)	3 (2.3%)	9 (2.1%)
Skin cancer	0	0	2 (0.5%)
Bowen's disease	1 (0.7%)	0	1 (0.2%)
Penile squamous cell carcinoma	0	0	1 (0.2%)
Squamous cell carcinoma of skin	1 (0.7%)	0	1 (0.2%)
Basosquamous carcinoma of skin	1 (0.7%)	0	0
Lip squamous cell carcinoma	0	1 (0.8%)	0
Melanoma skin cancer	0	1 (0.8%)	0
Malignant melanoma	0	1 (0.8%)	0
Non-skin cancer	6 (4.4%)	2 (1.5%)	10 (2.4%)
B-cell lymphoma	0	0	1 (0.2%)
Bladder cancer	0	0	1 (0.2%)
Fibrous histiocytoma	0	0	1 (0.2%)
Gastrointestinal carcinoma	0	0	1 (0.2%)
Lung adenocarcinoma metastatic	0	0	1 (0.2%)
Malignant histiocytosis	0	0	1 (0.2%)
Metastatic neoplasm	0	0	1 (0.2%)
Myelodysplastic syndrome	0	0	1 (0.2%)
Peripheral T-cell lymphoma unspecified	0	0	1 (0.2%)
Sarcoma	0	0	1 (0.2%)
Squamous cell carcinoma of lung	0	0	1 (0.2%)
Lung adenocarcinoma	1 (0.7%)	0	0
Non-small cell lung cancer	1 (0.7%)	1 (0.8%)	0
Prostate cancer	3 (2.2%)	1 (0.8%)	0
Squamous cell carcinoma	1 (0.7%)	0	0

Events include all other malignancies reported during the treatment and follow-up.
Note: Percentages calculated with the number of subjects in safety analysis set as denominator.
Current Monotherapy Label Pool includes Studies 1112, 1102, 1104, and 1118E.

A comparative, pooled, randomized Phase 3 clinical trial data analysis (including Studies 1112, 1115, MCL3001, and CLL3001) indicated that non-melanoma skin cancer was reported more frequently with ibrutinib than with the comparators, 6.1% vs 2.3%, respectively (Table 32).

Table 41. Incidence of Treatment-emergent Other Malignancy Events by Malignancy Type, Preferred Term PCYC-1112, PCYC-1115, MCL3001, CLL3001; Safety Population

	Ibrutinib [1]	Comparator [2]
Analysis Set: Safety Population	756	749
Subjects with any treatment-emergent other malignancy	66 (8.7%)	31 (4.1%)
Type		
Preferred term		
Non-Melanoma Skin Cancer	46 (6.1%)	17 (2.3%)
Basal cell carcinoma	28 (3.7%)	8 (1.1%)
Squamous cell carcinoma	17 (2.2%)	11 (1.5%)
Bowen's disease	4 (0.5%)	0
Squamous cell carcinoma of skin	4 (0.5%)	3 (0.4%)
Skin cancer	2 (0.3%)	2 (0.3%)
Basosquamous carcinoma	1 (0.1%)	0
Basosquamous carcinoma of skin	1 (0.1%)	0
Lip squamous cell carcinoma	0	1 (0.1%)
Non-Skin cancer (malignant)	20 (2.6%)	15 (2.0%)
Prostate cancer	4 (0.5%)	2 (0.3%)
Myelodysplastic syndrome	2 (0.3%)	2 (0.3%)
Anal squamous cell carcinoma	1 (0.1%)	0
Chronic myelomonocytic leukaemia	1 (0.1%)	0
Gastrointestinal carcinoma	1 (0.1%)	0
Gastrointestinal tract adenoma	1 (0.1%)	0
Lung adenocarcinoma	1 (0.1%)	1 (0.1%)
Lung adenocarcinoma metastatic	1 (0.1%)	0
Non-small cell lung cancer	1 (0.1%)	1 (0.1%)
Oropharyngeal squamous cell carcinoma	1 (0.1%)	0
Renal cell carcinoma	1 (0.1%)	0
Salivary gland cancer	1 (0.1%)	0
Sarcoma	1 (0.1%)	0
Squamous cell carcinoma	1 (0.1%)	0
Squamous cell carcinoma of lung	1 (0.1%)	0
Throat cancer	1 (0.1%)	0
Transitional cell carcinoma	1 (0.1%)	1 (0.1%)
Adenocarcinoma gastric	0	1 (0.1%)
Barrett's oesophagus	0	1 (0.1%)
Bladder neoplasm	0	1 (0.1%)
Fibrous histiocytoma	0	1 (0.1%)
Metastatic renal cell carcinoma	0	1 (0.1%)
Metastatic squamous cell carcinoma	0	2 (0.3%)
Myeloproliferative disorder	0	1 (0.1%)
Oesophageal carcinoma	0	1 (0.1%)
Renal cancer	0	1 (0.1%)
Renal cancer stage I	0	1 (0.1%)
Melanoma Skin Cancer	1 (0.1%)	1 (0.1%)
Malignant melanoma in situ	1 (0.1%)	0
Malignant melanoma	0	1 (0.1%)
Superficial spreading melanoma stage unspecified	0	1 (0.1%)

Hypersensitivity

In the ibrutinib group of Study 1115, a total of 6 subjects (4.4%) had hypersensitivity TEAEs, of which one (0.7%) had a Grade 3 or 4 event (angioedema, Grade 3). None of the hypersensitivity events were reported as serious, and none led to ibrutinib discontinuation or dose reduction.

Eight subjects (6.1%) in the chlorambucil group of Study 1115 had a hypersensitivity TEAE. For 1 subject, a hypersensitivity event (drug hypersensitivity) resulted in treatment discontinuation of

chlorambucil.

None of the hypersensitivity TEAEs (4.0%) in the current monotherapy label pool resulted in discontinuation of ibrutinib therapy or a reduction in the ibrutinib dose; 1 subject had an event that was serious (angioedema, 0.2%).

Eye disorders

In Study 1115, TEAEs of any grade in the MedDRA SOC Eye Disorders were reported in 54.8% of subjects in the ibrutinib group and 22.7% of subjects in the chlorambucil group. Grade 3 or higher TEAEs reported in more than 1 ibrutinib-treated subject in Study 1115 were cataract (2 subjects, 1.5%) and unilateral blindness (2 subjects, 1.5%). Of the 2 ibrutinib-treated subjects with unilateral blindness (both reported as serious), 1 subject had medical history of vision problems secondary to diabetes, bilateral pseudophakia and blindness in the left eye of vision, and the other developed bilateral blindness after experiencing central retinal vein occlusion caused by thromboembolic disease. For 1 ibrutinib-treated subject (0.7%) in Study 1115, the eye-related TEAE resulted in discontinuation of study treatment (vitreous haemorrhage, also reported as serious). No eye-related TEAE in the chlorambucil group was reported with a frequency of ≥10%, and 1 was assessed as Grade 3 (cataract).

The overall frequency of TEAEs in the SOC Eye Disorders in the ibrutinib treatment group of Study 1115 was higher than that reported in the current monotherapy label pool (29.5%), possibly due to the older median age and longer median treatment duration in Study 1115. In the current monotherapy label pool, 1 subject had an eye disorder TEAE that was Grade 3 or 4 in severity (retinal detachment), and none were serious and none resulted in ibrutinib discontinuation.

Severe gastrointestinal disorders

The percentage of subjects with a Grade 3 or 4 gastrointestinal (GI) TEAE was 9.6% for the ibrutinib group (4.5% for chlorambucil group), and no GI-related event was fatal. Diarrhoea (3.7%) and abdominal pain (3.0%) were the most frequent, Grade 3 or 4 GI TEAEs among ibrutinib-treated subjects in Study 1115, with all other individual, Grade 3 or 4 GI TEAEs reported in 1 subject each. For 3 ibrutinib-treated subjects (2.2%) in Study 1115, the GI TEAE was serious (Grade 3 abdominal pain upper, Grade 3 pancreatitis acute, and Grade 2 constipation). One subject had a GI TEAE that resulted in ibrutinib discontinuation (abdominal pain).

In the current monotherapy label pool, GI TEAEs of Grade 3 or 4 in severity were reported in 33 subjects, 7.9%. For 1 subject, the GI TEAE was fatal (ileus paralytic). Two subjects (0.5%) in the current monotherapy label pool had GI TEAEs that led to discontinuation of ibrutinib treatment (severe diarrhoea in both cases.

Pancreatitis-related TEAE were reported for 1 ibrutinib-treated subject in Study 1115 (pancreatitis acute), 1 subject in the current monotherapy label pool (pancreatitis chronic), and 1 subject in the chlorambucil group of Study 1115 (pancreatitis).

Renal events

Four subjects (3.0%) in the ibrutinib group had a Grade 3 or 4 event in this SOC (renal failure acute (2 subjects), renal impairment (1 subject), renal failure (1 subject), and renal failure chronic (1 subject). For 1 subject in Study 1115, ibrutinib treatment was discontinued as a result of renal-related TEAE (renal failure), and for 3 subjects (2.2%), the renal-related TEAE was serious (renal impairment; renal failure and renal failure chronic; renal failure acute). In the chlorambucil group of Study 1115, TEAEs in the MedDRA SOC Renal and Urinary Disorders were of grade 3 or 4 in 3 subjects (2.3%).

In the current monotherapy label pool, grade 3 and 4 events for this SOC were reported in 2.4% and serious events in 1.9%.

Hypertension

Hypertension TEAEs (including preferred terms of hypertension and blood pressure increased) were reported as a TEAE for 19 subjects (14.1%) in the ibrutinib group of Study 1115. For 6 subjects (4.4%) the event was assessed as Grade 3 or 4 in severity, and for 5 subjects (3.7%) the event assessed as treatment related. For all but 2 of the ibrutinib-treated subjects, the hypertension TEAEs were not serious, and none resulted in an ibrutinib dose reduction or treatment discontinuation. Nine of 19 subjects with a reported TEAE of hypertension had a medical history of hypertension prior to ibrutinib therapy, and all subjects were managed with addition and/or adjustment of anti-hypertensive therapy. One subject in the chlorambucil group of Study 1115 had a hypertension TEAE.

Among the 420 subjects treated with ibrutinib in the current monotherapy label pool, hypertension TEAEs was reported in 35 subjects (8.3%); 3.1% of subjects with Grade 3 or 4 event. None of the reported hypertension TEAEs in the current monotherapy label pool were serious or resulted in discontinuation of ibrutinib, and for 1 subject, the event resulted in an ibrutinib dose reduction.

Hepatic events

In Study 1115, TEAEs in the MedDRA SOC Hepatobiliary Disorders were reported for 8 ibrutinib-treated subjects (5.9%), of whom, 4 (3.0%) had a Grade 3 or 4 event. These latter TEAEs consisted for 2 reports of hepatic function abnormal (1.5%) and 1 report (0.7%) each of hyperbilirubinemia, bile duct stone, and cholangitis. Hepatobiliary TEAEs were reported for 5 subjects (3.8%) in the chlorambucil group of Study 1115, and for 1 subject, the event was Grade 3 or 4 (cholecystitis). Toxic hepatitis resulted in the death of a chlorambucil-treated subject.

In the current monotherapy label pool, TEAEs of any grade in this SOC were reported in 2.9% of subjects, with Grade 3 or 4 events reported for 2 subjects (0.5%) (hyperbilirubinemia and cholecystitis). No subject had a fatal hepatobiliary event, and serious hepatobiliary TEAEs were reported in 2 (0.5%) subjects (2 reports of cholecystitis). No subject experienced a hepatobiliary TEAE that resulted in discontinuation of ibrutinib treatment, although 1 subject had an event that led to dose reduction (hepatic function abnormal).

Serious adverse event / deaths / other significant events

Serious adverse event

Table 42. Serious Treatment-emergent Adverse Events with Subject Incidence of ≥2% in Study 1115 or the Current Monotherapy Label Pool; Safety Population

	PCYC-1115								
	Ibrutinib			Chlorambucil			Current Monotherapy Label Pool		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
Analysis Set: Safety Population	135			132			420		
Subjects with Any Serious TEAE	55 (40.7%)	42 (31.1%)	3 (2.2%)	33 (25.0%)	23 (17.4%)	4 (3.0%)	194 (46.2%)	142 (33.8%)	32 (7.6%)
System Organ Class									
Preferred Term									
Infections and infestations	20 (14.8%)	15 (11.1%)	1 (0.7%)	7 (5.3%)	6 (4.5%)	1 (0.8%)	96 (22.9%)	79 (18.8%)	9 (2.1%)
Pneumonia	5 (3.7%)	4 (3.0%)	0	2 (1.5%)	2 (1.5%)	0	29 (6.9%)	23 (5.5%)	4 (1.0%)
Urinary tract infection	2 (1.5%)	2 (1.5%)	0	0	0	0	9 (2.1%)	8 (1.9%)	0
General disorders and administration site conditions	4 (3.0%)	1 (0.7%)	2 (1.5%)	7 (5.3%)	3 (2.3%)	0	29 (6.9%)	16 (3.8%)	1 (0.2%)
Pyrexia	1 (0.7%)	0	0	5 (3.8%)	2 (1.5%)	0	12 (2.9%)	6 (1.4%)	0
Cardiac disorders	7 (5.2%)	5 (3.7%)	0	4 (3.0%)	2 (1.5%)	0	27 (6.4%)	22 (5.2%)	2 (0.5%)
Atrial fibrillation	2 (1.5%)	2 (1.5%)	0	1 (0.8%)	0	0	15 (3.6%)	14 (3.3%)	0
Blood and lymphatic system disorders	4 (3.0%)	4 (3.0%)	0	8 (6.1%)	8 (6.1%)	0	25 (6.0%)	24 (5.7%)	0
Febrile neutropenia	2 (1.5%)	2 (1.5%)	0	2 (1.5%)	2 (1.5%)	0	9 (2.1%)	9 (2.1%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	12 (8.9%)	7 (5.2%)	0	2 (1.5%)	0	1 (0.8%)	24 (5.7%)	8 (1.9%)	15 (3.6%)
Basal cell carcinoma	5 (3.7%)	1 (0.7%)	0	0	0	0	0	0	0
Metabolism and nutrition disorders	4 (3.0%)	3 (2.2%)	0	1 (0.8%)	0	0	7 (1.7%)	6 (1.4%)	0
Hyponatraemia	3 (2.2%)	2 (1.5%)	0	0	0	0	2 (0.5%)	1 (0.2%)	0

TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety population as denominator. Worst toxicity grade was used for subjects who had multiple events per system organ class or per preferred term. A subject who had event with missing toxicity grade was counted in the all grades column but not listed separately.
Current Monotherapy Label Pool includes Studies 1112, 1102, 1104, and 1118E.

Deaths

Table 43. Treatment-emergent Adverse Events Resulting in Death – Study 1115 and Current Monotherapy Label Pool; Safety Population

	PCYC-1115		
	Ibrutinib	Chlorambucil	Current Monotherapy Label Pool
Analysis set: safety	135	132	420
Subjects with Any TEAE Leading to Death	3 (2.2%)	4 (3.0%)	32 (7.6%)
System Organ Class Preferred Term			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.8%)	15 (3.6%)
Mantle cell lymphoma	0	0	7 (1.7%)
Chronic lymphocytic leukaemia	0	1 (0.8%)	2 (0.5%)
Gastrointestinal carcinoma	0	0	1 (0.2%)
Leukaemia	0	0	1 (0.2%)
Malignant histiocytosis	0	0	1 (0.2%)
Malignant pleural effusion	0	0	1 (0.2%)
Peripheral T-cell lymphoma unspecified	0	0	1 (0.2%)
Richter's syndrome	0	0	1 (0.2%)
Infections and infestations	1 (0.7%)	1 (0.8%)	9 (2.1%)
Pneumonia	0	0	4 (1.0%)
Sepsis	0	0	3 (0.7%)
Neutropenic sepsis	0	0	1 (0.2%)
Pneumocystis jirovecii pneumonia	0	0	1 (0.2%)
Acute hepatitis B	0	1 (0.8%)	0
Klebsiella infection	1 (0.7%)	0	0
Respiratory, thoracic and mediastinal disorders	0	0	3 (0.7%)
Dyspnoea	0	0	1 (0.2%)
Pleural effusion	0	0	1 (0.2%)
Respiratory failure	0	0	1 (0.2%)
Cardiac disorders	0	0	2 (0.5%)
Cardiac arrest	0	0	2 (0.5%)
Gastrointestinal disorders	0	0	1 (0.2%)
Ileus paralytic	0	0	1 (0.2%)
General disorders and administration site conditions	2 (1.5%)	0	1 (0.2%)
Systemic inflammatory response syndrome	0	0	1 (0.2%)
Death	2 (1.5%)	0	0
Renal and urinary disorders	0	0	1 (0.2%)
Renal failure acute	0	0	1 (0.2%)
Hepatobiliary disorders	0	1 (0.8%)	0
Hepatitis toxic	0	1 (0.8%)	0
Nervous system disorders	0	1 (0.8%)	0
Ischaemic stroke	0	1 (0.8%)	0

TEAE = Treatment-emergent adverse event.
Note: Percentages calculated with the number of subjects in safety analysis set as denominator.
Current Monotherapy Label Pool includes Studies 1112, 1102, 1104, and 1118E.

Laboratory findings

Haematology

In the ibrutinib group of Study 1115, no treatment-emergent, Grade 3 or 4 decreases in hemoglobin were observed, while treatment-emergent Grade 3 or 4 decreases in platelets and absolute neutrophil count (ANC) were observed for 7.4% and 28.1% of subjects, respectively.

The percentages of subjects with Grade 3 or 4 laboratory abnormalities in hemoglobin, platelet counts, and ANC for the chlorambucil group in Study 1115 were 1.5%, 13.6%, and 31.1%, respectively.

In study 1115, absolute lymphocyte count (ALC) values increased rapidly (but transiently) following initiation of ibrutinib to a peak median ALC of approximately 75 x 10^9/L, followed by a decrease toward normal values. The median time to treatment-emergent lymphocytosis (defined as an increase in ALC of at least 50% from baseline to an absolute value greater than 5.0 x 10^9/L) was 2.1 weeks, and 94.8% of ibrutinib-treated subjects who displayed treatment-emergent lymphocytosis achieved resolution (median time to resolution of 12.4 weeks; resolution defined as a decrease in ALC to baseline or to less than 5.0 x 10^9/L).

Hepatic function parameters

No subject in the ibrutinib group of Study 1115 had a treatment-emergent, Grade 4 elevation; 3 ibrutinib-treated subjects (2.3%) had a treatment-emergent, Grade 3 elevation in ALT, 1 subject (0.8%)

had a Grade 3 elevation in ALP, and no subject had a Grade 3 elevation in total bilirubin.

In the current monotherapy label pool, there were no treatment-emergent Grade 3 or 4 elevations in ALT or AST, and <1% of subjects had a treatment-emergent Grade 3 elevation in ALP or total bilirubin (none had a Grade 4 elevation in these parameters).

Based on case level review, no ibrutinib-treated subject in Study 1115 or the current monotherapy label pool met the Hy's law laboratory criteria without an alternative etiology.

In the chlorambucil group of Study 1115, Grade 3 or 4 elevations in ALT or AST were infrequent as well, reported for 2 (1.5%) subjects each; Grade 3 or 4 elevations in total bilirubin.

Serum creatinine

Treatment-emergent Grade 3 or 4 elevations in serum creatinine were observed for 1 subject (0.8%) in the ibrutinib group of Study 1115 (0 subjects in chlorambucil group of Study 1115) and for no subject in the current monotherapy label pool.

Among ibrutinib-treated subjects in Study 1115 or the current monotherapy label pool with normal baseline CrCl values of ⩾60 mL/min, <1% had a decrease in value to <30 mL/min while on treatment, and 15.2% and 10.1%, respectively, had a decrease in value to between ⩾30 and <60 mL/min on treatment.

Safety in special populations

Age

Table 44. Overall Summary of Treatment-emergent Adverse Events by Age Group (>=70 vs. <70) - PCYC-1115 and Current Monotherapy Label Pool; Safety Population (CLL/SLL/MCL/WM-ISS)

	PCYC-1115					
	Ibrutinib		Chlorambucil		Current Monotherapy Label Pool	
	Age (years)		Age (years)		Age (years)	
	>=70	<70	>=70	<70	>=70	<70
Analysis set: safety	95	40	93	39	164	256
Any TEAE	93 (97.9%)	40 (100.0%)	88 (94.6%)	36 (92.3%)	164 (100.0%)	255 (99.6%)
Grade >= 3	69 (72.6%)	20 (50.0%)	50 (53.8%)	18 (46.2%)	118 (72.0%)	145 (56.6%)
Drug related	81 (85.3%)	33 (82.5%)	74 (79.6%)	27 (69.2%)	139 (84.8%)	212 (82.8%)
Grade >= 3	32 (33.7%)	16 (40.0%)	38 (40.9%)	13 (33.3%)	65 (39.6%)	83 (32.4%)
Any TESAE	41 (43.2%)	14 (35.0%)	25 (26.9%)	8 (20.5%)	92 (56.1%)	102 (39.8%)
Grade >= 3	33 (34.7%)	12 (30.0%)	20 (21.5%)	7 (17.9%)	84 (51.2%)	90 (35.2%)
Drug related	11 (11.6%)	6 (15.0%)	11 (11.8%)	2 (5.1%)	39 (23.8%)	40 (15.6%)
TEAE leading to treatment discontinuation	8 (8.4%)	6 (15.0%)	21 (22.6%)	9 (23.1%)	22 (13.4%)	17 (6.6%)
TEAE leading to treatment dose reduction	13 (13.7%)	0	19 (20.4%)	6 (15.4%)	15 (9.1%)	17 (6.6%)
TEAE with outcome death	2 (2.1%)	1 (2.5%)	3 (3.2%)	1 (2.6%)	19 (11.6%)	13 (5.1%)
Death within 30 days after last dose of study treatment	2 (2.1%)	0	0	1 (2.6%)	18 (11.0%)	13 (5.1%)

Key: TEAE = Treatment-emergent adverse event, TESAE = Treatment-emergent serious adverse event.
[a] Includes any death that occurred post first dose of study treatment and within 30 days of the last dose of study treatment.
Note: Percentages calculated with the number of subjects in safety population as denominator.
Adverse events were coded using MedDRA version 17.1.
Current Monotherapy Label Pool includes PCYC-1102, PCYC-1104, PCYC-1112, and PCYC-1118.

Two of the 3 subjects with a TEAE that had an outcome of death were ≥70 years. An examination of

Grade 3 or 4 TEAEs by MedDRA SOC for the 2 age subgroups indicated that all Grade 3 or 4 cardiac disorder TEAEs in the ibrutinib group occurred in subjects ≥70 years (8 subjects, 8.4%), as did all Grade 3 or 4 neoplasm TEAEs (8 subjects, 8.4%).

Sex

Approximately two-thirds of the ibrutinib-treated subjects in Study 1115 were male (65.2%). The overall frequencies of TEAEs, Grade 3 or higher TEAEs, serious TEAEs, and TEAEs leading to discontinuation were similar (<10 % difference) in men and women in the ibrutinib group of this study.

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to adverse events

TEAEs leading to discontinuation in the experimental arm were atrial fibrillation (2 subjects, 1.5%), death of unknown cause (2 subjects), bronchopneumonia (1), Klebsiella infection (1), pneumonia legionella (1), non-small cell lung cancer (1), abdominal pain (1), vitreous haemorrhage (1), subdural hematoma (1), cerebral haemorrhage (1), subarachnoid haemorrhage (1), renal failure (1), rash macular (1), and rash maculo-papular (1).

Fifteen subjects (11.4%) in the control arm discontinued due to TEAEs in the Blood and Lymphatic System Disorders SOC compared with none among ibrutinib-treated subjects.

The most common TEAEs leading to treatment discontinuation in the current monotherapy label pool were pneumonia (1.2%), subdural hematoma (1.2%), and sepsis (1.0%). All other individual TEAEs leading to ibrutinib discontinuation in the safety population were reported in 2 or fewer subjects.

Approximately twice as many subjects in the chlorambucil group (compared to the ibrutinib group) of Study 1115 had a TEAE leading to dose reduction (25 subjects, 18.9%). The most common TEAEs resulting in a reduction of the chlorambucil dose (⩾2% of subjects) were neutropenia (6.8%), anemia (3.8%), and fatigue (2.3%). In the experimental arm, no individual TEAE (ie, preferred term) led to dose reduction in more than 1 subject and these events did not cluster within a particular SOC(s).

Diarrhoea (1.7%) and neutropenia (1.4%) were the only TEAEs leading to dose reduction in 1% or more of the current monotherapy label pool.

Post marketing experience

The first PBRER/PSUR for ibrutinib has been submitted in the EU and included data received worldwide for the reporting period from 21 October 2014 (date of first approval for ibrutinib in EU) through 20 April 2015. Based on the cumulative total of 1,429,641,360 milligrams of ibrutinib distributed (launch to 30 Apr 2015), the estimated exposure to this drug in the post marketing setting was 106,372 person-months (average daily dose of 448 mg).

A review of data for this reporting period indicated that the safety profile of ibrutinib remained acceptable, and the drug continues to have a favourable benefit-risk profile for the treatment of patients with the indications described in the Imbruvica SmPC.

2.5.1. Discussion on clinical safety

Randomised safety data from the 1115 study has been submitted (ibrutinib, n=135; chlorambucil, n=132) and data on ibrutinib compared to the current monotherapy label pool (n=420). The latter partly included time-truncated data as compared to the basis for the current SmPC; a re-analysis using non-truncated data was requested with reporting of any deviations regarding frequency of important AEs or ADR determination. The different treatment durations for the datasets should be noted when reviewing AE incidences: approximately 17 and 7 months for the ibrutinib and chlorambucil arms of study 1115, respectively, and 9 months for the monotherapy pool.

The most frequently reported TEAEs in the ibrutinib arm of study 1115 were diarrhoea (42%), fatigue (30%), nausea (22%) and cough (22%). A higher rate of eye disorders vs the monotherapy pool is noted (55% vs 30%), possibly related to a higher median age and the longer treatment duration, but few grade ≥ 3 events were reported. Although not adjusted for a declining number of subjects at risk over time, which, however, for the ibrutinib arm was quite low, an analysis suggests the lack of an increasing specific AE prevalence over time, except for hypertension. Generally, the highest AE rates were noted within the first 3 months of treatment.

When compared to the chlorambucil arm in study 1115, ibrutinib was associated with higher rates of grade ≥ 3 events (66% vs 52%) and SAEs (41% vs 25%), but fewer AEs leading to discontinuation or dose reduction. It is noted that an SAE related to basal cell carcinoma was reported in 3.7% of patients in the ibrutinib arm of study 1115 vs none in the monotherapy pool or the chlorambucil group.

As expected for a treatment-naïve population, the fraction of patients with AE leading to death was lower in the ibrutinib arm of the 1115 study (n=3; 2.2%) than in the monotherapy pool (7.6%); the corresponding fraction in the chlorambucil arm was 3%.

TEAEs leading to treatment discontinuation or dose reduction were both reported in 10% of patients in the ibrutinib arm of study 1115 vs 23% and 19% in the chlorambucil arm, respectively. For the ibrutinib arm, AEs leading to discontinuation were mainly related to infection, haemorrhage, atrial fibrillation and rash. As expected in a previously untreated population, the rates of TEAEs leading to death and deaths within 30 days of last dose were lower in the ibrutinib arm of the 1115 study compared to the monotherapy pool.

The safety profile observed in the 1115 study was generally consistent with previous reports but a comparison with the “current monotherapy label pool” (n=420 with data from the 1112, 1104, 1118E and 1102 studies in previously treated CLL, MCL and WM, and a few patients with treatment-naïve CLL) identified hypertension, muscle spasms and non-melanoma skin cancer as new ADRs. It should be noted in the comparisons that time on treatment vary widely between the study populations: approximately 17 and 7 months for the ibrutinib and chlorambucil arms of study 1115, respectively, and 9 months for the monotherapy pool.

Hypertension was identified as a new ADR for ibrutinib with a prevalence increasing over time. So far, only 1 event resulted in dose reduction, none led to treatment discontinuation. Hypertension and muscle spasms were identified as new ADRs in the 1115 study and are added in section 4.8 of the SmPC.

The rate of treatment-emergent other malignancies in the ibrutinib arm of study 1115, total 17% with 13% non-melanoma skin cancer vs a total 5% in the chlorambucil arm, may be of some concern. In the monotherapy pool, 8% of patients were reported with other malignancies. It is acknowledged that CLL per se is associated with a substantial increased risk for the development of other malignancies and that the different times on treatment may explain the observed differences between the safety populations.

A comparative, pooled, randomized Phase 3 clinical trial data analysis (including Studies 1112, 1115, MCL3001, and CLL3001) indicated that non-melanoma skin cancer was reported more frequently with

ibrutinib than with the comparators, 6.1% vs 2.3%, respectively. Patients should be monitored for the appearance of non-melanoma skin cancer (SmPC sections 4.4 and 4.8).

In addition, a time to event analyses for non-melanoma skin cancer for ibrutinib and comparator arms in the 1115 study and the pooled randomised phase 3 studies was presented. Genotoxic evaluation was regarded as negative for ibrutinib. However, the potential transformation of ibrutinib into genotoxic metabolites has not been addressed by the MAH. For the intended indication such transformation is regarded as a potential safety concern. Consequently, the MAH will perform, a (Q)SAR/DEREK analysis and AMES test for M21 and M34 (see discussion on non-clinical).

Further, the Risk Management Plan has been updated to include non-melanoma skin cancer as an important identified risk while other malignancies (excluding non-melanoma skin cancer) will be continued to be listed as an important potential risk. Second primary malignancies will continue to be monitored in ongoing clinical trials and through routine pharmacovigilance, and will be presented in the PSURs.

In the safety analysis of the Current monotherapy label pool, time-truncated data was used for the 1112 and 1104 studies. Given the importance of long-term safety data, not least in the 1st line setting, a re-analysis of the total data set was requested with reporting on frequency deviations regarding important AEs and the determination of ADRs. The only PTs that increased >1% were for Grade ≥ 3 events neutropenia (17.4% versus 16.2%), pneumonia (8.6% versus 6.9%) and hypertension (5.2% versus 3.1%); SAEs that increased by > 1% were pneumonia (9.0% versus 6.9%) and atrial fibrillation (4.8% versus 3.6%). No change in identified ADRs was detected and no new safety signals or late-onset toxicities were observed. Hypertension would change from the category Common to Very Common. The MAH argued for giving the highest weight to randomised data in the procedure for determining ADRs and to present follow-up data in DSURs/PSURs and also refers to the growing body of safety data with further randomised trials like CLL3001 and MCL3001, which are dealt with in the parallel II-17G procedure. This reasoning was considered reasonable and accepted.

No data of Long term use (>2 years) are available. An open-label extension study (PCYC-1116) in patients 65 years or older with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who participated in study PCYC-1115 is ongoing and a 2 years efficacy and safety update will be provided in support of the Missing Information of Long term use (>2 years) (see Risk Management Plan).

Safety data reflected in section 4.8 of the SmPC are now based on an analysis of the experience in 555 patients with B cell malignancies and, as a result, some ADR frequencies have been updated.

2.5.2. Conclusions on clinical safety

Safety data gathered in the 1115 study, with support from historical data were largely consistent with the known safety profile of ibrutinib with hypertension, muscle spasms and non-melanoma skin cancer being new adverse reactions observed in patients treated for CLL. Toxicity was generally manageable.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

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

The PRAC considered that the RMP version 5.0 (dated 08 October 2015) could be acceptable if the

applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed the above with comments.

The applicant implemented the changes in the RMP as requested by PRAC and CHMP.

The CHMP endorsed the RMP version 5.0.3 (dated 26 April 2016) with the following content:

Table 45 – *Summary of the Safety concerns*

Important Identified Risks	• Leukostasis • Haemorrhage • Tumour lysis syndrome • Non-melanoma skin cancer
Important Potential Risks	• Drug-drug interaction • Anaemia • Neutropenia • Thrombocytopenia • Infections • Cardiac arrhythmia • Severe GI disorders • Other malignancies (excluding non-melanoma skin cancer) • Hypersensitivity • Teratogenicity • Eye disorders • Renal failure • Hypertension
Missing Information	• Off-label use in paediatric patients • Use during breastfeeding • Use in patients with severe cardiac disease • Use in patients with severe renal impairment • Use in patients with severe hepatic impairment • Long term use (>2 years)

Pharmacovigilance plan

Table 46. *Ongoing and Planned Additional Pharmacovigilance Studies/Activities in the Pharmacovigilance Plan*

Study / activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
PCYC-PMR-2060-03 In Vitro Studies on the Effect of Ibrutinib on Platelet Function (category 3)	To evaluate the effect of ibrutinib on platelet aggregation as assessed by light transmission aggregometry	Haemorrhage	Started	4th Quarter 2016
PCYC-PMR-2060-04 Analysis of the risk of serious bleeding (category 3)	To study of the risk of serious bleeding from clinical trials and all post-marketing sources	Haemorrhage	Started	4th Quarter 2018
PCI-32765LYM1003 A drug-drug interaction study of Ibrutinib with moderate and strong CYP3A inhibitors in patients with B-cell malignancy (category 3)	To assess steady-state PK of repeated oral doses of ibrutinib alone in patients with B cell malignancies and when combined with a moderate and strong CYP3A inhibitor	Drug-drug interaction	Started	1st Quarter 2018
PCYC-1112-CA Yearly updates, including del17p/TP53 subgroups identified at baseline, for the randomised, multicentre, open-label; Subjects with CLL who have failed at least 1 prior line of therapy; Assess PFS by IRC trial. (category 1)	Yearly updates of trial results for progression and death	Overall safety profile	Yearly updates	2nd Quarter 2016 2nd Quarter 2017 4th Quarter 2017
PCI-32765 CLL1007 (planned) Thorough QT study (category 3)	To assess the effect of ibrutinib on ECG parameters	Cardiac arrhythmia	Planned	Final Report Submission: 4th Quarter 2016

Study / activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
PCI-1103-CA (ongoing)[a] Open-label, extension trial in subjects with B-cell lymphoma and CLL to determine the long-term safety of ibrutinib (category 3)	Determine the long-term safety and tolerability of a fixed daily dose of ibrutinib	Long-term use (>2 years)	Ongoing	Interim report 2nd Quarter 2016 4th Quarter 2027 final
PCI-32765 CAN3001[a] Open-label, extension study in subjects with MCL (category 3)	To determine the long-term safety of ibrutinib	Long-term use (>2 years)	Ongoing	Interim report 2nd Quarter 2016 4th Quarter 2027 final
PCI-32765MCL2001 Phase 2; Multicentre, single-arm; Subjects with MCL who have received ≥1 rituximab-containing regimen and progressed after receiving ≥2 cycles of bortezomib therapy (category 3)	Evaluate ORR	Overall safety profile	Ongoing	1st Quarter 2016 final
PCI-32765MCL3001 Phase 3; Randomised, controlled, open-label, multicentre; Subjects with relapsed/ refractory MCL who have received at least 1 prior rituximab-containing chemotherapy regimen (category 1)	Evaluate efficacy and safety of ibrutinib vs. temsirolimus.	Overall safety profile	Ongoing	1st Quarter 2016 final

Study / activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
PCI-32765MCL3002 Phase 3; Randomised, double-blind, placebo-controlled, multicentre; Subjects with newly diagnosed MCL with no prior therapies for MCL (category 3)	Evaluate efficacy and safety of ibrutinib in combination with BR vs. BR alone	Overall safety profile	Ongoing	3rd Quarter 2020 final
PCYC-1117-CA Phase 2; Open-label, single arm, multicentre; Subjects with relapsed or refractory CLL with 17p deletion (category 3)	Evaluate ORR by IRC and safety	Overall safety profile	Ongoing	4th Quarter 2015
PCI-32765CLL3001 Phase 3; Randomised, multicentre, double-blind, placebo-controlled; Subjects with relapsed or refractory CLL (excluding subjects with del 17p) (category 3)	Evaluate PFS of ibrutinib in combination with BR vs. BR alone	Overall safety profile	Ongoing	3rd Quarter 2018
A clinical interaction study to evaluate the effect of proton pump inhibitors (category 3)	Determine the effect of ibrutinib on proton pump inhibitors.	Drug-drug interaction	Planned	3rd Quarter 2016

Study / activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
A feasibility assessment for an interaction study between ibrutinib and bupropion as a substrate sensitive to CYP2B6 induction and as a model compound for assessing the potential of ibrutinib to induce the nuclear receptor CAR (constitutive androstane receptor). The assessment will include the possibility to combine the bupropion interaction study with the oral contraceptive interaction study (see Section III.5.2). (category 3)	Determine if conducting an interaction study of ibrutinib and bupropion is feasible.	Drug-drug interaction	Planned	Final feasibility assessment report: 4th Quarter 2015
A non-clinical study regarding the Transgenic (Tg) mouse range-finder study (category 3)	To characterise toxicity and establish appropriate doses for longer duration studies; to assess the metabolite profile.	Other malignancies	Planned	4th Quarter 2015
Following the mouse range-finder study: A non-clinical study regarding the Tg ras H2 6 month mouse carcinogenicity study. (category 3)	To evaluate the potential of ibrutinib to induce preneoplastic and neoplastic lesions.	Other malignancies	Planned	1st Quarter 2018

Study / activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
PCYC-1116-CA An Open-label Extension Study in Patients 65 Years or Older with Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) Who Participated in Study PCYC-1115-CA (Ibrutinib versus Chlorambucil) – 2 year safety update (category 3)	To further characterise the long-term efficacy and safety of ibrutinib	Non-melanoma skin cancer Other malignancies Long term use (>2 years)	Ongoing	2nd Quarter 2018
AMES assays of major human metabolites M21 and M34 (category 3)	Assess mutagenicity potential of major human metabolites	Long term use (>2 years)	Ongoing	Final report: 1st Quarter 2017
[a] Trial only collects grade 3 or 4 adverse events and not all adverse events				

Risk minimisation measures

Table 47 - *Risk Minimisation Measures*

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important identified risks		
Leukostasis	Wording in SmPC Sections 4.4 and 4.8	None
Haemorrhage	Wording in SmPC Section 4.4	None
Tumour lysis syndrome	Wording in SmPC Sections 4.4 and 4.8	None
Non-melanoma skin cancer	Wording in SmPC Sections 4.4 and 4.8	None
Important potential risks		
Drug-drug interactions	Wording in SmPC Sections 4.4 and 4.5	None
Anaemia	Wording in SmPC Sections 4.2, 4.4 and 4.8	None
Neutropenia	Wording in SmPC Sections 4.2, 4.4 and 4.8	None
Thrombocytopenia	Wording in SmPC Sections 4.2, 4.4 and 4.8	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Infections	Wording in SmPC Section 4.4	None
Cardiac arrhythmia	Wording in SmPC Section 4.4	None
Severe GI adverse events	Wording in SmPC Section 4.8	None
Other malignancies (excluding non-melanoma skin cancer)	None proposed	None
Hypersensitivity	Wording in SmPC Section 4.3	None
Teratogenicity	Wording in SmPC Sections 4.4 and 4.6	None
Eye disorders	Wording in SmPC Section 4.8	None
Renal failure	Wording in SmPC Section 4.2	None
Hypertension	None proposed.	None
Missing Information:		
Use in paediatric patients	Wording in SmPC Section 4.2	None
Use during breastfeeding	Wording in SmPC Section 4.6	None
Use in patients with severe cardiac disease	Wording in SmPC Sections 4.2 and 4.4	None
Use in patients with severe renal impairment	Wording in SmPC Section 4.2	None
Use in patients with severe hepatic impairment	Wording in SmPC Section 4.2	None
Long term use (>2 years)	None proposed	None
Mutagenic potential of M21 and M34	None proposed	None

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.4, 4.6, 4.8, 5.1 and 5.3 of the SmPC have been updated. Particularly, a new warning with regard to non-melanoma skin cancer has been added to the product information. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet

has been submitted by the applicant and has been found acceptable for the following reasons: No critical amendments of the product information have been proposed and a user consultation is not considered needed.

3. Benefit-Risk Balance

Benefits

Beneficial effects

In the 1115 study, efficacy was significantly superior with the ibrutinib regimen in terms of the primary endpoint PFS, compared to chlorambucil in previously untreated CLL patients with HR 0.161 (p<0.0001), based on 15 (11%) events in the ibrutinib arm and 64 (48%) events in the chlorambucil arm. The robustness of the PFS effect is supported by sensitivity analyses and by general consistency within subgroups.

The secondary endpoints including ORR by IRC (82% vs 35%, p<0.0001 MRD-negative response, sustained haematological improvement (in subjects with cytopenia at baseline in 77% vs 43% of patients for thrombocytopenia, p<0.0054, and 84% vs 46% for anaemia, p<0.0001, respectively), and EFS at 12 months (HR 0.165, p<0.0001) supported the primary efficacy endpoint and favoured the ibrutinib arm compared to the chlorambucil arm.

Collectively, the historical comparison data support the notion that ibrutinib monotherapy would provide efficacy in the same range as that seen with first-line combination regimens used in more fit patients.

Uncertainty in the knowledge about the beneficial effects

Overall survival data are still immature and the MAH will provide a 2-year efficacy and safety update of the long-term follow-up study PCYC-1116-CA, open-label extension of Study PCYC-1115-CA (see Risk Management Plan).

The 1115 study has been performed in a population of patients deemed unfit for full dose FCR therapy. The indication sought includes also patients who would be eligible for FCR, as well as for other chemo-immunotherapies as first line treatment of CLL. Estimates of efficacy in patients eligible for FCR is based on extrapolation to a more fit population and no direct estimate of efficacy is available. While cross-study comparisons are indicative that efficacy is not substantially lower than for alternatives, and this comparison may be conservative in the sense that patients were selected for the 1115 study based on an age and clinical status indicating that full dose FCR would not be tolerated, the absence of a direct, randomised comparison confers uncertainty to the knowledge of relative efficacy, for which no precise metric can be provided. However, in view of the benefits observed and plausible generalisations, this uncertainty does not raise concerns since based on indirect comparisons inferior efficacy can be ruled out.

Risks

Unfavourable effects

The ibrutinib safety profile observed in the 1115 study was generally consistent with previous reports but hypertension, muscle spasms and non-melanoma skin cancer were identified as new ADRs. TEAEs leading to treatment discontinuation or dose reduction were both reported in 10% of patients in the ibrutinib arm of study 1115 vs 23% and 19% in the chlorambucil arm, respectively.

As expected for a treatment-naïve population, the fraction of patients with AE leading to death was lower

in the ibrutinib arm of the 1115 study (n=3; 2.2%) than in the monotherapy pool (7.6%); the corresponding fraction in the chlorambucil arm was 3% (n=4).The most frequently reported TEAEs were diarrhoea (42%), fatigue (30%), nausea (22%) and cough (22%). When compared to the chlorambucil arm in study 1115, ibrutinib was associated with higher rates of grade ≥3 events (66% vs 52%) and SAEs (41% vs 25%), but as noted above, fewer AEs leading to discontinuation or dose reduction.

Uncertainty in the knowledge about the unfavourable effects

Ibrutinib as a single agent in the first line setting has been studied in a relatively elderly patient population deemed unfit for FCR. There are no estimates of the frequency of adverse events in a more fit population, but in comparison with pooled monotherapy data there are nothing indicating that "first-line" per se would increase the risk for adverse reactions; rather the opposite. To this may be added that a treatment with acceptable tolerability in unfit patients are likely to be better tolerated in fit patients.

A comparative, pooled, randomized Phase 3 clinical trial data analysis (including Studies 1112, 1115, MCL3001, and CLL3001) indicated that non-melanoma skin cancer was reported more frequently with ibrutinib than with the comparators, 6.1% vs 2.3%, respectively). This has been adequately reflected in the SmPC (see section 4.4 and 4.8) and is reflected in the Risk Management Plan.

In addition, second primary malignancies will continue to be monitored in ongoing clinical trials and through routine pharmacovigilance, and will be presented in the PSURs.

No data of Long term use (>2 years) are available. An open-label extension study (PCYC-1116) in patients 65 years or older with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who participated in study PCYC-1115 is ongoing and a 2 years efficacy and safety update will be provided in support of the Missing Information of Long term use (>2 years) (see Risk Management Plan).

Effects Table

Table 48. Effects Table for study 1115 (data cut-off: 28 May 2015)

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS by IRC	Duration from randomization to the time of PD or death	Months	Median NE (NE, NE) Censored: 89%	18.9 (14.1, 22.0) Censored: 51.9%	p<0.0001 HR 0.161 (0.091, 0.283)	AR (efficacy section of 1115 study)
ORR by IRC	proportion of subjects who achieved a best overall response of CR, CRi, nPR, or PR	%	82.4	35.3	p<0.0001	AR (efficacy section of 1115 study)

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
OS		Months	Median NE (NE, NE) Censored: 97.8%	NE (NE, NE) Censored: 87.2%	P<0.001 HR 0.163 (0.048, 0.558)	
Unfavourable Effects						
TEAEs grade ≥3		%	65.9	51.5	Note different times on treatment: 17 months for ibrutinib, 7 months for chlorambucil	
TESAEs grade ≥3		%	33.3	20.5		
TEAEs leading to treatment discontinuation		%	10.4	22.7		
TEAEs leading to dose reduction		%	9.6	18.9		
TEAEs leading to death		%	2.2	3.0		
Death within 30 days of treatment		%	1.5	0.8		
Hypertension		%	14.1	o		
Muscle spasms		%	11.1	5.3		
Non-melanoma skin cancer		%	13.3	3.8		

Abbreviations: AR: Assessment Report, HR: Hazard Ratio, NE: not estimated, ORR: overall response rate, OS: overall survival, PFS: Progression Free Survival, TEAEs: treatment-emergent adverse events, TESAEs: treatment-emergent serious adverse events

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The considerably better outcomes of the time-dependent measures, including OS, and also response rate vs chlorambucil, with generally good internal consistency, are deemed to be of definitive clinical relevance; furthermore, the magnitude of the effect seen in this study, supported by previous experiences such as results in the treatment of patients with 17p deletion, are indicative of a clinically relevant effect also in patients fit for various chemo-immunotherapies. This is supported by the relatively good tolerability of ibrutinib monotherapy

From a safety perspective the 1115 study compares ibrutinib, dosed until progression or unacceptable side effects, with chlorambucil dosed for a definite number of cycles (12). With the exception of hypertension, the incidence of particular AEs does not seem to increase over time and with respect to hypertension this AE is expected to be readily handled by the treating physician. In conjunction with the data presented for the monotherapy poo,l the safety profile of ibrutinib within the 9-17 months exposure window must be considered sufficiently well characterised. Given the considerably longer treatment duration expected for most patients when initiated in the 1st line setting, long-term safety of ibrutinib is addressed in the RMP.

Benefit-risk balance

In comparison to chlorambucil monotherapy, in the investigated population, the efficacy of ibrutinib is clearly superior. In relation to chlorambucil, the safety profile of ibrutinib is characterised by higher rates of grade $\geqslant$3 events and SAEs but eventually lower fractions of AEs leading to discontinuation or dose reductions.

The benefit-risk balance for the studied population is considered positive.

Discussion on the Benefit-Risk Balance

The 1115 study was a comparative study versus chlorambucil in previously untreated patients with CLL that are $\geqslant$ 65 years of age. In patients below 70 years of age, a comorbidity that could preclude the use of FCR was mandated for inclusion. Chlorambucil was selected as this was considered an acceptable treatment option for such patients at the time of initiation of the study. The treatment benefit was large (PFS HR 0.161, P <0.0001) and absolute B/R is undoubtedly favorable.

Furthermore, it has been shown that the activity of ibrutinib is unaffected by poor prognostic factors such as del 17p. Cross study comparisons are indicative that ibrutinib as monotherapy does not yield lower efficacy than does various chemo-immunotherapy combinations in more fit patients, though such comparisons are necessarily fraught with uncertainty. Further, the tolerability of this single agent in more fit patients is highly unlikely to be worse than in less fit patients.

As elaborated above, it appears that positive B/R may be inferred also in previously untreated patients that are eligible for FCR, and there are no indications that the use of ibrutinib until disease progression in such patients would impact the effectiveness of subsequent therapies. While the relative efficacy versus first line chemo-immunotherapy alternatives is not known, based on indirect comparisons single agent ibrutinib seems a reasonable alternative to consider among first line options for patients with CLL, regardless of fitness status and cytogenetics, along with chemo-immunotherapy alternatives.

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

Extension of indication to add the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) based on the results from the final CSR of study PCYC-1115-CA (MEA 021). As a consequence, sections 4.1, 4.4, 4.6, 4.8, 5.1 and 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial changes to the SmPC. A revised version of the RMP (version 5.0.3) has been approved as part of this application.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

REFERENCES

1 1. Arzerra (ofatumumab) [Product Information]. Camberley, United Kingdom, Novartis Europharm Limited ; 2015. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001131/WC500093091.pdf. Accessed 31 August 2015.

2. Benjamini O, Jain P, Trinh L, et al. Second cancers in patients with chronic lymphocytic leukemia who received frontline fludarabine, cyclophosphamide and rituximab therapy: distribution and clinical outcomes. Leuk Lymphoma. 2015;56(6):1643-1650.

3. Brown JR, Barrientos JC, Barr PM, et al. The Bruton tyrosine kinase inhibitor ibrutinib with chemoimmunotherapy in patients with chronic lymphocytic leukemia. Blood. 2015;125(19):2915-2922.

4. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med. 2013;369:32-42.

5. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014;371(3): 213–223.

6. Casak SJ, Lemery SJ, Shen YL, et al. U.S. Food and drug administration approval: rituximab in combination with fludarabine and cyclophosphamide for the treatment of patients with chronic lymphocytic leukemia. Oncologist. 2011;16(1):97-104.

7. Cheson BD, Byrd JC, Rai KR, et al. Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. J Clin Oncol. 2012;23:2820-2822.

8. Eichhorst BF, Busch R, Stilgenbauer S, et al. First-line therapy with fludarabine compared with

chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. Blood. 2009;114(16):3382-3391.

9. Eichhorst BF, Dreyling M, Robak T, et al. Chronic lymphocytic leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2011;22 (Suppl 6): vi50-vi54.

10. Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 (Suppl 5):v78-v84.

11. Gazyvaro (obinutuzumab) [Product Information]. Welwyn Garden City, United Kingdom, Roche Registration Limited. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002799/WC500171594.pdf. Accessed 31 August 2015.

12. Ghielmini M, Vitolo U, Kimby E, et al. ESMO Guidelines consensus conference on malignant lymphoma 2011 part 1: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL). Ann Oncol. 2013;24:561-574.

13. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus Chlorambucil in Patients with CLL and coexisting conditions. N Engl J Med. 2014;370:1101-1110.

14. Goede V, Fischer K, Engelke A, et al. Obinutuzumab as frontline treatment of chronic lymphocytic leukemia: updated results of the CLL11 study. Leukemia. 2015;29(7):1602-1604.

15. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukemia: A randomised, open-label, phase 3 trial. Lancet. 2010;376:1164-1174.

16. Hallek M, Cheson BD, Catovsky D, et al. Clarification of IWCLL criteria for a partial response to therapy. Blood. 13 Nov 2013; e-letter. Available at: http://www.bloodjournal.org/content/111/12/5446.e-letters. Accessed 17 August 2015.

17. Hallek M, Cheson BD, Catovsky D, et al. Response assessment in chronic lymphocytic leukemia treated with novel agents causing an increase of peripheral blood lymphocytes. Blood. 4 Jun 2012; e-letter. Available at: http://www.bloodjournal.org/content/111/12/5446.e-letters. Accessed 17 August 2015.

18. Hillmen P, Skotnicki AB, Robak T, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. J Clin Oncol. 2007;25:5616-5623.

19. Hillmen P. Using the biology of chronic lymphocytic leukemia to choose treatment. Hematology Am Soc Hematol Educ Program. 2011;2011:104-109.

20. Hillmen P, Robak T, Janssens A, et al. Chlorambucil plus ofatumumab versus chlorambucil alone in previously untreated patients with chronic lymphocytic leukaemia (COMPLEMENT 1): a randomised, multicentre, open-label phase 3 trial. Lancet. 2015;385:1873-1883.

21. Knauf WU, Lissichkov T, Aldaoud A, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. J Clin Oncol. 2009;27(26):4378-4384.

22. Maddocks KJ, Lin TS. Update in the management of chronic lymphocytic leukemia. J Hematol Oncol. 2009;2:29.

23. Molica S, Brugiatelli M, Morabito F, et al. Treatment of elderly patients with chronic lymphocytic leukemia: an unmet clinical need. Expert Rev Hematol. 2013 Aug;6(4):441-449.

24. Stilgenbauer S, Zenz T. Understanding and managing ultra high-risk chronic lymphocytic leukemia. Hematology Am Soc Hematol Educ Program. 2010;2010:481-488.

25. Stilgenbauer S, Chang BY, Furman R, et al. Tumor genomic profiling reveals mechanisms of resistance to BTK inhibitor ibrutinib in chronic lymphocytic leukemia. Presented at XV International Working Group for CLL Meeting, Cologne, Sept 2013.