EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 July 2014
EMA/CHMP/645137/2014
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Imbruvica

International non-proprietary name: ibrutinib

Procedure No.: EMEA/H/C/003791/0000

Note

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

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Administrative information

Name of the medicinal product:	Imbruvica
Applicant:	Janssen-Cilag International NV Turnhoutseweg 30 2340 Beerse BELGIUM
Active substance:	IBRUTINIB
International Non-proprietary Name/Common Name:	IBRUTINIB
Pharmaco-therapeutic group (ATC Code):	Antineoplastic agents, protein kinase inhibitors (L01XE27)
Therapeutic indications:	IMBRUVICA is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL). 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.
Pharmaceutical form:	Capsule, hard
Strength:	140 mg
Route of administration:	Oral use
Packaging:	bottle (HDPE)
Package sizes:	120 and 90

Table of contents

List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
App	appendix (used in cross-linking only)
AST	aspartate aminotransferase
Att	attachment (used in cross-linking only)
AUC	area under the plasma concentration versus time curve
AUC_{last}	area under the plasma concentration-time curve to the last quantifiable concentration
B-cells	B lymphocytes
BCR	B-cell antigen receptor
BR	bendamustine and rituximab
BTK	Bruton's tyrosine kinase
CI	confidence interval
CL/F	apparent oral clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration
CR	complete response
CSR	clinical study report
CV	coefficient of variation
CXC	chemokine receptors
CYP	cytochrome P450
Cys	cysteine residue
del(11q)	deletion of the long arm of chromosome 11
del(17p)	deletion of the short arm of chromosome 17
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
EU	European Union
FCR	fludarbarine + cyclophosphamide + rituximab
Fig	figure (used in cross-linking only)
GCLLSG08	German CLL Study Group 08
HED	human equivalent dose
IC_{50}	half-maximal inhibitory concentration
ICH	International Conference on Harmonisation
Ig	immunoglobulin
INR	international normalized ratio
IRC	independent review committee
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
IVIVC	in vitro-in vivo correlation
LDH	lactate dehydrogenase
MAA	Marketing Authorisation Application
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MIPI	mantle cell lymphoma international prognostic index

Mod	Module (used in cross-linking only)
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NE	not estimable (not evaluated)
NF-κB	nuclear factor kappa beta
NHL	non-Hodgkin lymphoma
PBMC	peripheral blood mononuclear cells
PFS	progression-free survival
P-gp	p-glycoprotein
PLCγ (or PLCγ2)	phospholipase-Cγ2
PR	partial response
QTcB	QT interval corrected for heart rate using Bazett formula
QTcF	QT interval corrected for heart rate using Fridericia formula
SAE	serious adverse event(s)
SCE	summary of clinical efficacy
SCS	summary of clinical safety
SCT	stem cell transplantation
SLL	small lymphocytic lymphoma
SmPC	Summary of Product Characteristics
SNV	single nucleoside variation
Syk	spleen tyrosine kinase
Tab	table (used in cross-linking only)
TEAE	treatment-emergent adverse event
t_{max}	time of maximum concentration
ULN	upper limit of normal

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Janssen-Cilag International NV submitted on 29 October 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Imbruvica, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 30 May 2013.

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

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Imbruvica as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/orphans/2012/06/human_orphan_001058.jsp&mid=WC0b01ac058001d12b
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/orphans/2013/04/human_orphan_001189.jsp&mid=WC0b01ac058001d12b

The applicant applied for the following indication:

- for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL)
- for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL)

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that ibrutinib was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0149/2013 on the granting of a (product-specific) waiver and the 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 applicant submitted a critical report addressing the possible similarity with authorised orphan medicinal products in a condition related to the proposed indication.

Applicant's request for consideration

Conditional Marketing Authorisation

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14(7) of the above mentioned Regulation based on the following claims:
The CHMP adopted a report on similarity of Imbruvica with Arzerra, Torisel and Gazyvaro on 24 July 2014

- The indications of relapsed or refractory MCL or CLL/SLL for which ibrutinib is proposed are life-threatening conditions for which there is an unmet medical need as current recommended therapies in the relapsed setting fail to show long-term clinical benefit and are often associated with significant toxicities.
- In addition, ibrutinib has been granted orphan drug status for the treatment of these conditions.

New active Substance status

The applicant requested the active substance ibrutinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 24 May 2012 and 19 July 2012. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

A new application was filed in the following countries at the time of submission of the application.: USA.

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

Janssen Pharmaceutica NV, Turnhoutseweg 30
Beerse, B-2340, Belgium

1.3. Steps taken for the assessment of the product

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

Rapporteur: Filip Josephson Co-Rapporteur: Jens Ersbøll

- The application was received by the EMA on 29 October 2013.
- The procedure started on 20 November 2013.

- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 February 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 26 February 2014.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 6 March 2014.
- During the meeting on 20 March 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 March 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 24 April 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 May 2014.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 12 June 2014
- During the CHMP meeting on 26 June 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 2 July 2014.
- PRAC RMP Advice and assessment overview as endorsed by PRAC via written procedure on 14 July 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 15 July 2014.
- The CHMP adopted a report on similarity of Imbruvica with to Arzerra, Gazyvaro and Torisel on 24 July 2014. During the meeting on 24 July 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Imbruvica.

2. Scientific discussion

2.1. Introduction

Mantle cell lymphoma (MCL) is a subtype of non-Hodgkin lymphoma (NHL) which represents approximately 6% of all new NHL cases per year. The estimated incidence of MCL is below 1 case per 100,000 persons throughout the world and was 0.45 cases (95% confidence interval [CI]: 0.42, 0.48) per 100,000 persons in an assessment of 44 cancer registries in Europe during the period from 2000 to 2002. The incidence of MCL increases with age, with the highest incidence observed in the 70 to 79 years age group (Morton 2006).

There is no curative therapy for MCL with the rare exception of patients who achieve long-term, disease-free survival after allogeneic stem cell transplantation (SCT). Among patients who relapse, median life expectancy is only 1 to 2 years following salvage therapies, which are often associated with significant toxicities. In the EU, temsirolimus is the only approved treatment for relapsed or refractory MCL. Lenalidomide was recently approved in the US for relapsed and refractory MCL.

Chronic lymphocytic leukemia (CLL) is a progressive hematologic disease characterized by an accumulation of monoclonal mature B cells in the blood, bone marrow, and secondary lymph organs, and diagnosis requires the presence of ≥5000 B-lymphocytes/µL in the peripheral blood for the duration of at least 3 months. It is the most common form of adult leukemia in the Western world, with an incidence of 4 per 100,000 persons per year. The median age of diagnosis in the EU is 72 years and only 10% of patients are less than 55 years old. The current WHO classification system recognizes and groups CLL and small lymphocytic lymphoma (SLL) as the same biological entity, with CLL clinically manifesting primarily in bone marrow and peripheral blood, and SLL primarily manifesting in the lymph nodes.

Current treatments for CLL are not curative. Fewer patients obtain responses with each subsequent regimen, and subjects become increasingly resistant to available therapy. Patients who relapse after a disease-free period of over 1 year (2-3 years for chemoimmunotherapy) are considered treatment sensitive and may be candidates for treatment reinitiation. Patients who relapse after a shorter interval, or are refractory to first-line treatment, or who harbour CLL cells with del17p present a more challenging group, particularly those who are older, have comorbid conditions, and/or harbor high-risk cytogenic abnormalities. A retrospective analysis of patients in the German CLL8 trial found that overall survival after the start of salvage treatment among patients whose disease had progressed within 2 years after the end of chemoimmunotherapy was about 2 years, comparable to that of truly refractory patients.

Patients with the del(17p) chromosomal abnormality represent a high risk group of CLL. According to the ESMO guidelines, there is no standard treatment for these patients, who have a median life expectancy of 2–3 years from front-line treatment. While only a small minority of CLL patients will have detectable del(17p) at the time of diagnosis, the proportion increases with successive chemotherapy treatments, so that in the relapsed setting up to 30% to 50% of patients have del(17p).

The monoclonal antibody ofatumumab, is currently approved in the EU for the treatment of CLL in the refractory setting as a single agent. The combination of the monoclonal antibody rituximab with chemotherapy (eg, fludarabine and cyclophosphamide) (FCR regimen) is approved in the EU for use in this setting. 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.

About the product

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 (see SmPC section 5.1). Ibrutinib is being developed for the treatment of various hematological malignancies. This application was seeking approval for ibrutinib in MCL and CLL/SLL.
The sponsor applied for the following indication:

- for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL)
- for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukaemia (CLL)/small lymphocytic lymphoma (SLL) or for patients with CLL/SLL

The final indication following CHMP review of this application is (see SmPC, section 4.1):

- IMBRUVICA is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).
- 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.

Treatment should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Imbruvica is presented as a hard capsule containing 140 mg of ibrutinib. The recommended dose for the treatment of MCL is 560 mg (four capsules) once daily.

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

Treatment should continue until disease progression or no longer tolerated by the patient.
The dose should be lowered to 140 mg once daily (one capsule) when used concomitantly with moderate CYP3A4 inhibitors. It should be reduced to 140 mg once daily (one capsule) or withheld for up to 7 days when it is used concomitantly with strong CYP3A4 inhibitors.

Recommended dose modifications for any new onset or worsening grade ≥ 3 non-haematological toxicity, grade 3 or greater neutropenia with infection or fever, or grade 4 haematological toxicities are described below:

Toxicity occurrence	MCL dose modification after recovery	CLL dose modification after recovery
First	restart at 560 mg daily	restart at 420 mg daily
Second	restart at 420 mg daily	restart at 280 mg daily
Third	restart at 280 mg daily	restart at 140 mg daily
Fourth	discontinue IMBRUVICA	discontinue IMBRUVICA

Dose modifications are described in Table 52 (Summary Table of Risk Minimization Measures) and the SmPC section 4.2.

Type of Application and aspects on development

• Legal basis

This application concerns a centralised procedure and is submitted in accordance with article 8(3) of Directive 2001/83/EC.

• Scientific advice

CHMP advice was sought by the Applicant on non-clinical program for ibrutinib mainly with regard to the extent of the non-clinical program and the use of the ICH S9 and ICH S8 Immunotoxicity for ibrutinib non-clinical development.

Scientific Advice was sought on clinical aspects mainly the choice of patient population and how they are defined in the study eligibility criteria, in study PCYC-1112-CA, the choice of progression-free survival (PFS) as primary endpoint, sensitivity analyses, maturity of OS data.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsule containing 140 mg of ibrutinib as active substance.

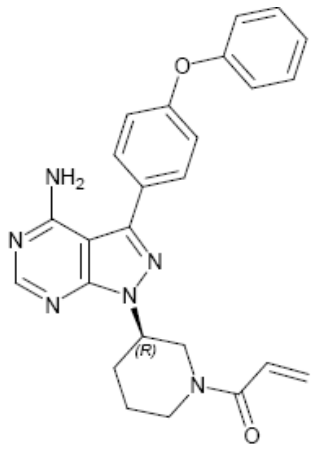
Other ingredients are: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, sodium laurilsulfate, gelatin and titanium dioxide (E171) for the capsule shell, shellac, iron oxide black (E172) and propylene glycol for the printing ink.

The product is available in HDPE bottles with a child resistant polypropylene closure.

2.2.2. Active Substance

General information

The chemical name of ibrutinib is 1-{(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl}prop-2-en-1-one and its molecular formula is $C_{25}H_{24}N_6O_2$. It has the following structure:



The active substance is a non-hygroscopic white to off-white solid which is practically insoluble in aqueous solutions of pH 4.5-8 and slightly soluble in HCl at pH 1.2. Ibrutinib is practically insoluble in non-polar solvents such as hexane and heptanes, sparingly soluble in ethyl acetate, ethanol and acetonitrile, soluble in acetone and methanol and freely soluble in N,N-dimethylformamide, tetrahydrofuran and dichloromethane.

Based on the solubility characteristics and in vitro permeability experiments, the applicant designated ibrutinib as a BCS Class 2 compound (low solubility and high permeability).

Ibrutinib has one chiral centre and the absolute stereochemistry of the drug substance was determined by single crystal X-ray crystallography as R. Enantiomeric purity is controlled routinely by chiral HPLC. Polymorphism was observed, three polymorphic forms of ibrutinib were identified and one of them which is the most thermodynamically stable is consistently formed during the active substance manufacturing process and used in the manufacturing of the finished product.

Chemical structure of ibrutinib was elucidated using the following techniques: elemental analysis, ultraviolet absorption spectroscopy (UV), Fourier Transform Infrared spectroscopy (FTIR), proton and carbon nuclear magnetic resonance spectroscopy (1H NMR and 13C NMR), and mass spectrometry (MS).

Manufacture, characterisation and process controls

Ibrutinib is manufactured in 6 main steps using commercially available well defined starting materials with acceptable specifications. The manufacturing process has been developed using a combination of conventional univariate studies and elements of QbD such as risk assessment. A criticality analysis was conducted to determine the critical quality attributes (CQA) of the active substance. The active substance synthesis process was evaluated, step by step, for its impact on the CQAs of ibrutinib. An overview of the control strategy for the drug substance has been provided in which critical control points (CCPs) are identified for each active substance CQA. A CCP can be a process parameter (PP), an in-process control (IPC) or a critical material attribute (CMA) of a process material. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Proven acceptable ranges have been defined for several steps. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Specification

The active substance specification includes tests for appearance, identity (IR, HPLC), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF), heavy metals (ICP-MS), and residue on ignition/sulphated ash (Ph. Eur.), particle size (laser diffraction analysis), crystal form (DSC).

Impurities present at higher level than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data are provided from about 30 batches of active substance used for non-clinical, clinical, stability, pre-process validation and process validation studies. Five batches are production scale batches. Twenty-two of the batches were manufactured according to the proposed process. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on three pilot scale batches of active substance from the proposed manufacturing sites stored in the intended commercial package for 12 months under long term conditions at 2-8 ºC, 25 ºC / 60% RH, 30 ºC / 75% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

In addition, stability data on three supportive registration stability batches were provided. These pilot batches were mainly produced by the proposed commercial manufacturing sites according to the proposed manufacturing process. The batches were stored in the intended commercial package for 12-24 months under long term conditions at 2-8 ºC, 25 ºC / 60% RH, for 12 months at 30 ºC / 65% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines.

The parameters tested are the same as for release. The analytical methods used were the same as for release and were stability indicating.

A forced degradation study has been conducted on one batch of the drug substance. Ibrutinib was subjected to the following conditions: acid (0.1 N HCl / 1 week 60 °C) , alkaline (0.1 N NaOH / 1 week 60 °C), oxidative (30% H_2O_2 / 5 hours 60°C) and thermal stress (in suspension 1 week at 60 °C; in solid state 2 week at 60 °C).

A photolysis study on the solid substance was also performed with harsher conditions than ICH conditions. Stressed and non-stressed samples were analysed for degradation products with the related substances method and also by LC/Q-TOF mass spectrometry to determine the mass or m/z for the degradation products found.

The forced degradation studies revealed that ibrutinib is sensitive to acid, alkaline and oxidative stress conditions. The drug substance was stable with respect to heat and light.

The stability results indicate that the active substance manufactured by the proposed supplier(s) is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

A capsule formulation was selected as the oral solid dosage form due to ease of administration and high patient compliance. The limited solubility of ibrutinib in aqueous media has been one challenge in the efforts to obtain an orally bioavailable formulation and the formulation optimization approach has mainly focussed on enhancement of dissolution rate and solubility. The effect of different surfactants and micronization of the active substance on rate of absorption were evaluated in a pilot pharmaco-kinetic dog study comprising different formulations. Based on the results from this study the particle size of the active substance and the type and amount of surfactant to be used for further development were selected.

Excipient compatibility was evaluated on selected mixtures of standard pharmaceutical excipients used in immediate-release solid oral dosage forms combined with ibrutinib. The pharmaceutical grade excipients were combined in a 1:1 ratio and held at 40 °C or 60 °C for 4 weeks. Based upon the findings from this study, excipients were selected. Different formulations have been used during clinical development. The modifications allowed for scale up and automation of the capsule filling process. In addition a change in the capsule colour has been introduced after completion of clinical studies

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The commercial process was developed through design of experiments and characterization of the process during clinical, registration and process scale-up manufacturing.

The manufacturing development was evaluated through the use of risk assessment and design of experiments to identify the critical product quality attributes and critical process parameters. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development, process design and scale-up studies. The critical process parameters were adequately identified.

The bioequivalence of the clinical formulation and the proposed commercial formulation is claimed based on an overall evaluation of the PK, efficacy/ safety, difference in formulations, dissolution profiles, all quality attributes and manufacturing process. A bioequivalence study was not performed. Results for Cmax and AUC obtained for the different formulations during individual clinical studies were evaluated,

dissolution profiles compared and overall conclusion is presented claiming that the modification of formulations did not have an impact on the pharmacokinetics and efficacy data.

The proposed QC dissolution method is considered suitable for quality control of the finished product.

The primary packaging is HDPE bottles with a child resistant polypropylene closure. The material complies with EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of six main steps including different blending steps, dry granulation, milling, encapsulation and packaging. In process controls are described and are considered adequate for this type of manufacturing process.

Major steps of the manufacturing process were validated based on manufacture of three consecutive full-scale batches. The validation report was not enclosed. The process validation scheme is presented. The absence of validation report was considered satisfactory taking into account manufacturing process development data provided and the fact that the process is considered to be a standard manufacturing process. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form visual appearance, identification by LC retention time and UV/VIS spectrometry, assay (HPLC or UPLC), degradation products (HPLC), content uniformity (Ph Eur), water content (Karl Fischer), dissolution and microbiological quality (Ph Eur). The same specifications apply at release and during shelf-life although identity of ibrutinib and content uniformity are tested only at release. The analytical methods used in the control of the drug product have been well described and satisfactorily validated according to ICH guidance.

Batch analysis results are provided for three production scale batches as well as for primary and supportive registration batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data of three pilot batches of finished product stored under long term conditions for 12 months at 25 ºC / 60% RH and 30 ºC / 75% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of Imbruvica are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Stability data from long term (25°C/60% RH) and accelerated (40°C/75% RH) conditions are also provided for three supportive pilot scale product batches representative of the commercial formulation. Six months accelerated data are reported for the supportive batches together with up to 24 months of long term results.

Samples were tested for appearance, assay, degradation products, water content, dissolution, microbial limits, chiral impurity, crystal form. The analytical procedures used are stability indicating.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.

For the primary registration stability batches, the data are all within proposed specifications and no large trends are seen. A small increase in degradation products is noted at the accelerated condition.

All results from the supportive batches are within acceptance criteria and no significant changes are observed although some increase in degradation products is seen.

The product has been shown stable against light exposure. Also, it has been shown that no change in polymorph of the drug substance occurs upon storage.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

2.2.3. Discussion on chemical, pharmaceutical and biological aspects

The ibrutinib drug substance has low solubility in aqueous media in the physiological pH range. The particle size of the substance has impact on the bioavailability and a micronized quality of ibrutinib is used in the drug product. For several of the specified drug related impurities of both the drug substance and drug product the specifications are above the ICH qualification limits. The proposed limits have been toxicologically qualified. The applicant has applied QbD principles in the development of the active substance and finished product and their manufacturing process, however no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.4. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.5. Recommendation(s) for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

The nonclinical testing strategy was designed to demonstrate and characterize the pharmacology, pharmacokinetics/toxicokinetics, and toxicology of ibrutinib. All pivotal toxicology / toxicokinetics studies were conducted according to the GLP principles.

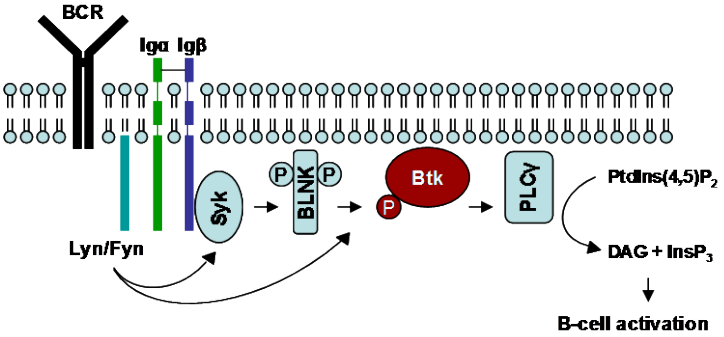
CHMP advice was sought by the Applicant on the overall non-clinical program for ibrutinib mainly with regard to the extent of the non-clinical program in order to support MAA and the use of the ICH S9 and ICH S8 Immunotoxicity for ibrutinib non-clinical development.

2.3.2. Pharmacology

Ibrutinib is a small-molecule inhibitor of Bruton's tyrosine kinase (BTK) that targets the ATP binding domain of BTK and forms a covalent bond with a cysteine residue (Cys-481) in the binding pocket that leads to sustained inhibition of BTK enzymatic activity.

BTK, is a critical component of the B-cell antigen receptor (BCR) signalling pathway, and has a well-established role in B lymphocytes (B cell) development. The generation and maintenance of (B-cells), both normally and in many B-cell malignancies, is controlled by biochemical signals transmitted by the BCR. Upon antigen engagement of the BCR, Btk is activated by the upstream Src-family kinases such as Lyn and Fyn (Afar 1996; Cheng 1994) and Btk in turn phosphorylates and activates Phospholipase-Cγ (PLCγ) (Humphries 2004), leading to Ca^{++} mobilization and activation of the oncogenic pathways MAPK, AKT, and NF-kB (Figure 1).

Figure 1. Activation of Btk Upon Antigen Engagement of the BCR



BCR = B cell antigen receptor; Btk = Bruton's kinase.

BTK's pivotal role in signalling through BCR results in activation of pathways necessary for B-cell activation/proliferation and development. In addition,. Activation of the BCR and chemokine-receptor signalling pathways is important for B-cell trafficking, chemotaxis, and adhesion. Ibrutinib binds covalently to a cysteine residue (Cys-481) near the Btk active site and inhibits Btk activity with a half maximal inhibitory concentration (IC_{50}) of 0.5 nM (Honigberg 2010; Pan 2007). Covalent binding of ibrutinib to Cys-481 results in irreversible inhibition of Btk.

Primary pharmacodynamic studies

In vitro *studies*

In order to characterize the selectivity and sensitivity of ibrutinib and its metabolite PCI -45227, an active-site dependent competition-binding assay as an initial screen was performed with a broad array of human kinases. Ibrutinib was most potent against Btk (IC50 = 0.39 nM). Inhibition of Btk was irreversible due to the formation of a stable covalent bond between ibrutinib with a specific cysteine residue (Cys-481) in the ATP binding pocket of Btk. Ibrutinib inhibited 9 other kinases with a similarly positioned cysteine in the active site: ErbB4/HER 4, Blk, Bmx/Etk, Txk), Tec, EGFR, ErbB2/HER2, JAK3 and Itk. Ibrutinib also reversibly inhibited Src-family kinases Fgr, Lck, and Yes/YES1. The PCI-45227 metabolite was determined to also inhibit Btk approximately 15 times less than the parent compound and is more selective for Btk inhibition relative to other kinases.

In the MCL cell line Mino, ibrutinib inhibited both auto-phosphorylation (pY223) and trans-phosphorylation (pY551) of Btk and the phosphorylation of downstream signaling proteins PLCγ2, Akt, Erk, and Jnk following stimulation with anti-IgM or with the chemokines CXCL12 and CXCL13. In normal human CD19+ B cells and in human primary MCL cells, 100 nM ibrutinib completely inhibited auto- and transphosphorylation of Btk and significantly inhibited the phosphorylation of PLCγ2.

Inhibition of B-Cell Activation was studied in human CD20+ B cells stimulated by BCR engagement with an anti-IgM antibody, continuous exposure to ibrutinib for 18 h at 10 nM completely prevented up-regulation of the early lymphocyte activation marker CD69. The effect of ibrutinib was studied in Diffuse Large B cell Lymphoma (DLBCL). Growth inhibition was evaluated in MCL cell lines Mino, JVM-2, Rec-1, Jeko-1, Granta-519, and Maver-1 exposed in culture to ibrutinib for 3 days at various concentrations. It was found that ibrutinib inhibits the proliferation of cell lines derived from DLBCL patients and MCL cell lines. The effect of ibrutinib on the proliferation of CLL cells was examined by measuring DNA incorporation of 3H-thymidine in isolated human CLL cells co-cultured with nurse-like stromal cells (NLCs).

Cellular assays were used to evaluate the effects of ibrutinib on proliferation, adhesion, and migration in B cell tumour cell lines. Btk has been shown to be expressed and constitutively active in primary MCL cells and in MCL cell lines (Ponader et al., 2011).

In follicular lymphoma cells (DOHH2), ibrutinib inhibited phosphorylation of PLCγ with an IC50 of 20 nM and the phosphorylation of Erk with an IC50 of 15 nM. 100 nM ibrutinib completely inhibited phosphorylation of Btk and PLCγ2 in normal human B-cells and human primary MCL cells (Mino cells).

Binding and inhibition of B-cell activation by ibrutinib (10 nM for 18h) resulted in complete prevention of up-regulation of the early lymphocyte activation marker CD69. A 1-hour washout of ibrutinib under these conditions did not change the activity of ibrutinib or affect the cell viability, suggesting irreversible mechanism of action by ibrutinib.

Relative levels of ibrutinib binding to Btk were measured using a specific active site-directed fluorescent probe linked to ibrutinib. Pre-incubation with ibrutinib effectively blocked probe binding to Btk and was used to determine ibrutinib concentration versus Btk occupancy profiles in mononuclear cells in human whole blood, and this was compared to the profile of ibrutinib-mediated inhibition of anti-IgM induced B-cell activation, as measured by CD69 up-regulation. 200 nM ibrutinib resulted in nearly complete (90%) occupancy of Btk in mononuclear blood cells, and this concentration led to approximately a 50% inhibition of CD69 expression in B cells.

Ibrutinib (10 nM for 18 h) completely and irreversibly prevented up-regulation of CD69 in B-cells. A site-directed fluorescent probe linked to ibrutinib demonstrated near complete occupancy of Btk by ibrutinib (200 nM) in mononuclear cells from human blood, a concentration which led to ~ 50% inhibition of CD69 expression in B-cells. Ibrutinib inhibited the growth of ABC-subtype of diffuse large B cell lymphoma (DLBCL) cell lines (TMD8, OCI-LY10)), in which “chronic active” BCR signalling is believed to be of important to the survival of ABC-DLBCL cells. Ibrutinib inhibited cell proliferations of ABC-DLBCL cell lines TMD8 and Ly10 with an EC50 of 1-10nM.

Ibrutinib reduced proliferation of CLL cells in a concentration-dependent manner tested by measuring DNA incorporation of 3H-thymidine in isolated human CLL cells co-cultured with nurse-like stromal cells.

Cell growth inhibition by ibrutinib (3 days incubation) was evaluated in various MCL cell lines. Mino cells were found to be the most sensitive cell type, in which Ibrutinib at concentrations of ≥ 100 nM inhibited cell growth by 50% or more.

In continuously cultured Mino Cells (MCL), resistance towards ibrutinib at low, but increasing drug concentrations was demonstrated. The resistance is stably maintained in Mino cells for up to 16 days after drug withdrawal.

The interaction of neoplastic B cells with stromal cells in the microenvironment plays a critical role in the progression of various B-cell malignancies including mantle cell lymphoma (MCL). The homing and trafficking of B cells is tightly controlled and regulated by the interaction of chemokine receptors (e.g. CXCR4) and adhesion molecules (integrins). In addition, BCR signaling within lymphoid tissues contributes to the control of homing and adhesion.

100 nM ibrutinib significantly inhibited (20-70%) adhesion of lymphoma (Jeko1, HBL2 and Mino) cells onto fibronectin or VCAM-1. In addition, ibrutinib inhibited the movement of MCL cell lines in a chemotaxis migration assay, the Mino and Jeko1 cells being most sensitive at ibrutinib concentrations of ≥ 0.1 nM. Ibrutinib concentration-dependently inhibits BCR- and chemokine-mediated adhesion and migration in MCL cell lines.

In vivo *studies*

Splenocytes harvested from BALB/c mice were found to exhibit complete Btk occupancy after dosing of 5 mg/kg ibrutinib via IV or IP routes and nearly complete occupancy after PO dosing and at 50 mg/kg for all three dosing routes, complete Btk occupancy by ibrutinib was found, which was also noted at 3 hours after dosing of ≥ 1 mg/kg and ≥ 10 mg/kg ibrutinib (SC and PO, respectively). In tumour-bearing mice, oral delivery of ibrutinib resulted in reduced proliferation of Mino cells, TCL1-192 cells, OCI-Ly10 cells, or TMD8 cells. Maximal suppression of cell proliferation occurred at doses of 12 to 25 mg/kg/day.

In the TCL1 adoptive transfer model, when treatment with ibrutinib started 2 weeks after CLL cell transfer, lymphocytosis was observed followed by a reduction of circulating lymphocyte counts. In this model, mice treated with ibrutinib had significantly smaller livers and spleens with reduced leukemic infiltration.

Oral administration of ibrutinib to 8 companion dogs with spontaneous B-cell lymphoma resulted in a partial tumour response in 3 dogs and stable disease in another 3 dogs. Full Btk active-site occupancy was achieved in the PBMCs of dogs at dose levels ≥ 2.5 mg/kg/day.

Mino (mantle cell lymphoma) cell-bearing and naïve CB17 SCID mice received medicated feed containing ibrutinib or vehicle ad libitum at an estimated dose level of 0 (vehicle) or 12 mg/kg/day for 70 consecutive days. FACS analysis of bone marrow, PBMC and lymph node preparations showed substantively lower numbers of hCD19+ Mino cells in tissues/preparations from ibrutinib-treated mice in comparison to tissues/preparations from vehicle-control mice. The differences were statistically significant ($P \leq 0.05$) for collective lymph nodes but not for bone marrow or PBMCs.

TCL1-192 cells were intravenously injected into the CLL Model CB17 SCID mice which were subsequently given drinking water containing ibrutinib at a concentration of either 0.016 or 0.16 mg/mL or drinking water containing vehicle alone. After 1 week of treatment, lymphocyte counts in the peripheral blood of mice in the 2.5 or 25 mg/kg/day groups were lower than those of the vehicle controls. After 2 weeks of treatment, lymphocyte counts in the high-dose group animals remained lower than in the controls.

Ibrutinib or vehicle only was administered to OCI-Ly10 (DLBCL) and to TMD8 (DLBCL) tumour cell-bearing female CB17 SCID mice once daily by oral gavage at a dose level of 0 (vehicle), 3 or 12 mg/kg/day. Mice were treated in cycles consisting of 5 consecutive days of dosing followed by 2 days without dosing for a total of 39 days. Tumour volumes in the 3 and 12 mg/kg/day dose groups were significantly smaller than in the vehicle controls on treatment days 10 through 39.

Secondary pharmacodynamics

Studies on the inhibition of release of mediators from human basophils activated in vitro, efficacy response in a collagen-induced arthritis mouse model, blockade of anaphylaxis response in a murine model of passive cutaneous anaphylaxis and inhibition of auto-antibody production and the development of kidney disease in the MRL/lpr murine lupus model, have been submitted.

In a report by MacGlaschan et al, ibrutinib inhibited the release of mediators from human basophils activated in vitro. After stimulation with anti- IgE, ibrutinib inhibited CD63 antigen expression, histamine, leukotriene C4, and interleukin 4 secretion/release with an IC50 of 3 to 6 nM(data not shown).

The ability of orally administered ibrutinib to inhibit progression of type II collagen-induced arthritis was shown in male DBA/1OlaHsd mice (data not shown).

Oral administration of ibrutinib at 12.5 or 50 mg/kg resulted in a significant inhibition of anaphylaxis response in dermal tissues of sensitized mice. These results were confirmed in a subsequent passive cutaneous anaphylaxis study at ibrutinib dose levels of 6.25 and 12.5 mg/kg (data not shown).

In a murine model of lupus nephritis, eight-week-old female mice (MRL/MpJ-Tnfrsf6lpr/J) were dosed with ibrutinib at dose levels of 0 (vehicle), 3.13, 12.5, and 50 mg/kg/day. Significant inhibition of urine protein levels, as compared to vehicle controls, was seen in mice at each dose level of ibrutinib. Reduction of summed histopathology scores was nearly significant for mice dosed at 50 mg/kg/day (P = 0.06). Serum double stranded DNA antibody levels were significantly reduced for animals dosed at 12.5 mg/kg (45% decrease; data not shown).

Safety pharmacology

Ibrutinib was evaluated in vitro for its ability to bind to 67 different targets. The target most inhibited by ibrutinib in these tests was the dopamine transporter (IC50 = 484 nM or 213 ng/mL). The IC50 for inhibition of dopamine transporter is 48 times the estimated mean steady state Cmax of unbound ibrutinib in patients (560 mg/day).

Ibrutinib did not have effects on the respiratory and central nervous systems of rats.

Ibrutinib inhibited hERG channel at a concentration 96 times the average maximum steady-state plasma concentration of unbound ibrutinib in patients. PCI-45227 inhibited hERG channel at a concentration 415 times the average maximum steady-state plasma concentration in patients. Based on these exposure margins, neither ibrutinib nor PCI-45227 is expected to adversely affect ventricular repolarization in humans.

Beagle dogs administered single oral doses were evaluated for potential cardiovascular effects of ibrutinib. Prolongation of RR interval, lowered heart rate, and increased blood pressure were noted at dose levels of 24 and 150 mg/kg. In addition, prolonged PR intervals and shortened QTCV intervals were noted at the 150 mg/kg dose level. The NOEL for oral administration of ibrutinib to dogs was set at 1.5 mg/kg (HED = 0.81 mg/kg). The changes in blood pressure, heart rate and RR interval noted at 24 mg/kg were not considered to be adverse.

In the 4- and 13-week dog studies increased RR interval was significantly increased in females (30 mg/kg/day, 1 hour after treatment in the first week) and heart rate was decreased (though non-significantly). The cardiovascular findings in the dog studies are considered clinically relevant, as similar changes are found in the clinical studies. The applicant has added relevant information in the SmPC regarding cardiovascular safety. The applicant is not able to establish etiology for the occurrence of the observed cardiovascular changes in both dog and humans the proposal to include additional information regarding cardiovascular safety in the SmPC is accepted.

Safety pharmacology studies have been conducted in receptor-ligand binding assays, in patch clamped HEK293 cells transfected with hERG, in female rats for CNS and respiratory evaluations and in dog for analysis of cardiovascular effects (Table 1).

Table 1. Safety pharmacology

Species, Type of study, GLP, Study no	Gender and no/grp	Method of Admin, Duration of dosing	Doses (mg/kg) or concentrations	Safety pharmacology findings
Off-target receptor binding, 38 receptors, non-GLP, 07-074-HU-X-RB	In vitro	NA	10 µM	At a concentration of 10,000 nM, ibrutinib inhibited radioligand binding to dopamine transporter (DAT) by 92%, to sodium channel (site 2) by 57%, to tachykinin NK1 receptor 53%, and to adenosine A2A receptor by 52%. In all other assays, radioligand-binding was not significantly inhibited (< 50%).
Off-target receptor binding, 29 receptors, non-GLP, 05-0383-V-X-RB	In vitro	NA	10 µM	
Dopamin transporter, non-GLP, 08-028-HU-X-RB	In vitro	NA	0.1-30 µM	IC50 = 0.484 µM (484 ± 50 nM)
hERG, GLP, 07-079-HEK-X-CT	In vitro	NA	0.3, 1, 3, and 10 µM	Ibrutinib inhibited hERG current by 8.3 ± 2.1% (mean ± SEM) at 0.3 µM, by 54.8 ± 2.9% at 1 µM, by 83.7± 1.7% at 3 µM, and by 93.8 ± 0.9% at 10 µM, compared to a 0.4 ± 0.2% inhibition observed for the vehicle treated controls. The IC50 hERG potassium current was 0.970 µM (427 ng/mL).
hERG with the PCI-5227 metabolite, GLP, 10-015-HEK-X-CT	In vitro	NA	3, 10, 30 and 100 µM	PCI-45227 inhibited hERG current by 18.2 ± 1.4% (mean ± SEM) at 3 µM, by 53.4 ± 1.8% at 10 µM, by 78.6 ± 0.4% at 30 µM, and by 94.1 ± 0.9% at 100 µM, compared to a 0.4 ± 0.2% inhibition observed for the vehicle-treated controls. The IC50 PCI-45227 on hERG potassium current was 9.6 µM (4555 ng/mL).
Rat, CNS, GLP, 06-024-R-PO-SP	F6	Po	0, 2.5, 40 and 150	No test article-related effects were seen at any dose.
Rat, Repiratory, GLP, 07-077-R-PO-SP	F8	Po	0, 2.5, 40 and 150	No test article-related effects were seen on respiratory frequency, tidal volume or minute volume at any dose.
Dog, Cardiovascula, GLP, 06-026-D-PO-SP	4M	Po	0, 1.5, 24, and 150 mg/kg	24 mg/kg; ↑pulse pressure 150 mg/kg; ↑pulse pressure, prolongation of PR interval and shortening of the heart rate-corrected QT interval (QTCV). There were no test article-related clinical findings or adverse effects on body temperature, QRS complex or blood pressure (systolic, diastolic, mean and pulse). The no-observed-effect level (NOEL) was determined to be 1.5 mg/kg.

Pharmacodynamic drug interactions

2.3.2.1. Potential Anti-proliferative Drug Interactions in Lymphoma Cell Lines

Ibrutinib as a single agent or in combination with fludarabine, doxorubicin, vincristine or dexamethasone was added to 96 well plates containing one of eight lymphoma cell lines (DB, Granta-519, DHL-4, DLCL2, Ly19, DOHH2, RAMOS and Jurkat) and incubated for 72 h. Cell viability was determined by AlamarBlue assay. In DLCL2 and DHL-4 cells, co-incubation with dexamethasone enhanced the inhibitory effect of ibrutinib on cell proliferation. In Ramos and DOHH2 cells, dexamethasone appeared to exhibit an additive effect when co-incubated with ibrutinib. In Ly19 cells, the combination of ibrutinib with any of the 4 chemotherapeutic agents exhibited a mild antagonistic effect. Dexamethasone did not enhance or inhibit the effect of ibrutinib in the Jurkat, Granta-519, or DB cell lines. Doxorubicin, fludarabine, and vincristine did not exhibit synergistic or antagonistic effects when studied in combination with ibrutinib in the DLCL2, DHL4, RAMOS, Jurkat, Granta-519, DB or DoHH2 cell lines.

2.3.3. Pharmacokinetics

Studies have been performed to characterise the absorption, pharmacokinetics, distribution, metabolism and excretion of ibrutinib in mouse, rat, rabbit, dog and in vitro. Studies related to the pivotal toxicity testing were conducted under GLP, whereas all other pharmacokinetic studies are non-GLP studies.

During the development program, analysis of ibrutinib and its metabolite PCI-45227 in plasma samples from nonclinical PK and TK studies was performed at various laboratories using liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS).

Carbon radiolabeled ibrutinib was synthesized as [14C]-ibrutinib (R-enantiomer), , or as a racemic mixture containing [14C]-ibrutinib (R-enantiomer) and [14C]-PCI-32769 (S-enantiomer) for drug metabolism and PK studies.

2.4. Absorption

Preclinical investigations to define the PK of ibrutinib were conducted in mice, rats, rabbits and dogs administered test compound by the oral or intravenous route and in mice and rats administered ibrutinib by the intraperitoneal or subcutaneous route.

After oral administration, ibrutinib exhibited rapid absorption in preclinical species. The mean Tmax of ibrutinib generally occurred within 2 h post-dose regardless of the formulation or feeding status. Ibrutinib is a high clearance compound in mice, rats and dogs with a moderate volume of distribution at steady-state. The mean terminal half-life of ibrutinib following oral administration ranged from 0.98 h in rats to 6.4 h in dogs. After oral dosing with ibrutinib, relevant levels of the PCI-45227 metabolite can be measured in the plasma of rats and dogs.

2.5. Metabolism

Table 2. Non-clinical metabolism studies

Study / Report	Species	Dose, regime	Findings
07-123-V-X-MT	Rat, Dog, Monkey and Human	liver microsomes, 1.32 µg/ml	Ibrutinib in the presence of NADPH was highly cleared in microsomes from all species. The rate of intrinsic clearance ± SE measured as µL/min/mg protein was: cynomolgus monkey = 629 ± 80.2; rat = 596 ± 60.9; human = 549 ± 68.8; dog 107 ± 5.47. The half-lives in minutes were: monkey = 2.20; rat = 2.33; human = 2.52; dog = 13.0.
12-080-V-X-MT	Rat, Rabbit, Dog and Human	liver microsomes and heaptocytes, 3 µM	Microsomes: In rat, dog and human, approximately 90%, 51% and 66% was metabolized after a 10 min incubation. In rabbit microsomes, 21% of was metabolised after 10 min. Hepatocytes: In rat and rabbit, approximately 87% and 98%, respectively, was metabolized after 60 min incubation. In dog and human hepatocytes, metabolism was somewhat slower, 72% and 70%, respectively. Data over metabolites is found in table 17B.
07-039-R-PO-ADME	Rat	Po, (10 mg/kg), iv (2 mg/kg)	Metabolite M19 was a major source of circulating radioactivity in the plasma and accounted for 23.69% of the sample radioactivity at 1 hour postdose. In urine, dihydrodiol-PCI-31532 represented 12.75% of the sample radioactivity for the 0- to 8-hour collection interval. M20 was the major metabolite in feces and accounted for 8.71% of the radioactive dose. M21 was the major metabolite in urine with 22.53% of the radioactivity in the sample collected from 0 to 8 hours postdose and 0.97% of the total radioactive dose through 24 hours.
11-022-R-PO-AME	Rat	po, 10 mg/kg	Two main metabolites were identified in faeces: M35 and M17. The hydroxylation on the phenyl (M35) give rise to M11, M16, M17, M18, M19, M21, M22, M28, M35 and M36, which represent just under half of the administered radioactive dose for male and female rats. Metabolites that can be linked to the piperidine ring opening pathway are: M11, M17, M18, M24, M25, and M29, and M34, which represent just under 20% of the administered radioactive dose for male and female rats. M37, M19 and M24 adding up to just under 10% of the administered radioactive dose for male and female rats. Metabolites identified in rat plasma (male and female) using the standard approach were M15, M34, M35, M37, M39, M40 and unchanged drug.
12-081-R-PO-EXC	Rat	po, 10 mg/kg	Bile; No parent compound, < 5% dose was M21 representing 7.85% of the dose, 2-5% were M6+M7, M9, M12+M13. Faeces; 1.1% parent compound, ≥5% were M17, M34, M35, 2-5% were M19, M28, M36. Urine; In the first 24h of urine collection, 1.15% of the administered radioactive dose was recovered. No unchanged drug was observed in urine. All detected metabolites less than 1% of the administered dose.
12-189-D-PO-AME	Dog	po, 30 mg/kg	In faeces, ibrutinib represented approximately 1.43 to 3.49 % of the administered dose. In urine, all peaks represented less than 1% of the administered dose. Feaces metabolites; >5%; M35, M17, M21 Main plasma metabolites; M37, M34, M35, M31, M21
12-188-Hu-PO-MT	Human	po, 140 mg	Faeces; The unchanged drug represented on average 0.77 % of the administered dose. Urine; M37, M34, M33 and M32, M29, M25, M24, M21, M20, M17, M10 and M7 were identified (5% of the administered dose total). Plasma and blood; M21, M25 (10% at 2h), M34 (14% at 2h), M37 (10% at 2h) (low amounts of M39 and M40). In plasma M23, M30, M1 and M4 were observed. In blood, M1 was not observed. Feces; unchanged ibrutinib (<1% of the administered dose), M11, M17, M20, M24, M25, M29, M34, M36 and M37 (2-9% of

	the administered dose)

Ibrutinib was extensively metabolized when administered orally to rats and dog. In total 41 metabolites were identified. The main circulating entities in humans were M21, M25, M34, PCI-45227 (dihydrodiol), and unchanged drug. Systemic exposure to the active metabolite PCI-45227 (based on AUC) in patients and healthy volunteers was comparable to that of ibrutinib.

2.6. Excretion

In rats, dogs and humans, excretion of ibrutinib-related radioactivity occurred principally via feces. In rats, dogs and humans, low amounts of unchanged ibrutinib are excreted in the feces after oral administration. Biliary excretion was found as the route of elimination of [^{14}C]-ibrutinib-derived radioactivity.

Table 3. Non-clinical excretion

Species, Study	N	Dose (mg/kg)	Route	Anal.	Urine (% dose)	Faeces (% dose)	Bile (% dose)	Recovery (% dose)	Time (h)
Rat, 07-039-R-PO-ADME	5M	2.0	Iv	^{14}C	5.16	83.5	ND	92.2	0-168
Rat, 11-022-R-PO-AME	3M, 3F	10	Oral	^{14}C	1.54M 1.75F	90.6M 89.1F	ND	92.3M 91.2F	0-96
Rat, 12-081-R-PO-EXC	5M	10	Oral	^{14}C	1.31	40.7	47	97.4	0-48
Dog, 12-189-D-PO-AME	3M	30	Oral	^{14}C	3.26	87.5	ND	90.7	0-72
Human, 12-188-Hu-PO-MT	6M	140	Oral	^{14}C	7.81 (5.5-9.3)	80.6 (75.9-83.5	ND	88.5 81.4-92.2	0-96

Studies to assess the excretion of ibrutinib in milk have not been submitted (see discussion on non-clinical aspects).

2.6.1. Toxicology

Single dose toxicity

Table 4. Single dose toxicity studies

Study ID, GLP	Species/ Sex/Number/ Group	Dose/Route	Approx. lethal dose / observed max non-lethal dose	Major findings
08-014-M-PO-ATI, Non-GLP	Mouse, 3M/3F	0, 500, 1000 and 2000, oral	2000 mg/kg – non-lethal dose	*500 and 1000 mg/kg:* Mild to moderate rough coat *2000 mg/kg:* Mild to moderate inactivity, ptosis and/or decreased body temperature and laboured respiration
06-022-R-PO-AT, GLP	Rat, 5M/5F	0, 400, 1000 and 2000, oral	400 mg/kg – maximum non-lethal dose for females, 1000 mg/kg – maximum non-lethal	*400 mg/kg:* ↓BWG (M) *1000 mg/kg:* 1F died on day 1 (no macroscopic findings), ↓BW M/F day 2, ↓BWG M/F day 0-2, ↑BWG F day 2-7. *2000 mg/kg:* 1M died on day 6 (distended stomach

			dose for males	and intestine), 1M and 1F died on day 7 (M, red matting of the skin and dark red contents of the stomach. F, without findings), ↓ BW and BWG day 0-2, ↑BWG day 7-14, abnormal excreta, various discoloured areas due to discharges/excreta, thin body, cool to the touch, red discharge from left eye (1M); abnormal respiration (rales), dermal atonia, hair loss on anogenital area or ventral trunk and swollen ears (1F).
07-109-R-IV, Non-GLP	Rat, 1-6F	0, 50, 100, 150, iv	50 mg/kg – maximum tolerated dose	*50 mg/kg:* Mild inactivity at 30 min postdosing. *100 and 150 mg/kg bolus:* All rats died within 10 min after dose administration, after showing ataxia, gasping, inactivity and tonic convulsions. *100 mg/kg 60 min infusion:* Mild ataxia and inactivity at end of infusion period, mild rough coat and inactivity at 1 h after infusion. *100 mg/kg 30 min infusion:* Moderate ataxia and inactivity
06-015-D-SC/PO-TXE, oral or sc (bolus), single dose escalation, GLP	Dog, M1/F1 or M2/F2	10, 20, 40, 100, 200, oral och sc (bolus),	ND	*10 mg/kg, oral:* No test-article related observations. *10 mg/kg, SC:* Flinching, scratching. ↑ leukocyte counts *20 mg/kg, SC:* Flinching, scratching. ↑ leukocyte counts *40 mg/kg, SC:* Squirming and thrashing. Biting and scratching at dose sites immediately after dosing. Ataxia and hypoactivity up to 4 h after dosing. ↑ leukocyte counts. *100 mg/kg, PO, solution:* Mild ataxia at 2 h postdosing. *100 mg/kg, PO, suspension:* Mild ataxia at 2 h postdosing *200 mg/kg, PO, suspension without sodium lauryl sulfate:* Mild ataxia and hypoactivity at 2 h postdosing; glassy appearance to the eyes at 1 to 8 h postdosing Complete occupancy of Btk for at least 24 h postdosing *200 mg/kg, PO, suspension with* sodium lauryl sulfate: Mild ataxia and hypoactivity at 2 h postdosing; glassy appearance to the eyes at 1 to 8 h postdosing Complete occupancy of Btk for at least 24 h postdosing

Repeat dose toxicity

Repeat dose toxicity studies were performed in rats and dogs. A 14 day repeat dose-range finding study was performed in rabbits, in order to establish the doses to be used in a preliminary embryo-foetal development study. The pivotal toxicity studies were all performed according to GLP.

Assessment of toxicity in the pivotal 13-week studies were based on mortality; clinical signs; body weight; food consumption; physical, ophthalmic, and electrocardiogram (ECG) examinations (dog only); clinical and anatomic pathology (including gross pathology, organ weights and histology). In addition, blood was collected for toxicokinetic, and immunophenotyping) analysis (rat study only). (summarised in table 5) :

Table 5.

Study ID GLP status Duration	**Species/Sex/ Number/Group**	**Dose/Route**	**NOEL/ NOAEL (mg/kg/ day)**	**Major findings**
07-146-R-PO-TXI Non-GLP 14 days	SD rats 4 M/F	0, 10, 200 mg/kg/day suspension Oral gavage	-	≥ 10 mg/kg Leukocyte↓ lymphocyte↓ ALB↓ F: RBC↓HB↓, HT↓ 200 mg/kg ALT↑, ALP (F)↓
11-042-R-PO-TX GLP 14 days	SD rats 10 M/F	0, 12, 35, 120 mg/kg/day Oral gavage	12 mg/kg/day	≥12mg/kg K↓, ≥36 mg/kg Pancreas acinar atrophy F: TP↓, M: HT↓ 120 mg/kg HDW↑, HT↓ M: MCV↓, F: NEU↑ ALT↑, ALB↓ Ca↓, TP↓ ALP↓
06-017-R-PO-TX GLP 28/29 days	SD rats Main study: 10 M/F Recovery (28 days): 5 M/F in group 1 and 4	0, 2.5, 40 and 300 (M) or 150 (F) mg/kg/day Oral gavage	2.5 mg/kg/day	≥40 mg/kg ALT↑ (F) Lymphoid hyperplasia mandibular lymphnode (M) Hepatocellular necrosis (1 female) 300/150 mg/kg 1 M found dead (Day 16) soft faeces FC↓, BW gain↓(M) HB ↓, HT ↓, MCV ↓, LYM ↓, RETIC ↑, NEU↑, MONO ↑, AST↑, ALB ↓, TP ↓ and Globulin ↓(M), Enlarged mandibular lymph nodes = lymphoid hyperplasia , Thymus weight ↓ (M), Liver weight↑ (F), Hepatocellular necrosis Lymphoid depletion spleen, single cell necrosis thymus Squamous hyperplasia glandular stomach Skin; epidermal necrosis, surface exudates, dermal abscess, inflammation (acute and subacute)

10-068-R-PO-TX GLP 13 week	SD rats Main study 15 M/F Recovery (6 week) 5 M/F group 1, 3 and 4	0, 30, 100, 300/175* mg/kg/day Oral gavage	30 mg/kg/day	≥30 mg/kg F: red facial discolouration Pancreatic acinar atrophy (mild) <u>≥100 mg/kg</u> Soft faeces, red facial discolouration NEU ↑ (M), MONO ↑ (M), RETIC (F)↑ RDW(F)↑ ALB↓, TP↓, ALT↑(M), G↓(F), BILI ↓(F), GLUC↓(F) Cortical and trabecular bone ↓(F) Pancreatic acinar atrophy (moderate) <u>300/175 mg/kg</u> Mortality 7M/1F associated with: lymphoid depletion, inflammation and ulceration of intestines general poor clinical condition FC↓ (M) RETIC↑, NEU↑, MONO↑, HDW (F)↑, MCV(F)↓, MCH(F)↓, MCHC(F)↓ M: G↓TRIG↓, UN↑, PHOS↑(F), Ca ↓(F) Cortical and trabecular bone ↓, Lymphoid depletion, lymph nodes, spleen and thymus (F), squamous epithelial atrophy of skin, vagina, oesophagus, stomach-> ulceration nonglandular stomach (F), intestinal ulceration/inflammation (F)
11-136-B-PO-TXE Non-GLP 7 day	Non-pregnant NZW Rabbit 3 F/group	0, 50, 100, 200 mg/kg/day Oral gavage	-	≥50 mg/kg defecation↓, soft/small faeces BW↓, FC↓ Severity of clinical signs increased with increasing dose
11-043-D-PO-TX GLP 14 day	Beagle dog 3 M/F	0, 4, 12 and 40 mg/kg Oral gavage	40 mg/kg	<u>≥4 mg/kg</u> Liver weight ↑(M), Hepatocellular glycogen↑(M) <u>≥12 mg/kg</u> Soft faeces (M) <u>40 mg/kg:</u> Soft faeces Liver weight↑, Hepatocellular glycogen↑
06-018-D-PO-TX GLP 28 day	Beagle dog 3 M/F +2 M/F for 29 days recovery in Group 1 and 4	0, 1.5, 24, 150 mg/kg/day Oral gavage	1.5 mg/kg/day	<u>≥24 mg/kg</u> EOS↓(F), ALP↓, ALT↓, GGT↓ Kidney; infarcts 1/3 female <u>150 mg/kg:</u> Soft faeces/diarrhoea LEU↑ (F), NEU↑(F), MONO↑(F), LYM↓, BASO↓ ALB↓, TP↓, A/G ratio↓, AST↑(F) Corneal dystrophy (3/6 animals) Inflammation of intestinal mucosa Kidney; infarct 2/3 females

10-069-D-PO-TX GLP 13 week	Beagle dog 3 M/F + 3 M/F for 91 days recover in Group 1, 3 and 4	0, 30, 80/60, 220/120** mg/kg/day Oral gavage	30 mg/kg/day	≥30 mg/kg Slightly decreased FC ≥80/60 mg/kg: 1 male euthanized Soft faeces/diarrhoea, emesis, gums; pale or redness, raised red/pale areas BW gain↓, FC ↓ RR interval increased ALB↓, A/G↓, ALT↓, GGT↓, G↑ Acute intestinal inflammation smooth muscle degeneration (stomach), Peyer's patches: lymphoid depletion 220/120 mg/kg: 1 male euthanized BW loss, Corneal dystrophy/degeneration (1 male) RBC↓, HB↓, HT↓, MCH↓, RDW↑, HDW↑, NEU↑, LYM↓ PT↑(F), APPT↑(F), Glucose↓

* female high dose reduced on –day 8 due to body weight losses. ** doses decreased on Day 42 due to decline in clinical condition, including body weight loss. A/G: albumin/globulin ratio, ALB: albumin, ALP: , ALT: alanine aminotransferase, AST: , BASO: basophile granulocyte count, EOS: eosinophile granulocyte count, FC: food consumption, G: globulin, GLUC: glucose, GGT: gamma globulin transferase, HB: haemoglobin, HT: hematocrit, MCH: mean haemoglobin concentration, LEU: leukocyte count, LYM: lymphocyte count, MONO; monocyte count, NEU: neutrophile granulocyte count, PT: platelet count, RBC: red blood cell count, TP: total protein,

In addition, a dose escalating study was performed in dogs, with SC and PO (gavage) administration (Study 06-015-SC-PO-TXE). In this non-GLP study, 10, 100 and 200 mg/kg were administered orally by gavage, and 10, 20 and 40 mg/kg was administered by SC injection. Both solution and suspension formulations were administered orally by gavage. Body weights, clinical signs were recorded, and blood samples for clinical pathology and toxicokinetics were collected. Following SC administration, ibrutinib appeared to be a local irritant which manifested as clinical reactions (e.g., scratching of the injection site, squirming during SC administration). In this study it was concluded that the solution formulation of ibrutinib was better absorbed than the suspension formulation. The maximum tolerated dose of ibrutinib following single oral administration was 200 mg/kg, whereas following repeated oral dosing for 6 consecutive days, 60 mg/kg/day was tolerated.

Genotoxicity

Table 6.

Type of test / study ID / GLP	Test system	Concentrations / Concentration range / Metabolising system	Results Positive / negative / equivocal
Gene mutations in bacteria, 06-027-Sal-X-MU, GLP	*S. typhimurium* strains TA98, TA100, TA1535 and *E. coli* strain WP2 uvrA	0, 15, 5.0, 15, 50, 150, 500, 1500, 5000 ug/plate, +/- Aroclor 1254-induced rat liver S9	No positive mutagenic responses were observed. Precipitate was observed beginning at dose levels of 500 or 1500 µg/plate.
Gene mutations in mammalian cells, 07-038-CHO-X-MU, GLP	CHO-cells, 4 and 20 hours	0, 5, 10, 12.5, 25, 32.5, 37.5 ug/ml, +/- Aroclor 1254-induced rat liver S9	Lot No. SCR-182-77 (micronized, non-GMP) was concluded to be positive for the induction of structural chromosome aberrations and negative for the induction of numerical chromosome aberrations in CHO cells in both non-activated and S9-activated test systems. Lot No. 082032 (clinical batch) was concluded to be negative for the induction of structural and numerical chromosome aberrations in CHO cells in the S9-activated test system.
Gene mutations in mammalian cells, 08-071-CHO-X-MU, GLP	CHO-cells, 4 and 20 hours	0, 5, 10, 20, 37.5 ug/ml, +/- Aroclor-induced, rat-liver S9	Negative for the induction of structural and numerical chromosome aberrations
Chromosomal aberrations in vivo, 07-037-M-PO-MU	Mouse, micronuclei in bone marrow	0, 500, 1000, 2000 mg/kg	Negative in the mouse bone marrow micronucleus assay

Carcinogenicity

Carcinogenicity studies have not been submitted (see discussion on non-clinical aspects).

Reproduction Toxicity

Fertility and early embryonic development studies with ibrutinib have not been submitted (see Discussion on non-clinical aspects). However, an assessment of potential effects on female and male fertility based on the histopathology findings in repeat dose toxicity studies has been performed (see repeat-dose toxicity section above). In rat and dog toxicity studies up to 92 days in duration, there were no treatment effects observed on reproductive tissues.

The following studies were performed on embryo/fetal development:

- An Oral (Gavage) Dose Range-Finding Study of PCI-32765 on Embryo/Fetal Development in Rats (10-063-R-PO-TTE, non-GLP)
- An Oral (Gavage) Embryo/Foetal Development Study of PCI-32765 in Rats (11-132-R-PO-TT, GLP)
- An Oral (Gavage) Dose Range-Finding Study of the Effects of PCI-32765 on Embryo/Fetal Development in Rabbits (10-064-B-PO-TTE, non-GLP)

Maternal and foetal toxicity was observed in the rat studies, including decreased maternal and foetal weight and early resorbtions. In the 80 mg/kg/day group, a higher overall incidence of visceral malformations were observed that consisted of dextrocardia, retroesophageal aortic arch, persistent truncus arteriosus, and a right-sided aortic arch. In addition, skeletal developmental variations were noted in the 80 mg/kg/day group. The treatment-related visceral malformations were considered to be of similar developmental origin (all involved the heart and major blood vessels). Body weight losses and reductions in food consumption were noted in the dams in the non-GLP rabbit study; A high litter proportion of post-implantation loss and lower fetal weights were noted in the high dose group, however, no external foetal malformations or developmental variations were noted.

Toxicokinetic data

Table 7. Toxicokinetics for ibrutinib

Species/Study/ Duration	Dose (mg/kg/day)	Sex	C_{max} (ng/ml)		AUC (ng*h/ml)	
			End of study	Animal to human ratio[a]	End of study	Animal to human ratio[a]
Human	5.3	M/F	132	-	680	-
	7.0	M/F	164	-	953	-
Rat/11-132-R-PO-TT/embryo-fetal	10	F	466	3.5/2.8	1278	1.9/1.3
	40		1310	9.9/8	5348	7.9/5.6
	80		2627	20/16	13729	20/14
Rat/-017-R-PO-TX/28 days	30	M/F	50M	4.7/3.8 M	140 M	0.2/0.1 M
			70F	11/8.6 F	180 F	0.3/0.2 F
	100	M/F	650 M	4.9/4.0 M	2800 M	4.1/2.9 M
			1700 F	13/10 F	4000F	5.9/4.2 F
	175	F	3130	24/19	19000	28/20
	300	M	2000	15/12	24000	35/25
Rat/10-068-R-PO-TX/13 week	30	M/F	618 M	4.7/3.8 M	2480 M	26/2.6 M
			1413 F	11/8.6 F	19712 F	29/21 F
	100	M/F	666 M	5.0/4.1 M	5506 M	8.1/5.8 M
			1923 F	15/12 F	20661 F	30/22 F
	175	F	3970	14/11	51549	76/54
	300	M	1847	30/24	21732	32/23
Dog/06-018-D-PO-TX/28 days	1.5	M/F	10 M	0.1/0.1 M	17 M	0.03/0.02 M
			12 F	0.1/0.1F	21 F	0.03/0.02 F
	24	M/F	682 M	5.2/4.2 M	1536 M	2.3/1.6 M
			911 F	6.9/5.6 F	1853 F	2.7/1.0 F
	150	M/F	1481 M	11/9.0 M	14079 M	21/15 M
			2183 F	17/13 F	15191 F	22/16 F
Dog/10-069-D-PO-TX/13 week	30	M/F	151 M	1.1/0.9 M	377 M	0.6/0.4 M
			451 F	3.4/2.8 F	1683 F	2.5/1.8 F
	60	M/F	1115 M	8.4/6.8 M	3414 M	5.0/3.6 M
			842 F	6.4/5.1 F	2211 F	3.3/2.3 F
	120	M/F	1859 M	14/11 M	12179 M	18/13 M
			1044 F	7.9/6.4 F	6628 F	9.7/7.0 F

[a] ratio at human dose 5.3 mg/kg/day/ratio at 7.0 mg/kg/day

Table 8. Toxicokinetics for PCI-45227

Species/Study/ Duration	Dose (mg/kg/day)	Sex	C_{max} (ng/ml)		AUC (ng*h/ml)	
			End of study	Animal to human ratio[a]	End of study	Animal to human ratio[a]
Human	5.3	M/F	122	-	1248	-
	7.0	M/F	122	-	1263	-
Rat/11-132-R-PO-TT/embryo-fetal	10	F	261	2.1/2.1	1203	1.0/1.0
	40		726	5.9/6.0	5110	4.1/4.0
	80		1665	14/13	12027	9.6/9.5
Rat/10-068-R-PO-TX/13 week	30	M/F	283 M	2.3/2.3 M	1536 M	1.2/1.2 M
			744 F	6.1/6.1 F	12758 F	10/10 F
	100	M/F	405 M	3.3/3.3 M	3698 M	3.0/2.9 M
			736 F	6.0/6.0 F	6872 F	5.5/5.4 F
	175	F	956	11/11	13055	10/10
	300	M	1322	7.8/7.8	17547	14/14
Dog/10-069-D-PO-TX/13 week	30	M/F	33.7 M	0.3/0.3 M	122 M	0.1/0.1 M
			67.9 F	0.6/0.6 F	347 F	0.3/0.3 F
	60	M/F	122 M	1.0/1.0 M	768 M	0.3/0.3 M
			102 F	0.8/0.8 F	352 F	0.6/0.6 F
	120	M/F	164 M	1.3/1.3 M	1488 M	1.2/1.2 M
			127 F	1.0/1.0 F	1131 F	0.9/0.9 F

Local Tolerance

Studies on local tolerance have not been submitted (see discussion on non-clinical aspects).

Other toxicity studies

Immunotoxicity

As part of the 13-week toxicology study in rat immunephenotyping was analysed in blood samples collected. The data show a treatment-related shift in the percentage of T cells and B cells with a lower percentage of B cells and a resultant higher percentage of total T cells and natural killer cells in the peripheral blood. No dedicated studies on metabolites are presented.

The applicant has additionally performed a functional immunotoxicity study in rat. The immune function data show that ibrutinib in a dose-dependent manner can inhibit TDAR responses and reversibly decrease total IgG concentrations following KLH injection. Such immune function toxicities are consistent with the pharmacologic mode of action, the data indicate recovery after cessation and the findings were not raising any concern.

Phototoxicity

Based on an evaluation of UV spectrum, photostability, and whole animal distribution data, the risk for phototoxic reactions in humans exposed orally to ibrutinib is considered minimal. While the UV absorption spectrum extends at a low level to 330 nm, the absorption maxima are seen at 259 and 287 nm, which are outside the 290-700 nm range of the electromagnetic spectrum that is associated with possible phototoxicity. Absorption above 290 nm is minimal, representing only 9% of the total absorption at wavelengths between 200 and 800 nm. Further, a photo stress study of ibrutinib using xenon lamp exposure for 4 days at rigorous conditions (27 times ICH guideline Q1B specified exposure of 1.2 million lux per hour) showed that ibrutinib was generally stable under this exposure condition, with approximately 2% degradation.

An in vitro phototoxicity assay in Balb/c 3T3 mouse fibroblasts by determining the relative reduction in viability (reduction in Neutral Red uptake) of cells exposed to the test article in the presence or absence of UV irradiation was completed which showed no phototoxic potential for ibrutinib.

Whole-body autoradiography data from pigmented rats dosed orally with radiolabeled ^{14}C-Ibrutinib indicate small amount of test article or metabolites distributes into the pigmented and non-pigmented skin and the eye structures; ^{14}C-ibrutinib distributes to the skin and eye of rats and the signal is above detection level in the skin also after 336 h. No accumulation in skin has been detected. See discussion on Clinical Safety

Impurities

Structures of actual impurities found at or above the ICH reporting threshold of 0.05% in at least 1 manufactured batch of ibrutinib at release or during stability testing were established based on mass spectrometry and/or NMR analyses. Structures of potential impurities reasonably expected to reside in ibrutinib based on theoretical considerations were also established. A total of 22 actual or potential impurities were identified. The potential of impurities to have mutagenic activity was assessed. All impurities were classified as non-mutagenic.

2.6.2. Ecotoxicity / environmental risk assessment

Table 9. Summary of main study results

Substance (INN / Invented Name): Ibrutinib, 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4- d]pyrimidin-1-yl]-1-piperidinyl]-2- propen-1-one			
CAS-number (if available): 936563-96-1			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	Log Pow = 3.8 (pH 4) Log Pow=4.0 (pH 7) Log Pow=4.0 (pH 9)	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	4.0 at pH 7	not B
	BCF OECD 305	$BCF_{low\ dose}$ = 13.5 $BCF_{high\ dose}$ = 68.0	not B
Persistence	DT50 OECD 308	$DT50_{water}$ = 4.2 -9,5 $DT50_{sediment}$ = 54-62 $DT50_{system}$ = 38-41	not P
Toxicity	NOEC or CMR	129 ug/L	not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined (e.g. prevalence, literature)	0.012	µg/L	> 0.01 threshold
Other concerns (e.g. chemical class)			None
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	Sludge K_{oc} = 2430-3820 L/kg Soil K_{oc} = 3220-6500 L/kg	A terrestrial assessment is not triggered!
Ready Biodegradability Test	OECD 301F	Not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308 Calwich Abbey Lake and Swiss Lake sediments	$DT50_{water}$ = 4.2 -9,5 $DT50_{sediment}$ = 54-62 $DT50_{system}$ = 38-41 More than 10 % shifting to the sediment.	A sediment assessment is triggered.

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Green algae *Pseudokirchneriella Subcapitata* Static test (72h)	OECD 201	NOEC	E_yC_{50} (72h) = 1.02 E_rC_{50} (72h) = 4.16 $NOEC_y$(72h) = 0.0370 $NOEC_r$ (72h) = 0.129	mg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	47.9	µg/L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	15.5	µg/L	Fathead minnow
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	EC50 (3h) > 1000 NOEC (3h) = 1000	mg/L	

Phase IIb Studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Bioaccumulation	OECD 305	BCF	Log Pow = 4.0 at pH 7 $BCF_{low\ dose}$ = 13.5 $BCF_{high\ dose}$ = 68.0		Rainbow trout
Aerobic and anaerobic transformation in soil	OECD 307 4 soils	DT50	DT50 = 22.7 DT50 = 6.9 DT50 = 166 DT50 = 39.4	days	Fulfil P
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect	NOEC = 0.235	mg/kg dry weight soil	
Terrestrial Plants, Growth Earthworms (*Eisenia fetida*) 14 days	OECD 208	NOEC	NOEC < 4.12 (tomato)	mg/kg dry weights oil	Cabbage, mung bean, sugar beet, tomato, ryegrass, wheat
Earthworm, Acute Toxicity Tests	OECD No. 207	NOEC	LC_{50} (14 days) > 1000 NOEC = 308.6	mg/kg	
Collembola, Reproduction Test	OECD No. 232	NOEC	EC_{50} (28 days) > 1000 NOEC = 1000	mg/kg	
Sediment dwelling organism	OECD No. 218	NOEC	NOEC = 47.4	mg/kg	*Chironomus riparius*

PECsurfacewater/PNECwater= 0.008; PECsurfacewater/PNECmicroorganisms = 1.2 x 10-7; PECgroundwater/PNECgroundwater = 0.0006

2.6.3. Discussion on non-clinical aspects

CHMP advice was sought by the Applicant on non-clinical program for ibrutinib mainly with regard to the extent of the non-clinical program, on immunotoxicity for ibrutinib non-clinical development. Further points raised by the CHMP concerned the characterization of the metabolite PCI-45227, the evaluation of the chiral conversion PCI-32765 - PCI-32769; potential concern with corneal dystrophy observed in dogs; risk of phototoxicity; The CHMP Scientific Advice has been followed by the Applicant.

Ibrutinib binds covalently to a cysteine residue (Cys-481) in the active site of Btk and inhibits the enzymatic activity of purified Btk with a median IC50 of 0.39 nM. Among the potential irreversibly inhibited non-Btk protein kinases, ErbB4/HER4, Blk, Bmx/Etk, Txk, and Tec are the most likely to be affected based on sensitivity to ibrutinib in biochemical assays. In vitro studies have shown that Btk inhibition effectively suppresses activity in BCR and chemokine-receptor signaling pathways. Ibrutinib, via Btk inhibition, impairs integrin-dependent, BCR-mediated adhesion and chemokine mediated adhesion and migration in both MCL and CLL cells (See section 5.1 of the SmPC). Inhibition of B-Cell Activation was studied in human CD20+ B cells stimulated by BCR engagement with an anti-IgM antibody, continuous exposure to ibrutinib for 18 h at 10 nM completely prevented up-regulation of the early lymphocyte activation marker CD69. A 1-hour (pulse) exposure did not change the activity of ibrutinib in the CD69 assay at 18 h post-treatment, a result consistent with an irreversible mechanism of action.

In murine non-clinical models of B-cell malignancies (MCL, CLL and DLBCL), ibrutinib has demonstrated maximal efficacy at doses consistent with ≥90% Btk active site occupancy in spleen and tumour cells. Orally administered ibrutinib resulted in objective clinical responses in dogs that spontaneously developed non-Hodgkin lymphoma. Btk occupancy has been determined in mouse, rat and dog. Sequence homology data which show that Btk is very conserved in all species as compared to human (98-99%), and although homology in the binding residues has not been confirmed, given the compiled data on pharmacology, pharmacokinetics, toxicity and the sequence homology the actual binding data against the Btk target and potential off-target kinases are considered relevant.

In the TCL1 adoptive transfer model, when treatment with ibrutinib started 2 weeks after CLL cell transfer, lymphocytosis was observed followed by a reduction of circulating lymphocyte counts. In this model, mice treated with ibrutinib had significantly smaller livers and spleens with reduced leukemic infiltration. These in vivo data, supported by anti-proliferative effects shown in co-cultured primary CLL cells, suggests that ibrutinib has a dual effect of 1) inhibiting leukemia cell migration and tissue retention/homing and 2) decreasing CLL cell survival and proliferation.

The IC50 values for inhibitory effect of ibrutinib and the dihydrodiol metabolite PCI-45227 on hERG channel current (427 and 4555 ng/mL, respectively) are 96 and 415 times the respective average maximum unbound plasma concentrations at steady-state in human subjects receiving a dose of 560 mg/day, indicating a low risk for effects on ventricular repolarization in humans.

In dog studies RR interval was significantly increased. The aetiology of these cardiovascular findings is not established. The ibrutinib exposure in the dog studies are similar or below the clinical exposure. Off-target kinase-effect of ibrutinib is deemed unlikely, but there are no other likely explanations for the observed changes. The cardiovascular findings in the dog studies are considered clinically relevant, as similar changes are found in the clinical studies. Additional information has been included in the SmPC regarding cardiovascular safety (see SmPC section 4.4 and discussion on clinical safety).

Ibrutinib was rapidly absorbed following oral administration in laboratory animal species, a finding consistent with the pharmacokinetic profile in humans. 41 metabolites were identified. After oral dosing with ibrutinib, substantial levels of the dihydrodiol metabolite PCI-45227 can be measured in the plasma of rats, dogs, and humans. Covalent binding was observed in plasma obtained from rats, dogs and humans after oral dosing with [14C]-ibrutinib as a single enantiomer. In rats, dogs and humans, excretion of ibrutinib-related radioactivity occurred principally via faeces. It is not known whether ibrutinib or its metabolites are excreted in human milk. A risk to the breast feeding infants cannot be excluded. Breast-feeding should be discontinued during treatment (See SmPC section 4.6).

Pivotal 13-week nonclinical toxicology studies were performed in rats and dogs administered ibrutinib once daily. In rats the following histopathologic changes were identified in target organs/tissues: lymphoid depletion in the lymph nodes, spleen, and thymus; edema and squamous epithelial atrophy in the non-glandular stomach; inflammation in the intestines, acinar atrophy in the pancreas; and thinning of cortical bone with fewer primary trabeculae. The primary toxicologic target in dogs dosed for 4 or 13 weeks was the intestinal tract (inflammation). Additional histopathologic changes noted in dogs dosed for 13 weeks included lymphoid depletion of Peyer's patches and smooth muscle degeneration of the stomach. In both rats and dogs, treatment-related soft feces and/or diarrhoea were a consistent clinical finding. In rats, red material around the nose was often observed and considered possibly related to epistaxis.

Most signals were completely or partly resolved after recovery indicating no permanently induced injury. Partial or incomplete recovery in the pancreas acinar atrophy found in rat was associated with fibrosis, deposition of brown pigment consistent with hemosiderin, and a mixed inflammatory infiltrate and pre-disposition of this species, consequently the risk for pancreas related toxicity in humans is considered low. Corneal dystrophy found in the 4 week dog study at exposure margin greater than 2.3-fold based on NOAEL; no corneal findings were detected in rat; it can be concluded that there is a low risk to patients developing corneal dystrophy. Ocular safety was given special attention on the clinical trials (See also Discussion on Clinical Safety.

Ibrutinib exposure levels not eliciting target organ toxicity in laboratory animals were generally higher than or comparable to exposure levels in human subjects.

While several target organs were identified, the specific mechanisms of toxicity are not known. However, considering the pharmacodynamic reversible and irreversible binding to off-target kinases ErbB4/HER4, ErbB2/HER2, JAK3, Blk, Bmx/Etk, Tkx, Tec, EGFR, Itk, Fgr, Lck, and Yes/YES1 expanded toxicity at high doses could be expected. For instance it is not unlikely that the GI effects are due to ErbB4/HER4 binding and the liver signals could potentially be attributed to Tec binding.

In the submitted studies, it can be concluded that ibrutinb has no genotoxic properties.

Studies on the carcinogenic potential of ibrutinib have not been submitted. Carcinogenicity studies are in general not required to support marketing for therapeutics intended to treat patients with advanced cancer. However, considering that life expectancy may be relatively long in some of these patients, in this particular case, there is a further need for carcinogenicty studies for Ibrutinib (see RMP). The applicant will conduct a transgenic mouse carcinogenicity study to address this concern (See also Discussion on Clinical safety, RMP).

In rat and dog toxicity studies up to 92 days in duration, there were no treatment effects observed on reproductive tissues. No male or female fertility studies have been conducted (see SmPC section 5.3). The lack of dedicated fertility and early embryonic development studies is acceptable in accordance with the ICH S9 guide line as generally, no fertility study is warranted to support the treatment in patients with late-stage disease, also confirmed by the CHMP within the Scientific Advice procedure.

Studies in animals have shown reproductive toxicity (see SmPC section 4.6, 5.3) Ibrutinib caused malformations of the heart and major vessels in rat foetuses, and is therefore considered to be teratogenic. Based on findings in animals, IMBRUVICA may cause foetal harm when administered to pregnant women. Women should avoid becoming pregnant while taking IMBRUVICA and for up to 3 months after ending treatment. Therefore, women of child-bearing potential must use highly effective contraceptive measures while taking IMBRUVICA and for three months after stopping treatment. This information is reflected in the SPC section (see SmPC section 4.6, 5.3) It is currently unknown whether ibrutinib may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method. (See also discussion on Clinical Pharmacokinetics). Regarding male patients, restriction to father a child was not required since ibrutinib is neither genotoxic nor induces testis toxicity.
Based on exposure at the 420 mg/day and 520 mg/kg/day clinical dose, animal-to-human Cmax ratios were 4.7/3.8 and 10.7/8.6 at the NOAEL in male and female rats, and 1.1/0.9 and 3.4/2.8 at the NOAEL in male and female dogs, respectively. The AUC ratios for exposure at the 420 mg/day and 520 mg/kg/day clinical dose were 3.6/2.6 and 29/21 at the NOAEL in male and female rats, and were 0.6/0.4 and 2.5/1.8 at the NOAEL in male and female dogs, respectively. Considering the indication and the pharmacological effect of ibrutinib the animal-human exposure is acceptable.

Local tolerance studies have not been submitted. As the intended clinical route of administration is oral, and this route of administration has been employed in the toxicity studies, dedicated stand-alone local tolerance studies are not necessary. The local tolerance of ibrutinib has been assessed in the general toxicity studies.

In rat a general treatment-related shift in the percentage of T cells and B cells with a lower percentage of B cells and a resultant higher percentage of total T cells and natural killer cells in the peripheral blood was recorded. These findings are generally consistent with lymphoid atrophy noted microscopically in the lymph nodes and spleen of rats administered doses of 100 to 300 mg/kg/day. No functional immunotoxicity study has been performed. The effects on B-cell population are expected as the Bruton's tyrosine kinase (Btk), the pharmacologic target of ibrutinib, is a critical component of the B cell antigen receptor-signalling pathway in B lymphocytes.

Absorption above 290 nm was minimal, representing only 9% of the total absorption at wavelengths between 200 and 800 nm. Ibrutinib was also distributed to the skin of pigmented rats. (See also clinical safety discussion). As in a 3T3 Neutral Red Uptake 186 Phototoxicity Test ibrutinib does not appear to have phototoxic properties, the skin toxicity signal is not considered to be related to light exposure.

Six impurities are above the qualification thresholds, all of which have been qualified with fortified ibrutinib batches. The data show no additional toxicity in these studies.

Ibrutinib and/or its metabolites are unlikely to represent a risk to the aquatic environment, sediment- or terrestrial compartment following prescribed usage in patients.

2.6.4. Conclusion on the non-clinical aspects

Overall, the non-clinical documentation submitted was considered adequate. The relevant information has been included in the SmPC (sections 4.4, 4.6, 5.1, 5.3).

The carcinogenicity of ibrutinib will be tested in a Transgenic (Tg) mouse range-finder study (to be submitted by 3Q 2015) followed by a Tg ras H2 6 month mouse carcinogenicity study (study report 1Q 2018) as a non-clinical post authorisation measure. (See RMP).

2.7. Clinical aspects

2.7.1. 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.

Table 10. Tabular overview of clinical efficacy studies in Support of the CLL Indication

Study Status	Study Name	Phase	Study Design/Dose	Subjects
PCYC-1102-CA Completed	A Phase 1b/2 fixed-dose study of Bruton's tyrosine kinase (BTK) inhibitor, PCI-32765, in chronic lymphocytic leukemia	1b/2	Safety, efficacy, PK, and PD study of 2 fixed doses of ibrutinib in relapsed/ refractory or treatment-naïve subjects at 420 mg and 840 mg continuous dosing; includes PK/PD of 16 fed/fasting subjects	132
PCYC-04753 Completed	Phase 1 dose-escalation study of Bruton's tyrosine kinase (BTK) inhibitor PCI-32765 in recurrent B-cell lymphoma	1	Safety, dose-finding, PK, and PD study of sequential cohorts of subjects who received ibrutinib from 1.25 to 12.5 mg/kg/day for 28 days of a 35-day cycle; and continuous dosing at 8.3 mg/kg/day or 560 mg fixed dose	66 16 with CLL/SLL;
PCYC-1112 Interim analysis (and subsequent cross over / early stop)	Phase 3 randomized, multi-center, open-label study of ibrutinib vs. ofatumumab in relapsed or refractory CLL	3	Efficacy and safety of 420 mg ibrutinib po once daily vs. ofatumumab 300 mg initial dose /2000 mg weekly i.v. in patients with relapsed or refractory CLL not appropriate for treatment with purine analogue based therapy.	Ibrutinib: 195, ofatumumab: 196

BTK=Bruton's tyrosine kinase; CLL=chronic lymphocytic leukemia; PD=pharmacodynamics; PK=pharmacokinetics; SLL=small lymphocytic lymphoma

Table 11. Tabular overview of clinical studies in support of the of the MCL Indication

Study Status	Study Name	Phase	Study Design/Dose	Number of Subjects
PCYC-1104-CA Completed	Multicenter, phase 2 study of Bruton's tyrosine kinase (BTK) inhibitor, PCI-32765, in relapsed or refractory mantle cell lymphoma	2	Efficacy and safety study in subjects with MCL stratified by bortezomib-naïve versus bortezomib-exposed; continuous fixed dose of 560 mg/day of ibrutinib	111
PCYC-04753 Completed	Phase 1 dose-escalation study of Bruton's tyrosine kinase (BTK) inhibitor PCI-32765 in recurrent B-cell lymphoma	1	Safety, dose-finding, PK, and PD study of sequential cohorts of subjects who received ibrutinib from 1.25 to 12.5 mg/kg/day for 28 days of a 35-day cycle; and continuous dosing at 8.3 mg/kg/day or 560 mg	66 9 subjects with MCL

fixed dose

BTK=Bruton's tyrosine kinase; CSR=clinical study report; MCL=mantle cell lymphoma; PD=pharmacodynamics; PK=pharmacokinetics

For clinical pharmacology studies, see Table 12.

2.7.2. Pharmacokinetics

The pharmacokinetics (PK) of ibrutinib has been assessed in subjects with B-cell malignancies as well as in healthy subjects in 6 Phase I and 2 Phase II studies (Table 12). In addition, preliminary data from a study in non-cancer patients with hepatic impairment have been submitted. Also, the disposition of ibrutinib has been evaluated in a number of in vitro studies, including metabolism studies, CYP inhibition and induction studies and studies to evaluate permeability, P-gp transport, transporter inhibition, protein binding, blood-plasma ratio and covalent binding to off-target proteins.

Table 12. Clinical pharmacology studies of ibrutinib

Type of Study	Study ID	Population	Number of Subjects[a]	Dose (mg)	Status
Phase 1					
DDI with CYP3A4 Inhibitor(ketoconazole), Single Dose	PCI-32765 CLL1002	Healthy subjects	18 3[b]	40, 120, 70	Completed Completed
DDI with CYP3A4 Inducer (Rifampin), Single Dose	PCI-32765 CLL1010	Healthy subjects	18	560	Completed
Mass-balance	PCI-32765 CLL1004	Healthy subjects	6	140	Completed
Food Effect	PCI-32765 CLL1001	Healthy subjects	44 8[c]	420 840	Completed Completed
Single and Multiple Ascending dose: Safety and Efficacy	PCYC-047 53	Subjects with B-cell malignancies	64	40-1400	Completed
Hepatic Impairment	PCI-32765 CLL1006	Non-cancer subjects with hepatic impairment	30[d]	140	Ongoing
Phase 2					
Safety and Efficacy	PCYC-110 2-CA	Subjects with CLL	131	420, 840	Completed
Safety and Efficacy	PCYC-110 4-CA	Subjects with MCL	48	560	Completed
Total			**370**		

[a] Refers only to subjects that were included for the PK analysis.
[b] 3 subjects were enrolled in an exploratory arm administering the oral solution in the DDI study.
[c] 8 subjects were enrolled in an exploratory arm administering 840 mg in fed condition.–
[d] 6 out of 30 subjects are pending enrolment.

The metabolite PCI-45227, binds to BTK in a reversible fashion with 1/15th of the affinity of ibrutinib. It has been quantified in laboratory animals and humans and its PK was investigated in most of the submitted in vivo and in vitro studies.

Pharmacokinetic data analysis

Standard statistical methods and non-compartmental methods were used to characterize the PK of ibrutinib. The population PK of ibrutinib was characterised by non-linear mixed effects modelling including data from the clinical studies in patients (study 04753, 1102-CA and 1104-CA). A physiologically based pharmacokinetic (PBPK) model was built and verified based on available clinical PK and DDI data for prediction of drug-drug interactions between ibrutinib and CYP3A inhibitors and inducers.

In all the completed clinical pharmacology studies included in the submission, plasma concentrations of ibrutinib and the active metabolite (PCI-45227) were quantified using validated LC-MS/MS bioanalytical methods.

Absorption

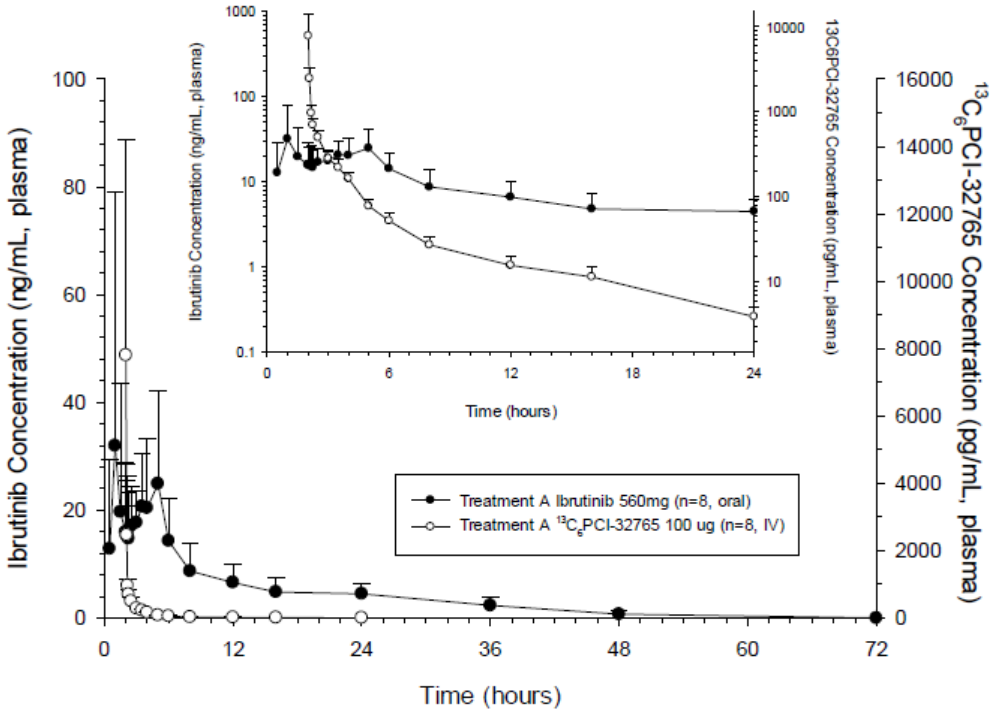
Ibrutinib is slightly soluble in HCI at pH 1.2 and practically insoluble in the pH range 3-8 in aqueous media. High in vitro permeability for ibrutinib has been demonstrated in Caco-2 cells.

Data on absolute bioavailability of ibrutinib initially indicated a bioavailability of approximately 4%, in line with preclinical, ketoconazole DDI study and human mass balance data that indicates that ibrutinib is completely absorbed and that absolute bioavailability, in fasted conditions, is less than 5% suggesting that the low bioavailability is mainly caused by extensive intestinal and hepatic first-pass. The clinical study report, PCI-32765CLL1011 was submitted at the request of the CHMP to further clarify the absolute bioavailability.

Study 1011 was an open-label, single-center, sequential and 2-way crossover-designed fasted PK study to investigate the bioavailability of oral ibrutinib and the effect of grapefruit juice on the bioavailability of ibrutinib in eight healthy subjects. All subjects were orally administered 560 mg ibrutinib itself in fasted state, 560 mg ibrutinib 30 minutes after drinking orange juice/sugary drink in fed state and 140 mg ibrutinib 30 minutes after grapefruit juice in fed state. In addition, the subjects received a single IV dose of 100 µg ^{13}C-ibrutinib 2 hours after each oral dose.

Results: The mean oral and IV PK profiles without coadministration of juices or sugary drinks are presented in the figure below. After dose adjusting the IV tracer dose to the oral dose (560 mg) the bioavailability was 2.9 and 3.9% for AUClast and AUC∞ respectively.

Figure 2.



Administration of the ibrutinib capsule as a single dose with a high-fat meal resulted in an increase in exposure by approximately two fold compared to administration in the fasted state. Further evaluation of the effect of timing of food intake in relation to drug administration showed that ibrutinib AUCs were comparable regardless if drug administration took place 30 minutes before, 30 minutes after (fed), or 2 hours after a high-fat breakfast. Food timing did however influence t_{max} and C_{max}, with the highest C_{max} observed when subjects were dosed 2 hours after the meal.

Administration of ibrutinib under fed conditions resulted in an increase in C_{max} and AUC_{last} with a geometric mean ratio of 3.15 and 1.86 compared to intake in fasted condition. When ibrutinib was administered either 30 minutes before or 2 hours after completing a high fat breakfast, the corresponding AUC_{last} were within 2-fold (ratio 1.62 and 1.78 for 30 minutes before and 2 hours after, respectively) compared to intake in fasted condition. For C_{max}, however, a significant difference was observed between 30 minutes before and 2 hours after compared to intake in the fasted condition (table 13).

Compared with fasted condition, PCI-45227 C_{max} was 1.7-, 2.3-, and 2.9-fold higher when dosed 30 minutes before, 30 minutes after, or 2 hours after a high-fat breakfast, respectively. AUC_{last} was 1.5-, 1.9, or 2.1-fold higher. Half-life was unchanged. No trend in metabolite-to-parent ratios was observed.

When administering twice the dose in fed condition (E), C_{max} and AUC were higher than those observed for the 420 mg dose (Treatment A), but the increase was less than 2-fold. The metabolite PCI-45227, however, did show dose-proportionality.

Table 13. Effect of Food on Ibrutinib PK Parameters. Study - CLL1001

Parameter[a]	Treatment[b]	N	Geometric Mean	Ratio: Test/Reference (%)[c]	90% Confidence Interval (%)	Intra-Subject CV (%)	Inter-Subject CV (%)
C_{max} (ng/mL)	D- Fasted	43	32.67	-	-	-	67.0
	A- Fed	44	102.86	314.9	271.70 - 364.89	43.2	79.3
	B- 30 min before	43	85.81	262.7	226.58 - 304.51		63.4
	C- 2h after	43	125.82	385.2	332.23 - 446.51		68.0
AUC_{last} (h.ng/mL)	D- Fasted	43	260.17	-	-	-	56.4
	A- Fed	44	483.45	185.8	169.07 - 204.23	26.9	57.1
	B- 30 min before	43	421.96	162.2	147.55 - 178.28		46.6
	C- 2h after	43	462.42	177.7	161.70 - 195.37		57.8
			Mean	**SD**	**Median**	**Range**	
t_{max} (h)	D- Fasted	43			1.5	1.00 - 8.00	
	A- Fed	44			4.0	2.00 - 6.00	
	B- 30 min before	43			1.5	1.00 - 4.00	
	C- 2h after	43			3.0	1.00 - 6.00	
$t_{1/2, term}$ (h)	D- Fasted	27	9.67	3.21			
	A- Fed	43	4.79	1.44			
	B- 30 min before	36	8.95	3.27			
	C- 2h after	39	5.17	1.92			

Distribution

Based on the results from the population PK analysis, ibrutinib has an estimated apparent volume of distribution (Vd/F) of approximately 10 000 L which indicates extensive distribution to tissue.

Ibrutinib exhibited high plasma protein binding in vitro (97.3%) without any concentration dependency in the studied range of concentrations (100-1000 ng/mL). The in vitro protein binding of the metabolite PCI-45227 was 91%.

The blood-plasma ratio for ibrutinib was approximately 0.8 indicating that ibrutinib is not widely distributed to blood cells. No determination of the blood/plasma concentration ratio for the metabolite was performed.

Ibrutinib has been designed to bind covalently to the cysteine residue in the active site of the target kinase (BTK). Evaluation of the binding to off-target proteins showed greater affinity for liver S9 compared to human plasma proteins or purified human albumin. The binding appears to be appreciably lower compared to target effects.

In the human mass balance study, elimination of covalently bound radioactivity was slower than total radioactivity. Approximately 10% of C_{max} and 27 % of AUC_{0-72} of total radioactivity in human plasma was accounted for by covalent binding following a single dose.

Elimination

Mean recovery of total radioactivity in urine and faeces accounted for 7.8% and 80.6% of the dose, respectively. Negligible amounts of parent ibrutinib and a small amount of the active metabolite PCI-45227 were detected in urine and faeces. The remaining identified radioactivity in excreta was made up by a large number of metabolites. The sum of identified drug related material in excreta, corrected for recovery and column recovery, was 64.1% of the dose. Since almost no ibrutinib was detected in urine and faeces it can be concluded that ibrutinib is almost completely absorbed and that metabolism is the major elimination pathway. The totality of the submitted data indicates that ibrutinib has a low bioavailability mainly caused by extensive intestinal and hepatic first-pass metabolism.

Ibrutinib is suggested to undergo a variety of biotransformations in vivo with three main primary metabolic clearance pathways. The drug interaction studies with ketoconazole and rifampin in combination with the in vitro metabolism data clearly indicate that CYP3A4 is responsible for the vast majority of ibrutinib elimination.

The elimnation half-life of ibrutininb is 4-13 hours.

Mean ibrutinib and PCI-45227 exposures together makes up less than 5% of the total radioactivity in blood and plasma. In addition, other identified metabolites also have a small individual contribution to the total radioactivity exposure and consequently the majority of blood and plasma radioactivity has not been identified.

Dose proportionality and time dependency

No indication for non-linearity in single and multiple dose data were observed under clinically relevant conditions.

Ibrutinib and PCI-45227 accumulate to a small degree, approximately 1.5-times after repeated dosing as compared to single dose. This is in line with the observed half-life of ibrutinib in the range of 4-14 hours. No signs of time-dependent PK of ibrutinib are present.

Intra- and inter-individual variability

The PK of Ibrutinib and PCI-45227 displays high inter-individual variability. For ibrutinib, CV% ranged from 58.5% to 136% for C_{max} and 60.1% to 107% for AUC_{0-24h} and for PCI-45227, CV% ranged from 48% to 64.9% for C_{max} and from 40.6% to 61.8% for AUC_{0-24h}.

The main reason for the high inter-subject variability is believed to be caused by the biological variation in CYP3A expression, leading to pronounced CYP3A-mediated intestinal and hepatic first-pass extraction.

Intra-subject mean variability for ibrutinib as measured in the food effect study (study 1002) in both fed and fasted subjects, ranged from 27% to 43% for AUC and $C_{max,}$ respectively.

Population PK analysis

An adequate predictive performance of the proposed model was demonstrated by prediction corrected visual predictive checks.The population PK of Imbruvica was described by a 2-compartment model with sequential zero-first order absorption, with an effect of food on absorption time and relative bioavailability and an allometric relationship for bodyweight implemented on the volume terms. The analysis suggested no significant effects of other covariates. Exceptions were the co-administration of ibrutinib with antacid drugs, which increased duration of the zero order absorption process by 61%. The analysis included PK information on ibrutinib obtained in subjects with different B-cell malignancies the phase I study 04753 and the phase II studies 1102-CA and 1104-CA.

Special populations

No formal study of the PK of ibrutinib in renal impairment has been conducted. The effect of creatinine clearance (Cockroft-Gault) in the range of mild (40.8 % of the patients CRCL ≥60 and <90 mL/min) and moderate renal impairment (21.2%, CRCL ≥60 and <90 mL/min) was evaluated in the population PK analysis. No influence of estimated creatinine clearance on the PK of ibrutinib was apparent. No data is available in severe renal impairment or in patients on dialysis. Since severe renal impairment might affect metabolism and hepatic transporters a clinical relevant effect of severe renal impairment on ibrutinib PK cannot be excluded. Treatment in severe renal impairment (less than 30 mL/min creatinine clearance) is thereby only recommended if the benefit outweighs the risk (see sections 4.2 and 5.2 of the SmPC).

Subjects with hepatic impairment have been excluded from participation in clinical trials. A study in non-cancer subjects with varying degrees of hepatic impairment has been conducted. Preliminary data has been submitted and a final report will be submitted as a post marketing commitment later in 2014. The preliminary data show a significant increase in ibrutinib exposure with increasing impairment, 4-, 8.2-, and 9.1-fold higher AUC_{last} in the mild, moderate, and severe cohort respectively. Terminal half-life trended slightly higher in moderately and severely impaired subjects. Fold increases taking into account the AUC of unbound drug were 4.0, 9.5, and 13 for the mild, moderate and severe impairment group, respectively. Based on the results, an initial reduced dose for patients with mild (280 mg) and moderate (140 mg) hepatic impairment is suggested. Treatment in severe hepatic impairment is not recommended (see sections 4.2, 4.4 and 5.2 of the SmPC).

The table below summarises the number of older people included in PK studies.

Table 14. Older subjects in PK trials.

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Human PK Trials			
PCI-32765CLL1001 PCI-32765CLL1002 PCI-32765CLL1004 PCI-32765CLL1010	0/89	0/89	0/89

No subjects aged 65 or older participated in PK studies in healthy volunteers. The effect of weight, gender, race and age on the PK of ibrutinib was evaluated in the population PK analysis. Body weight (mean 82.7, SD 19.1 kg) was identified as a significant covariate on peripheral volumes (V2/F and V3/F). The effect of on body weight on apparent clearance was negligible. No a priori dose adjustment based on weight appears necessary.

No statistically significant effects of gender (72.2 % male) or age (mean 53.3, SD 10.1 years) on the PK parameters were found. Limited data was available regarding the effect of race/ethnicity on ibrutinib PK and no conclusion on the effect of race on the PK can be drawn.

No studies have been conducted to investigate the pharmacokinetics of ibrutinib in paediatric patients.

Pharmacokinetic interaction studies

The drug-drug interaction potential of ibrutinib was investigated in a number of in vitro and in vivo studies.

In vitro: Neither ibrutinib nor PCI-45227 are considered clinically relevant systemic inhibitors or inducers of CYP-enzymes. Ibrutinib is not a substrate of P-gp and OATPs in vitro. In contrast, ibrutinib is an in vitro P-gp inhibitor (see Discussion on clinical pharmacology below).

In vivo: The CYP3A4 inhibitor ketoconazole increased ibrutinib Cmax and AUC 29- and 24-fold, respectively, with no apparent effect on the ibrutinib half-life. The CYP inducer rifampin resulted in a 13- and 9- to 10-fold decrease in ibrutinib C_{max} and AUC respectively with nearly unaffected half-life. These studies indicate that the interaction potential at CYP3A4 is mainly at the presystemic level. The results of the active metabolite PCI-45227 in the ketoconazole and rifampin study indicate that the further metabolism of PCI-45227 may also be governed by CYP3A4.

A PBPK model was built based on the available preclinical and clinical information and the aim of the model was to investigate the drug-drug interaction potential of CYP3A4 inhibitors/inducers on ibrutinib PK.

Pharmacokinetics using human biomaterials.

The applicant submitted a protein binding study of ibrutinib in human pre-dose plasma of subjects of the open-label pharmacokinetic study (PCI-32765CLL1002) in healthy male subjects. At a spiked total plasma concentration of 100 ng/mL, the unbound fraction of ibrutinib in plasma averaged 0.020 (2.0 % unbound), SD 0.002, range 0.017-0.025 (n=18; data not shown).

Protein binding of Ibrutinib was also assessed in pre-dosed plasma from subjects of an open-label Phase 1 Study to Determine the Absorption, Metabolism, and Routes of Excretion of ibrutinib in healthy male subjects. At a spiked total plasma concentration of 100 ng/mL, the unbound fraction of ibrutinib in plasma averaged 0.023 (2.3 % unbound), SD 0.003, range 0.020-0.026 (n=6; data not shown).

2.7.3. Pharmacodynamics

Mechanism of action

See non-clinical aspects.

Primary and Secondary pharmacology

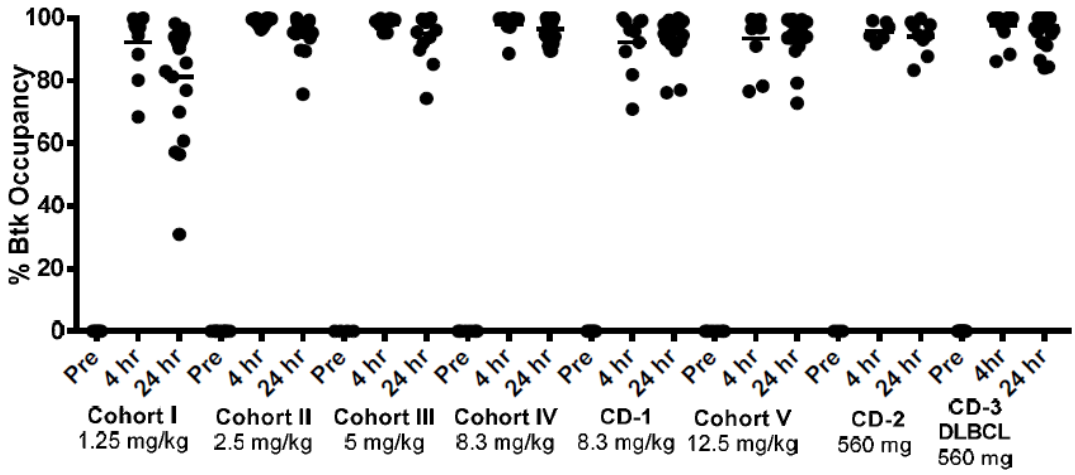
Study PCYC-04753 (See also Dose – Response section)

Primary Pharmacodynamics of ibrutinib in study 04753 was determined by monitoring the BTK occupancy of the subjects' PBMCs before and after treatment. The cohort in which >4 treated subjects demonstrated full occupancy of BTK (<5% remaining unoccupied BTK or below the lower limit of detection in the gel-based probe assay at 4 hours postdose) was defined as the "minimal occupying dose". In the absence of DLT (≤1 DLT in a cohort), dose escalation proceeded through 3 dose levels beyond the "minimal occupying dose." In the absence of DLT (≤1 DLT in a cohort), a "preferred occupying dose" was to be selected at the "minimal occupying dose" or one of subsequent higher dose levels based on assessment of other pharmacodynamic assays. Dose escalation was completed at that point.

In an analysis of BTK occupancy for subjects in this study, full occupancy was observed beginning with the 2.5 mg/kg/day cohort ("minimum occupying dose"). Therefore, the 12.5 mg/kg/day cohort (3 dose levels above 2.5 mg/kg/day) was the highest dose tested for dose escalation in this study. No subjects were enrolled into the 17.5 mg/kg/day cohort. Since no DLT was observed in the 12.5 mg/kg/day cohort and the MTD was not identified at this dose level on the intermittent schedule, 8.3 mg/kg/day (1 dose level below the 12.5 mg/kg/day dose level) was chosen as the "preferred occupying dose level".

After the “preferred occupying dose” was identified, 2 cohorts were added: Cohort C, which received 8.3 mg/kg/day using a 35-day cycle with no rest period; and Cohort F, which received a fixed dose (560 mg/dose) given once daily continuously. A final cohort (Cohort D) was then added for subjects with activated B-cell-like (ABC) subtype DLBCL, which received 560 mg/day continuously.

Figure 3. BTK Occupancy of Peripheral Blood Mononuclear Cells (Percent) at 4 Hours and 24 Hours After Ibrutinib Administration, by Dose Cohort



In summary, the BTK occupancies for the 2.5 mg/kg/day to 12.5 mg/kg/day cohorts were all above 90% at either 4 or 24 hours after drug administration. The mean BTK occupancies of continued dosing cohorts CD-1 (8.3 mg/kg/day), CD-2 (560 mg/day), and CD-3 (560 mg/day DLBCL) at 4 hours were 92.39%, 95.82%, and 97.79%, respectively; whereas the 24-hour occupancies were 93.36%, 94.18%, and 97.32%, respectively. In all cohorts above 2.5 mg/kg/day (or 200 mg), for both weight-based (ie, mg/kg) dosing and fixed dosing (ie, continuous dosing of 560 mg/day), the mean BTK occupancies were above 90% at 4 hours and 24 hours after drug administration.

Effects on electrocardiogram (ECG)

Results from formal ECG monitoring in 2 uncontrolled studies, study 04753 (n=45) and study 1102 (n=124), are presented.

In study 04753, a trend toward QTcB shortening was noted, especially in subjects receiving 12.5 mg/kg/day and in those on continuous dosing schedule. There was no significant QTc prolongation (>500 ms absolute value or >60 ms shift from baseline) was observed, and no evidence of QTcB prolongation with increasing plasma concentrations of ibrutinib ranging from 3.22 to 701 ng/mL in individual subjects was noted (non-significant negative slope of -0.0056 ms/ng/mL, p=0.5714).

In uncontrolled Study 1102 in 124 patients (described in Clinical Efficacy section) standard 12-lead ECGs were collected at several specified occasions during cycle 1 and at single specified occasions during further therapy and transmitted electronically to a central core lab. All ECGs were evaluated blindly by cardiologists for the presence of any clinically significant abnormalities. The study was not placebo controlled.

QTcF intervals were shorter by 8.9 ms on average relative to baseline in Treatment Group 1 (relapsed/refractory 420 mg, analysis set n=24), Treatment Group 2 (treatment-naïve 420 mg (elderly), n=23), and Treatment Group 3 (relapsed refractory 840 mg, n=34), and 7.5 ms on average for all groups combined,without evidence of dose-dependency. No such change was observed in Treatment Group 4 (high risk relapsed/refractory 420 mg, n=22) and in Treatment Group 6 (relapsed refractory food effect cohort 420 mg, n=16). Mean QTcF interval shortening was 7.5ms, no value <340ms.

Heart rate decreased by 6.8 beats per minute on average relative to baseline (screening) in both the 420 mg and 840 mg dose groups. There was no evidence of clinically meaningful bradycardia (i.e., <50 beats per minute).

PR interval duration was increased by 9.7 ms on average relative to baseline in both dose groups. There was no evidence of PR interval prolongation above 240 ms; a maximal value of PR interval of 242 ms was observed in one patient at one time-point only.

There were no treatment related effects on QRS duration in any of the treatment groups.

The exposure-response relationship between the plasma concentration of ibrutinib or PCI-45227 and change in QTcF and PR interval from baseline was conducted using a linear mixed effects modeling approach. The estimated slope of the linear mixed effect model was -0.0122 ms/ng/mL, which was statistically significant (p-value = 0.0002) indicating a decrease in QTcF by 1.2 ms with a 100 ng/mL increase in ibrutinib concentrations. Analysis of data for the metabolite PCI-45227 showed no evidence of QTcF prolongation with increasing PCI-45227 concentrations. The estimated population slope was -0.0197 ms/ng/ml with $p < 0.0001$ indicating a 2 ms decrease in QTcF per 100 ng/ml increase in PCI-45227 concentration. Similarly for PR, prolongation of 1.05 ms for each 100 ng/mL ibrutinib concentration increase was observed. The observed plasma concentrations of ibrutinib in CLL/SLL subjects dosed with 420 mg/day or 840 mg/day were in the range of 0 to 1170 ng/mL.

2.7.4. Discussion on clinical pharmacology

Ibrutinib has high permeability and low pH-dependent solubility. As such, the absorption of and subsequently the exposure of ibrutinib may be lowered by concomitant administrations of medicines that increase gastric pH (e.g. proton pump inhibitors), however population pharmacokinetic data and a subgroup efficacy analysis from the pivotal study 1112 (described in Clinical efficacy section) on patients with and without concomitant administration of proton-pump inhibitors (PPIs) indicate that a potential effect of increased gastric pH on ibrutinib PK is not clinically relevant. However, given that co-administration with PPIs is very common in the intended population and as a potential interaction could decrease efficacy this circumstantial evidence of a no-effect needs to be confirmed in a clinical study to evaluate the effect of a PPI on ibrutinib pharmacokinetics, which is requested post-approval (See RMP). Meanwhile, the information is included in the SmPC (under 4.5) until the study results are available.

Ibrutinib is rapidly absorbed after oral administration with a median T_{max} of 1 to 2 hours. Absolute bioavailability in fasted condition (n = 8) was 2.9% (90% CI = 2.1 – 3.9) and doubled when combined with a meal. Pharmacokinetics of ibrutinib does not significantly differ in patients with different B-cell malignancies. Ibrutinib exposure increases with doses up to 840 mg. The steady state AUC observed in patients at 560 mg is (mean ± standard deviation) 953 ± 705 ng h/mL. Administration of ibrutinib in fasted condition resulted in approximately 60% of exposure (AUC_{last}) as compared to either 30 minutes before, 30 minutes after (fed condition) or 2 hours after a high fat breakfast. The information is included in the SmPC and it is recommended that Imbruvica is taken at the same time every day without regard to meals.

Reversible binding of ibrutinib to human plasma protein in vitro was 97.3% with no concentration dependence in the range of 50 to 1,000 ng/mL. The apparent volume of distribution at steady state ($V_{d, ss}/F$) was approximately 10,000 L.

Ibrutinib is metabolised primarily by, CYP3A4 to produce a dihydrodiol metabolite with an inhibitory activity towards BTK approximately 15 times lower than that of ibrutinib. Involvement of CYP2D6 in the metabolism of ibrutinib appears to be minimal. Therefore, no precautions are necessary in patients with different CYP2D6 genotypes.

Apparent clearance (CL/F) is approximately 1,000 L/h. The half-life of ibrutinib is 4 to 13 hours.

After a single oral administration of radiolabeled [^{14}C]-ibrutinib in healthy subjects, approximately 90% of radioactivity was excreted within 168 hours, with the majority (80%) excreted in the faeces and less than 10% accounted for in urine. Unchanged ibrutinib accounted for approximately 1% of the radiolabeled excretion product in faeces and none in urine.

Ibrutinib has minimal renal clearance; urinary excretion of metabolites is < 10% of the dose. No specific studies have been conducted to date in subjects with impaired renal function. There are no data in patients with severe renal impairment or patients on dialysis (see section 4.2).

Ibrutinib is metabolised in the liver. In a dedicated hepatic impairment trial in non-cancer patients administered a single dose of 140 mg of medicinal product, preliminary data showed an approximate 4-, 8-, and 9-fold increase in ibrutinib exposure in subjects with mild (n = 6), moderate (n = 10) and severe (n = 8) hepatic impairment, respectively. The free fraction of ibrutinib also increased with degree of impairment, with 3.0, 3.8 and 4.8% in subjects with mild, moderate and severe liver impairment, respectively, compared to 3.3% in plasma from matched healthy controls within this study. An increase in unbound ibrutinib exposure is estimated to be 4-, 9-, and 13-fold in subjects with mild, moderate, and severe hepatic impairment, respectively (see section 4.2). As the hepatic impairment study report is not yet available, the final study report on the hepatic impairment study PCI-32765CLL1006 should be submitted post-approval (See RMP).

Co-administration of ketoconazole, a strong CYP3A4 inhibitor, in 18 fasted healthy subjects, increased exposure (C_{max} and AUC) of ibrutinib by 29- and 24-fold, respectively. Simulations using fasted conditions suggested that the strong CYP3A4 inhibitor clarithromycin may increase the AUC of ibrutinib by a factor of 14. Strong inhibitors of CYP3A4 (e.g., ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazadone and cobicistat) should therefore be avoided. If the benefit outweighs the risk and a strong CYP3A4 inhibitor must be used, reduce the IMBRUVICA dose to 140 mg (one capsule) or withhold treatment temporarily (for 7 days or less). Monitor patient closely for toxicity and follow dose modification guidance as needed (see sections 4.2 and 4.4).

Simulations using fasted conditions suggested that moderate CYP3A4 inhibitors, diltiazem, erythromycin and voriconazole, may increase the AUC of ibrutinib 5-9 fold. Moderate inhibitors (e.g., voriconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, fluconazole, fosamprenavir, imatinib, verapamil, amiodarone, dronedarone) should be avoided. Mild CYP3A4 inhibitors azithromycin and fluvoxamine may increase the AUC of ibrutinib by a factor of < 2-fold.

In the SmPC clinicians are instructed to reduce IMBRUVICA treatment to 140 mg in case a a moderate CYP3A4 inhibitor must be used but no dose adjustment is required in combination with mild inhibitors in both cases doctors are advised to monitor patient closely for toxicity and follow dose modification guidance as needed.

Co-administration of grapefruit juice, containing CYP3A4 inhibitors, in eight healthy subjects, increased exposure (C_{max} and AUC) of ibrutinib by approximately 4- and 2-fold, respectively. Grapefruit and Seville oranges should be avoided during IMBRUVICA treatment, as these contain moderate inhibitors of CYP3A4 (see section 4.2).

Administration of Imbruvica with inducers of CYP3A4 can decrease ibrutinib plasma concentrations.

Co-administration of rifampin, a strong CYP3A4 inducer, in 18 fasted healthy subjects, decreased exposure (C_{max} and AUC) of ibrutinib by 92 and 90%, respectively. Avoid concomitant use of strong or moderate CYP3A4 inducers (e.g., carbamazepine, rifampin, phenytoin). Preparations containing St. John's Wort are contraindicated during treatment with IMBRUVICA, as efficacy may be reduced. Doctors are advised to consider alternative agents with less CYP3A4 induction. If the benefit outweighs the risk and a strong or moderate CYP3A4 inducer must be used, monitor patient closely for lack of efficacy (see sections 4.3 and 4.4). Mild inducers may be used concomitantly with IMBRUVICA, however, patients should be monitored for potential lack of efficacy.

In vitro studies indicated that ibrutinib is a weak inhibitor toward CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. The dihydrodiol metabolite of ibrutinib is a weak inhibitor toward CYP2B6, CYP2C8, CYP2C9, and CYP2D6. Both ibrutinib and the dihydrodiol metabolite are at most weak inducers of CYP450 isoenzymes in vitro. Therefore, it is unlikely that the medicinal product has any clinically relevant drug-drug interactions with medicinal products that may be metabolised by the CYP450 enzymes.

In vitro studies indicated that ibrutinib is not a substrate of P-gp, OATP1B1 and OATP1B3. Ibrutinib is an *in vitro* inhibitor of P-gp (see section 4.5).
Time-dependent inhibition (TDI) data has not been submitted for a number of CYP enzymes. Thus, in vitro TDI data will be presented for CYP1A2, 2B6, 2C8, 2C9, 2C19 and 2D6 post-approval (See RMP). In addition, due to the poor stability of ibrutinib in hepatocytes the in vitro induction study is considered inconclusive. As ibrutinib was shown not to be a CYP3A4 inducer in vivo the applicant will submit new data on ibrutinib as an inducer of CYP1A2 and CYP2B6 (See RMP). Further, no data on the inhibitory potential of ibrutinib on drug transporters, except for P-gp, has been submitted. These studies are planned or ongoing and will be submitted post-approval (See RMP).

There is a risk that ibrutinib may inhibit intestinal CYP3A4 and thereby increasing the exposure of CYP3A4 substrates with a large contribution of intestinal CYP3A4 metabolism to its first pass extraction. This interaction has not been studied *in vivo* and its clinical relevance is currently unknown. (See SmPC section 5.2). Due to degradation of ibrutinib in vitro, the submitted in vitro and PBPK model data cannot be considered sufficient to exclude a risk for clinically relevant CYP3A4 intestinal inhibition by ibrutinib. Reversible CYP3A inhibition by ibrutinib will be studied in vitro by minimising the decline in ibrutinib concentration during incubations. If a risk for clinically relevant inhibition cannot be excluded an in vivo study will be considered (see RMP). Therefore, an in vivo interaction study between ibrutinib and a model CYP3A4 substrate, with a large contribution of intestinal CYP3A4 metabolism to its first pass extraction, will be performed and submitted post-approval (See RMP).

Concomitant use of Imbruvica and medicinal products that strongly or moderately inhibit CYP3A4 can increase ibrutinib exposure and should be avoided.

Ibrutinib is a P-gp inhibitor *in vitro*. As no clinical data are available on this interaction, it cannot be excluded that ibrutinib could inhibit intestinal P-gp after a therapeutic dose. To avoid a potential interaction in the GI tract, narrow therapeutic range P-gp substrates such as digoxin should be taken at least 6 hours before or after Imbruvica.

Ibrutinib is considered teratogenic (See Discussion on non-clinical aspects). The applicant will investigate the feasibility to conduct a drug interaction study between ibrutinib and oral contraceptives post-approval.

Population pharmacokinetics indicated that age and gender does not significantly influence ibrutinib clearance from the circulation. There are insufficient data to evaluate the potential effect of race on ibrutinib pharmacokinetics. Body weight (range: 41-146 kg; mean [SD]: 83 (19) kg) had a negligible effect on ibrutinib clearance.

No specific dose adjustment is required for elderly patients (aged ≥ 65 years)

No pharmacokinetic studies were performed with Imbruvica in patients under 18 years of age.

Ibrutinib therapy is associated with a mild decrease in the QTcF interval duration (mean 7.5 ms in study 1102). The clinical consequences of a shortened QTc duration are still largely unknown but may include an increased risk for arrhythmias (See discussion on Clinical safety and SmPC section 4.4), allowing the clinicians to use clinical judgment when assessing whether to prescribe ibrutinib to patients at risk from further shortening their QTc duration (e.g. Congenital Short QT Syndrome or patients with a family history of such a syndrome). Further information on this interaction will be provided from planned QTc study (PCI-32765CLL1007) (see RMP).

2.7.5. Conclusions on clinical pharmacology

The pharmacokinetic characteristics of ibrutinib and its active metabolite have been sufficiently characterized.

Awaiting data from the planned studies, the lack of information is addressed by appropriate warnings in the SmPC section 4.4 and 4.2.

The CHMP considers the following measures necessary –as part of the RMP- to address the issues related to pharmacology:

- Investigate the feasibility to conduct a drug interaction study between ibrutinib and oral contraceptives. If feasible, such a study will be conducted.
- Further evaluation of drug interactions, especially the potential interaction with PPI, the validity of the submitted in vitro studies and the potential intestinal interactions of ibrutinib will be performed
- An in vitro inhibition experiment for reversible CYP3A inhibition by ibrutinib, minimizing the decline in ibrutinib concentration during incubations.
- Submission of the final study report on the hepatic impairment study PCI-32765CLL1006
- An in vitro study to investigate the time dependent inhibition by ibrutinib on CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 should be submitted.
- In vitro studies investigating the inhibitory potential of ibrutinib towards BCRP, OATP1B1, OATP1B3, OCT2, OAT1 and OAT3 should be submitted.
- An in vivo interaction study between ibrutinib and a model CYP3A4 substrate, with a large contribution of intestinal CYP3A4 metabolism to its first pass extraction, should be performed and submitted.
- Submission of an in vitro study to investigate the induction by ibrutinib on CYP1A2 and CYP2B6 should be submitted.
- Submission of the study report from the planned QTc study (PCI-32765CLL1007).

2.8. Clinical efficacy

Overview of studies

For an overview of clinical efficacy studies, see Table 10-11.

The MAA for Imbruvica is based on a pivotal phase II study PCYC-1104-CA in relapsed or refractory MCL (n=111) and a phase Ib/II study, PCYC-1102-CA in relapsed or refractory CLL/SLL (n=132 whereof 101 with relapsed or refractory disease including 51 with the proposed 420 mg daily dose), with supportive evidence derived from the 04753 phase I study (MCL n=9; CLL/SLL n=16). Results from the interim analysis of a randomized, Phase 3 Study of ibrutinib versus ofatumumab in relapsed or refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (study PCYC 1112) was submitted within the Applicant's responses to CHMP List of questions.

2.8.1. Dose response study

Study PCYC-04753

Title: Phase I Dose-Escalation Study of Bruton's Tyrosine Kinase (BTK) Inhibitor PCI-32765 in Recurrent B-Cell Lymphoma

Objectives: The primary objectives of this study were to establish the safety and the MTD of orally administered ibrutinib in patients with recurrent B-cell lymphoma, to determine the PK of orally administered ibrutinib, and to measure pharmacodynamic parameters that include drug occupancy of BTK and the effect on biological markers of B-cell function. The secondary objective of this study was to evaluate tumor responses.

Methodology: This was a Phase 1, multicenter, open-label, dose-escalation study of ibrutinib in patients with recurrent surface immunoglobulin positive B-cell NHL according to WHO. Cohorts of 6 to 10 subjects each were to receive ibrutinib at 1.25, 2.5, 5.0, 8.3, 12.5, and 17.5 mg/kg/day until the MTD was established. A minimum of 4 evaluable subjects per cohort were included in the DLT and safety evaluations before a decision was made to dose escalate or initiate the next dosing cohort. Subjects were to receive daily treatment for 28 days followed by a 7-day rest period (1 cycle). Upon determination of the MTD, a cohort of 6 to 10 subjects was to be enrolled to receive ibrutinib at the MTD or"preferred occupying dose"continuously for 35 days with no rest period (1 cycle).

Key inclusion criteria included: measurable disease; failed ≥1 previous treatment for lymphoma and no standard therapy was available; ECOG performance status of ≤1.

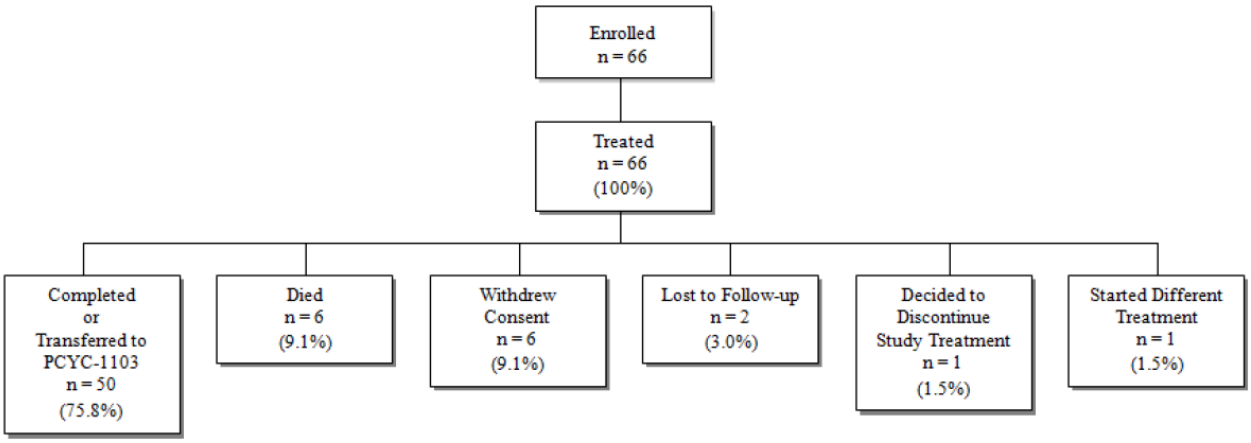
Key exclusion criteria included: more than 4 prior systemic therapies (not counting maintenance rituximab), except for CLL patients; prior allogeneic bone marrow transplant. The use of medications known to prolong corrected QT interval (QTc) interval or that may be associated with Torsades de Pointes were prohibited within 7 days of treatment start and during Cycle 1. Chemotherapy, immunotherapy, rituximab, prednisone (>20 mg/day), and radiotherapy were prohibited.

Results

Figure 4. Subject disposition

	Total	1.25 mg/kg	2.5 mg/kg	5.0 mg/kg	8.3 mg/kg	12.5 mg/kg	8.3 mg/kg cts	560 mg cts	560 mg DLBCL
No. (%)subjects, as enrolled	66	7	9 [a]	6	8	7	10	9	10
No. (%)subjects, as treated	66	8 [a]	8	6	8	7	10	9	10

	Total	CLL/SLL	MCL	DLBCL	FL	WM	Other Indolent NHL
No. (%)subjects as enrolled	66	16	9	17	16	4	4
No. (%)subjects as treated[a]	66	16	9	17	16	4	4



The study enrolled 66 patients: median age 65 (40-82) years; male 66.7%; white race 93.9%; ECOG 1 42.4%; median number of prior therapies 3 (1-10); CLL n=16, MCL n=9.

Table 15. Baseline Characteristics by Cohort (Safety Population)

	Total (N=66)	1.25 mg/kg (N=8)	2.5 mg/kg (N=8)	5.0 mg/kg (N=6)	8.3 mg/kg (N=8)	12.5 mg/kg (N=7)	8.3 mg/kg cts (N=10)	560 mg cts (N=9)	560 mg DLBCL (N=10)
Histology									
CLL/SLL	16 (24.2%)	0	3 (37.5%)	3 (50.0%)	1 (12.5%)	2 (28.6%)	6 (60.0%)	1 (11.1%)	0
MCL	9 (13.6%)	2 (25.0%)	1 (12.5%)	0	1 (12.5%)	0	0	5 (55.6%)	0
DLBCL	17 (25.8%)	2 (25.0%)	1 (12.5%)	0	2 (25.0%)	1 (14.3%)	1 (10.0%)	0	10 (100%)
FL	16 (24.2%)	4 (50.0%)	3 (37.5%)	1 (16.7%)	3 (37.5%)	3 (42.9%)	2 (20.0%)	0	0
WM	4 (6.1%)	0	0	0	0	1 (14.3%)	0	3 (33.3%)	0
Other indolent NHL	4 (6.1%)	0	0	2 (33.3%)	1 (12.5%)	0	1 (10.0%)	0	0

Table 16. Study Drug Exposure by Cohort (Safety Population)

	Total (N=66)	1.25 mg/kg/day (N=8)	2.5 mg/kg/day (N=8)	5.0 mg/kg/day (N=6)	8.3 mg/kg/day (N=8)	12.5 mg/kg/day (N=7)	8.3 mg/kg/day cts (N=10)	560 mg/day cts (N=9)	560 mg/day DLBCL (N=10)
Treatment duration (weeks)									
n	66	8	8	6	8	7	10	9	10
Median	29	9	22	17	43	34	45	30	8
Min-Max	1-98	2-80	2-64	4-80	1-74	1-49	2-66	6-45	2-98
Number of cycles of ibrutinib received									
n	66	8	8	6	8	7	10	9	10
Median	6	2	5	4	9	7	9	6	2
Min-Max	1-20	1-16	1-13	1-16	1-15	1-10	1-13	2-9	1-20
Total cumulative dose (mg)									
n	66	8	8	6	8	7	10	9	10
Median	54720	5600	29840	44920	183970	177560	204140	117040	29400
Min-Max	600-380240	600-52560	3600-54240	7280-267000	7360-235200	7420-296800	7040-308160	21840-176400	8400-380240
Number of subjects with dose missed for ≥7 days									
Yes	9 (13.6%)	1 (12.5%)	2 (25.0%)	0	1 (12.5%)	0	4 (40.0%)	1 (11.1%)	0
No	57 (86.4%)	7 (87.5%)	6 (75.0%)	6 (100.0%)	7 (87.5%)	7 (100.0%)	6 (60.0%)	8 (88.9%)	10 (100.0%)

In summary, the BTK occupancies for the 2.5 mg/kg/day to 12.5 mg/kg/day cohorts were all above 90% at either 4 or 24 hours after drug administration. The mean BTK occupancies of continued dosing cohorts CD-1 (8.3 mg/kg/day), CD-2 (560 mg/day), and CD-3 (560 mg/day DLBCL) at 4 hours were 92.39%, 95.82%, and 97.79%, respectively; whereas the 24-hour occupancies were 93.36%, 94.18%, and 97.32%, respectively. In all cohorts above 2.5 mg/kg/day (or 200 mg), for both weight-based (ie, mg/kg) dosing and fixed dosing (ie, continuous dosing of 560 mg/day), the mean BTK occupancies were above 90% at 4 hours and 24 hours after drug administration.

The MTD of ibrutinib was not reached using intermittent dosing cohorts up to 12.5 mg/kg/day and continuous dosing cohorts at 560 mg/day. Two DLTs occurred during the study conduct: 1 Grade 3 allergic hypersensitivity (8.3 mg/kg/day dosing cohort) and 1 dose interruption for more than 7 days secondary to Grade 2 neutropenia (2.5 mg/kg/day dosing cohort) (See also Supportive studies for description of efficacy in MCL, CLL).

2.8.2. Main studies

Study 1104

Study PCYC-1104-CA (hereafter “1104”) is a pivotal phase II study in relapsed or refractory MCL.

Methods

Study Participants

Key inclusion criteria:

- Men and women ≥18 years of age
- ECOG performance status of ≤2
- Pathologically confirmed MCL, with documentation of either overexpression of cyclin D1 or t(11;14), and measurable disease on cross sectional imaging that is ≥2 cm in the longest diameter and measurable in 2 perpendicular dimensions per CT
- Documented failure to achieve at least PR with, or documented disease progression after, the most recent treatment regimen
- At least 1, but no more than 5, prior treatment regimens for MCL (Note: “bortezomib exposed was defined as having received ≥2 cycles of prior treatment with bortezomib, either as a single agent or as part of a combination therapy regimen.)

Key exclusion criteria

- Prior chemotherapy within 3 weeks, nitrosoureas within 6 weeks, therapeutic anticancer antibodies within 4 weeks, radio- or toxin-immunoconjugates within 10 weeks, radiation therapy within 3 weeks, or major surgery within 2 weeks of first dose of study drug
- Known central nervous system (CNS) lymphoma
- Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 (moderate) or 4 (severe) cardiac disease as defined by the New York Heart Association Functional Classification

- Significant screening ECG abnormalities, including left bundle branch block, second-degree atrioventricular block Type II, third-degree block, bradycardia, or QTc interval ≥500 msec
- Any of the following laboratory abnormalities:
    - Absolute neutrophil count (ANC) <750 cells/mm3 (0.75 x 109/L) unless there is documented bone marrow involvement
    - Platelet count <50,000 cells/mm3 (50 x 109/L) independent of transfusion support unless there is documented bone marrow involvement
    - Serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≥3.0 x upper limit of normal(ULN) Creatinine >2.0 x ULN

Treatments

Ibrutinib 560 mg (4 x 140-mg capsules) was to be administered orally once daily until unacceptable toxicity. Each dose of ibrutinib was to be taken at least 30 minutes before eating or at least 2 hours after a meal, at approximately the same time each day.

Dosing was to be held for any of the following conditions: Grade ≥3 neutropenia with fever; Grade 4 neutropenia lasting >7 days (unless there was documented bone marrow involvement in which case study drug was to be held if there was >50% reduction in neutrophil count); Platelet counts <20 x 109/L (unless there was documented bone marrow involvement in which case dose was to be held if there was >50% reduction in platelet count); Any Grade ≥3 nonhematologic toxicity.

Use of hematopoietic growth factors was permitted after Cycle 1 according to the ASCO guidelines.

Concomitant use of strong CYP3A4/5 or CYP2D6 inhibitors, or strong CYP3A4/5 inducers, were to be avoided, if possible.

Objectives

The primary objective of this study was to evaluate the efficacy of ibrutinib in subjects with relapsed /refractory MCL.

The secondary objective was to evaluate the safety of a fixed daily dosing regimen of ibrutinib in this population.

Outcomes/endpoints

Primary efficacy endpoint: Overall response rate (ORR), defined as the percent of subjects who achieved either a PR or CR, according to the revised IWG criteria for NHL (Cheson 2007), as assessed by investigators.

Secondary efficacy endpoints: Assessed by the investigator

- Duration of response (DOR)
- Time to response was analyzed for subjects with CR/PR
- Progression-free survival (PFS)
- Overall survival (OS)

Other endpoint analyses: ECOG score

Exploratory analyses:

- ORR and DOR as assessed by the IRC
- The effect of the 2 manufacturing sites on efficacy, safety,and pharmacokinetics

Other analyses: Patient reported outcomes – EORTC QLQ-30

CT scans (with contrast unless contraindicated) of the chest, abdomen, and pelvis and any other disease sites were to be performed for tumour assessments within 7 days of Day 1 of Cycles 3, 5, 7 and then every 3 cycles until progressive disease. PET was mandatory to confirm any complete remission. Likewise, endoscopy was mandatory to confirm complete remission for any subjects with a documented history of gastrointestinal involvement at the time of screening and bone marrow biopsies were required to confirm complete response if bone marrow was involved at time of screening.

Sample size

Approximately 115 subjects were to be enrolled and grouped into 2 cohorts based upon prior exposure to bortezomib.

For the bortezomib-naïve cohort, a 2-stage design was used to test the null hypothesis that ORR would be ≤20% (not considered clinically compelling). Twenty-five subjects were to be included in the first stage, and, if there were at least 6 objective responses, a total of 65 subjects were to be enrolled in this cohort. A sample size of 65 subjects at final analysis would provide 91% power to test a difference of 20% versus 40% using a one-sided 0.01 significance level.

For the bortezomib-exposed cohort, a 2-stage design was used to test the null hypothesis that ORR would be ≤15% (not considered clinically compelling). Twenty-five subjects were to be included in the first stage, and, if there were at least 5 objective responses, a total of 50 subjects were to be enrolled in this cohort. A sample size of 50 subjects at final analysis would provide at least 80% power to test a difference of 15% versus 35% using a one-sided 0.01 significance level.

In both cohorts, the interim stopping rules were based on the stopping rules for Simon's 2-stage optimal Phase 2 design.

Randomisation

Study 1104 was not randomised.

Blinding (masking)

N/A

Statistical methods

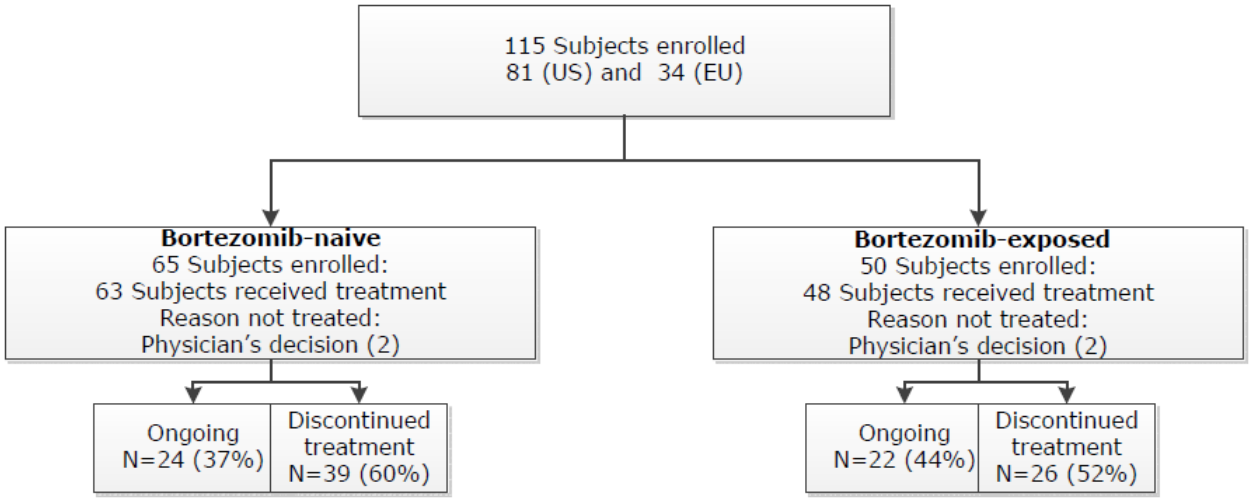
The primary analysis was based on the all treated population. The response rate was provided and the corresponding 95% 2-sided confidence interval (CI) was calculated using normal approximation to the binomial distribution.

Interim analysis

One interim analysis for futility based on response rate was planned for each cohort. The IA was performed in December 2011 when approximately 31 subjects were enrolled in the bortezomib-naive and 20 subjects were enrolled in the bortezomib-exposed cohorts and available for initial response evaluation.

Results

Figure 5. Participant flow



Subject Disposition and Treatment Withdrawal Information; All Treated Population

	Ibrutinib		
	Bortezomib-Naive	Bortezomib-Exposed	Combined
Population: all treated	63	48	111
Still on treatment	24 (38.1%)	22 (45.8%)	46 (41.4%)
Discontinued treatment	39 (61.9%)	26 (54.2%)	65 (58.6%)
Reason for discontinuation			
Adverse event	4 (6.3%)	5 (10.4%)	9 (8.1%)
Physician decision	1 (1.6%)	2 (4.2%)	3 (2.7%)
Progressive disease	32 (50.8%)	17 (35.4%)	49 (44.1%)
Withdrawal of consent	2 (3.2%)	2 (4.2%)	4 (3.6%)

Note: Percentages calculated with the number of subjects in all treated population as denominator

Out of the 115 patients enrolled 2 in each cohort were not treated at physician's decision. Reasons for Discontinuation in the All treated population (n=111) were death (36.9%) lost to follow up (1.8%) withdrawal of consent (7.2%) in the All Treated Population.

Recruitment

The study was initiated on 8 February 2011 and date of the clinical cut-off for primary analysis was 26 December 2012. Number of patients enrolled was 115 at 9 sites in US, 2 sites in Germany, 3 sites in Poland, and 4 sites in UK.

Conduct of the study

Protocol amendments were:

Amendment 1.0 (20 December 2010): Modification of inclusion criteria to include subjects who had either prior exposure to bortezomib therapy (n=50) or who were naïve to bortezomib therapy (n=50) (the original protocol excluded subjects with prior bortezomib exposure) and to allow up to 5 prior therapies (previously up to 3). Amendment 2.0 (3 October 2011): - to allow enrollment of 25 additional bortezomib- naïve subjects in the study. Amendment 3.0 (30 August 2012): Patients who did not progress and were on study treatment were required to continue treatment in a long-term extension study. In amendment 4, de-identified copies of all scans and radiology reports were to be provided for an independent response evaluation of the radiographic scans.

Protocol deviations

Protocol deviations were reported in 12 patients: 9 violations of eligibility criteria, 1 concomitant medication (filgrastim in cycle 1), 1 missing informed consent for a blood sample and 1 dispensing of 6 days expired drug.

Baseline data

Table 17. Baseline Disease Characteristics; All Treated Population (Study PCYC-1104-CA)

	Ibrutinib		
	Bortezomib-Naive	Bortezomib-Exposed	Combined
Population: all treated	63	48	111
Time from diagnosis to first dose (months)			
N	63	48	111
Mean (SD)	45.81 (45.45)	59.15 (39.62)	51.58 (43.35
Median	29.01	48.28	42.35
Range	(2.5; 213.2)	(6.6; 223.3)	(2.5; 223.3)
< 36 months	37 (58.7%)	11 (22.9%)	48 (43.2%)
≥ 36 months	26 (41.3%)	37 (77.1%)	63 (56.8%)
Tumor bulk (largest diameter)			
N	63	48	111
< 5 cm	37 (58.7%)	31 (64.6%)	68 (61.3%)
≥ 5 cm	26 (41.3%)	17 (35.4%)	43 (38.7%)
≥ 10 cm	6 (9.5%)	3 (6.3%)	9 (8.1%)
Tumor burden (cm^2)			
N	63	48	111
Mean (SD)	51.54 (53.68)	42.38 (49.04)	47.58 (51.70
Median	30.85	26.02	30.05
Range	(2.7; 288.8)	(1.4; 250.8)	(1.4; 288.8)
B-symptoms			
N	63	48	111
Yes	19 (30.2%)	10 (20.8%)	29 (26.1%)
No	39 (61.9%)	37 (77.1%)	76 (68.5%)
Unknown	5 (7.9%)	1 (2.1%)	6 (5.4%)
Simplified MIPI score [a]			
N	63	48	111
Low risk (0-3)	9 (14.3%)	6 (12.5%)	15 (13.5%)
Intermediate risk (4-5)	24 (38.1%)	18 (37.5%)	42 (37.8%)
High risk (6-11)	30 (47.6%)	24 (50.0%)	54 (48.6%)
Prior number of regimens			
N	63	48	111
Mean (SD)	2.60 (1.40)	3.25 (1.34)	2.88 (1.41)
Median	2.00	3.00	3.00
Range	(1.0; 5.0)	(1.0; 5.0)	(1.0; 5.0)
< 3	32 (50.8%)	18 (37.5%)	50 (45.0%)
≥ 3	31 (49.2%)	30 (62.5%)	61 (55.0%)
Refractory disease [b]			
N	63	48	111
Yes	27 (42.9%)	23 (47.9%)	50 (45.0%)
No	36 (57.1%)	25 (52.1%)	61 (55.0%)

Key: MIPI=Mantle cell lymphoma international prognostic index
[a] Derived using following 4 prognostic factors age, ECOG, LDH and WBC at baseline. If a subject had LDH and/or WBC values missing at baseline then it was derived using rest of the prognostic factors.

Table 18. Extent of Disease at Baseline; All Treated Population (Study PCYC-1104-CA)

	Ibrutinib		
	Bortezomib-Naive	Bortezomib-Exposed	Combined
Population: all treated	63	48	111
Molecular confirmation of MCL			
N	63	48	111
t(11;14) by cytogenetics/FISH	9 (14.3%)	6 (12.5%)	15 (13.5%)
Cyclin D1 expression by IHC	44 (69.8%)	33 (68.8%)	77 (69.4%)
Both t(11;14) and Cyclin D1	10 (15.9%)	9 (18.8%)	19 (17.1%)
MCL cytologic variant			
N	63	48	111
Typical	43 (68.3%)	35 (72.9%)	78 (70.3%)
Round cell (CLL-like)	2 (3.2%)	4 (8.3%)	6 (5.4%)
Blastoid	10 (15.9%)	7 (14.6%)	17 (15.3%)
Other	8 (12.7%)	2 (4.2%)	10 (9.0%)
Advanced disease			
N	63	48	111
Yes	49 (77.8%)	31 (64.6%)	80 (72.1%)
Bone marrow involvement	35 (55.6%)	19 (39.6%)	54 (48.6%)
Extranodal disease	40 (63.5%)	20 (41.7%)	60 (54.1%)
No	14 (22.2%)	17 (35.4%)	31 (27.9%)
Gastrointestinal disease			
N	63	48	111
Yes	13 (20.6%)	5 (10.4%)	18 (16.2%)
No	50 (79.4%)	43 (89.6%)	93 (83.8%)
LDH > upper limit normal			
N	62	48	110
Yes	47 (75.8%)	42 (87.5%)	89 (80.9%)
No	15 (24.2%)	6 (12.5%)	21 (19.1%)

Seventeen (15.3%) subjects were reported to have blastoid histology as reported by the investigator. Lactate dehydrogenase was above the ULN in the majority of subjects (89 subjects; 80.9%).

Table 19. Prior Therapy for Mantle Cell Lymphoma; All Treated Population (Study PCYC-1104-CA)

	Ibrutinib		
	Bortezomib-Naive	Bortezomib-Exposed	Combined
Population: all treated	63	48	111
Prior systemic therapy			
N	63	48	111
Yes	63 (100%)	48 (100%)	111 (100%)
No	0 (0%)	0 (0%)	0 (0%)
Prior radiation			
N	63	48	111
Yes	16 (25.4%)	12 (25%)	28 (25.2%)
No	47 (74.6%)	36 (75%)	83 (74.8%)
Prior high intensity therapy			
N	63	48	111
Yes	23 (36.5%)	16 (33.3%)	39 (35.1%)
Hyper CVAD	18 (28.6%)	15 (31.3%)	33 (29.7%)
Stem Cell Transplant	8 (12.7%)	4 (8.3%)	12 (10.8%)
No	40 (63.5%)	32 (66.7%)	72 (64.9%)
Prior Lenalidomide			
N	63	48	111
Yes	9 (14.3%)	18 (37.5%)	27 (24.3%)
No	54 (85.7%)	30 (62.5%)	84 (75.7%)
Prior Alkylator			
N	63	48	111
Yes	61 (96.8%)	46 (95.8%)	107 (96.4%)
No	2 (3.2%)	2 (4.2%)	4 (3.6%)
Prior Rituximab			
N	63	48	111
Yes	56 (88.9%)	43 (89.6%)	99 (89.2%)
No	7 (11.1%)	5 (10.4%)	12 (10.8%)
Prior Anthracycline			
N	63	48	111
Yes	50 (79.4%)	40 (83.3%)	90 (81.1%)
No	13 (20.6%)	8 (16.7%)	21 (18.9%)
Prior Vinca alkyloid			
N	63	48	111
Yes	44 (69.8%)	34 (70.8%)	78 (70.3%)
No	19 (30.2%)	14 (29.2%)	33 (29.7%)
Prior Purine analog			
N	63	48	111
Yes	17 (27%)	10 (20.8%)	27 (24.3%)
No	46 (73%)	38 (79.2%)	84 (75.7%)
Time from the end of last prior therapy to first dose (months)			
N	63	48	111
Mean (SD)	11.82 (17.81)	6.76 (8.51)	9.63 (14.70)
Median	4.40	2.65	3.50
Range	(0.8; 115.4)	(0.7; 30.7)	(0.7; 115.4)

Numbers analysed

The All treated population consisted of 111 patients.

Duration of treatment and follow-up

At the time of the clinical cut-off (chosen to ensure that last subject enrolled in the study in the final analysis had at least 9 months of follow-up) the median duration of ibrutinib treatment was 8.3 months (range, 0.7-21.4 months), 46 (41.4%) subjects continued to receive ibrutinib treatment and the median follow-up was 15.3 months.

Outcomes and estimation

Response rate

Table 20. ORR by investigator assessment: All-Treated Population - Ibrutinib ISE for MCL

	PCYC-1104-CA			PCYC-04753 MCL
	Bortezomib-Naive (N=63)	Bortezomib-Exposed (N=48)	Total (N=111)	Total (N=9)
Best Disease Response				
Complete Response (CR)	12 (19.0%)	11 (22.9%)	23 (20.7%)	3 (33.3%)
95% CI	(10.2%, 30.9%)	(12.0%, 37.3%)	(13.6%, 29.5%)	(7.5%, 70.1%)
Partial Response (PR)	31 (49.2%)	21 (43.8%)	52 (46.8%)	4 (44.4%)
Stable Disease (SD)	8 (12.7%)	8 (16.7%)	16 (14.4%)	1 (11.1%)
Progressive Disease (PD)	12 (19.0%)	7 (14.6%)	19 (17.1%)	1 (11.1%)
Not Evaluable[a]	0	1 (2.1%)	1 (0.9%)	0
Overall Response Rate (CR+PR)				
n (%)	43 (68.3%)	32 (66.7%)	75 (67.6%)	7 (77.8%)
95% CI[b]	(55.3%, 79.4%)	(51.6%, 79.6%)	(58.0%, 76.1%)	(40.0%, 97.2%)

Table 21. Response Assessment – Concordance between Investigator and Independent review Committee; All treated Population (Study PCYC-1104-CA)

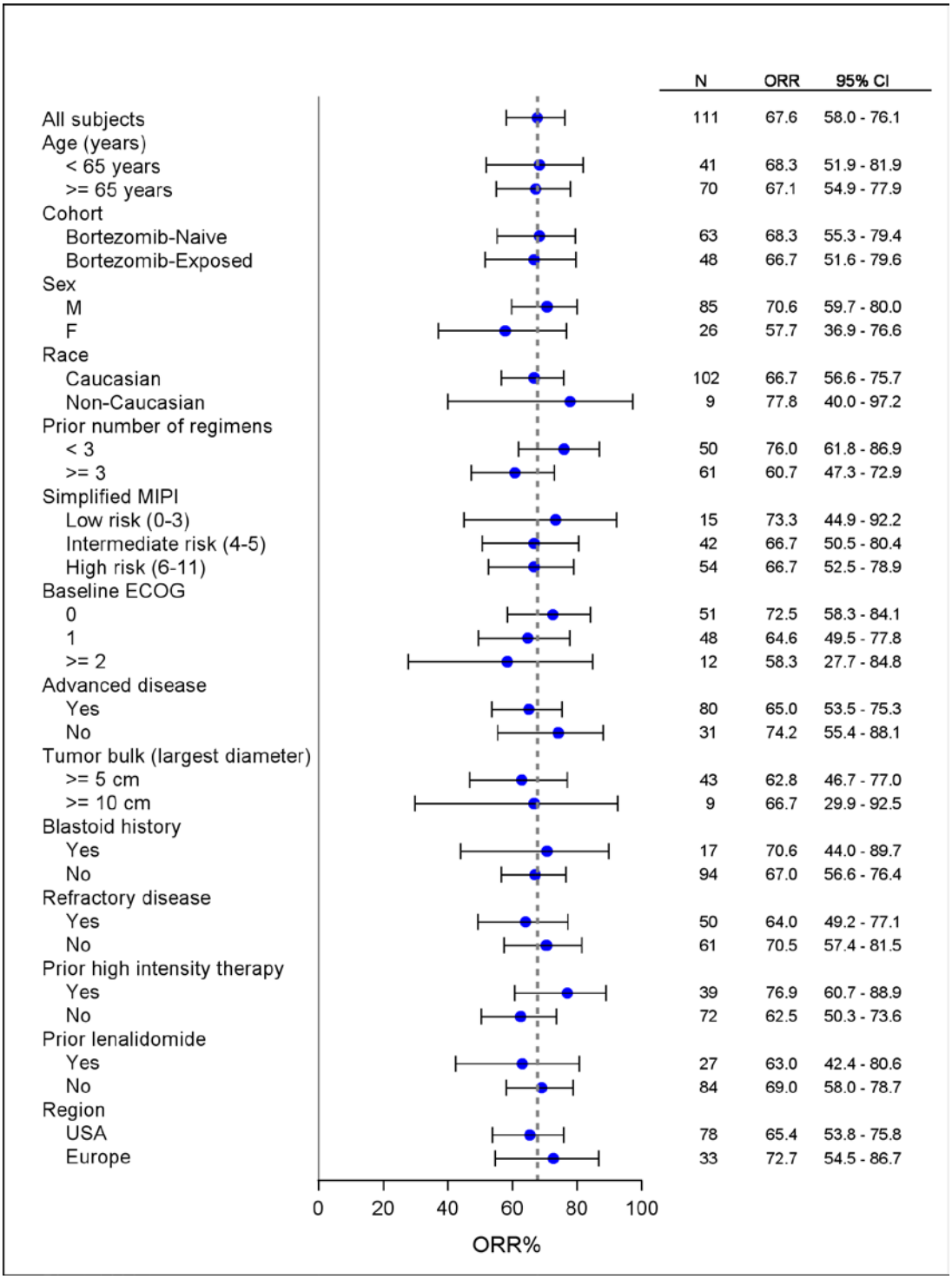
	Ibrutinib		
	Bortezomib-Naive	Bortezomib-Exposed	Combined
Population: all treated	63	48	111
Responder (CR or PR) by investigator	43	32	75
Responder (CR or PR) by IRC	40 (93.0%)	31 (96.9%)	71 (94.7%)
Complete agreement	33 (76.7%)	26 (81.3%)	59 (78.7%)
CR by investigator but PR by IRC	4 (9.3%)	2 (6.3%)	6 (8.0%)
PR by investigator but CR by IRC	3 (7.0%)	3 (9.4%)	6 (8.0%)
Non responder by IRC	3 (7.0%)	1 (3.1%)	4 (5.3%)
Non responder by investigator	20	16	36
CR by IRC	1 (5.0%)	0	1 (2.8%)
PR by IRC	4 (20.0%)	0	4 (11.1%)
Non responder by IRC	15 (75.0%)	16 (100.0%)	31 (86.1%)

Key: CR= complete response, IRC= independent review committee, PR= partial response

[TEFRSP06.rtf] [JNJ-54179060\PCYC_1104_CA\DBR_CSR\RE_CSR\tefrsp06.sas] 16APR2013, 16:34

In Study 1104, independent review of response by an IRC demonstrated an overall response rate of 68.5%, with a 20.7% CR rate and a 47.7% PR rate. A total of 94.7% of the investigator assessed responders were confirmed by the IRC. The IRC-estimated median duration of response was 19.6 months.

Table 22. Subgroup Analysis of Overall Response Rate by Investigator Assessment; All Treated Population (Study PCYC-1104-CA)



Time to response

The median time to initial response was 1.9 months (range: 1.4, 13.7; n=75).

The median time to CR was 5.5 months (range: 1.7, 11.5; n=23). The CR rate increased from 3.6% at 2 months to 20.7% at 12 months. The PR rate increased from 52.3% in 2 months to 67.6% in 15 months.

Duration of response

Table 23. Duration of Response: All-Treated Population – MCL (Note: All percentage calculations are based on the number of subjects with response (CR+PR)

	PCYC-1104-CA			PCYC-04753 MCL
	Bortezomib-Naive (N=63)	Bortezomib-Exposed (N=48)	Total (N=111)	Total (N=9)
Responders (CR+PR)	43	32	75	7
Events	17 (39.5%)	7 (21.9%)	24 (32.0%)	2 (28.6%)
Progressed	16 (37.2%)	6 (18.8%)	22 (29.3%)	2 (28.6%)
Died without documentation of progression	1 (2.3%)	1 (3.1%)	2 (2.7%)	0
Censored	26 (60.5%)	25 (78.1%)	51 (68.0%)	5 (71.4%)
Duration of response (months)[a]				
Median (95% CI)	15.8 (5.6, NE)	NE (NE, NE)	17.5 (15.8, NE)	9.1 (7.0, NE)
Min, Max	0.03+, 17.51+	1.68, 19.58+	0.03+, 19.58+	2.43+, 11.60+
6-month event-free rate (95% CI)	65.8 (49.1, 78.1)	86.5 (67.9, 94.8)	74.6 (62.7, 83.2)	100 (100, 100)
12-month event-free rate (95% CI)	63.1 (46.4, 75.9)	73.7 (52.2, 86.7)	67.9 (55.4, 77.7)	33.3 (0.9, 77.4)

TEFRSP09: Duration of Response by Best Response Categories Based on Investigator Assessment; All Treated Population (Study PCYC-1104-CA)

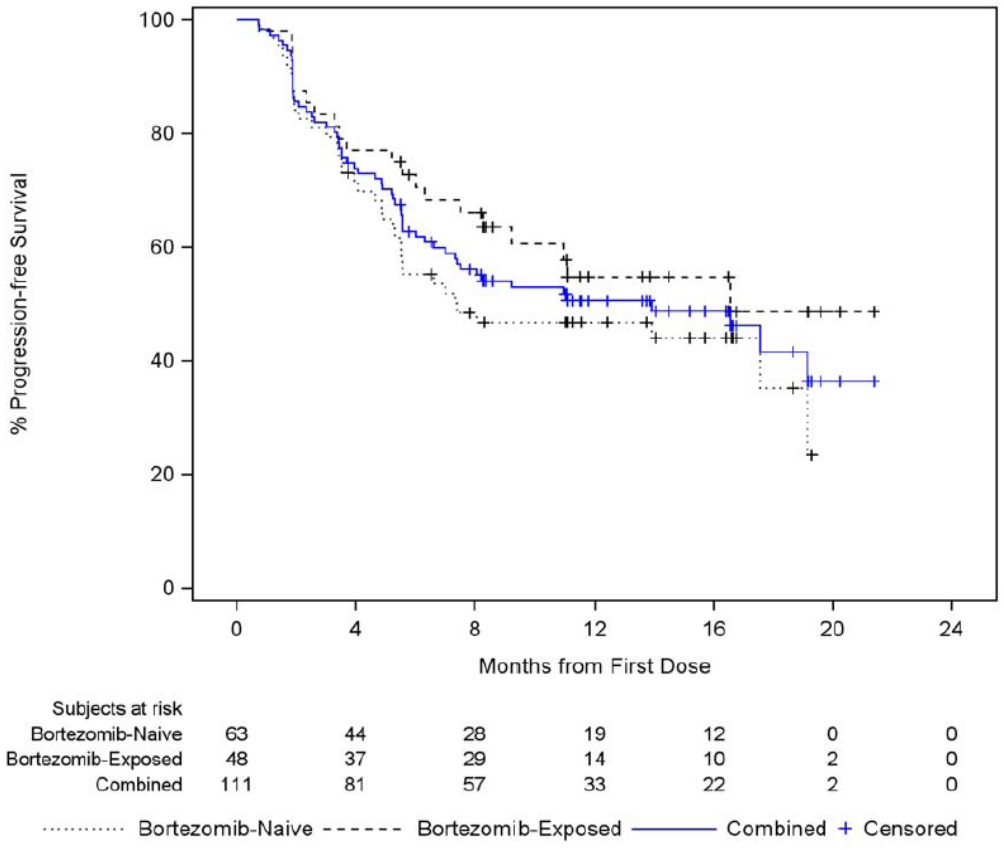
	Ibrutinib		
	Bortezomib-Naive	Bortezomib-Exposed	Combined
Population: all treated	63	48	111
Best response CR	12	11	23
Progressed or died (event)	1 (8.3%)	2 (18.2%)	3 (13.0%)
Censored	11 (91.7%)	9 (81.8%)	20 (87.0%)
Duration of response (months)			
Median (95% CI)	NE (2.83, NE)	NE (5.68, NE)	NE (NE, NE)
Range	(0.0+, 17.5+)	(1.9+, 18.5+)	(0.0+, 18.5+)
Best response PR	31	21	52
Progressed or died (event)	16 (51.6%)	5 (23.8%)	21 (40.4%)
Censored	15 (48.4%)	16 (76.2%)	31 (59.6%)
Duration of response (months)			
Median (95% CI)	15.80 (3.75, 17.51)	NE (7.23, NE)	15.80 (6.70, NE)
Range	(0.4, 17.5)	(1.7, 19.6+)	(0.4, 19.6+)

Progression-free survival

Table 24. Progression-Free Survival: All-Treated Population – MCL

	PCYC-1104-CA			PCYC-04753 MCL
	Bortezomib-Naive (N=63)	Bortezomib-Exposed (N=48)	Total (N=111)	Total (N=9)
Subject status				
Events	36 (57.1%)	21 (43.8%)	57 (51.4%)	3 (33.3%)
Progressed	35 (55.6%)	18 (37.5%)	53 (47.7%)	3 (33.3%)
Died without documentation of progression	1 (1.6%)	3 (6.3%)	4 (3.6%)	0
Censored	27 (42.9%)	27 (56.3%)	54 (48.6%)	6 (66.7%)
Progression-free survival (months)[a]				
Median (95% CI)	7.4 (5.3, 19.2)	16.6 (8.3, NE)	13.9 (7.0, NE)	11.6 (1.5, NE)
Min, Max	0.72, 19.29+	0.76, 21.39+	0.72, 21.39+	1.51, 18.43+
6-month progression-free survival rate (95% CI)	55.2 (42.0, 66.5)	72.8 (57.8, 83.2)	62.8 (53.0, 71.1)	88.9 (43.3, 98.4)
12-month progression-free survival rate (95% CI)	46.7 (34.0, 58.6)	54.7 (38.5, 68.3)	50.6 (40.6, 59.7)	47.4 (7.2, 80.9)
18-month progression-free survival rate (95% CI)	35.2 (17.7, 53.2)	48.6 (30.5, 64.6)	41.6 (28.7, 53.9)	47.4 (7.2, 80.9)

Figure 6. Kaplan-Meier Plot of Progression-free Survival by Investigator Assessment; All Treated Population (Study PCYC-1104-CA)



Note: Subjects who received subsequent anti-cancer therapy prior to disease progression were censored

Table 25. Reason of Censoring for Progression-free Survival by Investigator Assessment; All Treated Population (Study PCYC-1104-CA)

	Ibrutinib		
	Bortezomib-Naive	Bortezomib-Exposed	Combined
Population: all treated	63	48	111
Censored	27	27	54
Reason for censoring			
New anti-cancer therapy	0	1 (3.7%)	1 (1.9%)
Study cut-off	24 (88.9%)	24 (88.9%)	48 (88.9%)
Withdrew consent	3 (11.1%)	2 (7.4%)	5 (9.3%)

Note: Percentages calculated with the number of subjects censored as denominator

Overall survival

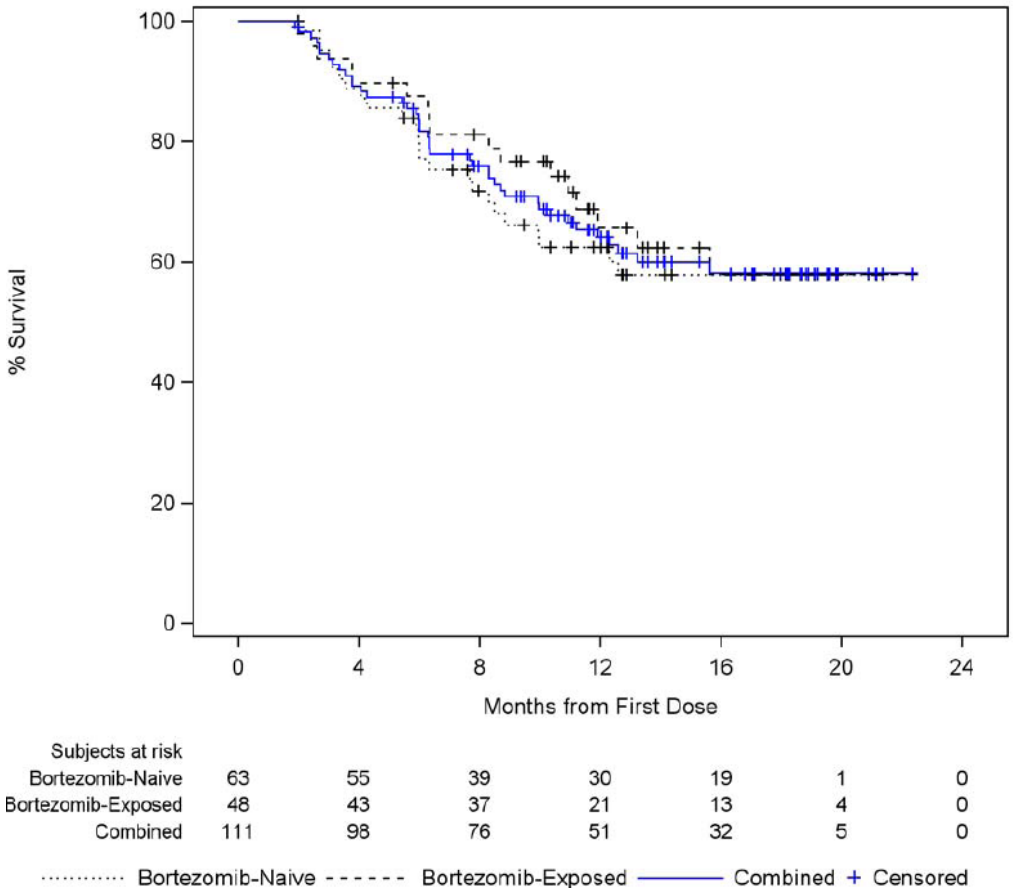
Table 26. Overall Survival: All-Treated Population – studies 1104 and 04753

	PCYC-1104-CA			PCYC-04753 MCL
	Bortezomib-Naive (N=63)	Bortezomib-Exposed (N=48)	Total (N=111)	Total (N=9)
Subject status				
Death of any cause (event)	24 (38.1%)	17 (35.4%)	41 (36.9%)	0
Censored	39 (61.9%)	31 (64.6%)	70 (63.1%)	9 (100%)
Overall survival (months)[a]				
Median (95% CI)	NE (10.0, NE)	NE (11.9, NE)	NE (13.2, NE)	NE (NE, NE)
Min, Max	1.97+, 21.16+	1.87, 22.34+	1.87, 22.34+	1.58+, 18.43+
6-month overall survival rate (95% CI)	80.4 (68.1, 88.4)	87.5 (74.2, 94.2)	83.5 (75.1, 89.3)	100 (100, 100)
12-month overall survival rate (95% CI)	62.4 (48.6, 73.5)	65.7 (49.2, 77.9)	64.2 (54.0, 72.7)	100 (100, 100)
18-month overall survival rate (95% CI)	57.8 (43.6, 69.6)	57.9 (40.0, 72.2)	58.2 (47.3, 67.6)	100 (100, 100)

TEFOS02: Reason of Censoring for Overall Survival ; All Treated Population (Study PCYC-1104-CA)

	Ibrutinib		
	Bortezomib-Naive	Bortezomib-Exposed	Combined
Population: all treated	63	48	111
Censored	39	31	70
Reason for censoring			
Lost to follow-up	2 (5.1%)	0	2 (2.9%)
Study cut-off	32 (82.1%)	28 (90.3%)	60 (85.7%)
Withdrew consent	5 (12.8%)	3 (9.7%)	8 (11.4%)

Figure 7. Kaplan-Meier Plot of Overall Survival ; All Treated Population (Study PCYC-1104-CA)



Efficacy data were collected in Study 1104 for subjects who continued to receive treatment or were in the post-treatment follow-up phase after the data cutoff for the CSR. - as of 14 March 2014, table xx

Table 27. Comparison of Efficacy Results for Study 1104 CSR and Recently Updated Results by Investigator Assessment; All Subjects

Efficacy Parameter	CSR Data	Updated Efficacy Data
ORR	75 (67.6%)	74 (66.7%)
95% CI	(58.9%, 76.3%)	(57.1%, 75.3%)
CR	23 (20.7%)	25 (22.5%)
PR	52 (46.8%)	49 (44.1%)
Median duration of response (95% CI)	17.5 months (15.80, NE)	17.5 months (14.92, NE)

Table 28. Summary of Efficacy for trial 1104

Title: A phase II, open-label, multi-center, single-arm, monotherapy study of ibrutinib in previously treated MCL patients who were resistant or relapsed after 1 to 5 prior treatment regimens			
Study identifier	BO21004 – stage 1a		
Design	Phase II open-label, non -randomized, multicenter monotherapy study in subjects with histologically documented MCL who were resistant or relapsed after 1 to 5 prior treatment regimens Stage 1 focuses on testing if ibrutinib is clinically compelling in terms of ORR Stage 2 focuses on estimating efficacy of ibrutinib in terms of ORR		
	Duration of main phase:		115 patients receiving daily treatment until progression or unacceptable toxicity.
	Duration of Run-in phase:		N/A
	Duration of Extension phase:		N/A
Hypothesis	• Bortezomib –naïve cohort: null hypothesis that ORR≤20% • Bortezomib –exposed cohort: null hypothesis that ORR≤15%		
Treatments groups	Ibrutinib		Ibrutinib 560 mg (4 x 140-mg capsules) orally once daily
Endpoints and definitions	Primary endpoint	ORR (Inv)	Overall response rate (ORR), defined as the percent of subjects who achieved either a PR or CR, according to the revised IWG criteria for NHL (Cheson 2007), as assessed by investigators**.**
	Secondary endpoint	DOR	Duration of response (DOR) was analyzed on subjects who achieved an overall response of partial response or better and was defined as the time from first evidence of response to either progression or death due to any cause.
Database lock	26 December 2012		

Results and Analysis	
Analysis description	**Primary Analysis**
Analysis population and time point description	All treated population; 26 December 2012
Overall response rate	67.6% (58.0%, 76.1%)
Duration of response (months)[f] Median (95% CI)	17.5 (15.8, NE)
Min, Max	(0.03+, 19.58+)

Supportive studies

Study PCYC -04753 described in the dose finding section is also considered supportive for efficacy in both indications. (See Efficacy results tables 42, 43 and 44)

Study 1112; pivotal in CLL

Title: A Randomized, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib versus Ofatumumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma.

Methods:

Study Participants

Main inclusion criteria:

- Performance status of ECOG 0-1,
- active disease requiring treatment, must have received at least one prior therapy for CLL/SLL and not be appropriate for treatment or retreatment with purine analogue based therapy, defined by at least one of the following criteria:
    - a) Failure to respond (stable disease [SD] or disease progression on treatment), or a progression-free interval of less than 3 years from first dose of treatment with a purine analogue based therapy and anti-CD20 containing chemoimmunotherapy regimen after at least two cycles,
    - b) Age ≥ 70 years, who had received 1 prior treatment including at least two cycles of an alkylating-agent based (or purine analogue based) anti-CD20 antibody containing chemoimmunotherapy regimen or ≥2 prior lines of systemic therapy including chemotherapy, anti-CD20 or anti-CD52 monoclonal antibodies, or immunomodulatory therapy with lenalidomide or thalidomide,

- c) Age ≥ 65 years with co-morbidities, who had received ≥1 prior treatment including at least two cycles of an alkylating-agent based (or purine analog based) anti-CD20 antibody containing chemoimmunotherapy regimen.

- Or d) The presence of deletion 17p

Key exclusion criteria:

- Known central nervous system (CNS) lymphoma or leukemia,
- history of Richter's transformation or prolymphocytic leukemia,
- missing or incomplete documentation of cytogenetic and/or FISH results reflecting the presence or absence of 17p del,
- currently active clinically significant cardiovascular disease, history of stroke or intracranial hemorrhage within 6 months prior to enrollment, requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists, requires treatment with a strong CYP3A4/5 inhibitor.

Treatments

Ofatumumab i.v. treatment for 12 i.v. doses over 24 weeks or until disease progression or unacceptable toxicity

ibrutinib p.o. treatment of 420 mg administered orally daily to continue until disease progression or unacceptable toxicity

Duration of Treatment: Subjects randomized to ibrutinib were to receive study drug daily until disease progression or unacceptable toxicity. Subjects randomized to ofatumumab were to receive treatment for up to 12 doses (approximately 6 months), until disease progression, or unacceptable toxicity as detailed in the package insert. Subjects were planned to be followed for 3 years (until June 2015) after the first subject was enrolled.

Objectives:

Primary Objective:

To evaluate the efficacy of ibrutinib compared to ofatumumab in terms of progression-free

survival (PFS) (IRC) per International Workshop on CLL Criteria (IWCLL, Hallek 2008) with incorporation of the clarification for treatment related lymphocytosis (Hallek 2012) (hereafter referred to as IWCLL 2008 criteria) in patients with relapsed or refractory CLL.

Secondary Objectives:

- To compare efficacy between the two treatment groups in terms of: overall survival (OS)
- To evaluate IRC-assessed overall response rate (ORR) per IWCLL 2008 criteria
- To evaluate patient-reported outcome (PRO) by FACiT-Fatigue
- To evaluate haematological improvement
- To evaluate event-free survival (EFS)
- To evaluate the safety and tolerability of ibrutinib compared to ofatumumab

Outcomes/endpoints

Primary efficacy endpoint:

The primary efficacy endpoint is PFS, which is defined as the time from the date of randomization until disease progression (assessed by the IRC per IWCLL 2008 criteria) or death from any cause, whichever occurs first. Patients who withdraw from the study or are considered lost to follow-up without prior documentation of disease progression will be censored on the date of the last adequate disease assessment. For patients without an adequate post-baseline disease assessment, PFS will be censored on the date of randomization.

Secondary efficacy endpoints:

Investigator-assessed PFS is defined as time from randomization until disease progression (assessed by the Investigator per IWCLL 2008 criteria) or death from any cause, whichever occurs first. Analysis methods for Investigator-assessed PFS will be similar to those described for PFS as assessed by the IRC per IWCLL 2008 criteria.

Overall response rate (ORR) is defined as the proportion of patients who achieve a CR, CRi, nPR, or PR over the course of the study as evaluated by the IRC and the investigator. Patients who do not have any post-baseline response assessment will be considered as non-responders.

Overall survival, overall response rate per IWCLL 2008 criteria by the IRC, FACIT-Fatigue, and

Time to improvement and percentage of patients with sustained haematological improvement measured in the subset of patients with cytopenia(s) at baseline (Hgb < 11 g/dL, platelets < 100,000, or ANC < 1500 cells/µL). Sustained haematological improvement is defined as improvement in cytopenia by ≥ 50%, or Hgb ≥ 11 g/dL, ANC ≥ 1500 cells/μL, platelets ≥ 100,000 with the duration of improvement lasting for ≥ 60 days without blood transfusion or growth factors.

Sample size

The study was expected to enrol a minimum of 350 patients with study duration of 23 months including an accrual period of 13 months. A minimum of 175 patients were to be centrally randomized at 1:1 ratio to each of the 2 arms of this study. A minimum of 176 PFS events provides 90% power to detect the target hazard ratio of 0.6 based on a log-rank test and a two-sided overall significance level of 0.05 adjusting for one interim analysis. This hazard ratio corresponds to an increase in median PFS from 8 months (ofatumumab arm) to 13.31 months (ibrutinib arm).

Randomisation

Patients were randomised to ibrutinib versus ofatumumab.

The randomization was stratified by important prognostic factors in CLL/SLL: whether the subject was positive for del17p and whether the subject was refractory to purine analogues administered in combination with an anti CD20 monoclonal antibody.

Two randomization schemes were generated: one for each geographic region (US versus non-US). Under each scheme, randomization was stratified using the following factors: 1) presence versus absence of refractory disease to purine analogue and anti-CD20 containing CIT regimen, and 2) presence versus absence of del17p.

Blinding / Masking

The study was open- label.

Statistical methods

All efficacy analyses will be performed using the intent-to-treat (ITT) population. All the stratified analyses will be based on the two randomization stratification factors: 1) refractory disease (presence versus absence) to purine analogue and anti-CD20 containing chemoimmunotherapy regimen, and 2) status of 17p del (presence versus absence).

PFS as determined by the IRC will be summarized for each treatment arm using Kaplan-Meier estimates and compared using stratified log rank test.

Overall response rate (ORR) as determined by the IRC will be compared using the Cochran –Mantel -Haenzel chi-square test, stratified by the two stratification factors (refractory disease and 17p del). Overall survival will be compared using stratified log rank test. Survival rate at landmark points will be summarized based on Kaplan-Meier point estimates and compared using the standard normal Z test.

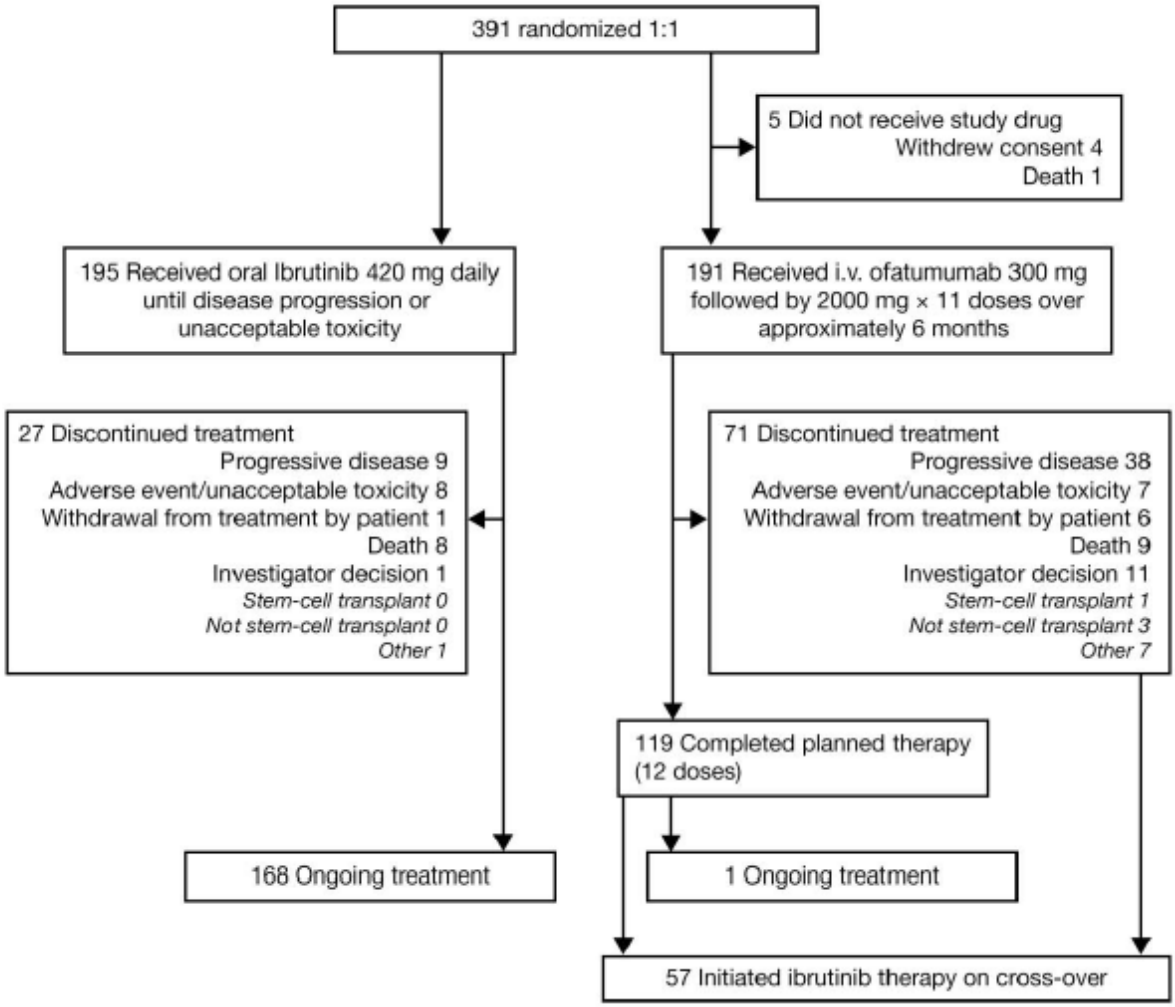
Descriptive statistics for change in scores from baseline to each assessment will be summarized for the PROs assessed by the FACiTFatigue.

Time to hematological improvement will be compared using unstratified log rank test.
A planned interim analysis for both superiority and futility (non-binding) at approximately 117 IRC-assessed PFS events, which is 66.5% of information fraction, based on a group sequential design with Lan-DeMets spending function with O'Brien-Fleming boundary was to be used.

Results

Participant flow

Figure



Recruitment

A total of 391 subjects were enrolled in the study from sites (n=67) located in the US (49.1%), Europe (43.5%), and Australia (7.4%). Study Period: 22 June 2012 (date first subject consented) to 06 November 2013 (data cutoff date).

Conduct of the study

Patient treatment and long-term follow-up is ongoing. Subjects were planned to be followed for 3 years (until June 2015) after the first subject was enrolled.

With the data cut-off of 06 November 2013 and database extract completed on 18 December 2013, the interim analysis was actually conducted with 146 PFS events representing 83% of the planned total PFS events. This interim analysis crossed the superiority boundary and therefore is considered as the final analysis for the study (see discussion on clinical efficacy), as triggered by DMC recommendation after the review of interim efficacy analysis results. Any future analyses will be considered supplemental.

Baseline data

A total of 391 subjects were enrolled in the study from sites located in the US (49.1%), Europe (43.5%), and Australia (7.4%) Total enrollment was higher than planned enrollment (N=350) in the ibrutinib arm, all 195 subjects received at least one dose of study drug. As of the data cutoff date, 27 subjects (13.8%) in the ibrutinib arm had completed/discontinued treatment; progressive disease was reported as the reason for discontinuation of treatment in 4.6% of subjects, AE in 4.1% of subjects, and death in 4.1% of subjects.

Table 29. Demographic characteristics (ITT Population)

	Ibrutinib (N=195)	Ofatumumab (N=196)	Total (N=391)
Age (Years)			
Mean (SD)	66.1 (10.15)	66.8 (8.88)	66.5 (9.53)
Median	67.0	67.0	67.0
Min, Max	30.0, 86.0	37.0, 88.0	30.0, 88.0
<65 years	77 (39.5%)	75 (38.3%)	152 (38.9%)
>=65 years	118 (60.5%)	121 (61.7%)	239 (61.1%)
Gender			
Male	129 (66.2%)	137 (69.9%)	266 (68.0%)
Female	66 (33.8%)	59 (30.1%)	125 (32.0%)
Race			
Asian	3 (1.5%)	2 (1.0%)	5 (1.3%)
Black Or African American	8 (4.1%)	9 (4.6%)	17 (4.3%)
White	174 (89.2%)	177 (90.3%)	351 (89.8%)
Multiple	1 (0.5%)	0 (0.0%)	1 (0.3%)
Patient Declined To Answer	9 (4.6%)	8 (4.1%)	17 (4.3%)

For those who discontinued due to AE, 2 (1.0%) were due to infection (*Pneumocystis jirovecii* infection and pneumonia); the remaining were single occurrences. In the ofatumumab arm, 191 subjects (97.4%) received at least one dose of study drug . Five subjects (2.6%) in the ofatumumab arm did not receive study drug: 4 withdrew consent and one died. As of the data cutoff date, 190 subjects (96.9%) had completed/discontinued treatment. Most subjects completed their planned treatment regimen. Progressive disease was reported as the reason for discontinuation of treatment in 19.4% of subjects, AE in 3.6% of subjects, and death in 4.6% of subjects.

A total of 18 subjects (9.2%) in the ibrutinib arm and 46 subjects (23.5%) in the ofatumumab arm discontinued the study. Death was the most common reason for discontinuation of study in both treatment groups (ibrutinib: 8.2%, ofatumumab: 19.4%). At the data cutoff date, 168 subjects (86.2%) in the ibrutinib arm and 1 subject (0.5%) in the ofatumumab arm were still undergoing treatment. The remaining 9 subjects (4.6%) in the ibrutinib arm and 149 subjects (76.0%) in the ofatumumab arm were in long-term follow-up. As of the data cutoff, 57 subjects (29.1%) originally randomized to ofatumumab subsequently received ibrutinib therapy.

The median (maximum) time on study was 9.6 (16.6) months for subjects in the ibrutinib arm and 9.2 (16.5) months for subjects in the ofatumumab arm.

Table 30. Baseline Disease Characteristics (ITT Population)

	Ibrutinib (N=195)	Ofatumumab (N=196)	Total (N=391)
Months from Initial Diagnosis to Randomization			
Median	92.3	90.7	91.3
Min, Max	4.9, 329.4	6.4, 345.8	4.9, 345.8
Histology at Diagnosis			
CLL	185 (94.9%)	188 (95.9%)	373 (95.4%)
SLL	10 (5.1%)	8 (4.1%)	18 (4.6%)
Rai Stage at Screening			
Stage 0	5 (2.6%)	2 (1.0%)	7 (1.8%)
Stage I	51 (26.2%)	42 (21.4%)	93 (23.8%)
Stage II	30 (15.4%)	39 (19.9%)	69 (17.6%)
Stage III	23 (11.8%)	35 (17.9%)	58 (14.8%)
Stage IV	86 (44.1%)	78 (39.8%)	164 (41.9%)
Baseline Eastern Cooperative Oncology Group (ECOG) Performance Score			
0	79 (40.5%)	80 (40.8%)	159 (40.7%)
1	116 (59.5%)	116 (59.2%)	232 (59.3%)
Bulky Disease [1]			
<5 cm	71 (36.4%)	92 (46.9%)	163 (41.7%)
>=5 cm	124 (63.6%)	101 (51.5%)	225 (57.5%)
Missing	0 (0.0)	3 (1.5%)	3 (0.8%)
Chromosome Abnormalities			
Del11q [2]			
Yes	63 (32.3%)	59 (30.1%)	122 (31.2%)
No	127 (65.1%)	132 (67.3%)	259 (66.2%)
Not Reported	5 (2.6%)	5 (2.6%)	10 (2.6%)
Del17p [3]			
Yes	63 (32.3%)	64 (32.7%)	127 (32.5%)
No	132 (67.7%)	132 (67.3%)	264 (67.5%)
Cytopenia (ANC ≤1.5 x 10^9/L, Hemoglobin ≤11g/dL, or Platelets <=100 x 10^9/L)	124 (63.6%)	123 (62.8%)	247 (63.2%)
ANC ≤1.5 x 10^9/L	41 (21.0%)	38 (19.4%)	79 (20.2%)
Hemoglobin ≤11g/dL	89 (45.6%)	86 (43.9%)	175 (44.8%)
Platelets ≤100 x 10^9/L	74 (37.9%)	64 (32.7%)	138 (35.3%)

	Ibrutinib (N=195)	Ofatumumab (N=196)	Total (N=391)

N=number of subjects in the specified population. Percentages are calculated by 100*n/N.
Baseline is defined as the last measurement taken on or prior to the first dose of study drug or the date of randomization for non-treated subjects.
[1] Based on the largest longest diameter of target lymph node at screening per the IRC assessment.
[2] Based on local lab
[3] Based on local lab captured as IWRS assignment

The presence or absence of del17p was locally evaluated in all enrolled subjects prior to randomization as one of the randomization stratification factors. Del17p was positive based on local lab/IWRS data for 32.5% of subjects. The Sponsor is also conducting central analysis (ie, Abbott CLL FISH Probe Kit) for del17p status at 3 central labs (US, EU, Australia). As of this CSR analysis, central FISH analysis results for 274 of the 391 randomized subjects were completed based on sample and processing availability. Out of 274 patient samples, 90 (32.9%) were positive for del17p.

Median time from initial diagnosis was approximately 7.5 years. Only 18 (5%) had SLL. Del 17p by local evaluation was detected in roughly a third of patients. The majority of patients had, expectedly, advanced disease with Rai stage III-IV and bulky disease. Baseline disease characteristics were generally well balanced between study arms. Comparison of the local FISH/IWRS captured results with central FISH results is ongoing, but so far indicates a good (concordance of 86%). Median number of prior therapies was 3 in the ibrutinib arm and 2 in the ofatumumab arm. The vast majority of patients had received CIT with anti-CD20. In terms of prior therapy, the ibrutinib population was slightly more exposed.

Table 31. Prior CLL/SLL Therapies (ITT Population)

	Ibrutinib (N=195)	Ofatumumab (N=196)	Total (N=391)
Number of prior CLL/SLL therapies [1]			
Median	3.0	2.0	2.0
Min, Max	1.0, 12.0	1.0, 13.0	1.0, 13.0
1	35 (17.9%)	54 (27.6%)	89 (22.8%)
2	57 (29.2%)	52 (26.5%)	109 (27.9%)
>=3	103 (52.8%)	90 (45.9%)	193 (49.4%)
Radiation Therapy			
Yes	4 (2.1)	6 (3.1)	10 (2.6)
No	191 (97.9)	190 (96.9)	381 (97.4)
Stem cell/bone marrow transplant			
Autologous	3 (1.5)	2 (1.0)	5 (1.3)
Allogeneic	3 (1.5)	1 (0.5)	4 (1.0)
Cytotoxic Therapy	190 (97.4)	189 (96.4)	379 (96.9)
Alkylating Agent	181 (92.8)	173 (88.3)	354 (90.5)
Bendamustine	84 (43.1)	73 (37.2)	157 (40.2)
Purine Analog	166 (85.1)	151 (77.0)	317 (81.1)
Immunotherapy (with monoclonal antibody)	188 (96.4)	183 (93.4)	371 (94.9)
Alemtuzumab	40 (20.5)	33 (16.8)	73 (18.7)
Anti-CD20	183 (93.8)	176 (89.8)	359 (91.8)
Chemoimmunotherapy (CIT) with any anti-CD20	174 (89.2)	167 (85.2)	341 (87.2)
Alkylating agent based	165 (84.6)	150 (76.5)	315 (80.6)
Purine analog based	139 (71.3)	130 (66.3)	269 (68.8)

Note: N=number of subjects in the specified population. Percentages are calculated by 100*n/N.
[1] Including radiation therapy, stem cell/bone marrow transplant, and drug treatment.

Numbers analysed

Table 32. Disposition of Study Treatment Phase (ITT Population)

	Ibrutinib (N=195) n (%)	Ofatumumab (N=196) n (%)	Total (N=391) n (%)
Study Treatment Phase Disposition			
Did Not Receive Study Drug	0 (0.0)	5 (2.6)	5 (1.3)
Discontinued/Completed	27 (13.8)	190 (96.9)	217 (55.5)
Ongoing	168 (86.2)	1 (0.5)	169 (43.2)
Primary Reason for Discontinuation of Study Treatment			
Progressive Disease	9 (4.6)	38 (19.4)	47 (12.0)
Adverse Event/unacceptable toxicity	8 (4.1)	7 (3.6)	15 (3.8)
Withdrawal from treatment by subject	1 (0.5)	6 (3.1)	7 (1.8)
Deaths	8 (4.1)	9 (4.6)	17 (4.3)
Investigator decision	1 (0.5)	11 (5.6)	12 (3.1)
Withdrawal Due To A New Anti-Cancer Therapy (Stem-Cell Transplant)	0 (0.0)	1 (0.5)	1 (0.3)
Withdrawal Due To A New Anti-Cancer Therapy (Not Stem-Cell Transplant)	0 (0.0)	3 (1.5)	3 (0.8)
Other	1 (0.5)	7 (3.6)	8 (2.0)
Completion of treatment regimen (ofatumumab treatment arm only)	0 (0.0)	119 (60.7)	119 (30.4)

In the ibrutinib arm, 27/195 (14%) patients discontinued treatment, mainly due to PD (5%), death (4%) and AE/toxicity (4%); 168 (86%) was still on study therapy at cutoff.

In the ofatumumab arm, 71/196 (36%) patients discontinued treatment, mainly due to PD (19%), investigator decision (6%) and death (5%); 4% discontinued treatment due AE/toxicity.

Outcomes and estimation

- **PFS**

Table 33. Progression-free Survival (ITT Population)

Progression-free Survival	Ibrutinib (N=195)	Ofatumumab (N=196)	Total (N=391)	Ibrutinib vs. Ofatumumab
Events	35 (17.9%)	111 (56.6%)	146 (37.3%)	
Disease Progression	26	93		
Death	9	18		
Censored at cut-off	160 (82.1%)	85 (43.4%)	245 (62.7%)	
Progression-free Survival (Months) [1]				
Median	NE	8.1		
Min, Max	0.03+ , 13.96+	0.03+ , 13.77		
P-value				<0.0001
Hazard Ratio (95% CI)				0.215 (0.146, 0.317)
Kaplan-Meier point estimate for PFS rate at				
6 Months	87.8%	64.6%		
12 Months	65.7%	5.9%		
18 Months	-	-		
24 Months	-	-		

Analysis is based on IRC assessment and subjects are not censored for initiation of subsequent antineoplastic treatment

[1] P-value is based on a log-rank test stratified by the two randomization stratification factors reported in the IWRS at the time of randomization. Hazard ratio is based on Cox regression model (with treatment as the only covariate) stratified by the same factors as for the p-value and is relative to ofatumumab with <1 favoring ibrutinib.
+ Indicating censored observation

Figure 8. Kaplan-Meier Curve of Progression-Free Survival (ITT population)

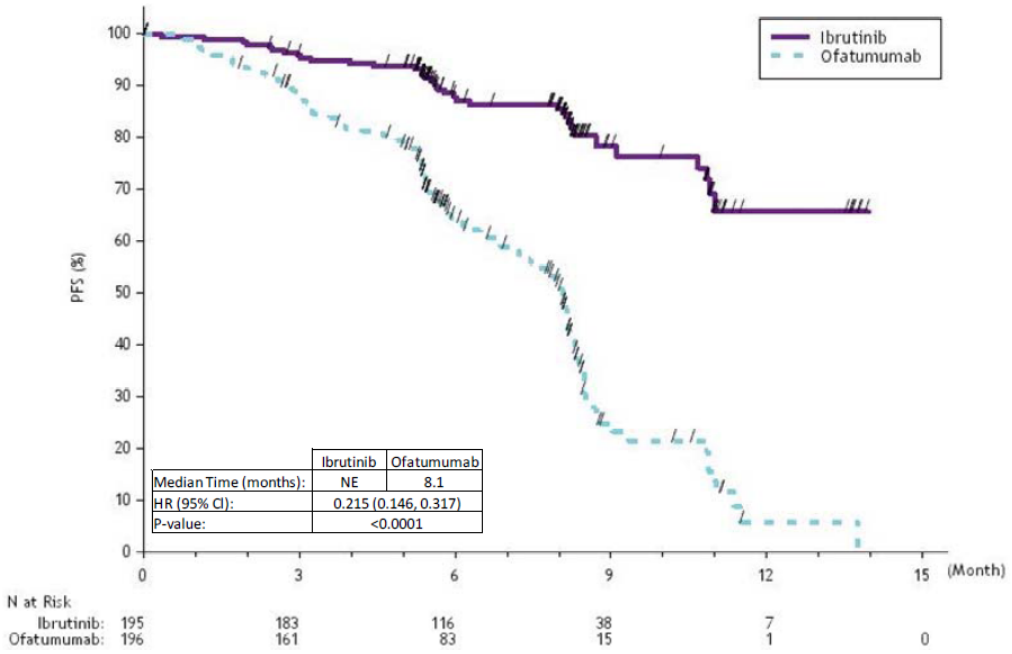


Figure 9. Kaplan-Meier Curve of Progression-Free Survival (PFS) – With del17p Stratification Factor (Based on Local FISH/IWRS) (ITT Population)

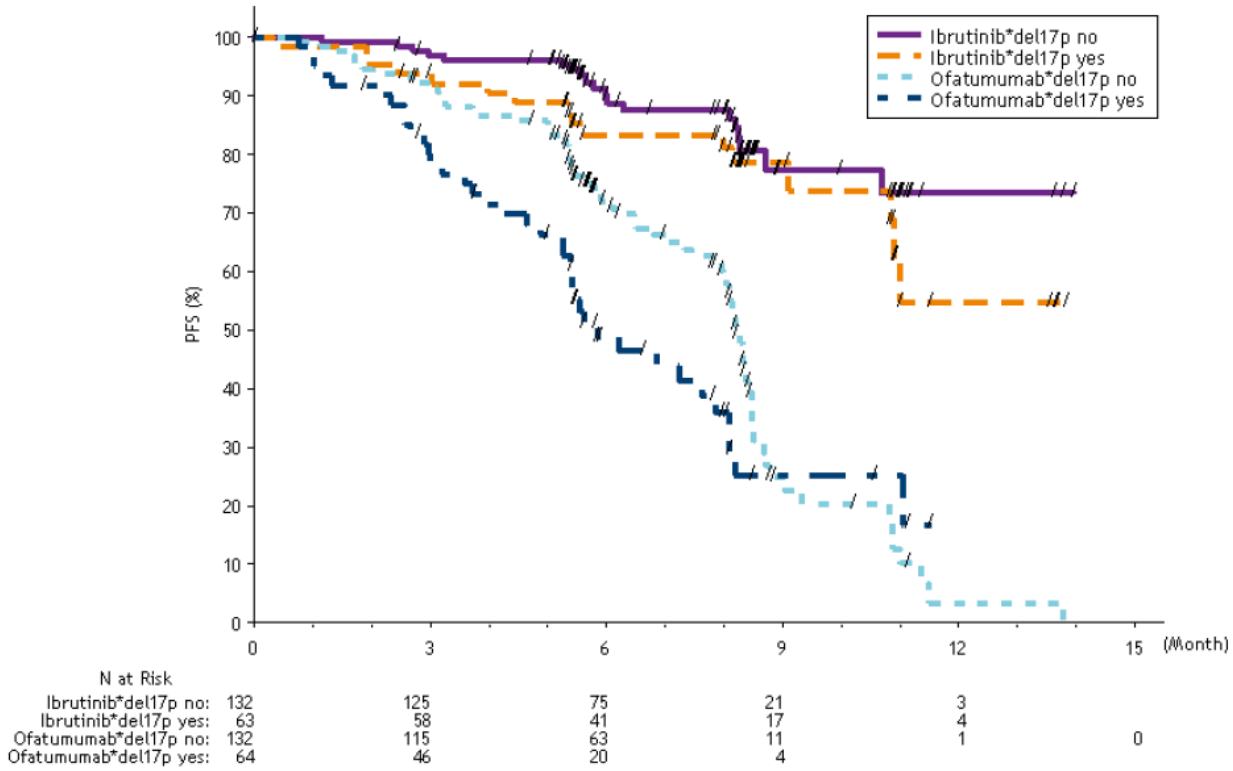
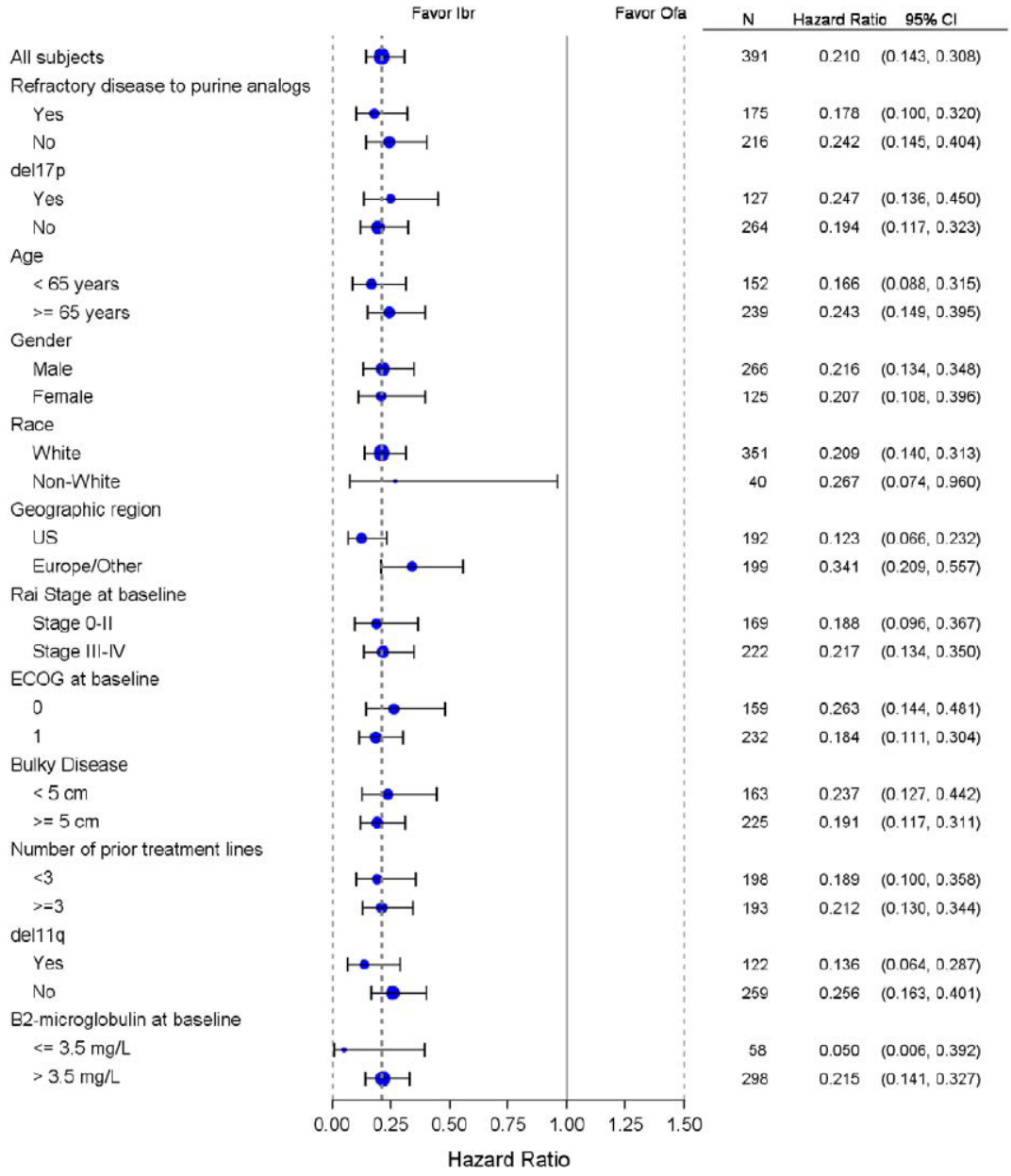


Figure 10. Forest Plot of Hazard Ratios for Progression-Free Survival (ITT Population)



The primary PFS analysis, based on IRC assessment and with no censoring for initiation of subsequent therapy, shows a large and statistically highly significant superiority for the ibrutinib arm, p <0.0001, HR = 0.215, 95% CI: 0.146, 0.317, with K-M curves separating over time. Median PFS was 8.1 months in the ofatumumab arm while not reached in the ibrutinib arm. Landmark K-M estimates at 6 month showed a PFS rate of 88% in the ibrutinib arm vs 65% in the ofatumumab arm. The robustness of the primary analysis is supported by performed sensitivity analyses and the general consistency in the subgroup analyses. The only aberrant signal noted in the subgroup analyses concerns the numerically higher HR noted in Europe/Other vs US (0.341 vs 0.123). To address this issue raised by the rapporteurs, a multivariate Cox proportional hazard analysis was employed, using a comprehensive list of baseline prognostic variables as covariates. After adjustment for the baseline covariates the HR is 0.22 (0.085, 0.564) for US and 0.20 (0.092, 0.451) for Europe/other. The selected covariates are considered clinically appropriate and while acknowledging the caveats of the presented post-hoc analysis there is no reason to anticipate major differences between the regions.

The results are based on very low event numbers, 26 disease progressions and 9 deaths in the ibrutinib arm.

PFS2

The applicant was asked by the CHMP to present data on PFS2 (defined as the time interval between randomization and progressive disease by investigator after the first subsequent therapy, death, or the start of the next subsequent therapy if no progressive disease is recorded in the ITT population), for the approximately 4% of subjects in the ibrutinib arm and 20% of subjects in the ofatumumab arm that received subsequent anti-neoplastic treatments. Analyses of PFS2 were performed in similar fashion as for the primary endpoint of PFS.

Generally, data for ibrutinib are too immature (8 patients receiving subsequent anti-neoplastic therapy, 16 events in the PFS2 analysis, and 2 events in the time on next anti-cancer therapy analysis) for a solid assessment per se. However, when comparing the 2 treatment arms, a statistically significant reduction in the risk of disease progression after 2 lines of therapy or death was noted in the ibrutinib arm (HR = 0.245, 95% CI: 0.140, 0.430), and while median PFS2 was 11.3 months for the ofatumumab arm it was not reached in the ibrutinib arm, due to a low event rate. Regarding time on next anti-cancer therapy, the median time on next therapy was 3.5 months for the 39 subjects in the ofatumumab arm but not reached in the ibrutinib patients (n=8), based on 32 and 2 events, respectively.

Collectively, available data does not indicate an adverse effect on PFS2 by ibrutinib. Updates should constitute part of the post-approval commitments.

OS

Table 34. Overall Survival (ITT Population)

Overall Survival	Ibrutinib (N=195)	Ofatumumab (N=196)	Total (N=391)	Ibrutinib vs. Ofatumumab
Deaths	16 (8.2%)	33 (16.8%)	49 (12.5%)	
Censored	179 (91.8%)	163 (83.2%)	342 (87.5%)	
Crossover	0 (0.0%)	57 (29.1%)	57 (14.6%)	
Cut-off date	179 (91.8%)	106 (54.1%)	285 (72.9%)	
Overall Survival (Months)				
Median	NE	NE		
Min, Max	0.33 , 16.62+	0.07+ , 16.49+		
P-value [1]				0.0049
Hazard Ratio (95% CI)				0.434 (0.238, 0.789)
Kaplan-Meier Point Estimate for Overall Survival Rates (%)				P-value [2]
6 Months	94.4%	87.4%		0.0167
12 Months	90.2%	81.3%		0.0283
18 Months	-	-		-
24 Months	-	-		-

[1] P-value is based on a log-rank test stratified by the two randomization stratification factors reported in the IWRS at the time of randomization. Hazard ratio is based on Cox regression model (with treatment as the only covariate) stratified by the same factors as for the p-value and is relative to ofatumumab with <1 favoring ibrutinib.
+ Indicating censored observation
[2] P-value is based on Z test

- **ORR**

Table 35. Overall Response Rate by IRC Assessment (ITT population)

	Ibrutinib (N=195)	Ofatumumab (N=196)	Ibrutinib vs. Ofatumumab P-value [1]
Overall Response Rate[2] (CR, CRi, nPR, or PR)	83 (42.6%)	8 (4.1%)	<0.0001
Overall Response Rate with PRL [2] (CR, CRi, nPR, PR, or PRL)	122 (62.6%)	8 (4.1%)	<0.0001
Best Response			
Partial response (PR)	83 (42.6%)	8 (4.1%)	
PR with lymphocytosis (PRL)	39 (20.0%)	0 (0.0%)	
Stable disease (SD)	63 (32.3%)	153 (78.1%)	
Progressive disease (PD)	5 (2.6%)	20 (10.2%)	
Not evaluable (NE)	0 (0.0%)	1 (0.5%)	
Unknown/Missing	5 (2.6%)	14 (7.1%)	

CR, CRi, nPR, and PR require confirmation with two response assessments including CT scan that were at least 56 days apart.
[1] P-value is based on Fisher's exact test.
[2] Response rate is estimated using the crude proportion of responders based on the best overall response.

Confirmed ORR per IRC was remarkably and statistically significantly higher in the ibrutinib arm, (43%), vs the ofatumumab arm (4%), p<0.0001, supported by the results of the investigator assessment. When including also PRL the results were even more pronounced, 63% vs 4%. Notably, no CR was reached in either arm.

FACIT-Fatigue

No significant difference was observed between the 2 treatment arms (p=0.8435). With this statistically non-significant result, the hierarchal testing stopped here.

Ancillary analyses

Hematologic improvement

In subjects with cytopenia at baseline, a markedly larger fraction achieved sustained haematological improvement of neutropenia or thrombocytopenia in the ibrutinib arm, 63% vs 32% and 72% vs 22%, respectively.

Summary of main efficacy results

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

Table 36. Summary of Efficacy for trial PCYC-1112

Title: A Phase 3 Study, randomized, multicenter, open-label, study of ibrutinib versus ofatumumab in subjects with relapsed or refractory CLL/SLL			
Study identifier	PCYC-1112-CA		
Design	A Randomized and stratified by known prognostic factors in CLL/SLL, Multicenter, Open-label, Phase 3 Study of the Bruton's Tyrosine Kinase (BTK) Inhibitor Ibrutinib versus Ofatumumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, comparing the efficacy and safety of ibrutinib (420 mg/day oral) with ofatumumab		
	Duration of main phase:		Planned interim analysis at approximately 117 IRC-assessed PFS events, patients treated until progressive disease or unacceptable toxicity
	Duration of Run-in phase:		
	Duration of Extension phase:		not applicable
Hypothesis	Superiority		
Treatments groups	ibrutinib		ibrutinib (420 mg/day oral)
	ofatumumab		ofatumumab (administered according to the dose and schedule per the package insert).
Endpoints and definitions	Primary endpoint	PFS (IRC)	Progression Free Survival assessed by the investigators is defined as the time from randomization to the first occurrence of progression, relapse, or death from any cause as assessed by the Independent Review Committee.
	Secondary endpoint	OS	Overall survival, defined as time from the date of randomization to the date of death from any cause
	Secondary endpoint	ORR	Overall Response Rate per IWCLL 2008 criteria by the IRC
Database lock	06 November 2013		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	With the data cut-off of 06 November 2013 and database extract completed on 18 December 2013, the interim analysis was actually conducted with 146 PFS events representing 83% of the planned total PFS events.		
Descriptive statistics and estimate variability and effect estimate per comparison	**Treatment group**	**ibrutinib**	**ofatumumab**
	Number of subject	**195**	**196**
	PFS (IRC) events (%)	35 (17.9%)	111 (56.6%)
	Median PFS in months (95% CI)	NR (0.03+, 13.96+) + indicated censored observation	8.1 (0.03+; 13.77)
	P-value (log-rank test)	< 0.0001	
	Hazard ratio (stratified)	0.215 (0.146 ; 0.317)	
	OS **Deaths (%)**	16 (8.2%)	33 (16.8%)
	Median OS in months (95% CI)	NE-	NE-
	P-value (log-rank test)	0.0049	
	Hazard ratio (stratified)	0.434	
	ORR (IRC) arm An additional 20.0% of subjects achieved a partial response in the ibrutinib arm.	(42.6%)	(4.1%).
	P-value (Chi-squared test)	<0.0001	
	Partial response with lymphocytosis (PRL)	20.0%	0%

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

Not applicable

Supportive studies

Study 1102 in CLL/SLL

Study 1102 was an open-label, non-randomized, multicenter phase Ib/II study of ibrutinib in subjects with treatment-naïve or relapsed/refractory CLL/SLL.

Study Participants

Key inclusion criteria

- **Relapsed / refractory Cohorts 1, 3, and 6 only:** Men and women 18 years of age or older with a confirmed diagnosis of relapsed/refractory CLL/SLL following previous therapy (ie, failed 2 or more previous treatments for CLL/SLL and at least 1 regimen had to have had a purine analog such as fludarabine for subjects with CLL)
- **High-risk Relapsed / refractory Cohort 4 only:** Men and women 18 years of age or older with a confirmed diagnosis of relapsed/refractory CLL/SLL with suboptimal response to at least 2 cycles of chemo-immunotherapy, defined as progression of disease within 24 months of initiation of a regimen containing a nucleoside analogue or bendamustine in combination with a monoclonal antibody or failure to respond to such a regimen
- **Treatment-naïve Cohorts 2 and 5 only:** Men and women ≥ 65 years of age with confirmed diagnosis of CLL/SLL, who require treatment per National Cancer Institute (NCI) or International Working Group guidelines
- Body weight ≥ 60 kg for any subject receiving an ibrutinib dose of 840 mg
- ECOG performance status of 0, 1, or 2

Key exclusion criteria

- Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the NYHA Functional Classification
- Malabsorption syndrome, disease significantly affecting gastrointestinal function
- Any immunotherapy, chemotherapy, radiotherapy, or experimental therapy within 4 weeks before first dose of study drug (corticosteroids for disease-related symptoms were allowed but required a 1-week washout before study drug administration)
- Concomitant use of medicines known to cause QT prolongation or torsades de pointes
- Central nervous system involvement by lymphoma
- Absolute neutrophil count (ANC) < 0.5 x 109/L or platelet count < 30 x 109/L
- Creatinine > 1.5 x institutional upper limit of normal (ULN), total bilirubin > 1.5 x ULN (unless due to Gilbert's disease), or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 x ULN unless disease related
- Significant screening ECG abnormalities including left bundle branch block, second degree AV block type II, third degree block, bradycardia, or QTc > 470 msec

- Concomitant use of warfarin
- History of Richter's transformation or prolymphocytic leukaemia

Treatments

Ibrutinib 420 mg (3 x 140 mg capsules) or 840 mg (6 x 140 mg capsules) was self-administered orally once daily, at least 2 hours after the previous meal and 30 minutes before the next meal at the same time each day.

Treatment with ibrutinib was held for any unmanageable toxicity that was either potentially study drug-related or Grade 3 or higher in severity. Study drug was held for a maximum of 28 consecutive days for toxicity; subjects were discontinued from treatment for required delays longer than 28 days.

Dose modifications were to be instituted in the following circumstances: treatment-emergent Grade 4 neutropenia for more than 7 days; Grade 3 or higher thrombocytopenia depending upon presence of bleeding; persistent Grade 3 or higher nausea, vomiting, or diarrhoea despite treatment; or any other Grade 4 or unmanageable Grade 3 toxicity. Separate instructions were provided for QTc prolongation. In subjects with baseline thrombocytopenia, dose modifications were based on percent decrease in platelets from baseline.

Subjects who required full-dose anticoagulant treatment (such as heparin or warfarin) were to have study drug temporarily suspended until on a stable anticoagulant dose. Dose reductions were to be permanent. No intrasubject dose escalation was allowed on this study.

Neutrophil growth factors were allowed. Corticosteroids (at dosages equivalent to prednisone > 20 mg/day), red blood cell growth factors, platelet growth factors, or sargramostim were prohibited.

Objectives

The primary objective of this study was to determine the safety of 2 fixed-dose daily regimens of ibrutinib in subjects with CLL/SLL.

The secondary objectives were to assess the preliminary efficacy, pharmacokinetics (including the effects of the fed-versus-fasted state), pharmacodynamics, and long-term safety of ibrutinib.

Outcomes/endpoints

Primary endpoint**:** Safety, as measured by the incidence, severity, and drug-relatedness of clinical AEs.

Secondary endpoints:

- Overall response rate: Response assessment was performed by the investigator and followed the IWCLL 2008 guidelines (Hallek 2008). For CLL subjects, treatment-related lymphocytosis was not considered progression and partial response with lymphocytosis was assessed according to clarification of the IWCLL criteria (Hallek 2012). For SLL subjects, the IWG for non-Hodgkin's Lymphoma 2007 criteria were used (Cheson 2007).
- Progression-free survival (PFS)
- Pharmacokinetics of ibrutinib and major metabolite PCI-45227
- Pharmacodynamics

- Tolerability of treatment as assessed by dose modifications due to treatment-related adverse events

Exploratory endpoints were: Identification of putative biomarkers of response, including but not limited to stimulated cytogenetics, interphase cytogenetics, IgVH mutational status, ZAP-70 methylation, CD38 expression, and serum β-2 microglobulin levels; Effects of fasted versus fed state on the pharmacokinetics of ibrutinib ; Time to response; Duration of response; Overall survival

A CT scan (with contrast unless contraindicated) was required of the chest, abdomen, and pelvis for pre-treatment tumour assessment of subjects with CLL. In addition, PET/CT was required for subjects with SLL. During treatment, the same scans were required at the end of Cycles 2, 5, 8, 12, 15, 18, 24, within 3 months prior to enrolling into the long-term extension study, or at any time to confirm progression.

Overall response assessments included investigator evaluation of radiological examination, physical examination, haematology, and, when appropriate, bone marrow results. Bone marrow aspirate/biopsy was collected pretreatment and to confirm a complete response, after which further on-treatment scans were only required to confirm disease progression. Peripheral blood and/or bone marrow aspirate/biopsy with flow cytometry assessments for minimal residual disease were also to be done in the event of a complete response.

Sample size

The sample size of 12 to 24 subjects per treatment cohort was considered sufficient to define the safety profile and pharmacokinetic characteristics of the 2 fixed-dose regimens of ibrutinib. No inferential statistical analyses were planned for this study.

Randomisation

The study was not randomised.

Blinding (masking)

N/A

Statistical methods

The following analysis sets were defined:

- Enrolled Population: All subjects who signed informed consent and were enrolled into Cohorts 1 through 5 of this study. This analysis set was used to summarize enrollment and disposition.
- All Treated Population: All enrolled subjects in Cohorts 1 through 5 who received at least 1 dose of study medication. Subjects in this population were analyzed according to the starting dose received. This analysis set was used for all efficacy and safety analyses.
- Response-evaluable Population: All enrolled subjects who received at least 1 dose of study medication and underwent at least 1 postbaseline tumour assessment. Subjects in this population were analyzed according to the starting dose received. This analysis set was used for a sensitivity analysis of tumour response rate.

- Del 17p Analysis Set: A subset of subjects from Cohorts 1 through 6 who received at least 1 dose of study medication and were positive for the del 17p by interphase cytogenetics. Safety and efficacy analyses on this subset of subjects are reported separately.

Results

Baseline data

Table 37. Baseline Demographic Characteristics: All-Treated Population -CLL/SLL

	PCYC-1102 Relapsed/Refractory			PCYC-04753 CLL/SLL
	420 mg (N=51)	840 mg (N=34)	Total (N=85)	Total (N=16)
Age (years)				
N	51	34	85	16
Mean (SD)	63.7 (11.31)	63.6 (9.28)	63.7 (10.49)	68.3 (8.35)
Median	68.0	63.5	66.0	65.5
Min, Max	37.0, 82.0	44.0, 80.0	37.0, 82.0	57.0, 82.0
Age Group				
<65 years	24 (47.1%)	18 (52.9%)	42 (49.4%)	6 (37.5%)
≥65 years	27 (52.9%)	16 (47.1%)	43 (50.6%)	10 (62.5%)
≥70 years	20 (39.2%)	10 (29.4%)	30 (35.3%)	5 (31.3%)
≥75 years	9 (17.6%)	5 (14.7%)	14 (16.5%)	5 (31.3%)
Sex				
Male	37 (72.5%)	28 (82.4%)	65 (76.5%)	12 (75.0%)
Female	14 (27.5%)	6 (17.6%)	20 (23.5%)	4 (25.0%)
Ethnicity				
Hispanic or Latino	3 (5.9%)	0	3 (3.5%)	0
Not Hispanic or Latino	48 (94.1%)	34 (100%)	82 (96.5%)	16 (100%)
Race				
Asian	0	0	0	0
Black or African-American	3 (5.9%)	1 (2.9%)	4 (4.7%)	0
White	48 (94.1%)	33 (97.1%)	81 (95.3%)	15 (93.8%)
Other	0	0	0	1 (6.3%)

Table 38. Baseline Disease Characteristics: All-Treated Population - Ibrutinib Monotherapy CLL / SLL

	PCYC-1102 Relapsed/Refractory			PCYC-04753 CLL/SLL
	420 mg (N=51)	840 mg (N=34)	Total (N=85)	Total (N=16)
Time since initial diagnosis (months)				
Mean (SD)	94.7 (62.13)	99.2 (49.09)	96.5 (57.01)	106 (78.24)
Median	80.0	98.6	88.8	93.8
Min, Max	14.2, 283.0	27.2, 232.0	14.2, 283.0	15.6, 293.6
Rai staging at baseline				
Stage 0	1 (2.0%)	1 (2.9%)	2 (2.4%)	1 (6.3%)
Stage I	15 (29.4%)	7 (20.6%)	22 (25.9%)	2 (12.5%)
Stage II	4 (7.8%)	0	4 (4.7%)	3 (18.8%)
Stage III	8 (15.7%)	2 (5.9%)	10 (11.8%)	0
Stage IV	20 (39.2%)	22 (64.7%)	42 (49.4%)	4 (25.0%)
Not Done/unknown	2 (3.9%)	0	2 (2.4%)	6 (37.5%)
Missing	1 (2.0%)	2 (5.9%)	3 (3.5%)	0
ECOG				
0	19 (37.3%)	16 (47.1%)	35 (41.2%)	9 (56.3%)
1	32 (62.7%)	16 (47.1%)	48 (56.5%)	6 (37.5%)
2	0	2 (5.9%)	2 (2.4%)	0
Diagnosis				
CLL	48 (94.1%)	33 (97.1%)	81 (95.3%)	11 (68.8%)
SLL	3 (5.9%)	1 (2.9%)	4 (4.7%)	5 (31.3%)
Chromosome abnormalities				
17p deletion Positive	18 (35.3%)	11 (32.4%)	29 (34.1%)	N/A
13q deletion Positive	23 (45.1%)	16 (47.1%)	39 (45.9%)	N/A
11q deletion Positive	16 (31.4%)	13 (38.2%)	29 (34.1%)	N/A
Trisomy 12 Positive	5 (9.8%)	5 (14.7%)	10 (11.8%)	N/A
IgVH Unmutated	38 (74.5%)	27 (79.4%)	65 (76.5%)	NA
ZAP-70 Methylated	18 (35.3%)	8 (23.5%)	26 (30.6%)	N/A
Bulky Disease Based on Largest Lymph Node				
LDi ≥5 cm	23 (45.1%)	20 (58.8%)	43 (50.6%)	N/A
LDi ≥10cm	3 (5.9%)	9 (26.5%)	12 (14.1%)	N/A
Absolute Lymphocyte Count (10^9/L)				
Mean (SD)	33.2 (55.26)	38.9 (62.12)	35.5 (57.80)	53.8 (109.8)
Median	10.8	8.4	8.9	11.7
Min, Max	0.1, 298.9	0.8, 233.6	0.1, 298.9	0.2, 439.3
Cytopenia				
ANC ≤1.5x10^9/L	14 (27.5%)	16 (47.1%)	30 (35.3%)	4 (25.0%)
HGB ≤11 g/dL	17 (33.3%)	20 (58.8%)	37 (43.5%)	4 (25.0%)
PLT ≤100x10^9/L	20 (39.2%)	23 (67.6%)	43 (50.6%)	3 (18.8%)
HGB ≤11 g/dL or PLT ≤100 x 10^9/L	26 (51.0%)	27 (79.4%)	53 (62.4%)	7 (43.8%)
Any of the above	28 (54.9%)	30 (88.2%)	58 (68.2%)	8 (50.0%)
LDH				
<350 unit/L	29 (56.9%)	16 (47.1%)	45 (52.9%)	8 (50.0%)
≥350 unit/L	22 (43.1%)	18 (52.9%)	40 (47.1%)	8 (50.0%)
Beta-2 Microglobulin (mg/L)				
≤3.0 mg/L	30 (58.8%)	11 (32.4%)	41 (48.2%)	N/A
>3.0 mg/L	18 (35.3%)	21 (61.8%)	39 (45.9%)	N/A
Missing	3 (5.9%)	2 (5.9%)	5 (5.9%)	N/A

Table 39. Prior Cancer-related Therapies: All-Treated Population - Relapsed / Refractory CLL / SLL

	PCYC-1102 Relapsed/Refractory			PCYC-04753 CLL/SLL
	420 mg (N=51)	840 mg (N=34)	Total (N=85)	Total (N=16)
Prior Surgery	0	3 (8.8%)	3 (3.5%)	3 (18.8%)
Prior Radiotherapy	6 (11.8%)	4 (11.8%)	10 (11.8%)	0
Prior Systemic Therapy	51 (100%)	34 (100%)	85 (100%)	16 (100%)
Number of prior induction/salvage therapy				
1	3 (5.9%)	0	3 (3.5%)	3 (18.8%)
2	15 (29.4%)	6 (17.6%)	21 (24.7%)	4 (25.0%)
3	6 (11.8%)	5 (14.7%)	11 (12.9%)	6 (37.5%)
≥4	27 (52.9%)	23 (67.6%)	50 (58.8%)	3 (18.8%)
Type of Prior Selected Systemic Therapy				
Nucleoside Analog	47 (92.2%)	34 (100%)	81 (95.3%)	15 (93.8%)
Rituximab	50 (98.0%)	33 (97.1%)	83 (97.6%)	15 (93.8%)
Alkylator	44 (86.3%)	32 (94.1%)	76 (89.4%)	12 (75.0%)
Bendamustine	20 (39.2%)	13 (38.2%)	33 (38.8%)	1 (6.3%)
Alemtuzumab	11 (21.6%)	7 (20.6%)	18 (21.2%)	1 (6.3%)
Ofatumumab	10 (19.6%)	12 (35.3%)	22 (25.9%)	1 (6.3%)
CAL-101 (GS1101, Idelalisib)	3 (5.9%)	2 (5.9%)	5 (5.9%)	0
Prior Bone Marrow or Stem Cell Transplant				
Autologous	0	0	0	0
Allogeneic	1 (2.0%)	3 (8.8%)	4 (4.7%)	N/A

Numbers analysed

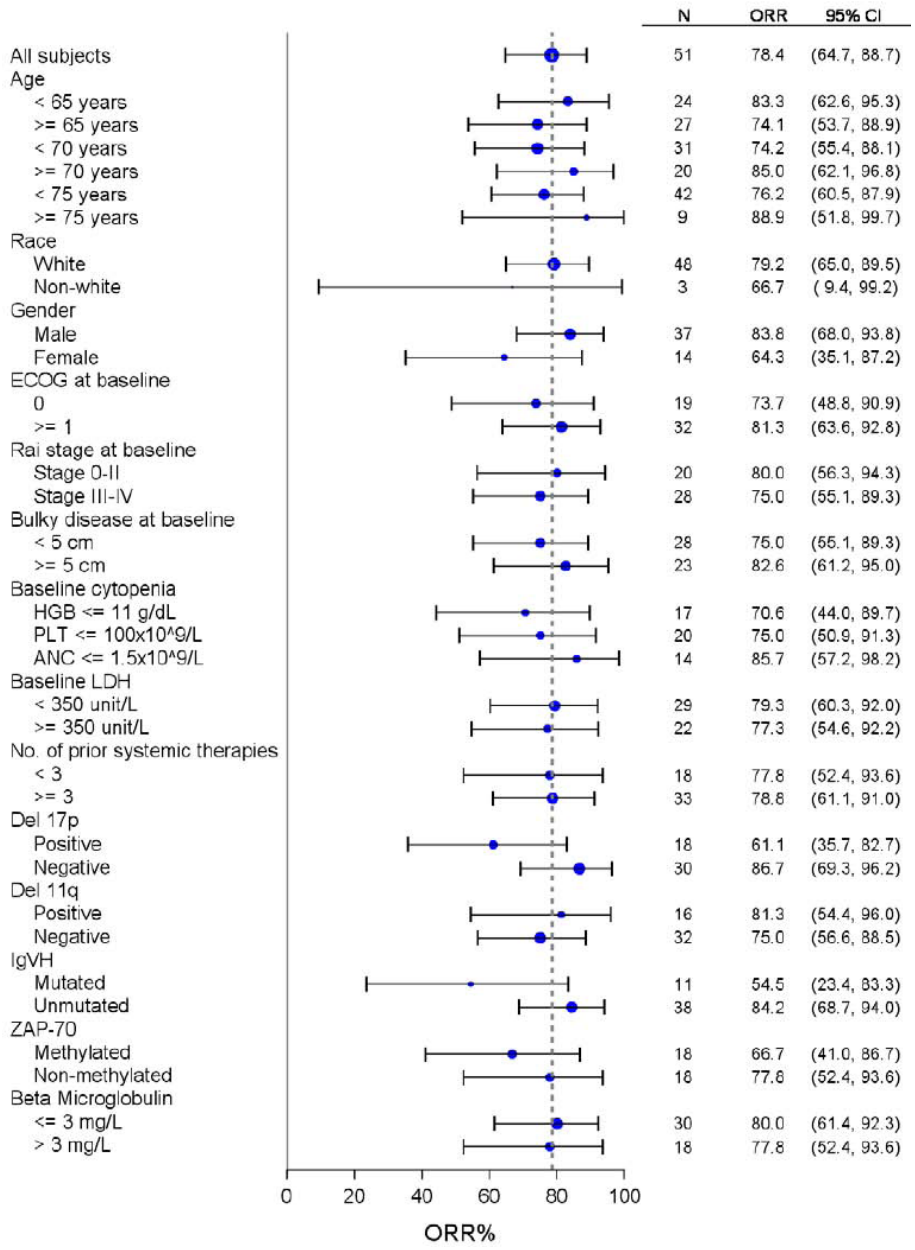
One hundred sixteen subjects were treated in 5 cohorts evaluable for primary efficacy, with primarily cohorts 1 and 4 (total n=51) supporting the application. In addition, cohort 6 recruited 16 patients for a randomized crossover substudy to assess the effects of the fed-versus-fasted state on the pharmacokinetics of ibrutinib, but due to a required shorter treatment period (6 cycles *vs* 12 or 24 cycles for cohort 1-5) this cohort was not used for efficacy analyses other than in patients with 17p deletion.

Outcomes and estimation

Table 40. Response Rate - All-Treated Population CLL/SLL

	PCYC-1102 Relapsed/Refractory			PCYC-04753 CLL/SLL
	420 mg (N=51)	840 mg (N=34)	Total (N=85)	Total (N=16)
Best Overall Response for the Study				
Complete response (CR)	2 (3.9%)	0	2 (2.4%)	2 (12.5%)
Partial response (PR)	38 (74.5%)	24 (70.6%)	62 (72.9%)	10 (62.5%)
Partial response with lymphocytosis (PRL)	7 (13.7%)	4 (11.8%)	11 (12.9%)	0
Stable disease (SD)	1 (2.0%)	3 (8.8%)	4 (4.7%)	2 (12.5%)
Progressive disease (PD)	2 (3.9%)	0	2 (2.4%)	0
Not evaluable[a] (NE)	1 (2.0%)	3 (8.8%)	4 (4.7%)	2 (12.5%)
Overall Response Rate (CR or PR)				
n (%)	40 (78.4%)	24 (70.6%)	64 (75.3%)	12 (75.0%)
95% CI[b]	(64.7%, 88.7%)	(52.5%, 84.9%)	(64.7%, 84.0%)	(47.6%, 92.7%)

Figure 11. Forest Plot for overall response rate by subgroup – relapsed / refractory CLL / SLL (420 mg dose group N = 51)



Median time to initial response in the 420 mg group, calculated as the number of months from first dose date of study treatment to first documented PR with lymphocytosis or better for subjects who achieved PR or better, was 1.8 months (range: 1.4 to 12.2 months).

The times to CR were 4.6 months and 11.2 months for the 2 subjects who achieved CR in the 420 mg dose group.

Table 41. Duration of Response: All-Treated Population CLL/SLL

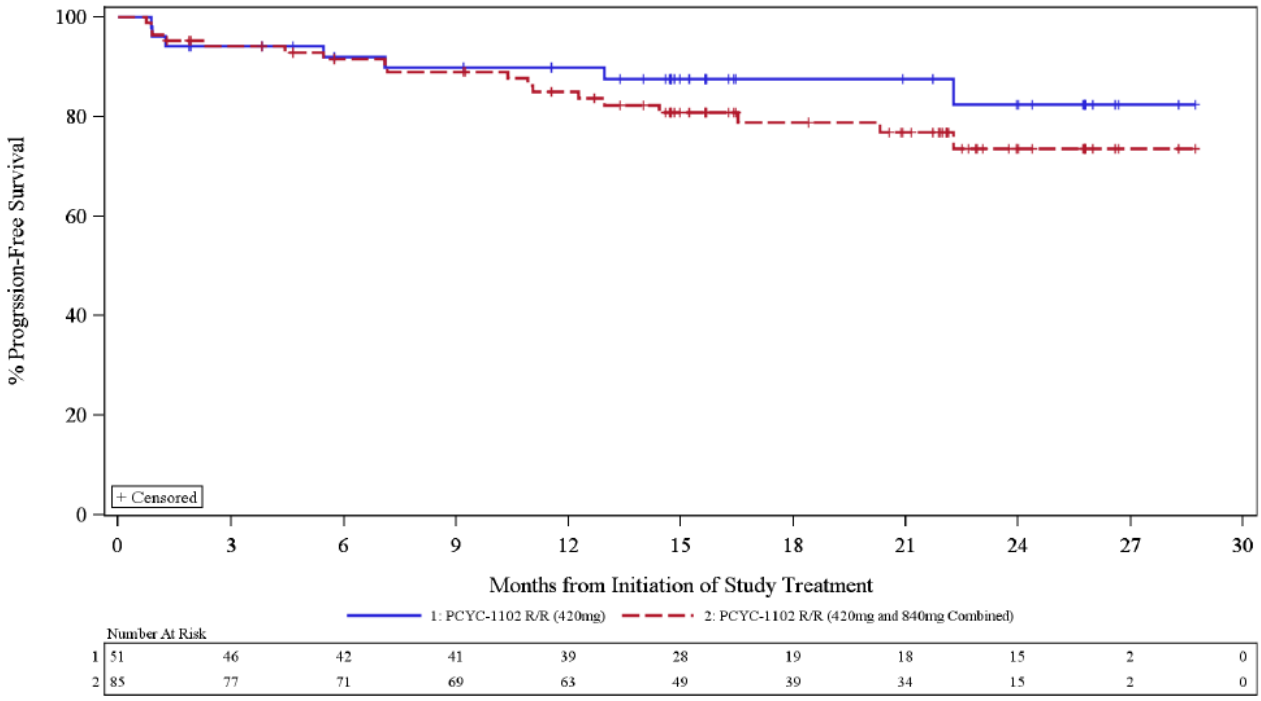
	PCYC-1102 Relapsed/Refractory			PCYC-04753 CLL/SLL
	420 mg (N=51)	840 mg (N=34)	Total (N=85)	Total (N=16)
Responders (CR+PR)	40	24	64	12
Events	3 (7.5%)	5 (20.8%)	8 (12.5%)	4 (33.3%)
Progressed	2 (5.0%)	4 (16.7%)	6 (9.4%)	4 (33.3%)
Died without documentation of progression	1 (2.5%)	1 (4.2%)	2 (3.1%)	0
Censored	37 (92.5%)	19 (79.2%)	56 (87.5%)	8 (66.7%)
Duration of response (months)[a]				
Median (95% CI)	NE (NE, NE)	NE (18.7, NE)	NE (NE, NE)	NE (2.9, NE)
Min, Max	0.03+, 26.87+	2.79+, 22.21+	0.03+, 26.87+	2.53, 16.46+
6-month event-free rate (95% CI)	97.1 (81.4, 99.6)	100 (100, 100)	98.3 (88.4, 99.8)	74.1 (39.1, 90.9)
12-month event-free rate (95% CI)	93.9 (77.7, 98.4)	90.9 (68.3, 97.6)	92.8 (82.0, 97.3)	61.7 (26.0, 84.1)
18-month event-free rate (95% CI)	87.6 (63.9, 96.2)	81.3 (57.6, 92.6)	85.2 (70.8, 92.8)	-[b]
24-month event-free rate (95% CI)	87.6 (63.9, 96.2)	-[b]	81.8 (65.9, 90.7)	-[b]

CLL=chronic lymphocytic leukemia; CR=complete response; NE=Not estimable; PR=partial response; SLL=small lymphocytic lymphoma
Note: + indicates censored observation.
Note: All percentage calculations are based on the number of subjects with response (CR+ PR).
[a] Kaplan-Meier product limit estimates.
[b] The event-free rate was not calculated if the last event was censored prior to the landmark time.

Table 42. Progression Free Survival: All-Treated Population CLL/SLL

	PCYC-1102 Relapsed/Refractory			PCYC-04753 CLL/SLL
	420 mg (N=51)	840 mg (N=34)	Total (N=85)	Total (N=16)
Subject status				
Events	7 (13.7%)	11 (32.4%)	18 (21.2%)	5 (31.3%)
Progressed	5 (9.8%)	6 (17.6%)	11 (12.9%)	4 (25.0%)
Died without documentation of progression	2 (3.9%)	5 (14.7%)	7 (8.2%)	1 (6.3%)
Censored	44 (86.3%)	23 (67.6%)	67 (78.8%)	11 (68.8%)
PFS (months)[a]				
Median (95% CI)	NE (NE, NE)	NE (16.5, NE)	NE (NE, NE)	NE (4.6, NE)
Min, Max	0.85, 28.71+	0.72, 23.95+	0.72, 28.71+	0.03+, 18.56+
6-month PFS rate (95% CI)	92.0 (80.0, 96.9)	91.0 (74.6, 97.0)	91.6 (83.1, 95.9)	80.0 (50.0, 93.1)
12-month PFS rate (95% CI)	89.8 (77.1, 95.6)	78.1 (59.4, 88.9)	85.0 (75.1, 91.2)	63.6 (32.7, 83.3)
18-month PFS rate (95% CI)	87.5 (74.2, 94.2)	68.0 (48.6, 81.4)	78.8 (67.5, 86.6)	63.6 (32.7, 83.3)
24-month PFS rate (95% CI)	82.3 (64.2, 91.8)	-[b]	73.6 (60.2, 83.1)	-[b]

Figure 12. Kaplan-Meier Curves of PFS - Subjects With r/r CLL/SLL in Study PCYC-1102

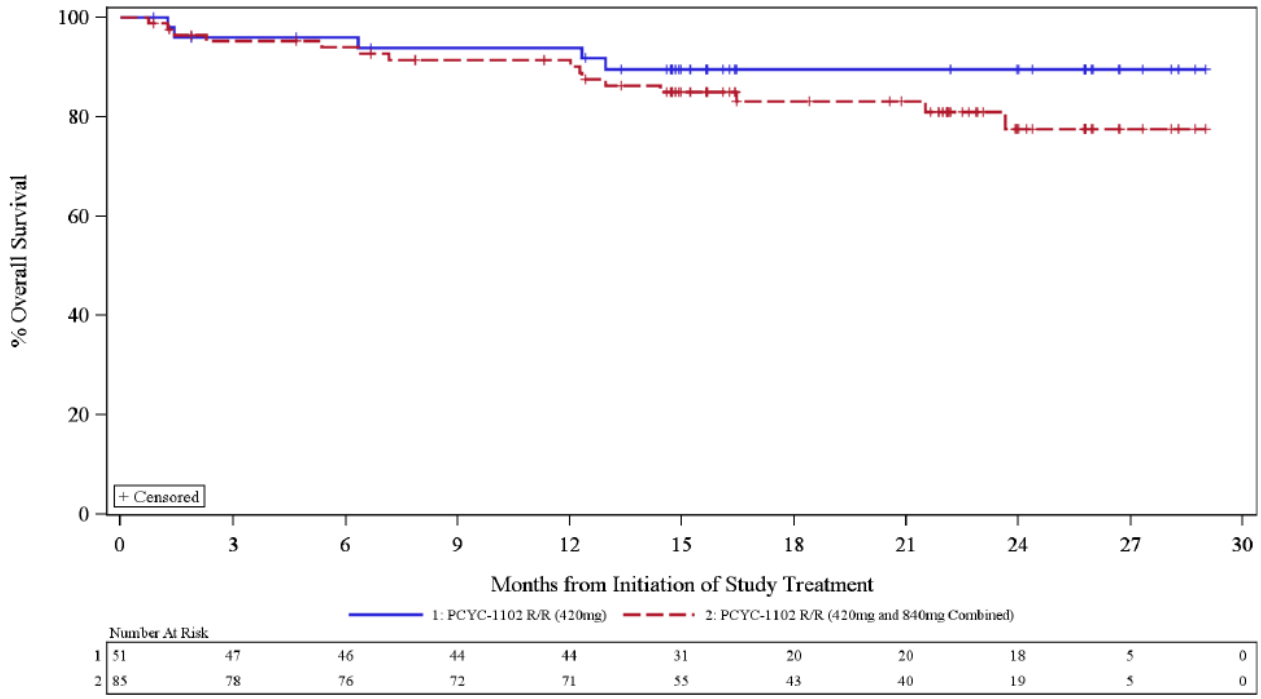


Overall survival

Table 43. Overall Survival: All-Treated Population CLL/SLL

	PCYC-1102 Relapsed/Refractory			PCYC-04753 CLL/SLL
	420 mg (N=51)	840 mg (N=34)	Total (N=85)	Total (N=16)
Subject status				
Death of any cause (event)	5 (9.8%)	10 (29.4%)	15 (17.6%)	2 (12.5%)
Censored	46 (90.2%)	24 (70.6%)	70 (82.4%)	14 (87.5%)
Overall survival (months)[a]				
Median (95% CI)	NE (NE, NE)	NE (23.7, NE)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.85+, 29.01+	0.72, 24.21+	0.72, 29.01+	0.82+, 19.88+
6-month OS rate (95% CI)	96.0 (84.9, 99.0)	91.0 (74.6, 97.0)	94.0 (86.1, 97.4)	86.7 (56.4, 96.5)
12-month OS rate (95% CI)	93.9 (82.3, 98.0)	88.0 (71.0, 95.3)	91.5 (83.0, 95.8)	86.7 (56.4, 96.5)
18-month OS rate (95% CI)	89.6 (76.8, 95.5)	74.9 (56.0, 86.6)	83.1 (72.5, 89.9)	86.7 (56.4, 96.5)
24-month OS rate (95% CI)	89.6 (76.8, 95.5)	53.4 (19.1, 78.8)	77.5 (63.9, 86.5)	-[b]

Figure 13. Kaplan-Meier Curves of OS - Subjects With r/r CLL/SLL in Study PCYC-1102



Ancillary analyses

- **Study 1102 Results in subjects with chromosome 17p deletion**

Table 44. Best Response and ORR. All Treated Population - Del17p Analysis Set

	420 mg (N=25)	840 mg (N=11)
Best Response		
Complete response (CR)	2 (8.0%)	0 (0.0%)
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)	14 (56.0%)	6 (54.5%)
PR with lymphocytosis (PRL)	6 (24.0%)	1 (9.1%)
Stable disease (SD)	1 (4.0%)	3 (27.3%)
Progressive disease (PD)	1 (4.0%)	0 (0.0%)
Not evaluable (NE)	0 (0.0%)	0 (0.0%)
Missing	1 (4.0%)	1 (9.1%)
ORR (CR+CRi+nPR+PR)	16 (64.0%)	6 (54.5%)
95% CI [1]	(42.5%,82.0%)	(23.4%,83.3%)
ORR with PRL (CR+CRi+nPR+PR+PRL)	22 (88.0%)	7 (63.6%)
95% CI [1]	(68.8%,97.5%)	(30.8%,89.1%)

With a median follow-up of 22.1 months, the median duration of response was 18.7 months for the 840-mg dose group but not reached for the 420-mg dose group. The 12-month duration of response rate for all treated subjects with del 17p was 95.2% (95% CI: 70.7, 99.3).

The median times to initial response and best response for all subjects were 1.9 months (range: 1.7 to 12.2 months) and 4.9 months (range: 1.7 to 16.6 months), respectively. The times to CR were 11.2 and 13.7 months for the 2 subjects who achieved CR.

Eleven (30.6%) subjects experienced progression events or died and the remaining 25 subjects (69.4%) had their data censored for the PFS analysis. The median PFS time was not reached. The 12-month PFS rate for all-treated subjects with del 17p was 78.2% (95% CI: 59.2, 89.1).

Ten (27.8%) subjects died and the remaining 26 (72.2%) subjects had their data censored for the overall survival analysis. The median overall survival time was not reached. The 12-month overall survival rate for all treated subjects with del 17p was 88.2% (95% CI: 71.6, 95.4).

- **Haematologic improvement**

Sustained Haematologic Improvement in r/r patients with Baseline Cytopenias (All Treated Population) was observed in 30/37 patients with anaemia (81.1%), 32/43 patients with thrombocytopenia (74.4%) 22/30 patients with neutropenia (73.3%).

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

N/A.

Clinical studies in special populations

No dedicated clinical studies were conducted in special populations. The below table provide information on the number of patients enrolled in the clinical development programme of ibrutinib by age group.

Table 45. Total Number of Subjects by Age Group for MCL and CLL/SLL

eCTD Module	Age 65-74 Number/total number (all ages) and percent	Age 75-84 Number/total number (all ages) and percent	Age 85+ Number/total number (all ages) and percent
Efficacy and Safety Studies[1] PCYC-04753 PCYC-1102-CA PCYC-1104-CA PCYC-1112-CA	279/700 (40%)	136/700 (19%)	4/700 (0.6%)
Human PD Studies	NA	NA	NA
Biopharmaceutical Studies	NA	NA	NA

1. Sum of patients involved in controlled, uncontrolled and other studies.

Supportive studies

Study PCYC -04753 described in the dose finding section is also considered supportive for efficacy in both indications. (Efficacy results tables 45, 46 and 47)

Table 46. Best Response and Overall Response Rate by Treated Cohort – Per Protocol Population

	Total N=62	1.25 mg/kg/day N=8	2.5 mg/kg/day N=6	5.0 mg/kg/day N=5	8.3 mg/kg/day N=8	12.5 mg/kg/day N=7	8.3 mg/kg/day cts N=9	560 mg/day cts N=9	560 mg/day DLBCL N=10
Complete response(CR)	10 (16.1%)	0 (0.0%)	1 (16.7%)	2 (40.0%)	3 (37.5%)	0 (0.0%)	1 (11.1%)	1 (11.1%)	2 (20.0%)
Partial response(PR)	23 (37.1%)	2 (25.0%)	3 (50.0%)	1 (20.0%)	1 (12.5%)	5 (71.4%)	5 (55.6%)	5 (55.6%)	1 (10.0%)
Stable disease(SD)	15 (24.2%)	2 (25.0%)	1 (16.7%)	1 (20.0%)	3 (37.5%)	2 (28.6%)	2 (22.2%)	2 (22.2%)	2 (20.0%)
Progressive disease(PD)	14 (22.6%)	4 (50.0%)	1 (16.7%)	1 (20.0%)	1 (12.5%)	0 (0.0%)	1 (11.1%)	1 (11.1%)	5 (50.0%)
Overall response rate	33 (53.2%)	2 (25.0%)	4 (66.7%)	3 (60.0%)	4 (50.0%)	5 (71.4%)	6 (66.7%)	6 (66.7%)	3 (30.0%)
95% CI[b]	(40.8%, 65.6%)	(0.0%, 55.0%)	(28.9%, 100%)	(17.1%, 100%)	(15.4%, 84.6%)	(38.0%, 100%)	(35.9%, 97.5%)	(35.9%, 97.5%)	(1.6%, 58.4%)

Table 47. Best Response and Overall Response Rate by Histology – Per Protocol Population

	CLL/SLL	MCL	DLBCL	FL	WM	Other Indolent NHL	Total
Per protocol population[a]	N=14	N=9	N=17	N=15	N=4	N=3	N=62
Complete response (CR)	2 (14.3%)	3 (33.3%)	2 (11.8%)	3 (20.0%)	0 (0.0%)	0 (0.0%)	10 (16.1%)
Partial response (PR)	10 (71.4%)	4 (44.4%)	3 (17.6%)	3 (20.0%)	2 (50.0%)	1 (33.3%)	23 (37.1%)
Stable disease (SD)	2 (14.3%)	1 (11.1%)	3 (17.6%)	6 (40.0%)	2 (50.0%)	1 (33.3%)	15 (24.2%)
Progressive disease (PD)	0 (0.0%)	1 (11.1%)	9 (52.9%)	3 (20.0%)	0 (0.0%)	1 (33.3%)	14 (22.6%)
Overall response rate	12 (85.7%)	7 (77.8%)	5 (29.4%)	6 (40.0%)	2 (50.0%)	1 (33.3%)	33 (53.2%)
95% CI[3]	(67.4%, 100%)	(50.6%, 100%)	(7.8%, 51.1%)	(15.2%, 64.8%)	(1.0%, 99.0%)	(0.0%, 86.7%)	(40.8%, 65.6%)

Table 48. Progression-free Survival by Histology – Per Protocol Population

	CLL/SLL	MCL	DLBCL	FL	WM	Other Indolent NHL	Total
Per Protocol Population[a]	N=14	N=9	N=17	N=15	N=4	N=3	N=62
Censored[b]	10 (71.4%)	6 (66.7%)	3 (17.6%)	8 (53.3%)	4 (100%)	0 (0.0%)	31 (50.0%)
Progressive disease or death	4 (28.6%)	3 (33.3%)	14 (82.4%)	7 (46.7%)	0 (0.0%)	3 (100%)	31 (50.0%)
Median PFS (months)[c]	NE	11.6	1.9	13.4	NE	7.0	9.2
95% CI	(8.6, NE)	(1.5, NE)	(0.7, 4.6)	(2.2, NE)	(NE, NE)	(2.1, 9.0)	(6.3, NE)

2.8.3. Discussion on clinical efficacy

Design and conduct of clinical studies

MCL

The efficacy evaluation is based on uncontrolled phase II data. The database is adequate in the context of the disease. Subject enrollment was non-randomized and based on prior bortezomib exposure. Efficacy was to be evaluated by the ORR based on investigator assessments, which was defined as the proportion of subjects achieving either a CR or a PR according to the revised IWG criteria for NHL. Duration of response for subjects achieving a response, PFS, and overall survival were to be assessed as secondary endpoints. In addition, response was to be confirmed by independent response assessment, as part of an exploratory analysis. There are no concerns regarding the design of the study, the patient population included or the presentation and interpretation of the efficacy data. The primary endpoint of ORR is considered clinically relevant and the response appears to be independent of relevant clinical characteristics such as age, sex, geographic region, number of prior treatments, prior bortezomib exposure, prior lenalidomide therapy, baseline ECOG score, and high-risk features including simplified high MIPI score, baseline refractory disease, or blastoid histology.

CLL

In the initially presented dossier, study 1102 was presented as the main study; the results of the interim analysis of 1112 were available during the procedure as part of the responses to the CHMP List of Questions.

CHMP advice was sought on the design and methodology of study PCYC-1112. The Advice received was followed by the applicant. With regard to defining the population, and according to the ESMO Clinical Practice Guideline (Eichhorst 2011), the decision on re-treatment is influenced by the fact of prior monotherapy or chemo-immunotherapy. It is accepted that patients with del17p do respond poorly to fludarabine-based therapy and that this cytogenetic abnormality is an important prognostic factor, and hence the proposed stratification on deletion status of 17p as a major prognostic factor is agreed upon. Patients who were negative in historical samples would have del17p FISH test repeated prior to randomisation. Prior treatment lines were recorded to enable evaluation of subgroups based on prior therapies, e.g. rituximab, bendamustine. Considering that the inclusion criteria define a population unfit for fludarabine as well as patients with prior fludarabine exposure and poor or short response, acknowledging that alemtuzumab has currently a limited use in CLL and is probably too toxic for elderly patients and that bendamustine is also quite toxic and not approved for second-line therapy, ofatumumab was considered an acceptable comparator.

The choice of progression-free survival (PFS) as primary endpoint is considered acceptable for the demonstration of clinical benefit in the proposed population, in accordance with existing guidelines, provided mature data are available at the time of analysis. Use of the IWCLL 2008 criteria for response was supported, as well as the schedule of response assessments.

In addition to the sensitivity analysis that addresses the influence of start of subsequent anti-leukaemia, sensitivity analyses addressing the influence of sources of missing data such as withdrawal of consent, loss of follow-up or missed scheduled visits, and analyses addressing detection of progression in unscheduled visits were pre-specified. The OS analysis was anticipated to be likely immature at the time of the planned interim analysis.

Efficacy data and additional analyses

MCL

The efficacy evaluation is based on data from the pivotal phase II study 1104 (n=111) and the supportive study 04753 (n=5 with the 520 mg daily dose), both single arm trials. With the limitations of uncontrolled data acknowledged, the robustness of the 1104 study is not challenged and, looking at the population under study, data should be roughly representative for the general population with r/r MCL.
ORR by investigator assessment, the primary endpoint in study 1104, was 67.6% with CR in 20.7%. This result was highly concordant with that obtained by the ICR. In addition, stable disease was noted in16 patients (14.4%), ending up to a disease control rate of 82% (91/111) at the study cut-off. With caution for some groups with small subject numbers, the treatment effect seemed fairly consistent throughout the analysed subgroups, including region, relapsed or refractory disease, bulky disease, number of prior regimens, simplified MIPI score, and prior therapy with bortezomib or lenalidomide. The median times to initial and complete responses were 1.9 and 5.5 months, respectively.

In an update on time-dependent outcomes provided during the procedure, based on final database lock of 14 March 2014, more mature data on duration of response, PFS, and OS was received. As of the data update, the median time on study for the 111 treated subjects was 26.7 months (range, 1.9, 32.5) compared with 15.3 months (range, 1.9 to 22.3 months) at the CSR cut-off. With the new cut-off, the median duration of response was unchanged, 17.5 months, median PFS 13.0 months (95% CI: 7.0, 28.7+) with 34% of subjects censored as compared to 13.9 months (95% CI: 7.0, not estimable) with 49% of subjects censored at the CSR cut-off, and median OS 22.5 months (95% CI: 13.73, not estimable) with 49% deaths as compared to not reached with 37% deaths at the CSR cut-off. For OS, approximately 50% of the survivors were censored due to treatment in the extension study. In summary, with more mature data, enough reassurance is provided on the sustained activity of ibrutinib in this indication.

From a historical perspective these results must be considered outstanding as responses of this magnitude have not been reported with other available monotherapies for R/R MCL.

A randomised trial in r/r MCL is currently ongoing, evaluating ibrutinib vs temsirolimus, and results will be provided post-approval as agreed. This is a Phase 3; Randomised, controlled, open-label, multicentre; in patients with relapsed/ refractory MCL who have received at least 1 prior rituximab-containing chemotherapy regimen (including analysis of treatment –related lymphocytosis). Time-dependent outcome measures for groups with and without treatment-related lymphocytosis will be presented.

CLL

In the data initially submitted, the efficacy evaluation in r/r CLL/SLL was primarily based on uncontrolled data in 51 subjects with the intended 420 mg daily dose in the pivotal phase Ib/II study 1102, (where efficacy was secondary endpoint) with support from data in 34 patients treated with 840 mg daily, and 16 subjects with various doses of study drug in study 04753. Additional analyses were presented for a population with del17p and are based on a heterogeneous population within the 1102 study: 36 subjects from Cohorts 1 through 6, whereof 2 were treatment-naïve (Cohort 2), and 5 subjects were from the food-effect cohort, Cohort 6; 25 subjects received 420 mg ibrutinib daily. All del17p patients had CLL. The median time since diagnosis was 78.4 months. Rai classification was high-risk for 61.1% of subjects. The median number of prior therapies was 4.0 in the subset of patients with r/r disease.

ORR by investigator assessment in the 420 mg daily dose group of study 1102 was 78.4% (including CR 3.9%). In addition, best response of PR with lymphocytosis was reported in 7 subjects;. Median time to first documented PR with lymphocytosis or better for subjects who achieved PR or better in the 420 mg group was 1.8 months (range: 1.4 to 12.2 months). An IRC review of responses was conducted, at FDA request, which was presented in the day 120 response. In this analysis, ORR was lower, 65%, and no patient had CR confirmed by IRC. The median PFS is not reached with median follow-up time of 16.4 months. The 24 month PFS rate is 82%. For the 36 del17p patients, ORR by investigator assessment is 61%. The median PFS is not reached with median follow-up time of 22.1 months. The 24 months PFS rate is 55%.

As part of the day 120 response the interim analysis report for the randomised study 1112, comparing ibrutinib (n=195) vs ofatumumab (n=196) in patients with r/r not appropriate for purine analogue based therapy, was provided. The study is considered well-conducted but was terminated early, at 146 PFS events, due to a positive interim analysis, with a median time on study at 9.6 and 9.2 months for the ibrutinib and ofatumumab arms, respectively. The primary PFS analysis, based on IRC assessment, shows a large and statistically highly significant superiority for the ibrutinib arm, $p < 0.0001$, HR = 0.215, 95% CI: 0.146, 0.317. Median PFS was 8.1 months in the ofatumumab arm while not reached in the ibrutinib arm. Kaplan - Meier estimates at 6 months showed a PFS rate of 88% in the ibrutinib arm vs 65% in the ofatumumab arm.

The robustness of the primary analysis is supported by performed sensitivity analyses and the general consistency in the subgroup analyses. Importantly, outcome in patients with and without del 17p in the ibrutinib arm was similar, seen also for refractoriness to purine analogue . These results are, however, based on only 26 disease progressions and 9 deaths in the ibrutinib arm, and further follow-up is needed. Data on OS were still immature, HR of 0.434 (95% CI: 0.238, 0.789), p=0.0049. Confirmed ORR per IRC was remarkably and statistically significantly higher in the ibrutinib arm, (43%), vs the ofatumumab arm (4%), $p<0.0001$, supported by the results of the investigator assessment. In addition a further 30% of subjects achived PRL on the ibrutinib arm. In subjects with cytopenia at baseline, a markedly larger fraction achieved sustained haematological improvement of neutropenia or thrombocytopenia in the ibrutinib arm, 63% vs 32% and 72% vs 22%, respectively; a clinically relevant finding.

These results are robust and convincing, with a p-value of 0.0049 and a HR of 0.434 (95% CI: 0.238, 0.789) in the primary analysis, and supportive sensitivity analyses and a relatively consistent result across subgroups. Future study updates will be impacted by the effect of cross-over.

2.8.4. Conclusions on the clinical efficacy

Initially the MAH requested a conditional MA as on the basis on the available data at the time of the submission. However with the availability of the updates of trial 1104 where a consistent effect in terms of responses and duration of response is noted in MCL and the data made available during the procedure from the interim analysis of study 1112 in CLL, the CHMP agreed that enough reassurance was provided to support the clinical efficacy of ibrutinib in the CLL and MCL indications as described in the SmPC.

The CHMP considers the following measures necessary to address issues related to efficacy:

- Submission of the MCL3001 study report
- Yearly updates of study 1112 results for progression and death should be provided until maturity in the ibrutinib arm, e.g. 70%, and preferably also include PFS2, or, at least, time on next therapy.

The CHMP also recommended that reports from studies on potential predictive biomarkers and mechanisms of resistance should be submitted when completed.

2.9. Clinical safety

Patient exposure

MCL

In MCL the cumulative data from study 1104 as of 15 May 2013 were integrated with data from 9 subjects treated in study 04753, comprising a safety population of 120 subjects with r/r MCL. The median duration on treatment for the integrated population was 8.3 months (range 0.7, 24.8). A total of 53 (44%) subjects received more than 12 months of treatment. Median cumulative dose was 125.2 g (range, 11.8, 411.6); median dose intensity was 98.2% (factoring in dose reductions and missed doses).

Table 49. Iburitinib Exposure for Subjects with MCL (Studies 1104 and 04753)

	PCYC-1104 (N=111)	PCYC-04753 (N=9)	Total (N=120)
Treatment Duration (months)			
Mean (SD)	11.2 (8.0)	9.7 (4.9)	11.1 (7.8)
Median	8.3	9.0	8.3
Min, Max	0.7, 24.8	1.3, 18.4	0.7, 24.8
Total Cumulative Dose Received (grams)			
Mean (SD)	176.3 (127.4)	97.0 (65.9)	170.4 (125.4)
Median	128.2	116.5	125.2
Min, Max	11.8, 411.6	17.8, 191.9	11.8, 411.6
Average Daily Dose (mg/day)			
Mean (SD)	521.0 (59.5)	425.4 (244.0)	513.9 (89.0)
Median	549.9	560.0	550.2
Min, Max	277.7, 566.7	80.0, 708.3	80.0, 708.3
Relative Dose Intensity [a] (%)			
Mean (SD)	93.0 (10.6)	98.6 (1.7)	93.5 (10.3)
Median	98.2	99.1	98.2
Min, Max	49.6, 101.2	95.3, 100.0	49.6, 101.2
Number of Dose Reduction[b]			
1	11 (10%)	NA	NA
2	7 (6%)	NA	NA

MCL=mantle cell lymphoma

[a.] Relative dose intensity (%) is calculated as the percentage of total cumulative dose received/planned total cumulative dose during the treatment

[b.] Dose reductions due to investigator decision; does not include inadvertent short-term underdosing. Dose reductions were not permitted in Study 04753.

NA: Not Applicable or data were not collected

CLL

The integrated CLL safety population presented represented 117 subjects with relapsed or refractory CLL/SLL: data from 101 subjects treated in Study 1102 (were integrated with data from 16 subjects treated in Study 04753. Median duration on treatment for the CLL/SLL population was 14.7 months (range, 0.3, 28.7). Median cumulative dose was 188.6 g (range, 3.6, 609.8). The median dose intensity across subjects was 99.1%.

Table 50.

Table 51. Ibrutinib exposure in CLL studies 1102 and 04753

	PCYC-1102 (N = 101)	PCYC-04753 (N = 16)	Total (N = 117)
Cumulative ibrutinib dose, g			
Mean (SD)	242.0 (176.5)	156.7 (114.9)	230.3 (171.5)
Median	188.6	174.2	188.6
Range	4.2, 609.8	3.6, 308.2	3.6, 609.8
Duration on treatment, months			
Mean (SD)	14.7 (8.3)	9.0 (5.3)	13.9 (8.2)
Median	15.0	9.9	14.7
Range	0.3, 28.7	0.5, 18.4	0.3, 28.7
Relative dose intensity, %			
Mean (SD)	95.0 (9.7)	97.5 (5.5)	95.3 (9.3)
Median	99.1	99.8	99.1
Range	33.5, 100.0	78.6, 100.9	33.5, 100.9
Subjects with ≥ 1 dose reductions, n (%)[a]	13 (12.9)	-	-

CLL=chronic lymphocytic leukemia; SLL=small lymphocytic lymphoma

[a] Dose reductions due to investigator decision; does not include inadvertent short-term underdosing. Dose reductions were not permitted in Study 04753.

AdditionaL safety data were obtained in the randomised 1112 study (CLL/SLL). The median duration of ibrutinib exposure was 8.6 months (range: 0.2 to 16.1) and 5.3 months (range: 0.0 to 7.4) for ofatumumab. In study 1102 the median duration on treatment for the integrated population was 14.7 months (range 0.3, 28.7). At the study cut-off, 78 (67%) subjects in the integrated population were continuing treatment. A total of 67 (57%) subjects received more than 12 months of treatment.

Adverse events

MCL

Table 52. Overall safety summary of subjects with MCL (Studies 1104 and 04753.

	All Subjects (N=120) n (%)
Any AE	119 (99.2)
Grade>=3	92 (76.7)
Any Related AE	108 (90.0)
Grade>=3	52 (43.3)
Any SAE	71 (59.2)
Grade>=3	62 (51.7)
Any Related SAE	29 (24.2)
Grade>=3	26 (21.7)
AE Leading to Study Drug Discontinuation	14 (11.7)[a]
All reported death	46 (38.3)
Death during treatment or within 30 days of last dose	17 (14.2)

AE=adverse event; MCL=mantle cell lymphoma; SAE=serious adverse event

[a] This total does not include 1 subject who had an AE leading to discontinuation more than 30 days after last dose of drug.

Table 53. AEs Occurring in 10% or More Subjects with MCL by SOC (Studies 1104 and 04753)

System Organ Class MedDRA Preferred Term	All Subjects (N=120) Any Grade n (%)	 Grade 3 + 4 n (%)
Subjects with an event	119 (99.2)	75 (62.5)
Blood and lymphatic system disorders	53 (44.2)	37 (30.8)
Thrombocytopenia	24 (20.0)	14 (11.7)
Neutropenia	22 (18.3)	20 (16.7)
Anaemia	18 (15.0)	11 (9.2)
Gastrointestinal disorders	100 (83.3)	14 (11.7)
Diarrhoea	63 (52.5)	6 (5.0)
Nausea	38 (31.7)	1 (0.8)
Constipation	32 (26.7)	0 (0.0)
Vomiting	28 (23.3)	0 (0.0)
Abdominal pain	21 (17.5)	6 (5.0)
Dyspepsia	14 (11.7)	0 (0.0)
Stomatitis	14 (11.7)	1 (0.8)
General disorders and administration site conditions	88 (73.3)	13 (10.8)
Fatigue	52 (43.3)	5 (4.2)
Oedema peripheral	34 (28.3)	2 (1.7)
Pyrexia	23 (19.2)	1 (0.8)
Asthenia	15 (12.5)	4 (3.3)
Infections and infestations	91 (75.8)	26 (21.7)
Upper respiratory tract infection	29 (24.2)	0 (0.0)
Sinusitis	17 (14.2)	1 (0.8)
Urinary tract infection	16 (13.3)	3 (2.5)
Pneumonia	14 (11.7)	6 (5.0)
Injury, poisoning and procedural complications	39 (32.5)	5 (4.2)
Contusion	21 (17.5)	0 (0.0)
Metabolism and nutrition disorders	65 (54.2)	16 (13.3)
Decreased appetite	28 (23.3)	2 (1.7)
Hyperuricaemia	19 (15.8)	5 (4.2)
Dehydration	16 (13.3)	4 (3.3)
Musculoskeletal and connective tissue disorders	70 (58.3)	5 (4.2)
Muscle spasms	20 (16.7)	0 (0.0)
Myalgia	19 (15.8)	0 (0.0)
Arthralgia	16 (13.3)	0 (0.0)
Back pain	16 (13.3)	1 (0.8)
Pain in extremity	15 (12.5)	0 (0.0)
Nervous system disorders	50 (41.7)	3 (2.5)
Dizziness	18 (15.0)	0 (0.0)
Headache	15 (12.5)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	66 (55.0)	8 (6.7)
Dyspnoea	31 (25.8)	4 (3.3)
Cough	24 (20.0)	0 (0.0)
Epistaxis	12 (10.0)	0 (0.0)
Oropharyngeal pain	12 (10.0)	0 (0.0)
Skin and subcutaneous tissue disorders	82 (68.3)	4 (3.3)
Rash	18 (15.0)	2 (1.7)

The most commonly reported SOCs were gastrointestinal disorders (83.3%), infections and infestations (75.8%), and general disorders and administrative site conditions (73.3%). The most commonly reported grade 3-4 SOCs were blood and lymphatic system disorders (30.8%), infections and infestations (21.7%), metabolism and nutrition disorders (13.3%), and gastrointestinal disorders (11.7%).

The most commonly reported events were diarrhoea (52.5%), fatigue (43.3%), nausea (31.7%), peripheral oedema (28.3%), constipation (26.7%), and dyspnoea (25.8%). The most commonly reported grade 3-4 events were neutropenia (16.7%), thrombocytopenia (11.7%), anaemia (9.2%), diarrhoea (5.0%), abdominal pain (5.0%), and pneumonia (5.0%).

Adverse Events leading to treatment discontinuation:

Fourteen of the 15 patients (12.5%) that discontinued treatment due to AE did so within 30 days of last dose of study drug; out of these, 9 (7.5%) were not related to disease progression. The only event not related to MCL/progression occurring twice was subdural hematoma (1.7%). Two patients discontinued treatment due to infection-related events. No clear pattern in terms of time on treatment before discontinuation is noted. Ten of the 15 patients discontinuing treatment had achieved PR. Overall, 12.5% discontinuations due to AE, 7.5% not related to disease progression, is considered a relatively low rate, indicating that side effects generally were clinically manageable.

Adverse Events leading to dose reduction:

Fourteen percent of patients in study 1104 had the dose reduced due to AE. The only events >2% leading to dose reduction were: neutropenia (grade 3-4, 4.5%) and diarrhoea (grade 3-4, 2.7%).

Adverse Events over time:

Importantly, the incidence of new-onset AEs all grade and grade ≥3 was highest during the first cycle and generally decreased over time through cycle 1 to 16. This trend was clear for diarrhoea and also infections showed a globally slightly decreasing incidence over time

CLL

Table 54. Overall Safety Summary for Subjects with CLL/SLL (Studies 1102 and 04753)

	Total (N = 117) n (%)
Subjects with 1 or more adverse event	
Any	117 (100.0)
Grade 3 or higher	81 (69.2)
Subjects with an ibrutinib-related event	
Any	105 (89.7)
Grade 3 or higher	30 (25.6)
Subjects with a serious event	
Any	67 (57.3)
Ibrutinib-related	10 (8.5)
Subjects with an event leading to ibrutinib discontinuation	13 (11.1)
Deaths during treatment or within 30 days of last dose of ibrutinib	9 (7.7)

CLL=chronic lymphocytic leukemia; SLL=small lymphocytic lymphoma

Table 55. Adverse Events Occuring in 10% or More Subjects with CLL/SLL by System Organ Class (Studies 1102 and 04753).

		Total (N = 117)	
System Organ Class	Preferred term	All, n (%)	Grade 3/4, n (%)
Blood and lymphatic system disorders	Neutropenia	18 (15.4)	15 (12.8)
	Anemia	17 (14.5)	2 (1.7)
Gastrointestinal disorders	Diarrhea	64 (54.7)	4 (3.4)
	Constipation	21 (17.9)	1 (0.9)
	Vomiting	21 (17.9)	1 (0.9)
	Nausea	20 (17.1)	1 (0.9)
	Abdominal pain	13 (11.1)	2 (1.7)
	Stomatitis	12 (10.3)	0 (0.0)
General disorders and administration site conditions	Fatigue	38 (32.5)	5 (4.3)
	Pyrexia	30 (25.6)	3 (2.6)
	Edema peripheral	28 (23.9)	0 (0.0)
	Chills	17 (14.5)	0 (0.0)
Infections and infestations	Upper respiratory tract infection	35 (29.9)	0 (0.0)
	Pneumonia	19 (16.2)	14 (12.0)
	Sinusitis	17 (14.5)	5 (4.3)
Injury, poisoning and procedural complications	Contusion	23 (19.7)	0 (0.0)
Metabolism and nutrition disorders	Decreased appetite	17 (14.5)	4 (3.4)
Musculoskeletal and connective tissue disorders	Arthralgia	35 (29.9)	1 (0.9)
	Muscle spasms	23 (19.7)	1 (0.9)
	Myalgia	14 (12.0)	0 (0.0)
	Pain in extremity	14 (12.0)	0 (0.0)
	Back pain	12 (10.3)	2 (1.7)
Nervous system disorders	Headache	24 (20.5)	1 (0.9)
	Dizziness	17 (14.5)	1 (0.9)
Psychiatric disorders	Insomnia	13 (11.1)	0 (0.0)
	Anxiety	12 (10.3)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	Cough	31 (26.5)	0 (0.0)
	Oropharyngeal pain	15 (12.8)	0 (0.0)
	Dyspnea	13 (11.1)	1 (0.9)
	Epistaxis	13 (11.1)	0 (0.0)
Skin and subcutaneous tissue disorders	Increased tendency to bruise	15 (12.8)	0 (0.0)
	Petechiae	15 (12.8)	0 (0.0)
Vascular disorders	Hypertension	23 (19.7)	9 (7.7)

CLL=chronic lymphocytic leukemia; SLL=small lymphocytic lymphoma

- **Study 1112**

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Table 56. Overview of Adverse Events (Safety Population)

	Ibrutinib (N=195) n (%)	Ofatumumab (N=191) n (%)
Subjects with any TEAE	194 (99.5)	187 (97.9)
Grade ≥ 3	111 (56.9)	90 (47.1)
Subjects with any at least possibly treatment related TEAE [1]	164 (84.1)	150 (78.5)
Grade ≥ 3	65 (33.3)	53 (27.7)
Subjects with any AE leading to dose reduction	8 (4.1)	1 (0.5) [3]
Subjects with any AE leading to discontinuation of study drug [2]	16 (8.2)	16 (8.4)
Subjects with any SAE	81 (41.5)	58 (30.4)
Grade ≥ 3	69 (35.4)	55 (28.8)
Treatment related SAEs[1]	36 (18.5)	27 (14.1)
Fatal AE	12 (6.2)	16 (8.4)

AE = adverse event, SAE = serious AE, TEAE = treatment-emergent AE,
N = Number of subjects in the analysis population.
[1] Possibly Related or Related to study drug per investigator's judgment.
[2] Includes AEs with action taken as study drug permanently withdrawn.
[3] One subject in the ofatumumab arm had an AE that was captured incorrectly in the clinical database as an AE leading to dose reduction; the same AE was correctly captured in the clinical database as an AE leading to dose interruption.

Table 57. Adverse Events with Subject Incidence ≥ 10% in Either Arm by System Organ Class, Preferred Term, and Maximum Severity Grade (Safety Population)

System Organ Class MedDRA Preferred Term	Ibrutinib (N=195) Any Grade n (%)	Ibrutinib (N=195) Grade 3+4 n (%)	Ofatumumab (N=191) Any Grade n (%)	Ofatumumab (N=191) Grade 3+4 n (%)
Subjects with any TEAE	194 (99.5)	99 (50.8)	187 (97.9)	74 (38.7)
Blood and lymphatic system disorders	98 (50.3)	51 (26.2)	67 (35.1)	45 (23.6)
Anaemia	44 (22.6)	9 (4.6)	33 (17.3)	15 (7.9)
Neutropenia	42 (21.5)	32 (16.4)	28 (14.7)	26 (13.6)
Thrombocytopenia	33 (16.9)	11 (5.6)	22 (11.5)	8 (4.2)
Gastrointestinal disorders	153 (78.5)	17 (8.7)	105 (55.0)	7 (3.7)
Diarrhoea	93 (47.7)	8 (4.1)	34 (17.8)	3 (1.6)
Nausea	51 (26.2)	3 (1.5)	35 (18.3)	0 (0.0)
Constipation	30 (15.4)	0 (0.0)	18 (9.4)	0 (0.0)
Vomiting	28 (14.4)	0 (0.0)	12 (6.3)	1 (0.5)
Stomatitis	21 (10.8)	1 (0.5)	4 (2.1)	1 (0.5)
General disorders and administration site conditions	113 (57.9)	11 (5.6)	104 (54.5)	6 (3.1)
Fatigue	54 (27.7)	4 (2.1)	57 (29.8)	3 (1.6)
Pyrexia	46 (23.6)	3 (1.5)	28 (14.7)	2 (1.0)
Oedema peripheral	22 (11.3)	0 (0.0)	15 (7.9)	0 (0.0)
Infections and infestations	137 (70.3)	41 (21.0)	104 (54.5)	33 (17.3)
Upper respiratory tract infection	31 (15.9)	1 (0.5)	20 (10.5)	3 (1.6)
Sinusitis	21 (10.8)	1 (0.5)	12 (6.3)	0 (0.0)
Injury poisoning and procedural complications	43 (22.1)	3 (1.5)	66 (34.0)	8 (4.2)
Contusion	21 (10.8)	0 (0.0)	6 (3.1)	0 (0.0)
Infusion related reaction	0 (0.0)	0 (0.0)	53 (27.7)	6 (3.1)
Musculoskeletal and connective tissue disorders	93 (47.7)	8 (4.1)	68 (35.6)	3 (1.6)
Arthralgia	34 (17.4)	2 (1.0)	13 (6.8)	0 (0.0)
Muscle spasms	25 (12.8)	0 (0.0)	16 (8.4)	0 (0.0)
Back pain	22 (11.3)	2 (1.0)	12 (6.3)	1 (0.5)
Pain in extremity	20 (10.3)	1 (0.5)	8 (4.2)	0 (0)
Nervous system disorders	64 (32.8)	2 (1.0)	58 (30.4)	1 (0.5)
Headache	27 (13.8)	2 (1.0)	11 (5.8)	0 (0.0)
Dizziness	22 (11.3)	0 (0.0)	10 (5.2)	0 (0.0)
Peripheral sensory neuropathy	8 (4.1)	0 (0.0)	24 (12.6)	0 (0.0)
Respiratory thoracic and mediastinal disorders	93 (47.7)	6 (3.1)	83 (43.5)	9 (4.7)
Cough	38 (19.5)	0 (0.0)	44 (23.0)	2 (1.0)
Dyspnoea	23 (11.8)	4 (2.1)	20 (10.5)	1 (0.5)
Skin and subcutaneous tissue disorders	108 (55.4)	7 (3.6)	88 (46.1)	4 (2.1)
Petechiae	27 (13.8)	0 (0.0)	2 (1.0)	0 (0.0)
Night sweats	10 (5.1)	1 (0.5)	24 (12.6)	0 (0.0)

Adverse events are coded by MedDRA Version 16.1. N = number of subjects in safety population. Percentages are calculated by 100*n/N.

Grade 3 or 4 AEs were reported for 50.8% of subjects in the ibrutinib arm and 38.7% of subjects in the ofatumumab arm. The most common Grade 3 or 4 AE (≥5% of subjects in either treatment arm) was neutropenia (ibrutinib: 16.4%, ofatumumab: 13.6%) pneumonia (6.7%, 4.7%), thrombocytopenia (5.6%, 4.2%), and anaemia (4.6%, 7.9%).

Grade 3 or 4 AEs reported that occurred at higher incidence (≥2% difference) in the ibrutinib arm than in the ofatumumab arm included neutropenia (ibrutinib: 16.4%, ofatumumab: 13.6%), pneumonia (6.7%, 4.7%), diarrhea (4.1%, 1.6%), urinary tract infection (3.6%, 0.5%), leukocytosis (3.1%, 0%), atrial fibrillation (3.1%, 0%), and lung infection (2.6%, 0%).

AE leading to treatment discontinuation: Sixteen patients in each treatment arm discontinued due to AEs. In the ibrutinib arm, infection was the leading cause. The only events occurring in more than 1 patient in the ibrutinib arm were pneumonia (n=4) and atrial fibrillation (n=2).

AE leading to dose reduction: Due to the study design dose reduction was not applicable for the ofatumumab arm. In the ibrutinib arm, 4% of patients discontinued treatment due to AEs, with the most common AE being diarrhoea (n=3).

Adverse drug reactions

MCL

Overall, 108 (90%) of the 120 treated subjects in the MCL population experienced an AE that was considered related to ibrutinib by the investigator. The most common related events were diarrhoea (38.3%), fatigue (26.7%), nausea (18.3%), and neutropenia and upper respiratory tract infection (14.2% each). Few of these events were Grade 3 or 4 in severity, with the exception of neutropenia; 16 (13.3%) of the 17 subjects with neutropenia had a Grade 3 or 4 event (Table 57).

Table 58. Ibrutinib-related Adverse Events Occurring in 10% or More Subjects with MCL in Descending order of incidence (studies 1104 and 04753).

	All Subjects (N=120)	
	Any Grade n (%)	Grade 3+4 n (%)
Subjects with an event	108 (90.0)	50 (41.7)
Diarrhea	46 (38.3)	5 (4.2)
Fatigue	32 (26.7)	2 (1.7)
Nausea	22 (18.3)	0
Neutropenia	17 (14.2)	16 (13.3)
Upper respiratory tract infection	17 (14.2)	0
Decreased appetite	15 (12.5)	0
Thrombocytopenia	14 (11.7)	8 (6.7)
Constipation	12 (10.0)	0
Muscle spasms	12 (10.0)	0
Rash	12 (10.0)	2 (1.7)
Vomiting	12 (10.0)	0

MCL=mantle cell lymphoma.
A subject with multiple severity ratings for a given AE was counted only once under the maximum severity.

CLL

Overall (studies 1102, 04753), 89.7% of subjects in the CLL/SLL population experienced an AE that was considered related to ibrutinib by the investigator. Four events occurred at an incidence greater than 10%: diarrhoea (39.3%), fatigue (13.7%), arthralgia (12.8%), and contusion (10.3%) (Table 58).

Table 59. Ibrutinib-related Adverse Events Occurring in 10% or More Subjects with CCL/SLL in Descending order of incidence (studies 1104 and 04753).

	Total (N = 117)	
Preferred term	All, n (%)	Grade 3/4, n (%)
Diarrhea	46 (39.3)	3 (2.6)
Fatigue	16 (13.7)	3 (2.6)
Arthralgia	15 (12.8)	1 (0.9)
Contusion	12 (10.3)	0 (0.0)

CLL=chronic lymphocytic leukemia; SLL=small lymphocytic lymphoma

PCYC-1112-CA: Adverse events considered by the investigator to be related to treatment were reported for 84.1% of subjects in the ibrutinib arm and 78.5% of subjects in the ofatumumab arm (Table 59). The most common treatment-related AE in the ibrutinib arm (≥ 20% of subjects) was diarrhoea (32.8%). The most common treatment-related AE in the ofatumumab arm (≥ 20% of subjects) was infusion-related reaction (27.7%). The only treatment-related AE that occurred at a higher incidence (≥ 10% difference) in the ibrutinib arm than in the ofatumumab arm was diarrhoea (ibrutinib: 32.8%, ofatumumab: 8.4%) (Table 59). The only treatment-related AE that occurred at a higher incidence (≥ 10% difference) in the ofatumumab arm than in the ibrutinib arm was infusion-related reaction (ibrutinib: 0%, ofatumumab: 27.7%).

Table 60. Treatment-Related Adverse Events with Subject Incidence ≥10% in Either Arm by Preferred Term and Maximum Severity Grade (Safety Population)

	Ibrutinib (N=195)		Ofatumumab (N=191)	
MedDRA Preferred Term	Any Grade n (%)	Grade 3+4 n (%)	Any Grade n (%)	Grade 3+4 n (%)
Subjects with any TEAE	164 (84.1)	64 (32.8)	150 (78.5)	51 (26.7)
Diarrhoea	64 (32.8)	4 (2.1)	16 (8.4)	1 (0.5)
Nausea	31 (15.9)	2 (1.0)	16 (8.4)	0 (0.0)
Neutropenia	26 (13.3)	21 (10.8)	18 (9.4)	17 (8.9)
Arthralgia	22 (11.3)	2 (1.0)	4 (2.1)	0 (0.0)
Petechiae	22 (11.3)	0 (0.0)	1 (0.5)	0 (0.0)
Infusion-related reaction	0 (0.0)	0 (0.0)	53 (27.7)	6 (3.1)

AEs are coded by MedDRA Version 16.1. N=number of subjects in the specified treatment arm in safety the population. %= 100*n/N.
Subjects with multiple events for a given preferred term are counted once only using maximum severity under each preferred term.
Events are sorted by decreasing frequency of preferred term by Any Grade column in the ibrutinib arm.

One single list of ADRs has been generated by pooling safety data from 357 patients across studies 1104, 1102 and 1112, and the use of the following criteria:

- Any AE for which the incidence is 5% greater in the ibrutinib arm when compared with the ofatumumab arm in the randomized, controlled Phase 3 Study 1112, or
- Any AE of any incidence, (including those whose incidence is ≤5% in the ibrutinib arm when compared with the ofatumumab arm in Study 1112), which based on biological plausibility, could be related to ibrutinib.

The most commonly occurring adverse reactions (≥ 20%) were diarrhoea, musculoskeletal pain, upper respiratory tract infection, bruising, rash, nausea, pyrexia, neutropenia and constipation. The most common grade 3/4 adverse reactions (≥ 5%) were anaemia, neutropenia, pneumonia and thrombocytopenia. (table … below by system organ class and frequency defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness (See SmPC section 4.8).

Table 61. Treatment-emergent Adverse drug reactions (ADR) in MCL, CLL/SLL patients treated with ibrutinib (N = 357)

System organ class	Frequency (All grades)	Adverse drug reactions
Infections and infestations	Very common	Pneumonia* Upper respiratory tract infection Sinusitis*
	Common	Sepsis* Urinary tract infection Skin infection*
Blood and lymphatic system disorders	Very common	Neutropenia Thrombocytopenia Anaemia
	Common	Febrile neutropenia Leukocytosis Lymphocytosis
	Uncommon	Leukostasis
Metabolism and nutrition disorders	Common	Dehydration Hyperuricaemia
Nervous system disorders	Very common	Dizziness Headache
Eye disorders	Common	Vision blurred
Cardiac disorders	Common	Atrial fibrillation
Vascular disorders	Very common	Haemorrhage* Bruising* Petechiae
	Common	Subdural haematoma Epistaxis
Gastrointestinal disorders	Very common	Diarrhoea Vomiting Stomatitis* Nausea Constipation
	Common	Dry mouth
Skin and subcutaneous tissue disorders	Very common	Rash*
Musculoskeletal and connective tissue disorders	Very common	Arthralgia Musculoskeletal pain*
General disorders and administration site conditions	Very common	Pyrexia Oedema peripheral

* Includes multiple adverse reaction terms.

Selected events (MCL, CLL)

- **Haemorrhage**

Fifty-seven (47.5%) of 120 subjects in the integrated MCL population experienced a treatment-emergent haemorrhage event of any severity; the most common were contusion (17.5%) and epistaxis (10.0%). Major haemorrhage was reported in 8 (6.7%) patients, whereof 3 led to discontinuation of study drug. Platelet counts were below 50 in 1 or 2 of these patients. Confounders for bleeding were present in all cases.

In study 1102, haemorrhagic events were reported in 65 (56%) of subjects, with major events in 5 (4%), including 2 patients with subdural hematoma. Upon inspection of tabulated data on the major events, strong confounders were present for all events except for 1 of the subdural hematoma events.

In study 1112, haemorrhagic events were reported for 43.6% of subjects in the ibrutinib arm and 11.5% of subjects in the ofatumumab arm. Major haemorrhagic events were reported for 1% of subjects (n=2; subdural hematoma at platelets 64, and postoperative haemorrhage at platelets 105) in the ibrutinib arm and 1.6% of subjects (n=3) in the ofatumumab arm.

Haemorrhage, also in the absence of thrombocytopenia, is considered an ADR related to ibrutinib. The proposed wording in SmPC 4.4 is considered appropriate. The contributing mechanism is not clear.

- **Other malignancies**

In studies 04753, 1104 and 1102 (n=309), additional malignancies were reported in 27 (8.7%) subjects. An imbalance between indications is noted with 19 (16.2%) and 5 (4.2%) patients reported with additional malignancy in CLL/SLL and MCL, respectively, mainly due to a higher incidence of skin carcinoma in the CLL/SLL group. In the 1104 study in MCL, the incidence of additional malignancies was 4% whereas 16% noted in the 1102 CLL/SLL study.

Reporting of other malignancies was initially required only during the treatment emergent period in study 1112; an amendment requiring the reporting of other malignancies during the entire study period was implemented as late as 3 months prior to data cut-off. In the 1112 study “other malignancy” in terms of skin cancer was noted in 5% in the ibrutinib arm vs 2% in the ofatumumab arm, and non-skin cancers in 2.6% vs 1%, respectively during a median duration of treatment of 8.6 months for the ibrutinib arm vs 5.3 months for the ofatumumab arm. An overestimation of the difference in the incidence of other malignancies between the two study arms cannot be excluded (The risk is included in the RMP).

- **Progressive multifocal leukoencephalopathy**

One single case of PML, in a 57-year-old woman with heavily pretreated r/r del 17p CLL on day 323, in the total experience of 1800 patients has been observed, however prior rituximab and the disease itself are considered strong confounders.

- **Diarrhoea**

In MCL, gastrointestinal side effects were the most common seen during ibrutinib therapy, with diarrhoea being the prominent event, although most patients, absolutely and relatively, experienced the event during the first 3 months of treatment. However, only 6 events being grade 3 (no grade 4) and only 3 dose reductions and no discontinuations due to the event are considered reassuring.

Also in CLL/SLL diarrhoea was the most frequently reported AE (55% in 1102, 48% in 1112). However, in 1102 only 4 patients had grade 3 events, dose reduction was rare (2) and no patient discontinued treatment due to the event. The incidence rate declined markedly after 3 months of treatment. In study 1112, 4% of patients were reported with grade 3+4 events, 1 patient discontinued treatment due to diarrhoea and 3 had the dosed reduced. The AE of diarrhoea is deemed clinically manageable.

- **Infections**

Infections occurred in 76% of MCL patients with grade 3-4 in 22%, with a relatively constant incidence rate during 1-24 months. Pneumonia was the most prevalent event with 17 (14%) cases overall with 2 leading to death. Overall 3 patients died from infectious events.

In study 1102, infections occurred in 76% of patients with grade ≥3 in 38%. The incidence rate of new-onset grouped infectious AEs remained relatively stable over time. Fatal outcome was reported for 3 cases, all related to pneumonia. Pooling of pneumonia-related events showed an overall incidence rate of 21% with grade ≥3 pneumonia in 17% of subjects.

In study 1112, AEs in the Infections and Infestations SOC were reported for 70.3% of subjects in the ibrutinib arm and 54.5% of subjects in the ofatumumab arm, but no large difference in terms of grade ≥3 or fatal events were noted between study arms.

Considering ibrutinib's MoA, an increased susceptibility to infections might be expected. Considering infection as an ADR for ibrutinib is reasonable.

Lymphocytosis and leukostasis

Lymphocytosis (transient) is part of ibrutinib's MoA and was in MCL reported in 41 patients (34.5%); in 13 (32%) of these lymphocytosis was ongoing at the cut-off (censored). Median time to treatment-emergent lymphocytosis was 1.1 weeks but it is noted that lymphocytosis occurred as late as after 64.3 weeks. Median duration was 8 weeks with a maximum duration of 35 weeks.

In study 1102, a reversible increase in lymphocyte counts (≥50% increase from baseline and above absolute count 5,000/mcL) was reported in 88 (75%) patients. Median time to the phenomenon was 1.1 weeks but occurred as late as after 16 weeks; median duration was 18.7 weeks with an upper range of 104 weeks.

At the time of the MAA submission, 4 events of leukostasis had been reported in clinical studies of ibrutinib to that date: 2 patients with MCL and 2 with CLL. Three of the 4 events were possibly confounded by transformation/progressive disease. In study 1112, no event of leukostasis was reported in the ibrutinib arm. In the updated results, the Applicant informs that to date a total of 5 isolated cases of leukostasis in subjects treated with ibrutinib have been reported. Three subjects experienced concurrent intracranial haemorrhage.

Cardiac AEs

In MCL, cardiac AEs were reported in 21% of patients with grade 3-4 in 9%. The only "cardiac-related" death was due to pulmonary embolism, deep vein thrombosis, and hypertensive heart disease. Atrial fibrillation was the most commonly reported event (n=11; 9%); myocardial infarction, Torsade de pointes and ventricular tachycardia were reported in 1 patient each.

In study 1102, cardiac AEs were reported in 19.7% of subjects with atrial fibrillation (5.1%) being the most common. In study 1112, AEs events in the SOC of Cardiac Disorders were reported for 11.8% of subjects in the ibrutinib arm and 7.9% of subjects in the ofatumumab arm. A higher subject incidence of atrial fibrillation was observed in the ibrutinib arm (10 subjects [5.1%]) compared with the ofatumumab arm (1 subject [0.5%]). These events were assessed with maximum severity as grade 3 or 4 for 3.1% (n=6) and 0% (n=0) of subjects, respectively. Six of the 10 subjects in the ibrutinib arm experienced SAEs of atrial fibrillation. One event resulted in study drug discontinuation for a subject in the ibrutinib arm.

Ibrutinib is associated with exposure-dependent QTc shortening, prolonged PR interval and reduction in heart rate. Although all these effects are of limited magnitude, and no obvious and suspicious AE pattern is identified, especially the clinical consequences of QTc shortening generally remain obscure.

In the setting of a randomised trial with similar baseline characteristics, supported by phase Ib/II data, it must be assumed that the clearly higher incidence of atrial fibrillation/flutter in the ibrutinib arm is associated with therapy. This is correctly included in the SmPC 4.8. However, whether this is related to the QT-shortening property of the drug remains to be elucidated. Considering the obscure clinical significance of the QT shortening associated with ibrutinib, cardiac safety should be part of the RMP. A thorough QT-study (PCI-32765CLL1007) will be conducted as a post-approval commitment.

Hypersensitivity

Due to the low frequency of individual events suggestive of hypersensitivity in combination with the lack of a placebo control, and uncertainties regarding possible co-medication/exposure to environmental factors etc, a definitive causal relationship with ibrutinib cannot be concluded. Comparison with data obtained with ofatumumab is of little value.

Inclusion of hypersensitivity as an important potential risk in the RMP seems reasonable.

Eye disorders

The incidence of AEs in the SOC of eye disorders was double as high in the ibrutinib arm (36% vs 19%); none was grade ≥3. Further, ocular toxicity was noted in animal studies. Therefore, inclusion of "vision blurred" in the SmPC 4.8 is endorsed, but the SOC of eye disorders should also be part of the RMP for further vigilance.

Serious adverse event / deaths / other significant events

Deaths

MCL

Of the 17 (14%) patients that died during treatment or within 30 days of treatment discontinuation, all in study 1104, 12 died from MCL or events associated with disease progression. The remaining causes of death were cardiac arrest (1; pulmonary embolism identified at autopsy), hypovolemic shock (1), infection (3; pneumonia 2, sepsis 1). No obvious pattern in terms of time on treatment is noted. Therefore, 5 (4.3%) patients in the integrated population of 116 patients with r/r MCL and treated with the 520 mg daily dose died for reasons not related to PD during treatment or within 30 days of treatment discontinuation. Out of these 5 deaths, 3 were due to infection.

CLL

In total in study 1102, 9 patients died during or within 30 days of treatment, whereof 3 in the setting of progressive disease. The cause of death in the remaining 6 (5% of the study population) was related to infection in 4 (pneumonia 3, sepsis 1) and to secondary malignancy in 2 (malignant histiocytosis, PTCL). None of the subjects with MCL in Study 04753 died.

In study 1112, the fraction of patients with fatal SAEs was numerically slightly more common in the ofatumumab arm; 8.4% vs 6.2% in the ibrutinib arm. The most common AEs leading to death in either treatment arm were pneumonia (ibrutinib: 1.5%, ofatumumab: 1.0%), CLL (disease progression) (1.0%, 1.0%), and sepsis (1.0%, 0%). No event was reported at a frequency ≥2%. This result is considered reassuring.

Other Serious Adverse Events:

MCL

SAEs were reported in 59% of patients; grade 3-4 in 38%. The most commonly reported SAEs (Preferred Terms) (excluding disease progression) were atrial fibrillation (5.8%), pneumonia (5.0%), febrile neutropenia (3.3%), and urinary tract infection (3.3%). The highest frequencies of grade 3-4 events were reported for atrial fibrillation (5%) and pneumonia (4.2%). Generally, the SOC with most all grade as well as grade 3-4 SAEs was infections and infestations.

Table 62. Serious Adverse Events Occurring in 2% or More of Subjects with MCL by System Organ Class (Studies 1104 and 04753)

	All Subjects (N=120)	
System Organ Class MedDRA Preferred Term	Any Grade n (%)	Grade 3 + 4 n (%)
Subjects with an event	71 (59.2)	45 (37.5)
Blood and lymphatic system disorders	10 (8.3)	9 (7.5)
Febrile neutropenia	4 (3.3)	3 (2.5)
Cardiac disorders	10 (8.3)	8 (6.7)
Atrial fibrillation	7 (5.8)	6 (5.0)
Gastrointestinal disorders	8 (6.7)	6 (5.0)
Abdominal pain	3 (2.5)	3 (2.5)
General disorders and administration site conditions	12 (10.0)	6 (5.0)
Oedema peripheral	3 (2.5)	2 (1.7)
Pyrexia	3 (2.5)	1 (0.8)
Infections and infestations	24 (20.0)	19 (15.8)
Pneumonia	6 (5.0)	5 (4.2)
Urinary tract infection	4 (3.3)	3 (2.5)
Cellulitis	3 (2.5)	3 (2.5)
Injury, poisoning and procedural complications	6 (5.0)	4 (3.3)
Subdural haematoma	3 (2.5)	2 (1.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	12 (10.0)	4 (3.3)
Mantle cell lymphoma	10 (8.3)	3 (2.5)
Renal and urinary disorders[a]	6 (5.0)	5 (4.2)
Renal failure acute	3 (2.5)	2 (1.7)

MCL=mantle cell lymphoma; MedDRA=Medical Dictionary for Regulatory Activities

Counts represent number of subjects reporting the event, individual event counts may not sum to SOC totals because of multiple events per subject.

A subject with multiple severity ratings for a given AE was counted only once under the maximum severity.

[a] One (0.8%) additional subject with an SAE coded with the preferred term 'renal failure' is not included in this table because the incidence was less than 2%. This subject is discussed in Section 2.2.1.1.1.

CLL

One or more SAEs were reported in 67 of the 117 subjects (57.3%) in the CLL/SLL population. The majority of individual events occurred at an incidence of 2% or less; those more prevalent are shown in Table 62. The most common serious events were pneumonia (12.8%), febrile neutropenia (4.3%), bacteraemia, cellulitis, and sinusitis (all 3.4%), and sepsis (2.6%). Overall, the most common events were infectious. The SAE most frequently considered related to ibrutinib was pneumonia (2.6%).

Table 63. Serious Adverse Events Occuring in 2% or More of Subjects with CLL/SLL by System Organ Class (Studies 1102 and 04753).

		Total (N = 117)	
System Organ Class	Preferred term	All, n (%)	Related, n (%)
Blood/lymphatic	Febrile neutropenia	5 (4.3)	0 (0.0)
Cardiac	Atrial fibrillation	3 (2.6)	1 (0.9)
Infections	Pneumonia	15 (12.8)	3 (2.6)
	Bacteremia	4 (3.4)	0 (0.0)
	Cellulitis	4 (3.4)	0 (0.0)
	Sinusitis	4 (3.4)	0 (0.0)
	Sepsis	3 (2.6)	0 (0.0)

CLL=chronic lymphocytic leukemia; SLL=small lymphocytic lymphoma

Study 1112: Serious AEs were reported for 41.5% in the ibrutinib arm and 30.4% of subjects in the ofatumumab arm. The most common SAE in both treatment arms was pneumonia (ibrutinib: 8.7%, ofatumumab: 6.3%). SAEs for atrial fibrillation, pneumonia, lung infection and urinary tract infection were reported with ≥2% higher frequency in the ibrutinib arm.

Table 64. Serious Adverse Events with Subjects incidence of ≥2% in Either Arm by System Organ Class and Preferred Term (Safety Population)

System Organ Class MedDRA Preferred Term	Ibrutinib (N=195) n (%)	Ofatumumab (N=191) n (%)
Number of subjects reporting at least one SAE	81 (41.5)	58 (30.4)
Blood and lymphatic system disorders	8 (4.1)	11 (5.8)
Febrile neutropenia	3 (1.5)	4 (2.1)
Anaemia	2 (1.0)	4 (2.1)
Cardiac disorders	13 (6.7)	6 (3.1)
Atrial fibrillation	6 (3.1)	1 (0.5)
General disorders and administration site conditions	12 (6.2)	4 (2.1)
Pyrexia	6 (3.1)	4 (2.1)
Infections and infestations	46 (23.6)	39 (20.4)
Pneumonia	17 (8.7)	12 (6.3)
Lung infection	5 (2.6)	0 (0.0)
Lower respiratory tract infection	4 (2.1)	2 (1.0)
Urinary tract infection	4 (2.1)	0 (0.0)
Upper respiratory tract infection	1 (0.5)	4 (2.1)

Adverse events are coded by MedDRA Version 16.1. N = number of subjects in the specified population.
Percentages are calculated by 100*n/N.
Subjects with multiple events for a given preferred term or system organ class are counted once only under each preferred term or system organ class, respectively.
Events are sorted by system organ class alphabetically and decreasing frequency of preferred term in the ibrutinib arm.

Laboratory findings

Haematology

MCL

A review of haematological parameters during treatment with ibrutinib was conducted on the 120 subjects in the integrated MCL population. Laboratory hematologic toxicities were not uncommon in the integrated MCL population, although most were Grade 1 or 2 in severity. Thrombocytopenia of any grade was observed in 55.8% of treated subjects, followed by neutropenia (43.7%) and anaemia (38.3%) (Table 64). Neutropenia was the most common Grade 3 or higher hematologic toxicity (23.5%). Thrombocytopenia grade ≥3 was reported in 13% of patients. Twelve (10.1%) subjects experienced treatment-emergent Grade 4 neutropenia. Six (5.0%) subjects experienced treatment-emergent Grade 4 thrombocytopenia. Four (3.3%) subjects had treatment-emergent Grade 3 anaemia and there was no reports of Grade 4 anaemia.

Table 65. Subject Incidence of Treatment-emergent Hematological Laboratory Low Abnormalities (Studies 1104 and 04753)

Max Grade: n (%)	N	Any Grade n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	>= Grade 3 n (%)
Platelets	120	67 (55.8)	19 (15.8)	10 (8.3)	6 (5.0)	16 (13.3)
Hemoglobin	120	46 (38.3)	24 (20.0)	4 (3.3)	0	4 (3.3)
ANC	119	52 (43.7)	15 (12.6)	16 (13.4)	12 (10.1)	28 (23.5)
White Blood Cell	120	32 (26.7)	14 (11.7)	8 (6.7)	4 (3.3)	12 (10.0)

ANC=absolute neutrophil count.
Hematology assay results were graded using CTCAE version 4.03.
N=total number of subjects for whom a baseline measurement and post treatment measurement is available.
n=number of those subjects whose worst post-baseline grade is higher than their baseline grade.
A value of 0 for n means the criteria has not been met for subjects with baseline and post treatment measurements

CLL

A review of haematological parameters and shift analysis during treatment with ibrutinib was conducted on the 116 subjects in the integrated CLL/SLL population. Thrombocytopenia was the most common hematologic toxicity (all grades) observed in the CLL/SLL population (59.5%), followed by neutropenia (56.0%) and anaemia (48.3%). Neutropenia had the highest incidence of severity Grade 3 and higher (31.9%). There was no Grade 3 and higher anaemia (Table 65).

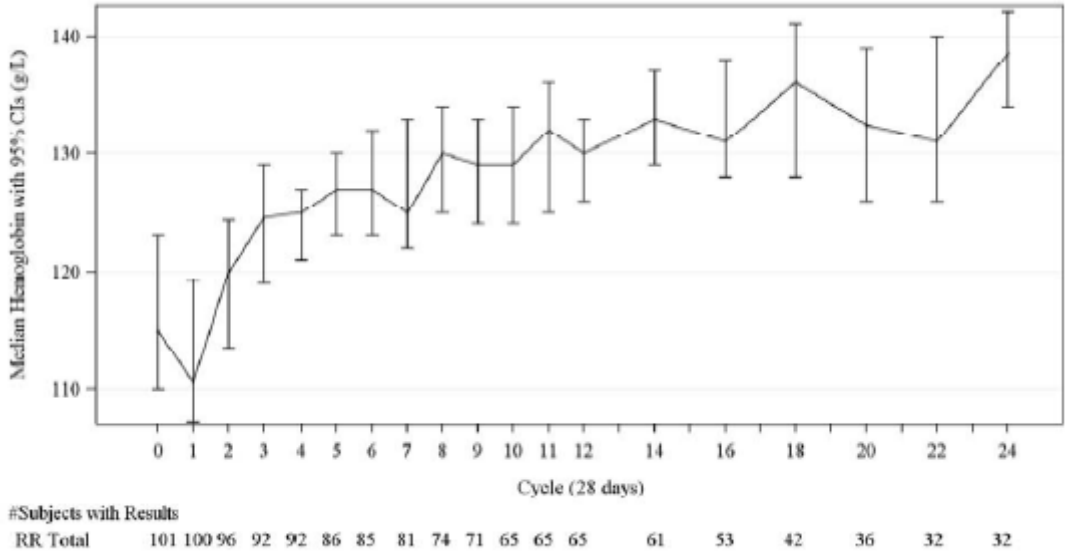
Table 66. Treatment-emergent Laboratory Hematologic Toxicity in Subjects with CLL/SLL (Studies 1102 and 04753).

	N	Any grade n (%)	Grade 3 and higher n (%)
Hemoglobin	116	56 (48.3)	0 (0.0)
Platelets	116	69 (59.5)	12 (10.3)
ANC	116	65 (56.0)	37 (31.9)
WBC	116	24 (20.7)	8 (6.9)

CLL=chronic lymphocytic leukemia; SLL=small lymphocytic lymphoma

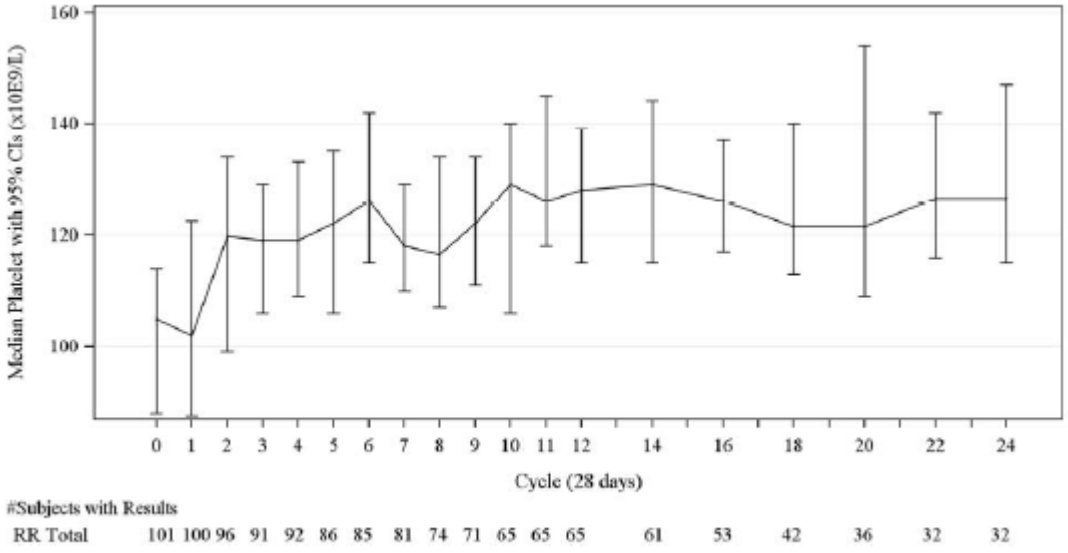
During treatment median haemoglobin, and to certain extent also median platelet levels, increased while median ANC remained within normal range.

Figure 14. Median Haemoglobin over time for subjects with CLL/SLL (Study 1102 Only)



CI=confidence interval; CLL=chronic lymphocytic leukemia; SLL=small lymphocytic lymphoma

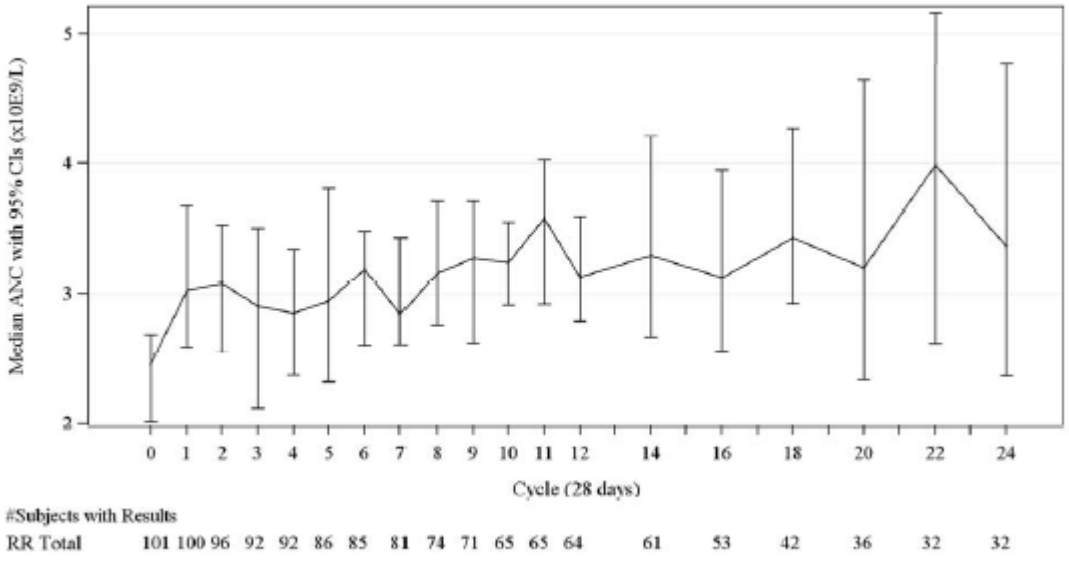
Figure 15. Median Platelets over time for subjects with CLL/SLL (Study 1102 Only)



CI=confidence interval; CLL=chronic lymphocytic leukemia; SLL=small lymphocytic lymphoma

Figure 16. Median Neutrophils over Time for Subjects with CLL/SLL (Study 1102 Only)

Figure 7: Median Neutrophils over Time for Subjects with CLL/SLL (Study 1102 Only)



ANC=absolute neutrophil count; CI=confidence interval; CLL=chronic lymphocytic leukemia; SLL=small lymphocytic lymphoma

PCYC-1112-CA:

Treatment-emergent Grade 3 or 4 decreases in platelet counts were reported for 5.1% of subjects in the ibrutinib arm and 9.9% of subjects in the ofatumumab arm. Treatment-emergent Grade 3 or 4 decreases in ANCs were observed for 23.1% of subjects in the ibrutinib arm and 26.2% of subjects in the ofatumumab arm. No subject in either treatment arm had treatment-emergent Grade 3 or 4 decreases in haemoglobin (Table 66). Grade 3 and 4 haemoglobin and platelet decreases were defined as reduction from baseline of ≥ 50% and ≥ 75%, respectively (IWCLL 2008 criteria).

Table 67. Worst Toxicity Grade in Neutrophils, Haemoglobin, and Platelet Counts During Treatment (Safety Population).

		Ibrutinib (N=195)		Ofatumumab (N=191)	
Hematology Laboratory Parameter	Direction of Toxicity	Any Grade n (%)	Grade 3 + 4 n (%)	Any Grade n (%)	Grade 3 + 4 n (%)
Hemoglobin	Lower	71 (36.4)	0	41 (21.5)	0
Platelet	Lower	101 (51.8)	10 (5.1)	86 (45.0)	19 (9.9)
Absolute Neutrophil Count	Lower	100 (51.3)	45 (23.1)	109 (57.1)	50 (26.2)

Platelet counts, hemoglobin, and absolute neutrophils counts were graded using the IWCLL 2008 guidelines. Only includes subjects whose grade worsened from baseline in the numerator. Denominator (N) is the number of subjects in the specific treatment arm in the safety population. These analyses are based on results from the central laboratory.

Clinical chemistry

MCL

Concerning serum chemistries, the most common abnormalities of any grade were creatinine elevation (74.2%), hypocalcaemia (56.7%), hyperglycaemia (41.7%), hypomagnesaemia (39.0%), low creatinine clearance (33.3%), and hypernatraemia (30.8%). Most of these abnormalities were Grade 1 or 2. The only notable Grade 3 or higher laboratory abnormality was hyponatremia (5.8%). Other Grade 3 or 4 abnormalities occurred in 4 subjects or less.

Table 68. Treatment-emergent Blood Chemistry Abnormalities in Subjects with MCL (Studies 1104 and 04753)

Max Grade: n (%)	N	Abnormal Direction	Any Grade n (%)	Grade 3 and higher n (%)
Alanine Aminotransferase	120	High	11 (9.2)	0
Alkaline Phosphatase	120	High	33 (27.5)	1 (0.8)
Aspartate Aminotransferase	119	High	33 (27.7)	0 (0.0)
Bilirubin	120	High	16 (13.3)	0 (0.0)
Calcium	120	High	1 (0.8)	0 (0.0)
	120	Low	68 (56.7)	1 (0.8)
Creatinine	120	High	89 (74.2)	0 (0.0)
Creatinine Clearance	120	Low	40 (33.3)	2 (1.7)
Magnesium	118	High	17 (14.4)	0 (0.0)
	118	Low	46 (39.0)	0 (0.0)
Phosphate	118	Low	25 (21.2)	0 (0.0)
Potassium	120	High	22 (18.3)	0 (0.0)
	120	Low	13 (10.8)	1 (0.8)
Serum Albumin	120	Low	35 (29.2)	1 (0.8)
Serum Glucose	120	High	50 (41.7)	4 (3.3)
	120	Low	26 (21.7)	1 (0.8)
Sodium	120	High	37 (30.8)	0 (0.0)
	120	Low	18 (15.0)	7 (5.8)

CTCAE version 4.03 was used for grading.
N=total number of subjects for whom a baseline measurement and post treatment measurement is available.
n=number of those subjects whose worst post-baseline grade is higher than their baseline grade. A value of 0 for n means the criteria has not been met for subjects with baseline and post treatment measurements.
Lab results with any treatment emergent abnormalities were presented on this table. Lab results with no treatment emergent abnormalities were excluded.

A shift analysis of creatinine clearance showed that 77.5% of subjects maintained their baseline grade, 18.3% shifted from ≥ 60 mL/min to between 60 and 30 mL/min, and 1.7% shifted to <30 mL/min at some time during treatment. This analysis presents only worst value and does not portray reversibility or irreversibility.Deterioration of kidney function did not seem to be a major side effect of ibrutinib in this patient population.

No patient fulfilled Hy's law. Although median serum bilirubin and AST remained relatively constant over time, acknowledging the decreasing number of patients at risk, median ALT increased beyond cycle 17 (data not shown).

CLL

The most common treatment-emergent serum chemistry abnormalities for the CLL/SLL population were hypocalcaemia (69.8%), hyperglycaemia (54.3%), hypomagnesaemia (39.5%), and AST elevation (31.9%). Most of these abnormalities were Grade 1 or 2. The most common Grade 3 or higher abnormalities were hyperglycaemia (6.9%), hypophosphataemia (6.1%), hyponatraemia (6.0%) and hypocalcaemia (4.3%). All other Grade 3/4 abnormalities occurred in 1 or 2 subjects each. No concerns for renal or hepatic toxicity were noted. Median serum creatinine levels were roughly stable over time, also in patients with baseline creatinine clearance value <60 mL/min. Median ALT, AST and bilirubin levels were also roughly stable over time. One subject transiently met the criteria for drug-induced liver injury (ALT/AST criteria and total bilirubin criteria both met and alkaline phosphatase ≤ 2 times upper limit of normal on any day) but the event was attributed to sepsis.

Table 69. Treatment-emergent Blood Chemistry Abnormalities in Subjects with CLL/SLL (Studies 1104 and 04753)

Analyte	N	Abnormal direction	Any grade n (%)	Grade 3 and higher n (%)
ALT	116	High	27 (23.3)	0 (0.0)
Alkaline Phosphatase	116	High	26 (22.4)	1 (0.9)
AST	113	High	36 (31.9)	0 (0.0)
Bilirubin	116	High	33 (28.4)	4 (3.4)
Calcium	116	High	3 (2.6)	1 (0.9)
	116	Low	81 (69.8)	5 (4.3)
Creatinine	116	High	33 (28.4)	0 (0.0)
Creatinine Clearance	116	Low	31 (26.7)	2 (1.7)
Magnesium	114	High	27 (23.7)	0 (0.0)
	114	Low	45 (39.5)	1 (0.9)
Phosphate	115	Low	25 (21.7)	7 (6.1)
Potassium	116	High	23 (19.8)	3 (2.6)
	116	Low	12 (10.3)	2 (1.7)
Serum Glucose	116	High	63 (54.3)	8 (6.9)
	116	Low	27 (23.3)	3 (2.6)
Sodium	116	High	32 (27.6)	0 (0.0)
	116	Low	27 (23.3)	7 (6.0)

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CLL=chronic lymphocytic leukemia; SLL=small lymphocytic lymphoma

PCYC-1112-CA:

Table 70. Worst Toxicity Grade in Clinical Chemistry Parameters during Treatment (Safety Population).

Chemistry Laboratory Parameter	Direction of Toxicity	Ibrutinib (N=195) Any Grade n (%)	Ibrutinib (N=195) Grade 3 + 4 n (%)	Ofatumumab (N=191) Any Grade n (%)	Ofatumumab (N=191) Grade 3 + 4 n (%)
Alanine Aminotransferase	High	23 (11.8)	0	20 (10.5)	0
Albumin	Low	31 (15.9)	0	18 (9.4)	2 (1.0)
Alkaline Phosphatase	High	16 (8.2)	1 (0.5)	17 (8.9)	0
Aspartate Aminotransferase	High	11 (5.6)	0	16 (8.4)	0
Bilirubin	High	24 (12.3)	2 (1.0)	11 (5.8)	0
Calcium	High	3 (1.5)	0	1 (0.5)	0
Calcium	Low	17 (8.7)	2 (1.0)	11 (5.8)	0
Creatinine	High	12 (6.2)	0	16 (8.4)	1 (0.5)
Creatinine Clearance	Low	31 (15.9)	2 (1.0)	33 (17.3)	7 (3.7)
Glucose	High	74 (37.9)	5 (2.6)	87 (45.5)	11 (5.8)
Glucose	Low	23 (11.8)	0	10 (5.2)	0
Phosphate	Low	17 (8.7)	2 (1.0)	15 (7.9)	1 (0.5)
Potassium	High	3 (1.5)	0	4 (2.1)	1 (0.5)
Potassium	Low	20 (10.3)	1 (0.5)	5 (2.6)	0
Sodium	High	11 (5.6)	0	9 (4.7)	0
Sodium	Low	29 (14.9)	6 (3.1)	14 (7.3)	1 (0.5)

Only includes subjects whose grade worsened from baseline in the numerator. Denominator is N that is the number of subjects in the specific treatment arm in the safety population. For crossover ofatumumab subjects, only lab tests that were taken before crossing over are included. These analyses are based on results from the central laboratory.

Safety in special populations

MCL

Table 71. Safety Summary for Subjects with MCL by Age (Studies 1104 and 04753)

	< 65 yrs (N=44)	>= 65 yrs (N=76)	Total (N=120)
Any AE	43 (97.7)	76 (100.0)	119 (99.2)
Grade >=3	29 (65.9)	63 (82.9)	92 (76.7)
Any SAE	18 (40.9)	53 (69.7)	71 (59.2)
Grade >=3	13 (29.5)	49 (64.5)	62 (51.7)
All reported death	14 (31.8)	32 (42.1)	46 (38.3)
Death within 30 days of last dose	4 (9.1)	13 (17.1)	17 (14.2)

AE=adverse event; MCL=mantle cell lymphoma; SAE=serious adverse event.

Table 72. Safety Summary for Subjects with CLL/SLL by Age (Studies 1102 and 04753)

	< 65 years (N = 57)	≥ 65 years N = 60)
Subjects with 1 or more adverse event, n (%)		
Any	57 (100.0)	60 (100.0)
Grade 3 or higher	35 (61.4)	46 (76.7)
Subjects with a serious event, n (%)	31 (54.4)	36 (60.0)
Deaths within 30 days of last dose of ibrutinib, n (%)	5 (8.8)	4 (6.7)

CLL=chronic lymphocytic leukemia; SLL=small lymphocytic lymphoma

CLL

Safety related to drug-drug interactions and other interactions

There were no dedicated PD interaction studies; with respect to PK interactions, see section 2.4.2.

Discontinuation due to adverse events

MCL: Fifteen (12.5%) of the 120 subjects in the integrated MCL population discontinued treatment due to AEs; all were in Study 1104. Fourteen of these subjects had AEs that occurred within 30 days of last dose of ibrutinib. One subject had a discontinuation due to cardiac failure congestive more than 30 days after last study drug dose. The most frequent AE leading to treatment discontinuation was subdural hematoma (1.7%). Four of the AEs leading to treatment discontinuation were considered possibly related to ibrutinib: pneumonia, sepsis, subdural hematoma, and metastatic neoplasm (associated with liver adenocarcinoma, an additional primary malignancy). See also section on adverse events.

CLL: Thirteen (11.1%) of the 117 subjects in the CLL/SLL population experienced an AE that led to discontinuation of study treatment. The study day of the precipitating event ranged from Day 9 to Day 589. Seven of the 13 events were infectious in nature and 2 events were related to disease progression. Five of the 13 subjects recovered from the event, 5 subjects died, and the event was ongoing at last contact in 3 subjects. Only 1 of the events leading to treatment discontinuation (influenza) was considered possibly related to ibrutinib.

PCYC-1112: Adverse events resulting in treatment discontinuation, including AEs with fatal outcomes, were reported for 8.2% of subjects in the ibrutinib arm and 8.4% of subjects in the ofatumumab arm . The most common AEs leading to treatment discontinuation in either treatment armwere pneumonia (ibrutinib: 2.1%, ofatumumab: 2.1%) and sepsis (1%, 0%). All other AEs leading to treatment discontinuation occurred in only 1 subject each in a given treatment arm. See also section on adverse events.

Post marketing experience

Not available.

2.9.1. Discussion on clinical safety

In CLL/SLL, the initially (at MAA) submitted safety database for ibrutinib monotherapy consisted of 117 patients, including 51 patients at the intended 420 mg daily dose (primary safety population) and 34 patients at a higher daily dose of 840 mg. The median duration on treatment for the integrated population was 14.7 months and ranged up to 29 months. During the procedure, the study 1112 CSR was provided, adding randomised data from 195 patients to the total safety database. At study cut-off, the median duration of ibrutinib exposure was 8.6 months while 5.3 months for ofatumumab.

There are limited data on the effects of IMBRUVICA overdose. No maximum tolerated dose was reached in the phase 1 study in which patients received up to 12.5 mg/kg/day (1,400 mg). There is no specific antidote for IMBRUVICA. Patients who ingested more than the recommended dose should be closely monitored and given appropriate supportive treatment.

Patients with severe cardiovascular disease were excluded from IMBRUVICA clinical studies.

In summary the safety profile is based on pooled data from 357 patients treated with IMBRUVICA in two phase 2 clinical studies and one randomised phase 3 study. Patients treated for MCL received IMBRUVICA at 560 mg once daily and patients treated for CLL/SLL received IMBRUVICA at 420 mg once daily. All patients received IMBRUVICA until disease progression or no longer tolerated.

The most commonly occurring adverse reactions (≥ 20%,) were diarrhoea, musculoskeletal pain, upper respiratory tract infection, bruising, rash, nausea, pyrexia, neutropenia and constipation. The most common grade 3/4 adverse reactions (≥ 5%) were anaemia, neutropenia, pneumonia and thrombocytopenia.
Overall grade ≥3 events, AEs leading to dose reduction, and SAEs including grade ≥3 were all numerically more common in the ibrutinib arm. Incidence of discontinuation of study drug due to AE was similar between study arms (8%) while fatal AEs were slightly more common in the ofatumumab arm (8% vs 6%). Thus, while frequency as well as severity of side effects was more pronounced in the ibrutinib arm, discontinuation rate due to AE was not worryingly high and similar between study arms, indicating that the toxicity of ibrutinib is reasonably clinically manageable.

AE patterns were generally relatively similar in the two indications, dominated by GI symptoms, mainly diarrhoea, and in a conservative interpretation, associated with infections. Infections, cardiac AEs, haemorrhage, ocular events, and new primary malignancies (especially for the CLL/SLL indication) deserve further attention. (see RMP) Importantly, AE incidence generally decreased over time, and with relatively low discontinuation rates and dose reductions due to AEs, side effects overall seem clinically manageable by dose modifications as described in the SmPC section 4.2.

With a cut-off at 65 years, grade ≥3 events, SAEs and death within 30 days of last dose were all more common in the elderly group; notably, SAEs grade ≥3 were more than twice as common. A higher frequency of AEs with increasing age is generally an expected finding.

Only 22% (n=27) of the subjects in the integrated population were female, making an evaluation of AEs by sex difficult. It is noted that grade ≥3 AEs, any SAE and grade ≥3 AEs were slightly more common among females; 82% vs 75%, 63% vs 58%, and 56% vs 50%, respectively.

Creatinine >2.0 x ULN was an exclusion criterion in study 1104. It is noted that overall AEs grade ≥3 and death within 30 days of last dose were more common in patients with creatinine clearance below 30 mL/min. In a comparison of events, the following notable differences in the incidence of grade 3 and 4 AEs between subjects with lower versus higher creatinine clearance were identified: dyspnoea (12.5% versus 1.0%), diarrhoea (12.5% versus 3.1%), and anaemia (16.7% versus 7.3%), respectively. These findings might be confounded by age-related factors.

The AE profile in the randomised study 1112, overall and grade ≥3, was qualitatively consistent with was seen in the phase Ib/II study 1102 but generally less prominent. However, the 2 studies are not fully comparable due to various dosages in the 1102 study.

IMBRUVICA therapy should be withheld for any new onset or worsening grade ≥ 3 non-haematological toxicity, grade 3 or greater neutropenia with infection or fever, or grade 4 haematological toxicities. Once the symptoms of the toxicity have resolved to grade 1 or baseline (recovery), IMBRUVICA therapy may be reinitiated at the starting dose. If the toxicity reoccurs, the once daily dose should be reduced by one capsule (140 mg). A second reduction of dose by 140 mg may be considered as needed. If these toxicities persist or recur following two dose reductions, discontinue the medicinal product.

Recommended dose modifications are described below:

Toxicity occurrence	MCL dose modification after recovery	CLL/SLL dose modification after recovery
First	restart at 560 mg daily	restart at 420 mg daily
Second	restart at 420 mg daily	restart at 280 mg daily
Third	restart at 280 mg daily	restart at 140 mg daily
Fourth	discontinue IMBRUVICA	discontinue IMBRUVICA

Further follow-up to establish long-term safety will be provided within 1112 study update and in the upcoming MCL3001.

There have been reports of haemorrhagic events in patients treated with IMBRUVICA, both with and without thrombocytopenia. These include minor haemorrhagic events such as contusion, epistaxis, and petechiae; and major haemorrhagic events including gastrointestinal bleeding, intracranial haemorrhage, and haematuria.

Patients were excluded from participation in IMBRUVICA phase 2 and 3 studies if they required warfarin or other vitamin K antagonists. Warfarin or other vitamin K antagonists should not be administered concomitantly with IMBRUVICA. Supplements such as fish oil and vitamin E preparations should be avoided. Use of IMBRUVICA in patients requiring other anticoagulants or medicinal products that inhibit platelet function may increase the risk of bleeding, and particular care should be taken if anticoagulant therapy is used. Patients with congenital bleeding diathesis have not been studied.

IMBRUVICA should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Cases of leukostasis have been reported in patients treated with IMBRUVICA. (see also Pharmacodynamics discussion) A high number of circulating lymphocytes (> 400,000/mcL) may confer increased risk. Consider temporarily holding IMBRUVICA. Patients should be closely monitored. Administer supportive care including hydration and/or cytoreduction as indicated.

Infections (including sepsis, neutropenic sepsis, bacterial, viral, or fungal infections) were observed in patients treated with IMBRUVICA. Some of these infections have been associated with hospitalisation and death. Most patients with fatal infections also had neutropenia. Patients should be monitored for fever, neutropenia and infections and appropriate anti-infective therapy should be instituted as indicated.

Treatment-emergent grade 3 or 4 cytopenias (neutropenia, thrombocytopenia and anaemia) were reported in patients treated with IMBRUVICA. Monitor complete blood counts monthly.

Atrial fibrillation and atrial flutter have been reported in patients treated with IMBRUVICA, particularly in patients with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Periodically monitor all patients clinically for atrial fibrillation. Patients who develop arrhythmic symptoms or new onset of dyspnoea should be evaluated clinically and if indicated have an electrocardiogram (ECG) performed.

In patients with pre-existing atrial fibrillation requiring anticoagulant therapy, alternative treatment options to IMBRUVICA should be considered. In patients who develop atrial fibrillation on therapy with IMBRUVICA a thorough assessment of the risk for thromboembolic disease should be undertaken. In patients at high risk and where alternatives to IMBRUVICA are non-suitable, tightly controlled treatment with anticoagulants should be considered.

In a phase 2 study, ECG evaluations showed IMBRUVICA produced a mild decrease in QTcF interval (mean 7.5 ms). Although the underlying mechanism and safety relevance of this finding is not known, clinicians should use clinical judgment when assessing whether to prescribe ibrutinib to patients at risk from further shortening their QTc duration (e.g., Congenital Short QT Syndrome or patients with a family history of such a syndrome).

In studies 04753, 1104 and 1102 (n=309), additional malignancies were reported in 27 (8.7%) subjects. An imbalance between indications is noted with 19 (16.2%) and 5 (4.2%) patients reported with additional malignancy in CLL/SLL and MCL, respectively, mainly due to a higher incidence of skin carcinoma in the CLL/SLL group. Increased incidences of other malignant neoplasms have been frequently reported in patients with CLL/SLL and non-Hodgkin's Lymphomas; in particular for CLL/SLL, retrospective analysis indicated an approximate 8-fold increase of skin carcinomas and 2-fold higher frequency for all cancers excluding skin carcinomas compared to an age- and sex-matched control population.

In the 1112 study other malignancy in terms of skin cancer was noted in 5% in the ibrutinib arm vs 2% in the ofatumumab arm, and non-skin cancers in 2.6% vs 1%, respectively. Current data therefore indicate that treatment with ibrutinib may be associated with an increased risk for development of secondary malignancies, especially skin cancers. However, and importantly, in the 1112 study, the longer median duration of treatment for the ibrutinib arm vs the ofatumumab arm (8.6 and 5.3 months, respectively) and circumstances related to the reporting procedure for "other malignancies" confound the interpretation of the results, and an overestimation of the difference in the incidence of "other malignancies" between the two study arms is possible. Therefore, and as further controlled data is expected, it is considered reasonable to keep "Other malignancies" as an important potential risk in the RMP not to include this term in the SmPC at present.

Special attention was paid to ocular events as of the suspected non-clinical signal. Due to the age of the patient group and the disease population AEs in the eye is not unexpected and ocular AEs were reported for 31 (27.9%) subjects in Study 1104. None of the reported events were, according to the applicant, considered related to the treatment with ibrutinib. Concerning both the pancreas and corneal signal the risk to patients is regarded as low due to species pre-disposition, exposure margins and clinical safety data.

In the clinic 68.3% of patients experience skin and subcutaneous tissue SAEs, which was in line with non-clinical signals for skin SAEs/toxicity.

Ibrutinib is clinically associated with exposure-dependent QTc shortening, prolonged PR interval and reduction in heart rate. Cardiac AEs were reported in approximately 20% of patients with atrial fibrillation in 5-9%; Torsade de pointes and ventricular tachycardia were reported in 1 patient each in the MCL population. Considering the obscure clinical significance of the QT shortening associated with ibrutinib, cardiac safety should be part of the RMP. In contrast, the preclinical data package shows hERG inhibition at concentrations above clinical exposure and in vivo safety pharmacology generated in dog also show cardiac effects.
With a cut-off at 65 years, only grade ≥3 events were slightly more common in the elderly group. A higher incidence of grade ≥3 dehydration and atrial fibrillation among the elderly is not surprising.

By preferred term, the only notable differences in the incidence of grade 3 and 4 AEs between subjects with lower versus higher creatinine clearance were, respectively, sinusitis (13.0% vs 2.1%) and hypertension (13.0% vs 6.4%). These findings might be confounded by age-related factors.

No specific clinical studies have been conducted in patients with renal impairment. Patients with mild or moderate renal impairment were treated in IMBRUVICA clinical studies. No dose adjustment is needed for patients with mild or moderate renal impairment (greater than 30 mL/min creatinine clearance). Hydration should be maintained and serum creatinine levels monitored periodically. Administer IMBRUVICA to patients with severe renal impairment (less than 30 mL/min creatinine clearance) only if the benefit outweighs the risk and monitor patients closely for signs of toxicity. There are no data in patients with severe renal impairment or patients on dialysis (see section 5.2).

Ibrutinib is metabolised in the liver. Patients with serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≥ 3 x upper limit of normal (ULN) were excluded from IMBRUVICA clinical studies. In a dedicated hepatic impairment trial in non-cancer patients, preliminary data showed an increase in ibrutinib exposure (see section 5.2). For patients with mild liver impairment (Child-Pugh class A), the recommended dose is 280 mg daily (two capsules). For patients with moderate liver impairment (Child-Pugh class B), the recommended dose is 140 mg daily (one capsule). Monitor patients for signs of IMBRUVICA toxicity and follow dose modification guidance as needed. It is not recommended to administer IMBRUVICA to patients with severe hepatic impairment (Child-Pugh class C).

The safety and efficacy of IMBRUVICA in children aged 0 to 18 years have not been established. No data are available.

The safety data bases for both indications derive from a relatively short follow-up; long term safety is to be addressed in future study updates (see RMP) and within the PSURs.

Submission of the study report from the planned thorough QTc study (PCI-32765CLL1007) when completed is awaited in order to clarify concerns discussed in connection to the Pharmacology section.

A specific safety issue relates to the concomitant use of CYP3A4 inhibitors and inducers as discussed in the Pharmacology section is appropriately addressed in the SmPC with dose modifications and warnings.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics section 4.8.

2.9.2. Conclusions on the clinical safety

The safety profile is based on pooled data from 357 patients treated with IMBRUVICA in two phase 2 clinical studies and one randomised phase 3 study. Patients treated for MCL received IMBRUVICA at 560 mg once daily and patients treated for CLL received IMBRUVICA at 420 mg once daily. All patients received IMBRUVICA until disease progression or no longer tolerated. The most commonly occurring adverse reactions (⩾ 20%,) were diarrhoea, musculoskeletal pain, upper respiratory tract infection, bruising, rash, nausea, pyrexia, neutropenia and constipation. The most common grade 3/4 adverse reactions (⩾ 5%) were anaemia, neutropenia, pneumonia and thrombocytopenia.

The CHMP considers the following measures necessary to address issues related to safety:

- Submission of the study report from the planned thorough QTc study (PCI-32765CLL1007) when completed.

2.10. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.11. Risk Management Plan

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

Based on the PRAC review of the Risk Management Plan version 3.1, the PRAC considers by consensus that the risk management system for ibrutinib (Imbruvica) in:

- the treatment of adult patients with relapsed or refractory MCL

  and 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 could be acceptable with some minor amendments as detailed in the attached PRAC Rapporteur's RMP AR.

The CHMP endorsed this advice, but considered that it would not be necessary to include the studies on potential predictive biomarkers for responders and/or drug/disease resistance in the Pharmacovigilance Plan as a required additional pharmacovigilance activity.

Following the CHMP meeting the applicant implemented the changes in the RMP as requested by the PRAC and the CHMP in RMP version 3.2 with the following content:

- ***Safety concerns***

Table 73. Summary of the Safety Concerns

Important Identified Risks	Leukostasis Haemorrhage
Important Potential Risks	Drug-drug interaction Anaemia Neutropenia Thrombocytopenia Infections Cardiac arrhythmia Severe GI disorders Other malignancies Hypersensitivity Teratogenicity Tumour lysis syndrome 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 74. On-going and planned studies in the Post-authorisation Pharmacovigilance Development 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	Planning stages	To be determined
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 postmarketing sources	Haemorrhage	Planning stages	To be determined
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	Planning stages	To be determined
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 3)	Yearly updates of trial results for progression and death.	Overall safety profile	Yearly updates	2nd Quarter 2015 2nd Quarter 2016 2nd Quarter 2017 4th Quarter 2017
JNJ-54179060/FK10654 Study on the inhibition potential of JNJ-54179060 and four metabolites on OATP1B1 (SLCO1B1) and OATP1B3 (SLCO1B3) transport in HEK293 cell lines overexpressing this transporter. (category 3)	To evaluate the potential inhibitory effect of ibrutinib and 4 metabolites on drug transporting proteins OATP1B1 (SLCO1B1) and OATP1B3 (SLCO1B3.	Drug-drug interaction	Started	1st Quarter 2015
JNJ-54179060/FK10655 Study on the inhibition potential of JNJ-54179060 and four metabolites on OAT3 (SLC22A8) transport in MDCK-II cell lines overexpressing this transporter. (category 3)	To evaluate the potential inhibitory effect of ibrutinib and 4 metabolites on drug transporting protein OAT3 (SLC22A8).	Drug-drug interaction	Started	1st Quarter 2015

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)
JNJ-54179060/FK10656 Study on the inhibition potential of JNJ-54179060 and four metabolites on OAT1 (SLC22A6) and OCT2 (SLC22A2) transport in CHO cell lines overexpressing this transporter. (category 3)	To evaluate the potential inhibitory effect of ibrutinib and 4 metabolites on drug transporting proteins OAT1 (SLC22A6) and OCT2 (SLC22A2).	Drug-drug interaction	Started	1st Quarter 2015
JNJ-54179060/FK10657 An in vitro study on the possible BRCP (ABCG2) transport inhibition by JNJ-54179060 and four metabolites. (category 3)	To evaluate the potential inhibitory effect of ibrutinib and 4 metabolites on drug transporting protein BRCP (ABCG2).	Drug-drug interaction	Started	1st Quarter 2015
In vitro study of inhibition by ibrutinib on CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 (category 3)	To investigate the time dependent inhibition by ibrutinib on CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6	Drug-drug interaction	Planned	1st Quarter 2015
An in vitro inhibition experiment for reversible CYP3A inhibition by ibrutinib minimising the decline in ibrutinib concentration during incubations. (category 3)	To better estimate the actual in vitro ibrutinib CYP3A Ki.	Drug-drug interaction	Planned	1st Quarter 2015
An in vitro study into hepatic CYP1A2 and CYP2B6 induction with the inclusion of unchanged ibrutinib recovery assessment during and at the end of the incubation. (category 3)	To evaluate the potential inducing effect of ibrutinib on hepatic CYP1A2 and CYP2B6.	Drug-drug interaction	Planned	1st Quarter 2015
PCI-32765 CLL1006 (enrolment completed) Phase 1, open-label, single-dose, multicentre, non-randomised in healthy subjects and subjects with hepatic impairment. (category 3)	Evaluate the effect of hepatic impairment on ibrutinib PK	Use in patients with severe hepatic impairment	Trial completion: 30 March 2014	Ongoing Planned final report submission: 4th Quarter 2014
PCI-32765 CLL1007 (planned) Thorough QT study (category 3)	To assess the effect of ibrutinib on ECG parameters	Cardiac arrhythmia	Planned	Final Protocol Submission: 4th Quarter 2014 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
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
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 3)	Evaluate efficacy and safety of ibrutinib vs. temsirolimus.	Overall safety profile	Ongoing	1st Quarter 2016 final
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
PCYC-1115-CA Phase 3; Randomised, multicentre, open-label; Subjects ≥65 years with treatment naive CLL	Assess efficacy of ibrutinib compared with chlorambucil based on PFS by IRC	Overall safety profile	Ongoing	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-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
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	3rd 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

[a] Trial only collects grade 3 or 4 adverse events and not all adverse events

Risk minimisation measures

Table 75. Summary Table of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important identified risks:		
Leukostasis	The SmPC (Sections 4.4 and 4.8) states that patients should be closely monitored. Supportive care should be administer including hydration and/or cytoreduction as indicated, and/or consider temporarily holding ibrutinib.	None
Haemorrhage	The SmPC (Section 4.4) states that warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in patients requiring anticoagulants or medications that inhibit platelet function. Patients with congenital bleeding diathesis have not been studied. Ibrutinib should be withheld for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding.	None
Drug-drug interactions	The SmPC (Section 4.4 and 4.5) states that the concomitant use of ibrutinib with strong or moderate CYP3A inhibitors and moderate and strong and moderate inducers should be avoided when possible. Preparations containing St. John's wort are	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	contraindicated during treatment with ibrutinib, as efficacy may be reduced.	
Anaemia	The SmPC (Sections 4.4 and 4.8) states that treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia and anaemia) were reported in patients treated with ibrutinib. Complete blood counts should be monitored monthly.	None

Important potential risks:

Neutropenia	The SmPC (Sections 4.4 and 4.8) states that treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia and anaemia) were reported in patients treated with ibrutinib. Complete blood counts should be monitored monthly.	None
Thrombocytopenia	The SmPC (Sections 4.4 and 4.8) states that treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia and anaemia) were reported in patients treated with ibrutinib. Complete blood counts should be monitored monthly.	None
Infections	The SmPC (Section 4.4) states that infections (including sepsis, neutropenic sepsis, bacterial, viral, or fungal infections) have been observed in patients treated with ibrutinib. Some of these infections have been associated with hospitalisation and death. Most patients with fatal infections also had neutropenia. Patients should be monitored for fever and infections and appropriate anti-infective therapy should be instituted as indicated.	None
Cardiac arrhythmia	The SmPC (Section 4.4) states that atrial fibrillation and atrial flutter have been reported in patients treated with ibrutinib, particularly in patients with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Periodically monitor patients clinically for atrial fibrillation. If clinically indicated, the use of anti coagulants or anti platelet agents may be considered for the thromboprophylaxis of atrial fibrillation. In a Phase 2 study, ECG evaluation showed, ibrutinib produced a decrease in QTc interval.	None
Severe GI adverse events	The SmPC (Section 4.8) states that the most commonly occurring GI adverse events (≥5%) were diarrhoea and abdominal pain.	None
Other malignancies	None proposed.	None
Hypersensitivity	The SmPC (Section 4.3) recommends that ibrutinib should not be administered to patients who have known hypersensitivity to ibrutinib or to the excipients in its formulation.	None
Teratogenicity	The SmPC (Sections 4.4 and 4.6) discuss that based on findings in animals, ibrutinib may cause fetal harm when administered to pregnant women.	None

Important potential risks:

Tumour lysis syndrome	None proposed.	None
Eye disorders	The SmPC (Section 4.8) states vision blurred is a common adverse event.	None
Renal failure	The SmPC (Section 4.2) states that hydration should be maintained and serum creatinine levels monitored periodically. Ibrutinib should be administered to patients with severe renal impairment (less than 30 mL/min creatinine clearance) only if the benefit outweighs the risk and patients should be monitored closely for signs of toxicity.	None
Hypertension	None proposed.	None

Missing Information:

Use in paediatric patients	The safety and efficacy of ibrutinib in children aged < 18 years have not yet been established. (SmPC Section 4.2).	None
Use during breastfeeding	The SmPC (Section 4.6) states that it is not known whether ibrutinib or its metabolites are excreted in human milk. A risk to breastfeeding newborns/infants cannot be excluded. Breastfeeding should be discontinued during treatment with ibrutinib.	None
Use in patients with severe cardiac disease	The SmPC (Section 4.2) states that patients with severe cardiovascular disease were excluded from ibrutinib clinical trials.	None
Use in patients with severe renal impairment	The SmPC (Section 4.2) states that no specific clinical studies have been conducted in patients with renal impairment, but patients with mild or moderate renal impairment were treated in ibrutinib clinical trials. No dose adjustment is needed for patients with mild or moderate renal impairment (>30 mL/min creatinine clearance), but ibrutinib should be administered to patients with severe renal impairment (<30 mL/min creatinine clearance) only if the benefit outweighs the risk and patients should be monitored closely. Hydration should be maintained and serum creatinine levels monitored periodically. There are no data in patients with severe renal impairment or patients on dialysis.	None
Use in patients with severe hepatic impairment	The SmPC (Section 4.2) state that ibrutinib is metabolised in the liver. Hepatic impairment has been associated with substantial increase in ibrutinib exposure. For patients with mild liver impairment (Child Pugh class A), the recommended dose is 280 mg daily (2 capsules). For patients with moderate liver impairment (Child Pugh class B), the recommended dose is 140 mg daily (1 capsule). Patients should be monitored and dose modification guidance followed as needed. Ibrutinib should not be administered to patients with severe hepatic impairment (Child-Pugh class C).	None
Long term use (>2 years)	None proposed.	None

2.12. Product information

2.13. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

MCL: In a single arm ibrutinib monotherapy study conducted in patients with relapsed / refractory MCL an ORR of 67.6% a PFS rate of 63% (95% CI 53, 71%) at 6 months and a duration of response of 17.5 months were observed. In an update on time-dependent outcomes as of 14 March 2014, the beneficial effects were sustained.

The treatment effect seemed fairly consistent throughout the analysed subgroups, including region, relapsed or refractory disease, bulky disease, number of prior regimens, simplified MIPI score, and prior therapy with bortezomib or lenalidomide.

CLL/SLL: Ibrutinib in a randomised study in CLL patients showed a statistically highly significant superiority, with a PFS HR = 0.215, compared to ofatumumab. Median PFS was 8.1 months in the ofatumumab arm while not reached in the ibrutinib arm. Kaplan- Meier estimates at 1 year showed a PFS rate of 66% in the ibrutinib arm vs 6% in the ofatumumab arm. In secondary analyses OS data also showed a favourable effect for the ibrutinib arm with a HR of 0.434. Confirmed ORR was remarkably and statistically significantly higher in the ibrutinib arm, (43%), vs the ofatumumab arm (4%).

The robustness of the primary analysis is supported by performed sensitivity analyses and the general consistency in the subgroup analyses. Importantly, outcome in patients with and without del 17p in the ibrutinib arm was similar, independently of resistance to purine analogue. In subjects with cytopenia at baseline, a markedly larger fraction achieved sustained haematological improvement of neutropenia or thrombocytopenia in the ibrutinib arm, 63% vs 32% and 72% vs 22%, respectively; a clinically relevant finding.

Uncertainty in the knowledge about the beneficial effects.

The evaluation of the efficacy of ibrutinib in r/r MCL is based on non-randomised data. A randomized trial is currently ongoing, evaluating ibrutinib vs temsirolimus, and results should be provided, as a post-approval measure by 1Q 2016.

The important results in the CLL population are from an interim analysis and are based on only 26 disease progressions and 9 deaths in the ibrutinib arm, and further follow-up will be provided. The early availability of the positive interim analysis, imposes uncertainties on the final analysis as future study updates will be impacted by the effect of cross-over, however the outstanding results seen are already sufficiently robust. (see Annex II of the opinion)

Risks

Unfavourable effects

The reported AE pattern is roughly similar across clinical trials and indications. The most commonly occurring adverse reactions are: pneumonia, upper respiratory tract infection, sinusitis, neutropenia, thrombocytopenia, anaemia, dizziness, headache, haemorrhage, bruising, petechiae, diarrhoea, vomiting, stomatitis, nausea, constipation, rash, arthralgia, musculoskeletal pain, pyrexia and peripheral oedema.

Discontinuation rate due to AE was at acceptable levels and similar across indications (4% of MCL patients discontinued treatment due to AEs, and 8% in both treatment groups in study 1112 in CLL/SLL, indicating that the toxicity of ibrutinib is reasonably clinically manageable with dose modifications.

As ibrutinib is primarily metabolised by CYP3A4, there are a significant changes in ibrutinib exposure seen for CYP3A4 inhibitors and inducers.

Uncertainty in the knowledge about the unfavourable effects

In the clinical studies additional malignancies were reported. In the 1104 study in MCL, the incidence of additional malignancies was 4%; In the 1112 study other malignancy in terms of skin cancer was noted in 5% in the ibrutinib arm vs 2% in the ofatumumab arm, and non-skin cancers in 2.6% vs 1%, respectively. However, in the 1112 study, the longer median duration of treatment for the ibrutinib arm vs the ofatumumab arm (8.6 and 5.3 months, respectively) and circumstances related to the reporting procedure for "other malignancies" confound the interpretation of the results, and an overestimation of the difference in the incidence of "other malignancies" between the two study arms is possible. CLL is associated with an increased incidence of skin cancer assumed to be related to immune suppressive effects of the disease and treatment, e.g. with alkylating agents. Therefore, and as further controlled data are expected, the risk of "Other malignancies" is added in the RMP and events will be addressed as events of special interest in ongoing and future clinical trials (see RMP).

Ibrutinib is clinically associated with exposure-dependent QTc shortening, prolonged PR interval and reduction in heart rate. Cardiac AEs were reported in approximately 20% of patients with atrial fibrillation in 5-9%; Torsade de pointes and ventricular tachycardia were reported in 1 patient each in the MCL population. Cardiac safety is part of the RMP.

A weakness of the safety data bases for both indications is the relatively short follow-up; long term safety is to be addressed in future study updates and within the RMP.

Benefit-risk balance

Importance of favourable and unfavourable effects

The results from studies conducted in the CLL indication are of high clinical relevance. The activity of ibrutinib was demonstrated across trials. The positive results in the high risk patients with del17p / TP53 mutations are of particular importance and support an indication in first line for those patients who are unsuitable for chemo-immunotherapy.

Clinically relevant results were observed in patients with MCL treated with ibrutinib monotherapy. Although the pivotal study is a single arm study, the dramatic activity seen in terms of ORR, and DOR is unprecedented historically and considered sufficiently important in this heavily pre-treated patient population to support approval.

The most frequent adverse reactions related to the use of the ibrutinib are infections, neutropenia, and diarrhoea. However, discontinuation due to toxicity was infrequent and overall the toxicity was considered manageable.

The safety profile was similar across clinical trials and indications with diarrhoea and infections as predominant events and most common grade 3/4 adverse reactions (≥ 5%) were anaemia, neutropenia, pneumonia and thrombocytopenia. Discontinuation due to toxicity was infrequent and overall the toxicity was considered manageable with dose modifications.

Benefit-risk balance

The important benefits observed in the two indications outweigh the risks related to the use of ibrutinib.

Discussion on the benefit-risk balance

Of major importance in the assessment of benefit is the consistently shown dramatic activity of ibrutinib irrespective of refractoriness to prior therapy or unfavourable prognostic factors in patients with MCL and CLL.

The high response rates and long durations of response at acceptable toxicity are acknowledged, although the long-term data are not yet available. As a consequence, efficacy and safety data from ongoing studies will be regularly updated to provide additional information about long-term benefits and risks.

The benefit- risk balance in the indication:

- treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).

Is positive, as outstanding activity is shown in terms of high response rate in this patient population of an unmet clinical need

The benefit- risk balance in the indication:

- 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 unlikely to benefit from chemo-immunotherapy.

is positive considering that patients who had received prior therapies included in the pivotal study had a statistically significant reduction in the risk of death or progression. The efficacy was similar across all of the subgroups examined, including in patients with and without deletion 17p, a pre-specified stratification factor, patients who are unlikely to benefit from chemo – immunotherapy.

In patients with del17p/TP53 mutations limited options such as fludarabine or alemtuzumab combination regimens may be available; however these regimens are too toxic for large proportions of patients, therefore benefit-risk is considered clearly favourable for patients non-suitable for immuno-chemotherapy in case of mutations del17p/TP53, regardless of prior treatment experience.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Imbruvica is not similar to Arzerra, Gazyvaro and Torisel and within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Imbruvica in the treatment of

- adult patients with relapsed or refractory mantle cell lymphoma (MCL).
- 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 unlikely to benefit from chemo-immunotherapy

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Obligation to complete post-authorisation measures**

Description	**Due date**
Submission of the final study report of study MCL3001	1Q 2016
Submission of yearly updates of study 1112 results for progression and death - to be provided until maturity in the ibrutinib arm, e.g. 70%, and preferably also include PFS2, or, at least, time on next therapy.	2Q 2015

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that Imbruvica (ibrutinib) is qualified as a new active substance.