European Union Risk Management Plan (EU-RMP)
IMBRUVICA (Ibrutinib)

Data lock point for current RMP	30 Sep 2021	Version number	22.1

QPPV Sign-off Date: 02 November 2023
RMP Version Number: 22.1
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QPPV Name(s):	Dr. Laurence Oster-Gozet, PharmD, PhD
QPPV Signature:	The MAH QPPV has either reviewed and approved this RMP, or approved with an electronic signature appended to this RMP, as applicable.

Details of this RMP Submission	
Version Number	22.1
Rationale for submitting an updated RMP	Type IB variation to update the RMP.
Summary of significant changes in this RMP	Update of the due date for the final report of the additional pharmacovigilance activity "Analysis of aggregate randomized controlled clinical trial data" to further evaluate the risk of hemorrhage from 1st Quarter 2024 to 4th Quarter 2024.

Other RMP Versions Under Evaluation:

RMP Version Number	Submitted on	Procedure Number
Not applicable		

Details of the Currently Approved RMP:

Version number of last agreed RMP	21.2
Approved within procedure	EMEA/H/C/003791/IB/0079
Date of approval (opinion date)	17 May 2023

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PART I: PRODUCT(S) OVERVIEW

Active substance(s) **(International Nonproprietary Name [INN] or common name)**	Ibrutinib
Pharmacotherapeutic group(s) (Anatomic Therapeutic Chemical [ATC] Code)	Antineoplastic agents, protein kinase inhibitors (L01EL01)
Marketing Authorization Holder (MAH)	Janssen-Cilag International, NV
Medicinal products to which the Risk Management Plan refers	IMBRUVICA®
Invented name(s) in the European Economic Area (EEA)	IMBRUVICA
Marketing authorization procedure	Centralized procedure
Brief description of the product	**Chemical class** Small-molecule inhibitor of Bruton's tyrosine kinase (BTK)
	Summary of mode of action Ibrutinib is a potent, small-molecule inhibitor of BTK and forms a stable 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 signaling molecule of the B-cell antigen receptor and cytokine receptor pathways. The B-cell antigen receptor pathway is implicated in the pathogenesis of several B-cell malignancies, including mantle cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, and B-cell chronic lymphocytic leukemia (CLL). BTK's pivotal role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. Ibrutinib effectively inhibits malignant B-cell proliferation and survival as well as cell migration and substrate adhesion. In preclinical tumor models, the combination of ibrutinib and venetoclax resulted in increased cellular apoptosis and anti-tumor activity compared to either agent alone. BTK inhibition by ibrutinib increases CLL cell dependence on BCL-2, a cell survival pathway, while venetoclax inhibits BCL-2 leading to apoptosis.
	Important information about its composition Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Reference to the Product Information	Module 1.3.1 Summary of Product Characteristics, Labeling and Package Leaflet
Indication(s) in the EEA	Current: IMBRUVICA as a single agent is indicated for the treatment of adult patients with relapsed or refractory MCL. IMBRUVICA as a single agent or in combination with rituximab or obinutuzumab or venetoclax is indicated for the treatment of adult patients with previously untreated CLL. IMBRUVICA as a single agent or in combination with bendamustine and rituximab (BR) is indicated for the treatment of adult patients with CLL who have received at least one prior therapy. IMBRUVICA as a single agent is indicated for the treatment of adult patients with Waldenström's macroglobulinemia (WM) who have received at least one prior therapy, or in first-line treatment for patients unsuitable for chemo-immunotherapy. IMBRUVICA in combination with rituximab is indicated for the treatment of adult patients with WM.
	Proposed: Not applicable.
Dosage in the EEA	Current: MCL The recommended dose of ibrutinib for the treatment of MCL is 560 mg once daily. CLL The recommended dose of ibrutinib for the treatment of CLL, either as a single agent or in combination, is 420 mg once daily. In combination with venetoclax, ibrutinib should be administered as a single agent for 3 cycles (1 cycle is 28 days), followed by 12 cycles of ibrutinib plus venetoclax. WM The recommended dose for the treatment of WM, either as a single agent or in combination, is 420 mg once daily. When administering ibrutinib in combination with anti-CD20 therapy, it is recommended to administer ibrutinib prior to anti-CD20 therapy when given on the same day.
	Proposed: Not applicable.

Pharmaceutical form(s) and strengths	Current: Ibrutinib comes in 140 mg hard capsules marked with “ibr 140 mg” in black ink and in film-coated tablets in the following strengths: *140 mg* Yellow-green to green round tablet, debossed on one side with “ibr” and “140” on the other side. *280 mg* Purple oblong tablet, debossed on one side with “ibr” and “280” on the other side. *420 mg* Yellow-green to green oblong tablet, debossed on one side with “ibr” and “420” on the other side. *560 mg* Yellow to orange oblong tablet, debossed on one side with “ibr” and “560” on the other side.		
	Proposed: Not applicable.		
Is/will the product subject to additional monitoring in the EU?		☐ **Yes**	☑ **No**

PART II: SAFETY SPECIFICATION

Module SI: Epidemiology of the Indication(s) and Target Population(s)

Indication: Mantle Cell Lymphoma

Incidence:

Mantle cell lymphoma represents approximately 6% to 8% of all new non-Hodgkin's lymphoma (NHL) cases per year (Rule, 2019). Estimates of the incidence of MCL in the total population are below 1 case per 100,000 persons throughout the world. The incidence of MCL in Europe has been estimated at 0.45 per 100,000 population and 0.71 per 100,000 population in the United States (US) based on registry data from 2002 to 2007 (Botta et al, 2020). Other national databases have estimated an incidence of 0.9 per 100,000 persons for the years 2010 to 2016 in the United Kingdom (UK) (Hematological Malignancy Research Network [HMRN], 2019) and 1.80 per 100,000 persons in Finland for 2019 (Finnish Cancer Registry, 2021).

Prevalence:

MCL represents 7% to 9% of lymphomas in Europe (Vose, 2017) and 1.3% of all hematological malignancies in the United Kingdom (HMRN, 2019). Prevalence in Europe is estimated to be about 3.5 per 100,000 population (Orphanet, 2021). The 10-year prevalence in the United Kingdom for 2007 to 2016 is estimated at 3.7 per 100,000 population (HMRN, 2019). A study by Sant analyzed 16,955 NHL cases diagnosed from 1990 to 1994 in 27 of 67 population-based cancer registries participating in European Cancer Registry (EUROCARE), and 22,713 NHL cases diagnosed over the same period in 9 US cancer registries. Of the 4 NHL groupings (follicular lymphoma, DLBCL, MCL, and "other NHL" subtypes), MCL had similar frequencies in EUROCARE overall and in Surveillance, Epidemiology, and End Results (SEER) (5.9% and 4.4% of total NHL cases), but a much higher frequency in Estonia (20.3%) likely due to incorrect coding conversions in diagnostic disease codes (Sant et al, 2008). The Committee for Orphan Medicinal Products at the European Medicines Agency (EMA) reported that the prevalence rate of MCL for the period from 2004 to 2015 was stable at approximately 0.5 in 10,000 (Polsinelli et al, 2017).

Demographics of the Population in the Authorized Indication - Sex, Age, Racial and/or Ethnic Origin, and Risk Factors for the Disease

<u>Sex</u>

MCL is more than twice as common among men compared with women both in Europe (male-to-female-ratio 2.3:1) and in the United States (male-to-female ratio 2.65:1) (Aschebrook-Kilfoy et al, 2013). In the United Kingdom, the male-to-female ratio is 2.6:1 (HMRN, 2019). Specifically, in the United States, the incidence rate of MCL in men was reported to be 1.3 per 100,000 person-years for 2007 to 2016, and among women, the rate was 0.4 per 100,000 person-years (Howlader et al, 2019).

Age

In the United Kingdom, the median age at diagnosis is 72.9 years (HMRN, 2019). In the United Kingdom, the incidence increases with age going from 0.52 per 100,000 population for 45- to 49-year-olds, with the highest rate being 4.69 per 100,000 population for 75- to 79-year-olds, and 4.02 per 100,000 population for those aged 80 and older (HMRN, 2019).

In the United States, from 2007 to 2016, the overall incidence rate per 100,000 person-years was 0.4 in 20- to 64-year-olds and 4.4 in those aged 65 and older (Howlader et al, 2019).

Race/Ethnicity

MCL incidence does not show an association with ethnicity in the United Kingdom (Cancer Research UK, Non-Hodgkin Lymphoma Incidence Statistics, 2016). In the United States, for the years 2004 to 2013, 82.7% of MCL patients were white non-Hispanic, 3.9% were black, 6.0% were Hispanic, and 7.3% were other populations (Shah et al, 2019). There is evidence that the incidence of MCL in Asian countries is lower than in western countries (Jain and Wang, 2019).

Risk Factors for the Disease

Risk factors for MCL include being above the age of 60 years and being male. There is also a strong link between immune suppression and lymphoma. Those who are human immunodeficiency virus (HIV)-positive are at a higher risk than those without. Another infectious disease associated with an increased risk of MCL is Lyme disease.

Family history of the disease is also associated with a 2-fold increase (Smedby and Hjalgrim, 2011). It has been observed that patients with MCL may have a first-degree relative who is also affected with this lymphoma or other NHLs. The tumor in these relatives appears at a younger age than in the parents, thus suggesting a genetic predisposition (Cortelazzo et al, 2012).

It has also been suggested that people exposed to causative agents for an extended period of time, such as pesticides, organophosphate insecticides, and phenoxy herbicides, have a greater risk of developing MCL (Cortelazzo et al, 2012).

Main Existing Treatment Options:

Most patients with MCL receive treatment following diagnosis and staging. For younger, fit patients with MCL, the therapeutic strategy has been to use aggressive induction chemotherapy followed by autologous stem cell transplantation. For older patients who cannot tolerate intensive chemotherapy or autologous stem cell transplantation, historically, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy has been used, and other chemotherapy options include VR-CAP (a combination of bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone) and BR (Chen et al, 2016).

The prognosis for patients with MCL who have progressed after first-line therapy is dismal. In the European Union (EU), temsirolimus and ibrutinib are approved for treating relapsed and refractory MCL (Dreyling et al, 2014). Bortezomib is approved in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone for the treatment of previously untreated MCL in patients who are unsuitable for hematopoietic stem cell transplantation (SCT) in the European Union (Dreyling et al, 2014). Lenalidomide is used for the treatment of relapsed MCL and has also been used in combination with rituximab (Vose, 2017).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

MCL is an aggressive B-cell subtype of NHL which generally arises from naïve, pre–germinal center lymphocytes. MCL characteristically exhibits small-to-medium–sized tumor cells that can infiltrate the lymph nodes, spleen, bone marrow, blood, and gastrointestinal (GI) system. It has an aggressive disease course and a high rate of relapse. Most patients are initially diagnosed with stage III or IV disease, and are usually symptomatic at presentation. Common features include widespread lymphadenopathy and splenomegaly, and bone marrow infiltration. Leukemic involvement is found in 20% to 30% of patients. Extranodal involvement is common, and most frequently involves the GI tract and liver. More than 90% of patients have extranodal involvement at diagnosis, and between 30% and 50% of patients show infiltration in more than 2 extranodal areas. The clinical course of MCL is not uniform, as disease course usually corresponds with the particular subtype of the disease (Rosen et al, 2013). In approximately 10% to 20% of patients, the clinical course of MCL is smoldering nodal/extra-nodal or asymptomatic non-blastoid leukemic non-nodal. These are variants that do not need immediate systemic treatment and the watch-and-wait strategy is used (Jain and Wang, 2019). However, most cases follow a relatively rapid disease progression, short response to treatment, inevitable relapses, and continuously declining survival curve (Li et al, 2013).

Mortality and Morbidity

There is no curative therapy for MCL, with the rare exception of patients who achieve long-term, disease-free survival after allogeneic SCT (Goy, 2011). The median duration of remission according to most studies is 1.5 to 3 years and the median survival is 3 to 6 years with standard chemotherapy (Leukemia & Lymphoma Society MCL, 2018). In the United Kingdom, the 5-year relative survival has been estimated to be 41.9% (HMRN, 2019). Some patients succumb to their disease in less than 6 months, whereas others (8%) survive more than 10 years. The blastoid and pleomorphic variants appear more aggressive, with a median overall survival (OS) of 18 months. The median OS of patients with advanced non-blastoid or pleomorphic MCL almost doubled during the past 30 years from 2.7 years up to 4.8 years in recent studies. The superior outcome may be a result of the improvement of treatment regimens (Cortelazzo et al, 2012). Data suggest that survival also improved in Germany, with the 5-year relative survival for MCL increasing from 51.6% in 2003 to 2007 to 58.5% in 2008 to 2012 (Pulte et al, 2017). One study reported a median OS of 70 months, a 5-year OS of 54.9% and 10-year OS of 33.5% (Chihara et al, 2019).

Important Comorbidities:

Important comorbidities in patients with MCL include infections, cardiovascular diseases (CVD), renal insufficiencies (Schmidt et al, 2011), and other malignancies (Chihara et al, 2016).

Indication: Chronic Lymphocytic Leukemia

Incidence:

CLL, a B-cell lymphoid malignancy, is the most common leukemia among adults in the United States and Europe with annual incidence ranging between 4 to 6 cases per 100,000 persons (Scarfò et al, 2016). In the United Kingdom, for the years 2010 to 2016, the incidence was estimated at 7.2 per 100,000 population, with 4,680 new cases in 2016 (HMRN, 2019), and in Finland the age-standardized incidence for 2019 was estimated to be 4.64 per 100,000 population (Finnish Cancer Registry, 2021). Based on the Cancer Registry of Norway, the age-standardized incidence increased from 0.6 per 100,000 person-years in 1953 to 3.1 per 100,000 person-years in 2012. There was a 68% increase in incidence between 1993 to 2002 (1,557 patients) and 2003 to 2012 (2,636 patients) (Lenartova et al, 2016). For 2014 to 2018, the age-adjusted incidence of CLL in the United States was 4.9 per 100,000 population (SEER Explorer, 2021). A Canadian study conducted in the province of British Columbia observed a world age-standardized incidence rate of CLL to be 1.71 per 100,000 in that province (Mak et al, 2014).

Approximately 5% to 8% of patients have a detectable deletion of the short arm of chromosome 17 (del17p) at diagnosis (Stilgenbauer and Zenz, 2010). The del17p results in the deletion of one allele of *TP53*, the gene encoding for the important tumor suppressor p53 (Sellner et al, 2013). A further 4% to 5% of patients have *TP53* mutation without del17p at the time of diagnosis. The proportion of patients with del17p increases with successive chemotherapy treatments, so that in the relapsed setting up to 30% to 50% of patients have del17p (Badoux et al, 2011; Stilgenbauer and Zenz, 2010).

Prevalence:

In Europe, the prevalence of CLL has been estimated to be 48 per 100,000 population (Orphanet, 2021). The worldwide prevalence of CLL in 2016 was 460,000 (Global Burden of Disease and Injury Incidence and Prevalence Collaborators, 2017). In the United Kingdom, CLL accounts for 10.6% of all hematological malignancies (HMRN, 2019). In the United States, there were an estimated 195,129 (0.060%) people living with CLL in 2018 (SEER Explorer, 2021).

Demographics of the Population in the Authorized Indication - Sex, Age, Racial and/or Ethnic Origin, and Risk Factors for the Disease

<u>Sex</u>

Globally, the age-standardized incidence rate per 100,000 person-years for CLL in 2015 was estimated to be 3.4 (3.2-3.7) for men and 2.4 (2.2-2.6) for women (Global Burden of Disease Cancer Collaboration, 2017). In Europe, the incidence rate of CLL varies from 2.2 to 3.36 per 100,000 population in men and 0.9 to 1.52 per 100,000 population in women (Panovska et al, 2010). In the United Kingdom, the age-standardized incidence rate has been estimated to be 9.2 per 100,000 population for men and 5.2 per 100,000 population for women (HMRN, 2019). For the

Nordic countries (Denmark, Finland, Greenland, Iceland, Norway, and Sweden), the age-standardized incidence rate was 3.6 per 100,000 population for men and 1.8 per 100,000 population for women in 2016 (Nordcan, 2019). In the United States, the incidence rate is 6.7 per 100,000 population for men and 3.5 per 100,000 population for women for 2014 to 2018 (SEER Explorer, 2021).

Age

This disorder is often considered to be a disease of the elderly: the median age of diagnosis in the European Union is 72 years and only 10% of patients are less than 55 years old (Eichhorst et al, 2021). In the United Kingdom, the median age at diagnosis was 71.8 years for 2010 to 2016 (HMRN, 2019). In the United States, in the years 2014 to 2018, the incidence rate was 0.4 per 100,000 for people under 50 years, 7.9 per 100,000 for those aged 50 to 64 years, and 27.1 for those 65 years or older (SEER Explorer, 2021). The mean age at diagnosis has been reported as 69.8 years (Blansky et al, 2020).

Race/Ethnicity

Race in the European CLL population is not described. In the United States, the incidence rate in 2014 to 2018 was 6.0 per 100,000 population for non-Hispanic whites, 3.2 per 100,000 population for blacks, and 2.1 per 100,000 population for Hispanics (SEER Explorer, 2021). The incidence rate for the Asian population in the United States for the same time period was lower (1.6 and 0.8 per 100,000 population for men and women, respectively) (SEER Explorer, 2021). Specifically, a Canadian study conducted by combining data from British Columbia databases and Hong Kong Cancer Registry observed world age-standardized incidence rates of CLL per 100,000 to be 0.28 in Hong Kong and 0.4 in Chinese living in British Columbia (Mak et al, 2014).

Risk Factors for the Disease

Factors that may increase the risk of CLL include older age, white race, a family history of the disease or of another form of blood and bone marrow cancers, and exposure to certain herbicides and insecticides including Agent Orange used during the Vietnam War (Mayo Clinic, Chronic lymphocytic leukaemia: Symptoms & causes, 2019). Exposure to several solvents, including benzene, toluene, and xylene, has been found to increase the risk of CLL (Wang and Ma, 2014).

Main Existing Treatment Options:

Current treatments for CLL are not curative, are limited by inevitable relapse as well as by toxicity, and are complicated by eventual resistance to therapy. Fewer patients obtain responses with each subsequent regimen, and subjects become increasingly resistant to available therapy (Hillmen, 2011; Maddocks and Lin, 2009). While SCT is a potentially curative therapy, few patients are able to undergo this treatment (Gribben and O'Brien, 2011).

Treatment for CLL depends on the stage of the disease, the signs and symptoms, and the fitness of the patient. The standard treatment of patients with early disease is a watch-and-wait strategy (Eichhorst et al, 2021). When treatment is indicated, several options exist for most CLL patients: a combination of venetoclax with obinutuzumab, ibrutinib monotherapy, or chemoimmunotherapy. For physically fit patients younger than 65 years, chemoimmunotherapy with fludarabine, cyclophosphamide, and rituximab remains a standard therapy (Hallek, 2019).

In more advanced stages, when patients develop symptomatic or progressive disease per International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria for treatment (Hallek et al, 2018), treatment agent options may include:

- Chemotherapy such as fludarabine, cyclophosphamide, bendamustine, or chlorambucil
- Immunotherapy: rituximab, ofatumumab, obinutuzumab
- Targeted drug therapy: ibrutinib, idelalisib, venetoclax
- SCT

Most often, chemotherapy is combined with immunotherapy, eg, fludarabine, cyclophosphamide, rituximab (FCR), BR, and chlorambucil in combination with obinutuzumab are commonly used regimens. Novel targeted agents may be given with or without immunotherapy.

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

CLL is a lymphoproliferative disorder, involving peripheral blood, bone marrow, and lymphoid organs (Scarfò et al, 2016). The clinical manifestations of CLL range from an asymptomatic patient with minimal B-cell lymphocytosis to a progressive clinical picture of enlarging lymph nodes, splenomegaly, anemia, thrombocytopenia, and life-threatening infections (Kempin, 2013). Some patients live with stable disease for many years without intervention, while 20% to 30% follow an aggressive course, sometimes with rapid progression requiring treatment (Huang et al, 2014). Advanced stage patients can show fatigue and intolerance to physical exercise due to anemia, secondary to bone marrow infiltration, while the presence of bleeding manifestations due to low platelet count is very rare. The nonspecific ‘B’ symptoms, which include fever, chills, night sweats, weight loss, fatigue, and/or malaise, are indicators of increased disease activity and need for treatment. Other symptoms indicating the need for treatment are anemia, thrombocytopenia, and progressive lymphadenopathy (Tees and Flinn, 2017). Patients with CLL have a higher vulnerability to infections, with bacterial infections involving upper and lower respiratory tract and urinary tract being the most frequent, though an increased risk of viral reactivation (eg, herpes zoster infection) has also been reported (Scarfò et al, 2016). About 5% to 10% of patients with CLL develop "Richter's transformation" which refers to the development of aggressive lymphoma with rapidly enlarging lymph nodes (Jain and O’Brien, 2012). Advanced disease is frequently characterized by worsening infectious complications which represent the main cause of death (Scarfò et al, 2016).

Mortality and Morbidity

For CLL, the 5-year relative survival in Europe was estimated to be 70.4%, was better in women than men (73.7% versus 68%), and ranged from 58% in Eastern Europe to about 74% in Central and Northern Europe (De Angelis et al, 2015). In the United States, the 5-year survival was estimated at 87.2% for 2011 to 2017 (SEER Explorer, 2021). CLL has 3 stages. When diagnosed in the earlier stage, people generally live for 10 years or more. For those diagnosed in the most advanced stage, people usually live for approximately 6.5 years. For all others, people generally live more than 8 years (Cancer Research UK, Chronic Lymphocytic Leukaemia, 2018).

The mortality rate was 1.1 per 100,000 population for 2014 to 2018 in the United States (SEER Explorer, 2021). Of the CLL deaths, mortality for patients under the age of 50 was 0.0 per 100,000 population, 0.6 per 100,000 population for those aged 50 to 64 years, and 8.2 per 100,000 population for those 65 years or older. During this same period, the mortality was 1.6 per 100,000 population for men and 0.8 per 100,000 population for women (SEER Explorer, 2021). The death rates by race between 2014 and 2018 in the United States are detailed in the table below (SEER Explorer, 2021).

Death Rates by Race, United States, 2014-2018

Race/Ethnicity	Deaths per 100,000
All Races	1.1
White	1.3
Black	1.0
Asian/Pacific Islander	0.2
American Indian/Alaska Native	0.3
Hispanic	0.4

Important Comorbidities:

Important comorbidities in patients with CLL include infections, autoimmune disorders (Kipps et al, 2017), neurological disorders (Lopes da Silva, 2012), other malignancies (NCI, 2019), CVD, and renal insufficiencies (Schmidt et al, 2011).

Indication: Waldenström's Macroglobulinemia

Incidence:

WM accounts for 1% to 2% of hematological neoplasms (Steingrímsson et al, 2017). In Europe, the incidence is estimated to be 0.81 per 100,000 population (Orphanet, 2021). Another study of patients with WM recorded within the South Thames Hematology Registry from 1999 to 2001 in the United Kingdom, estimated the age-standardized annual incidence of WM at 5.5 per million persons per year (Phekoo et al, 2008). In Sweden, the age-adjusted incidence of WM/lymphoplasmacytic lymphoma (LPL) was estimated to be 11.5 per million persons per year for the years 2000 to 2014 (Brandefors et al, 2018). In the United States, the incidence was 0.48 per 100,000 population for 1980 to 2016 (Yin et al, 2020).

Prevalence:

WM is a subtype of LPL, which is a rare type of NHL. In the World Health Organization's (WHO) classification of neoplasms of the hematopoietic and lymphoid tissues (Hossfeld, 2002), LPL includes patients with WM, in whom the malignant cells produce immunoglobulin (Ig)M protein. A Swedish study reported that 86.1% of LPL patients diagnosed between 2000 and 2014 met the criteria for WM (Brandefors et al, 2018).

Demographics of the Population in the Authorized Indication - Sex, Age, Racial and/or Ethnic Origin, and Risk Factors for the Disease

Sex

WM is found at a higher proportion in men than women. For example, in a Swedish population-based study of 1,555 LPL/WM patients, men constituted 57.9% of these patients (Kristinsson et al, 2013). A UK registry-based study reported the age-standardized incidence rates of WM to be 0.73 and 0.42 per 100,000 European standard population in men and women, respectively (Phekoo et al, 2008). Similarly, in the United States, the incidence rate in men was 0.6 per 100,000 population and 0.3 per 100,000 population in women for the 2007 to 2016 period (Howlader et al, 2019). Consistent findings were also seen in the EUROCARE-based project, HAEMACARE study, where the crude incidence rate of immunoproliferative disease (inclusive of LPL, WM, and not otherwise specified immunoproliferative disease and heavy chain disease) was 1.00 and 0.67 per 100,000 in men and women, respectively (Sant et al, 2010).

Age

WM is a disease of the elderly, with incidence increasing with age. In a population-based study in Sweden that included 1,555 LPL/WM patients diagnosed from 1980 to 2005, the overall median age of diagnosis was 72 years (Kristinsson et al, 2013). Similarly, 1 study in patients with WM recorded within the South Thames Hematology Registry from 1999 to 2001 in the United Kingdom, observed a median age at diagnosis of 75 years (range 45-93 years) (Phekoo et al, 2008). In the United States, based on 20-year SEER data (2007 to 2016), the overall annual age-adjusted incidence of WM ranged from 0.2 per 100,000 person-years in patients aged 20 to 64 years to 2.4 per 100,000 person-years in patients aged 65 years or older (Howlader et al, 2019).

Race/Ethnicity

WM occurs predominantly in the white population compared with the black population representing only 5% of all patients. Approximately 20% of WM patients have an Ashkenazi (Eastern European) Jewish ethnic background (Treon et al, 2008). In the United States, based on 20-year SEER data (1988 to 2007), WM incidence rates were higher in the white population (4.1) than in the black population (1.8) or other races (2.1) per million persons (Wang et al, 2012). In the United States, based on SEER data from 2012 to 2017, the 5-year relative survival was 0.87 (95% CI: 0.84-0.90) for the white population, 0.82 (95% CI: 0.75-0.90) for the black population, and 0.80 (95% CI: 0.74-0.88) for the Asian/Pacific Islander population. The 10-year relative survival from 2000 to 2017 for these same populations was 0.70 (95% CI: 0.67-0.73), 0.62 (95% CI: 0.52-0.75), and 0.59 (95% CI: 0.50-0.69), respectively (Vaughn et al, 2021).

Risk Factors for the Disease

WM is a rare cancer and mostly affects the elderly, aged over 65 years. The main risk factor is the presence of monoclonal gammopathy of undetermined significance (MGUS), and some studies have shown an increased risk of WM with the presence of autoimmune disorders or infection history (Simon et al, 2018). The potential role of hepatitis C virus (HCV) infection in the etiology of WM is inconclusive. A high frequency of MYD88 L265P mutation has been observed in WM patients in multiple studies (Poulain et al, 2013; Treon et al, 2012). The disease has a familial component. Around 20% to 25% of patients with WM have been observed to have a relative with either WM or a similar condition such as CLL or another NHL (Lymphoma Action, 2019; Treon et al, 2006). A Swedish study found that first-degree relatives of LPL/WM patients have a 20-fold (95% CI: 4.1-98.4) increased risk of developing the disease compared with controls (Kristinsson et al, 2008). Another important risk factor for the development of WM is pre-existing IgM monoclononal gammopathy of undetermined significance, which confers a 46-fold higher relative risk of developing WM compared with the general population. In addition, there may be a potential role for immune-related factors in the pathogenesis of WM (Ghobrial, 2012).

Main Existing Treatment Options:

WM is not curable, but is a slow growing cancer. Asymptomatic patients can be kept under observation without therapy. Choice of therapy is highly personalized, dictated by symptoms, age, and comorbidities (Benevolo et al, 2017). Current European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines recommend bortezomib/dexamethasone/rituximab (BDR), BR, dexamethasone/rituximab/cyclophosphamide (DRC), bortezomib/rituximab (VR), or ibrutinib, depending on symptoms (Kastritis et al, 2018; NCCN, 2018). Other possible agents can include cladribine, carfilzomib, and fludarabine (NCCN, 2018). SCT is sometimes considered for salvage therapy mainly in younger patients with WM (Kastritis et al, 2018). Plasmapheresis is used to manage hyperviscosity or for IgM-related complications (Kastritis et al, 2018).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

WM is defined as a B-cell LPL. WM is an indolent, chronic disease in most patients. The median survival varied in studies, from 5 years to nearly 11 years (Oza and Rajkumar, 2015). A German study reported 3-year progression-free survival from the start of first-line treatment to be 83% and 3-year OS to be 87% (Knauf et al, 2020). At least 25% of patients are asymptomatic at diagnosis, and 50% of asymptomatic patients who are observed will not require therapy within 3 years and one in 10 will not require therapy for 10 years (Morel and Merlini, 2012). Most patients present with symptoms attributable to tumor burden, including anemia, pancytopenia, organomegaly, neuropathy, amyloidosis, cryoglobulinemia, night sweats and symptomatic hyperviscosity (Oza and Rajkumar, 2015). Approximately 20% of patients will experience hepatosplenomegaly and lymphadenopathy, and some patients may present with ‘B’ symptoms, including night sweats, fever, and weight loss (Ghobrial, 2012). Median life expectancy at diagnosis is between 5 and 10 years, but varies considerably according to disease aggressiveness and tumor mass (Souchet-Compain et al, 2014). The main causes of death of WM include disease progression, transformation to high-grade lymphoma or complications of therapy (Oza and Rajkumar, 2015).

However, due to the advanced age of these patients, approximately 50% die of unrelated causes (Ansell et al, 2010).

Mortality and Morbidity

A retrospective study of 587 symptomatic WM patients conducted by 7 cooperative groups or institutions in Europe and the United States reported that the 5-year survival rate for patients with symptomatic WM is 87% for those with low-risk disease, 68% for those with intermediate-risk disease, and 36% for those with high-risk disease (Kasi et al, 2015; Morel et al, 2009).

A Swedish population-based study of 1,555 LPL/WM patients diagnosed from 1980 to 2005 observed survival of LPL/WM patients to have improved significantly over time (Kristinsson et al, 2013). Specifically, the 5-year relative survival ratios increased from 0.57 (95% CI: 0.46-0.68) to 0.78 (95% CI: 0.71-0.85) for patients diagnosed during the calendar periods 1980 to 2005. In a UK study of patients with WM recorded within the South Thames Hematology Registry from 1999 to 2001, the estimated 5-year survival was 57% (95% CI: 47%-66%). Relative 5-year survival was 70% among patients <70 years and 50% for patients aged 70 and older (Phekoo et al, 2008). SEER data from the United States report the 5-year OS for WM to be 83.4%, 92.5% for patients 20 to 64 years, and 78.2% for those 65 years or older (Howlader et al, 2019).

Important Comorbidities:

Important comorbidities in patients with WM include peripheral neuropathy, infection (McShane et al, 2014), and other malignancies (Castillo et al, 2015).

PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

Key Safety Findings	Relevance to Human Usage
Toxicity	
Single-dose toxicity	
Single-dose studies were conducted in mice and rats. The maximum nonlethal total dose of ibrutinib following administration by oral gavage was 2,000 mg/kg for mice (human equivalent dose [HED]=160 mg/kg), 400 mg/kg for female rats (HED=64 mg/kg), and 1,000 mg/kg for male rats (HED=160 mg/kg). In rats, mortality with orally administered ibrutinib was 10% at a dose of 1,000 mg/kg and 30% at 2,000 mg/kg.	The margins for single-dose studies are high; therefore, there is minimal risk of acute toxicities in humans.
Multiple dose toxicities	
Multiple dose studies with a duration of 6 months in rats and 9 months in dogs were conducted. The no observed adverse effect level (NOAEL) was determined to be 100/50 mg/kg/day for male/female rats and 80 mg/kg/day for dogs in both genders. This corresponds to HEDs of 16/8 mg/kg/day for male/female rat and 43 mg/kg/day in dog, respectively.	In general, the toxicity of ibrutinib was similar across species and was related to the pharmacological activity of ibrutinib. Overall, based on animal studies the most likely human findings are GI events and pharmacologically mediated changes in the lymphoid organs.
Reproductive and developmental toxicity	
The potential effects of ibrutinib on embryofetal development were evaluated in pregnant rats and rabbits. Rats were administered oral doses of 10, 40, and 80 mg/kg on gestation Days 6 through 17 (the period of organogenesis) and were euthanized on gestation Day 20 for assessment of implantation and litter parameters. The fetuses were examined for external, visceral, and skeletal malformations. There were no remarkable treatment-related maternal effects; therefore, the NOAEL for maternal toxicity was set at 80 mg/kg/day (HED=12.8 mg/kg/day). Based on a higher mean litter proportion of post-implantation loss and a corresponding lower mean number of viable fetuses and test article-related effects on fetal morphology (visceral [heart and major vessels] malformations and skeletal variations) at the 80 mg/kg/day dose level, as well as lower mean fetal body weights at the 40 and 80 mg/kg/day dose levels, 10 mg/kg/day was considered to be the NOAEL for effects on embryofetal development (HED=1.6 mg/kg/day).	Based on findings in animals, ibrutinib is teratogenic and may cause fetal harm when administered to pregnant women.

Key Safety Findings	Relevance to Human Usage
Rabbits were dosed with 5, 15, or 45 mg/kg/day on gestation Days 6 to 19; rabbits were euthanized on Day 28 of pregnancy and examined for macroscopic abnormalities, pregnancy status, corpora lutea, implantations, early and late resorptions, and live and dead fetuses. The fetuses were weighed, sexed, and examined for external, visceral, and skeletal abnormalities. Ibrutinib dosed at 45 mg/kg/day in rabbits was associated with increased post-implantation loss; when dosed at ≥15 mg/kg/day, fetal malformations (fused sternebrae) were induced. The NOAEL for effects on rabbit embryo/fetal development was 5 mg/kg/day. Relative to a human dose of 560 mg/day, the area under the curve (AUC)-based safety margin was 0.75-fold. The NOAEL for rabbit maternal toxicity was 15 mg/kg/day (HED=4.8 mg/kg/day).	
In repeated-dose studies in rats and dogs, no morphological changes were identified in the male and female reproductive organs.	
Fertility and early embryonic development	
The potential effects of ibrutinib on fertility and reproductive capacity, including conception and implantation were evaluated in male and female rats (22/group). Male rats received ibrutinib (lot 131439) at oral doses of 0 (vehicle; 0.5% w/v methylcellulose and 0.1% w/v sodium lauryl sulfate), 25, 50, or 100 mg/kg/day once daily for 4 weeks prior to pairing, during pairing, and continuing until study termination. Female rats were administered the same dose levels once daily for 14 days prior to pairing, during pairing, and continuing until Day 7 of pregnancy [Day 0 of pregnancy = day of copulation]. Estrous cycles were recorded and the pre-coital interval was noted. The females were sacrificed on Day 14 of pregnancy for evaluation of pregnancy status. The males were sacrificed once the fertility rate in females had been established and sperm evaluation was conducted.	Based on the preclinical findings, no fertility and reproductive findings were identified.
The NOAEL for fertility and reproductive capacities of adult female and male rats was considered to be 100 mg/kg/day (HED=16 mg/kg/day).	

Key Safety Findings	Relevance to Human Usage
Genotoxicity	
Ibrutinib was not genotoxic in studies evaluating reverse gene mutations in bacteria and erythrocyte micronuclei in the bone marrow of mice. Clinical grade ibrutinib did not induce chromosome aberrations in Chinese hamster ovary cells. Major human metabolites M25 and M37 were not mutagenic in studies evaluating the ability to induce reverse gene mutations in bacteria with an added rat S9 metabolic activation system. Major metabolites M21 and M34 were not mutagenic in studies evaluating the ability to induce reverse gene mutations in bacteria with an added rat S9 metabolic activation system and the sulfate conjugation cofactor adenosine 3'-phosphate-5'-phosphosulfate present. M21, M25, M34, and M37 were considered negative for clastogenicity or disruption of mitotic spindle apparatus in a study evaluating micronucleated erythrocytes in the bone marrow of mice.	Based on the preclinical findings, no genotoxic risk was identified. No mutagenic or clastogenic risk was identified for M21, M25, M34, or M37.
Carcinogenicity	
Ibrutinib was not carcinogenic in a 6-month study in the transgenic (Tg.rasH2) mouse at oral doses up to 2,000 mg/kg/day with an exposure margin of approximately 23 (males) to 37 (females) times the human AUC of ibrutinib at a dose of 560 mg/day.	Based on the preclinical findings, no carcinogenic risk was identified.
Safety pharmacology	
Cardiovascular system (including potential for QT interval prolongation)	
The effects of ibrutinib and metabolite PCI-45227 on human Ether-à-go-go-Related Gene (hERG) channel-mediated ion current were evaluated in voltage-clamped HEK293 cells that stably express hERG potassium channels. The half maximal inhibitory concentration (IC_{50}) for inhibitory effect of ibrutinib on hERG channel current was 970 nM (427 ng/mL). The IC_{50} for inhibitory effect of metabolite PCI-45227 on hERG channel current was 9,600 nM (4,555 ng/mL).	The IC_{50} for inhibitory effect of ibrutinib on hERG channel current (970 nM or 427 ng/mL) is 96 times the average maximum steady-state plasma concentration of unbound ibrutinib (4.43 ng/mL) in patients receiving a dose of 560 mg/day. The IC_{50} for inhibitory effect of metabolite PCI-45227 on hERG channel current (9,600 nM or 4,555 ng/mL) is 415 times the average maximum steady-state plasma concentration of unbound PCI-45227 (11.0 ng/mL) in patients receiving a dose of 560 mg/day. Based on these margins of safety, neither ibrutinib nor metabolite PCI-45227 is expected to adversely affect ventricular repolarization in humans.

Key Safety Findings	Relevance to Human Usage
Human cardiac ion channels interrogated using the whole-cell voltage clamp technique indicated ibrutinib inhibits hERG-mediated I_{Kr} (Kv11.1) by 19% at 1 µM and by 36.6% at 3 µM, inhibits late and peak I_{Na} (Nav1.5) only at 3 µM (by 35.8% and 27.5%, respectively), and inhibits I_{Kur} (Kv1.5) by 15.5% only at 3 µM. Ibrutinib up to 3 µM had no relevant effects on I_{Ks} (KvLQT1/minK), $I_{Ca}L$ (Cav1.2), $I_{Ca}T$ (Cav3.2), I_{K1} (Kir2.1), I_{to} (Kv4.3/KChiP2.2), I_f (HCN4), I_{KAch} (Kir3.1/Kir3.4), and I_{KATP} (Kir6.2/SUR2A).	Ibrutinib's marginal inhibition of I_{Kr} (hERG) at 1 and 3 µM and of I_{Na} (Nav1.5) and I_{Kur} (an atrial specific channel) at 3 µM occurs at concentrations that are over 100 times therapeutic free maximum concentration (C_{max}) in human and is considered unlikely to be the basis for an enhanced susceptibility to atrial fibrillation within the therapeutic exposure range.
Ibrutinib was also evaluated in synchronously beating human induced pluripotent stem cell-derived cardiomyocytes at concentrations of 0.03, 0.1, 0.3, 1, and 3 µM nominal during 30 minutes incubations. Up to 3 µM nominal there was no relevant effect on amplitude, beat rate, or CTD_{90} (a surrogate for QT-interval) and ibrutinib did not elicit arrhythmias, such as early after depolarization-like, ventricular tachycardia-like, and ventricular fibrillation-like events. However, ibrutinib induced cessation of beating with an incidence of 50% at 1 and 3 µM nominal.	There were no findings in cardiomyocytes except for cessation of beating with an incidence of 50% at concentrations 1 and 3 µM that are over 100 times higher than the therapeutic free C_{max} in humans. The mechanism for the cessation of beating is unknown but may be a result of the weak Na+ channel inhibition identified with high concentration of ibrutinib. Similar findings have been noted with other weak Na+ channel blockers such as the positive control phenytoin, which is not known to be overtly pro-arrhythmic in clinical use.
The potential cardiovascular effects of orally administered ibrutinib were evaluated in telemetry-monitored male dogs. Prolongation of RR interval, lowered heart rate, and increased pulse pressure were noted at dose levels of 24 and 150 mg/kg. In addition, prolonged PR intervals and shortened QT intervals, corrected according to Vandewater were noted at the 150 mg/kg dose level. There were no treatment-related effects on QTc (QT interval corrected for heart rate) intervals at any dose level. The no-observed-effect level (NOEL) was determined to be 1.5 mg/kg (HED=0.81 mg/kg). The changes observed in RR interval, heart rate, and pulse pressure at the 24-mg/kg dose level (HED=13 mg/kg) were considered to be non-adverse because of the relatively small magnitude of maximum or overall change. Thus, 24 mg/kg was considered to be the NOAEL.	The estimated C_{max} for ibrutinib at the NOAEL of 24 mg/kg is approximately 6 times the mean C_{max} measured in patients receiving ibrutinib 560 mg/day. No evidence of QT prolongation with increasing plasma concentrations of ibrutinib, as well as no evidence of QT prolongation with increasing concentrations of the metabolite PCI-45227 was observed in 2 of the completed clinical trials. Based on the nonclinical observations of prolonged PR intervals and lowered heart rates, and the available clinical data, the risk of cardiac arrhythmia (excluding atrial fibrillation and ventricular tachyarrhythmias) is considered an important potential risk with the use of ibrutinib. Atrial fibrillation and ventricular tachyarrhythmias have been included as important identified risks based on Phase 3 clinical data although these were not observed in nonclinical data.

Key Safety Findings	Relevance to Human Usage
Nervous system	
No treatment-related changes were noted in studies to evaluate potential effects of orally administered ibrutinib on the neurological function of rats. The NOEL for neurological in rats was set at 150 mg/kg (HED=24 mg/kg), the highest dose administered.	In the rat neurological functional assay, there were no relevant observations at plasma exposures that were 18-fold higher than the plasma exposure measured in humans at the C_{max} after administration of the highest clinical dose of 560 mg. Therefore, the risks for adverse neurological effects associated with the use of ibrutinib are negligible.
Respiratory function	
No treatment-related changes were noted in studies to evaluate potential effects of orally administered ibrutinib on the respiratory function of rats. The NOEL for respiratory in rats was set at 150 mg/kg (HED=24 mg/kg), the highest dose administered.	In the rat respiratory function assay, there were no relevant observations at plasma exposures that were 18-fold higher than the plasma exposure measured in humans at the C_{max} after administration of the highest clinical dose of 560 mg. Therefore, the risks for adverse respiratory effects associated with the use of ibrutinib are negligible.
Other toxicity-related information or data	
Lymphoid organs	
Lymphoid depletion of the spleen occurred in high-dose group male and female rats that received ibrutinib for 4 weeks. In rats dosed for 13 weeks, minimal to severe lymphoid depletion of the mantle zone of the spleen and minimal to moderate lymphoid depletion of the cortex of the lymph nodes (axillary, mandibular, and/or mesenteric) were noted. Depletion of the lymphocytes in the mantle zone of the spleen correlated to the lower absolute B cells observed in the toxicokinetic group animals. Lymphoid depletion of Peyer's patches was evident in the small and/or large intestines in dogs that received doses of 60 to 220 mg/kg/day in the 13-week toxicity study. The changes were minimal to mild and characterized by reduced size of the germinal center and mantle zones of the Peyer's patches. Lymphoid findings were completely reversible following a 6-week recovery period.	Effects on lymphoid organs, particularly B lymphocytes as observed in animal studies, are consistent with the pharmacological effects of BTK inhibition, and therefore, are relevant to humans but do not indicate a specific unanticipated safety risk. At high dose levels, where other adverse effects were present the lymphoid depletion was more generalized and consistent with a cortisol-mediated stress response. Because of the margin where these findings occur the risk to humans is considered low.

Key Safety Findings	Relevance to Human Usage
Exocrine pancreas	
In rats dosed for 2 or 13 weeks, minimal to moderate acinar atrophy was observed in the pancreas of males and females. Acinar atrophy included a combination of fibrosis, brown pigment (interpreted as hemosiderin), small acini with fewer zymogen granules, and mixed inflammatory cell infiltrate (predominantly neutrophils, lymphocytes, and plasma cells, consistent with a chronic inflammatory infiltrate). These lesions were noted at doses ranging from 12 to 300 mg/kg/day and considered adverse (moderate severity or greater) at doses from 36 to 300 mg/kg/day (HED=5.8 to 48 mg/kg/day). Atrophy of pancreatic acinar cells was more prominent in male rats and showed partial recovery in the 13-week study 6 weeks after the cessation of dosing. In the 2-week study in rats, where serum amylase and lipase levels were assessed, no correlative changes in these biochemical markers were observed. No pancreatic changes were observed in the dog studies.	The mechanism of the pancreatic changes in rats is unknown; however, the finding showed partial reversibility over a 6-week recovery period, was not associated with any clinically relevant biochemical markers, and was seen in only one species. There have been no relevant safety signals attributable to effects of ibrutinib on the pancreas in patient trials. The risk to humans is considered low.
Gastrointestinal system	
Mild squamous epithelial hyperplasia was present in the non-glandular stomach of male rats administered ibrutinib for 4 weeks at 300 mg/kg/day. Minimal to moderate edema and squamous epithelial atrophy were noted for the non-glandular stomach of female rats dosed at 175 mg/kg/day for 13 weeks. Because neither of these findings was seen in both genders or in more than one study, their toxicological relevance is uncertain. Effects on the intestinal tract of rats dosed at 175 or 300 mg/kg/day for 13 weeks included minimal to mild acute inflammation in the cecum, colon, and/or rectum. Clinically, these animals had soft feces and presented with brown material on the anogenital areas during the course of the treatment period. Notable GI findings were not seen in rats administered ibrutinib for 6 months at dose levels up to 100 mg/kg/day in males and 80 mg/kg/day in females.	Both rats and dogs had abnormal excreta with reversible lesions attributable to GI inflammation and with correlating reversible decreases in serum protein levels. Abnormal excreta (eg, diarrhea) are also a common adverse effect in clinical trials. Most of the events observed from human clinical trials were grade 1 or 2. GI adverse events (AEs) are common in patients but are generally mild, reversible, and manageable by routine standard of care.

Key Safety Findings	Relevance to Human Usage
In dogs dosed for 4 weeks, minimal to mild inflammation of the intestinal mucosa of dogs was observed microscopically in 2 of 3 males and 1 of 3 females at the 150 mg/kg/day dose level. These changes correlated with soft feces and diarrhea noted clinically and with higher neutrophil, monocyte, and/or eosinophil counts noted in the peripheral blood of affected dogs. In the 13-week toxicity study in dogs, a male dosed at 220 mg/kg/day was euthanized in extremis on study Day 31 with acute inflammation of the intestines as well as ulceration of the duodenum and erosions of the stomach epithelium. Minimal to mild muscle degeneration was noted in the stomach of the 220/120 mg/kg/day group females on the 13-week study. Clinically, dogs in the 80/60 and 220/120 mg/kg/day dose groups on the 13-week study had abnormal excreta (soft feces, mucoid feces, diarrhea and/or diarrhea containing red material) throughout the dosing period. Dogs dosed up to 80 mg/kg/day for 9 months had no significant GI findings. The clinical and histopathologic changes in the GI tract of rats and dogs were completely reversible.	
Bone	
In the 13-week toxicity study in rats, bone changes were characterized by minimal to mild thinning of cortical bone with fewer primary trabeculae. These lesions were observed primarily in the sternum and femur of the females dosed at 100 and 175 mg/kg/day (HED=16 and 28 mg/kg/day) only in the 13-week study. Notable bone findings were not seen in rats dosed up to 100/80 mg/kg/day (males/females) for 6 months. Histopathologic changes in the bone resolved after the 6-week non-dosing recovery period. No morphological changes of the bones were seen in the dog studies.	The mechanism of the bone changes in rats is unknown; however, the finding was minimal to mild in nature, was reversible, and seen at >5-fold AUC exposures. Therefore, the risk to humans is low.

Key Safety Findings	Relevance to Human Usage
Cornea	
Slight to moderate corneal dystrophy/opacity was noted during ophthalmic examinations for 3 of 10 high-dose group dogs (150 mg/kg/day) in the 4-week study and for 1 high-dose group dog (220/120 mg/kg/day) in the subsequent 13-week study. The corneal changes were noted both during the treatment periods and during the non-dosing recovery periods. Corneal lesions were not seen in dogs dosed up to 80 mg/kg/day for 9 months.	Serial ophthalmic examinations in completed clinical trials have revealed no clinical correlate to this finding.
Hepatotoxicity	
Based on in vitro data, ibrutinib is not transported by major transporter proteins involved in hepatic uptake or hepatic efflux.	Hepatic accumulation of ibrutinib due to hepatic transporter inhibition by coadministered drugs is not expected.
Based on in vitro data, a clinically relevant systemic inhibition of major transporter proteins by ibrutinib or its major human metabolites tested can be excluded, with the exception of the hepatic efflux transporter breast cancer resistance protein, for which a clinically relevant systemic inhibition by parent compound ibrutinib cannot be excluded based on in vitro data.	There are no clinical data available. Ibrutinib may increase the exposure of coadministered drugs that undergo breast cancer resistance protein-mediated hepatic efflux, such as rosuvastatin.
Formation of the glutathione adduct M26 and the glutathione conjugate M27 has been observed in vitro in human hepatocytes in the presence of additional glutathione, with or without additional recombinant human glutathione-S-transferase. In control human hepatocyte incubations, formation of M26 or M27 was not observed. In the human mass balance study, M26 or M27 were not observed; however, corresponding downstream metabolites were observed (M31, M32, and M33). Based on the human mass balance data, the combined glutathione-related pathways are a minor route of overall ibrutinib metabolism making up less than 5% in man.	Given the known high intracellular glutathione content, neither glutathione depletion caused by ibrutinib treatment at the recommended therapeutic dose, nor drug interactions related to glutathione conjugation or addition, would be anticipated.
In in vitro studies, ibrutinib was observed to bind covalently to hepatic proteins such as cytochrome P450 (CYP)3A4/5 and human hepatic microsomes, with and without metabolic activation. However, in vitro studies using human hepatic microsomes did not indicate a clinically relevant reversible or time-dependent CYP inhibition by ibrutinib.	CYP isozyme activity and microsomal function were not affected by the covalent binding of ibrutinib.

Key Safety Findings	Relevance to Human Usage
Despite the observed in vitro covalent binding to (hepatic) proteins, there was no hepatic safety signal from the general toxicity program, eg, no adverse treatment-related changes in liver function parameters were noted and no adverse test article-mediated hepatic histopathology changes were observed.	Based on the general toxicity program, the liver is not a target organ for ibrutinib toxicity. However, based on the available postmarketing spontaneous case reports and a grade 4 hepatic enzyme elevation in a healthy volunteer, the risk of hepatotoxicity (including hepatic failure) is considered an important identified risk with the use of ibrutinib (see Module SVII).

Summary of Nonclinical Safety Concerns

Important identified risks	Atrial fibrillation Ventricular tachyarrhythmias
Important potential risks	Cardiac arrhythmia (excluding atrial fibrillation and ventricular tachyarrhythmias)
Missing information	None

PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

SIII.1. Brief Overview of Development

The following clinical trials are included in this European Union Risk Management Plan (EU-RMP):

- Trial PCYC-04753 (hereafter referred to as Trial 04753): First-in-human Phase 1, open-label, multicenter, dose-escalation trial of ibrutinib in subjects with recurrent B-cell lymphoma (including WM, MCL, CLL, follicular lymphoma, and LPL, or DLBCL)

MCL trials:

- Trial PCYC-1104-CA (hereafter referred to as Trial 1104): Phase 2, open-label, non-randomized, multicenter trial in subjects with histologically documented MCL who relapsed after at least 1 (but not more than 5) prior treatment regimens
- Trial PCI-32765MCL2001 (hereafter referred to as Trial MCL2001): Phase 2, single-arm, multicenter trial in subjects with relapsed or refractory MCL who received prior bortezomib therapy
- Trial PCI-32765MCL3001 (hereafter referred to as Trial MCL3001): Phase 3, open-label, randomized, controlled, international, multicenter trial in subjects with relapsed or refractory MCL in which ibrutinib monotherapy was compared with treatment with temsirolimus

CLL trials:

- Trial PCYC-1102-CA (hereafter referred to as Trial 1102): Phase 2, open-label, non-randomized, multicenter trial of 2 different CLL populations (treatment-naïve and relapsed/refractory) and 2 different fixed doses of ibrutinib (420 and 840 mg/day)
- Trial PCYC-1108-CA (hereafter referred to as Trial 1108): Phase 1b, open-label, non-randomized, multicenter trial in subjects with relapsed/refractory CLL, in which subjects received ibrutinib + chemo-immunotherapy (BR or FCR)
- Trial PCYC-1109-CA (hereafter referred to as Trial 1109): Phase 1b/2, open-label, non-randomized trial in subjects with relapsed/refractory CLL and prolymphocytic leukemia, in which subjects received ibrutinib + ofatumumab
- Trial PCYC-1112-CA (hereafter referred to as Trial 1112): Phase 3, open-label, randomized, multicenter trial in subjects with CLL who have failed at least 1 prior line of therapy, in which subjects received ibrutinib or ofatumumab
- Trial PCYC-1115-CA (hereafter referred to as Trial 1115): Phase 3, open-label, randomized, multicenter trial in subjects ≥65 years with treatment-naïve CLL, in which subjects received ibrutinib or chlorambucil
- Trial PCYC-1117-CA (hereafter referred to as Trial 1117): Phase 2, open-label, single-arm, multicenter trial in subjects with relapsed or refractory CLL with 17p deletion, in which subjects received ibrutinib monotherapy

- Trial PCI-32765CLL3001 (hereafter referred to as Trial CLL3001): Phase 3, double-blind, placebo-controlled, randomized, multicenter trial in subjects with relapsed or refractory CLL (excluding subjects with del 17p), in which subjects received ibrutinib + BR or placebo + BR
- Trial PCYC-1130-CA (hereafter referred to as Trial 1130): Phase 3, open-label, randomized, multicenter trial in subjects with treatment-naïve CLL, in which subjects received either ibrutinib or chlorambucil in combination with obinutuzumab
- Trial PCYC-1126e-CA (Eastern Cooperative Oncology Group-American College of Radiology Imaging Network [ECOG-ACRIN]-1912, hereafter referred to as Trial E1912): Phase 3, open-label, randomized, multicenter trial in younger (≤70 years) subjects with treatment-naïve CLL, in which subjects received either ibrutinib + rituximab or FCR
- Trial 54179060CLL3011 (hereafter referred to as Trial CLL3011): Phase 3, open-label, randomized, multicenter trial in subjects with previously untreated CLL who meet the iwCLL treatment criteria, in which subjects received ibrutinib + venetoclax or chlorambucil + obinutuzumab for fixed durations
- Trial PCYC-1142-CA (hereafter referred to as Trial 1142): Phase 2, 2-cohort, multicenter trial in subjects with previously untreated CLL, in which subjects received ibrutinib + venetoclax in a minimal residual disease-guided treatment discontinuation cohort and in a fixed duration treatment cohort

WM trials:

- Trial PCYC-1118E-CA (hereafter referred to as Trial 1118E): Phase 2, open-label, single-arm, multicenter trial in subjects with WM
- Trial PCYC-1127-CA (hereafter referred to as Trial 1127): Phase 3, double-blind, randomized, multicenter trial in subjects with treatment-naïve or previously treated WM, in which subjects received either ibrutinib or placebo in combination with rituximab. Trial 1127 also included an open-label subtrial in adult subjects with WM who were refractory to the last prior rituximab-containing therapy, in which subjects received ibrutinib as monotherapy.

DLBCL trial:

- Trial PCI-32765DBL3001 (hereafter referred to as Trial DBL3001), a Phase 3, randomized, double-blind, placebo-controlled, multicenter trial in subjects with newly diagnosed non-germinal center B-cell subtype DLBCL in which subjects received either ibrutinib or placebo in combination with R-CHOP.

Use of ibrutinib for treatment of DLBCL and use of ibrutinib in combination with R-CHOP are not within the currently submitted/approved ibrutinib indications. Therefore, the DLBCL trial is not included in the 'randomized clinical trials population' or the 'all clinical trials population' in the risk management plan (RMP). However, safety data from Trial DBL3001 are included for the relevant important risks in the ‘Characterization of the Risk’ subsection of Section SVII.3.1.

SIII.2. Clinical Trial Exposure

Exposure in Randomized Clinical Trials

The randomized clinical trials population includes 8 trials:

- Trial MCL3001
- Trial 1112
- Trial 1115
- Trial CLL3001
- Trial 1130
- Trial E1912
- Trial CLL3011
- Trial 1127

Exposure to ibrutinib in the **randomized clinical trials population** is summarized in Tables SIII.1 through SIII.5 for all subjects by duration, by age group and sex, by dose, by ethnic or racial origin, by baseline renal status, and by baseline hepatic status.

Table SIII.1: Duration of Ibrutinib Exposure: Randomized Clinical Trials Population

Cumulative for all indications (person-months)		
Duration of exposure	**Patients**	**Person-Months**
Cumulative up to 6 months	158	
Cumulative up to 12 months	257	
Cumulative up to 18 months	468	
Cumulative up to 24 months	586	
Cumulative up to 36 months	802	
Cumulative up to 48 months	1,084	
Cumulative up to 60 months	1,216[a]	32,021.8
Total person-months	**1,402**	**44,071.8**
Indication: MCL		
Duration of exposure	**Patients**	**Person-Months**
Cumulative up to 6 months	40	
Cumulative up to 12 months	59	
Cumulative up to 18 months	73	
Cumulative up to 24 months	83	
Cumulative up to 36 months	103	
Cumulative up to 48 months	139	2,673.3
Cumulative up to 60 months	NA	
Total person-months	**139**	**2,673.3**

Table SIII.1: Duration of Ibrutinib Exposure: Randomized Clinical Trials Population

Indication: CLL		
Duration of exposure	**Patients**	**Person-Months**
Cumulative up to 6 months	114	
Cumulative up to 12 months	192	
Cumulative up to 18 months	382	
Cumulative up to 24 months	486	
Cumulative up to 36 months	676	
Cumulative up to 48 months	905	
Cumulative up to 60 months	1,002	26,327.5
Total person-months	**1,188**	**38,377.5**

Indication: WM		
Duration of exposure	**Patients**	**Person-Months**
Cumulative up to 6 months	4	
Cumulative up to 12 months	6	
Cumulative up to 18 months	13	
Cumulative up to 24 months	17	
Cumulative up to 36 months	23	
Cumulative up to 48 months	40	
Cumulative up to 60 months	75	3,021.0
Total person-months	**75**	**3,021.0**

[a] This number includes all subjects from all indications in the randomized clinical trials population who were exposed for ≤60 months.
MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia; NA = no subjects were exposed beyond 48 months.
Note: Trials included: MCL3001, PCYC-1112-CA, PCYC-1115-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1127-CA.
Note: Exposures beyond 60 months were included in the total person-months row.
[TRMEXP01 RTF] [JNJ-54179060/Z_RMP/DBR_RMP_2021_GLOW/RE_RMP_EU_UPDATE/PROD/TRMEXP01.SAS] 10FEB2022, 23:24

Table SIII.2: Age Group and Sex: Randomized Clinical Trials Population

Cumulative for all indications				
Age group	**Men**		**Women**	
	Patients	**Person-Months**	**Patients**	**Person-Months**
18 - <35 years	3	115.7	2	51.4
>=35 - 49 years	57	1,957.9	36	1,295.3
>=50 - 64 years	380	13,104.8	171	5,848.1
>=65 - 69 years	167	5,374.2	92	2,889.7
>=70 - 74 years	144	4,022.3	93	2,439.6
>=75 years	163	4,066.3	94	2,906.6
Total	**914**	**28,641.1**	**488**	**15,430.7**

Indication: MCL				
Age group	**Men**		**Women**	
	Patients	**Person-Months**	**Patients**	**Person-Months**
18 - <35 years	0	0.0	0	0.0
>=35 - 49 years	3	82.3	2	56.8
>=50 - 64 years	37	741.2	11	269.6
>=65 - 69 years	19	334.1	9	258.4
>=70 - 74 years	18	329.9	11	183.5
>=75 years	23	353.2	6	64.3
Total	**100**	**1,840.7**	**39**	**832.7**

Table SIII.2: Age Group and Sex: Randomized Clinical Trials Population

Indication: CLL				
Age group	**Men**		**Women**	
	Patients	**Person-Months**	**Patients**	**Person-Months**
18 - <35 years	3	115.7	2	51.4
>=35 - 49 years	52	1,807.5	33	1,187.1
>=50 - 64 years	329	11,746.0	149	5,207.1
>=65 - 69 years	144	4,828.4	79	2,436.8
>=70 - 74 years	121	3,467.5	78	2,139.0
>=75 years	120	2,960.3	78	2,430.7
Total	**769**	**24,925.5**	**419**	**13,452.0**

Indication: WM				
Age group	**Men**		**Women**	
	Patients	**Person-Months**	**Patients**	**Person-Months**
18 - <35 years	0	0.0	0	0.0
>=35 - 49 years	2	68.2	1	51.4
>=50 - 64 years	14	617.6	11	371.4
>=65 - 69 years	4	211.6	4	194.5
>=70 - 74 years	5	224.9	4	117.1
>=75 years	20	752.7	10	411.6
Total	**45**	**1,875.0**	**30**	**1,146.0**

MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia.
Note: Trials included: MCL3001, PCYC-1112-CA, PCYC-1115-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1127-CA.
[TRMEXP05.RTF] [JNJ-54179060/Z_RMP/DBR_RMP_2021_GLOW/RE_RMP_EU_UPDATE/PROD/TRMEXP05.SAS] 10FEB2022, 23:25

Table SIII.3: Ibrutinib Exposure by Dose: Randomized Clinical Trials Population

Cumulative for all indications		
Dose of exposure	**Patients**	**Person-Months**
420 mg/day	1,263	41,398.5
560 mg/day	139	2,673.3
Total	**1,402**	**44,071.8**

Indication: MCL		
Dose of exposure	**Patients**	**Person-Months**
560 mg/day	139	2,673.3
Total	**139**	**2,673.3**

Indication: CLL		
Dose of exposure	**Patients**	**Person-Months**
420 mg/day	1,188	38,377.5
Total	**1,188**	**38,377.5**

Indication: WM		
Dose of exposure	**Patients**	**Person-Months**
420 mg/day	75	3,021.0
Total	**75**	**3,021.0**

MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia.
Note: Trials included: MCL3001, PCYC-1112-CA, PCYC-1115-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1127-CA.
[TRMEXP03.RTF] [JNJ-54179060/Z_RMP/DBR_RMP_2021_GLOW/RE_RMP_EU_UPDATE/PROD/TRMEXP03.SAS] 10FEB2022, 23:24

Table SIII.4: Ibrutinib Exposure by Ethnic or Racial Origin: Randomized Clinical Trials Population

Cumulative for all indications		
Race	**Patients**	**Person-Months**
White	1,230	38,656.0
Black or African American	41	1,183.2
Asian	38	970.2
American Indian or Alaska Native	0	0.0
Hispanic or Latino [a,c,e]	39	1,207.8
Other [b,d,f]	54	2,054.6
Total	**1,402**	**44,071.8**

Indication: MCL		
Race	**Patients**	**Person-Months**
White	113	2,034.7
Black or African American	0	0.0
Asian	15	375.8
American Indian or Alaska Native	0	0.0
Hispanic or Latino [a]	7	186.5
Other [b]	4	76.3
Total	**139**	**2,673.3**

Indication: CLL		
Race	**Patients**	**Person-Months**
White	1,061	34,381.6
Black or African American	40	1,156.1
Asian	20	493.1
American Indian or Alaska Native	0	0.0
Hispanic or Latino [c]	29	909.7
Other [d]	38	1,436.9
Total	**1,188**	**38,377.5**

Table SIII.4: Ibrutinib Exposure by Ethnic or Racial Origin: Randomized Clinical Trials Population

Indication: WM		
Race	**Patients**	**Person-Months**
White	56	2,239.7
Black or African American	1	27.2
Asian	3	101.3
American Indian or Alaska Native	0	0.0
Hispanic or Latino [e]	3	111.5
Other [f]	12	541.4
Total	**75**	**3,021.0**

[a,c,e] Race: Declined (3 subjects), Other (4 subjects), 32 subjects identified their ethnicity as Hispanic or Latino and checked their race as being Asian (1 subject), black or African American (5 subjects), American Indian or Alaska Native (1 subject), or white (25 subjects). These 32 subjects were not included in the Asian, black or African American, American Indian or Alaska Native, nor white population exposures but are included in the Hispanic or Latino count.
[b,d,f] Declined (48 subjects), Other (3 subjects), Haitian (1 subject), Multiracial (1 subject), North African (1 subject).
[a] Race: Other (4 subjects), 3 subjects identified their ethnicity as Hispanic or Latino and checked their race as being Asian (1 subject) or white (2 subjects). These 3 subjects were not included in the Asian, black or African American, American Indian or Alaska Native, nor white population exposures but are included in the Hispanic or Latino count.
[b] Declined (4 subjects).
[c] Race: Declined (2 subjects), 27 subjects identified their ethnicity as Hispanic or Latino and checked their race as being black or African American (5 subjects), American Indian or Alaska Native (1 subject), or white (21 subjects). These 27 subjects were not included in the black or African American, American Indian or Alaska Native, nor white population exposures but are included in the Hispanic or Latino count.
[d] Declined (32 subjects), Other (3 subjects), Haitian (1 subject), Multiracial (1 subject), North African (1 subject).
[e] Race: Declined (1 subject), 2 subjects identified their ethnicity as Hispanic or Latino and checked their race as being white. These subjects were not included in the white population exposures but are included in the Hispanic or Latino count.
[f] Other (12 subjects).
MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia.
Note: Trials included: MCL3001, PCYC-1112-CA, PCYC-1115-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1127-CA.
[TRMEXP07.RTF] [JNJ-54179060/Z_RMP/DBR_RMP_2021_GLOW/RE_RMP_EU_UPDATE/PROD/TRMEXP07.SAS] 10FEB2022, 23:25

Table SIII.5: Ibrutinib Exposure by Special Populations (by Baseline Renal Status and by Baseline Hepatic Status): Randomized Clinical Trials Population

Cumulative for all indications		
Population	**Patients**	**Person-Months**
Renal impairment at baseline		
Normal (CrCl >= LLN)	633	21,120.9
Mild (CrCl < LLN to >= 60 mL/min)	452	14,149.0
Moderate (CrCl < 60 to >= 30 mL/min)	310	8,615.4
Severe (CrCl < 30 mL/min)	6	166.1
Missing	1	20.3
Hepatic function abnormality at baseline		
ALT		
<= ULN (normal)	1,041	31,850.0
> ULN to <= 3.0 x ULN	54	1,733.2
> 3.0 to <= 5.0 x ULN	0	0.0
> 5.0 x ULN	0	0.0
Missing	307	10,488.6

Table SIII.5: Ibrutinib Exposure by Special Populations (by Baseline Renal Status and by Baseline Hepatic Status): Randomized Clinical Trials Population

AST		
<= ULN (normal)	1,279	40,230.7
> ULN to <= 3.0 x ULN	121	3,761.7
> 3.0 to <= 5.0 x ULN	1	19.2
> 5.0 x ULN	0	0.0
Missing	1	60.2
Bilirubin		
<= ULN (normal)	1,319	41,551.3
> ULN to <= 1.5 x ULN	68	2,039.0
> 1.5 to <= 3.0 x ULN	14	480.8
> 3.0 x ULN	1	0.7
Missing	0	0.0

Indication: MCL

Population	Patients	Person-Months
Renal impairment at baseline		
Normal (CrCl >= LLN)	51	1,096.5
Mild (CrCl < LLN to >= 60 mL/min)	58	1,189.2
Moderate (CrCl < 60 to >= 30 mL/min)	29	382.9
Severe (CrCl < 30 mL/min)	1	4.7
Missing	0	0.0
Hepatic function abnormality at baseline		
ALT		
<= ULN (normal)	127	2,494.1
> ULN to <= 3.0 x ULN	12	179.2
> 3.0 to <= 5.0 x ULN	0	0.0
> 5.0 x ULN	0	0.0
Missing	0	0.0
AST		
<= ULN (normal)	125	2,567.7
> ULN to <= 3.0 x ULN	14	105.7
> 3.0 to <= 5.0 x ULN	0	0.0
> 5.0 x ULN	0	0.0
Missing	0	0.0
Bilirubin		
<= ULN (normal)	130	2,537.6
> ULN to <= 1.5 x ULN	7	92.0
> 1.5 to <= 3.0 x ULN	1	43.0
> 3.0 x ULN	1	0.7
Missing	0	0.0

Indication: CLL

Population	Patients	Person-Months
Renal impairment at baseline		
Normal (CrCl >= LLN)	545	18,494.1
Mild (CrCl < LLN to >= 60 mL/min)	371	12,065.9
Moderate (CrCl < 60 to >= 30 mL/min)	266	7,635.7
Severe (CrCl < 30 mL/min)	5	161.4
Missing	1	20.3
Hepatic function abnormality at baseline		
ALT		
<= ULN (normal)	841	26,436.9
> ULN to <= 3.0 x ULN	40	1,452.0
> 3.0 to <= 5.0 x ULN	0	0.0
> 5.0 x ULN	0	0.0
Missing	307	10,488.6

Table SIII.5: Ibrutinib Exposure by Special Populations (by Baseline Renal Status and by Baseline Hepatic Status): Randomized Clinical Trials Population

AST		
<= ULN (normal)	1,081	34,717.4
> ULN to <= 3.0 x ULN	105	3,580.6
> 3.0 to <= 5.0 x ULN	1	19.2
> 5.0 x ULN	0	0.0
Missing	1	60.2
Bilirubin		
<= ULN (normal)	1,117	36,097.3
> ULN to <= 1.5 x ULN	58	1,842.4
> 1.5 to <= 3.0 x ULN	13	437.8
> 3.0 x ULN	0	0.0
Missing	0	0.0

Indication: WM		
Population	**Patients**	**Person-Months**
Renal impairment at baseline		
Normal (CrCl >= LLN)	37	1,530.3
Mild (CrCl < LLN to >= 60 mL/min)	23	894.0
Moderate (CrCl < 60 to >= 30 mL/min)	15	596.8
Severe (CrCl < 30 mL/min)	0	0.0
Missing	0	0.0
Hepatic function abnormality at baseline		
ALT		
<= ULN (normal)	73	2,919.0
> ULN to <= 3.0 x ULN	2	102.0
> 3.0 to <= 5.0 x ULN	0	0.0
> 5.0 x ULN	0	0.0
Missing	0	0.0
AST		
<= ULN (normal)	73	2,945.6
> ULN to <= 3.0 x ULN	2	75.4
> 3.0 to <= 5.0 x ULN	0	0.0
> 5.0 x ULN	0	0.0
Missing	0	0.0
Bilirubin		
<= ULN (normal)	72	2,916.3
> ULN to <= 1.5 x ULN	3	104.7
> 1.5 to <= 3.0 x ULN	0	0.0
> 3.0 x ULN	0	0.0
Missing	0	0.0

MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia; CrCl = creatinine clearance; ALT = alanine aminotransferase; AST = aspartate aminotransferase; LLN = lower limit of normal; ULN = upper limit of normal.
Note: Trials included: MCL3001, PCYC-1112-CA, PCYC-1115-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1127-CA.
[TRMEXP09.RTF] [JNJ-54179060/Z_RMP/DBR_RMP_2021_GLOW/RE_RMP_EU_UPDATE/PROD/TRMEXP09.SAS] 10FEB2022, 23:26

Exposure in All Clinical Trials

The all clinical trials population includes the randomized trials population (MCL3001, 1112, 1115, CLL3001, 1130, E1912, CLL3011, and 1127) and 9 open-label trials:

- Trial 04753
- Trial 1104
- Trial MCL2001
- Trial 1102
- Trial 1108
- Trial 1109
- Trial 1117
- Trial 1142
- Trial 1118E

Exposure to ibrutinib in the **all clinical trials population** is summarized in Tables SIII.6 through SIII.10 for all subjects by duration, by age group and sex, by dose, by ethnic or racial origin, by baseline renal status, and by baseline hepatic status.

Table SIII.6: Duration of Ibrutinib Exposure: All Clinical Trials Population Including Open Extensions

Cumulative for all indications (person months)		
Duration of exposure	**Patients**	**Person-Months**
Cumulative up to 6 months	406	
Cumulative up to 12 months	701	
Cumulative up to 18 months	1,335	
Cumulative up to 24 months	1,610	
Cumulative up to 36 months	2,042	
Cumulative up to 48 months	2,492	
Cumulative up to 60 months	2,723[a]	62,523.1
Total person-months	**2,912**	**74,755.5**
Indication: MCL		
Duration of exposure	**Patients**	**Person-Months**
Cumulative up to 6 months	146	
Cumulative up to 12 months	221	
Cumulative up to 18 months	275	
Cumulative up to 24 months	325	
Cumulative up to 36 months	385	
Cumulative up to 48 months	421	5,957.9
Cumulative up to 60 months	NA	
Total person-months	**421**	**5,957.9**

Table SIII.6: Duration of Ibrutinib Exposure: All Clinical Trials Population Including Open Extensions

Indication: CLL		
Duration of exposure	**Patients**	**Person-Months**
Cumulative up to 6 months	241	
Cumulative up to 12 months	425	
Cumulative up to 18 months	980	
Cumulative up to 24 months	1,183	
Cumulative up to 36 months	1,529	
Cumulative up to 48 months	1,915	
Cumulative up to 60 months	2,097	50,698.7
Total person-months	**2,283**	**62,748.6**

Indication: WM		
Duration of exposure	**Patients**	**Person-Months**
Cumulative up to 6 months	19	
Cumulative up to 12 months	55	
Cumulative up to 18 months	80	
Cumulative up to 24 months	102	
Cumulative up to 36 months	128	
Cumulative up to 48 months	156	
Cumulative up to 60 months	205	5,866.5
Total person-months	**208**	**6,048.9**

[a] This number includes all subjects from all indications in the all clinical trials population who were exposed for ≤60 months.
MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia; NA = no subjects were exposed beyond 48 months.
Note: Trials included: PCYC-04753, PCYC-1104-CA, MCL2001, MCL3001, PCYC-1102-CA, PCYC-1108-CA, PCYC-1109-CA, PCYC-1112-CA, PCYC-1115-CA, PCYC-1117-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1142-CA, PCYC-1118e-CA, PCYC-1127-CA. Cross-over period exposure from Trials MCL3001, PCYC-1112-CA, CLL3001, PCYC-1130-CA, CLL3011, and PCYC-1127-CA, as well as exposures from open-label subtrial in PCYC-1127-CA are included in the summary.
Note: Exposures beyond 60 months were included in the total person-months row.
[TRMEXP11.RTF] [JNJ-54179060/Z_RMP/DBR_RMP_2021_GLOW/RE_RMP_EU_UPDATE/PROD/TRMEXP11.SAS] 10FEB2022, 23:26

Table SIII.7: Age Group and Sex: All Clinical Trials Population Including Open Extensions

Cumulative for all indications				
Age group	**Men**		**Women**	
	Patients	**Person-Months**	**Patients**	**Person-Months**
18 - <35 years	4	130.0	4	136.3
>=35 - 49 years	137	3,711.8	67	1,991.7
>=50 - 64 years	861	23,214.6	352	9,545.8
>=65 - 69 years	385	9,653.9	181	4,840.5
>=70 - 74 years	286	6,642.3	161	4,066.1
>=75 years	311	6,651.0	163	4,171.5
Total	**1,984**	**50,003.6**	**928**	**24,751.9**

Table SIII.7: Age Group and Sex: All Clinical Trials Population Including Open Extensions

Indication: MCL				
Age group	**Men**		**Women**	
	Patients	**Person-Months**	**Patients**	**Person-Months**
18 - <35 years	0	0.0	0	0.0
>=35 - 49 years	15	174.3	3	60.9
>=50 - 64 years	116	1,816.0	31	430.0
>=65 - 69 years	61	852.7	20	358.2
>=70 - 74 years	69	919.8	19	307.5
>=75 years	65	800.4	22	238.3
Total	**326**	**4,563.1**	**95**	**1,394.8**

Indication: CLL				
Age group	**Men**		**Women**	
	Patients	**Person-Months**	**Patients**	**Person-Months**
18 - <35 years	4	130.0	4	136.3
>=35 - 49 years	114	3,378.7	56	1,695.2
>=50 - 64 years	690	19,864.8	303	8,590.5
>=65 - 69 years	303	8,133.8	151	4,138.7
>=70 - 74 years	198	5,142.3	132	3,543.1
>=75 years	207	4,753.0	121	3,242.2
Total	**1,516**	**41,402.7**	**767**	**21,346.0**

Indication: WM				
Age group	**Men**		**Women**	
	Patients	**Person-Months**	**Patients**	**Person-Months**
18 - <35 years	0	0.0	0	0.0
>=35 - 49 years	8	158.8	8	235.6
>=50 - 64 years	55	1,533.8	18	525.3
>=65 - 69 years	21	667.4	10	343.6
>=70 - 74 years	19	580.2	10	215.5
>=75 years	39	1,097.6	20	691.0
Total	**142**	**4,037.8**	**66**	**2,011.1**

MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia.
Note: Trials included: PCYC-04753, PCYC-1104-CA, MCL2001, MCL3001, PCYC-1102-CA, PCYC-1108-CA, PCYC-1109-CA, PCYC-1112-CA, PCYC-1115-CA, PCYC-1117-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1142-CA, PCYC-1118e-CA, PCYC-1127-CA. Cross-over period exposure from Trials MCL3001, PCYC-1112-CA, CLL3001, PCYC-1130-CA, CLL3011, and PCYC-1127-CA, as well as exposures from open-label subtrial in PCYC-1127-CA are included in the summary.
[TRMEXP15.RTF] [JNJ-54179060/Z_RMP/DBR_RMP_2021_GLOW/RE_RMP_EU_UPDATE/PROD/TRMEXP15.SAS] 10FEB2022, 23:27

Table SIII.8: Ibrutinib Exposure by Dose: All Clinical Trials Population Including Open Extensions

Cumulative for all indications		
Dose of exposure	**Patients**	**Person-Months**
420 mg/day	2,432	68,022.1
560 mg/day	417	5,904.6
840 mg/day	39	601.8
Other [a,b,c]	24	227.0
Total	**2,912**	**74,755.5**
Indication: MCL		
Dose of exposure	**Patients**	**Person-Months**
560 mg/day	417	5,904.6
Other [a]	4	53.4
Total	**421**	**5,957.9**
Indication: CLL		
Dose of exposure	**Patients**	**Person-Months**
420 mg/day	2,228	62,002.9
840 mg/day	39	601.8
Other [b]	16	143.9
Total	**2,283**	**62,748.6**
Indication: WM		
Dose of exposure	**Patients**	**Person-Months**
420 mg/day	204	6,019.2
Other [c]	4	29.7
Total	**208**	**6,048.9**

[a] For MCL; 1.25 mg/kg (2 subjects), 2.5 mg/kg (1 subject), and 8.3 mg/kg (1 subject) once daily for 28 consecutive days followed by a 7-day rest.
[b] For CLL; for the 16 subjects with CLL from Trial 04753 who received ibrutinib treatment in 6 of the 8 dose cohorts evaluated: 2.5 mg/kg (3 subjects); 5.0 mg/kg (3 subjects); 8.3 mg/kg (1 subject); 12.5 mg/kg (2 subjects); 8.3 mg/kg continuous daily dosing (6 subjects); and 560 mg continuous daily dosing (1 subject).
[c] For WM; for the 4 subjects with WM from Trial 04753 who received ibrutinib treatment 1 subject received 12.5 mg/kg/day and 3 received 560 mg continuous daily dosing.
MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia.
Note: Trials included: PCYC-04753, PCYC-1104-CA, MCL2001, MCL3001, PCYC-1102-CA, PCYC-1108-CA, PCYC-1109-CA, PCYC-1112-CA, PCYC-1115-CA, PCYC-1117-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1142-CA, PCYC-1118e-CA, PCYC-1127-CA. Cross-over period exposure from Trials MCL3001, PCYC-1112-CA, CLL3001, PCYC-1130-CA, CLL3011, and PCYC-1127-CA, as well as exposures from open-label subtrial in PCYC-1127-CA are included in the summary.
[TRMEXP13.RTF] [JNJ-54179060/Z_RMP/DBR_RMP_2021_GLOW/RE_RMP_EU_UPDATE/PROD/TRMEXP13.SAS] 10FEB2022, 23:27

Table SIII.9: Ibrutinib Exposure by Ethnic or Racial Origin: All Clinical Trials Population Including Open Extensions

Cumulative for all indications		
Race	**Patients**	**Person-Months**
White	2,568	65,567.9
Black or African American	79	1,923.1
Asian	54	1,330.6
American Indian or Alaska Native	2	49.9
Hispanic or Latino [a,c,e]	100	2,653.0
Other [b,d,f]	109	3,231.0
Total	**2,912**	**74,755.5**

Indication: MCL		
Race	**Patients**	**Person-Months**
White	365	4,918.5
Black or African American	7	97.6
Asian	16	399.7
American Indian or Alaska Native	1	10.3
Hispanic or Latino [a]	20	372.8
Other [b]	12	159.0
Total	**421**	**5,957.9**

Indication: CLL		
Race	**Patients**	**Person-Months**
White	2,029	55,717.2
Black or African American	70	1,794.6
Asian	33	743.7
American Indian or Alaska Native	1	39.6
Hispanic or Latino [c]	75	2,117.4
Other [d]	75	2,336.2
Total	**2,283**	**62,748.6**

Table SIII.9: Ibrutinib Exposure by Ethnic or Racial Origin: All Clinical Trials Population Including Open Extensions

Indication: WM		
Race	**Patients**	**Person-Months**
White	174	4,932.2
Black or African American	2	30.9
Asian	5	187.2
American Indian or Alaska Native	0	0.0
Hispanic or Latino [e]	5	162.8
Other [f]	22	735.8
Total	**208**	**6,048.9**

[a,c,e] Race: Declined (8 subjects), Other (7 subjects), 85 subjects identified their ethnicity as Hispanic or Latino and checked their race as being Asian (1 subject), black or African American (6 subjects), American Indian or Alaska Native (1 subject), or white (77 subjects). These subjects were not included in the Asian, black or African American, American Indian or Alaska Native, nor white population exposures but are included in the Hispanic or Latino count.
[b,d,f] Declined (71 subjects), Other (31 subjects), Haitian (1 subject), Iranian (1 subject), Multirace (1 subject), North African (1 subject), Unknown (3 subjects).
[a] Race: Declined (1 subject), Other (3 subjects), 16 subjects identified their ethnicity as Hispanic or Latino and checked their race as being Asian (1 subject) or white (15 subjects). These subjects were not included in the Asian or white population exposures but are included in the Hispanic or Latino count.
[b] Declined (9 subjects), Other (2 subjects), Native Hawaiian or other Pacific Islander (1 subject).
[c] Race: Declined (7 subjects), Other (3 subjects), 65 subjects identified their ethnicity as Hispanic or Latino and checked their race as being black or African American (6 subjects), American Indian or Alaska Native (1 subject), or white (58 subjects). These subjects were not included in the black or African American, American Indian or Alaska Native, nor white population exposures but are included in the Hispanic or Latino count.
[d] Declined (62 subjects), Other (7 subjects), Haitian (1 subject), Iranian (1 subject), Multirace (1 subject), North African (1 subject), Unknown (2 subjects).
[e] Race: Other (1 subject), 4 subjects identified their ethnicity as Hispanic or Latino and checked their race as being white. These subjects were not included in the white population exposure but are included in the Hispanic or Latino count.
[f] Other (22 subjects).
MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia.
Note: Trials included: PCYC-04753, PCYC-1104-CA, MCL2001, MCL3001, PCYC-1102-CA, PCYC-1108-CA, PCYC-1109-CA, PCYC-1112-CA, PCYC-1115-CA, PCYC-1117-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1142-CA, PCYC-1118e-CA, PCYC-1127-CA. Cross-over period exposure from Trials MCL3001, PCYC-1112-CA, CLL3001, PCYC-1130-CA, CLL3011, and PCYC-1127-CA, as well as exposures from open-label subtrial in PCYC-1127-CA are included in the summary.
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Table SIII.10: Ibrutinib Exposure by Special Populations (by Baseline Renal Status and by Baseline Hepatic Status): All Clinical Trials Population Including Open Extensions

Cumulative for all indications		
Population	**Patients**	**Person-Months**
Renal impairment at baseline		
Normal (CrCl >= LLN)	1,395	36,894.1
Mild (CrCl < LLN to >= 60 mL/min)	908	23,487.2
Moderate (CrCl < 60 to >= 30 mL/min)	587	13,891.2
Severe (CrCl < 30 mL/min)	12	279.4
Missing	10	203.6
Hepatic function abnormality at baseline		
ALT		
<= ULN (normal)	2,473	60,725.3
> ULN to <= 3.0 x ULN	126	3,392.0
> 3.0 to <= 5.0 x ULN	0	0.0
> 5.0 x ULN	0	0.0
Missing	313	10,638.2
AST		
<= ULN (normal)	2,641	68,266.3
> ULN to <= 3.0 x ULN	259	6,254.1
> 3.0 to <= 5.0 x ULN	2	36.8
> 5.0 x ULN	0	0.0
Missing	10	198.3
Bilirubin		
<= ULN (normal)	2,762	71,060.6
> ULN to <= 1.5 x ULN	117	2,865.7
> 1.5 to <= 3.0 x ULN	28	710.0
> 3.0 x ULN	3	74.7
Missing	2	44.5

Indication: MCL		
Population	**Patients**	**Person-Months**
Renal impairment at baseline		
Normal (CrCl >= LLN)	190	2,760.2
Mild (CrCl < LLN to >= 60 mL/min)	141	2,127.1
Moderate (CrCl < 60 to >= 30 mL/min)	85	997.4
Severe (CrCl < 30 mL/min)	3	31.0
Missing	2	42.2
Hepatic function abnormality at baseline		
ALT		
<= ULN (normal)	397	5,662.6
> ULN to <= 3.0 x ULN	24	295.4
> 3.0 to <= 5.0 x ULN	0	0.0
> 5.0 x ULN	0	0.0
Missing	0	0.0
AST		
<= ULN (normal)	381	5,657.9
> ULN to <= 3.0 x ULN	39	296.1
> 3.0 to <= 5.0 x ULN	0	0.0
> 5.0 x ULN	0	0.0
Missing	1	3.9
Bilirubin		
<= ULN (normal)	398	5,671.9
> ULN to <= 1.5 x ULN	19	218.9
> 1.5 to <= 3.0 x ULN	3	66.4
> 3.0 x ULN	1	0.7
Missing	0	0.0

Table SIII.10: Ibrutinib Exposure by Special Populations (by Baseline Renal Status and by Baseline Hepatic Status): All Clinical Trials Population Including Open Extensions

Indication: CLL		
Population	**Patients**	**Person-Months**
Renal impairment at baseline		
Normal (CrCl >= LLN)	1,094	30,714.0
Mild (CrCl < LLN to >= 60 mL/min)	718	19,892.9
Moderate (CrCl < 60 to >= 30 mL/min)	458	11,780.7
Severe (CrCl < 30 mL/min)	8	244.7
Missing	5	116.5
Hepatic function abnormality at baseline		
ALT		
<= ULN (normal)	1,876	49,305.6
> ULN to <= 3.0 x ULN	96	2,849.3
> 3.0 to <= 5.0 x ULN	0	0.0
> 5.0 x ULN	0	0.0
Missing	311	10,593.7
AST		
<= ULN (normal)	2,059	56,709.8
> ULN to <= 3.0 x ULN	215	5,852.1
> 3.0 to <= 5.0 x ULN	2	36.8
> 5.0 x ULN	0	0.0
Missing	7	150.0
Bilirubin		
<= ULN (normal)	2,165	59,564.2
> ULN to <= 1.5 x ULN	93	2,529.4
> 1.5 to <= 3.0 x ULN	24	638.1
> 3.0 x ULN	1	17.0
Missing	0	0.0

Indication: WM		
Population	**Patients**	**Person-Months**
Renal impairment at baseline		
Normal (CrCl >= LLN)	111	3,419.8
Mild (CrCl < LLN to >= 60 mL/min)	49	1,467.2
Moderate (CrCl < 60 to >= 30 mL/min)	44	1,113.2
Severe (CrCl < 30 mL/min)	1	3.7
Missing	3	44.9
Hepatic function abnormality at baseline		
ALT		
<= ULN (normal)	200	5,757.1
> ULN to <= 3.0 x ULN	6	247.4
> 3.0 to <= 5.0 x ULN	0	0.0
> 5.0 x ULN	0	0.0
Missing	2	44.5
AST		
<= ULN (normal)	201	5,898.6
> ULN to <= 3.0 x ULN	5	105.9
> 3.0 to <= 5.0 x ULN	0	0.0
> 5.0 x ULN	0	0.0
Missing	2	44.5

Table SIII.10: Ibrutinib Exposure by Special Populations (by Baseline Renal Status and by Baseline Hepatic Status): All Clinical Trials Population Including Open Extensions

Bilirubin		
<= ULN (normal)	199	5,824.5
> ULN to <= 1.5 x ULN	5	117.3
> 1.5 to <= 3.0 x ULN	1	5.6
> 3.0 x ULN	1	57.0
Missing	2	44.5

MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CrCl = creatinine clearance; LLN = lower limit of normal; ULN = upper limit of normal.
Note: Trials included: PCYC-04753, PCYC-1104-CA, MCL2001, MCL3001, PCYC-1102-CA, PCYC-1108-CA, PCYC-1109-CA, PCYC-1112-CA, PCYC-1115-CA, PCYC-1117-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, PCYC-1118e-CA, CLL3011, PCYC-1142-CA, PCYC-1127-CA. Cross-over period exposure from Trials MCL3001, PCYC-1112-CA, CLL3001, PCYC-1130-CA, CLL3011, and PCYC-1127-CA, as well as exposures from open-label subtrial in PCYC-1127-CA are included in the summary.
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PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 1	**Hypersensitivity**
Reason for being an exclusion criterion	Ibrutinib is contraindicated for patients with a hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 of the Summary of Product Characteristics (SmPC).
Considered to be included as missing information	No
Rationale (if not included as missing information)	This is a standard contraindication in SmPCs. To date, there were very few severe hypersensitivity reactions observed in association with ibrutinib treatment and there is currently no way allowing the identification of patients who could be hypersensitive to ibrutinib. None of the excipients is considered as potentially causing hypersensitivity reactions.
Criterion 2	**Central nervous system (CNS) involvement by lymphoma**
Reason for being an exclusion criterion	Standard practice in oncology clinical trials. Inclusion of patients with known CNS involvement can confound the efficacy and safety assessments of the trial.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Patients may have their lymphoma treated with ibrutinib but need additional therapy to treat the CNS involvement.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Criterion 3	**Creatinine >1.5 x institutional upper limit of normal (ULN)**
Reason for being an exclusion criterion	Early in the development program, the effects of renal clearance on ibrutinib pharmacokinetics and safety were not fully elucidated.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Ibrutinib has minimal renal clearance; urinary excretion of ibrutinib and its metabolites is <10% of the dose. There is no scientific rationale to expect a different safety profile in this population.
Criterion 4	**Total bilirubin >1.5 x institutional ULN (unless elevated from documented Gilbert's syndrome).** **Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 x institutional ULN**
Reason for being an exclusion criterion	Ibrutinib is metabolized in the liver. Early in the development program, the effects of hepatic impairment on ibrutinib pharmacokinetics and safety were not fully elucidated.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Trial PCI-32765CLL1006, which evaluated the effect of hepatic impairment on ibrutinib exposure, was completed. As a result, a dose recommendation has been included in the SmPC, advising dose reductions for patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. The SmPC states that it is not recommended to administer ibrutinib to patients with severe hepatic impairment (Child-Pugh class C).
Criterion 5	**Concomitant use of medicines known to cause QT prolongation or torsades de pointes**[1]
Reason for being an exclusion criterion	Cardiac electrocardiogram (ECG) monitoring was part of the assessments for the trial; therefore, medications that can cause significant abnormalities were prohibited. It is common practice to exclude such treatments prior to availability of QT data.

[1] This was an exclusion criterion in Trials 04753, 1102, 1108, and 1118E-CA, but not in the other trials in the ibrutinib development program.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Considered to be included as missing information	No
Rationale (if not included as missing information)	Concomitant use of such medications was only prohibited in earlier trials with ibrutinib. Clinical data show that QTc intervals are not prolonged by ibrutinib. In a thorough QT study (PCI-32765CLL1007), a concentration-dependent shortening in the QTc interval was observed.
Criterion 6	**Significant screening ECG abnormalities including left bundle branch block, 2nd degree AV block type II, 3rd degree block, bradycardia, or QTc ≥500 msec**[2]
Reason for being an exclusion criterion	Cardiac ECG monitoring was part of the assessments for the trial; therefore, significant abnormalities at entry were excluded.
Considered to be included as missing information	No
Rationale (if not included as missing information)	There were no findings in the clinical trials and the thorough QT study indicating that ibrutinib administration was associated with prolongation of QTc interval.
Criterion 7	**History of myocardial infarction, acute coronary syndromes (including unstable angina), coronary angioplasty, and/or stenting within the past 6 months**
Reason for being an exclusion criterion	It is common clinical practice to exclude subjects with severe and potentially life-threatening concurrent cardiac conditions in clinical trials.
Considered to be included as missing information	Yes (Use in patients with severe cardiac disease)
Rationale (if not included as missing information)	Mild to Moderate Cardiac Disease: The observed cardiac AEs following exposure to ibrutinib in trials were mainly mild to moderate and not unexpected for trial populations (generally older males and with multiple pre-existing CVD). There are no specific data available for use of ibrutinib in patients with severe cardiac disease. The treating physician would be expected to weigh the benefit and risks for each individual patient.

[2] This was an exclusion criterion in Trials 04753, 1104, 1102, and 1108, but not in the other trials in the ibrutinib development program.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Criterion 8	**Pregnant or lactating women (female patients of childbearing potential must have a negative serum pregnancy test within 14 days of first day of drug dosing, or, if positive, a pregnancy ruled out by ultrasound)**
Reason for being an exclusion criterion	Based on findings in animals, ibrutinib may cause fetal harm when administered to pregnant women.
Considered to be included as missing information	No
Rationale (if not included as missing information)	The SmPC states that ibrutinib should not be used during pregnancy and that women of childbearing potential must use highly effective contraceptive measures while taking ibrutinib and for 3 months after stopping treatment. Breastfeeding should be discontinued during treatment with ibrutinib as a risk to the newborns/infants cannot be excluded.
Criterion 9	**Known history of HIV or active infection with HCV or hepatitis B virus (HBV) or any uncontrolled active systemic infection**
Reason for being an exclusion criterion	It is common clinical practice to exclude subjects with severe active infections because they potentially confound the interpretation of safety.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Infections (including viral reactivation) are included as an important identified risk. The treating physician would be expected to weigh the benefit and risks for each individual patient.
Criterion 10	**If subjects required anticoagulation with warfarin or other vitamin K antagonists**
Reason for being an exclusion criterion	During the early Phase 1 and 2 trials in October 2011, a cluster of CNS hemorrhagic events were identified. Two external consultants (a hematologist and a neurosurgeon) reviewed the intracranial hemorrhage cases and felt that the causations were most likely due to a recent fall or use of warfarin. Patients were excluded from participation in ibrutinib Phase 2 and 3 trials if they required warfarin or other vitamin K antagonists.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Considered to be included as missing information	No
Rationale (if not included as missing information)	Hemorrhage is an important identified risk. SmPC Section 4.4 states that there have been reports of bleeding events in patients treated with ibrutinib, both with and without thrombocytopenia. These include minor bleeding events such as contusion, epistaxis, and petechiae; and major bleeding events, some fatal, including GI bleeding, intracranial hemorrhage, and hematuria. Warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib. Use of either anticoagulants or medicinal products that inhibit platelet function (antiplatelet agents) concomitantly with ibrutinib increases the risk of major bleeding. A higher risk for major bleeding was observed with anticoagulant than with antiplatelet agents. The risks and benefits of anticoagulant or antiplatelet therapy should be considered when coadministered with ibrutinib and patients should be monitored for signs and symptoms of bleeding. Supplements such as fish oil and vitamin E preparations should be avoided. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding. The mechanism for the bleeding-related events is not fully understood. Patients with congenital bleeding diathesis have not been studied. The treating physician would be expected to weigh the benefit and risks for each individual patient.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program(s)

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Children	The efficacy of ibrutinib in children aged 0 to <18 years has not yet been established as MCL, CLL, and WM are not present in the pediatric population. A Paediatric Investigation Plan for ibrutinib has been agreed and closed for the condition "Treatment of mature B-cell neoplasm". A trial in pediatric subjects with relapsed or refractory mature B-cell NHL (Trial 54179060LYM3003) was completed and has shown no benefit of adding ibrutinib to standard-of-care chemoimmunotherapy. In that trial, 56 subjects were exposed to ibrutinib (21 subjects aged 1 to <18 years and 35 subjects aged 1 to 30 years [initial diagnosis of mature B cell NHL was made before 18 years of age]). No new adverse reactions were observed in this study. A Paediatric Investigation Plan for ibrutinib has been agreed for the condition "Treatment of cGVHD". Two trials in pediatric subjects with cGVHD have been conducted (Trials PCYC-1146-IM and PCYC-1140-IM). In total, 62 pediatric subjects (aged 1 to <22 years) were exposed to ibrutinib.
Pregnant or breastfeeding women	There are no adequate and well controlled trials of ibrutinib in pregnant women. Ibrutinib should not be used during pregnancy. Breastfeeding should be discontinued during treatment with ibrutinib.
Population with relevant different racial and/or ethnic origin	Of the 2,912 adult subjects in the all clinical trials population, 2,568 (88%) subjects were white, while 79 (3%) subjects were black or African American and 265 (9%) subjects were Hispanic or Latino, Asian, American Indian or Alaska Native, or "Other" race.
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Patients with relevant comorbidities:	
• Patients with hepatic impairment	Of the 2,912 adult subjects in the all clinical trials population, 126 (4%) subjects had ALT >ULN to ≤3.0 x ULN, 259 (9%) subjects had AST >ULN to ≤3.0 x ULN, 2 (<1%) subjects had AST >3.0 x ULN to ≤5.0 x ULN, 117 (4%) subjects had bilirubin > ULN to ≤1.5 x ULN, 28 (1%) subjects had bilirubin >1.5 x ULN to ≤3.0 x ULN, and 3 (<1%) subjects had bilirubin >3.0 x ULN at baseline.

• Patients with renal impairment	No specific clinical trials have been conducted in patients with renal impairment. Of the 2,912 adult subjects in the all clinical trials population, 908 (31%) of the subjects had mild (creatinine clearance [CrCl] <lower limit of normal to ≥60 mL/min), 587 (20%) of the subjects had moderate (CrCl <60 to ≥30 mL/min), and 12 (<1%) subjects had severe (CrCl <30 mL/min) renal impairment at baseline.
• Patients with cardiovascular impairment	The subjects in the clinical trials included older subjects with multiple pre-existing CVD. However, patients with severe cardiac diseases (eg, New York Heart Association class III or higher) were excluded from ibrutinib clinical trials. **Use in patients with severe cardiac disease is considered Missing Information.**
• Immunocompromised patients	Not applicable
• Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable

Summary of Missing Information Due to Limitations of the Clinical Trial Program

Use in patients with severe cardiac disease

PART II: SAFETY SPECIFICATION

Module SV: Postauthorization Experience

SV.1. Postauthorization Exposure

SV.1.1. Method used to Calculate Exposure

Reporting frequencies calculated using exposure data do not reflect occurrence rates. Multiple factors influence the reporting of spontaneous experiences and therefore, caution must be exercised in the analysis and evaluation of spontaneous reports. In addition, product exposure is estimated at the time of distribution, not at the time of usage. There is a delay between the times a medication is distributed until it is used by a patient. Patient exposure was estimated by calculation from distribution data. Estimates of exposure are based upon finished product. Ibrutinib is marketed for 3 indications: MCL, CLL, and WM. The recommended dosing for the MCL indication is 560 mg once daily and for the CLL and WM indications is 420 mg once daily. The treatment pattern between MCL:CLL is close to 1:4. Taking this indication ratio into consideration, the average use regardless of indications per patient per day was calculated to be 448 mg (0.2*560 mg + 0.8*420 mg).

SV.1.2. Exposure

Exposure to Ibrutinib (Cumulative to 30 September 2021)

Mg Distributed[a]	Average Daily Dose	Person-Years
51,438,828,707	448 mg	330,980

a: Distribution was first observed in January 2014. This estimate includes commercial exposure for Ibrutinib. Specific ATU and named patient program information are not available for various programs by country and may be captured in other clinical sections of the report.

Based on the total 51,438,828,707 mg distributed (cumulative to 30 September 2021) the estimated exposure is 330,980 person-years.

Market research sources for non-study exposure data (nonclinical) are unavailable for breakdowns such as usage in children, pregnant or breastfeeding women, severe hepatic impairment population, or renal impairment population.

PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Ibrutinib is an antineoplastic agent and has no abuse potential. Therefore, there is no concern for potential illegal use.

PART II: SAFETY SPECIFICATION

Module SVII: Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Not applicable.

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

Reason for not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Not applicable.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

Per Health Authority request for Procedure No. EMEA/H/C/003791/IB/0079, the MAH has reclassified the important potential risk "Infections (including viral reactivation)" to an important identified risk. This is based on the totality of data and the inclusion of serious infections in Sections 4.4 and 4.8 of the SmPC.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

The important identified risks, important potential risks, and missing information with ibrutinib are based on the nonclinical and clinical trial experience, as well as on postmarketing experience.

Important identified risks:

1. Hemorrhage
2. Hepatotoxicity (including hepatic failure)
3. Atrial fibrillation
4. Ventricular tachyarrhythmias
5. Hypertension
6. Ischemic stroke
7. Cardiac failure
8. Infections (including viral reactivation)

Important potential risks:

1. Progressive multifocal leukoencephalopathy (PML)
2. Cardiac arrhythmia (excluding atrial fibrillation and ventricular tachyarrhythmias)
3. Other malignancies (excluding non-melanoma skin cancer)

Missing information:

1. Use in patients with severe cardiac disease

Medical Dictionary for Regulatory Activities (MedDRA) version 23.1 was used to classify the clinical trials AE information that is summarized in this Section.

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk - Hemorrhage

Potential Mechanisms:

In an in vitro study (PCYC-1132-NT), ibrutinib demonstrated inhibition of collagen-induced platelet aggregation in samples from the cohorts of subjects with either renal dysfunction, those on warfarin, or healthy subjects. The magnitude of inhibition of collagen-induced platelet aggregation in the cohort of subjects on aspirin was less pronounced since collagen-induced platelet aggregation was already reduced without ibrutinib. Ibrutinib did not show meaningful inhibition of platelet aggregation for the 4 agonists adenosine diphosphate, arachidonic acid,

ristocetin, and thrombin receptor-activating peptide 6 across any of these cohorts of subjects or healthy subjects.

Evidence Source(s) and Strength of Evidence:

Cases of hemorrhagic events in association with ibrutinib have been reported in completed clinical trials. These events, in addition to recommendations for patients requiring anticoagulants or medication that inhibits platelet function, are also described in the current prescribing information for ibrutinib.

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of Hemorrhage in Clinical Trials; (The Randomized Clinical Trials Population)

	All Randomized Trials Population	
	Ibrutinib n (%)	**Placebo/Comparator n (%)**
Indication: MCL		
Number of subjects treated	139	139
Frequency[a]	55 (39.6%)	46 (33.1%)
Odds Ratio	1.324	
95% confidence interval	(0.811, 2.161)	
Seriousness		
Was Serious	11 (7.9%)	6 (4.3%)
Outcomes		
Resulted in Death	2 (1.4%)	0
Did not recover (Persisted)	12 (8.6%)	2 (1.4%)
Recovering with treatment	2 (1.4%)	0
Recovering without treatment	1 (0.7%)	1 (0.7%)
Recovered with treatment	11 (7.9%)	15 (10.8%)
Recovered without treatment	27 (19.4%)	28 (20.1%)
Missing	0	0
Severity/Nature of Risk		
Worst Grade=1	29 (20.9%)	34 (24.5%)
Worst Grade=2	14 (10.1%)	5 (3.6%)
Worst Grade=3	4 (2.9%)	6 (4.3%)
Worst Grade=4	6 (4.3%)	1 (0.7%)
Worst Grade=5	2 (1.4%)	0
Missing Grade	0	0
Indication: CLL		
Number of subjects treated	1,188	988
Frequency[a]	574 (48.3%)	128 (13.0%)
Odds Ratio	6.280	
95% confidence interval	(5.051, 7.807)	
Severity/Nature of Risk		
Worst Grade=1	412 (34.7%)	96 (9.7%)
Worst Grade=2	113 (9.5%)	19 (1.9%)
Worst Grade=3	39 (3.3%)	9 (0.9%)
Worst Grade=4	4 (0.3%)	4 (0.4%)
Worst Grade=5	5 (0.4%)	0
Missing Grade	1 (0.1%)	0
Number of subjects assessed (exclude E1912)	836	830
Seriousness*		
Was Serious	46 (5.5%)	7 (0.8%)
Outcomes*		
Resulted in Death	5 (0.6%)	0
Did not recover (Persisted)	111 (13.3%)	11 (1.3%)
Recovering with treatment	2 (0.2%)	0
Recovering without treatment	4 (0.5%)	1 (0.1%)
Recovered with treatment	45 (5.4%)	9 (1.1%)

Frequency, Seriousness, Outcomes, and Severity of Hemorrhage in Clinical Trials; (The Randomized Clinical Trials Population)

	All Randomized Trials Population	
	Ibrutinib n (%)	**Placebo/Comparator n (%)**
Recovered without treatment	221 (26.4%)	89 (10.7%)
Missing	0	0
Indication: WM		
Number of subjects treated	75	75
Frequency[a]	40 (53.3%)	16 (21.3%)
Odds Ratio	4.214	
95% confidence interval	(2.062, 8.613)	
Seriousness		
Was Serious	4 (5.3%)	3 (4.0%)
Outcomes		
Resulted in Death	0	1 (1.3%)
Did not recover (Persisted)	13 (17.3%)	0
Recovering with treatment	0	0
Recovering without treatment	0	0
Recovered with treatment	3 (4.0%)	0
Recovered without treatment	24 (32.0%)	15 (20.0%)
Missing	0	0
Severity/Nature of Risk		
Worst Grade=1	25 (33.3%)	9 (12.0%)
Worst Grade=2	10 (13.3%)	4 (5.3%)
Worst Grade=3	5 (6.7%)	2 (2.7%)
Worst Grade=4	0	0
Worst Grade=5	0	1 (1.3%)
Missing Grade	0	0

[a] Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA preferred terms representative of hemorrhage; the subject is counted only once regardless of the number of events or the number of occurrences.
The outcome of Unknown is not presented in the summary.
MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia.
Note: Trials included: MCL3001, PCYC-1112-CA, PCYC-1115-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1127-CA. Comparator drugs include temsirolimus (MCL3001), ofatumumab (PCYC-1112-CA), chlorambucil (PCYC-1115-CA), placebo + bendamustine + rituximab (CLL3001), chlorambucil + obinutuzumab (PCYC-1130-CA, CLL3011), fludarabine + cyclophosphamide + rituximab (E1912/PCYC-1126e-CA), and a combination of placebo + rituximab (PCYC-1127-CA).
* Trial E1912 collected neither AE seriousness, nor outcome, thus is excluded from seriousness and outcome summaries.

[TRMRSK04A.RTF] [JNJ-54179060/Z RMP/DBR RMP 2021 GLOW/RE RMP EU UPDATE/PROD/TRMRSKA-ALL.SAS] 10FEB2022, 23:29

Frequency, Seriousness, Outcomes, and Severity of Hemorrhage in Clinical Trials; (The All Clinical Trials Population Including Open Extensions)

	Monotherapy [a]	**Combination [a]**	**All Clinical Trials Population**
Indication: MCL			
Number of subjects treated	421	0	421
Frequency[a]	169 (40.1%)	0	169 (40.1%)
Seriousness			
Was Serious	22 (5.2%)	0	22 (5.2%)
Outcomes			
Resulted in Death	2 (0.5%)	0	2 (0.5%)
Did not recover (Persisted)	49 (11.6%)	0	49 (11.6%)
Recovering with treatment	3 (0.7%)	0	3 (0.7%)
Recovering without treatment	2 (0.5%)	0	2 (0.5%)
Recovered with treatment	24 (5.7%)	0	24 (5.7%)
Recovered without treatment	89 (21.1%)	0	89 (21.1%)
Missing	0	0	0

Frequency, Seriousness, Outcomes, and Severity of Hemorrhage in Clinical Trials; (The All Clinical Trials Population Including Open Extensions)

	Monotherapy [a]	Combination [a]	All Clinical Trials Population
Severity/Nature of Risk			
Worst Grade=1	111 (26.4%)	0	111 (26.4%)
Worst Grade=2	35 (8.3%)	0	35 (8.3%)
Worst Grade=3	13 (3.1%)	0	13 (3.1%)
Worst Grade=4	8 (1.9%)	0	8 (1.9%)
Worst Grade=5	2 (0.5%)	0	2 (0.5%)
Missing Grade	0	0	0
Indication: CLL			
Number of subjects treated	998	1,285	2,283
Frequency[a]	515 (51.6%)	660 (51.4%)	1,175 (51.5%)
Severity/Nature of Risk			
Worst Grade=1	353 (35.4%)	514 (40.0%)	867 (38.0%)
Worst Grade=2	101 (10.1%)	107 (8.3%)	208 (9.1%)
Worst Grade=3	51 (5.1%)	30 (2.3%)	81 (3.5%)
Worst Grade=4	5 (0.5%)	4 (0.3%)	9 (0.4%)
Worst Grade=5	5 (0.5%)	4 (0.3%)	9 (0.4%)
Missing Grade	0	1 (0.1%)	1 (<0.1%)
Number of subjects assessed (exclude E1912)	998	933	1,931
Seriousness*			
Was Serious	66 (6.6%)	30 (3.2%)	96 (5.0%)
Outcomes*			
Resulted in Death	5 (0.5%)	4 (0.4%)	9 (0.5%)
Did not recover (Persisted)	196 (19.6%)	127 (13.6%)	323 (16.7%)
Recovering with treatment	2 (0.2%)	0	2 (0.1%)
Recovering without treatment	5 (0.5%)	1 (0.1%)	6 (0.3%)
Recovered with treatment	55 (5.5%)	38 (4.1%)	93 (4.8%)
Recovered without treatment	250 (25.1%)	304 (32.6%)	554 (28.7%)
Missing	0	0	0
Indication: WM			
Number of subjects treated	133	75	208
Frequency[a]	57 (42.9%)	40 (53.3%)	97 (46.6%)
Seriousness			
Was Serious	4 (3.0%)	4 (5.3%)	8 (3.8%)
Outcomes			
Resulted in Death	0	0	0
Did not recover (Persisted)	13 (9.8%)	13 (17.3%)	26 (12.5%)
Recovering with treatment	0	0	0
Recovering without treatment	0	0	0
Recovered with treatment	3 (2.3%)	3 (4.0%)	6 (2.9%)
Recovered without treatment	13 (9.8%)	24 (32.0%)	37 (17.8%)
Missing	28 (21.1%)	0	28 (13.5%)

Frequency, Seriousness, Outcomes, and Severity of Hemorrhage in Clinical Trials; (The All Clinical Trials Population Including Open Extensions)

	Monotherapy [a]	Combination [a]	All Clinical Trials Population
Severity/Nature of Risk			
Worst Grade=1	46 (34.6%)	25 (33.3%)	71 (34.1%)
Worst Grade=2	8 (6.0%)	10 (13.3%)	18 (8.7%)
Worst Grade=3	3 (2.3%)	5 (6.7%)	8 (3.8%)
Worst Grade=4	0	0	0
Worst Grade=5	0	0	0
Missing Grade	0	0	0

[a] Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA preferred terms representative of hemorrhage; the subject is counted only once regardless of the number of events or the number of occurrences.
The outcome of Unknown is not presented in the summary.
MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia.
Note: Trials included: PCYC-04753, PCYC-1104-CA, MCL2001, MCL3001, PCYC-1102-CA, PCYC-1108-CA, PCYC-1109-CA, PCYC-1112-CA, PCYC-1115-CA, PCYC-1117-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1142-CA, PCYC-1118e-CA, PCYC-1127-CA.
Data for cross-over subjects from Trials MCL3001, PCYC-1112-CA, CLL3001, PCYC-1130-CA, CLL3011, and PCYC-1127-CA, as well as data for subjects from open-label subtrial in PCYC-1127-CA are included in the monotherapy pool.
* Trial E1912 collected neither AE seriousness, nor outcome, thus is excluded from seriousness and outcome summaries.
Note: Subjects who crossed over from the comparator treatment group are counted towards monotherapy. All subjects in Trial PCYC-1142-CA are counted towards combination therapy. Subjects in Trial CLL3011 who received experimental treatment and who were re-exposed to study ibrutinib are also counted towards combination therapy.

[TRMRSK04B.RTF] [JNJ-54179060/Z RMP/DBR RMP 2021 GLOW/RE RMP EU UPDATE/PROD/TRMRSKB-ALL.SAS] 10FEB2022, 23:41

There have been reports of bleeding events in subjects treated with ibrutinib, both with and without thrombocytopenia. These include predominantly minor bleeding events such as contusion, epistaxis, and petechiae; but also some major bleeding events, some fatal, including GI bleeding, intracranial hemorrhage, and hematuria.

Mild to moderate hemorrhage is one of the most commonly occurring adverse reactions. Severe hemorrhage, which occurs less frequently, is a potentially life-threatening or fatal complication, also known to occur in the context of the underlying diseases of WM, MCL, or CLL. Patients with hemorrhage are treated as per standard of care.

No new safety information that impacts the risk-benefit balance of the product has emerged from postmarketing experience.

Risk Factors and Risk Groups:

Predictors include increasing age (>60 years), history of bleeding, dose of chemotherapy, baseline platelet count, poor performance and/or nutritional status, and concomitant use of antiplatelet or anticoagulant therapy, especially warfarin use in the elderly population.

Preventability:

As stated in Section 4.4 of the SmPC, warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib. Use of either anticoagulants or medicinal products that inhibit platelet function (antiplatelet agents) concomitantly with ibrutinib increases the risk of major bleeding. A higher risk for major bleeding was observed with anticoagulant than with antiplatelet agents. The risks and benefits of anticoagulant or antiplatelet therapy should be considered when coadministered with ibrutinib and patients should be monitored for signs and symptoms of bleeding. Supplements such as fish oil and vitamin E preparations should be avoided. The mechanism for the bleeding-related events is not fully understood. Patients with congenital bleeding diathesis have not been studied. Ibrutinib should be withheld at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Impact on the Risk-benefit Balance of the Product:

While occurring frequently in patients treated with ibrutinib, most cases of bleeding were mild or moderate and therefore had no significant impact on the risk-benefit balance of the product. Major hemorrhage occurs less frequently but has led to death in rare cases. The SmPC and package leaflet (PL) provide information to the prescriber and patient on how to manage the risk. Overall, the risk-benefit balance is positive for the product considering the severity of the diseases treated and the established efficacy and safety profile of ibrutinib.

Public Health Impact:

In consideration of the relatively small number of patients in the targeted populations and the relatively small number of major hemorrhage cases reported with ibrutinib therapy, the impact on public health is expected to be low.

Annex 1 MedDRA Term:

Haemorrhage (Standardized MedDRA Query [SMQ])

Important Identified Risk – Hepatotoxicity (Including Hepatic Failure)

Potential Mechanisms:

In in vitro studies, ibrutinib was observed to bind covalently to hepatic proteins such as CYP3A4/5 and human hepatic microsomes, with and without metabolic activation. However, in vitro studies using human hepatic microsomes did not indicate a clinically relevant reversible or time-dependent CYP inhibition by ibrutinib. Despite the observed in vitro covalent binding to (hepatic) proteins, there was no hepatic safety signal from the general toxicity program, eg, no treatment-related changes in liver function parameters were noted and no hepatic histopathology changes were observed.

Based on in vitro data, ibrutinib is not transported by major transporter proteins involved in hepatic uptake or hepatic efflux. A potential mechanism for ibrutinib-induced hepatotoxicity is unknown.

Evidence Source(s) and Strength of Evidence:

A grade 4 hepatic enzyme elevation in association with ibrutinib has been observed in a healthy volunteer in a clinical trial. Hepatic failure has been identified as an adverse reaction during postmarketing experience. These events are described in the current prescribing information for ibrutinib.

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of Hepatotoxicity (Including Hepatic Failure) in Clinical Trials; (The Randomized Clinical Trials Population)

	All Randomized Trials Population	
	Ibrutinib n (%)	**Placebo/Comparator n (%)**
Indication: MCL		
Number of subjects treated	139	139
Frequency[a]	15 (10.8%)	20 (14.4%)
Odds Ratio	0.720	
95% confidence interval	(0.352, 1.472)	
Seriousness		
Was Serious	1 (0.7%)	1 (0.7%)
Outcomes		
Resulted in Death	0	0
Did not recover (Persisted)	4 (2.9%)	3 (2.2%)
Recovering with treatment	0	0
Recovering without treatment	1 (0.7%)	3 (2.2%)
Recovered with treatment	3 (2.2%)	3 (2.2%)
Recovered without treatment	7 (5.0%)	11 (7.9%)
Missing	0	0
Severity/Nature of Risk		
Worst Grade=1	5 (3.6%)	12 (8.6%)
Worst Grade=2	6 (4.3%)	7 (5.0%)
Worst Grade=3	3 (2.2%)	1 (0.7%)
Worst Grade=4	1 (0.7%)	0
Worst Grade=5	0	0
Missing Grade	0	0

Frequency, Seriousness, Outcomes, and Severity of Hepatotoxicity (Including Hepatic Failure) in Clinical Trials; (The Randomized Clinical Trials Population)

	All Randomized Trials Population	
	Ibrutinib n (%)	**Placebo/Comparator n (%)**
Indication: CLL		
Number of subjects treated	1,188	988
Frequency[a]	328 (27.6%)	143 (14.5%)
Odds Ratio	2.254	
95% confidence interval	(1.812, 2.803)	
Severity/Nature of Risk		
Worst Grade=1	185 (15.6%)	83 (8.4%)
Worst Grade=2	84 (7.1%)	40 (4.0%)
Worst Grade=3	53 (4.5%)	16 (1.6%)
Worst Grade=4	6 (0.5%)	1 (0.1%)
Worst Grade=5	0	3 (0.3%)
Missing Grade	0	0
Number of subjects assessed (exclude E1912)	836	830
Seriousness*		
Was Serious	3 (0.4%)	8 (1.0%)
Outcomes*		
Resulted in Death	0	3 (0.4%)
Did not recover (Persisted)	28 (3.3%)	6 (0.7%)
Recovering with treatment	0	0
Recovering without treatment	1 (0.1%)	1 (0.1%)
Recovered with treatment	7 (0.8%)	2 (0.2%)
Recovered without treatment	80 (9.6%)	46 (5.5%)
Missing	0	0
Indication: WM		
Number of subjects treated	75	75
Frequency[a]	7 (9.3%)	4 (5.3%)
Odds Ratio	1.827	
95% confidence interval	(0.512, 6.524)	
Seriousness		
Was Serious	0	0
Outcomes		
Resulted in Death	0	0
Did not recover (Persisted)	3 (4.0%)	1 (1.3%)
Recovering with treatment	0	0
Recovering without treatment	0	0
Recovered with treatment	0	0
Recovered without treatment	4 (5.3%)	3 (4.0%)
Missing	0	0

Frequency, Seriousness, Outcomes, and Severity of Hepatotoxicity (Including Hepatic Failure) in Clinical Trials; (The Randomized Clinical Trials Population)

	All Randomized Trials Population	
	Ibrutinib n (%)	**Placebo/Comparator n (%)**
Severity/Nature of Risk		
Worst Grade=1	1 (1.3%)	0
Worst Grade=2	2 (2.7%)	2 (2.7%)
Worst Grade=3	4 (5.3%)	2 (2.7%)
Worst Grade=4	0	0
Worst Grade=5	0	0
Missing Grade	0	0

[a] Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA preferred terms representative of hepatotoxicity including hepatic failure; the subject is counted only once regardless of the number of events or the number of occurrences.
The outcome of Unknown is not presented in the summary.
MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia.
Note: Trials included: MCL3001, PCYC-1112-CA, PCYC-1115-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1127-CA. Comparator drugs include temsirolimus (MCL3001), ofatumumab (PCYC-1112-CA), chlorambucil (PCYC-1115-CA), placebo + bendamustine + rituximab (CLL3001), chlorambucil + obinutuzumab (PCYC-1130-CA, CLL3011), fludarabine + cyclophosphamide + rituximab (E1912/PCYC-1126e-CA), and a combination of placebo + rituximab (PCYC-1127-CA).
* Trial E1912 collected neither AE seriousness, nor outcome, thus is excluded from seriousness and outcome summaries.

[TRMRSK17A.RTF] [JNJ-54179060/Z_RMP/DBR_RMP_2021_GLOW/RE_RMP_EU_UPDATE/PROD/TRMRSKA-ALL.SAS] 10FEB2022, 23:29

Frequency, Seriousness, Outcomes, and Severity of Hepatotoxicity (Including Hepatic Failure) in Clinical Trials; (The All Clinical Trials Population Including Open Extensions)

	Monotherapy [a]	**Combination [a]**	**All Clinical Trials Population**
Indication: MCL			
Number of subjects treated	421	0	421
Frequency[a]	46 (10.9%)	0	46 (10.9%)
Seriousness			
Was Serious	3 (0.7%)	0	3 (0.7%)
Outcomes			
Resulted in Death	0	0	0
Did not recover (Persisted)	16 (3.8%)	0	16 (3.8%)
Recovering with treatment	0	0	0
Recovering without treatment	1 (0.2%)	0	1 (0.2%)
Recovered with treatment	4 (1.0%)	0	4 (1.0%)
Recovered without treatment	25 (5.9%)	0	25 (5.9%)
Missing	0	0	0
Severity/Nature of Risk			
Worst Grade=1	12 (2.9%)	0	12 (2.9%)
Worst Grade=2	19 (4.5%)	0	19 (4.5%)
Worst Grade=3	14 (3.3%)	0	14 (3.3%)
Worst Grade=4	1 (0.2%)	0	1 (0.2%)
Worst Grade=5	0	0	0
Missing Grade	0	0	0
Indication: CLL			
Number of subjects treated	998	1,285	2,283
Frequency[a]	96 (9.6%)	350 (27.2%)	446 (19.5%)
Severity/Nature of Risk			
Worst Grade=1	44 (4.4%)	195 (15.2%)	239 (10.5%)
Worst Grade=2	32 (3.2%)	89 (6.9%)	121 (5.3%)
Worst Grade=3	15 (1.5%)	60 (4.7%)	75 (3.3%)
Worst Grade=4	1 (0.1%)	6 (0.5%)	7 (0.3%)
Worst Grade=5	4 (0.4%)	0	4 (0.2%)
Missing Grade	0	0	0

Frequency, Seriousness, Outcomes, and Severity of Hepatotoxicity (Including Hepatic Failure) in Clinical Trials; (The All Clinical Trials Population Including Open Extensions)

	Monotherapy [a]	Combination [a]	All Clinical Trials Population
Number of subjects assessed (exclude E1912)	998	933	1,931
Seriousness*			
Was Serious	6 (0.6%)	4 (0.4%)	10 (0.5%)
Outcomes*			
Resulted in Death	4 (0.4%)	0	4 (0.2%)
Did not recover (Persisted)	30 (3.0%)	28 (3.0%)	58 (3.0%)
Recovering with treatment	0	0	0
Recovering without treatment	2 (0.2%)	0	2 (0.1%)
Recovered with treatment	5 (0.5%)	8 (0.9%)	13 (0.7%)
Recovered without treatment	55 (5.5%)	102 (10.9%)	157 (8.1%)
Missing	0	0	0
Indication: WM			
Number of subjects treated	133	75	208
Frequency[a]	5 (3.8%)	7 (9.3%)	12 (5.8%)
Seriousness			
Was Serious	0	0	0
Outcomes			
Resulted in Death	0	0	0
Did not recover (Persisted)	2 (1.5%)	3 (4.0%)	5 (2.4%)
Recovering with treatment	0	0	0
Recovering without treatment	0	0	0
Recovered with treatment	0	0	0
Recovered without treatment	1 (0.8%)	4 (5.3%)	5 (2.4%)
Missing	2 (1.5%)	0	2 (1.0%)
Severity/Nature of Risk			
Worst Grade=1	3 (2.3%)	1 (1.3%)	4 (1.9%)
Worst Grade=2	1 (0.8%)	2 (2.7%)	3 (1.4%)
Worst Grade=3	1 (0.8%)	4 (5.3%)	5 (2.4%)
Worst Grade=4	0	0	0
Worst Grade=5	0	0	0
Missing Grade	0	0	0

[a] Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA preferred terms representative of hepatotoxicity including hepatic failure; the subject is counted only once regardless of the number of events or the number of occurrences.
The outcome of Unknown is not presented in the summary.
MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia.
Note: Trials included: PCYC-04753, PCYC-1104-CA, MCL2001, MCL3001, PCYC-1102-CA, PCYC-1108-CA, PCYC-1109-CA, PCYC-1112-CA, PCYC-1115-CA, PCYC-1117-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1142-CA, PCYC-1118e-CA, PCYC-1127-CA.
Data for cross-over subjects from Trials MCL3001, PCYC-1112-CA, CLL3001, PCYC-1130-CA, CLL3011, and PCYC-1127-CA, as well as data for subjects from open-label subtrial in PCYC-1127-CA are included in the monotherapy pool.
* Trial E1912 collected neither AE seriousness, nor outcome, thus is excluded from seriousness and outcome summaries.
Note: Subjects who crossed over from the comparator treatment group are counted towards monotherapy. All subjects in Trial PCYC-1142-CA are counted towards combination therapy. Subjects in Trial CLL3011 who received experimental treatment and who were re-exposed to study ibrutinib are also counted towards combination therapy.

[TRMRSK17B.RTF] [JNJ-54179060/Z RMP/DBR RMP 2021 GLOW/RE RMP EU UPDATE/PROD/TRMRSKB-ALL.SAS] 10FEB2022, 23:41

In a thorough QTc Study (PCI-32765CLL1007), a healthy volunteer experienced reversible grade 4 ALT/AST elevation after receiving a supratherapeutic dose (1,680 mg) of ibrutinib in accordance with the protocol. The subject's hepatic enzyme levels returned to normal approximately 5 weeks following the peak elevation. The Sponsor considered that a causal

relationship of the liver function abnormalities in this subject to ibrutinib could not be ruled out. The investigator assessment was "possibly related."

Liver abnormalities are generally non-severe. However, drug-induced liver injury could be serious and potentially fatal or require liver transplant. The majority of cases reporting hepatotoxicity associated with ibrutinib were mild to moderate and resolved with discontinuation or dose modification.

No new safety information that impacts the risk-benefit balance of the product has emerged from postmarketing experience.

Risk Factors and Risk Groups:

Risk factors for drug-induced liver toxicity include increasing age, HIV/acquired immunodeficiency syndrome infection and antiretroviral drug use, chronic HBV or HCV infection, obesity, and nonalcoholic fatty liver disease. Patients taking other anti-cancer agents, anti-infectives, psychotropics, lipid-lowering agents, herbal and dietary supplements, and nonsteroidal anti-inflammatory drugs are also at risk (Bahirwani and Reddy, 2014; Bell and Chalasani, 2009).

Preventability:

The SmPC (Section 4.4) states that liver function and viral hepatitis status should be assessed before initiating treatment with ibrutinib. Patients should be periodically monitored for changes in liver function parameters during treatment. For patients diagnosed with hepatic events, consulting a liver disease expert for management should be considered. As stated in the SmPC (Section 4.9), patients who ingest more than the recommended dose should be closely monitored and given appropriate supportive treatment.

Impact on the Risk-benefit Balance of the Product:

The observed incidence of significant hepatotoxicity cases is low and therefore does not have a significant impact on the risk-benefit balance of the product. Hepatic failure is included as an adverse reaction in the SmPC. Overall, the risk-benefit balance is positive for the product considering the severity of the diseases treated and the established efficacy and safety profile of ibrutinib.

Public Health Impact:

In consideration of the relatively small number of patients in the targeted populations and the relatively small number of significant hepatotoxicity cases reported with ibrutinib therapy, the impact on public health is expected to be low.

Annex 1 MedDRA Term:

Hepatic disorders (SMQ)

Important Identified Risk – Atrial Fibrillation

Potential Mechanisms:

The potential mechanism by which ibrutinib causes atrial fibrillation is unknown at this time.

Evidence Source(s) and Strength of Evidence:

Cases of atrial fibrillation in association with ibrutinib have been reported in completed clinical trials (particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation), and are also described in the current prescribing information for ibrutinib.

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of Atrial Fibrillation in Clinical Trials; (The Randomized Clinical Trials Population)

	All Randomized Trials Population	
	Ibrutinib n (%)	**Placebo/Comparator n (%)**
Indication: MCL		
Number of subjects treated	139	139
Frequency[a]	10 (7.2%)	3 (2.2%)
Odds Ratio	3.513	
95% confidence interval	(0.946, 13.052)	
Seriousness		
Was Serious	7 (5.0%)	2 (1.4%)
Outcomes		
Resulted in Death	0	0
Did not recover (Persisted)	2 (1.4%)	0
Recovering with treatment	0	0
Recovering without treatment	0	0
Recovered with treatment	8 (5.8%)	3 (2.2%)
Recovered without treatment	0	0
Missing	0	0
Severity/Nature of Risk		
Worst Grade=1	0	0
Worst Grade=2	3 (2.2%)	1 (0.7%)
Worst Grade=3	5 (3.6%)	2 (1.4%)
Worst Grade=4	2 (1.4%)	0
Worst Grade=5	0	0
Missing Grade	0	0
Indication: CLL		
Number of subjects treated	1,188	988
Frequency[a]	126 (10.6%)	15 (1.5%)
Odds Ratio	7.695	
95% confidence interval	(4.474, 13.236)	
Severity/Nature of Risk		
Worst Grade=1	8 (0.7%)	2 (0.2%)
Worst Grade=2	64 (5.4%)	9 (0.9%)
Worst Grade=3	51 (4.3%)	3 (0.3%)
Worst Grade=4	3 (0.3%)	1 (0.1%)
Worst Grade=5	0	0
Missing Grade	0	0
Number of subjects assessed (exclude E1912)	836	830
Seriousness*		
Was Serious	42 (5.0%)	4 (0.5%)

Frequency, Seriousness, Outcomes, and Severity of Atrial Fibrillation in Clinical Trials; (The Randomized Clinical Trials Population)

	All Randomized Trials Population	
	Ibrutinib n (%)	**Placebo/Comparator n (%)**
Outcomes*		
Resulted in Death	0	0
Did not recover (Persisted)	37 (4.4%)	3 (0.4%)
Recovering with treatment	0	0
Recovering without treatment	2 (0.2%)	0
Recovered with treatment	34 (4.1%)	3 (0.4%)
Recovered without treatment	25 (3.0%)	5 (0.6%)
Missing	0	0
Indication: WM		
Number of subjects treated	75	75
Frequency[a]	14 (18.7%)	2 (2.7%)
Odds Ratio	8.377	
95% confidence interval	(1.832, 38.303)	
Seriousness		
Was Serious	8 (10.7%)	1 (1.3%)
Outcomes		
Resulted in Death	0	0
Did not recover (Persisted)	8 (10.7%)	0
Recovering with treatment	0	0
Recovering without treatment	0	0
Recovered with treatment	6 (8.0%)	1 (1.3%)
Recovered without treatment	0	1 (1.3%)
Missing	0	0
Severity/Nature of Risk		
Worst Grade=1	1 (1.3%)	0
Worst Grade=2	1 (1.3%)	1 (1.3%)
Worst Grade=3	12 (16.0%)	1 (1.3%)
Worst Grade=4	0	0
Worst Grade=5	0	0
Missing Grade	0	0

[a] Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA preferred term of atrial fibrillation; the subject is counted only once regardless of the number of events or the number of occurrences.
The outcome of Unknown is not presented in the summary.
MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia.
Note: Trials included: MCL3001, PCYC-1112-CA, PCYC-1115-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1127-CA. Comparator drugs include temsirolimus (MCL3001), ofatumumab (PCYC-1112-CA), chlorambucil (PCYC-1115-CA), placebo + bendamustine + rituximab (CLL3001), chlorambucil + obinutuzumab (PCYC-1130-CA, CLL3011), fludarabine + cyclophosphamide + rituximab (E1912/PCYC-1126e-CA), and a combination of placebo + rituximab (PCYC-1127-CA).
* Trial E1912 collected neither AE seriousness, nor outcome, thus is excluded from seriousness and outcome summaries.

[TRMRSK21A.RTF] [JNJ-54179060/Z RMP/DBR RMP 2021 GLOW/RE RMP EU UPDATE/PROD/TRMRSKA-ALL.SAS] 10FEB2022, 23:29

Frequency, Seriousness, Outcomes, and Severity of Atrial Fibrillation in Clinical Trials; (The All Clinical Trials Population Including Open Extensions)

	Monotherapy [a]	Combination [a]	All Clinical Trials Population
Indication: MCL			
Number of subjects treated	421	0	421
Frequency[a]	38 (9.0%)	0	38 (9.0%)
Seriousness			
Was Serious	20 (4.8%)	0	20 (4.8%)
Outcomes			
Resulted in Death	0	0	0
Did not recover (Persisted)	9 (2.1%)	0	9 (2.1%)
Recovering with treatment	0	0	0
Recovering without treatment	0	0	0
Recovered with treatment	27 (6.4%)	0	27 (6.4%)
Recovered without treatment	2 (0.5%)	0	2 (0.5%)
Missing	0	0	0
Severity/Nature of Risk			
Worst Grade=1	3 (0.7%)	0	3 (0.7%)
Worst Grade=2	12 (2.9%)	0	12 (2.9%)
Worst Grade=3	20 (4.8%)	0	20 (4.8%)
Worst Grade=4	3 (0.7%)	0	3 (0.7%)
Worst Grade=5	0	0	0
Missing Grade	0	0	0
Indication: CLL			
Number of subjects treated	998	1,285	2,283
Frequency[a]	105 (10.5%)	121 (9.4%)	226 (9.9%)
Severity/Nature of Risk			
Worst Grade=1	10 (1.0%)	10 (0.8%)	20 (0.9%)
Worst Grade=2	59 (5.9%)	63 (4.9%)	122 (5.3%)
Worst Grade=3	31 (3.1%)	45 (3.5%)	76 (3.3%)
Worst Grade=4	5 (0.5%)	3 (0.2%)	8 (0.4%)
Worst Grade=5	0	0	0
Missing Grade	0	0	0
Number of subjects assessed (exclude E1912)	998	933	1,931
Seriousness*			
Was Serious	39 (3.9%)	40 (4.3%)	79 (4.1%)
Outcomes*			
Resulted in Death	0	0	0
Did not recover (Persisted)	45 (4.5%)	33 (3.5%)	78 (4.0%)
Recovering with treatment	3 (0.3%)	0	3 (0.2%)
Recovering without treatment	2 (0.2%)	2 (0.2%)	4 (0.2%)
Recovered with treatment	34 (3.4%)	30 (3.2%)	64 (3.3%)
Recovered without treatment	21 (2.1%)	28 (3.0%)	49 (2.5%)
Missing	0	0	0
Indication: WM			
Number of subjects treated	133	75	208
Frequency[a]	7 (5.3%)	14 (18.7%)	21 (10.1%)
Seriousness			
Was Serious	2 (1.5%)	8 (10.7%)	10 (4.8%)
Outcomes			
Resulted in Death	0	0	0
Did not recover (Persisted)	0	8 (10.7%)	8 (3.8%)
Recovering with treatment	0	0	0
Recovering without treatment	0	0	0
Recovered with treatment	2 (1.5%)	6 (8.0%)	8 (3.8%)
Recovered without treatment	0	0	0
Missing	5 (3.8%)	0	5 (2.4%)

Frequency, Seriousness, Outcomes, and Severity of Atrial Fibrillation in Clinical Trials; (The All Clinical Trials Population Including Open Extensions)

	Monotherapy [a]	Combination [a]	All Clinical Trials Population
Severity/Nature of Risk			
Worst Grade=1	1 (0.8%)	1 (1.3%)	2 (1.0%)
Worst Grade=2	3 (2.3%)	1 (1.3%)	4 (1.9%)
Worst Grade=3	3 (2.3%)	12 (16.0%)	15 (7.2%)
Worst Grade=4	0	0	0
Worst Grade=5	0	0	0
Missing Grade	0	0	0

[a] Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA preferred term of atrial fibrillation; the subject is counted only once regardless of the number of events or the number of occurrences.
The outcome of Unknown is not presented in the summary.
MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia.
Note: Trials included: PCYC-04753, PCYC-1104-CA, MCL2001, MCL3001, PCYC-1102-CA, PCYC-1108-CA, PCYC-1109-CA, PCYC-1112-CA, PCYC-1115-CA, PCYC-1117-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1142-CA, PCYC-1118e-CA, PCYC-1127-CA.
Data for cross-over subjects from Trials MCL3001, PCYC-1112-CA, CLL3001, PCYC-1130-CA, CLL3011, and PCYC-1127-CA, as well as data for subjects from open-label subtrial in PCYC-1127-CA are included in the monotherapy pool.
* Trial E1912 collected neither AE seriousness, nor outcome, thus is excluded from seriousness and outcome summaries.
Note: Subjects who crossed over from the comparator treatment group are counted towards monotherapy. All subjects in Trial PCYC-1142-CA are counted towards combination therapy. Subjects in Trial CLL3011 who received experimental treatment and who were re-exposed to study ibrutinib are also counted towards combination therapy.

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With rare exceptions, atrial fibrillation is generally not life-threatening, but it can have considerable effects on quality of life and can cause considerable distress for some patients. Occasionally, if uncontrolled, it may increase the risk of thromboembolism.

No new safety information that impacts the risk-benefit balance of the product has emerged from postmarketing experience.

Risk Factors and Risk Groups:

Atrial fibrillation is more common in men than women. Other risk factors for atrial fibrillation include advanced age, hypertension and other cardiac conditions, obesity, and metabolic syndrome. There are also indications that individuals of white European descent have a higher risk of atrial fibrillation compared with individuals of other races (Chugh et al, 2014). Specifically, among CLL patients, a Mayo Clinic study observed that increased risk of incident atrial fibrillation was associated with older age, male sex, valvular heart disease, and hypertension in multivariable analysis (Shanafelt et al, 2015).

Preventability:

The SmPC (Section 4.4) states that fatal and serious cardiac arrhythmias and cardiac failure have occurred in patients treated with ibrutinib. Patients with advanced age, ECOG performance status ≥2, or cardiac comorbidities may be at greater risk of events including sudden fatal cardiac events. Atrial fibrillation, atrial flutter, ventricular tachyarrhythmia, and cardiac failure have been reported, particularly in patients with acute infections or cardiac risk factors including hypertension, diabetes mellitus, and a previous history of cardiac arrhythmia. Appropriate clinical evaluation of cardiac history and function should be performed prior to initiating ibrutinib. Patients should be carefully monitored during treatment for signs of clinical deterioration of cardiac function and clinically managed. Further evaluation (eg, ECG, echocardiogram), as indicated for patients in whom there are cardiovascular concerns, should be considered. For patients with relevant risk factors for cardiac events, the benefit/risk should be carefully assessed before initiating treatment with ibrutinib; alternative treatment may be considered. In patients with pre-existing atrial fibrillation requiring anticoagulant therapy, alternative treatment options to ibrutinib should be considered. In patients who develop atrial fibrillation on therapy with ibrutinib, a thorough assessment of the risk for thromboembolic disease should be undertaken. In patients at high risk and where alternatives to ibrutinib are nonsuitable, tightly controlled treatment with anticoagulants should be considered.

Additional risk minimization measures for this important identified risk are described in Section V.2.

Impact on the Risk-benefit Balance of the Product:

Treatment with ibrutinib is associated with an increased incidence of atrial fibrillation with most cases grade 3 or lower. The SmPC and PL provide information to the prescriber and patient on risk factors and how to appropriately manage the risk. Overall, the risk-benefit balance is positive for the product considering the severity of the diseases treated and the established efficacy and safety profile of ibrutinib.

Public Health Impact:

Although the incidence of atrial fibrillation in patients receiving ibrutinib was higher than in patients receiving placebo/comparator in the randomized clinical trials population, in consideration of the relatively small number of patients in the targeted populations and the relatively small number of significant atrial fibrillation cases reported with ibrutinib therapy, the impact on public health is expected to be low.

Annex 1 MedDRA Term:

Atrial fibrillation (Preferred Term [PT])

Important Identified Risk - Ventricular Tachyarrhythmias

Potential Mechanisms:

The potential mechanism by which ibrutinib causes ventricular tachyarrhythmias is unknown at this time.

Evidence Source(s) and Strength of Evidence:

Cases of ventricular tachyarrhythmia in association with ibrutinib have been reported in completed clinical trials. Ventricular tachyarrhythmia has been included as an adverse reaction in the SmPC. These events are described in the current prescribing information for ibrutinib.

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of Ventricular Tachyarrhythmias in Clinical Trials; (The Randomized Clinical Trials Population)

	All Randomized Trials Population	
	Ibrutinib n (%)	**Placebo/Comparator n (%)**
Indication: MCL		
Number of subjects treated	139	139
Frequency[a]	2 (1.4%)	1 (0.7%)
Odds Ratio	2.015	
95% confidence interval	(0.181, 22.477)	
Seriousness		
Was Serious	0	0
Outcomes		
Resulted in Death	0	0
Did not recover (Persisted)	0	0
Recovering with treatment	0	0
Recovering without treatment	0	0
Recovered with treatment	1 (0.7%)	1 (0.7%)
Recovered without treatment	1 (0.7%)	0
Missing	0	0
Severity/Nature of Risk		
Worst Grade=1	1 (0.7%)	0
Worst Grade=2	1 (0.7%)	1 (0.7%)
Worst Grade=3	0	0
Worst Grade=4	0	0
Worst Grade=5	0	0
Missing Grade	0	0
Indication: CLL		
Number of subjects treated	1,188	988
Frequency[a]	14 (1.2%)	2 (0.2%)
Odds Ratio	5.879	
95% confidence interval	(1.333, 25.929)	
Severity/Nature of Risk		
Worst Grade=1	9 (0.8%)	2 (0.2%)
Worst Grade=2	2 (0.2%)	0
Worst Grade=3	2 (0.2%)	0
Worst Grade=4	0	0
Worst Grade=5	1 (0.1%)	0
Missing Grade	0	0
Number of subjects assessed (exclude E1912)	836	830
Seriousness*		
Was Serious	2 (0.2%)	0
Outcomes*		
Resulted in Death	1 (0.1%)	0
Did not recover (Persisted)	3 (0.4%)	0

Frequency, Seriousness, Outcomes, and Severity of Ventricular Tachyarrhythmias in Clinical Trials; (The Randomized Clinical Trials Population)

	All Randomized Trials Population	
	Ibrutinib n (%)	**Placebo/Comparator n (%)**
Recovering with treatment	0	0
Recovering without treatment	0	0
Recovered with treatment	0	0
Recovered without treatment	6 (0.7%)	2 (0.2%)
Missing	0	0
Indication: WM		
Number of subjects treated	75	75
Frequency[a]	1 (1.3%)	2 (2.7%)
Odds Ratio	0.493	
95% confidence interval	(0.044, 5.559)	
Seriousness		
Was Serious	0	0
Outcomes		
Resulted in Death	0	0
Did not recover (Persisted)	0	0
Recovering with treatment	0	0
Recovering without treatment	0	0
Recovered with treatment	1 (1.3%)	1 (1.3%)
Recovered without treatment	0	1 (1.3%)
Missing	0	0
Severity/Nature of Risk		
Worst Grade=1	1 (1.3%)	1 (1.3%)
Worst Grade=2	0	1 (1.3%)
Worst Grade=3	0	0
Worst Grade=4	0	0
Worst Grade=5	0	0
Missing Grade	0	0

[a] Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA preferred terms representative of ventricular tachyarrhythmias; the subject is counted only once regardless of the number of events or the number of occurrences.
The outcome of Unknown is not presented in the summary.
MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia.
Note: Trials included: MCL3001, PCYC-1112-CA, PCYC-1115-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1127-CA. Comparator drugs include temsirolimus (MCL3001), ofatumumab (PCYC-1112-CA), chlorambucil (PCYC-1115-CA), placebo + bendamustine + rituximab (CLL3001), chlorambucil + obinutuzumab (PCYC-1130-CA, CLL3011), fludarabine + cyclophosphamide + rituximab (E1912/PCYC-1126e-CA), and a combination of placebo + rituximab (PCYC-1127-CA).
* Trial E1912 collected neither AE seriousness, nor outcome, thus is excluded from seriousness and outcome summaries.

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Frequency, Seriousness, Outcomes, and Severity of Ventricular Tachyarrhythmias in Clinical Trials; (The All Clinical Trials Population Including Open Extensions)

	Monotherapy [a]	Combination [a]	All Clinical Trials Population
Indication: MCL			
Number of subjects treated	421	0	421
Frequency[a]	6 (1.4%)	0	6 (1.4%)
Seriousness			
Was Serious	0	0	0
Outcomes			
Resulted in Death	0	0	0
Did not recover (Persisted)	0	0	0
Recovering with treatment	0	0	0
Recovering without treatment	0	0	0
Recovered with treatment	3 (0.7%)	0	3 (0.7%)
Recovered without treatment	2 (0.5%)	0	2 (0.5%)
Missing	0	0	0
Severity/Nature of Risk			
Worst Grade=1	3 (0.7%)	0	3 (0.7%)
Worst Grade=2	3 (0.7%)	0	3 (0.7%)
Worst Grade=3	0	0	0
Worst Grade=4	0	0	0
Worst Grade=5	0	0	0
Missing Grade	0	0	0
Indication: CLL			
Number of subjects treated	998	1,285	2,283
Frequency[a]	11 (1.1%)	12 (0.9%)	23 (1.0%)
Severity/Nature of Risk			
Worst Grade=1	8 (0.8%)	6 (0.5%)	14 (0.6%)
Worst Grade=2	1 (0.1%)	1 (0.1%)	2 (0.1%)
Worst Grade=3	1 (0.1%)	3 (0.2%)	4 (0.2%)
Worst Grade=4	1 (0.1%)	1 (0.1%)	2 (0.1%)
Worst Grade=5	0	1 (0.1%)	1 (<0.1%)
Missing Grade	0	0	0
Number of subjects assessed (exclude E1912)	998	933	1,931
Seriousness*			
Was Serious	3 (0.3%)	3 (0.3%)	6 (0.3%)
Outcomes*			
Resulted in Death	0	1 (0.1%)	1 (0.1%)
Did not recover (Persisted)	6 (0.6%)	2 (0.2%)	8 (0.4%)
Recovering with treatment	0	0	0
Recovering without treatment	0	0	0
Recovered with treatment	0	2 (0.2%)	2 (0.1%)
Recovered without treatment	5 (0.5%)	3 (0.3%)	8 (0.4%)
Missing	0	0	0
Indication: WM			
Number of subjects treated	133	75	208
Frequency[a]	0	1 (1.3%)	1 (0.5%)
Seriousness			
Was Serious	0	0	0
Outcomes			
Resulted in Death	0	0	0
Did not recover (Persisted)	0	0	0
Recovering with treatment	0	0	0
Recovering without treatment	0	0	0
Recovered with treatment	0	1 (1.3%)	1 (0.5%)
Recovered without treatment	0	0	0
Missing	0	0	0

Frequency, Seriousness, Outcomes, and Severity of Ventricular Tachyarrhythmias in Clinical Trials; (The All Clinical Trials Population Including Open Extensions)

	Monotherapy [a]	Combination [a]	All Clinical Trials Population
Severity/Nature of Risk			
Worst Grade=1	0	1 (1.3%)	1 (0.5%)
Worst Grade=2	0	0	0
Worst Grade=3	0	0	0
Worst Grade=4	0	0	0
Worst Grade=5	0	0	0
Missing Grade	0	0	0

[a] Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA preferred terms representative of ventricular tachyarrhythmias; the subject is counted only once regardless of the number of events or the number of occurrences.
The outcome of Unknown is not presented in the summary.
MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia.
Note: Trials included: PCYC-04753, PCYC-1104-CA, MCL2001, MCL3001, PCYC-1102-CA, PCYC-1108-CA, PCYC-1109-CA, PCYC-1112-CA, PCYC-1115-CA, PCYC-1117-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1142-CA, PCYC-1118e-CA, PCYC-1127-CA.
Data for cross-over subjects from Trials MCL3001, PCYC-1112-CA, CLL3001, PCYC-1130-CA, CLL3011, and PCYC-1127-CA, as well as data for subjects from open-label subtrial in PCYC-1127-CA are included in the monotherapy pool.
* Trial E1912 collected neither AE seriousness, nor outcome, thus is excluded from seriousness and outcome summaries.
Note: Subjects who crossed over from the comparator treatment group are counted towards monotherapy. All subjects in Trial PCYC-1142-CA are counted towards combination therapy. Subjects in Trial CLL3011 who received experimental treatment and who were re-exposed to study ibrutinib are also counted towards combination therapy.

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Ventricular tachyarrhythmias could be serious and potentially fatal.

No other safety information that impacts the risk-benefit balance of the product has emerged from postmarketing experience.

Risk Factors and Risk Groups:

Ventricular tachyarrhythmias are common in older people. Risk factors include myocardial infarction, heart failure or cardiomyopathy, cardiac hypertrophy, incompetent or stenotic heart valves, or congenital heart defects. Risk can also be increased if the patient has hypertension, myocarditis, pericarditis, diabetes mellitus, sleep apnea, electrolyte imbalance (eg, hyperkalemia and hypomagnesemia), hypothyroidism, or hyperthyroidism (National Heart, Lung, and Blood Institute, 2011).

Preventability:

The SmPC (Section 4.4) states that fatal and serious cardiac arrhythmias and cardiac failure have occurred in patients treated with ibrutinib. Patients with advanced age, ECOG performance status ≥2, or cardiac comorbidities may be at greater risk of events including sudden fatal cardiac events. Atrial fibrillation, atrial flutter, ventricular tachyarrhythmia, and cardiac failure have been reported, particularly in patients with acute infections or cardiac risk factors including hypertension, diabetes mellitus, and a previous history of cardiac arrhythmia. Appropriate clinical evaluation of cardiac history and function should be performed prior to initiating ibrutinib. Patients should be carefully monitored during treatment for signs of clinical deterioration of cardiac function and clinically managed. Further evaluation (eg, ECG, echocardiogram), as indicated for patients in whom there are cardiovascular concerns, should be considered. For patients with relevant risk factors for cardiac events, the benefit/risk should be carefully assessed before initiating treatment with ibrutinib; alternative treatment may be considered. In patients who develop signs and/or symptoms of ventricular tachyarrhythmia, ibrutinib should be temporarily discontinued and a thorough clinical benefit/risk assessment should be performed before possibly restarting therapy.

Additional risk minimization measures for this important identified risk are described in Section V.2.

Impact on the Risk-benefit Balance of the Product:

The observed incidence of ventricular tachyarrhythmias is low and therefore does not have a significant impact on the risk-benefit balance of the product. The SmPC and PL provide information to the prescriber and patient on how to manage the risk. Overall, the risk-benefit balance is positive for the product considering the severity of the diseases treated and the established efficacy and safety profile of ibrutinib.

Public Health Impact:

In consideration of the relatively small number of patients in the targeted populations and the relatively small number of significant cases of ventricular tachyarrhythmias reported with ibrutinib therapy, the impact on public health is expected to be low.

Annex 1 MedDRA Term:

Ventricular tachyarrhythmias (SMQ narrow)

Important Identified Risk – Hypertension

Potential Mechanisms:

A mechanism of action for the identified risk of hypertension in subjects treated with ibrutinib is unknown.

Evidence Source(s) and Strength of Evidence:

Hypertension has been identified as an adverse reaction associated with ibrutinib.

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of Hypertension in Clinical Trials; (The Randomized Clinical Trials Population)

	All Randomized Trials Population	
	Ibrutinib n (%)	**Placebo/Comparator n (%)**
Indication: MCL		
Number of subjects treated	139	139
Frequency[a]	17 (12.2%)	6 (4.3%)
Odds Ratio	3.089	
95% confidence interval	(1.180, 8.087)	
Seriousness		
Was Serious	0	0
Outcomes		
Resulted in Death	0	0
Did not recover (Persisted)	7 (5.0%)	1 (0.7%)
Recovering with treatment	5 (3.6%)	0
Recovering without treatment	0	0
Recovered with treatment	4 (2.9%)	4 (2.9%)
Recovered without treatment	1 (0.7%)	1 (0.7%)
Missing	0	0
Severity/Nature of Risk		
Worst Grade=1	2 (1.4%)	1 (0.7%)
Worst Grade=2	6 (4.3%)	3 (2.2%)
Worst Grade=3	9 (6.5%)	2 (1.4%)
Worst Grade=4	0	0
Worst Grade=5	0	0
Missing Grade	0	0
Indication: CLL		
Number of subjects treated	1,188	988
Frequency[a]	303 (25.5%)	68 (6.9%)
Odds Ratio	4.632	
95% confidence interval	(3.505, 6.121)	
Severity/Nature of Risk		
Worst Grade=1	38 (3.2%)	16 (1.6%)
Worst Grade=2	138 (11.6%)	27 (2.7%)
Worst Grade=3	125 (10.5%)	24 (2.4%)
Worst Grade=4	2 (0.2%)	1 (0.1%)
Worst Grade=5	0	0
Missing Grade	0	0
Number of subjects assessed (exclude E1912)	836	830
Seriousness*		
Was Serious	10 (1.2%)	1 (0.1%)
Outcomes*		
Resulted in Death	0	0
Did not recover (Persisted)	84 (10.0%)	6 (0.7%)
Recovering with treatment	3 (0.4%)	2 (0.2%)
Recovering without treatment	2 (0.2%)	1 (0.1%)
Recovered with treatment	28 (3.3%)	9 (1.1%)

Frequency, Seriousness, Outcomes, and Severity of Hypertension in Clinical Trials; (The Randomized Clinical Trials Population)

	All Randomized Trials Population	
	Ibrutinib n (%)	**Placebo/Comparator n (%)**
Recovered without treatment	38 (4.5%)	15 (1.8%)
Missing	0	0
Indication: WM		
Number of subjects treated	75	75
Frequency[a]	21 (28.0%)	4 (5.3%)
Odds Ratio	6.903	
95% confidence interval	(2.238, 21.289)	
Seriousness		
Was Serious	1 (1.3%)	1 (1.3%)
Outcomes		
Resulted in Death	0	0
Did not recover (Persisted)	12 (16.0%)	0
Recovering with treatment	0	0
Recovering without treatment	0	0
Recovered with treatment	6 (8.0%)	1 (1.3%)
Recovered without treatment	3 (4.0%)	3 (4.0%)
Missing	0	0
Severity/Nature of Risk		
Worst Grade=1	3 (4.0%)	1 (1.3%)
Worst Grade=2	7 (9.3%)	0
Worst Grade=3	11 (14.7%)	3 (4.0%)
Worst Grade=4	0	0
Worst Grade=5	0	0
Missing Grade	0	0

[a] Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA preferred terms representative of hypertension; the subject is counted only once regardless of the number of events or the number of occurrences.
The outcome of Unknown is not presented in the summary.
MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia.
Note: Trials included: MCL3001, PCYC-1112-CA, PCYC-1115-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1127-CA. Comparator drugs include temsirolimus (MCL3001), ofatumumab (PCYC-1112-CA), chlorambucil (PCYC-1115-CA), placebo + bendamustine + rituximab (CLL3001), chlorambucil + obinutuzumab (PCYC-1130-CA, CLL3011), fludarabine + cyclophosphamide + rituximab (E1912/PCYC-1126e-CA), and a combination of placebo + rituximab (PCYC-1127-CA).
* Trial E1912 collected neither AE seriousness, nor outcome, thus is excluded from seriousness and outcome summaries.

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Frequency, Seriousness, Outcomes, and Severity of Hypertension in Clinical Trials; (The All Clinical Trials Population Including Open Extensions)

	Monotherapy [a]	Combination [a]	All Clinical Trials Population
Indication: MCL			
Number of subjects treated	421	0	421
Frequency[a]	46 (10.9%)	0	46 (10.9%)
Seriousness			
Was Serious	1 (0.2%)	0	1 (0.2%)
Outcomes			
Resulted in Death	0	0	0
Did not recover (Persisted)	20 (4.8%)	0	20 (4.8%)
Recovering with treatment	5 (1.2%)	0	5 (1.2%)
Recovering without treatment	0	0	0
Recovered with treatment	15 (3.6%)	0	15 (3.6%)
Recovered without treatment	6 (1.4%)	0	6 (1.4%)
Missing	0	0	0
Severity/Nature of Risk			
Worst Grade=1	6 (1.4%)	0	6 (1.4%)
Worst Grade=2	20 (4.8%)	0	20 (4.8%)
Worst Grade=3	20 (4.8%)	0	20 (4.8%)
Worst Grade=4	0	0	0
Worst Grade=5	0	0	0
Missing Grade	0	0	0
Indication: CLL			
Number of subjects treated	998	1,285	2,283
Frequency[a]	200 (20.0%)	305 (23.7%)	505 (22.1%)
Severity/Nature of Risk			
Worst Grade=1	30 (3.0%)	38 (3.0%)	68 (3.0%)
Worst Grade=2	88 (8.8%)	137 (10.7%)	225 (9.9%)
Worst Grade=3	82 (8.2%)	128 (10.0%)	210 (9.2%)
Worst Grade=4	0	2 (0.2%)	2 (0.1%)
Worst Grade=5	0	0	0
Missing Grade	0	0	0
Number of subjects assessed (exclude E1912)	998	933	1,931
Seriousness*			
Was Serious	9 (0.9%)	8 (0.9%)	17 (0.9%)
Outcomes*			
Resulted in Death	0	0	0
Did not recover (Persisted)	122 (12.2%)	80 (8.6%)	202 (10.5%)
Recovering with treatment	5 (0.5%)	0	5 (0.3%)
Recovering without treatment	5 (0.5%)	1 (0.1%)	6 (0.3%)
Recovered with treatment	33 (3.3%)	32 (3.4%)	65 (3.4%)
Recovered without treatment	35 (3.5%)	44 (4.7%)	79 (4.1%)
Missing	0	0	0
Indication: WM			
Number of subjects treated	133	75	208
Frequency[a]	20 (15.0%)	21 (28.0%)	41 (19.7%)
Seriousness			
Was Serious	0	1 (1.3%)	1 (0.5%)
Outcomes			
Resulted in Death	0	0	0
Did not recover (Persisted)	10 (7.5%)	12 (16.0%)	22 (10.6%)
Recovering with treatment	0	0	0
Recovering without treatment	0	0	0
Recovered with treatment	2 (1.5%)	6 (8.0%)	8 (3.8%)
Recovered without treatment	3 (2.3%)	3 (4.0%)	6 (2.9%)
Missing	5 (3.8%)	0	5 (2.4%)

Frequency, Seriousness, Outcomes, and Severity of Hypertension in Clinical Trials; (The All Clinical Trials Population Including Open Extensions)

	Monotherapy [a]	Combination [a]	All Clinical Trials Population
Severity/Nature of Risk			
Worst Grade=1	4 (3.0%)	3 (4.0%)	7 (3.4%)
Worst Grade=2	8 (6.0%)	7 (9.3%)	15 (7.2%)
Worst Grade=3	8 (6.0%)	11 (14.7%)	19 (9.1%)
Worst Grade=4	0	0	0
Worst Grade=5	0	0	0
Missing Grade	0	0	0

[a] Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA preferred terms representative of hypertension; the subject is counted only once regardless of the number of events or the number of occurrences.
The outcome of Unknown is not presented in the summary.
MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia.
Note: Trials included: PCYC-04753, PCYC-1104-CA, MCL2001, MCL3001, PCYC-1102-CA, PCYC-1108-CA, PCYC-1109-CA, PCYC-1112-CA, PCYC-1115-CA, PCYC-1117-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1142-CA, PCYC-1118e-CA, PCYC-1127-CA.
Data for cross-over subjects from Trials MCL3001, PCYC-1112-CA, CLL3001, PCYC-1130-CA, CLL3011, and PCYC-1127-CA, as well as data for subjects from open-label subtrial in PCYC-1127-CA are included in the monotherapy pool.
* Trial E1912 collected neither AE seriousness, nor outcome, thus is excluded from seriousness and outcome summaries.
Note: Subjects who crossed over from the comparator treatment group are counted towards monotherapy. All subjects in Trial PCYC-1142-CA are counted towards combination therapy. Subjects in Trial CLL3011 who received experimental treatment and who were re-exposed to study ibrutinib are also counted towards combination therapy.

[TRMRSK16B.RTF] [JNJ-54179060/Z RMP/DBR RMP 2021 GLOW/RE RMP EU UPDATE/PROD/TRMRSKB-ALL.SAS] 10FEB2022, 23:41

Long-term safety data presented in the Year 5 Long-term Safety Study 3038-1 final report showed an increase in prevalence rate of hypertension events (identified based on hypertension SMQ narrow) over the first 5 years of ibrutinib treatment in the Long-Term Safety population. The prevalence rate of hypertension events of any grade was 20.2% overall (0-5 years): 10.2% in the first period (0-1 year), 13.0% in the second period (1-2 years), 18.6% in the third period (2-3 years), 19.4% in the fourth period (3-4 years), and 20.5% in the fifth period (4-5 years). For events of Grade 3 or higher, the prevalence rate was 10.9% overall: 4.2% in the first period, 6.3% in the second period, 8.4% in the third period, 8.9% in the fourth period, and 9.4% in the fifth period. The prevalence rate of serious hypertension events was 0.9% overall: 0.4% in the first period, 0.6% in the second period, 0.1% in the third period, 0.2% in the fourth period, and 0% in the fifth period. Hypertensive retinopathy and hypertension resulted in the discontinuation of ibrutinib for 0.1% of subjects each, and there were no fatal hypertension events. The median time to first onset of hypertension events of Grade 3 or higher severity was 17.9 months and the median time to onset of the first serious hypertension event was 14.9 months.

The incidence rates of hypertension events were 20.2% overall: 10.2% in the first period, 6.6% in the second period, 8.9% in the third period, 8.2% in the fourth period, and 8.4% in the fifth period. The decline in incidence rates of hypertension events to a lower stable rate after the first yearly period suggests the increased prevalence over time was due to ongoing hypertension rather than an increase in new events.

Of the 238 subjects with treatment-emergent hypertension events, 70.2% had 1 or more relevant risk factors for developing hypertension, including history of hypertensive disorders/conditions (56.3%) and/or other relevant risk factors (44.5%) derived from medical histories.

Hypertension is a major risk factor for stroke, ischemic heart disease (including myocardial infarction), heart failure, aneurysms of the arteries (eg, aortic aneurysm), and peripheral arterial disease, and is also a cause of chronic kidney disease. Even moderate elevation of arterial blood pressure is associated with a shortened life expectancy. Quality of life of individuals with hypertension is worse than that of normotensive individuals. However, an overall improved quality of life of an individual patient is expected if a better control of blood pressure can be achieved.

No new safety information that impacts the risk-benefit balance of the product has emerged from postmarketing experience. However, changes to the characterization of this risk have been made based on clinical trial data from long-term Safety Study 3038-1.

Risk Factors and Risk Groups:

Risk factors for hypertension include increasing age, black race, family history of hypertension, being overweight or obese, physical inactivity, tobacco use, excess salt (sodium) in diet, too little potassium and vitamin D in diet, excess alcohol use, and stress (Mayo Clinic, High blood Pressure [Hypertension], 2018).

Preventability:

The incidence of hypertension is high in this patient population. A heart-healthy lifestyle such as healthy diet with reduced salt, regular physical activity, maintaining a healthy weight, avoiding tobacco smoke, and limiting alcohol intake can help to prevent high blood pressure. As stated in Section 4.4 of the SmPC, blood pressure should be regularly monitored in patients treated with ibrutinib and antihypertensive medication should be initiated or adjusted throughout treatment with ibrutinib as appropriate.

Impact on the Risk-benefit Balance of the Product:

Hypertension has been observed at a higher incidence with ibrutinib than with comparators in randomized, controlled Phase 3 trials; most events were grade 3 or lower. Long-term safety data showed an increase in prevalence rate of hypertension events (any grade and grade 3 or higher) over 5 years of ibrutinib treatment; however, few events were serious or resulted in discontinuation of ibrutinib. Hypertension is an acknowledged adverse reaction and Section 4.4 of the SmPC provides recommendations for blood pressure monitoring and management of patients with hypertension. Overall, the risk-benefit balance remains positive for the product considering the severity of the diseases treated and the established efficacy and safety profile of ibrutinib.

Public Health Impact:

In consideration of the relatively small number of patients in the targeted populations and the relatively small number of significant cases of hypertension reported with ibrutinib therapy, the impact on public health is expected to be low.

Annex 1 MedDRA Term:

Hypertension (SMQ narrow)

Important Identified Risk – Ischemic Stroke

Potential Mechanisms:

An increased risk of stroke in patients taking ibrutinib is theoretically possible, given the known association of stroke with ibrutinib-associated cardiovascular adverse effects of atrial fibrillation and hypertension. However, from a direct mechanism standpoint and based on available data, a causal relationship cannot be established between ibrutinib and the occurrence of stroke. Patients treated with ibrutinib are generally at an increased risk for stroke events based on their advanced age as well as the underlying malignancy (ie, hypercoagulable state).

Evidence Source(s) and Strength of Evidence:

Cases of ischemic stroke in association with ibrutinib have been reported in completed clinical trials. Cerebrovascular accident, transient ischemic attack, and ischemic stroke have been included as adverse reactions in the SmPC, based on the Pharmacovigilance Risk Assessment Committee (PRAC) assessment (procedure EMA/PRAC/510313/2019, European Pharmacovigilance Issues Tracking Tool [EPITT] number 19369) of the signal evaluation of ischemic stroke conducted by the MAH, considering the established cardiac risks of atrial fibrillation and hypertension associated with ibrutinib administration. Although, from a direct mechanism standpoint and based on available data, causality between stroke and treatment with ibrutinib has not been established, ischemic stroke was added to the EU-RMP as an important identified risk as requested by PRAC (procedure EMEA/H/C/003791/II/0061), in conjunction with the addition of ischemic stroke to Sections 4.4 and 4.8 of the SmPC.

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of Ischemic Stroke in Clinical Trials; (The Randomized Clinical Trials Population)

	All Randomized Trials Population	
	Ibrutinib n (%)	**Placebo/Comparator n (%)**
Indication: MCL		
Number of subjects treated	139	139
Frequency[a]	3 (2.2%)	3 (2.2%)
Odds Ratio	1.000	
95% confidence interval	(0.198, 5.042)	
Seriousness		
Was Serious	1 (0.7%)	3 (2.2%)
Outcomes		
Resulted in Death	0	1 (0.7%)
Did not recover (Persisted)	0	1 (0.7%)
Recovering with treatment	0	0
Recovering without treatment	0	0
Recovered with treatment	1 (0.7%)	0
Recovered without treatment	2 (1.4%)	1 (0.7%)
Missing	0	0
Severity/Nature of Risk		
Worst Grade=1	1 (0.7%)	0
Worst Grade=2	2 (1.4%)	1 (0.7%)
Worst Grade=3	0	0
Worst Grade=4	0	1 (0.7%)
Worst Grade=5	0	1 (0.7%)
Missing Grade	0	0

Frequency, Seriousness, Outcomes, and Severity of Ischemic Stroke in Clinical Trials; (The Randomized Clinical Trials Population)

	All Randomized Trials Population	
	Ibrutinib n (%)	**Placebo/Comparator n (%)**
Indication: CLL		
Number of subjects treated	1,188	988
Frequency[a]	32 (2.7%)	5 (0.5%)
Odds Ratio	5.442	
95% confidence interval	(2.112, 14.020)	
Severity/Nature of Risk		
Worst Grade=1	6 (0.5%)	2 (0.2%)
Worst Grade=2	15 (1.3%)	1 (0.1%)
Worst Grade=3	10 (0.8%)	1 (0.1%)
Worst Grade=4	0	0
Worst Grade=5	1 (0.1%)	1 (0.1%)
Missing Grade	0	0
Number of subjects assessed (exclude E1912)	836	830
Seriousness*		
Was Serious	16 (1.9%)	3 (0.4%)
Outcomes*		
Resulted in Death	1 (0.1%)	1 (0.1%)
Did not recover (Persisted)	4 (0.5%)	0
Recovering with treatment	0	0
Recovering without treatment	1 (0.1%)	1 (0.1%)
Recovered with treatment	11 (1.3%)	1 (0.1%)
Recovered without treatment	12 (1.4%)	1 (0.1%)
Missing	0	0
Indication: WM		
Number of subjects treated	75	75
Frequency[a]	1 (1.3%)	0
Odds Ratio	> 999.999	
95% confidence interval	(< 0.001, > 999.999)	
Seriousness		
Was Serious	0	0
Outcomes		
Resulted in Death	0	0
Did not recover (Persisted)	1 (1.3%)	0
Recovering with treatment	0	0
Recovering without treatment	0	0
Recovered with treatment	0	0
Recovered without treatment	0	0
Missing	0	0

Frequency, Seriousness, Outcomes, and Severity of Ischemic Stroke in Clinical Trials; (The Randomized Clinical Trials Population)

	All Randomized Trials Population	
	Ibrutinib n (%)	**Placebo/Comparator n (%)**
Severity/Nature of Risk		
Worst Grade=1	1 (1.3%)	0
Worst Grade=2	0	0
Worst Grade=3	0	0
Worst Grade=4	0	0
Worst Grade=5	0	0
Missing Grade	0	0

[a] Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA preferred terms representative of ischemic stroke; the subject is counted only once regardless of the number of events or the number of occurrences.
The outcome of Unknown is not presented in the summary.
MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia.
Note: Trials included: MCL3001, PCYC-1112-CA, PCYC-1115-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1127-CA. Comparator drugs include temsirolimus (MCL3001), ofatumumab (PCYC-1112-CA), chlorambucil (PCYC-1115-CA), placebo + bendamustine + rituximab (CLL3001), chlorambucil + obinutuzumab (PCYC-1130-CA, CLL3011), fludarabine + cyclophosphamide + rituximab (E1912/PCYC-1126e-CA), and a combination of placebo + rituximab (PCYC-1127-CA).
* Trial E1912 collected neither AE seriousness, nor outcome, thus is excluded from seriousness and outcome summaries.

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Frequency, Seriousness, Outcomes, and Severity of Ischemic Stroke in Clinical Trials; (The All Clinical Trials Population Including Open Extensions)

	Monotherapy [a]	**Combination [a]**	**All Clinical Trials Population**
Indication: MCL			
Number of subjects treated	421	0	421
Frequency[a]	5 (1.2%)	0	5 (1.2%)
Seriousness			
Was Serious	3 (0.7%)	0	3 (0.7%)
Outcomes			
Resulted in Death	0	0	0
Did not recover (Persisted)	0	0	0
Recovering with treatment	0	0	0
Recovering without treatment	0	0	0
Recovered with treatment	3 (0.7%)	0	3 (0.7%)
Recovered without treatment	2 (0.5%)	0	2 (0.5%)
Missing	0	0	0
Severity/Nature of Risk			
Worst Grade=1	1 (0.2%)	0	1 (0.2%)
Worst Grade=2	3 (0.7%)	0	3 (0.7%)
Worst Grade=3	1 (0.2%)	0	1 (0.2%)
Worst Grade=4	0	0	0
Worst Grade=5	0	0	0
Missing Grade	0	0	0

Frequency, Seriousness, Outcomes, and Severity of Ischemic Stroke in Clinical Trials; (The All Clinical Trials Population Including Open Extensions)

	Monotherapy [a]	Combination [a]	All Clinical Trials Population
Indication: CLL			
Number of subjects treated	998	1,285	2,283
Frequency[a]	21 (2.1%)	28 (2.2%)	49 (2.1%)
Severity/Nature of Risk			
Worst Grade=1	2 (0.2%)	7 (0.5%)	9 (0.4%)
Worst Grade=2	9 (0.9%)	11 (0.9%)	20 (0.9%)
Worst Grade=3	7 (0.7%)	8 (0.6%)	15 (0.7%)
Worst Grade=4	3 (0.3%)	0	3 (0.1%)
Worst Grade=5	0	2 (0.2%)	2 (0.1%)
Missing Grade	0	0	0
Number of subjects assessed (exclude E1912)	998	933	1,931
Seriousness*			
Was Serious	13 (1.3%)	15 (1.6%)	28 (1.5%)
Outcomes*			
Resulted in Death	0	2 (0.2%)	2 (0.1%)
Did not recover (Persisted)	2 (0.2%)	6 (0.6%)	8 (0.4%)
Recovering with treatment	0	0	0
Recovering without treatment	0	1 (0.1%)	1 (0.1%)
Recovered with treatment	8 (0.8%)	9 (1.0%)	17 (0.9%)
Recovered without treatment	11 (1.1%)	7 (0.8%)	18 (0.9%)
Missing	0	0	0
Indication: WM			
Number of subjects treated	133	75	208
Frequency[a]	3 (2.3%)	1 (1.3%)	4 (1.9%)
Seriousness			
Was Serious	1 (0.8%)	0	1 (0.5%)
Outcomes			
Resulted in Death	0	0	0
Did not recover (Persisted)	1 (0.8%)	1 (1.3%)	2 (1.0%)
Recovering with treatment	0	0	0
Recovering without treatment	0	0	0
Recovered with treatment	1 (0.8%)	0	1 (0.5%)
Recovered without treatment	0	0	0
Missing	1 (0.8%)	0	1 (0.5%)

Frequency, Seriousness, Outcomes, and Severity of Ischemic Stroke in Clinical Trials; (The All Clinical Trials Population Including Open Extensions)

	Monotherapy [a]	Combination [a]	All Clinical Trials Population
Severity/Nature of Risk			
Worst Grade=1	1 (0.8%)	1 (1.3%)	2 (1.0%)
Worst Grade=2	1 (0.8%)	0	1 (0.5%)
Worst Grade=3	1 (0.8%)	0	1 (0.5%)
Worst Grade=4	0	0	0
Worst Grade=5	0	0	0
Missing Grade	0	0	0

[a] Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA preferred terms representative of ischemic stroke; the subject is counted only once regardless of the number of events or the number of occurrences.
The outcome of Unknown is not presented in the summary.
MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia.
Note: Trials included: PCYC-04753, PCYC-1104-CA, MCL2001, MCL3001, PCYC-1102-CA, PCYC-1108-CA, PCYC-1109-CA, PCYC-1112-CA, PCYC-1115-CA, PCYC-1117-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1142-CA, PCYC-1118e-CA, PCYC-1127-CA.
Data for cross-over subjects from Trials MCL3001, PCYC-1112-CA, CLL3001, PCYC-1130-CA, CLL3011, and PCYC-1127-CA, as well as data for subjects from open-label subtrial in PCYC-1127-CA are included in the monotherapy pool.
* Trial E1912 collected neither AE seriousness, nor outcome, thus is excluded from seriousness and outcome summaries.
Note: Subjects who crossed over from the comparator treatment group are counted towards monotherapy. All subjects in Trial PCYC-1142-CA are counted towards combination therapy. Subjects in Trial CLL3011 who received experimental treatment and who were re-exposed to study ibrutinib are also counted towards combination therapy.

[TRMRSK24B.RTF] [JNJ-54179060/Z RMP/DBR RMP 2021 GLOW/RE RMP EU UPDATE/PROD/TRMRSKB-ALL.SAS] 10FEB2022, 23:41

There have been reports of cerebrovascular accident, transient ischemic attack, and ischemic stroke including fatalities in subjects treated with ibrutinib, both with and without concomitant atrial fibrillation and/or hypertension. Latency from the initiation of treatment with ibrutinib to the onset of ischemic central nervous vascular conditions was in the most cases after several months (more than 1 month in 78% and more than 6 months in 44% of cases), emphasizing the need for regular monitoring of patients.

Risk Factors and Risk Groups:

The most frequent causes of ischemic stroke in cancer patients are cerebrovascular risk factors such as hypertension, hyperlipidemia, diabetes, atrial fibrillation, and tobacco use. Additionally, patients receiving treatment with ibrutinib are mostly elderly and most strokes occur in people aged >65 years.

Preventability:

A heart-healthy lifestyle such as healthy diet with reduced cholesterol/saturated fat, regular physical activity, maintaining a healthy weight, avoiding tobacco smoke, and limiting stress and alcohol intake can help to prevent a stroke, as well as regular heart rate and blood pressure monitoring. As stated in Section 4.4 of the SmPC, patients treated with ibrutinib should be regularly monitored, as among cases with reported latency, the initiation of ibrutinib treatment to the onset of ischemic central nervous vascular conditions was in most cases after several months.

Impact on the Risk-benefit Balance of the Product:

The observed incidence of ischemic stroke is low and therefore does not have a significant impact on the risk-benefit balance of the product. Cerebrovascular accident, transient ischemic attack, and ischemic stroke have been added as adverse reactions in the SmPC. Overall, the risk-benefit balance remains positive for the product considering the severity of the diseases treated and the established efficacy and safety profile of ibrutinib.

Public Health Impact:

In consideration of the relatively small number of patients in the targeted populations and the relatively small number of significant cases of ischemic stroke reported with ibrutinib therapy, the impact on public health is expected to be low.

Annex 1 MedDRA Term:

Ischaemic central nervous system vascular conditions (SMQ narrow)

Important Identified Risk – Cardiac Failure

Potential Mechanisms:

The potential mechanism by which ibrutinib may cause cardiac failure is unknown at this time. However, ibrutinib is known to be associated with atrial fibrillation, a risk factor that could lead to reduced cardiac output.

Evidence Source(s) and Strength of Evidence:

Cases of cardiac failure in association with ibrutinib have been reported in completed clinical trials. Although no direct causal association between ibrutinib and cardiac failure was established, based on the number of cardiac failure cases from the postmarketing setting and the known association between ibrutinib and atrial fibrillation (a risk factor that could lead to reduced cardiac output), cardiac failure has been included as an adverse reaction in the SmPC.

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of Cardiac Failure in Clinical Trials; (The Randomized Clinical Trials Population)

	All Randomized Trials Population	
	Ibrutinib n (%)	**Placebo/Comparator n (%)**
Indication: MCL		
Number of subjects treated	139	139
Frequency[a]	5 (3.6%)	5 (3.6%)
Odds Ratio	1.000	
95% confidence interval	(0.283, 3.534)	
Seriousness		
Was Serious	2 (1.4%)	4 (2.9%)
Outcomes		
Resulted in Death	1 (0.7%)	2 (1.4%)
Did not recover (Persisted)	2 (1.4%)	1 (0.7%)
Recovering with treatment	1 (0.7%)	0
Recovering without treatment	0	0
Recovered with treatment	1 (0.7%)	2 (1.4%)
Recovered without treatment	0	0
Missing	0	0
Severity/Nature of Risk		
Worst Grade=1	1 (0.7%)	0
Worst Grade=2	1 (0.7%)	1 (0.7%)
Worst Grade=3	2 (1.4%)	0
Worst Grade=4	0	2 (1.4%)
Worst Grade=5	1 (0.7%)	2 (1.4%)
Missing Grade	0	0
Indication: CLL		
Number of subjects treated	1,188	988
Frequency[a]	30 (2.5%)	7 (0.7%)
Odds Ratio	3.631	
95% confidence interval	(1.588, 8.302)	
Severity/Nature of Risk		
Worst Grade=1	2 (0.2%)	0
Worst Grade=2	7 (0.6%)	3 (0.3%)
Worst Grade=3	16 (1.3%)	3 (0.3%)
Worst Grade=4	2 (0.2%)	0
Worst Grade=5	3 (0.3%)	1 (0.1%)
Missing Grade	0	0

Frequency, Seriousness, Outcomes, and Severity of Cardiac Failure in Clinical Trials; (The Randomized Clinical Trials Population)

	All Randomized Trials Population	
	Ibrutinib n (%)	**Placebo/Comparator n (%)**
Number of subjects assessed (exclude E1912)	836	830
Seriousness*		
Was Serious	16 (1.9%)	3 (0.4%)
Outcomes*		
Resulted in Death	3 (0.4%)	1 (0.1%)
Did not recover (Persisted)	8 (1.0%)	3 (0.4%)
Recovering with treatment	1 (0.1%)	0
Recovering without treatment	1 (0.1%)	0
Recovered with treatment	9 (1.1%)	3 (0.4%)
Recovered without treatment	6 (0.7%)	0
Missing	0	0
Indication: WM		
Number of subjects treated	75	75
Frequency[a]	3 (4.0%)	0
Odds Ratio	> 999.999	
95% confidence interval	(< 0.001, > 999.999)	
Seriousness		
Was Serious	3 (4.0%)	0
Outcomes		
Resulted in Death	0	0
Did not recover (Persisted)	0	0
Recovering with treatment	0	0
Recovering without treatment	0	0
Recovered with treatment	3 (4.0%)	0
Recovered without treatment	0	0
Missing	0	0
Severity/Nature of Risk		
Worst Grade=1	0	0
Worst Grade=2	0	0
Worst Grade=3	3 (4.0%)	0
Worst Grade=4	0	0
Worst Grade=5	0	0
Missing Grade	0	0

[a] Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA preferred terms representative of cardiac failure; the subject is counted only once regardless of the number of events or the number of occurrences.
The outcome of Unknown is not presented in the summary.
MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia.
Note: Trials included: MCL3001, PCYC-1112-CA, PCYC-1115-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1127-CA. Comparator drugs include temsirolimus (MCL3001), ofatumumab (PCYC-1112-CA), chlorambucil (PCYC-1115-CA), placebo + bendamustine + rituximab (CLL3001), chlorambucil + obinutuzumab (PCYC-1130-CA, CLL3011), fludarabine + cyclophosphamide + rituximab (E1912/PCYC-1126e-CA), and a combination of placebo + rituximab (PCYC-1127-CA).
* Trial E1912 collected neither AE seriousness, nor outcome, thus is excluded from seriousness and outcome summaries.

[TRMRSK27A.RTF] [JNJ-54179060/Z RMP/DBR RMP 2021 GLOW/RE RMP EU UPDATE/PROD/TRMRSKA-ALL.SAS] 10FEB2022, 23:29

Frequency, Seriousness, Outcomes, and Severity of Cardiac Failure in Clinical Trials; (The All Clinical Trials Population Including Open Extensions)

	Monotherapy [a]	Combination [a]	All Clinical Trials Population
Indication: MCL			
Number of subjects treated	421	0	421
Frequency[a]	11 (2.6%)	0	11 (2.6%)
Seriousness			
Was Serious	4 (1.0%)	0	4 (1.0%)
Outcomes			
Resulted in Death	2 (0.5%)	0	2 (0.5%)
Did not recover (Persisted)	5 (1.2%)	0	5 (1.2%)
Recovering with treatment	1 (0.2%)	0	1 (0.2%)
Recovering without treatment	0	0	0
Recovered with treatment	2 (0.5%)	0	2 (0.5%)
Recovered without treatment	1 (0.2%)	0	1 (0.2%)
Missing	0	0	0
Severity/Nature of Risk			
Worst Grade=1	1 (0.2%)	0	1 (0.2%)
Worst Grade=2	3 (0.7%)	0	3 (0.7%)
Worst Grade=3	5 (1.2%)	0	5 (1.2%)
Worst Grade=4	0	0	0
Worst Grade=5	2 (0.5%)	0	2 (0.5%)
Missing Grade	0	0	0
Indication: CLL			
Number of subjects treated	998	1,285	2,283
Frequency[a]	20 (2.0%)	19 (1.5%)	39 (1.7%)
Severity/Nature of Risk			
Worst Grade=1	1 (0.1%)	2 (0.2%)	3 (0.1%)
Worst Grade=2	6 (0.6%)	3 (0.2%)	9 (0.4%)
Worst Grade=3	10 (1.0%)	9 (0.7%)	19 (0.8%)
Worst Grade=4	0	2 (0.2%)	2 (0.1%)
Worst Grade=5	3 (0.3%)	3 (0.2%)	6 (0.3%)
Missing Grade	0	0	0
Number of subjects assessed (exclude E1912)	998	933	1,931
Seriousness*			
Was Serious	12 (1.2%)	10 (1.1%)	22 (1.1%)
Outcomes*			
Resulted in Death	3 (0.3%)	3 (0.3%)	6 (0.3%)
Did not recover (Persisted)	6 (0.6%)	5 (0.5%)	11 (0.6%)
Recovering with treatment	1 (0.1%)	0	1 (0.1%)
Recovering without treatment	0	1 (0.1%)	1 (0.1%)
Recovered with treatment	6 (0.6%)	4 (0.4%)	10 (0.5%)
Recovered without treatment	4 (0.4%)	4 (0.4%)	8 (0.4%)
Missing	0	0	0
Indication: WM			
Number of subjects treated	133	75	208
Frequency[a]	2 (1.5%)	3 (4.0%)	5 (2.4%)
Seriousness			
Was Serious	2 (1.5%)	3 (4.0%)	5 (2.4%)
Outcomes			
Resulted in Death	0	0	0
Did not recover (Persisted)	1 (0.8%)	0	1 (0.5%)
Recovering with treatment	0	0	0
Recovering without treatment	0	0	0
Recovered with treatment	1 (0.8%)	3 (4.0%)	4 (1.9%)
Recovered without treatment	0	0	0
Missing	0	0	0

Frequency, Seriousness, Outcomes, and Severity of Cardiac Failure in Clinical Trials; (The All Clinical Trials Population Including Open Extensions)

	Monotherapy [a]	Combination [a]	All Clinical Trials Population
Severity/Nature of Risk			
Worst Grade=1	0	0	0
Worst Grade=2	0	0	0
Worst Grade=3	1 (0.8%)	3 (4.0%)	4 (1.9%)
Worst Grade=4	1 (0.8%)	0	1 (0.5%)
Worst Grade=5	0	0	0
Missing Grade	0	0	0

[a] Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA preferred terms representative of cardiac failure; the subject is counted only once regardless of the number of events or the number of occurrences.
The outcome of Unknown is not presented in the summary.
MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia.
Note: Trials included: PCYC-04753, PCYC-1104-CA, MCL2001, MCL3001, PCYC-1102-CA, PCYC-1108-CA, PCYC-1109-CA, PCYC-1112-CA, PCYC-1115-CA, PCYC-1117-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1142-CA, PCYC-1118e-CA, PCYC-1127-CA.
Data for cross-over subjects from Trials MCL3001, PCYC-1112-CA, CLL3001, PCYC-1130-CA, CLL3011, and PCYC-1127-CA, as well as data for subjects from open-label subtrial in PCYC-1127-CA are included in the monotherapy pool.
* Trial E1912 collected neither AE seriousness, nor outcome, thus is excluded from seriousness and outcome summaries.
Note: Subjects who crossed over from the comparator treatment group are counted towards monotherapy. All subjects in Trial PCYC-1142-CA are counted towards combination therapy. Subjects in Trial CLL3011 who received experimental treatment and who were re-exposed to study ibrutinib are also counted towards combination therapy.

[TRMRSK27B.RTF] [JNJ-54179060/Z RMP/DBR RMP 2021 GLOW/RE RMP EU UPDATE/PROD/TRMRSKB-ALL.SAS] 10FEB2022, 23:41

Cardiac failure can be debilitating and potentially fatal. Cases of cardiac failure including fatalities have been reported in patients treated with ibrutinib, with and without concomitant atrial fibrillation. The majority of the cases occurred in elderly patients (≥65 years) with the median age being 76. In some of the cases, cardiac failure resolved or improved after ibrutinib withdrawal or dose reduction.

Risk Factors and Risk Groups:

Patients with known cardiac risk factors (eg, age 65 years or older, diabetes mellitus, hyperlipidemia, chronic kidney disease, hypertension, smoking), pre-existing heart disease, acute severe infection, and a previous history of cardiotoxic cancer therapy, such as anthracyclines, are at higher risk for developing cardiac failure. Concomitant atrial fibrillation is a risk factor that could lead to reduced cardiac output. African Americans and South Asians are ethnic groups with higher risk (Lawson et al, 2020).

Preventability:

The SmPC (Section 4.4) states that fatal and serious cardiac arrhythmias and cardiac failure have occurred in patients treated with ibrutinib. Patients with advanced age, ECOG performance status ≥2, or cardiac comorbidities may be at greater risk of events including sudden fatal cardiac events. Atrial fibrillation, atrial flutter, ventricular tachyarrhythmia, and cardiac failure have been reported, particularly in patients with acute infections or cardiac risk factors including hypertension, diabetes mellitus, and a previous history of cardiac arrhythmia. Appropriate clinical evaluation of cardiac history and function should be performed prior to initiating ibrutinib. Patients should be carefully monitored during treatment for signs of clinical deterioration of cardiac function and clinically managed. Further evaluation (eg, ECG, echocardiogram), as indicated for patients in whom there are cardiovascular concerns, should be considered. For patients with relevant risk factors for cardiac events, the benefit/risk should be carefully assessed before initiating treatment with ibrutinib; alternative treatment may be considered. Patients should be monitored for signs and symptoms of cardiac failure during ibrutinib treatment. In some of these cases cardiac failure resolved or improved after ibrutinib withdrawal or dose reduction.

Additional risk minimization measures for this important identified risk are described in Section V.2.

Impact on the Risk-benefit Balance of the Product:

Cardiac failure has been observed in patients treated with ibrutinib and has been added as an adverse reaction in the SmPC. The SmPC and PL provide information to the prescriber and patient on how to manage the risk. Overall, the risk-benefit balance remains positive for the product considering the severity of the diseases treated and the established efficacy and safety profile of ibrutinib.

Public Health Impact:

In consideration of the relatively small number of patients in the targeted populations and the relatively small number of significant cases of cardiac failure reported with ibrutinib therapy, the impact on public health is expected to be low.

Annex 1 MedDRA Term:

Cardiac failure (SMQ narrow)

Important Identified Risk - Infections (Including Viral Reactivation)

Potential Mechanisms:

Patients with underlying hematological diseases often have an impaired immune system, making them more prone to infections. The underlying mechanism for increased risk of infection during ibrutinib treatment is not fully understood. Many factors should be taken into consideration, such as biological features of the disease (low vs high-risk), hypogammaglobulinemia with or without ongoing Ig substitution, previous and concomitant treatment (eg, steroids, anti-CD20 antibodies, or chemotherapies), exposure to environmental risk factors, concurrent neutropenia, and the effect of BTK inhibition on native and adaptive immunity. Baseline factors such as diabetes mellitus, chronic obstructive pulmonary disease/asthma, and/or lymphopenia may increase the risk.

Evidence Source(s) and Strength of Evidence:

Cases of infections (including sepsis, neutropenic sepsis, bacterial, viral, or fungal infection) in association with ibrutinib have been reported in completed clinical trials and are also described in the current prescribing information for ibrutinib.

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of Infections (Including Viral Reactivation) in Clinical Trials; (The Randomized Clinical Trials Population)

	All Randomized Trials Population	
	Ibrutinib n (%)	**Placebo/Comparator n (%)**
Indication: MCL		
Number of subjects treated	139	139
Frequency[a]	99 (71.2%)	99 (71.2%)
Odds Ratio	1.000	
95% confidence interval	(0.595, 1.681)	
Seriousness		
Was Serious	31 (22.3%)	43 (30.9%)
Outcomes		
Resulted in Death	6 (4.3%)	3 (2.2%)
Did not recover (Persisted)	16 (11.5%)	13 (9.4%)
Recovering with treatment	1 (0.7%)	3 (2.2%)
Recovering without treatment	1 (0.7%)	0
Recovered with treatment	70 (50.4%)	76 (54.7%)
Recovered without treatment	5 (3.6%)	3 (2.2%)
Missing	0	0
Severity/Nature of Risk		
Worst Grade=1	5 (3.6%)	5 (3.6%)
Worst Grade=2	60 (43.2%)	49 (35.3%)
Worst Grade=3	23 (16.5%)	35 (25.2%)
Worst Grade=4	5 (3.6%)	7 (5.0%)
Worst Grade=5	6 (4.3%)	3 (2.2%)
Missing Grade	0	0

Frequency, Seriousness, Outcomes, and Severity of Infections (Including Viral Reactivation) in Clinical Trials; (The Randomized Clinical Trials Population)

	All Randomized Trials Population	
	Ibrutinib n (%)	**Placebo/Comparator n (%)**
Indication: CLL		
Number of subjects treated	1,188	988
Frequency[a]	861 (72.5%)	538 (54.5%)
Odds Ratio	2.202	
95% confidence interval	(1.842, 2.633)	
Severity/Nature of Risk		
Worst Grade=1	56 (4.7%)	68 (6.9%)
Worst Grade=2	490 (41.2%)	303 (30.7%)
Worst Grade=3	243 (20.5%)	127 (12.9%)
Worst Grade=4	44 (3.7%)	18 (1.8%)
Worst Grade=5	27 (2.3%)	22 (2.2%)
Missing Grade	1 (0.1%)	0
Number of subjects assessed (exclude E1912)	836	830
Seriousness*		
Was Serious	253 (30.3%)	133 (16.0%)
Outcomes*		
Resulted in Death	27 (3.2%)	21 (2.5%)
Did not recover (Persisted)	120 (14.4%)	35 (4.2%)
Recovering with treatment	11 (1.3%)	3 (0.4%)
Recovering without treatment	5 (0.6%)	2 (0.2%)
Recovered with treatment	280 (33.5%)	213 (25.7%)
Recovered without treatment	199 (23.8%)	207 (24.9%)
Missing	0	0
Indication: WM		
Number of subjects treated	75	75
Frequency[a]	60 (80.0%)	32 (42.7%)
Odds Ratio	5.375	
95% confidence interval	(2.596, 11.127)	
Seriousness		
Was Serious	21 (28.0%)	4 (5.3%)
Outcomes		
Resulted in Death	1 (1.3%)	0
Did not recover (Persisted)	11 (14.7%)	3 (4.0%)
Recovering with treatment	0	0
Recovering without treatment	0	0
Recovered with treatment	42 (56.0%)	22 (29.3%)
Recovered without treatment	6 (8.0%)	7 (9.3%)
Missing	0	0

Frequency, Seriousness, Outcomes, and Severity of Infections (Including Viral Reactivation) in Clinical Trials; (The Randomized Clinical Trials Population)

	All Randomized Trials Population	
	Ibrutinib n (%)	**Placebo/Comparator n (%)**
Severity/Nature of Risk		
Worst Grade=1	12 (16.0%)	9 (12.0%)
Worst Grade=2	26 (34.7%)	17 (22.7%)
Worst Grade=3	20 (26.7%)	5 (6.7%)
Worst Grade=4	1 (1.3%)	1 (1.3%)
Worst Grade=5	1 (1.3%)	0
Missing Grade	0	0

[a] Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA preferred terms representative of infections including viral reactivation, and excluding preferred terms representative of PML; the subject is counted only once regardless of the number of events or the number of occurrences.
The outcome of Unknown is not presented in the summary.
MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia.
Note: Trials included: MCL3001, PCYC-1112-CA, PCYC-1115-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1127-CA. Comparator drugs include temsirolimus (MCL3001), ofatumumab (PCYC-1112-CA), chlorambucil (PCYC-1115-CA), placebo + bendamustine + rituximab (CLL3001), chlorambucil + obinutuzumab (PCYC-1130-CA, CLL3011), fludarabine + cyclophosphamide + rituximab (E1912/PCYC-1126e-CA), and a combination of placebo + rituximab (PCYC-1127-CA).
* Trial E1912 collected neither AE seriousness, nor outcome, thus is excluded from seriousness and outcome summaries.

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Frequency, Seriousness, Outcomes, and Severity of Infections (Including Viral Reactivation) in Clinical Trials; (The All Clinical Trials Population Including Open Extensions)

	Monotherapy [a]	**Combination [a]**	**All Clinical Trials Population**
Indication: MCL			
Number of subjects treated	421	0	421
Frequency[a]	290 (68.9%)	0	290 (68.9%)
Seriousness			
Was Serious	93 (22.1%)	0	93 (22.1%)
Outcomes			
Resulted in Death	15 (3.6%)	0	15 (3.6%)
Did not recover (Persisted)	57 (13.5%)	0	57 (13.5%)
Recovering with treatment	3 (0.7%)	0	3 (0.7%)
Recovering without treatment	1 (0.2%)	0	1 (0.2%)
Recovered with treatment	195 (46.3%)	0	195 (46.3%)
Recovered without treatment	19 (4.5%)	0	19 (4.5%)
Missing	0	0	0
Severity/Nature of Risk			
Worst Grade=1	30 (7.1%)	0	30 (7.1%)
Worst Grade=2	156 (37.1%)	0	156 (37.1%)
Worst Grade=3	79 (18.8%)	0	79 (18.8%)
Worst Grade=4	10 (2.4%)	0	10 (2.4%)
Worst Grade=5	15 (3.6%)	0	15 (3.6%)
Missing Grade	0	0	0
Indication: CLL			
Number of subjects treated	998	1,285	2,283
Frequency[a]	799 (80.1%)	906 (70.5%)	1,705 (74.7%)
Severity/Nature of Risk			
Worst Grade=1	87 (8.7%)	107 (8.3%)	194 (8.5%)
Worst Grade=2	364 (36.5%)	542 (42.2%)	906 (39.7%)
Worst Grade=3	267 (26.8%)	203 (15.8%)	470 (20.6%)
Worst Grade=4	34 (3.4%)	34 (2.6%)	68 (3.0%)
Worst Grade=5	47 (4.7%)	19 (1.5%)	66 (2.9%)
Missing Grade	0	1 (0.1%)	1 (<0.1%)
Number of subjects assessed (exclude E1912)	998	933	1,931

Frequency, Seriousness, Outcomes, and Severity of Infections (Including Viral Reactivation) in Clinical Trials; (The All Clinical Trials Population Including Open Extensions)

	Monotherapy [a]	Combination [a]	All Clinical Trials Population
Seriousness*			
Was Serious	325 (32.6%)	195 (20.9%)	520 (26.9%)
Outcomes*			
Resulted in Death	47 (4.7%)	19 (2.0%)	66 (3.4%)
Did not recover (Persisted)	183 (18.3%)	89 (9.5%)	272 (14.1%)
Recovering with treatment	15 (1.5%)	3 (0.3%)	18 (0.9%)
Recovering without treatment	6 (0.6%)	3 (0.3%)	9 (0.5%)
Recovered with treatment	409 (41.0%)	346 (37.1%)	755 (39.1%)
Recovered without treatment	136 (13.6%)	227 (24.3%)	363 (18.8%)
Missing	0	0	0
Indication: WM			
Number of subjects treated	133	75	208
Frequency[a]	88 (66.2%)	60 (80.0%)	148 (71.2%)
Seriousness			
Was Serious	21 (15.8%)	21 (28.0%)	42 (20.2%)
Outcomes			
Resulted in Death	0	1 (1.3%)	1 (0.5%)
Did not recover (Persisted)	6 (4.5%)	11 (14.7%)	17 (8.2%)
Recovering with treatment	0	0	0
Recovering without treatment	0	0	0
Recovered with treatment	31 (23.3%)	42 (56.0%)	73 (35.1%)
Recovered without treatment	5 (3.8%)	6 (8.0%)	11 (5.3%)
Missing	46 (34.6%)	0	46 (22.1%)
Severity/Nature of Risk			
Worst Grade=1	25 (18.8%)	12 (16.0%)	37 (17.8%)
Worst Grade=2	44 (33.1%)	26 (34.7%)	70 (33.7%)
Worst Grade=3	18 (13.5%)	20 (26.7%)	38 (18.3%)
Worst Grade=4	1 (0.8%)	1 (1.3%)	2 (1.0%)
Worst Grade=5	0	1 (1.3%)	1 (0.5%)
Missing Grade	0	0	0

[a] Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA preferred terms representative of infections including viral reactivation, and excluding preferred terms representative of PML; the subject is counted only once regardless of the number of events or the number of occurrences.
The outcome of Unknown is not presented in the summary.
MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia.
Note: Trials included: PCYC-04753, PCYC-1104-CA, MCL2001, MCL3001, PCYC-1102-CA, PCYC-1108-CA, PCYC-1109-CA, PCYC-1112-CA, PCYC-1115-CA, PCYC-1117-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1142-CA, PCYC-1118e-CA, PCYC-1127-CA.
Data for cross-over subjects from Trials MCL3001, PCYC-1112-CA, CLL3001, PCYC-1130-CA, CLL3011, and PCYC-1127-CA, as well as data for subjects from open-label subtrial in PCYC-1127-CA are included in the monotherapy pool.
* Trial E1912 collected neither AE seriousness, nor outcome, thus is excluded from seriousness and outcome summaries.
Note: Subjects who crossed over from the comparator treatment group are counted towards monotherapy. All subjects in Trial PCYC-1142-CA are counted towards combination therapy. Subjects in Trial CLL3011 who received experimental treatment and who were re-exposed to study ibrutinib are also counted towards combination therapy.

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Development of infections such as pneumonia or sepsis, either in the context of underlying neutropenia (neutropenic sepsis) or occurring without neutropenia, has been reported during ibrutinib treatment. Infection is also known to occur in the context of the underlying diseases of WM, MCL, and CLL. Patients with infection are treated as per standard of care.

In Trial DBL3001, the overall safety population showed a higher incidence of serious treatment-emergent adverse events (TEAEs), grade ≥3 serious TEAEs, and TEAEs leading to study drug discontinuation in the ibrutinib 560 mg+R-CHOP treatment group compared to the placebo+R-CHOP treatment group. The difference was more pronounced for older subjects (aged ≥65 years) compared with younger subjects. Infections were reported with a higher incidence for the ibrutinib+R-CHOP treatment group (57.2%) versus the placebo+R-CHOP treatment group (43.5%) regardless of age and were reported more frequently in the ibrutinib+R-CHOP treatment group (63.6%) versus the placebo+R-CHOP treatment group (46.9%) for subjects aged ≥65 years. The most common infections were respiratory related (pneumonia, upper respiratory tract infections). Infections were the most commonly reported TEAE with an outcome of death for subjects aged ≥65 years in the ibrutinib+R-CHOP treatment group. Fewer younger subjects died compared with older subjects. Febrile neutropenia was reported with a higher incidence for the ibrutinib+R-CHOP treatment group (25.5%) versus the placebo+R-CHOP treatment group (14.8%) regardless of age and was reported more frequently in the ibrutinib+R-CHOP treatment group (29.4%) versus the placebo+R-CHOP treatment group (16.9%) for subjects aged ≥65 years. The observed adverse reactions that occurred with ibrutinib in combination with R-CHOP were consistent with the known adverse reaction profile of ibrutinib in the B-cell malignancy randomized controlled trial population. Use of ibrutinib for treatment of DLBCL and use of ibrutinib in combination with R-CHOP are not submitted/approved ibrutinib indications.

No new safety information that impacts the risk-benefit balance of the product has emerged from postmarketing experience.

Risk Factors and Risk Groups:

Predictors include increasing age (>60 years), underlying immunosuppression that is inherent to the primary disease process, therapy-related immunosuppression, concomitant chemotherapy, absence of antibiotic prophylaxis, and poor performance and/or nutritional status.

Preventability:

The SmPC (Section 4.4) states that prophylaxis should be considered according to standard of care in patients who are at increased risk for opportunistic infections. Patients should be monitored for fever, abnormal liver function tests, neutropenia, and infections and appropriate anti-infective therapy should be instituted as indicated. Liver function and viral hepatitis status should be assessed before initiating treatment with ibrutinib. As clinically indicated, viral load and serological testing for infectious hepatitis should be performed per local medical guidelines. For patients diagnosed with viral hepatitis, consulting a liver disease expert for management should be considered.

Impact on the Risk-benefit Balance of the Product:

Infections are frequently observed in patients with hematological malignancies and a potential association with the use of ibrutinib cannot be excluded. The SmPC and PL provide information to the prescriber and patient on how to manage the risk. Overall, the risk-benefit balance is positive for the product considering the severity of the diseases treated and the established efficacy and safety profile of ibrutinib.

Public Health Impact:

Overall, the frequency of grade 3 or higher infections tends to be higher in ibrutinib versus comparators used in Phase 3 randomized controlled clinical trials. Given that most of these events are clinically manageable and reversible, and that the number of patients in the targeted populations is relatively small, infections associated with ibrutinib therapy is not likely to have a significant impact on public health.

Annex 1 MedDRA Term:

Infections and infestations System Organ Class (SOC)

Important Potential Risk - Progressive Multifocal Leukoencephalopathy (PML)

Potential Mechanisms:

PML is caused by the John Cunningham (JC) virus, which is normally kept under control by the immune system. JC virus is harmless, unless the immune system has been severely weakened.

Evidence Source(s) and Strength of Evidence:

Cases of PML (within the context of a prior or concomitant immunosuppressive therapy) in association with ibrutinib have been reported in completed clinical trials and during postmarketing experience, and are also described in the current prescribing information for ibrutinib. PML has not been identified as an adverse reaction.

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of Progressive Multifocal Leukoencephalopathy (PML) in Clinical Trials; (The Randomized Clinical Trials Population)

	All Randomized Trials Population	
	Ibrutinib n (%)	**Placebo/Comparator n (%)**
Indication: MCL		
No subjects participating in clinical trials for MCL with ibrutinib reported an AE of PML.		
Indication: CLL		
Number of subjects treated	1,188	988
Frequency[a]	3 (0.3%)	0
Odds Ratio	> 999.999	
95% confidence interval	(< 0.001, > 999.999)	
Severity/Nature of Risk		
Worst Grade=1	1 (0.1%)	0
Worst Grade=2	0	0
Worst Grade=3	0	0
Worst Grade=4	0	0
Worst Grade=5	2 (0.2%)	0
Missing Grade	0	0
Number of subjects assessed (exclude E1912)	836	830
Seriousness*		
Was Serious	2 (0.2%)	0
Outcomes*		
Resulted in Death	2 (0.2%)	0
Did not recover (Persisted)	1 (0.1%)	0
Recovering with treatment	0	0
Recovering without treatment	0	0
Recovered with treatment	0	0
Recovered without treatment	0	0
Missing	0	0

Frequency, Seriousness, Outcomes, and Severity of Progressive Multifocal Leukoencephalopathy (PML) in Clinical Trials; (The Randomized Clinical Trials Population)

	All Randomized Trials Population	
	Ibrutinib n (%)	**Placebo/Comparator n (%)**
Indication: WM		
Number of subjects treated	75	75
Frequency[a]	1 (1.3%)	0
Odds Ratio	> 999.999	
95% confidence interval	(< 0.001, > 999.999)	
Seriousness		
Was Serious	0	0
Outcomes		
Resulted in Death	0	0
Did not recover (Persisted)	1 (1.3%)	0
Recovering with treatment	0	0
Recovering without treatment	0	0
Recovered with treatment	0	0
Recovered without treatment	0	0
Missing	0	0
Severity/Nature of Risk		
Worst Grade=1	0	0
Worst Grade=2	1 (1.3%)	0
Worst Grade=3	0	0
Worst Grade=4	0	0
Worst Grade=5	0	0
Missing Grade	0	0

[a] Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA preferred terms representative of PML; the subject is counted only once regardless of the number of events or the number of occurrences.
The outcome of Unknown is not presented in the summary.
MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia.
Note: Trials included: MCL3001, PCYC-1112-CA, PCYC-1115-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1127-CA. Comparator drugs include temsirolimus (MCL3001), ofatumumab (PCYC-1112-CA), chlorambucil (PCYC-1115-CA), placebo + bendamustine + rituximab (CLL3001), chlorambucil + obinutuzumab (PCYC-1130-CA, CLL3011), fludarabine + cyclophosphamide + rituximab (E1912/PCYC-1126e-CA), and a combination of placebo + rituximab (PCYC-1127-CA).
* Trial E1912 collected neither AE seriousness, nor outcome, thus is excluded from seriousness and outcome summaries.

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Frequency, Seriousness, Outcomes, and Severity of Progressive Multifocal Leukoencephalopathy (PML) in Clinical Trials; (The All Clinical Trials Population Including Open Extensions)

	Monotherapy [a]	**Combination [a]**	**All Clinical Trials Population**
Indication: MCL			
No subjects participating in clinical trials for MCL with ibrutinib reported an AE of PML.			
Indication: CLL			
Number of subjects treated	998	1,285	2,283
Frequency[a]	3 (0.3%)	2 (0.2%)	5 (0.2%)
Severity/Nature of Risk			
Worst Grade=1	1 (0.1%)	0	1 (<0.1%)
Worst Grade=2	1 (0.1%)	0	1 (<0.1%)
Worst Grade=3	0	0	0
Worst Grade=4	0	0	0
Worst Grade=5	1 (0.1%)	2 (0.2%)	3 (0.1%)
Missing Grade	0	0	0

Frequency, Seriousness, Outcomes, and Severity of Progressive Multifocal Leukoencephalopathy (PML) in Clinical Trials; (The All Clinical Trials Population Including Open Extensions)

	Monotherapy [a]	Combination [a]	All Clinical Trials Population
Number of subjects assessed (exclude E1912)	998	933	1,931
Seriousness*			
Was Serious	2 (0.2%)	2 (0.2%)	4 (0.2%)
Outcomes*			
Resulted in Death	1 (0.1%)	2 (0.2%)	3 (0.2%)
Did not recover (Persisted)	1 (0.1%)	0	1 (0.1%)
Recovering with treatment	0	0	0
Recovering without treatment	0	0	0
Recovered with treatment	0	0	0
Recovered without treatment	1 (0.1%)	0	1 (0.1%)
Missing	0	0	0
Indication: WM			
Number of subjects treated	133	75	208
Frequency[a]	0	1 (1.3%)	1 (0.5%)
Seriousness			
Was Serious	0	0	0
Outcomes			
Resulted in Death	0	0	0
Did not recover (Persisted)	0	1 (1.3%)	1 (0.5%)
Recovering with treatment	0	0	0
Recovering without treatment	0	0	0
Recovered with treatment	0	0	0
Recovered without treatment	0	0	0
Missing	0	0	0
Severity/Nature of Risk			
Worst Grade=1	0	0	0
Worst Grade=2	0	1 (1.3%)	1 (0.5%)
Worst Grade=3	0	0	0
Worst Grade=4	0	0	0
Worst Grade=5	0	0	0
Missing Grade	0	0	0

[a] Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA preferred terms representative of PML; the subject is counted only once regardless of the number of events or the number of occurrences.
The outcome of Unknown is not presented in the summary.
MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia.
Note: Trials included: PCYC-04753, PCYC-1104-CA, MCL2001, MCL3001, PCYC-1102-CA, PCYC-1108-CA, PCYC-1109-CA, PCYC-1112-CA, PCYC-1115-CA, PCYC-1117-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1142-CA, PCYC-1118e-CA, PCYC-1127-CA.
Data for cross-over subjects from Trials MCL3001, PCYC-1112-CA, CLL3001, PCYC-1130-CA, CLL3011, and PCYC-1127-CA, as well as data for subjects from open-label subtrial in PCYC-1127-CA are included in the monotherapy pool.
* Trial E1912 collected neither AE seriousness, nor outcome, thus is excluded from seriousness and outcome summaries.
Note: Subjects who crossed over from the comparator treatment group are counted towards monotherapy. All subjects in Trial PCYC-1142-CA are counted towards combination therapy. Subjects in Trial CLL3011 who received experimental treatment and who were re-exposed to study ibrutinib are also counted towards combination therapy.

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In general, PML has a mortality rate of 30% to 50% in the first few months and those who survive can be left with severe neurological disabilities.

No new safety information that impacts the risk-benefit balance of the product has emerged from postmarketing experience.

Risk Factors and Risk Groups:

PML is a demyelinating disorder of the CNS, caused by the reactivation of the commonly occurring JC virus, which remains inactive in healthy individuals, and causes disease only when the immune system has been compromized (Lopes da Silva, 2012). PML usually occurs during severe immunosuppression and the most common causes are represented by HIV infection, lymphoproliferative disorders, and other forms of cancer. The use of monoclonal antibodies (eg, natalizumab, rituximab, efalizumab) in the treatment of several dysimmune diseases such as multiple sclerosis, rheumatoid arthritis, psoriasis, and systemic lupus erythematosus, has led to an increased incidence of PML (Tavazzi et al, 2011). Chemotherapy and immunosuppressive therapy are considered to be the primary risk factors in addition to HIV infection (Carson et al, 2009). In one analysis, 3 significant risk factors for developing PML in CLL patients were identified: age (>55 years), male sex, and CD4 cell count <200 cells/µL (Lopes da Silva, 2012).

A retrospective, monocentric cohort study of 976 NHL patients, including 517 patients who received at least one dose of rituximab, concluded that the inclusion of rituximab into standard chemotherapy regimens for NHL caused a significantly higher incidence of PML cases (rate difference: 2.2 every 1,000 patient-years; 95% CI: 0.1-4.3) (Tuccori et al, 2010).

Preventability:

The SmPC (Section 4.4) states that physicians should consider PML in the differential diagnosis in patients with new or worsening neurological, cognitive, or behavioral signs or symptoms. If PML is suspected, appropriate diagnostic evaluations should be undertaken and treatment suspended until PML is excluded. If any doubt exists, referral to a neurologist and appropriate diagnostic measures for PML, including magnetic resonance imaging scan preferably with contrast, cerebrospinal fluid testing for JC viral DNA and repeat neurological assessments, should be considered.

Impact on the Risk-benefit Balance of the Product:

The observed incidence of PML is low and therefore does not have a significant impact on the risk-benefit balance of the product. The SmPC and PL provide information to the prescriber and patient on how to manage the risk. Overall, the risk-benefit balance is positive for the product considering the severity of the diseases treated and the established efficacy and safety profile of ibrutinib.

Public Health Impact:

In consideration of the relatively small number of patients in the targeted populations and the small number of PML cases reported with ibrutinib therapy, the impact on public health is expected to be low.

Annex 1 MedDRA Term:

Progressive multifocal leukoencephalopathy (PT)

Important Potential Risk - Cardiac Arrhythmia (Excluding Atrial Fibrillation and Ventricular Tachyarrhythmias)

Potential Mechanisms:

The potential mechanism by which ibrutinib causes cardiac arrhythmia is unknown at this time.

Evidence Source(s) and Strength of Evidence:

Cases of cardiac arrhythmia in association with ibrutinib have been reported in completed clinical trials, and are also described in the current prescribing information for ibrutinib.

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of Cardiac Arrhythmia (Excluding Atrial Fibrillation and Ventricular Tachyarrhythmias) in Clinical Trials; (The Randomized Clinical Trials Population)

	All Randomized Trials Population	
	Ibrutinib n (%)	**Placebo/Comparator n (%)**
Indication: MCL		
Number of subjects treated	139	139
Frequency[a]	10 (7.2%)	11 (7.9%)
Odds Ratio	0.902	
95% confidence interval	(0.370, 2.198)	
Seriousness		
Was Serious	4 (2.9%)	1 (0.7%)
Outcomes		
Resulted in Death	0	1 (0.7%)
Did not recover (Persisted)	2 (1.4%)	1 (0.7%)
Recovering with treatment	1 (0.7%)	0
Recovering without treatment	0	0
Recovered with treatment	2 (1.4%)	3 (2.2%)
Recovered without treatment	5 (3.6%)	6 (4.3%)
Missing	0	0
Severity/Nature of Risk		
Worst Grade=1	4 (2.9%)	4 (2.9%)
Worst Grade=2	2 (1.4%)	3 (2.2%)
Worst Grade=3	4 (2.9%)	3 (2.2%)
Worst Grade=4	0	0
Worst Grade=5	0	1 (0.7%)
Missing Grade	0	0
Indication: CLL		
Number of subjects treated	1,188	988
Frequency[a]	196 (16.5%)	66 (6.7%)
Odds Ratio	2.760	
95% confidence interval	(2.059, 3.700)	
Severity/Nature of Risk		
Worst Grade=1	96 (8.1%)	33 (3.3%)
Worst Grade=2	48 (4.0%)	23 (2.3%)
Worst Grade=3	33 (2.8%)	9 (0.9%)
Worst Grade=4	7 (0.6%)	1 (0.1%)
Worst Grade=5	12 (1.0%)	0
Missing Grade	0	0
Number of subjects assessed (exclude E1912)	836	830
Seriousness*		
Was Serious	31 (3.7%)	9 (1.1%)
Outcomes*		
Resulted in Death	12 (1.4%)	0
Did not recover (Persisted)	32 (3.8%)	4 (0.5%)
Recovering with treatment	1 (0.1%)	0
Recovering without treatment	3 (0.4%)	0

Frequency, Seriousness, Outcomes, and Severity of Cardiac Arrhythmia (Excluding Atrial Fibrillation and Ventricular Tachyarrhythmias) in Clinical Trials; (The Randomized Clinical Trials Population)

	All Randomized Trials Population	
	Ibrutinib n (%)	**Placebo/Comparator n (%)**
Recovered with treatment	12 (1.4%)	10 (1.2%)
Recovered without treatment	71 (8.5%)	37 (4.5%)
Missing	0	0
Indication: WM		
Number of subjects treated	75	75
Frequency[a]	12 (16.0%)	6 (8.0%)
Odds Ratio	2.190	
95% confidence interval	(0.776, 6.184)	
Seriousness		
Was Serious	1 (1.3%)	0
Outcomes		
Resulted in Death	0	0
Did not recover (Persisted)	3 (4.0%)	2 (2.7%)
Recovering with treatment	0	0
Recovering without treatment	0	0
Recovered with treatment	1 (1.3%)	1 (1.3%)
Recovered without treatment	8 (10.7%)	3 (4.0%)
Missing	0	0
Severity/Nature of Risk		
Worst Grade=1	8 (10.7%)	3 (4.0%)
Worst Grade=2	2 (2.7%)	2 (2.7%)
Worst Grade=3	2 (2.7%)	1 (1.3%)
Worst Grade=4	0	0
Worst Grade=5	0	0
Missing Grade	0	0

[a] Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA preferred terms representative of cardiac arrhythmia, excluding terms representative of ventricular tachyarrhythmias and the preferred term of atrial fibrillation; the subject is counted only once regardless of the number of events or the number of occurrences.
The outcome of Unknown is not presented in the summary.
MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia.
Note: Trials included: MCL3001, PCYC-1112-CA, PCYC-1115-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1127-CA. Comparator drugs include temsirolimus (MCL3001), ofatumumab (PCYC-1112-CA), chlorambucil (PCYC-1115-CA), placebo + bendamustine + rituximab (CLL3001), chlorambucil + obinutuzumab (PCYC-1130-CA, CLL3011), fludarabine + cyclophosphamide + rituximab (E1912/PCYC-1126e-CA), and a combination of placebo + rituximab (PCYC-1127-CA).
* Trial E1912 collected neither AE seriousness, nor outcome, thus is excluded from seriousness and outcome summaries.

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Frequency, Seriousness, Outcomes, and Severity of Cardiac Arrhythmia (Excluding Atrial Fibrillation and Ventricular Tachyarrhythmias) in Clinical Trials;
(The All Clinical Trials Population Including Open Extensions)

	Monotherapy [a]	Combination [a]	All Clinical Trials Population
Indication: MCL			
Number of subjects treated	421	0	421
Frequency[a]	51 (12.1%)	0	51 (12.1%)
Seriousness			
Was Serious	9 (2.1%)	0	9 (2.1%)
Outcomes			
Resulted in Death	2 (0.5%)	0	2 (0.5%)
Did not recover (Persisted)	7 (1.7%)	0	7 (1.7%)
Recovering with treatment	1 (0.2%)	0	1 (0.2%)
Recovering without treatment	0	0	0
Recovered with treatment	12 (2.9%)	0	12 (2.9%)
Recovered without treatment	29 (6.9%)	0	29 (6.9%)
Missing	0	0	0
Severity/Nature of Risk			
Worst Grade=1	23 (5.5%)	0	23 (5.5%)
Worst Grade=2	15 (3.6%)	0	15 (3.6%)
Worst Grade=3	11 (2.6%)	0	11 (2.6%)
Worst Grade=4	0	0	0
Worst Grade=5	2 (0.5%)	0	2 (0.5%)
Missing Grade	0	0	0
Indication: CLL			
Number of subjects treated	998	1,285	2,283
Frequency[a]	159 (15.9%)	216 (16.8%)	375 (16.4%)
Severity/Nature of Risk			
Worst Grade=1	82 (8.2%)	118 (9.2%)	200 (8.8%)
Worst Grade=2	38 (3.8%)	44 (3.4%)	82 (3.6%)
Worst Grade=3	29 (2.9%)	34 (2.6%)	63 (2.8%)
Worst Grade=4	3 (0.3%)	8 (0.6%)	11 (0.5%)
Worst Grade=5	7 (0.7%)	12 (0.9%)	19 (0.8%)
Missing Grade	0	0	0
Number of subjects assessed (exclude E1912)	998	933	1,931
Seriousness*			
Was Serious	29 (2.9%)	27 (2.9%)	56 (2.9%)
Outcomes*			
Resulted in Death	7 (0.7%)	12 (1.3%)	19 (1.0%)
Did not recover (Persisted)	40 (4.0%)	29 (3.1%)	69 (3.6%)
Recovering with treatment	1 (0.1%)	0	1 (0.1%)
Recovering without treatment	1 (0.1%)	2 (0.2%)	3 (0.2%)
Recovered with treatment	21 (2.1%)	14 (1.5%)	35 (1.8%)
Recovered without treatment	88 (8.8%)	95 (10.2%)	183 (9.5%)
Missing	0	0	0
Indication: WM			
Number of subjects treated	133	75	208
Frequency[a]	14 (10.5%)	12 (16.0%)	26 (12.5%)
Seriousness			
Was Serious	4 (3.0%)	1 (1.3%)	5 (2.4%)
Outcomes			
Resulted in Death	0	0	0
Did not recover (Persisted)	4 (3.0%)	3 (4.0%)	7 (3.4%)
Recovering with treatment	0	0	0
Recovering without treatment	0	0	0
Recovered with treatment	0	1 (1.3%)	1 (0.5%)
Recovered without treatment	4 (3.0%)	8 (10.7%)	12 (5.8%)
Missing	6 (4.5%)	0	6 (2.9%)

Frequency, Seriousness, Outcomes, and Severity of Cardiac Arrhythmia (Excluding Atrial Fibrillation and Ventricular Tachyarrhythmias) in Clinical Trials;
(The All Clinical Trials Population Including Open Extensions)

	Monotherapy [a]	Combination [a]	All Clinical Trials Population
Severity/Nature of Risk			
Worst Grade=1	9 (6.8%)	8 (10.7%)	17 (8.2%)
Worst Grade=2	1 (0.8%)	2 (2.7%)	3 (1.4%)
Worst Grade=3	4 (3.0%)	2 (2.7%)	6 (2.9%)
Worst Grade=4	0	0	0
Worst Grade=5	0	0	0
Missing Grade	0	0	0

[a] Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA preferred terms representative of cardiac arrhythmia, excluding terms representative of ventricular tachyarrhythmias and the preferred term of atrial fibrillation; the subject is counted only once regardless of the number of events or the number of occurrences.
The outcome of Unknown is not presented in the summary.
MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia.
Note: Trials included: PCYC-04753, PCYC-1104-CA, MCL2001, MCL3001, PCYC-1102-CA, PCYC-1108-CA, PCYC-1109-CA, PCYC-1112-CA, PCYC-1115-CA, PCYC-1117-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1142-CA, PCYC-1118e-CA, PCYC-1127-CA.
Data for cross-over subjects from Trials MCL3001, PCYC-1112-CA, CLL3001, PCYC-1130-CA, CLL3011, and PCYC-1127-CA, as well as data for subjects from open-label subtrial in PCYC-1127-CA are included in the monotherapy pool.
* Trial E1912 collected neither AE seriousness, nor outcome, thus is excluded from seriousness and outcome summaries.
Note: Subjects who crossed over from the comparator treatment group are counted towards monotherapy. All subjects in Trial PCYC-1142-CA are counted towards combination therapy. Subjects in Trial CLL3011 who received experimental treatment and who were re-exposed to study ibrutinib are also counted towards combination therapy.

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The effect of ibrutinib on the QTc interval was evaluated in 20 healthy male and female subjects in a randomized, double-blind thorough QT trial (Trial PCI-32765CLL1007) with placebo and positive controls. At a supratherapeutic dose of 1,680 mg, ibrutinib did not prolong the QTc interval to any clinically relevant extent. The largest upper bound of the 2-sided 90% CI for the baseline-adjusted mean differences between ibrutinib and placebo was below 10 ms. In this same trial, a concentration-dependent shortening in the QTc interval was observed (-5.3 ms [90% CI: -9.4, -1.1] at a C_{max} of 719 ng/mL following the supratherapeutic dose of 1,680 mg) that was considered not clinically relevant.

Cardiac arrhythmia can be debilitating and potentially fatal. Patients with cardiac arrhythmias experience various symptoms that could result in decreased quality of life. In rare cases, sudden death could occur as an outcome of cardiac arrhythmias (Huikuri et al, 2001). The search strategy for Cardiac arrhythmias (SMQ) includes the PTs of Sudden death and Sudden cardiac death. In the company-sponsored pooled randomized clinical trials, an imbalance in exposure-adjusted incidence rate for sudden death and sudden cardiac death events was observed in the ibrutinib arm (0.0002) versus the comparator arm (0.0001). The subjects who had such events mostly presented with preexisting cardiac comorbidities at baseline. The postmarketing reporting frequency of sudden death or sudden cardiac death was 15.8 cases per 100,000 person-years (assigned as rare), considerably lower than the rate in the general population (40-100 per 100,000) (Hayashi et al, 2015).

No other relevant new safety information that impacts the risk-benefit balance of the product has emerged from postmarketing experience.

Risk Factors and Risk Groups:

Arrhythmias are common in older people. Risk factors include myocardial infarction, heart failure or cardiomyopathy, cardiac hypertrophy, incompetent or stenotic heart valves, or congenital heart defects. Risk can also be increased if the patient has hypertension, myocarditis, pericarditis, diabetes mellitus, sleep apnea, electrolyte imbalance (eg, hyperkalemia and hypomagnesemia), hypothyroidism, or hyperthyroidism (National Heart, Lung, and Blood Institute, 2011).

Preventability:

The SmPC (Section 4.4) states that fatal and serious cardiac arrhythmias and cardiac failure have occurred in patients treated with ibrutinib. Patients with advanced age, ECOG performance status ≥2, or cardiac comorbidities may be at greater risk of events including sudden fatal cardiac events. Atrial fibrillation, atrial flutter, ventricular tachyarrhythmia and cardiac failure have been reported, particularly in patients with acute infections or cardiac risk factors including hypertension, diabetes mellitus, and a previous history of cardiac arrhythmia. Appropriate clinical evaluation of cardiac history and function should be performed prior to initiating ibrutinib. Patients should be carefully monitored during treatment for signs of clinical deterioration of cardiac function and clinically managed. Further evaluation (eg, ECG, echocardiogram), as indicated for patients in whom there are cardiovascular concerns, should be considered. For patients with relevant risk factors for cardiac events, the benefit/risk should be carefully assessed before initiating treatment with ibrutinib; alternative treatment may be considered.

Additional risk minimization measures for this important potential risk are described in Section V.2.

Impact on the Risk-benefit Balance of the Product:

Cardiac arrhythmia (excluding atrial fibrillation and ventricular tachyarrhythmias) has been observed in patients treated with ibrutinib. The SmPC and PL provide information to the prescriber and patient on how to manage the risk. Overall, the risk-benefit balance is positive for the product considering the severity of the diseases treated and the established efficacy and safety profile of ibrutinib.

Public Health Impact:

In consideration of the relatively small number of patients in the targeted populations and the relatively small number of significant cases of cardiac arrhythmia reported with ibrutinib therapy, the impact on public health is expected to be low.

Annex 1 MedDRA Term:

Cardiac arrhythmias (SMQ)

Important Potential Risk - Other Malignancies (Excluding Non-melanoma Skin Cancer)

Potential Mechanisms:

It is not known if ibrutinib is associated with second primary malignancy.

Evidence Source(s) and Strength of Evidence:

Cases of other malignancies (including solid tumors and hematologic tumors) in association with ibrutinib have been reported in ongoing and completed clinical trials. Other malignancies has not been identified as an adverse reaction.

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of Other Malignancies (Excluding Non-melanoma Skin Cancer) in Clinical Trials; (The Randomized Clinical Trials Population)

	All Randomized Trials Population	
	Ibrutinib n (%)	**Placebo/Comparator n (%)**
Indication: MCL		
Number of subjects treated	139	139
Frequency[a]	6 (4.3%)	1 (0.7%)
Odds Ratio	6.225	
95% confidence interval	(0.740, 52.404)	
Seriousness		
Was Serious	5 (3.6%)	1 (0.7%)
Outcomes		
Resulted in Death	1 (0.7%)	0
Did not recover (Persisted)	2 (1.4%)	0
Recovering with treatment	0	0
Recovering without treatment	0	0
Recovered with treatment	2 (1.4%)	1 (0.7%)
Recovered without treatment	0	0
Missing	0	0
Severity/Nature of Risk		
Worst Grade=1	0	0
Worst Grade=2	2 (1.4%)	0
Worst Grade=3	3 (2.2%)	1 (0.7%)
Worst Grade=4	0	0
Worst Grade=5	1 (0.7%)	0
Missing Grade	0	0
Indication: CLL		
Number of subjects treated	1,188	988
Frequency[a]	72 (6.1%)	24 (2.4%)
Odds Ratio	2.591	
95% confidence interval	(1.620, 4.146)	
Severity/Nature of Risk		
Worst Grade=1	3 (0.3%)	1 (0.1%)
Worst Grade=2	16 (1.3%)	8 (0.8%)
Worst Grade=3	34 (2.9%)	12 (1.2%)
Worst Grade=4	4 (0.3%)	0
Worst Grade=5	8 (0.7%)	2 (0.2%)
Missing Grade	7 (0.6%)	1 (0.1%)
Number of subjects assessed (exclude E1912)	836	830
Seriousness*		
Was Serious	40 (4.8%)	10 (1.2%)
Outcomes*		
Resulted in Death	8 (1.0%)	1 (0.1%)
Did not recover (Persisted)	18 (2.2%)	3 (0.4%)
Recovering with treatment	0	0
Recovering without treatment	1 (0.1%)	0

Frequency, Seriousness, Outcomes, and Severity of Other Malignancies (Excluding Non-melanoma Skin Cancer) in Clinical Trials; (The Randomized Clinical Trials Population)

	All Randomized Trials Population	
	Ibrutinib n (%)	**Placebo/Comparator n (%)**
Recovered with treatment	6 (0.7%)	2 (0.2%)
Recovered without treatment	19 (2.3%)	13 (1.6%)
Missing	0	0
Indication: WM		
Number of subjects treated	75	75
Frequency[a]	6 (8.0%)	1 (1.3%)
Odds Ratio	6.435	
95% confidence interval	(0.755, 54.814)	
Seriousness		
Was Serious	4 (5.3%)	1 (1.3%)
Outcomes		
Resulted in Death	0	0
Did not recover (Persisted)	4 (5.3%)	0
Recovering with treatment	0	0
Recovering without treatment	0	0
Recovered with treatment	0	0
Recovered without treatment	2 (2.7%)	1 (1.3%)
Missing	0	0
Severity/Nature of Risk		
Worst Grade=1	1 (1.3%)	0
Worst Grade=2	3 (4.0%)	0
Worst Grade=3	1 (1.3%)	1 (1.3%)
Worst Grade=4	1 (1.3%)	0
Worst Grade=5	0	0
Missing Grade	0	0

[a] Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA preferred terms representative of other malignancies other than the underlying indication or non-melanoma skin cancer; the subject is counted only once regardless of the number of events or the number of occurrences.
The outcome of Unknown is not presented in the summary.
MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia.
Note: Trials included: MCL3001, PCYC-1112-CA, PCYC-1115-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1127-CA. Comparator drugs include temsirolimus (MCL3001), ofatumumab (PCYC-1112-CA), chlorambucil (PCYC-1115-CA), placebo + bendamustine + rituximab (CLL3001), chlorambucil + obinutuzumab (PCYC-1130-CA, CLL3011), fludarabine + cyclophosphamide + rituximab (E1912/PCYC-1126e-CA), and a combination of placebo + rituximab (PCYC-1127-CA).
* Trial E1912 collected neither AE seriousness, nor outcome, thus is excluded from seriousness and outcome summaries.

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Frequency, Seriousness, Outcomes, and Severity of Other Malignancies (Excluding Non-melanoma Skin Cancer) in Clinical Trials; (The All Clinical Trials Population Including Open Extensions)

	Monotherapy [a]	Combination [a]	All Clinical Trials Population
Indication: MCL			
Number of subjects treated	421	0	421
Frequency[a]	11 (2.6%)	0	11 (2.6%)
Seriousness			
Was Serious	7 (1.7%)	0	7 (1.7%)
Outcomes			
Resulted in Death	1 (0.2%)	0	1 (0.2%)
Did not recover (Persisted)	7 (1.7%)	0	7 (1.7%)
Recovering with treatment	0	0	0
Recovering without treatment	0	0	0
Recovered with treatment	2 (0.5%)	0	2 (0.5%)
Recovered without treatment	0	0	0
Missing	0	0	0
Severity/Nature of Risk			
Worst Grade=1	0	0	0
Worst Grade=2	3 (0.7%)	0	3 (0.7%)
Worst Grade=3	7 (1.7%)	0	7 (1.7%)
Worst Grade=4	0	0	0
Worst Grade=5	1 (0.2%)	0	1 (0.2%)
Missing Grade	0	0	0
Indication: CLL			
Number of subjects treated	998	1,285	2,283
Frequency[a]	56 (5.6%)	61 (4.7%)	117 (5.1%)
Severity/Nature of Risk			
Worst Grade=1	5 (0.5%)	4 (0.3%)	9 (0.4%)
Worst Grade=2	11 (1.1%)	19 (1.5%)	30 (1.3%)
Worst Grade=3	25 (2.5%)	24 (1.9%)	49 (2.1%)
Worst Grade=4	7 (0.7%)	2 (0.2%)	9 (0.4%)
Worst Grade=5	8 (0.8%)	5 (0.4%)	13 (0.6%)
Missing Grade	0	7 (0.5%)	7 (0.3%)
Number of subjects assessed (exclude E1912)	998	933	1,931
Seriousness*			
Was Serious	41 (4.1%)	26 (2.8%)	67 (3.5%)
Outcomes*			
Resulted in Death	9 (0.9%)	5 (0.5%)	14 (0.7%)
Did not recover (Persisted)	25 (2.5%)	10 (1.1%)	35 (1.8%)
Recovering with treatment	1 (0.1%)	0	1 (0.1%)
Recovering without treatment	0	1 (0.1%)	1 (0.1%)
Recovered with treatment	7 (0.7%)	4 (0.4%)	11 (0.6%)
Recovered without treatment	14 (1.4%)	21 (2.3%)	35 (1.8%)
Missing	0	0	0
Indication: WM			
Number of subjects treated	133	75	208
Frequency[a]	4 (3.0%)	6 (8.0%)	10 (4.8%)
Seriousness			
Was Serious	2 (1.5%)	4 (5.3%)	6 (2.9%)
Outcomes			
Resulted in Death	1 (0.8%)	0	1 (0.5%)
Did not recover (Persisted)	1 (0.8%)	4 (5.3%)	5 (2.4%)
Recovering with treatment	0	0	0
Recovering without treatment	0	0	0
Recovered with treatment	0	0	0
Recovered without treatment	1 (0.8%)	2 (2.7%)	3 (1.4%)
Missing	1 (0.8%)	0	1 (0.5%)

Frequency, Seriousness, Outcomes, and Severity of Other Malignancies (Excluding Non-melanoma Skin Cancer) in Clinical Trials; (The All Clinical Trials Population Including Open Extensions)

	Monotherapy [a]	Combination [a]	All Clinical Trials Population
Severity/Nature of Risk			
Worst Grade=1	1 (0.8%)	1 (1.3%)	2 (1.0%)
Worst Grade=2	1 (0.8%)	3 (4.0%)	4 (1.9%)
Worst Grade=3	1 (0.8%)	1 (1.3%)	2 (1.0%)
Worst Grade=4	0	1 (1.3%)	1 (0.5%)
Worst Grade=5	1 (0.8%)	0	1 (0.5%)
Missing Grade	0	0	0

[a] Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA preferred terms representative of other malignancies other than the underlying indication or non-melanoma skin cancer; the subject is counted only once regardless of the number of events or the number of occurrences.
The outcome of Unknown is not presented in the summary.
MCL = mantle cell lymphoma; CLL = chronic lymphocytic leukemia; WM = Waldenström's macroglobulinemia.
Note: Trials included: PCYC-04753, PCYC-1104-CA, MCL2001, MCL3001, PCYC-1102-CA, PCYC-1108-CA, PCYC-1109-CA, PCYC-1112-CA, PCYC-1115-CA, PCYC-1117-CA, CLL3001, PCYC-1130-CA, E1912/PCYC-1126e-CA, CLL3011, PCYC-1142-CA, PCYC-1118e-CA, PCYC-1127-CA.
Data for cross-over subjects from Trials MCL3001, PCYC-1112-CA, CLL3001, PCYC-1130-CA, CLL3011, and PCYC-1127-CA, as well as data for subjects from open-label subtrial in PCYC-1127-CA are included in the monotherapy pool.
* Trial E1912 collected neither AE seriousness, nor outcome, thus is excluded from seriousness and outcome summaries.
Note: Subjects who crossed over from the comparator treatment group are counted towards monotherapy. All subjects in Trial PCYC-1142-CA are counted towards combination therapy. Subjects in Trial CLL3011 who received experimental treatment and who were re-exposed to study ibrutinib are also counted towards combination therapy.

[TRMRSK07B.RTF] [JNJ-54179060/Z RMP/DBR RMP 2021 GLOW/RE RMP EU UPDATE/PROD/TRMRSKB-ALL.SAS] 10FEB2022, 23:41

Second primary malignancies have become an increasingly important concern in oncology during the last 2 decades, as they now comprise the sixth most common group of malignancies after skin, colorectal, lung, breast, and prostate cancers.

Some second malignancies appear to be less amenable to treatment than primary tumors of the same histologic type. The best example of this is therapy-related acute myelogenous leukemia (AML) where the prognosis is much worse than for de novo AML. Presumably, this reflects enhanced mutations and other molecular genetic abnormalities stemming from exposure to chemotherapy or radiation. Treatment for a second cancer must also take into account the toxicity from the initial therapy (Rheingold et al, 2003).

Therapeutic options for second primary cancers are often compromised by the therapy for the first neoplasm, but early diagnosis can often lead to successful treatment of most second primary cancers.

No new safety information that impacts the risk-benefit balance of the product has emerged from postmarketing experience.

Risk Factors and Risk Groups:

The chance of developing a second cancer depends on a number of factors including type of primary cancer, age at diagnosis, sex, types of therapy given, environmental exposures, genetic predisposition, and health decisions. Radiation has long been associated with the development of primary cancers and, when used as treatment, imparts a risk for the development of a second cancer.

Leukemia as a second primary cancer can occur following treatment with chemotherapy. Although AML is the most common type of therapy-related leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, and myelodysplastic syndrome have also been reported. Chemotherapy-induced myeloid leukemias are relatively resistant to subsequent therapy and have a cure rate of only 10% to 20%, stressing the importance of primary prevention (Bhatia et al, 1999; Neugut et al, 1990; Felix, 1999).

Preventability:

Identifying those who are at greater risk for multiple neoplasms can help medical providers to better monitor for second neoplasms and advise patients on ways of reducing risks.

Many groups of high-risk individuals are already known, and several ways of reducing the incidence of second cancers are underway. The knowledge that certain agents and regimens increase the risk of second malignancies has prompted oncologists to modify therapy.

Impact on the Risk-benefit Balance of the Product:

The observed incidence of other malignancies (excluding non-melanoma skin cancer) is relatively low. Based on available data, other malignancies have not been identified as an adverse reaction in the SmPC. Overall, the risk-benefit balance is positive for the product considering the severity of the diseases treated and the established efficacy and safety profile of ibrutinib.

Public Health Impact:

In consideration of the relatively small number of patients in the targeted populations and the relatively small number of serious or severe events of other malignancies reported with ibrutinib therapy, the impact on public health is expected to be low.

Annex 1 MedDRA Term:

Malignant tumours (SMQ narrow)

SVII.3.2. Presentation of the Missing Information

Missing information: Use in patients with severe cardiac disease
Evidence source: The subjects in the clinical trials included older subjects with multiple pre-existing CVD. However, patients with severe cardiac diseases (eg, New York Heart Association class III or higher) were excluded from ibrutinib clinical trials.
Population in need of further characterization: For the use of ibrutinib in patients with severe cardiac disease, a risk cannot be defined based upon currently available evidence.

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1: Summary of Safety Concerns

Important identified risks	Hemorrhage
	Hepatotoxicity (including hepatic failure)
	Atrial fibrillation
	Ventricular tachyarrhythmias
	Hypertension
	Ischemic stroke
	Cardiac failure
	Infections (including viral reactivation)
Important potential risks	Progressive multifocal leukoencephalopathy (PML)
	Cardiac arrhythmia (excluding atrial fibrillation and ventricular tachyarrhythmias)
	Other malignancies (excluding non-melanoma skin cancer)
Missing information	Use in patients with severe cardiac disease

PART III: PHARMACOVIGILANCE PLAN (Including Postauthorization Safety Studies)

III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

Specific Follow-up Questionnaires for Safety Concerns

Safety Concern	Purpose/Description
Hemorrhage	Targeted follow-up of AEs through a guided questionnaire.
Hepatotoxicity (including hepatic failure)	Targeted follow-up of AEs through a guided questionnaire.
Ischemic stroke	Targeted follow-up of AEs through a guided questionnaire.
Cardiac failure	Targeted follow-up of AEs through a guided questionnaire.
Progressive multifocal leukoencephalopathy (PML)	Targeted follow-up of AEs through a guided questionnaire.
Cardiac arrhythmia (excluding atrial fibrillation and ventricular tachyarrhythmias)	Targeted follow-up of AEs through a guided questionnaire.

Other Forms of Routine Pharmacovigilance Activities

Activity	Objective/Description	Milestones
None.		

III.2. Additional Pharmacovigilance Activities

Additional Pharmacovigilance Activities

Analysis of aggregate randomized controlled clinical trial data

Study name and title	Additional pharmacovigilance study to further evaluate the risk of hemorrhage in subjects receiving ibrutinib and concomitant anticoagulant and/or antiplatelet drugs
Rationale and study objectives	Rationale: To perform an analysis of randomized controlled clinical trial data to further understand the risk of major hemorrhage in subjects receiving ibrutinib and concomitant vitamin K antagonists with or without antiplatelet drugs Objective: To further evaluate the risk of major hemorrhage in subjects receiving ibrutinib and concomitant vitamin K antagonists with or without antiplatelet drugs
Safety concern addressed	Hemorrhage
Study design	Analysis of aggregate data from randomized controlled clinical trials
Study population	Subjects in randomized controlled clinical trials
Milestones	Final report: 4th Quarter 2024

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Analysis of aggregate randomized controlled clinical trial data Planned	To further evaluate the risk of major hemorrhage in subjects receiving ibrutinib and concomitant vitamin K antagonists with or without antiplatelet drugs	Hemorrhage	Final report	4th Quarter 2024

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Table Part IV.1: Planned and Ongoing Postauthorization Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Efficacy Studies which are conditions of the marketing authorizations				
Not applicable				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				

PART V: RISK MINIMIZATION MEASURES (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Hemorrhage	**Routine risk communication:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Warning not to use warfarin or other vitamin K antagonists concomitantly with ibrutinib, to avoid supplements such as fish oil and vitamin E, advice on use of ibrutinib in patients requiring other anticoagulants or medicinal products that inhibit platelet function, and advice on use pre- and post-surgery is provided in SmPC Section 4.4 • Warning for patients with prior unusual bruising or bleeding and advice on concomitant use of medicines that increase the risk of bleeding is provided in PL Section 2 **Other routine risk minimization measures beyond the Product Information:** • Legal status: restricted medical prescription
Hepatotoxicity (including hepatic failure)	**Routine risk communication:** • SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 4.9 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendations regarding assessment of liver function and viral hepatitis status prior to ibrutinib initiation and periodic monitoring for changes in liver function parameters during treatment are provided in SmPC Section 4.4 • A recommendation for patients diagnosed with hepatic events regarding consultation of a liver disease expert for management is provided in SmPC Section 4.4

Safety Concern	Routine Risk Minimization Activities
	• Warning for patients who have liver problems is provided in PL Section 2 **Other routine risk minimization measures beyond the Product Information:** • Legal status: restricted medical prescription
Atrial fibrillation	**Routine risk communication:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendations regarding clinical evaluation of cardiac history and function prior to ibrutinib initiation, monitoring during treatment for signs of clinical deterioration of cardiac function and clinical management are provided in SmPC Section 4.4 • A recommendation regarding further evaluation (eg, ECG, echocardiogram) for patients in whom there are cardiovascular concerns is provided in SmPC Section 4.4 • A recommendation for careful assessment of the benefit/risk before initiating treatment with ibrutinib in patients with relevant risk factors for cardiac events, including consideration of alternative treatment, is provided in SmPC Section 4.4 • Recommendations regarding monitoring and management of patients with pre-existing atrial fibrillation requiring anticoagulant therapy, and of patients who develop atrial fibrillation on therapy with ibrutinib are provided in SmPC Section 4.4 • Advice for patients experiencing (a history of) irregular heart beat is provided in PL Section 2 **Other routine risk minimization measures beyond the Product Information:** • Legal status: restricted medical prescription

Safety Concern	Routine Risk Minimization Activities
Ventricular tachyarrhythmias	**Routine risk communication:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendations regarding clinical evaluation of cardiac history and function prior to ibrutinib initiation, monitoring during treatment for signs of clinical deterioration of cardiac function and clinical management are provided in SmPC Section 4.4 • A recommendation regarding further evaluation (eg, ECG, echocardiogram) for patients in whom there are cardiovascular concerns is provided in SmPC Section 4.4 • A recommendation for careful assessment of the benefit/risk before initiating treatment with ibrutinib in patients with relevant risk factors for cardiac events, including consideration of alternative treatment, is provided in SmPC Section 4.4 • Recommendations regarding monitoring and management of patients who develop signs and/or symptoms of ventricular tachyarrhythmia (including treatment interruption) are provided in SmPC Section 4.4 • Warning for patients with (history of) irregular heart beat is provided in PL Section 2 **Other routine risk minimization measures beyond the Product Information:** • Legal status: restricted medical prescription

Safety Concern	Routine Risk Minimization Activities
Hypertension	**Routine risk communication:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendations regarding blood pressure monitoring and management of patients with hypertension are provided in SmPC Section 4.4 • Advice for patients having high blood pressure is provided in PL Section 2 **Other routine risk minimization measures beyond the Product Information:** • Legal status: restricted medical prescription
Ischemic stroke	**Routine risk communication:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Signs and symptoms of stroke are provided in PL Section 2 **Other routine risk minimization measures beyond the Product Information:** • Legal status: restricted medical prescription

Safety Concern	Routine Risk Minimization Activities
Cardiac failure	**Routine risk communication:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendations regarding clinical evaluation of cardiac history and function prior to ibrutinib initiation, monitoring during treatment for signs of clinical deterioration of cardiac function and clinical management are provided in SmPC Section 4.4 • A recommendation regarding further evaluation (eg, ECG, echocardiogram) for patients in whom there are cardiovascular concerns is provided in SmPC Section 4.4 • A recommendation for careful assessment of the benefit/risk before initiating treatment with ibrutinib in patients with relevant risk factors for cardiac events, including consideration of alternative treatment, is provided in SmPC Section 4.4 • Recommendations regarding monitoring and management of patients who develop signs and symptoms of cardiac failure are provided in SmPC Section 4.4 • Instructions and criteria for ibrutinib treatment interruption, dose modification, and treatment discontinuation in patients who develop grade 2 or higher cardiac failure are provided in SmPC Section 4.2 • Warning for patients with a history of severe heart failure or with signs and symptoms of heart failure are provided in PL Section 2 **Other routine risk minimization measures beyond the Product Information:** • Legal status: restricted medical prescription

Safety Concern	Routine Risk Minimization Activities
Infections (including viral reactivation)	**Routine risk communication:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendations regarding preventive measures in patients who are at increased risk for opportunistic infections and for monitoring and management of infections are provided in SmPC Section 4.4 • A recommendation regarding viral load and serological testing for infectious hepatitis is provided in SmPC Section 4.4 • Warning for patients who had or have a hepatitis B infection is provided in PL Section 2 **Other routine risk minimization measures beyond the Product Information:** • Legal status: restricted medical prescription
Progressive multifocal leukoencephalopathy (PML)	**Routine risk communication:** • SmPC Section 4.4 • PL Section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendations regarding management of patients with suspected PML are provided in SmPC Section 4.4 • Signs and symptoms of PML are provided in PL Section 2 **Other routine risk minimization measures beyond the Product Information:** • Legal status: restricted medical prescription

Safety Concern	Routine Risk Minimization Activities
Cardiac arrhythmia (excluding atrial fibrillation and ventricular tachyarrhythmias)	**Routine risk communication:** • SmPC Section 4.4 • SmPC Section 5.1 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendations regarding clinical evaluation of cardiac history and function prior to ibrutinib initiation, monitoring during treatment for signs of clinical deterioration of cardiac function and clinical management are provided in SmPC Section 4.4 • A recommendation regarding further evaluation (eg, ECG, echocardiogram) for patients in whom there are cardiovascular concerns is provided in SmPC Section 4.4 • A recommendation for careful assessment of the benefit/risk before initiating treatment with ibrutinib in patients with relevant risk factors for cardiac events, including consideration of alternative treatment, is provided in SmPC Section 4.4 • Instructions and criteria for ibrutinib treatment interruption, dose modification, and treatment discontinuation in patients who develop grade 3 or higher cardiac arrhythmias are provided in SmPC Section 4.2 • Warning for patients with (history of) irregular heart beat is provided in PL Section 2 **Other routine risk minimization measures beyond the Product Information:** • Legal status: restricted medical prescription
Other malignancies (excluding non-melanoma skin cancer)	**Other routine risk minimization measures beyond the Product Information:** • Legal status: restricted medical prescription

Safety Concern	Routine Risk Minimization Activities
Use in patients with severe cardiac disease	**Routine risk communication:** • SmPC Section 4.2 • SmPC Section 4.4 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendations regarding clinical evaluation of cardiac history and function prior to ibrutinib initiation, monitoring during treatment for signs of clinical deterioration of cardiac function and clinical management are provided in SmPC Section 4.4 • A recommendation regarding further evaluation (eg, ECG, echocardiogram) for patients in whom there are cardiovascular concerns is provided in SmPC Section 4.4 • A recommendation for careful assessment of the benefit/risk before initiating treatment with ibrutinib in patients with relevant risk factors for cardiac events, including consideration of alternative treatment, is provided in SmPC Section 4.4 • Recommendations regarding monitoring and management of patients who develop signs and/or symptoms of ventricular tachyarrhythmia (including treatment interruption) are provided in SmPC Section 4.4 • Recommendations regarding monitoring and management of patients with pre-existing atrial fibrillation requiring anticoagulant therapy, and of patients who develop atrial fibrillation on therapy with ibrutinib are provided in SmPC Section 4.4 • Warning for patients having severe heart failure is provided in PL Section 2 **Other routine risk minimization measures beyond the Product Information:** • Legal status: restricted medical prescription

V.2. Additional Risk Minimization Measures

Additional Risk Minimization Activity 1 A Direct Healthcare Professional Communication (DHPC) will be distributed in EU Member States	
Objective(s):	The aim of this DHPC is to increase awareness of the following important risks associated with the use of ibrutinib and to provide guidance on how to manage these risks: <u>Important identified risks</u> • Atrial fibrillation • Ventricular tachyarrhythmias • Cardiac failure <u>Important potential risks</u> • Cardiac arrhythmia (excluding atrial fibrillation and ventricular tachyarrhythmias) <u>Missing information</u> • Use in patients with severe cardiac disease
Rationale for the additional risk minimization activity:	The rationale of this DHPC is to inform prescribers of important cardiac risks associated with the use of ibrutinib, provide background and recommendations on how to manage these risks, and to direct the prescriber's attention to follow the new dose modification guidelines for patients with new onset or worsening cardiac arrhythmia or cardiac failure.
Target audience and planned distribution path:	Hematologists, oncologists, cardiologists, and any other relevant target groups like hospital pharmacists as agreed at national level.
Plans to evaluate the effectiveness of the interventions and criteria for success:	Routine pharmacovigilance surveillance systems are used to detect safety signals based on AE reporting rates and trends. In addition, reporting trend analyses from postmarketing safety data are monitored in the Periodic Benefit Risk Evaluation Report (PBRER)/Periodic Safety Update Report (PSUR). Assessments are conducted at the end of each PBRER/PSUR reporting interval. Stable or declined AE reporting rates and trends from the postmarketing safety data are the criteria for success.

V.2.1. Removal of Additional Risk Minimization Activities

Not applicable.

V.3. Summary of Risk Minimization Measures and Pharmacovigilance Activities

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Hemorrhage	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Warning not to use warfarin or other vitamin K antagonists concomitantly with ibrutinib, to avoid supplements such as fish oil and vitamin E, advice on use of ibrutinib in patients requiring other anticoagulants or medicinal products that inhibit platelet function, and advice on use pre- and post-surgery is provided in SmPC Section 4.4 • Warning for patients with prior unusual bruising or bleeding and advice on concomitant use of medicines that increase the risk of bleeding is provided in PL Section 2 • Legal status: restricted medical prescription **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Targeted follow-up of AEs through a guided questionnaire **Additional pharmacovigilance activities:** • Analysis of aggregate randomized controlled clinical trial data Final report: 4th Quarter 2024

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Hepatotoxicity (including hepatic failure)	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 4.9 • PL Section 2 • PL Section 4 • Recommendations regarding assessment of liver function and viral hepatitis status prior to ibrutinib initiation and periodic monitoring for changes in liver function parameters during treatment are provided in SmPC Section 4.4 • A recommendation for patients diagnosed with hepatic events regarding consultation of a liver disease expert for management is provided in SmPC Section 4.4 • Warning for patients who have liver problems is provided in PL Section 2 • Legal status: restricted medical prescription **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Targeted follow-up of AEs through a guided questionnaire **Additional pharmacovigilance activities:** • None

Atrial fibrillation	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendations regarding clinical evaluation of cardiac history and function prior to ibrutinib initiation, monitoring during treatment for signs of clinical deterioration of cardiac function and clinical management are provided in SmPC Section 4.4 • A recommendation regarding further evaluation (eg, ECG, echocardiogram) for patients in whom there are cardiovascular concerns is provided in SmPC Section 4.4 • A recommendation for careful assessment of the benefit/risk before initiating treatment with ibrutinib in patients with relevant risk factors for cardiac events, including consideration of alternative treatment, is provided in SmPC Section 4.4 • Recommendations regarding monitoring and management of patients with pre-existing atrial fibrillation requiring anticoagulant therapy, and of patients who develop atrial fibrillation on therapy with ibrutinib are provided in SmPC Section 4.4 • Advice for patients experiencing (a history of) irregular heart beat is provided in PL Section 2	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• Legal status: restricted medical prescription **Additional risk minimization measures:** • DHPC to inform prescribers of important cardiac risks associated with the use of ibrutinib, provide background and recommendations on how to manage these risks, and to direct the prescriber's attention to follow the new dose modification guidelines for patients with new onset or worsening cardiac arrhythmia or cardiac failure	
Ventricular tachyarrhythmias	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendations regarding clinical evaluation of cardiac history and function prior to ibrutinib initiation, monitoring during treatment for signs of clinical deterioration of cardiac function and clinical management are provided in SmPC Section 4.4 • A recommendation regarding further evaluation (eg, ECG, echocardiogram) for patients in whom there are cardiovascular concerns is provided in SmPC Section 4.4 • A recommendation for careful assessment of the benefit/risk before initiating treatment with ibrutinib in patients with relevant risk factors for cardiac events, including consideration of alternative treatment, is provided in	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	SmPC Section 4.4 • Recommendations regarding monitoring and management of patients who develop signs and/or symptoms of ventricular tachyarrhythmia (including treatment interruption) are provided in SmPC Section 4.4 • Warning for patients with (history of) irregular heart beat is provided in PL Section 2 • Legal status: restricted medical prescription **Additional risk minimization measures:** • DHPC to inform prescribers of important cardiac risks associated with the use of ibrutinib, provide background and recommendations on how to manage these risks, and to direct the prescriber's attention to follow the new dose modification guidelines for patients with new onset or worsening cardiac arrhythmia or cardiac failure	

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Hypertension	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendations regarding blood pressure monitoring and management of patients with hypertension are provided in SmPC Section 4.4 • Advice for patients having high blood pressure is provided in PL Section 2 • Legal status: restricted medical prescription **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None
Ischemic stroke	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Signs and symptoms of stroke are provided in PL Section 2 • Legal status: restricted medical prescription **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Targeted follow-up of AEs through a guided questionnaire **Additional pharmacovigilance activities:** • None

Cardiac failure	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendations regarding clinical evaluation of cardiac history and function prior to ibrutinib initiation, monitoring during treatment for signs of clinical deterioration of cardiac function and clinical management are provided in SmPC Section 4.4 • A recommendation regarding further evaluation (eg, ECG, echocardiogram) for patients in whom there are cardiovascular concerns is provided in SmPC Section 4.4 • A recommendation for careful assessment of the benefit/risk before initiating treatment with ibrutinib in patients with relevant risk factors for cardiac events, including consideration of alternative treatment, is provided in SmPC Section 4.4 • Recommendations regarding monitoring and management of patients who develop signs and symptoms of cardiac failure are provided in SmPC Section 4.4 • Instructions and criteria for ibrutinib treatment interruption, dose modification, and treatment discontinuation in patients who develop grade 2 or higher cardiac failure are provided in SmPC Section 4.2 • Warning for patients with a history of severe heart failure or with signs and symptoms	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Targeted follow-up of AEs through a guided questionnaire **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	of heart failure are provided in PL Section 2 • Legal status: restricted medical prescription **Additional risk minimization measures:** • DHPC to inform prescribers of important cardiac risks associated with the use of ibrutinib, provide background and recommendations on how to manage these risks, and to direct the prescriber's attention to follow the new dose modification guidelines for patients with new onset or worsening cardiac arrhythmia or cardiac failure	

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Infections (including viral reactivation)	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendations regarding preventive measures in patients who are at increased risk for opportunistic infections and for monitoring and management of infections are provided in SmPC Section 4.4 • A recommendation regarding viral load and serological testing for infectious hepatitis is provided in SmPC Section 4.4 • Warning for patients who had or have a hepatitis B infection is provided in PL Section 2 • Legal status: restricted medical prescription **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Progressive multifocal leukoencephalopathy (PML)	**Routine risk minimization measures:** • SmPC Section 4.4 • PL Section 2 • Recommendations regarding management of patients with suspected PML are provided in SmPC Section 4.4 • Signs and symptoms of PML are provided in PL Section 2 • Legal status: restricted medical prescription **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Targeted follow-up of AEs through a guided questionnaire for PML **Additional pharmacovigilance activities:** • None
Cardiac arrhythmia (excluding atrial fibrillation and ventricular tachyarrhythmias)	**Routine risk minimization measures:** • SmPC Section 4.4 • SmPC Section 5.1 • PL Section 2 • PL Section 4 • Recommendations regarding clinical evaluation of cardiac history and function prior to ibrutinib initiation, monitoring during treatment for signs of clinical deterioration of cardiac function and clinical management are provided in SmPC Section 4.4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • Targeted follow-up of AEs through a guided questionnaire **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• A recommendation regarding further evaluation (eg, ECG, echocardiogram) for patients in whom there are cardiovascular concerns is provided in SmPC Section 4.4 • A recommendation for careful assessment of the benefit/risk before initiating treatment with ibrutinib in patients with relevant risk factors for cardiac events, including consideration of alternative treatment, is provided in SmPC Section 4.4 • Instructions and criteria for ibrutinib treatment interruption, dose modification, and treatment discontinuation in patients who develop grade 3 or higher cardiac arrhythmias are provided in SmPC Section 4.2 • Warning for patients with (history of) irregular heart beat is provided in PL Section 2 • Legal status: restricted medical prescription **Additional risk minimization measures:** • DHPC to inform prescribers of important cardiac risks associated with the use of ibrutinib, provide background and recommendations on how to manage these risks, and to direct the prescriber's attention to follow the new dose modification guidelines for patients with new onset or worsening cardiac arrhythmia or cardiac failure	

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Other malignancies (excluding non-melanoma skin cancer)	**Routine risk minimization measures:** • Legal status: restricted medical prescription **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None
Use in patients with severe cardiac disease	**Routine risk minimization measures:** • SmPC Section 4.2 • SmPC Section 4.4 • PL Section 2 • PL Section 4 • Recommendations regarding clinical evaluation of cardiac history and function prior to ibrutinib initiation, monitoring during treatment for signs of clinical deterioration of cardiac function and clinical management are provided in SmPC Section 4.4 • A recommendation regarding further evaluation (eg, ECG, echocardiogram) for patients in whom there are cardiovascular concerns is provided in SmPC Section 4.4 • A recommendation for careful assessment of the benefit/risk before initiating treatment with ibrutinib in patients with relevant risk factors for cardiac events, including consideration of alternative treatment, is provided in SmPC Section 4.4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• Recommendations regarding monitoring and management of patients who develop signs and/or symptoms of ventricular tachyarrhythmia (including treatment interruption) are provided in SmPC Section 4.4 • Recommendations regarding monitoring and management of patients with pre-existing atrial fibrillation requiring anticoagulant therapy, and of patients who develop atrial fibrillation on therapy with ibrutinib are provided in SmPC Section 4.4 • Warning for patients having severe heart failure is provided in PL Section 2 • Legal status: restricted medical prescription **Additional risk minimization measures:** • DHPC to inform prescribers of important cardiac risks associated with the use of ibrutinib, provide background and recommendations on how to manage these risks, and to direct the prescriber's attention to follow the new dose modification guidelines for patients with new onset or worsening cardiac arrhythmia or cardiac failure.	

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for IMBRUVICA (ibrutinib)

This is a summary of the risk management plan (RMP) for IMBRUVICA. The RMP details important risks of IMBRUVICA, how these risks can be minimized, and how more information will be obtained about IMBRUVICA's risks and uncertainties (missing information).

IMBRUVICA's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals (HCPs) and patients on how IMBRUVICA should be used.

This summary of the RMP for IMBRUVICA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report.

Important new concerns or changes to the current ones will be included in updates of IMBRUVICA's RMP.

I. The Medicine and What it is Used For

IMBRUVICA is authorized for treatment of adult patients with chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), or Waldenström's macroglobulinemia (WM) (see SmPC for the full indications). It contains ibrutinib as the active substance and it is given as 140 mg capsules or as immediate release film-coated tablets for oral administration (140, 280, 420, and 560 mg).

Further information about the evaluation of IMBRUVICA's benefits can be found in IMBRUVICA's European Public Assessment Report, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/imbruvica

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of IMBRUVICA, together with measures to minimize such risks and the proposed studies for learning more about IMBRUVICA's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;

- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Benefit Risk Evaluation Report/Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of IMBRUVICA is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of IMBRUVICA are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of IMBRUVICA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	Hemorrhage Hepatotoxicity (including hepatic failure) Atrial fibrillation Ventricular tachyarrhythmias Hypertension Ischemic stroke Cardiac failure Infections (including viral reactivation)
Important potential risks	Progressive multifocal leukoencephalopathy (PML) Cardiac arrhythmia (excluding atrial fibrillation and ventricular tachyarrhythmias) Other malignancies (excluding non-melanoma skin cancer)
Missing information	Use in patients with severe cardiac disease

II.B. Summary of Important Risks

Important Identified Risk: Hemorrhage	
Evidence for linking the risk to the medicine	Cases of hemorrhagic events in association with ibrutinib have been reported in completed clinical trials. These events, in addition to recommendations for patients requiring anticoagulants or medication that inhibits platelet function, are also described in the current prescribing information for ibrutinib.
Risk factors and risk groups	Predictors include increasing age (>60 years), history of bleeding, dose of chemotherapy, baseline platelet count, poor performance and/or nutritional status, and concomitant use of antiplatelet or anticoagulant therapy, especially warfarin use in the elderly population.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Warning not to use warfarin or other vitamin K antagonists concomitantly with ibrutinib, to avoid supplements such as fish oil and vitamin E, advice on use of ibrutinib in patients requiring other anticoagulants or medicinal products that inhibit platelet function, and advice on use pre- and post-surgery is provided in SmPC Section 4.4 • Warning for patients with prior unusual bruising or bleeding and advice on concomitant use of medicines that increase the risk of bleeding is provided in PL Section 2 • Legal status: restricted medical prescription Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • Analysis of aggregate randomized controlled clinical trial data Final report: 4th Quarter 2024 See Section II.C of this summary for an overview of the post-authorization development plan.

Important Identified Risk: Hepatotoxicity (including hepatic failure)	
Evidence for linking the risk to the medicine	A grade 4 hepatic enzyme elevation in association with ibrutinib has been observed in a healthy volunteer in a clinical trial. Hepatic failure has been identified as an adverse reaction during postmarketing experience. These events are described in the current prescribing information for ibrutinib.
Risk factors and risk groups	Risk factors for drug-induced liver toxicity include increasing age, human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome infection and antiretroviral drug use, chronic hepatitis B virus or hepatitis C virus infection, obesity, and nonalcoholic fatty liver disease. Patients taking other anti-cancer agents, anti-infectives, psychotropics, lipid-lowering agents, herbal and dietary supplements, and nonsteroidal anti-inflammatory drugs are also at risk.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 4.9 • PL Section 2 • PL Section 4 • Recommendations regarding assessment of liver function and viral hepatitis status prior to ibrutinib initiation and periodic monitoring for changes in liver function parameters during treatment are provided in SmPC Section 4.4 • A recommendation for patients diagnosed with hepatic events regarding consultation of a liver disease expert for management is provided in SmPC Section 4.4 • Warning for patients who have liver problems is provided in PL Section 2 • Legal status: restricted medical prescription Additional risk minimization measures: • None

Important Identified Risk: Atrial fibrillation	
Evidence for linking the risk to the medicine	Cases of atrial fibrillation in association with ibrutinib have been reported in completed clinical trials (particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation), and are also described in the current prescribing information for ibrutinib.
Risk factors and risk groups	Atrial fibrillation is more common in men than women. Other risk factors for atrial fibrillation include advanced age, hypertension and other cardiac conditions, obesity and metabolic syndrome. There are also indications that individuals of white European descent have a higher risk of atrial fibrillation compared with individuals of other races. Specifically, among CLL patients, a Mayo Clinic study observed that increased risk of incident atrial fibrillation was associated with older age, male sex, valvular heart disease, and hypertension in multivariable analysis.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendations regarding clinical evaluation of cardiac history and function prior to ibrutinib initiation, monitoring during treatment for signs of clinical deterioration of cardiac function and clinical management are provided in SmPC Section 4.4 • A recommendation regarding further evaluation (eg, ECG, echocardiogram) for patients in whom there are cardiovascular concerns is provided in SmPC Section 4.4 • A recommendation for careful assessment of the benefit/risk before initiating treatment with ibrutinib in patients with relevant risk factors for cardiac events, including consideration of alternative treatment, is provided in SmPC Section 4.4 • Recommendations regarding monitoring and management of patients with pre-existing atrial fibrillation requiring anticoagulant therapy, and of patients who develop atrial fibrillation on therapy with ibrutinib are provided in SmPC Section 4.4 • Advice for patients experiencing (a history of) irregular heart beat is provided in PL Section 2 • Legal status: restricted medical prescription

	Additional risk minimization measures: • DHPC to inform prescribers of important cardiac risks associated with the use of ibrutinib, provide background and recommendations on how to manage these risks, and to direct the prescriber's attention to follow the new dose modification guidelines for patients with new onset or worsening cardiac arrhythmia or cardiac failure

Important Identified Risk: Ventricular tachyarrhythmias	
Evidence for linking the risk to the medicine	Cases of ventricular tachyarrhythmia in association with ibrutinib have been reported in completed clinical trials. Ventricular tachyarrhythmia has been included as an adverse reaction in the SmPC. These events are described in the current prescribing information for ibrutinib.
Risk factors and risk groups	Ventricular tachyarrhythmias are common in older people. Risk factors include myocardial infarction, heart failure or cardiomyopathy, cardiac hypertrophy, incompetent or stenotic heart valves, or congenital heart defects. Risk can also be increased if the patient has hypertension, myocarditis, pericarditis, diabetes mellitus, sleep apnea, electrolyte imbalance (eg, hyperkalemia and hypomagnesemia), hypothyroidism, or hyperthyroidism.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendations regarding clinical evaluation of cardiac history and function prior to ibrutinib initiation, monitoring during treatment for signs of clinical deterioration of cardiac function and clinical management are provided in SmPC Section 4.4 • A recommendation regarding further evaluation (eg, ECG, echocardiogram) for patients in whom there are cardiovascular concerns is provided in SmPC Section 4.4 • A recommendation for careful assessment of the benefit/risk before initiating treatment with ibrutinib in patients with relevant risk factors for cardiac events, including consideration of alternative treatment, is provided in SmPC Section 4.4 • Recommendations regarding monitoring and management of patients who develop signs and/or symptoms of ventricular tachyarrhythmia (including treatment interruption) are provided in SmPC Section 4.4 • Warning for patients with (history of) irregular heart beat is provided in PL Section 2

	• Legal status: restricted medical prescription Additional risk minimization measures: • DHPC to inform prescribers of important cardiac risks associated with the use of ibrutinib, provide background and recommendations on how to manage these risks, and to direct the prescriber's attention to follow the new dose modification guidelines for patients with new onset or worsening cardiac arrhythmia or cardiac failure

Important Identified Risk: Hypertension	
Evidence for linking the risk to the medicine	Hypertension has been identified as an adverse reaction associated with ibrutinib.
Risk factors and risk groups	Risk factors for hypertension include increasing age, black race, family history of hypertension, being overweight or obese, physical inactivity, tobacco use, excess salt (sodium) in diet, too little potassium and vitamin D in diet, excess alcohol use, and stress.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendations regarding blood pressure monitoring and management of patients with hypertension are provided in SmPC Section 4.4 • Advice for patients having high blood pressure is provided in PL Section 2 • Legal status: restricted medical prescription Additional risk minimization measures: • None

Important Identified Risk: Ischemic stroke	
Evidence for linking the risk to the medicine	Cases of ischemic stroke in association with ibrutinib have been reported in completed clinical trials. Cerebrovascular accident, transient ischemic attack, and ischemic stroke have been included as adverse reactions in the SmPC, based on the Pharmacovigilance Risk Assessment Committee (PRAC) assessment of the signal evaluation of ischemic stroke conducted by the Marketing Authorization Holder, considering the established cardiac risks of atrial fibrillation and hypertension associated with ibrutinib administration. Although, from a direct mechanism standpoint and based on available data, causality between stroke and treatment with ibrutinib has not been established, ischemic stroke was added to the European Union Risk Management Plan as an important identified risk as requested by PRAC, in conjunction with the addition of ischemic stroke to Sections 4.4 and 4.8 of the SmPC.
Risk factors and risk groups	The most frequent causes of ischemic stroke in cancer patients are cerebrovascular risk factors such as hypertension, hyperlipidemia, diabetes, atrial fibrillation, and tobacco use. Additionally, patients receiving treatment with ibrutinib are mostly elderly and most strokes occur in people aged >65 years.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Signs and symptoms of stroke are provided in PL Section 2 • Legal status: restricted medical prescription Additional risk minimization measures: • None

Important Identified Risk: Cardiac failure	
Evidence for linking the risk to the medicine	Cases of cardiac failure in association with ibrutinib have been reported in completed clinical trials. Although no direct causal association between ibrutinib and cardiac failure was established, based on the number of cardiac failure cases from the postmarketing setting and the known association between ibrutinib and atrial fibrillation (a risk factor that could lead to reduced cardiac output), cardiac failure has been included as an adverse reaction in the SmPC.

Risk factors and risk groups	Patients with known cardiac risk factors (eg, age 65 years or older, diabetes mellitus, hyperlipidemia, chronic kidney disease, hypertension, smoking), pre-existing heart disease, acute severe infection, and a previous history of cardiotoxic cancer therapy, such as anthracyclines, are at higher risk for developing cardiac failure. Concomitant atrial fibrillation is a risk factor that could lead to reduced cardiac output. African Americans and South Asians are ethnic groups with higher risk.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendations regarding clinical evaluation of cardiac history and function prior to ibrutinib initiation, monitoring during treatment for signs of clinical deterioration of cardiac function and clinical management are provided in SmPC Section 4.4 • A recommendation regarding further evaluation (eg, ECG, echocardiogram) for patients in whom there are cardiovascular concerns is provided in SmPC Section 4.4 • A recommendation for careful assessment of the benefit/risk before initiating treatment with ibrutinib in patients with relevant risk factors for cardiac events, including consideration of alternative treatment, is provided in SmPC Section 4.4 • Recommendations regarding monitoring and management of patients who develop signs and symptoms of cardiac failure are provided in SmPC Section 4.4 • Instructions and criteria for ibrutinib treatment interruption, dose modification, and treatment discontinuation in patients who develop grade 2 or higher cardiac failure are provided in SmPC Section 4.2 • Warning for patients with a history of severe heart failure or with signs and symptoms of heart failure are provided in PL Section 2 • Legal status: restricted medical prescription Additional risk minimization measures: • DHPC to inform prescribers of important cardiac risks associated with the use of ibrutinib, provide background and recommendations on how to manage these risks, and to direct the prescriber's attention to follow the new dose modification guidelines for patients with new onset or worsening cardiac arrhythmia or cardiac failure

Important Identified Risk: Infections (including viral reactivation)	
Evidence for linking the risk to the medicine	Cases of infections (including sepsis, neutropenic sepsis, bacterial, viral, or fungal infection) in association with ibrutinib have been reported in completed clinical trials and are also described in the current prescribing information for ibrutinib.
Risk factors and risk groups	Predictors include increasing age (>60 years), underlying immunosuppression that is inherent to the primary disease process, therapy-related immunosuppression, concomitant chemotherapy, absence of antibiotic prophylaxis, and poor performance and/or nutritional status.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendations regarding preventive measures in patients who are at increased risk for opportunistic infections and for monitoring and management of infections are provided in SmPC Section 4.4 • A recommendation regarding viral load and serological testing for infectious hepatitis is provided in SmPC Section 4.4 • Warning for patients who had or have a hepatitis B infection is provided in PL Section 2 • Legal status: restricted medical prescription Additional risk minimization measures: • None

Important Potential Risk: Progressive multifocal leukoencephalopathy (PML)	
Evidence for linking the risk to the medicine	Cases of PML (within the context of a prior or concomitant immunosuppressive therapy) in association with ibrutinib have been reported in completed clinical trials and during postmarketing experience, and are also described in the current prescribing information for ibrutinib. PML has not been identified as an adverse reaction.
Risk factors and risk groups	PML is a demyelinating disorder of the central nervous system, caused by the reactivation of the commonly occurring John Cunningham virus, which remains inactive in healthy individuals, and causes disease only when the immune system has been compromised. PML usually occurs during severe immunosuppression and the most common causes are represented by HIV infection, lymphoproliferative disorders, and other forms of cancer. The use of monoclonal antibodies (eg, natalizumab, rituximab, efalizumab) in the treatment of several dysimmune diseases such as multiple sclerosis, rheumatoid arthritis, psoriasis, and systemic lupus erythematosus, has led to an increased incidence of PML. Chemotherapy and immunosuppressive therapy are considered to be the primary risk factors in addition to HIV infection. In one analysis, 3 significant risk factors for developing PML in CLL patients were identified: age (>55 years), male sex, and CD4 cell count <200 cells/µL. A retrospective, monocentric cohort study of 976 non-Hodgkin's lymphoma patients, including 517 patients who received at least one dose of rituximab, concluded that the inclusion of rituximab into standard chemotherapy regimens for non-Hodgkin's lymphoma caused a significantly higher incidence of PML cases (rate difference: 2.2 every 1,000 patient-years; 95% confidence interval: 0.1-4.3).
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • PL Section 2 • Recommendations regarding management of patients with suspected PML are provided in SmPC Section 4.4 • Signs and symptoms of PML are provided in PL Section 2 • Legal status: restricted medical prescription Additional risk minimization measures: • None

Important Potential Risk: Cardiac arrhythmia (excluding atrial fibrillation and ventricular tachyarrhythmias)	
Evidence for linking the risk to the medicine	Cases of cardiac arrhythmia in association with ibrutinib have been reported in completed clinical trials, and are also described in the current prescribing information for ibrutinib.
Risk factors and risk groups	Arrhythmias are common in older people. Risk factors include myocardial infarction, heart failure or cardiomyopathy, cardiac hypertrophy, incompetent or stenotic heart valves, or congenital heart defects. Risk can also be increased if the patient has hypertension, myocarditis, pericarditis, diabetes mellitus, sleep apnea, electrolyte imbalance (eg, hyperkalemia and hypomagnesemia), hypothyroidism, or hyperthyroidism.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 5.1 • PL Section 2 • PL Section 4 • Recommendations regarding clinical evaluation of cardiac history and function prior to ibrutinib initiation, monitoring during treatment for signs of clinical deterioration of cardiac function and clinical management are provided in SmPC Section 4.4 • A recommendation regarding further evaluation (eg, ECG, echocardiogram) for patients in whom there are cardiovascular concerns is provided in SmPC Section 4.4 • A recommendation for careful assessment of the benefit/risk before initiating treatment with ibrutinib in patients with relevant risk factors for cardiac events, including consideration of alternative treatment, is provided in SmPC Section 4.4 • Instructions and criteria for ibrutinib treatment interruption, dose modification, and treatment discontinuation in patients who develop grade 3 or higher cardiac arrhythmias are provided in SmPC Section 4.2 • Warning for patients with (history of) irregular heart beat is provided in PL Section 2 • Legal status: restricted medical prescription Additional risk minimization measures: • DHPC to inform prescribers of important cardiac risks associated with the use of ibrutinib, provide background and recommendations on how to manage these risks, and to direct the prescriber's attention to follow the new dose modification guidelines for patients with new onset or worsening cardiac arrhythmia or cardiac failure

Important Potential Risk: Other malignancies (excluding non-melanoma skin cancer)	
Evidence for linking the risk to the medicine	Cases of other malignancies (including solid tumors and hematologic tumors) in association with ibrutinib have been reported in ongoing and completed clinical trials. Other malignancies has not been identified as an adverse reaction.
Risk factors and risk groups	The chance of developing a second cancer depends on a number of factors including type of primary cancer, age at diagnosis, sex, types of therapy given, environmental exposures, genetic predisposition, and health decisions. Radiation has long been associated with the development of primary cancers and, when used as treatment, imparts a risk for the development of a second cancer. Leukemia as a second primary cancer can occur following treatment with chemotherapy. Although acute myelogenous leukemia is the most common type of therapy-related leukemia, acute lymphocytic leukemia, chronic myelogenous leukemia, and myelodysplastic syndrome have also been reported. Chemotherapy-induced myeloid leukemias are relatively resistant to subsequent therapy and have a cure rate of only 10% to 20%, stressing the importance of primary prevention.
Risk minimization measures	Routine risk minimization measures: • Legal status: restricted medical prescription

Missing Information: Use in patients with severe cardiac disease	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 • SmPC Section 4.4 • PL Section 2 • PL Section 4 • Recommendations regarding clinical evaluation of cardiac history and function prior to ibrutinib initiation, monitoring during treatment for signs of clinical deterioration of cardiac function and clinical management are provided in SmPC Section 4.4 • A recommendation regarding further evaluation (eg, ECG, echocardiogram) for patients in whom there are cardiovascular concerns is provided in SmPC Section 4.4 • A recommendation for careful assessment of the benefit/risk before initiating treatment with ibrutinib in patients with relevant risk factors for cardiac events, including consideration of alternative treatment, is provided in SmPC Section 4.4

	• Recommendations regarding monitoring and management of patients who develop signs and/or symptoms of ventricular tachyarrhythmia (including treatment interruption) are provided in SmPC Section 4.4 • Recommendations regarding monitoring and management of patients with pre-existing atrial fibrillation requiring anticoagulant therapy, and of patients who develop atrial fibrillation on therapy with ibrutinib are provided in SmPC Section 4.4 • Warning for patients having severe heart failure is provided in PL Section 2 • Legal status: restricted medical prescription Additional risk minimization measures: • DHPC to inform prescribers of important cardiac risks associated with the use of ibrutinib, provide background and recommendations on how to manage these risks, and to direct the prescriber's attention to follow the new dose modification guidelines for patients with new onset or worsening cardiac arrhythmia or cardiac failure

II.C. Postauthorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of IMBRUVICA.

II.C.2. Other Studies in Postauthorization Development Plan

Analysis of aggregate randomized controlled clinical trial data – Additional pharmacovigilance study to further evaluate the risk of hemorrhage in subjects receiving ibrutinib and concomitant anticoagulant and/or antiplatelet drugs

Purpose of the study: To further evaluate the risk of major hemorrhage in subjects receiving ibrutinib and concomitant vitamin K antagonists with or without antiplatelet drugs

Annex 4: Specific Adverse Drug Reaction Follow-up Forms

A standard AE follow-up form (see Annex 4.7) to obtain complete reporter, patient, and product information is used in conjunction with specific adverse drug reaction follow-up forms (Topic of Interest Targeted Follow-up Questionnaires).

Table of Contents

Specific Adverse Drug Reaction Follow-up Questionnaires	
Safety Concern	Purpose/Description
Hemorrhage	Targeted follow-up of AEs through a guided questionnaire.
Hepatotoxicity (including hepatic failure)	Targeted follow-up of AEs through a guided questionnaire.
Ischemic stroke	Targeted follow-up of AEs through a guided questionnaire.
Cardiac failure	Targeted follow-up of AEs through a guided questionnaire.
Progressive multifocal leukoencephalopathy (PML)	Targeted follow-up of AEs through a guided questionnaire.
Cardiac arrhythmia (excluding atrial fibrillation and ventricular tachyarrhythmias)	Targeted follow-up of AEs through a guided questionnaire.

Annex 4.1 Ibrutinib (IMBRUVICA®) Targeted Follow-up Questionnaire for Hemorrhage

Manufacturer Control Number: _____ Date of Report [dd-MMM-yyyy]

Person providing this information:			
Name:			
Address:			
City:		State:	ZIP/Postal Code:
Country:		Telephone:	Fax:
Relationship to patient:	☐ Physician	☐ Nurse	☐Pharmacist
	☐ Other health care professional (please explain)		
	☐ Other (please explain)		
Signature:		Date: [dd-MMM-yyyy]	

Note to LSOs: The following statement may be removed or modified in accordance with local requirements.

For reports originating from the United States: The Health Insurance Portability and Accountability Act (HIPAA) specifically permits covered entities (such as pharmacists, physicians or hospitals) to report adverse events and other information related to the quality, effectiveness and safety of FDA regulated products both to the manufacturers and directly to the FDA.

1. Patient Demographics

Note: If regarding a clinical trial subject, please provide ONLY the demographics under 1a, before completing the rest of the questionnaire.

a. Clinical Trials Only

Patient DOB: [dd-MMM-yyyy] Subject ID Number:
Site ID Number: Protocol Number:

b. Non-Clinical Trials

Patient name: (unless prohibited by data privacy/local law)
Patient DOB: [dd-MMM-yyyy] Patient gender: ☐ M ☐ F
Patient's country of origin: Patient height: Patient weight: lbs kg
Patient's ethnicity: ☐ White ☐ Hispanic ☐ Black ☐ Asian/Pacific Islander
☐ Native American ☐ Unknown

2. ibrutinib (IMBRUVICA®) Details

Indication for Use:
Dose/unit/frequency at time of event:
Route/formulation:
Start Date: [dd-MMM-yyyy] End date: [dd-MMM-yyyy]
Recent dose change? (Elaborate on timing/amount of dose change):
Lot#:

Action taken with Ibrutinib (IMBRUVICA®) following event:

☐ Discontinued
☐ Interrupted
☐ Dose reduced
☐ Dose increased
☐ Dose not changed
☐ Unknown
☐ Not applicable

Did the event/reaction abate after Ibrutinib (imbruvica®) was withdrawn, interrupted, or reduced?

☐ No ☐ Yes

If Ibrutinib (IMBRUVICA®) was reintroduced, did reaction recur?

☐ No ☐ Yes

Causality assessment -- Is the event/reaction related to Ibrutinib (imbruvica®)?

☐ Not related ☐ Doubtful ☐ Possible ☐ Probable ☐ Very likely

Co-suspect medications – Attach additional pages as needed.

Medication	Indication	Dose/route of administration	Start Date/Stop Date [dd-MMM-yyyy]	Lot #

Concomitant medications and supplements – Attach additional pages as needed

Medication	Indication	Dose/route of administration	Start Date/Stop Date [dd-MMM-yyyy]	Lot #

3. Medical History and Concurrent Conditions

Does the patient have any history of previous bleeding? (e.g. petechiae, bruise, ecchymosis, purpura, epistaxis, subdural hematoma) Does the patient have any known risk factors for bleeding? (e.g. coagulopathy or history of bleeding disorder such as von Willebrand disease, hemophilia A or B, etc.)

Any history of? (Check all that apply, describe positive responses below)

☐ Autoimmune disorders ☐ Severe anemia ☐ Diabetes Mellitus
☐ Hypertension ☐ Obesity ☐ Chronic liver disease
☐ Peptic ulcer disease ☐ Renal impairment ☐ Stroke
☐ Recent myocardial infarction ☐ Recent injury/trauma
☐ Tobacco use ☐ Alcohol use
☐ Drug allergies ☐ Family history of bleeding problems

4. Bleeding Event Details

Bleeding event (Final diagnosis, report symptoms only if diagnosis not available):

Date and time of onset of bleeding event:

Time from first dose of ibrutinib (IMBRUVICA®) until the onset of event:

Was this the surgical site? ☐ Yes ☐ No Date of surgery: Duration of Surgery:

Was the bleeding event associated with a decrease in hemoglobin of 2g/dl or more? ☐ Yes ☐ No

Was the patient on an antiplatelet/anticoagulant drug at the time of the bleeding event? ☐Yes ☐No

Please specify: Drug name: Dose:

Was the patient using NSAIDs? ☐ Yes ☐ No If yes please specify and provide dose:

In the case of an intracranial bleed, did the patient had evidence of CNS involvement with lymphoma/ leukaemia? ☐ Yes ☐ No

Brief description of the course of events:

5. Laboratory Data Use additional page if necessary

Lab Test	Units	Normal Range	Baseline (dd/MMM/yyyy)	At the time of event onset (dd/MMM/yyyy)	Current (dd/MMM/yyyy)
Hemoglobin					
Hematocrit					
White blood cell count					
Lyphocyte count					
Platelets					
ALT					
AST					
PT					
Creatinine					
PTT					
INR					
Other					

Other relevant laboratory results:

6. Treatment Use additional page if necessary.

Describe patient treatment regimen. Specify the type and amount of any transfusions or other supportive or corrective actions for the bleeding. Include dates of treatment, response to treatment

☐ Required surgical intervention / re-operation

☐ Required an infusion of 2 or more units of blood. How many units?

☐ The patient was treated in an emergency department and discharged. Date:

☐ The patient was hospitalized due to event. Dates

7. Outcome

☐ Recovered/resolved Date recovered:
☐ Recovering/resolving
☐ Recovered/resolved with sequelae (If sequelae, please describe):
☐ Not recovered/not resolved (i.e. ongoing)
☐ Fatal (Cause of death):
☐ Unknown
Did the patient experience permanent disability? ☐ Yes ☐ No If yes please describe:

8. Suspected causes/risk factors

9. Comments:

Annex 4.2 Ibrutinib (IMBRUVICA®) Targeted Follow-up Questionnaire (TFUQ) for Hepatotoxicity

Manufacturer Control Number: _____ Date of Report [dd-MMM-yyyy]

Person providing this information:			
Name:			
Address:			
City:		State:	ZIP/Postal Code:
Country:		Telephone:	Fax:
Relationship to patient:	☐ Physician	☐ Nurse	☐ Pharmacist
	☐ Other health care professional (please explain)		
	☐ Other (please explain)		
Signature:		Date: [dd-MMM-yyyy]	

Note to LSOs: The following statement may be removed or modified in accordance with local requirements.
For reports originating from the United States: The Health Insurance Portability and Accountability Act (HIPAA) specifically permits covered entities (such as pharmacists, physicians or hospitals) to report adverse events and other information related to the quality, effectiveness and safety of FDA regulated products both to the manufacturers and directly to the FDA.

1. Patient Demographics

Note: If regarding a clinical trial subject, please provide ONLY the demographics under 1a, before completing the rest of the questionnaire.

a. Clinical Trials Only

Patient DOB: [dd-MMM-yyyy] Subject ID Number:
Site ID Number: Protocol Number:

b. Non-Clinical Trials

Patient name: (unless prohibited by data privacy/local law)
Patient DOB: [dd-MMM-yyyy] Patient gender: ☐ M ☐ F
Patient's country of origin: Patient height: Patient weight: lbs kg
Patient's ethnicity: ☐ White ☐ Hispanic ☐ Black ☐ Asian/Pacific Islander
☐ Native American ☐ Unknown

2. ibrutinib (IMBRUVICA®) Details

Indication for Use:
Dose/unit/frequency at time of event:
Route/formulation:
Start Date: [dd-MMM-yyyy] End date: [dd-MMM-yyyy]
Recent dose change? (Elaborate on timing/amount of dose change):
Lot#:

Action taken with **ibrutinib (IMBRUVICA®)** following event:

☐ Discontinued ☐ Interrupted ☐ Dose reduced ☐ Dose increased
☐ Dose not changed ☐ Unknown ☐ Not applicable

Did the event/reaction abate after **ibrutinib (IMBRUVICA®)** was withdrawn, interrupted, or reduced?

☐ No ☐ Yes

If **ibrutinib (IMBRUVICA®)** was reintroduced, did reaction recur?

☐ No ☐ Yes

Causality assessment -- Is the event/reaction related to **ibrutinib (IMBRUVICA®)**?

☐ Not related ☐ Doubtful ☐ Possible ☐ Probable ☐ Very likely

Co-suspect medications – Attach additional pages as needed.

Medication	Indication	Dose/route of administration	Start Date/Stop Date [dd-MMM-yyyy]	Lot #

Concomitant medications and supplements – Attach additional pages as needed

Medication	Indication	Dose/route of administration	Start Date/Stop Date [dd-MMM-yyyy]	Lot #

3. Medical History and Concurrent Conditions

Hepatitis? ☐ No ☐ Yes – details:
Heart failure? ☐ No ☐ Yes – details:
Blood transfusion? ☐ No ☐ Yes – details:
Other Malignancy: ☐ No ☐ Yes – details:
Viral infection/HIV/EBV? ☐ No ☐ Yes – details:
Autoimmune diseases? ☐ No ☐ Yes – details:
Recent live vaccination? ☐ No ☐ Yes – details:
Alcohol consumption? ☐ No ☐ Yes – details:
Recent travel? ☐ No ☐ Yes – details:

List relevant family history:

4. Adverse Event Description

Time from initiation of ibrutinib (IMBRUVICA®) to event:
Onset date of Event: [dd-MMM-yyyy])
Detailed description of Event:
Underlying medical cause of liver necrosis/ liver failure:

Clinical signs and symptoms:

☐ Jaundice ☐ Fatigue ☐ Stomach pain ☐ Nausea
☐ Vomiting ☐ Not feeling well ☐ Disorientation or confusion ☐ Sleepiness

Other clinical findings:

Diagnostic procedures: (*Please enclose copies of results)*

Imaging: e.g. Sonography/CT…):

☐ Not Done ☐ Done, specify:

Puncture: Ascites/Liver: (Indication: Date: dd-MMM-yyyy)

☐ Not done ☐ Done, specify:

Serology: Hepatitis: Date(s): dd-MMM-yyyy ☐ not done ☐ Unknown

Please provide Titers/Values and Units or enclose copies of Lab-Results

5. Diagnosis

6. Relevant results of diagnostic tests including laboratory tests, imaging, biopsies, etc (Please note positive/negative, and date performed) ***(ADD or REMOVE APPROPRIATE CHOICES FOR EVENT OF INTEREST):***

			Before Start of Drug			**Normalized after end of Drug**
			Date	**Date**	**Date**	**Date**
Lab Test:	**Units**	**Normal range**	dd-MM-yy	dd-MM-yy	dd-MM-yy	dd-MM-yy
ALT (SGPT)						☐ yes ☐ no
AST (SGOT)						☐ yes ☐ no
GGT						☐ yes ☐ no
Alkphos						☐ yes ☐ no
Tot. Bili (TB)						☐ yes ☐ no
Conj.Bili (CB)						☐ yes ☐ no
Albumin						☐ yes ☐ no
Amylase						☐ yes ☐ no
Lipase						☐ yes ☐ no
Ammonia						☐ yes ☐ no
PT/INR						☐ yes ☐ no
Others						☐ yes ☐ no

7. Treatment and Outcome

Patient was treated after the event? ☐ No ☐ Yes (Details of treatment:)
Patient had an emergency department visit?
☐ No ☐ Yes (If yes provide Start date: , Discharge date:) (dd/MMM/yyyy)
Patient was hospitalized ☐ No ☐ Yes
(If yes, provide Start date: , Dischage date:) (dd/MMM/yyyy)
Patient died? ☐ No ☐ Yes (If yes, elaborate on cause of death)
Date of death: (dd/MMM/yyyy)
Patient recovered? ☐ No ☐ Yes (If yes, date of recovery: (dd/MMM/yyyy)
Associated, or any preceding relevant, treatment emergent adverse events

8. Suspected causes/risk factors

9. Comments:

Annex 4.3 Topic of Interest Targeted Follow-up Questionnaire (TOI TFUQ) for Cerebrovascular Events/Ischemic Stroke

Topic of Interest Targeted Follow-Up Questionnaire (TOI TFUQ) for Cerebrovascular Events/Ischemic Stroke

To the Health Care Provider: Please complete this form as a supplement to the Health Care Professional Adverse Event Follow-Up Form provided, in order to define if the patient or his/her family members has a medical condition predisposing him/her to cerebrovascular events or stroke, and to add specific details regarding the cerebrovascular event or stroke.

Manufacturer Control Number: Product generic (TRADE) Name:
Date of Report: [dd-MMM-yyyy]

1. Relevant Medical/Family History
(Check all that apply)

	Patient Medical History Date/Details	**Family History** Family Member(s) Affected Details
Cerebrovascular disease	☐	☐
Ischemic stroke	☐ [ ]	☐ [ ]
Hemorrhagic stroke	☐	☐
TIA	☐	☐
Other	☐	☐
Intracranial aneurysm	☐	☐
Carotid artery disease	☐	☐
Hypertension	☐	☐
Diabetes mellitus	☐	☐
Dyslipidemia/Hypercholesterolemia	☐	☐
Atrial fibrillation	☐	☐
Arrhythmia, other	☐	☐
Coronary artery disease	☐	☐
Angina	☐	☐
Myocardial infarction	☐	☐
Coronary revascularization	☐	☐
Peripheral arterial disease	☐	☐
Venous thromboembolism	☐	☐
Chronic kidney disease	☐	☐
Hypercoagulability	☐	☐
Elevated fibrinogen	☐	☐
Autoimmune disease	☐	☐
Demyelinating disease	☐	☐
Congenital heart disease	☐	☐
Congenital cerebrovascular disease	☐	☐
Obesity	☐	☐
Sleep-related breathing disorder	☐	☐
Radiotherapy to head/neck	☐	☐
Lifestyle risks	☐	☐

MCN:

	Patient Medical History Date/Details	**Family History** Family Member(s) Affected Details
Smoking (amount)	☐	☐
Alcohol intake (amount)	☐	☐
Physical inactivity	☐	☐
Other disease (specify)	☐	☐
Additional details regarding Medical or Family History:		

2. Adverse Event Details
(Check/list all that apply)

- ☐ Sudden numbness in the limbs; Right or left side, specify:
- ☐ Sudden weakness in the limbs; Right or left side, specify:
- ☐ Sudden confusion
- ☐ Trouble speaking
- ☐ Trouble understanding speech
- ☐ Difficulty walking
- ☐ Loss of balance or lack of coordination
- ☐ Unilateral visual impairment
- ☐ Bilateral visual impairment
- ☐ Speed of onset - sudden
- ☐ Speed of onset - gradual
- ☐ Did the patient experience pain/headache? Specify location:
- ☐ If there was pain, was it affected by movement of the eyes
  Specify ophthalmologic and neurologic physical findings:
- ☐ Changes in consciousness
- ☐ Neck stiffness
- ☐ Vomiting
- ☐ Other signs or symptoms, specify:

Annex 4.4 Topic of Interest Questionnaire (TOIQ) for Cardiac Failure

Topic of Interest Questionnaire (TOIQ) for Cardiac Failure

To the Health Care Provider: Please complete this form as a supplement to the Health Care Professional Adverse Event Follow-Up Form provided.

Manufacturer Control Number: Product generic (TRADE) Name:
Date of Report [dd-MMM-yyyy]

1. **Adverse Event/Patient's Symptoms** *(Check all that apply and provide details below.)*
   - ☐ Dizziness ☐ Exercise intolerance ☐ Fluid retention/weight gain
   - ☐ Chest discomfort ☐ Palpitations ☐ Dyspnea
   - ☐ Specific Triggering event (i.e., dietary indiscretion recent missed doses of medication, systemic infection, uncontrolled hypertension, de novo arrhythmia etc.) Details:
   - ☐ Other; Specify:

2. **Relevant Medical/Family History**
   (Check all that apply)

	Patient Medical History Date/Details	**Family History** Family Member(s) Effected/Details
Valvular Heart Disease	☐	☐
Cardiomyopathy	☐	☐
Anaemia	☐	☐
Sleep Apnea	☐	☐
Hypertension	☐	☐
Hyperlipidemia	☐	☐
Diabetes mellitus	☐	☐
Coronary artery disease	☐	☐
Autoimmune or Rheumatoid disease	☐	☐
Congenital heart disease	☐	☐
Cardiac failure	☐	☐
Previous MI	☐	☐
Angina Pectoris	☐	☐
Arrhythmia	☐	☐
Hyperthyroidism	☐	☐
Pulmonary disease	☐	☐
Obesity	☐	☐
Malignant neoplasm progression	☐	☐
Previous exposure to cardiotoxic drugs/chemotherapy	☐	☐
Lifestyle risks		
Smoking (amount)	☐	☐
Alcohol intake (amount)	☐	☐
Drug abuse (specific)	☐	☐
Physical inactivity	☐	☐

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Topic of Interest Questionnaire (TOIQ) for Cardiac Failure
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MCN:

3. Relevant results of baseline and periodic cardiac monitoring including dates of testing and normal ranges. Please provide copies of results:

Test	Baseline	During therapy	After withdrawal of therapy
Cardiac monitoring: (please specify cardiac test, eg. ECG, Echo, Holter, etc.)			
Ejection Fraction (%)			
Concurrent atrial fibrillation and/or other arrhythmia (please specify)*			

**Please specify type of arrhythmia/s and provide details including time course (eg. arrhythmia occurred along with cardiac failure or arryhthmia led to cardiac failure). Please provide copies of results.*

Annex 4.5 Ibrutinib (IMBRUVICA®) Targeted Follow-up Questionnaire (TFUQ) for Progressive Multifocal Leukoencephalopathy (PML)

Manufacturer Control Number: _____ Date of Report [dd-MMM-yyyy]

Person providing this information:			
Name:			
Address:			
City:		State:	ZIP/Postal Code:
Country:		Telephone:	Fax:
Relationship to patient:	☐ Physician	☐ Nurse	☐Pharmacist
	☐ Other health care professional (please explain)		
	☐ Other (please explain)		
Signature:		Date: [dd-MMM-yyyy]	

Note to LSOs: The following statement may be removed or modified in accordance with local requirements.
For reports originating from the United States: The Health Insurance Portability and Accountability Act (HIPAA) specifically permits covered entities (such as pharmacists, physicians or hospitals) to report adverse events and other information related to the quality, effectiveness and safety of FDA regulated products both to the manufacturers and directly to the FDA.

1. Patient Demographics

Note: If regarding a clinical trial subject, please provide ONLY the demographics under 1a, before completing the rest of the questionnaire.

a. Clinical Trials Only

Patient DOB: [dd-MMM-yyyy] Subject ID Number:

Site ID Number: Protocol Number:

b. Non-Clinical Trials

Patient name: (unless prohibited by data privacy/local law)

Patient DOB: [dd-MMM-yyyy] Patient gender: ☐ M ☐ F

Patient's country of origin: Patient height: Patient weight: lbs kg

Patient's ethnicity: ☐ White ☐ Hispanic ☐ Black ☐ Asian/Pacific Islander

☐ Native American ☐ Unknown

2. Medical History and Concurrent Conditions

List relevant past medical history including dates *(e.g., immune deficiency, HIV, autoimmune disorders, hepatitis, tuberculosis, malignancies, sarcoidosis)*. Please list the details with dates of diagnoses, therapies received, including radiation.

List relevant concurrent/pre-existing conditions *(e.g., Hodgkin's CLL, CML, AML, ongoing GVHD, long term immunosuppression, pre-existing neurological features/disorders, and any relevant previous imaging or laboratory test results.) Please list the details with dates of diagnosis*.

☐ Alcohol consumption: if yes, specify:
☐ History of drug abuse; if yes, provide details

3. Event details:

Onset date of Event: [dd-MMM-yyyy]
Clinical signs and symptoms:
Detailed description of Event:

Neurological Evaluation, please include the neurology report

Has the patient been evaluated by a neurologist? ☐ Yes ☐ No

Patient's findings, including dates (e.g., clinical features observed - central nervous system and other symptoms and their progression, including dates [these could include neurological deficits such as motor symptoms (e.g., hemiparesis), cognitive dysfunction or changes in behavior or personality, language or speech disturbances (e.g., aphasia/dysarthria), visual disturbances (e.g., hemianopsia), ataxia/loss of motor coordination, seizures, etc.)

4. Laboratory/Radiographic Evaluation results as appropriate and accompanying normal ranges, if available (please note positive/negative, and date performed and other test results as appropriate)

a. MRI: Date: [dd-MMM-yyyy]
Results:

b. JC Virus DNA
1) CSF Fluid: Date: [dd-MMM-yyyy], Results:
2) Brain tissue: Biopsy date: [dd-MMM-yyyy], Results:
3) Non CSF sources for JCV DNA testing: Date: [dd-MMM-yyyy], Results:

c. Histopathology of brain biopsy: Date: [dd-MMM-yyyy]
Results:

d. **Results of other imaging studies** (e.g., CT scan, etc.):

Date of CT scan, if done:

e. **Other relevant test results** (list additional details below and attach report(s) if available)

Lab Test	Units	Normal Range	Baseline (dd/MMM/yyyy)	At the time of event onset (dd/MMM/yyyy)	Current (dd/MMM/yyyy)
Hemoglobin					
Hematocrit					
White blood cell count					
Lyphocyte count					
Platelets					
ALT					
AST					
PT					
Creatinine					
Other					

5. Ibrutinib (IMBRUVICA®) Details

Indication for Use:
Dose/unit/frequency at time of event:
Route/formulation:
Start Date: [dd-MMM-yyyy] End date [dd-MMM-yyyy]
Recent dose change? (Elaborate on timing/amount of dose change):
Lot#:

Co-suspect medications – Please include details of any other drugs including prior or concurrent chemotherapies, corticosteroids, and radiation), attach additional pages as needed..

Medication	Indication	Dose/route of administration	Start Date/Stop Date [dd-MMM-yyyy]	Lot #

Concomitant medications and supplements – (include prior or concurrent immunosuppressant medications – e.g., chemotherapy agents, radiation, transplant regimens, immunotherapy with monoclonal antibodies such as anti-CD-20 monoclonal antibodies), also include over the counter and herbal medications attach additional pages as needed.

Medication	Indication	Dose/route of administration	Start Date/Stop Date [dd-MMM-yyyy]	Lot #

6. Treatment and Outcome *(list patient treatment regimen and outcome of event below. Include dates of treatment, response to treatment, and hospitalization dates if relevant)*

Patient had an emergency department visit and was discharged ☐ Yes ☐ No
Patient was hospitalized ☐ Yes ☐ No
Patient died ☐ Yes ☐ No
Was PML cause of death ☐ Yes ☐ No (if no, provide cause of death:)
Associated, or any preceding relevant, treatment emergent adverse events
Recovered/resolved ☐ Yes ☐ No Date recovered:
Recovering/resolving ☐ Yes ☐ No
Recovered/resolved with sequelae ☐ Yes ☐ No (If sequelae, please describe):
Not recovered/not resolved (i.e. ongoing) ☐ Yes ☐ No
Unknown ☐ Yes ☐ No
Did the patient experience permanent disability? ☐ Yes ☐ No If yes please describe: :

7. Comments:

Annex 4.6 Ibrutinib (IMBRUVICA®) Targeted Follow-up Questionnaire (TFUQ) for Cardiac Arrhythmias

Manufacturer Control Number: _____ Date of Report [dd-MMM-yyyy]

Person providing this information:			
Name:			
Address:			
City:		State:	ZIP/Postal Code:
Country:		Telephone:	Fax:
Relationship to patient:	☐ Physician	☐ Nurse	☐ Pharmacist
	☐ Other health care professional (please explain)		
	☐ Other (please explain)		
Signature:		Date: [dd-MMM-yyyy]	

Note to LSOs: The following statement may be removed or modified in accordance with local requirements.
For reports originating from the United States: The Health Insurance Portability and Accountability Act (HIPAA) specifically permits covered entities (such as pharmacists, physicians or hospitals) to report adverse events and other information related to the quality, effectiveness and safety of FDA regulated products both to the manufacturers and directly to the FDA.

1. Patient Demographics

Note: If regarding a clinical trial subject, please provide ONLY the demographics under 1a, before completing the rest of the questionnaire.

a. Clinical Trials Only

Patient DOB: [dd-MMM-yyyy] Subject ID Number:
Site ID Number: Protocol Number:

b. Non-Clinical Trials

Patient name: (unless prohibited by data privacy/local law)
Patient DOB: [dd-MMM-yyyy] Patient gender: ☐ M ☐ F
Patient's country of origin: Patient height: Patient weight: lbs kg
Patient's ethnicity: ☐ White ☐ Hispanic ☐ Black ☐ Asian/Pacific Islander
☐ Native American ☐ Unknown

2. ibrutinib (IMBRUVICA®) Details

Indication for Use:
Dose/unit/frequency at time of event:
Route/formulation:
Start Date: [dd-MMM-yyyy] End date: [dd-MMM-yyyy]
Recent dose change? (Elaborate on timing/amount of dose change):
Lot#:

Action taken with **ibrutinib (IMBRUVICA®)** following event:

☐ Discontinued ☐ Interrupted ☐ Dose reduced ☐ Dose increased
☐ Dose not changed ☐ Unknown ☐ Not applicable

Did the event/reaction abate after **ibrutinib (IMBRUVICA®)** was withdrawn, interrupted, or reduced?

☐ No ☐ Yes If yes, when?

If **ibrutinib (IMBRUVICA®)** was reintroduced, did reaction recur?

☐ No ☐ Yes If yes, when?

Causality assessment -- Is the event/reaction related to **ibrutinib (IMBRUVICA®)**?

☐ Not related ☐ Doubtful ☐ Possible ☐ Probable ☐ Very likely

Co-suspect medications – Attach additional pages as needed.

Medication	Indication	Dose/route of administration	Start Date/Stop Date [dd-MMM-yyyy]	Lot #

Concomitant medications and supplements – Attach additional pages as needed

Medication	Indication	Dose/route of administration	Start Date/Stop Date [dd-MMM-yyyy]	Lot #

3. Medical History and Concurrent Conditions *(Provide prior diagnoses relevant laboratory data [including echo and ischemic evaluation], dates, etc. below.)*

☐ Coronary Artery Disease ☐ Myocardial Infarction ☐ Hypertension
☐ Hyperlipidemia/Hypercholesterolemia ☐ Diabetes Mellitus ☐ Obesity
☐ Peripheral Artery Disease ☐ Prior Stroke or Transient Ischemic Attack
☐ Congestive Heart Failure ☐ Prior Coronary Revascularization/Angioplasty
☐ Cardiac Arrest ☐ Ventricular Tachycardia ☐ Bradycardia
☐ Prolonged QT ☐ Angina Pectoris ☐ Atrial Arrhythmias
☐ Ventricular Arrhythmia ☐ Preexcitation Syndrome
☐ Decreased Left Ventricular Fraction ☐ Drowning or Other Accidents
☐ Unexplained Seizures ☐ Syncope/Pre-Syncope
☐ Unexplained Fainting ☐ Low Potassium ☐ Low Magnesium
☐ Low Calcium ☐ Elevated Potassium
☐ Other Electrolyte Abnormality (Specify Details):
☐ Other Cardiac Disease (Specify Details):
☐ Thyroid Disorders (Specify Details):
☐ Smoking (Specify Number Of Packs/Years):
☐ Alcohol Consumption (Specify Details):
☐ Illicit Drug Use (Specify Details):
☐ Family History of Cardiac Disease or Early Coronary Disease
☐ Family History of Strokes ☐ Family History of Sudden Death
☐ Family History of Long QT Syndrome

4. **Drug History** *(Include prior drug exposure that are cardiotoxic, such as anthracyclines, alkylating agents, paclitaxel, etoposide, teniposide, the vinca alkaloids, fluorouracil, cytarabine, amsacrine, cladribine, asparaginase, tretinoin and pentostatin.)*

   Drug:
   Exposure date:
   Dose details:

5. **Other Relevant Medical Conditions:**

6. **Adverse Event Description**

   Time from initiation of ibrutinib (IMBRUVICA®) to event:
   Onset date of Event: [dd-MMM-yyyy])
   Detailed description of Event:

   Clinical signs and symptoms:
   ☐ Dizziness ☐ Lightheadedness
   ☐ Fainting (syncope) or near-fainting spells
   ☐ Tachycardia ☐ Fatigue
   ☐ Palpitations ☐ Shortness of breath
   ☐ Chest discomfort ☐ Sudden death
   ☐ Other

7. **Diagnosis** *(Specify diagnosis and how event was diagnosed including type of arrhythmia)* Date of diagnosis: [dd-MMM-yyyy]

8. Relevant results of diagnostic tests including laboratory tests, imaging, etc. *(List all relevant **laboratory data below with results, including Echocardiogram, Holter, rhythm strips, lipids, cardiac enzymes, ECG. Please provide copies of results.**)*

			Before Start of Drug			**Normalized After End Of Drug**
			Date	**Date**	**Date**	**Date**
Lab Test:	**Units**	**Normal Range**	**dd-MMM-yyyy**	**dd-MMM-yyyy**	**dd-MMM-yyyy**	**dd-MMM-yyyy**
Creatine Kinase						☐ Yes ☐ No
Troponin						☐ Yes ☐ No
Myoglobin						☐ Yes ☐ No
Potassium						☐ Yes ☐ No
Calcium						☐ Yes ☐ No
Magnesium						☐ Yes ☐ No
Resting Heart Rate						☐ Yes ☐ No
QT Interval						☐ Yes ☐ No

			Before Start of Drug			Normalized After End Of Drug
			Date	Date	Date	Date
Lab Test:	**Units**	**Normal Range**	**dd-MMM-yyyy**	**dd-MMM-yyyy**	**dd-MMM-yyyy**	**dd-MMM-yyyy**
Others						☐ Yes ☐ No

☐ Electrocardiogram (ECG) including ECG before start treatment:
☐ Echocardiogram:
☐ Holter monitor and event recorders:
☐ Electrophysiology (EP) study:

9. Treatment and Outcome (List any treatments regimen and outcome of event below. Include dates of ***treatment, response to treatment, and hospitalization dates if relevant.)***

Did the event resolve? ☐ No ☐ Yes
If yes, list date that event was considered resolved? [dd-MMM-yyyy]

Was the patient treated for the adverse event? ☐ No ☐ Yes (Specify details:)

Did the patient receive outpatient treatment? ☐ No ☐ Yes (Specify details:)

Has the patient had an emergency department visit? ☐ No ☐ Yes (Date: [dd-MMM-yyyy])

Was the patient hospitalized? ☐ No ☐ Yes (Admission date: [dd-MMM-yyyy], Discharge date: [dd-MMM-yyyy])

Has the patient died? ☐ No ☐ Yes (Specify cause of death and provide autopsy results if any:)

If the patient died, was the arrhythmia/cardiogenic death documented by ECG or a rhythm strip?
☐ No ☐ Yes

10. Suspected causes/risk factors (List any conditions that may have contributed to patient's death, or *any alternative explanations.)*

11. Any additional comments:

Annex 4.7 Health Care Professional Adverse Event Follow-up Form

HEALTH CARE PROFESSIONAL ADVERSE EVENT FOLLOW-UP FORM
Return in postage-paid envelope enclosed, or fax to +1 215-293-9955

Product:	**AER No.:**	**Other ID No.:**

Patient					
Patient Name (Print):					
Height:	**Weight:**	**Gender:**	**Age:**	**Date of Birth:**	**Age Group (if age or DOB is not available)** ☐ Birth – 28 days ☐ 29 days – 24 months ☐ 24 months – 13 years ☐ 14 years – 18 years ☐ 19 years – 65 years ☐ Over 65 years

	PRIMARY Suspect Medication	**OTHER Suspect Medication**		
		#1	**#2**	**#3**
Generic name				
Trade/brand name				
Biosimilar?	Y ☐ N ☐ Unknown ☐ N/A ☐	Y ☐ N ☐ Unk ☐ N/A ☐	Y ☐ N ☐ Unk ☐ N/A ☐	Y ☐ N ☐ Unk ☐ N/A ☐
Indication				
Dose/unit/frequency				
Approximate total number of doses/ injections/infusions patient received				
Route/formulation				
Therapy dates (start and stop)				
Lot #				
Expiration date				

Does the patient have allergies?	☐ No ☐ Yes – details:
Was the patient pregnant?	☐ No ☐ Yes – last menstrual period date:
Does the patient drink alcohol?	☐ No ☐ Yes – units per week:
Does the patient smoke?	☐ No ☐ Yes – how much per day:
Is there a history of drug abuse?	☐ No ☐ Yes – details:

Device/Combo Product Device			
	Is the complaint related to a specific part used to administer the product?	No ☐ Yes ☐ **If Yes, document the specific details about how the issue occurred (complete questions below by checking the boxes):**	Describe which specific part of the Device or device component was involved:
	When did the problem occur?	Before use/in package ☐ During preparation ☐ During use/administration ☐ After use/during disposal ☐ Unknown ☐	
	Did the patient experience harm from the product problem?	No ☐ Yes ☐ Unk ☐ Describe:	
	Were the product instructions for use followed?	No ☐ Yes ☐ Unk ☐ If not, explain why:	Number of units involved?
	Who was using the Device (Operator of device)?	Health Professional ☐ Lay User/Patient ☐ Other ☐ If Other, describe:	Single use device was reprocessed and reused? No ☐ Yes ☐
	Usage of Device	Initial Use ☐ Reuse ☐ Unk ☐	

Reporter		
	Reporter's Name:	
	☐ **Nurse** ☐ **Physician - Specialty:** ☐ **Pharmacist** ☐ **Other - Specify:**	
	Address:	
	Telephone:	**Fax:**

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Product: **AER No.:** **Other ID No.:**

Concomitant Therapy: Other medication (including botanical remedies and nutraceuticals) received no longer than 2 weeks prior to event				
Name	Indication	Dates of therapy	Dose	Lot #

Provide the underlying clinical diagnosis – if unknown, list as relevant signs and symptoms						
	Adverse Event #1		**Adverse Event #2**		**Adverse Event #3**	
Adverse Event Diagnosis						
Seriousness	☐ Non-serious ☐ Serious - Specify: ☐ Event directly led to death ☐ Event was an immediate threat to life ☐ Hospitalization ☐ Persistent/significant disability ☐ Congenital anomaly/birth defect ☐ Other medically important condition		☐ Non-serious ☐ Serious - Specify: ☐ Event directly led to death ☐ Event was an immediate threat to life ☐ Hospitalization ☐ Persistent/significant disability ☐ Congenital anomaly/birth defect ☐ Other medically important condition		☐ Non-serious ☐ Serious - Specify: ☐ Event directly led to death ☐ Event was an immediate threat to life ☐ Hospitalization ☐ Persistent/significant disability ☐ Congenital anomaly/birth defect ☐ Other medically important condition	
Onset Date						
Primary Suspect Medication	Causality	Action taken with drug	Causality	Action taken with drug	Causality	Action taken with drug
	☐ Not related ☐ Related	☐ Drug withdrawn ☐ Drug interrupted ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable	☐ Not related ☐ Related	☐ Drug withdrawn ☐ Drug interrupted ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable	☐ Not related ☐ Related	☐ Drug withdrawn ☐ Drug interrupted ☐ Dose reduced ☐ Dose increased ☐ Dose not changed ☐ Unknown ☐ Not applicable
	Recent dose change? (Elaborate on timing/amount of dose change)[ ]		Recent dose change? (Elaborate on timing/amount of dose change):		Recent dose change? (Elaborate on timing/amount of dose change):	
	Did the reaction abate after the drug was withdrawn, interrupted, or reduced? ☐ Yes ☐ No		Did the reaction abate after the drug was withdrawn, interrupted, or reduced? ☐ Yes ☐ No		Did the reaction abate after the drug was withdrawn, interrupted, or reduced? ☐ Yes ☐ No	
	If drug reintroduced, did reaction recur? ☐ Yes ☐ No		If drug reintroduced, did reaction recur? ☐ Yes ☐ No		If drug reintroduced, did reaction recur? ☐ Yes ☐ No	

Product: AER No.: Other ID No.:

Provide the underlying clinical diagnosis – if unknown, list as relevant signs and symptoms			
	Adverse Event #1	Adverse Event #2	Adverse Event #3
Outcome	☐ Recovered without sequelae ☐ Recovered with sequelae Recovery date: ☐ Recovering ☐ Not recovered ☐ Fatal (event directly led to death) ☐ Unknown	☐ Recovered without sequelae ☐ Recovered with sequelae Recovery date: ☐ Recovering ☐ Not recovered ☐ Fatal (event directly led to death) ☐ Unknown	☐ Recovered without sequelae ☐ Recovered with sequelae Recovery date: ☐ Recovering ☐ Not recovered ☐ Fatal (event directly led to death) ☐ Unknown
If Applicable	Hospital admission date: Patient had emergency department visit and discharged? ☐ Yes ☐ No		Hospital discharge date:
	Date of death:	Was an autopsy performed? ☐ No ☐ Yes (attach copy of report if available)	

Describe the course of events including timing with respect to drug administration (use additional pages if necessary)		
Adverse Event Description	Relevant medical history and family history	
	Signs & Symptoms	
	Course of Event	
	Relevant results of diagnostic tests (imaging, laboratory tests, biopsies, etc.)	
	Diagnosis	
	Treatment & response	
	Suspected causes/risk factors	

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Annex 6: Details of Proposed Additional Risk Minimization Activities

Approved Key Messages of the Additional Risk Minimization Measures

Direct Healthcare Professional Communication (DHPC)

The DHPC addresses the important identified risks 'atrial fibrillation', 'ventricular tachyarrhythmias', and 'cardiac failure'; the important potential risk 'cardiac arrhythmia (excluding atrial fibrillation and ventricular tachyarrhythmias)'; and the missing information 'use in patients with severe cardiac disease'.

The specific objective is to increase awareness of HCPs to the possible safety concerns described above and to provide guidance for risk mitigation.

Content of the DHPC – Messages for the HCP

- Inform that the Special Warnings and Precautions for Use section (Section 4.4) of the IMBRUVICA SmPC has been revised with additional information on cardiac arrhythmias, cardiac failure, and sudden fatal cardiac events, including a description of risk factors and guidelines for assessment and management to help prescribers.

- Inform that the dose modification recommendations in the Posology and Method of Administration section (Section 4.2) of the SmPC have been updated for events of cardiac failure or cardiac arrhythmias, and for non-cardiac events.

- Provide background information on the evaluation of cardiac events and the related SmPC update.