Johnson & Johnson Private Limited

Phase IV Clinical Trial Protocol

A prospective, multicenter, open label single arm Phase IV clinical trial to assess safety of ImbruvicaTM (Ibrutinib capsules 140 mg) in Indian patients with chronic lymphocytic leukemia or mantle cell lymphoma who have received at least one prior therapy or chronic lymphocytic leukemia with 17p deletion

Protocol 54179060LYM4005; Phase [IV]

54179060 Imbruvica (Ibrutinib capsule 140 mg)

is approved for marketing in India for:

(a) Imbruvica™ is indicated for the treatment of adult patients with mantle cell lymphoma who have received at least one prior therapy.
(b) Imbruvica™ is indicated for the treatment of patients with chronic lymphocytic leukemia who have received at least one prior therapy.
(c) Imbruvica™ is indicated for the treatment of patients with chronic lymphocytic leukemia with 17p deletion.

Status: Approved (Version 2.0)
Date: 20 October 2022
Prepared by: Johnson & Johnson Private Limited
EDMS number: EDMS-ERI-133399729, 2.0

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

Confidentiality Statement

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PROTOCOL AMENDMENTS

SUMMARY OF CHANGES

Protocol Version	Issue Date
Original Protocol	27-Sep-2016
Amendment 1	20-Oct-2022

Amendments below are listed beginning with the most recent amendment.
Amendment -1 (20-Oct-2022)

Protocol Section	Description of Change
SYNOPSIS	Added description regarding referring to attachment 3 for dose modification guidelines "Refer to the locally approved prescribing information for Imbruvica™ and Attachment 3 regarding the updated dose modification guidelines, special warnings, precautions for use, and other important information."
1.2 Overall Rationale for study	Added description regarding referring to attachment 3 for dose modification guidelines "For atrial fibrillation which persists, consider the risks and benefits of ibrutinib treatment and follow the dose modification guidelines as per Attachment 3 in conjunction with local prescribing information"
6.0 Dosage and Administration	Added description regarding referring to attachment 3 for dose modification guidelines "Refer to the locally approved prescribing informationfor Imbruvica™ and Attachment 3 regarding the updated dose modification guidelines, special warnings, precautions for use, and other important information."
Attachments	Added attachment 3
Investigator Agreement (Last Page)	Change in Sponsor's Responsible Medical Officer: PPD to PPD

SYNOPSIS

Protocol Title

A prospective, multicenter, open label single arm Phase IV clinical trial to assess safety of ImbruvicaTM (Ibrutinib capsules 140 mg) in Indian patients with chronic lymphocytic leukemia or mantle cell lymphoma who have received at least one prior therapy or chronic lymphocytic leukemia with 17p deletion

Sponsor's Responsible Medical Officer: PPD, Medical Advisor, Johnson & Johnson Private Limited, India.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided separately.

BACKGROUND AND RATIONALE

Ibrutinib is a first-in-class potent, orally-administered, covalently-binding small molecule inhibitor of Bruton's tyrosine kinase (BTK) currently approved by the United States (US) FDA for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy; for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy; and for the treatment of patients with CLL with 17p deletion. Drug Controller General (India) first approved ibrutinib for the treatment of patients with CLL or MCL who have received at least one prior therapy or CLL with 17p deletion in October 2015.

Post-marketing study is useful in identifying new safety issues and trends, which were not observed in previously conducted clinical studies. The data obtained from the present study will help to understand the safety profile of ibrutinib in a real-world Indian scenario compared with that obtained in a controlled clinical environment.

OBJECTIVES

The aim of the present phase IV clinical trial is to assess the safety of ibrutinib in a routine clinical set-up in Indian patients to address the regulatory requirement.

Objective

Primary Objective

The primary objective of this study is to evaluate the post-marketing safety of Imbruvica^{TM} (ibrutinib capsule 140 mg) under actual conditions of use, and to understand the following:

- Incidence of adverse events (AEs) (Serious and Non-serious AEs);

Exploratory Objective(s)

To analyse the following outcomes with ibrutinib:

- Baseline patient and disease characteristics
- Response assessment and progression
- Change in patient reported outcomes as measured by
    - Quality of Life by EORTC QLQ C-30 instrument (European Organization for Research and Treatment of Cancer Quality of Life Questionnaires Core 30)
    - Fatigue by FACIT Fatigue instrument (Functional Assessment of Chronic Illness Therapy Fatigue)

PHASE IV CLINICAL STUDY DESIGN

This is a prospective open label, single arm, multicentre, phase IV interventional study to describe the safety of Imbruvica™ in Indian subjects. Approximately, 75 subjects, selected by investigators and determined to be eligible for ibrutinib treatment as per protocol eligibility criteria will be enrolled into the study, after written informed consent is obtained. Subjects will be monitored for AEs during treatment of Imbruvica™. Participating investigators will be trained on the locally approved prescribing information of Imbruvica™ by the sponsor designee before the enrolment of first patient

The decision of subjects to participate in this study must not, in any way, impact upon the standard of care that they are receiving or any benefits to which they are otherwise entitled. Prior to data collection, all subjects must sign an informed consent form (ICF) allowing data collection and source data verification in accordance with local requirements and/or sponsor policy. Sponsor shall provide reimbursement for the investigations haematological profile and coagulation profile to monitor the safety as per protocol throughout the study period. Commercial stocks of Ibrutinib affixed with additional investigational labels (to meet local regulatory requirements) will be provided free of cost by the sponsor to clinical trial subject from the existing distribution channel as per the mentioned duration in the study protocol.

Screening cum Enrolment Visit (Day 1):
Data collected at this visit may include but not limited to demographics, medical history, disease related history, concomitant medications, patient-reported outcomes (PROs), laboratory investigations (hematological and coagulation profile) etc. The use of Imbruvica™ is expected to follow the locally approved prescribing information.

Treatment Period: Subjects will be observed for up to 12 months from the treatment initiation. During the study period, data will be collected at monthly intervals for the first 6 months, (monthly visit ± 7 days; Visit 1 to 6) . Subsequent visit would be at 9 months ± 7 days [Visit 7], Data collected at this visit will include demographics, medical history, disease related history, AEs, disease progression assessment, concomitant medications, patient-reported outcomes (PROs), laboratory investigations (haematological and coagulation profile) as listed in the TIME AND EVENTS SCHEDULE. The End-of-Treatment (EOT) visit will be conducted after the completion of 12-months Imbruvica™ treatment (at Visit 8) or on the day at which the patient discontinued the Imbruvica™ treatment or study. The rationale for such schedule is that in the RESONATE Trial, on long term follow up it was found that the prevalence rates for infection, diarrhoea, and bleeding events were highest for the first 6 months and gradually declined thereafter. Subjects will have post-trial access to Imbruvica™ for at least one year or as decided by EC whichever is more as per the recommendations of Subject Expert Committee (Oncology & Haematology) made in its 70th meeting held on 23rd May 2018 at Central Drugs Standard Control Organization HQ, New Delhi communicated vide F.N. 12-10/2017-DC (Pt-Johnson-snd).

Follow up period (End of Study Visit): A telephonic follow-up will be conducted 30 days after the EOT Visit.

The observation period including the Enrolment Visit and telephonic follow-up will be up to a maximum duration of 13 months for each patient. The subjects can continue with their prescribed Imbruvica™ treatment after the end of treatment in consultation with the participating physician. The overall duration of the study, including recruitment [and/or follow up], is expected to be 36 months.

The expected frequency and timing of data collection in this phase IV clinical trial are summarized in the **Error! Reference source not found.Error! Reference source not found.** presented after the synopsis.

SUBJECT POPULATION

The phase IV clinical trial population will include Indian subjects with CLL or MCL who have received at least one prior therapy or CLL with 17p deletion who are newly initiated on Imbruvica™ treatment based on the independent clinical judgment of the treating physician in clinical practice setting.

Participating sites will be encouraged to enrol subjects in a consecutive manner when subjects come for their regular consultation, in order to minimize bias in patient selection. All eligible patients should be offered enrolment for data collection within the phase IV clinical trial.

Each potential patient must satisfy the following criteria to be eligible for participation in this study:

1. Patient of either sex and >18 years of age
2. CLL or MCL patients being newly initiated on Imbruvica™ treatment (Ibrutinib capsule 140 mg) based on independent clinical judgment of treating physicians as per locally approved prescribing information
3. Must give written informed consent indicating that they understand the purpose and are willing to participate in the study and allowing data collection and source data verification in accordance with regulatory requirements

Potential patients who meet any of the following criteria will not be eligible for this study:

1. Patients who are not eligible to receive Imbruvica™ as per the locally approved prescribing information.
2. Patients participating or planning to participate in any interventional drug trial during the course of this study.

TREATMENT WITH IMBRUVICA™

Imbruvica™ will be prescribed to the subjects as per locally approved Prescribing Information. The recommended dose of Imbruvica™ is 420 mg (three 140 mg capsules) as a single daily dose for CLL and 560 mg (four 140 mg capsules) as a single daily dose for MCL.

Imbruvica™ should continue until disease progression or no longer tolerated by the patient.

Refer to the locally approved prescribing information for Imbruvica™ and Attachment 3 regarding the updated dose modification guidelines, special warnings, precautions for use, and other important information.

DATA SOURCES AND COLLECTION METHODS

The primary data source for this phase IV interventional study will be the medical records of each patient. Source documentation should be in subjects' medical records for all data entered into the CRF. Additionally, patient- completed questionnaires requested by the sponsor will be recorded and will be considered source data.

At each participating site, the same physician must do assessments for an individual patient through the course of study, if possible. Response assessment and progression criteria will be recorded

Patient-reported outcomes will be measured by 2 questionnaires. The EORTC QLQ-C30 is a general cancer assessment, and the FACIT Fatigue Scale specifically assesses aspects of fatigue. Samples of the PRO scales are provided in Attachments 1, and 2. The PRO questionnaires will be collected at the beginning of the clinic visits prior to any procedures or physician interactions according to the **Error! Reference source n ot found.**

Safety Assessment

All AEs, with the exception of progression of CLL/MCL, will be reported from the time a signed and dated informed consent form is obtained until 30 days following the end of treatment period or until the start of a subsequent systemic antineoplastic therapy, if earlier. All non-haematological AEs including laboratory

AEs and AEs leading to dose reductions or discontinuation will be graded and reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0. All haematological AEs will be graded and reported according to the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) 2008 criteria for grading of haematological toxicities in CLL studies. Results of physical examinations including vital signs and clinical laboratory investigations if performed during routine clinical visit will also be recorded.

Clinical Response Measures
Response assessment and progression criteria will be recorded as per IWCLL criteria for CLL and revised response criteria for malignant lymphoma for MCL as per participating physicians' routine clinical practice.

Patient-Reported Outcomes
Patient-reported outcomes (PROs) will be measured by 2 questionnaires. The EORTC QLQ-C30 is a general cancer assessment, and the FACIT Fatigue Scale specifically assesses aspects of fatigue. The PRO questionnaires will be collected at the beginning of the clinic visits prior to any procedures or physician interactions. Data will be collected using electronic Case Report Form (eCRF). **The EORTC QLQ-C30** includes 30 separate items with a recall period of last 1 week. Administration time is approximately 11 minutes. **FACIT Fatigue** is an instrument for use as a measure of the effect of fatigue in patients with cancer and other chronic diseases

STATISTICAL METHODS

The primary objective of this study is to estimate the incidence of AEs in Indian subjects under actual conditions of use of Imbruvica™. A sample size of 75 subjects is as per the recommendations of Subject Expert Committee (Oncology & Haematology) made in its 70th meeting held on 23rd May 2018 at Central Drugs Standard Control Organization HQ, New Delhi communicated vide F.N. 12-10/2017-DC (Pt-Johnson-snd).

Parameters of Interest

Primary Endpoint:

- The number and type of AEs reported by the investigator or the patient

The safety variables to be analysed include AEs and clinical laboratory tests

Exploratory Endpoints

- Proportion of participants experiencing clinical response as per assessment criteria defined in section 9.1
- Change from baseline in patient-reported outcomes as per EORTC QLQ C-30 and FACIT Fatigue

The safety analysis population will include all subjects who sign the ICF and receive at least one dose of Imbruvica™. The verbatim terms used by participating physicians to document AEs in the CRF will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized. Adverse events and serious adverse events will be summarized for the study duration by body system, preferred term, intensity, and relationship to Imbruvica™ using descriptive statistics. Where appropriate, additional summaries, listings, or narratives may be provided for any deaths, serious adverse events, or any adverse events of clinical interest. Changes from baseline to the worst AE grade experienced by a patient during the study will be provided as shift tables. Results of investigations data including vital signs, if any, will be summarized using descriptive statistics.

All subjects who have received at least one dose of Imbruvica™ and have completed one post-treatment PRO assessment will be considered for exploratory analysis. Exploratory endpoints will be summarized using descriptive statistics. Shift tables will be provided to determine the change in reported outcomes from baseline (Enrolment Visit) until Visit 8 /EOT.

Statistical Analysis of Data

No formal hypothesis testing will be conducted for this phase IV interventional study. Data will be summarized using descriptive statistics. Continuous variables will be summarized using descriptive statistics, which will include the number of subjects, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequencies and percentages, as appropriate.

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Data Collection		Observation Period				Unscheduled Visit
		Treatment with Imbruvica™			Follow up *(telephonic)*[i]	
	Screening / Enrolment Visit	**Monthly Visits (Month 1 to Month 6) Monthly Visit (±7 days)**	**Visit 7 Month 9 (±7 days)**	**Visit 8 / End of Treatment[h]** (EOT) **Months 12/ (±7 days)**	**30 days after EoT visit (EOS) (±7 days)**	
Screening/Patient information						
Eligibility criteria	X					
Patient information/consent [a]	X					
Demographics	X					
Medical history	X					
Baseline disease characteristics [b]	X					
Relevant treatment history [c]	X					
Physical exam, vital signs & Disease-related symptoms [d]	X	X	X	X		X
Clinical response						
Disease progression assessment [e]		X	X	X		X
Patient-reported outcomes						
EORTC QLQ C-30 questionnaire	X	X	X	X		
FACIT Fatigue questionnaire	X	X	X	X		
Ongoing patient review						
Adverse events [f]	X	X	X	X	X	X
Compliance Assessment		X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X
Other safety measures	X	X	X	X	X	X
Investigations[g]						
Hematology		X	X	X		
Coagulation (PT, INR and aPTT)		X		X		
Discontinuation visit[h]				X		

a. Before the start of data collection in this study, all subjects (and/or their legally-acceptable representative where applicable) must sign an informed consent form (ICF) allowing data collection and source data verification in accordance with local requirements.
b. Includes number of years of diagnosis, stage, and extent of disease.
c. Includes prior medications and any prior CLL/MCL therapies.

d. May include but not limited to blood pressure, pulse rate, respiratory rate, body temperature, and weight including ECOG performance status.
e. Based on the criteria described in Section 9.1 implemented by the participating physician
f. All AEs and special situations following exposure to ibrutinib will be to be recorded in the CRF, regardless of seriousness or causality. AE collection should start from the time a signed and dated informed consent form is obtained and will apply to all adverse events that occur up until 30 days after a patient's last use within the study. It includes the incidence of deaths, AEs, and AEs reported/observed any time during the course of the study, either during any study visit or through any other mode of communication. AE follow-up required for 30 days after last dose to determine if any new or ongoing drug-related AEs or any SAEs regardless of relationship to Imbruvica™ exists. Follow-up would be conducted by participating site via telephone contact.
g. Investigations including haematological and coagulation profile
h. A discontinuation visit is the visit at which the participating physician is discontinuing Imbruvica™ or first routine clinic visit after the patient stopped taking Imbruvica™ on his own. At the discontinuation visit information on date and reason(s) for Imbruvica™ discontinuation will be collected, if available.
i. For follow-up assessments, a telephonic follow-up call will be made by the participating physician 30 days (±7 days) after last dose of Imbruvica™ or 30 days (±7 days) after completion of 12 months of Imbruvica™ treatment (whichever is earlier), to inquire about any AEs observed.

Abbreviation:
EORTC QLQ C-30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaires Core 30
FACIT Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue

ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
BTK	Bruton's Tyrosine Kinase
CLL	Chronic Lymphocytic Leukaemia
CR	Complete Response
CRF	Case Report Form
del17p	deletions in the short arm of chromosome 17
ECOG	Eastern Cooperative Oncology Group
eDC	Electronic Data Capture
EORTC QLQ C-30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaires Core 30
EOT	End-Of-Treatment
FACIT	Functional Assessment of Chronic Illness Therapy
GCP	Good Clinical Practice
ICF	Informed Consent Form/Document
ICH	International Conference on Harmonization
IRB	Institutional Review Board
IWCLL	International Workshop on Chronic Lymphocytic Leukaemia
MCL	Mantle Cell Lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Overall Response Rate
PD	Progressive Disease
PQC	Product Quality Complaint
PR	Partial Response
PRO	Patient-Reported Outcome
SAE	Serious Adverse Event
SD	Stable Disease
SLL	Small Lymphocytic Lymphoma
TEAE	Treatment-Emergent Adverse Event

1. INTRODUCTION

Ibrutinib (PCI-32765; JNJ-54179060) is a first-in-class potent, orally-administered, covalently-binding small molecule inhibitor of Bruton's tyrosine kinase (BTK) currently under development for the treatment of B-cell malignancies. Ibrutinib is being co-developed by Pharmacyclics, Inc. and Janssen Research & Development, LLC (JRD). The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

Ibrutinib is an oral formulation in a hard gelatin capsule form containing micronized ibrutinib. The initial approval of ibrutinib by the United States (US) FDA for the treatment of an adult patient with mantle cell lymphoma (MCL) who has received at least one prior therapy was received on 13 November 2013. This indication is based on overall response rate. Subsequently it received approval in the US for the treatment of patient with chronic lymphocytic leukemia (CLL) who has received at least one prior therapy, and for the treatment of CLL patient with 17p deletion. It is also approved in the EU for the treatment of adult patients with CLL who have received at least one prior therapy, or in first line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy. Approvals have also been obtained in a number of other countries worldwide. Drug Controller General (India) first approved Ibrutinib for the treatment of patients of CLL or MCL who have received at least one prior therapy or CLL with 17p deletion on October 2015.

The following nonclinical and clinical information summarizes Imbruvica™ (Ibrutinib capsule 140 mg) (Appendix 1). The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

1.1. Background

The generation and maintenance of normal and malignant B cells is controlled by biochemical signals transmitted by the BCR. Bruton's tyrosine kinase is an enzyme required for BCR signalling. Selective BTK inhibition is a novel approach to target diseases driven by BCR activation, such as CLL/SLL (Small Lymphocytic Lymphoma).

In vitro studies have shown that ibrutinib binds covalently to a cysteine residue (Cys-481) in the BTK active site, leading to potent and irreversible inhibition of BTK enzymatic activity.[1] In cellular signal transduction assays with a B-cell lymphoma cell line, ibrutinib inhibited auto-phosphorylation of BTK, phosphorylation of BTK's physiological substrate, phospholipaseCγ (PLCγ), and phosphorylation of a further downstream kinase, extracellular signal-regulated kinase (ERK). Ibrutinib also inhibited the growth of a subset of B-cell lymphoma derived cell lines, with 50% growth inhibition (GI50) values ranging from 0.1 to 5.5 μM.[2] When added directly to human whole blood, ibrutinib inhibits signal transduction from the B-cell receptor and blocks primary B-cell activation (IC50 = 80 nM) as assayed by anti-IgM stimulation followed by CD69 expression.[3]

1.2. Overall Rationale for the Study

CLL is a progressive hematologic disease characterized by an accumulation of monoclonal mature B cells (CD5+ CD23+) in the blood, bone marrow, and secondary lymph organs; diagnosis requires the presence of ≥ 5000 B-lymphocytes/µL in the peripheral blood. The clinical course for CLL ranges from asymptomatic lymphocytosis to aggressive disease involving lymphatic and myelopoietic organs.

Although there have been impressive gains in treatment and in the understanding of the biology of CLL, the disease is incurable using chemotherapy or CIT. Stem cell transplant may be curative, but few patients are able to undergo this treatment. The more relapses patients incur, the more resistant patients become to therapy. Therefore, there is a need for further development of therapies for CLL. The most recent guidelines on the management of CLL states that the biological parameters useful for guiding treatment for CLL are deletions in the short arm of chromosome 17 (del17p), p53, and in the long arm of chromosome 11 (del11q). In particular, patients with the del17p abnormality have an increased risk of relapse and death; the median life expectancy is 2 to 3 years from first-line treatment, and no standard treatment exists for this patient group.

While a minority of patients with CLL will have del17p at the time of diagnosis, the proportion increases with successive chemotherapy treatments to between 30% and 50% of patients having del17p in the relapsed setting. This chromosomal defect results in a loss of functional p53, which thereby confers resistance to subsequent salvage treatments.

CLL has been categorized under lymphoid leukaemia (as C91 in ICD-10) in *Consolidated report of Hospital-Based Cancer Registry of India for year 2007-2011*.[4] Exact number of cases is not reported in the reported but overall number of lymphoid leukaemia cases is as followed:

HBCR	Male N (% of total cancer cases)	Female N (% of total cancer cases)
Mumbai	662 (2.9)	251 (1.4)
Bangalore	390 (3.5)	207 (1.6)
Chennai	450 (2.9)	232 (1.3)
Thiruvananthapuram	739 (3.8)	446 (2.4)
Dibrugarh	27 (0.9)	7 (0.3)
Guwahati	26 (0.4)	19 (0.4)
Chandigarh	155 (5.9)	41 (2.0)

MCL is a rare and incurable subtype of non-Hodgkin Lymphoma (NHL). It accounts for about 6% of all NHL cases in the Western world. At the molecular level, MCL is uniquely characterized by overexpression of the cell cycle regulator protein cyclin D1. This is due to the chromosomal translocation t(11;14)(q13;q32), which puts the cyclin D1 gene, B-cell leukaemia/lymphoma-1 (bcl-1), under the control of the immunoglobulin heavy chain enhancer with subsequent overexpression of cyclin D1. In association with overexpression of cyclin D1, other markers such as CD20 and CD5 are also evident in MCL.

Current initial therapy for the treatment of MCL includes cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine (Hyper-CVAD), often in combination with rituximab (R-CHOP or R-Hyper CVAD). However, many other chemotherapeutic regimens have been evaluated. Younger patients with good performance status are frequently considered for more intensive induction therapy with combinations such as R-Hyper CVAD or alternating R-CHOP and rituximab, dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP) followed by consolidation therapy with autologous stem cell transplant (SCT). Intensive therapy is not an option for most patients with MCL because of their age and comorbidities. Once the disease has progressed after first-line therapy, the prognosis is dismal. Many agents/regimens have been studied and are used. However, there is no globally accepted standard treatment for patients with MCL who progress after initial therapy.

MCL has been categorized under NHL (as C83.1 in ICD-10) in "*Consolidated report of Hospital-Based Cancer Registry of India for year 2007-2011"*.[4] Exact number of MCL cases is not reported in the reported but overall number of NHL cases is as followed:

HBCR	Male N (% of total cancer cases)	Female N(% of total cancer cases)
Mumbai	1381 (6.1)	647(3.5)
Bangalore	520 (4.6)	254 (1.9)
Chennai	655 (4.2)	301 (1.7)
Thiruvananthapuram	954 (5.0)	516 (2.7)
Dibrugarh	83 (2.9)	33 (1.4)
Guwahati	127 (1.9)	60 (1.3)
Chandigarh	114 (4.3)	45 (2.2)

MCL represents around 2-3% of all cases of non-Hodgkin's lymphoma in India [2.1% by Gujral S et al.[11], 3.4% by Naresh KN et al.[12], 1.8% by Nimmagadda RB[13]].

Efficacy in CLL

Extensive pharmacokinetic (PK) sampling has been performed on approximately 186 subjects across 4 studies [Studies PCYC-04753[5], PCYC-1102-CA[6], PCYC-1104-CA[7], and PCYC-1109-CA[8]]. Results show that plasma concentrations of ibrutinib generally increased with increasing dosages from 1.25 to 12.5 mg/kg/day. An increase in ibrutinib AUC was approximately proportional to dose. The coefficient of variation for the AUC ranged from 60% to 107% across all studies. The mean apparent terminal half-life of ibrutinib ranged from 4.3 to 8.9 hours, with median T_{max} of 2 hours. There was no apparent accumulation of ibrutinib exposure after repeated daily dosing.[5,6]

In Study PCYC-1102-CA, ibrutinib was administered as a fixed dosage of 420 mg/day to subjects with relapsed/refractory CLL/SLL. Approximately 95% of subjects had steady-state ibrutinib AUC values ≥160 ng·h/mL, indicating that the 420-mg/day dose is adequate to achieve exposures yielding full BTK active-site occupancy.

Study PCI-32765CLL1002 was an open-label drug-drug interaction study of 18 men, in which ibrutinib was administered alone at a 120-mg dose or in combination with ketoconazole at a 40-mg dose. Results demonstrated a 24-fold increase in ibrutinib area under the plasma concentration-time curve ($AUC_{0\text{-last}}$) and a 29-fold increase in C_{max} following co-administration with ketoconazole. Terminal half-life was not increased. Ibrutinib single-dose administration was well tolerated. No drug-related adverse events (AEs) were reported. No Grade 3 or 4 toxicities or serious adverse events (SAEs) were reported.

Patients with various B-cell malignancies have received ibrutinib across 7 clinical studies, 4 of which included patients with CLL/SLL. Patients with CLL or SLL have received single-agent ibrutinib across 2 clinical studies: Study PCYC-04753, a Phase 1 dose-finding study in patients with recurrent B-cell lymphoma, and Study PCYC-1102-CA, a Phase 1b/2 study in patients with CLL/SLL. Two additional Phase 1b/2 studies are ongoing to evaluate the safety and efficacy of ibrutinib in combination with chemoimmunotherapy (CIT) or CD20 monoclonal antibody therapy in patients with relapsed or refractory CLL/SLL, specifically with BR or FCR in Study PCYC-1108-CA, and with ofatumumab in Study PCYC-1109-CA.

In **Study 1112**, a Phase 3 randomized, comparator-controlled, pivotal study in subjects with CLL/SLL ibrutinib improved efficacy outcomes in subjects with previously treated CLL/SLL compared to that ofatumumab. Analysis of PFS (per the Independent Review Committee [IRC]) demonstrated a statistically significant reduction in the risk of disease progression or death in the ibrutinib arm compared to the ofatumumab arm (HR=0.215, $p<0.0001$). Analysis of OS showed that subjects in the ibrutinib arm had a statistically significant reduction in the risk of death (HR=0.434, p=0.0049). The ORR (per the IRC) was significantly higher ($p<0.0001$) for subjects in the ibrutinib arm (42.6%) than those in the ofatumumab arm (4.1%). The ORR, when including partial response with lymphocytosis (PR-L) (per IRC assessment), was 62.6% for the ibrutinib arm and 4.1% for the ofatumumab arm ($p<0.0001$).

Study **PCYC-04753** was a Phase 1, multicentre, dose-escalation study of ibrutinib in subjects with surface immunoglobulin positive B-cell Non-Hodgkin's Lymphoma (NHL).[5] Subjects were observed for dose-limiting toxicities (DLTs) and other AEs as well as for laboratory and physical examination changes. Fifty subjects were evaluable for efficacy. The ORR was 60%, with 7 CRs and 23 PRs. The maximum tolerated dose (MTD) of ibrutinib was not reached.[5]

Study **PCYC-1102-CA** is a Phase 1b/2, open-label, multicentre study. One hundred seventeen subjects with CLL/SLL were enrolled into 1 of 5 treatment groups, each receiving 1 of 2 fixed dose levels (420 mg/day or 840 mg/day) of ibrutinib. Of the 61 subjects in Groups 1 (relapsed/refractory; 420 mg) and 3 (relapsed/refractory; 840 mg) with relapsed or refractory disease had received a median of 4 (range: 1 to 12) prior therapies, with all subjects receiving nucleoside analogues. The median age for subjects in Groups 1 and 3 was 64 years. Thirty-nine percent of subjects had an ECOG performance score of 0 and 61% had a score of 1 or 2.[6]

Molecular, clinical, and prior treatment characteristics reflected a poor-risk population. 28 (46%) subjects from Groups 1 and 3 were considered refractory to purine analogue therapy (ie, <12-month treatment-free interval following purine analogue regimen). 54% had bulky disease

(defined as single lymph nodes measuring ≥5 cm). 79% of subjects had at least 1 molecular poor-risk feature. (immunoglobulin variable heavy gene [IgVH] unmutated, del [17p], del [11q], or β2 microglobulin >3 mg/L), with 36% of subjects having del (17p).[6]

The ORR was 67% with 2% CRs. An additional 23% of subjects had >50% shrinkage of lymphadenopathy (nodal response) and 3% had stable disease. The 840-mg cohort was stopped after comparable efficacy and safety between 420 mg and 840 mg was shown. The 12-month PFS estimate for Group 1 was 88% and for Group 3 was 82%.[6]

Study **PCYC-1108-CA** is an ongoing combination CIT Phase 1b/2 study which has completed enrolment. Among 33 subjects with relapsed and refractory CLL/SLL enrolled, 30 have received BR and ibrutinib and 3 have received FCR and ibrutinib.[9] The FCR cohort enrolment was suspended due to slow enrolment related to the lack of subjects at participating sites with relapsed CLL in whom the FCR regimen was considered appropriate. For subjects receiving the BR combination, bendamustine 70 mg/m^2 was administered on Day 1 and Day 2, combined with rituximab at 375 mg/m^2 on Day 1 of Cycle 1 and 500 mg/m^2 on Day 1 for all subsequent courses for a maximum of 6 cycles. Ibrutinib was administered as a continuous daily oral dose of 420 mg. The median number of prior therapies was 2 (range 1 to 4). There were 37% and 13% of subjects, respectively, who were considered either refractory to a purine analogue-containing regimen or to BR (treatment-free interval prior to enrolment was <12 months). Bulky disease was present in 52% of subjects.[9]

At a median follow-up of 4.9 months (range 2.7 to 8.3 months), the ORR was 90% (CR 10%, partial response [PR] 80%). Two additional subjects achieved a nodal response with residual lymphocytosis. Responses appear to be independent of high-risk clinical or genomic features. Ninety percent of subjects currently remain on study. Three subjects have discontinued, 2 for progressive disease (PD) and 1 in pursuit of a stem cell transplant.[9]

Study **PCYC-1109-CA** is an ongoing Phase 1b/2 study combining ibrutinib with ofatumumab. Based on preliminary data from 27 subjects with relapsed or refractory CLL/SLL/prolymphocytic leukaemia (PLL) (n=24) or Richter's transformation (RT, n=3), all subjects achieved a PR (100% ORR). The median follow-up is 6.5 months (range: 5.3 to 10.2 months).[8,10]

In Study 1112, a Phase 3 randomized, comparator-controlled, pivotal study in subjects with CLL/SLL ibrutinib improved efficacy outcomes in subjects with previously treated CLL/SLL compared to that ofatumumab. Efficacy results from Studies PCYC-04753, PCYC-1102-CA, PCYC-1108-CA, and PCYC-1109-CA demonstrate that ibrutinib has robust activity in CLL both as a single agent and in combination. All studies included patients with relapsed and refractory disease. Response rates for the 4 studies were independent of high-risk factors or genomic features. The predictable and characteristic pattern of response, with rapid reduction in lymphadenopathy, frequent and early hematologic improvement, and transient lymphocytosis, is consistent with the established anti-homing, anti-adhesion, pro-apoptotic, and anti-proliferative effects of BTK inhibition in CLL cells. Of particular note, high response rates have been demonstrated with continuing therapy in Studies PCYC-1102-CA, PCYC-1108-CA, and PCYC-1109-CA.[6–8]

With these results, Imbruvica™ (Ibrutinib capsule 140 mg). has been approved in various regions of the world including India in patients with CLL who have received at least one prior therapy or CLL with 17p deletion.

Efficacy in MCL

Study **PCI- 32765CLL1002** was an open-label drug-drug interaction study of 18 men, in which ibrutinib was administered alone at a 120 mg dose or in combination with ketoconazole at a 40 mg dose.[14] Results demonstrated that ketoconazole, a strong CYP3A4 inhibitor, increased ibrutinib exposure (C_{max} and AUC_{last}) by 29- and 24-fold, respectively. Terminal half-life was not increased. Ibrutinib single-dose administration was well-tolerated in Study PCI-32765CLL1002. No drug-related AEs were reported. No Grade 3 or 4 toxicities or SAEs were reported.[14]

Efficacy results from **Study PCYC-04753** and Study **PCYC-1104-CA** demonstrate that ibrutinib has activity as a single-agent in treatment of subjects with relapsed or refractory MCL.

Study PCYC-04753 was a Phase 1, multicentre, multi-cohort, open-label, dose-escalation study, in which 56 subjects with relapsed or refractory NHL including CLL and Waldenström's macroglobulinemia were enrolled across 7 dose cohorts.[8] Nine of 56 subjects had a diagnosis of MCL and were evaluable for response. Seven of them achieved an objective response by the Revised Response Criteria for Malignant Lymphoma, including 3 CRs and 4 partial responses [PRs]; 1 subject had stable disease and 1 subject had progressive disease. All of the subjects responding to treatment achieved response at the time of the first post-baseline response assessment (after 2 cycles of treatment). Of the 3 subjects who achieved a CR, 2 subjects had CR on initial post-baseline assessment, and 1 subject achieved a PR initially and they had a CR after 8 cycles (28-days cycle duration) of therapy. Five subjects who entered a long-term follow-up study have durations of response ranging from 10.5 to 27.5 months.[8]

This is an ongoing multicentre Phase 2 study in subjects with MCL who are relapsed or refractory to their previous treatment. Subjects are stratified based on their previous exposure to the chemotherapeutic agent bortezomib.[7] The objectives include studying the efficacy of ibrutinib given as a continuous fixed dose of 560 mg/day. Preliminary results were recently presented on 68 subjects, of whom 51 were evaluable for efficacy. Overall best response (CR + PR) was 69%—71% among the bortezomib naive subjects (N = 31) and 65% among bortezomib-exposed subjects (N = 20). In some patients, treatment with ibrutinib was associated with a transient increase in peripheral lymphocyte count representing a compartmental shift of cells with the CD19+/CD5+ phenotype from nodal tissues to peripheral blood.[7]

In a single arm ibrutinib monotherapy study conducted in patients with relapsed / refractory MCL an ORR of 67.6% a PFS rate of 63% (95% CI 53, 71%) at 6 months and a duration of response of 17.5 months were observed. In an update on time-dependent outcomes till March 2014, the beneficial effects were sustained. The treatment effect seemed fairly consistent throughout the analysed subgroups, including region, relapsed or refractory disease, bulky disease, number of prior regimens, simplified MIPI score, and prior therapy with bortezomib or lenalidomide.

The benefit- risk balance in the indication "treatment of adult patients with relapsed or refractory MCL" is considered positive, as outstanding activity is shown in terms of high response rate in this patient population of previously treated & relapsed or refractory MCL with an unmet clinical need, along with the added convenience of oral dosing once daily. With these results, Imbruvica™ (Ibrutinib capsule 140 mg) has been approved in various regions of the world including India in patients with MCL who have received at least one prior therapy.

Safety Overview

Pooled safety data for subjects treated with ibrutinib monotherapy in 9 studies that have completed primary analysis as of the cutoff date for this Investigator's Brochure update (6 April 2015) (Studies 04753, 1102, 1112, 1117, 1104, MCL2001, 1106, 1118E, and JPN-101) are summarized below. The data presented also include subjects enrolled in Studies 1112 (N=57) and CLL3001 (N=90) who crossed over from ofatumumab or placebo, respectively, to receive treatment with ibrutinib monotherapy after progression and/or positive interim analysis results. Median duration on treatment was 8.3 months (range: 0.0 to 32.3 months).

Treatment-emergent AEs in more than 10% of subjects receiving ibrutinib as monotherapy (N=1071) The most frequently reported treatment-emergent AEs were diarrhea, fatigue, nausea, cough, anemia, pyrexia, and neutropenia.

Treatment-emergent AEs assessed as related to ibrutinib by the investigators in more than 5% of subjects receiving ibrutinib as monotherapy (N=1071). Adverse events that were considered by the investigator to be related to ibrutinib monotherapy were reported in 75.5% of subjects. The most frequently reported AEs related to ibrutinib were diarrhea, fatigue, neutropenia, and nausea.

Treatment-emergent AEs of Grade 3 or 4 in severity in more than 2% of subjects receiving ibrutinib as monotherapy (N=1071). Adverse events of Grade 3 or 4 were reported in 49.3% of subjects. The most commonly reported Grade 3 or 4 AEs that were hematologic in nature were neutropenia, thrombocytopenia, and anemia. Pneumonia, hypertension, and atrial fibrillation were the most frequently reported nonhematologic Grade 3 or 4 AEs.

The incidence of treatment-emergent SAEs reported in more than 1% of subjects receiving ibrutinib as monotherapy (N=1071). Serious AEs were reported in 43.2% of subjects. The most frequently reported SAEs were pneumonia, atrial fibrillation, febrile neutropenia, and pyrexia. The most frequently reported SAEs (any grade) that were considered related to ibrutinib were pneumonia, atrial fibrillation, and febrile neutropenia.

Among the 1071 subjects in the pooled analysis of monotherapy studies, 11.8% discontinued ibrutinib therapy due to an AE. The most frequently reported AEs leading to treatment discontinuation included infections (ie, pneumonia [1.4%] and sepsis [0.8%]), respiratory failure (0.6%), and subdural hematoma (0.5%). Fatal AEs were reported in 9.3% of subjects during study treatment or within 30 days of discontinuation of treatment. The most frequently reported causes of fatal AEs included pneumonia (1.7%), sepsis (0.7%), progressive disease (MCL [0.7%] in

subjects from MCL studies, CLL [0.6%] and Richter's syndrome (0.4%) in subjects from CLL studies).

Upon initiation of treatment, a reversible increase in lymphocyte counts (i.e. ≥ 50% increase from baseline and above absolute count 5000/mcL), often associated with reduction of lymphadenopathy, has been observed in most subjects (approximately 69% to 75%) with CLL/SLL treated with single agent ibrutinib. This effect has also been observed in some patients (33%) with MCL treated with single agent ibrutinib. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first few weeks of ibrutinib therapy (median time 1.1 weeks) and typically resolves within a median of 8.0 weeks in subjects with MCL and 18.7 weeks in subjects with CLL/SLL.

Lymphocytosis appeared to occur in lower incidence and at lesser magnitude in subjects with CLL/SLL receiving ibrutinib in combination with chemo-immunotherapy (i.e. 27% of subjects receiving ibrutinib + BR in Study 1108) or immunotherapy (i.e. 55% of subjects receiving ibrutinib plus ofatumumab in Group 2 of Study 1109).

There were isolated cases of leukostasis reported in subjects treated with ibrutinib. A high number of circulating lymphocytes (> 400000/mcL) may confer increased risk. Subjects should be closely monitored. Administer supportive care including hydration and/or cytoreduction as indicated.

There have been reports of haemorrhagic events in subjects treated with ibrutinib in both monotherapy and combination clinical studies. The majority of these haemorrhagic AEs were of Grade 1 or 2 in severity; those included contusion, epistaxis, and petechiae. Haemorrhagic events of Grade 3 or higher, including central nervous system (CNS) haemorrhage of any grade severity, occurred in 3.4% (17/506) of subjects treated in monotherapy studies and in 3.1% (4/130) of subjects treated in combination therapy studies; none were reported in the healthy volunteer studies (N=100). In the extension study, PCYC-1103-CA, two additional Grade 3 events associated with bleeding were reported ('gastrointestinal haemorrhage' and 'haematotympanum'). It is not clear whether or not these events are attributable to ibrutinib. Subjects were excluded from participation in specific ibrutinib Phase 2 and 3 studies if they required warfarin or other vitamin K antagonists.

However, it is possible that treatment with ibrutinib could increase the risk of bruising or bleeding. Subjects in the current study will be monitored closely for haemorrhagic AEs. Guidance on use of antiplatelet agents and anticoagulants is provided in locally approved prescribing information.

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects treated with ibrutinib therapy. In non-randomized clinical trials, infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects with MCL (≥Grade 3; 25.2%) and CLL/SLL (≥Grade 3; 37.6%). Some of these infections have been associated with hospitalization and death. Although causality has not been established, cases of progressive multifocal leukoencephalopathy have occurred in subjects treated with ibrutinib. Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anaemia) were reported in subjects treated with ibrutinib.

Subjects should be monitored for fever and infections and appropriate anti-infective therapy should be instituted as indicated.

Atrial fibrillation and atrial flutter have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, acute infections, and a previous history of atrial fibrillation. Periodically monitor subjects clinically for atrial fibrillation. Subjects who develop arrhythmic symptoms (e.g., palpitations, lightheadedness) or new onset of dyspnea should be evaluated clinically, and if indicated, have an ECG performed. For atrial fibrillation which persists, consider the risks and benefits of ibrutinib treatment and follow the dose modification guidelines as per Attachment 3 in conjunction with local prescribing information

Other malignant diseases have been observed in subjects who have been treated with ibrutinib, including skin cancers, adenocarcinomas, and other hematologic malignancies. It is not clear whether or not these events are attributable to ibrutinib. Subjects in the current study will be monitored for other malignancies.

Tumour lysis syndrome has been reported with ibrutinib therapy. Subjects at risk of tumour lysis syndrome are those with high tumour burden prior to treatment.

Diarrhoea is the most frequently reported nonhaematologic AEs with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe and are generally managed with supportive therapies including antidiarrheal and antiemetic.

Mild to moderate rash has been commonly reported in subjects treated with either single-agent ibrutinib or in combination with chemotherapy. Rash occurred at a higher rate in the ibrutinib arm than in the ofatumumab arm in Study PCYC-1112-CA.[15] Most rashes were mild to moderate in severity. One case of Stevens-Johnson Syndrome (SJS) was reported in a subject with CLL. The subject received ibrutinib (420 mg/day) and was also receiving various antibiotics and anti-gout medication (allopurinol) known to be associated with SJS. Subjects should be monitored closely for signs and symptoms suggestive of SJS.

Overall Rationale

Post-marketing phase IV clinical trial is useful in identifying new safety issues and trends, which were not observed in previously conducted clinical studies. The data obtained from the present study will help to understand the safety profile of ibrutinib in a real-world Indian scenario compared with that obtained in a controlled clinical environment. The objective of the present study is to address the mandatory regulatory requirement regarding conduct of study in Indian population to monitor the adverse events with Imbruvica™ (Ibrutinib capsule 140 mg). The study will assess the safety of Imbruvica™ prescribed as per locally approved Prescribing Information in Indian patients of CLL or MCL who have received at least one prior therapy or CLL with 17p deletion.

2. OBJECTIVES AND HYPOTHESIS

2.1. Objectives

The aim of the present study is to assess the safety of ibrutinib in a routine clinical set-up in Indian subjects to address the regulatory requirement.

2.1.1. Objectives

Primary Objective

The primary objective of this study is to evaluate the safety of Imbruvica™ (ibrutinib capsule 140 mg) under actual conditions of use.

Exploratory Objectives

To analyse the following outcomes with ibrutinib:

- Baseline patient and disease characteristics
- Response assessment and progression criteria as per International Workshop on Chronic Lymphocytic Leukaemia (IWCLL) criteria[16–18] for CLL and revised response criteria for malignant lymphoma[19] for MCL.
- Change in patient reported outcomes as measured by
    - Quality of Life by EORTC QLQ C-30 instrument (European Organization for Research and Treatment of Cancer Quality of Life Questionnaires Core 30)
    - Fatigue by FACIT Fatigue instrument (Functional Assessment of Chronic Illness Therapy Fatigue)

2.2. Hypothesis

No formal hypothesis testing will be conducted. Data will be summarized using descriptive statistics. Continuous variables will be summarized using the number of observations, mean, SD, coefficient of variation, median, and range as appropriate. Categorical values will be summarized using the number of observations and percentages as appropriate.

3. STUDY DESIGN AND RATIONALE

This is a prospective open label, single arm, multicentre, phase IV interventional study to describe the safety of Imbruvica™ in Indian subjects. Approximately, 75 subjects, selected by investigators and determined to be eligible for ibrutinib treatment as per protocol eligibility criteria will be enrolled in the study, after written informed consent is obtained. Subjects will be monitored for AEs during treatment of Imbruvica™.

3.1. Overview of Study Design

Relapsed/refractory CLL and MCL patients who have received at least one therapy or CLL patients with deletion 17p selected by investigators and determined to be eligible for ibrutinib treatment as per protocol eligibility criteria will be enrolled in the study. Each subject will receive ibrutinib treatment for a period of 12 months or till disease progression, whichever is earlier. Enrolled subjects will be followed up to 12 months from the treatment initiation. During the study period, data will be collected at monthly intervals for the first 6 months, (monthly visit ± 7 days; Visit 1 to 6) . Subsequent visit would be at 9 months ± 7 days [Visit 7]. The End-of-Treatment (EOT) visit will be conducted after the completion of 12-months Imbruvica™ treatment (at Visit 8) or on the day at which the patient discontinued the Imbruvica™ treatment or study. A telephonic follow-up will be conducted 30 days after the EOT Visit.

Screening cum Enrolment Visit (Day 1):
Indian subjects who are eligible to receive Imbruvica™ will be considered in the present study. Prior to data collection, all subjects [and/or their legally acceptable representative where applicable] must sign an informed consent form (ICF) allowing data collection and source data verification in accordance with local regulations. Data collected at this visit may include but not limited to demographics, medical history, disease related history, concomitant medications, patient-reported outcomes (PROs), laboratory investigations, etc. The use of Imbruvica™ is expected to follow dosing and frequency stipulated in the locally approved prescribing information. The recommended dose of Imbruvica™ as per the locally approved Prescribing Information (Appendix 1) is 420 mg (three 140 mg capsules) as a single daily dose for CLL and 560 mg (four 140 mg capsules) as a single daily dose for MCL.

Treatment Period (Visit 1 to 6 and Visit 7):

Enrolled subjects will be followed up to 12 months from the treatment initiation. During the study period, data will be collected at monthly intervals for the first 6 months, (monthly visit ± 7 days; Visit 1 to 6). Subsequent visit would be at 9 months ± 7 days [Visit 7], Data collected at this visit may include but not limited to demographics, medical history, disease related history, AEs, disease progression assessment, concomitant medications, patient-reported outcomes (PROs), laboratory investigations, etc.

End-of-Treatment (EOT) (Visit 8)

The End-of-Treatment (EOT) visit will be conducted after the completion of 12-months Imbruvica™ treatment (at Visit 8) or on the day at which the patient discontinued the Imbruvica™ treatment or study.

The rationale for such schedule is that in the RESONATE Trial, on long term follow up it was found that the prevalence rates for infection, diarrhea, and bleeding events were highest for the first 6 months and gradually declined thereafter

Follow up period (End of Study): A telephonic follow-up will be conducted 30 days after the EOT Visit.

The expected frequency and timing of data collection in this phase IV study are summarized in the TIME AND EVENTS SCHEDULE presented after the synopsis.

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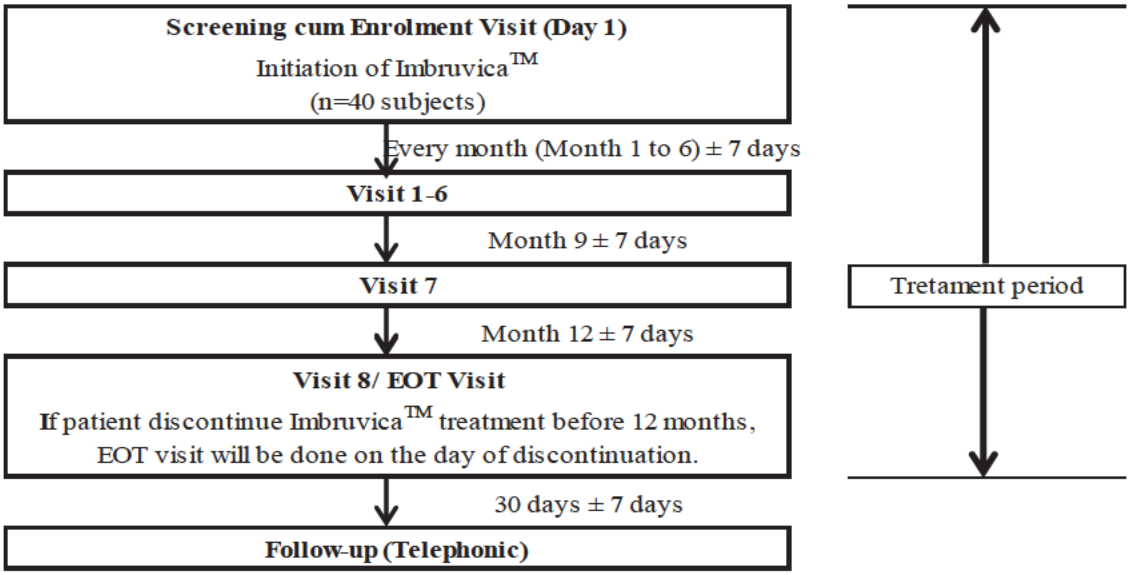


Figure 1: Schematic Overview of the phase IV clinical study for a single patient

Follow up period: A telephonic follow-up will be conducted 30 days after the EOT Visit.

The observation period including the Enrolment Visit and telephonic Follow-up will be up to a maximum duration of 13 months for each patient. The subjects can continue with their prescribed Imbruvica™ treatment after the end of treatment in consultation with the participating physician. The end of the treatment will be the End of Treatment visit within the study for the last participating patient. The overall duration of the study, including recruitment [and/or follow up], is expected to be 36 months.

The expected frequency and timing of data collection in this phase IV clinical study are summarized in the TIME AND EVENTS SCHEDULE presented after the synopsis.

A diagram of the study design is provided in Figure 1.

3.2. Study Design Rationale

Clinical study Design

This is a prospective open label, single arm, multicentre, phase IV interventional tudy to describe the safety of Imbruvica™ in Indian subjects. Approximately, 75 subjects selected by investigators and determined to be eligible for ibrutinib treatment as per protocol eligibility criteria will be enrolled in the study, after written informed consent. Subjects will be monitored for AEs during treatment of Imbruvica™. Participating investigator will be trained on the locally approved prescribing information of Imbruvica™ by the sponsor designee before the enrolment of first subject . The prospective study design facilitates collection of a sufficient quantity of defined variables, where available in clinical practice, to address the study objectives; classical database mining, in contrast, typically provides

only a limited amount of such data. Commercial stocks of Ibrutinib affixed with additional investigational labels (to meet local regulatory requirements) will be used for the subjects enrolled in the study. Subjects will procure Ibrutinib from the existing distribution channel (regular supply chain) as obtained by routine subjects but the drug will be free of cost for clinical trial subjects as per the mentioned duration in the study protocol.

4. SUBJECT POPULATION

The study population will include Indian subjects with CLL or MCL who have received at least one prior therapy or CLL with 17p deletion who are newly initiated on Imbruvica™ treatment as per protocol eligibility criteria. .

Participating sites will be encouraged to enrol subjects in a consecutive manner when subjects come for their regular consultation, in order to minimize bias in patient selection. All eligible subjects should be offered enrolment for data collection within the study.

At each participating site, the participating physician will assess subjects to determine their eligibility for data collection within the study based on the selection criteria listed below. If there is a question about any of the selection criteria, the participating physician should consult with the appropriate sponsor representative before enrolling the patient.

A subject will be considered to have completed the study if he has completed the end of study telephonic follow-up 30 days after EOT visit. Subjects who prematurely discontinue Imbruvica™ for any reason will be considered as completed the study after they have completed the telephonic follow-up post-end of treatment visit at discontinuation.

A subject will be withdrawn from data collection within the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death

If a patient is lost to follow-up, every reasonable effort should be made by the participating site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up should be documented.

When a patient withdraws before completing the study, the reason for withdrawal is to be documented in the case report form (CRF) and in the source document. Subjects who withdraw will not be replaced.

Starting or stopping therapies during the study period will not impact data collection for this study. If treatment with Imbruvica™ needs to be discontinued at the discretion of the participating physician or the patient discontinues Imbruvica™ before the end of the 12-month follow-up, this will not result in automatic withdrawal of the patient from the study. In this scenario, subsequently end of treatment assessments should be documented and EOS will be conducted 30days after EOT.

Treatment with Imbruvica™ should be discontinued if:

- The participating physician believes that for safety reasons (e.g., AEs) it is in the best interest of the patient to discontinue Imbruvica™.
- Disease progression as per participating physician's assessment

4.1. Inclusion Criteria

Each potential patient must satisfy the following criteria to be eligible for data collection in this study:

1. Patient of either sex and ≥18 years of age
2. CLL or MCL patients being newly initiated on Imbruvica™ treatment (ibrutinib capsule 140 mg) based on independent clinical judgment of treating physicians as per locally approved prescribing information
3. Must give a written informed consent indicating that they understand the purpose and are willing to participate in the study and allowing data collection and source data verification in accordance with regulatory requirements

4.2. Exclusion Criteria

Potential patients who meet any of the following criteria will not be eligible for this study:

1. Patients who are not eligible to receive Imbruvica™ as per the locally approved prescribing information.
2. Patients participating or planning to participate in any interventional drug trial during the course of this study.

5. TREATMENT ALLOCATION

Participating investigator will be trained on the protocol as well as on the locally approved prescribing information of Imbruvica™ by the sponsor designee before the enrolment of first patient. The TIME AND EVENTS SCHEDULE summarizes the frequency and timing of safety and other measurements applicable to this study. The exploratory assessments of EORTC QLQ-30, FACIT Fatigue will be scored according to the scores described in Attachment 1: EORTC OLQ C-30 (Specimen Sample)

The primary data source for this study will be the medical records of each participating patient. Source documentation should be available in subjects' medical records for all data entered into the CRF.

Screening cum enrolment visit (Day 1)

The below mentioned procedure and measurements will be performed.

- Written Informed Consent

- Eligibility Criteria
- Demographic data
- Diagnosis and medical history
- Previous and/or current CLL/MCL characteristics
  - Date of initial diagnosis
  - Date of first symptoms
  - Current hospitalization information (reason for admission, date of admission, physical examination including vitals)
  - Prior treatment before enrolment in the study, including chemotherapies, observation, and other CLL or MCL treatments including transplants since diagnosis till screening visit will be documented:
  - Drug name, start/stop dates, dosing regimen, dose modifications, route of administration, and indication.
- Patient-completed PRO instruments (questionnaires and scales)
  - FACIT Fatigue Instrument
  - EORTC QLQ-30
- AEs
- Type, dosage and duration of concomitant medication

Observation Visits (Visit 1 to Visit 8)

The subjects will be followed up at every monthly interval during Visit 1 to Visit 6 for the first 6 months, followed by seventh visit at month 9 and eighth visit at month 12, and as outlined in the TIME AND EVENTS SCHEDULE The below mentioned procedure and measurements will be performed

- Current medical history (symptoms & signs if any, physical examination including vitals)
- Disease progression assessment
- Compliance Assessment
- Patient-completed PRO instruments (questionnaires and scales)
  - FACIT Fatigue Instrument
  - EORTC QLQ-30
- Type, dosage and duration of concomitant medication
- AEs for Imbruvica™ (see Section
- Investigations (Hematology and coagulation profile); as per TIME AND EVENTS SCHEDULE.

Note*: Visit 8 or discontinuation visit will be the EOT Visit.*
A discontinuation visit is the visit at which the participating physician is discontinuing Imbruvica™ or first routine clinic visit after the patient stopped taking Imbruvica™ on his own.

At the discontinuation visit, information on date and reason(s) for Imbruvica™ discontinuation will be collected, if available. The data for discontinuation visit will be collected on the EOT Visit page in CRF.

Telephonic follow up (End of Study)

A follow-up will be performed via a telephonic contact by the participating physician 30 days (±7 days) after last dose of Imbruvica™ or 30 days (±7 days) after completion of 12 months of Imbruvica™ treatment (whichever is earlier). In this follow-up call, enquiry about any AEs observed or concomitant medications taken will be made and recorded in the CRF unless the patient has died, or is lost to follow-up, or has withdrawn consent. Since the information on safety is obtained via telephone contact, written documentation of the communication must be available for review in the source documents. If the patient has died, the date and cause of death will be collected and documented in the CRF. Investigations and their results, if any performed within last 12 weeks will be recorded.

Unscheduled Visit

During an unscheduled visit, below mentioned procedures and measurements may be performed but are not limited to.

- Current medical history (symptoms & signs if any, physical examination including vitals)
- Disease progression assessment
- Compliance Assessment
- Type, dosage and duration of concomitant medication
- AEs for Imbruvica™

6. DOSAGE AND ADMINISTRATION

Dosing Regimen and Administration

Imbruvica™ will be prescribed to the subjects as per locally approved Prescribing Information. The recommended dose of Imbruvica™ is 420 mg (three 140 mg capsules) as a single daily dose for CLL and 560 mg (four 140 mg capsules) as a single daily dose for MCL.

Imbruvica™ should be administered orally once daily with a glass of water at approximately the same time each day. The capsules should be swallowed whole with water and should not be opened, broken, or chewed. Imbruvica™ must not be taken with grapefruit juice.

Imbruvica™ should continue until disease progression or no longer tolerated by the patient.

Refer to the locally approved prescribing informationfor Imbruvica™ and Attachment 3 regarding the updated dose modification guidelines, special warnings, precautions for use, and other important information.

Subjects will have post-trial access to Imbruvica™ for at least one year or as decided by EC whichever is more as per the recommendations of ethics committee as per the recommendations of Subject Expert Committee (Oncology & Haematology) made in its 70th meeting held on 23rd May 2018 at Central Drugs Standard Control Organization HQ, New Delhi communicated vide F.N. 12-10/2017-DC (Pt-Johnson-snd)

Dosing Schedule

Enrolled subjects will receive ibrutinib treatment for the duration of 12 months or till EOT visit. Each subject will receive a monthly supply (90 capsules for CLL and 120 capsules for MCL) at the enrolment visit till month 6. Subsequent refill will be provided at the end of the month or after consumption of the dose provided. Sufficient dose for subsequent 3 months will be provided at the beginning of month 7 and month 10.

	Enrolment visit (beginning of month 1)	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Ibrutinib monthly refill	X	X	X	X	X	X	X X X				X X X	

The following data will be documented during the study period:

- Indication for Imbruvica™
- Start/stop dates and reason for initiation/discontinuation of Imbruvica™
- Date and reason for dose reductions. If dosage reduction of Imbruvica™ is needed, the decision will be taken as per participating physician's discretion and it should be based on and consistent with the recommendation given in the locally approved Prescribing Information.

7. TREATMENT COMPLIANCE

The participating physician or designated personnel will check with the subjects for treatment compliance at each visit (Visits 1 to 8) will accordingly document in the CRF.

8. CONCOMITANT THERAPY

The following data, including drug name, start/stop dates, dose, frequency, dose modifications route of administration, and indication, will be documented at baseline and during the prospective clinical trial.

- Other therapy administered as part of Imbruvica™ treatment regimen
- All concomitant medications

Concomitant therapies for AEs or SAEs during the study should be recorded from the onset of the event, including the dose, frequency of administration, and duration of use where available in the CRF.

Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0.[20] All haematological AEs will be graded and reported according to the IWCLL 2008 criteria for grading of haematological toxicities in CLL studies.[16] The study will include the following evaluations of safety and tolerability according to the time points provided in the TIME AND EVENTS SCHEDULE.

9. STUDY EVALUATIONS

9.1. Efficacy Evaluations

At each participating site, any physician assessments should be performed by the same physician on each occasion for an individual patient, if possible and in accordance with local clinical practice only. Response assessment and progression criteria will be recorded as per International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria[16–18] for CLL and revised response criteria for malignant lymphoma[19] for MCL

Patient-reported outcomes will be measured by **2 questionnaires**. The EORTC QLQ-C30 is a general cancer assessment, and the FACIT Fatigue Scale specifically assesses aspects of fatigue. Samples of the PRO scales are provided in Attachments 1, and 2. The PRO questionnaires will be collected preferably at the beginning of the clinic visits prior to any procedures or physician interactions according to the TIME AND EVENTS SCHEDULE.[21]

The EORTC QLQ-C30 includes 30 separate items resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 Global Health Status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties).[22] The recall period is 1 week (the past week). The EORTC QLQ-C30 has been widely used among cancer patients in general and specifically in CLL patients.[23,24] Scale scores range from 0 to 100. A change of 10 points is considered clinically meaningful for the functioning scales. Administration time is approximately 11 minutes.

FACIT Fatigue is an instrument for use as a measure of the effect of fatigue in patients with cancer and other chronic diseases (http://www.facit.org). Responses to the 13-item FACIT Fatigue Scale are reported on a 5-point categorical response scale ranging from 0 (not at all) to 4 (very much). Higher scores indicate poorer health status. The FACIT Fatigue Scale has been validated in the general population[25] as well as for patients with cancer and rheumatoid arthritis.

Clinical Response and Patient-Reported Outcomes
Exploratory Endpoints

- Proportion of participants experiencing clinical response as per assessment criteria
- Change from baseline in patient-reported outcomes as per EORTC QLQ C-30 and FACIT Fatigue

9.2. Safety Evaluations

Any clinically relevant changes occurring during the study will be recorded in the Adverse Event section of the CRF. Any clinically significant abnormalities persisting at the end of the study or at discontinuation will be followed by the participating physician until resolution or until a clinically stable outcome is reached.

All non-haematological AEs including laboratory AEs and AEs leading to dose reductions or discontinuation will be graded and reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0.[20] All haematological AEs will be graded and reported according to the IWCLL 2008 criteria for grading of haematological toxicities in CLL studies.[16] The study will include the evaluations of safety and tolerability according to the time points provided in the TIME AND EVENTS SCHEDULE.

Safety assessments will be based on medical review of adverse event reports and the results of vital sign measurements, physical examinations, clinical laboratory tests, ECOG performance status, and other safety evaluations at specified time points as described in the Time and Events Schedules

All AEs, with the exception of progression of CLL/MCL, will be reported from the time a signed and dated informed consent form is obtained until 30 days following the end of observation period or until the start of a subsequent systemic antineoplastic therapy, if earlier. AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the subject's legally-acceptable representative) for the duration of the study. AEs if any reported by the patient through means other than physical visit (e.g. telephonically) will also be captured. AEs will be followed by the participating physician, Adverse Event Reporting. Non-hematologic AEs and hematologic AEs events will be graded according to specifications. It will include the incidence of deaths, SAEs, and AEs reported/observed any time during the course of the study, either during any visit or through any other mode of communication. Follow-up will be conducted by participating site via telephone contact. SAEs reported after 30 days of follow up period or 30 days after early discontinuation of Imbruvica™ should also be reported if considered related to Imbruvica™. Follow-up for an AE will be required for 30 days after last dose to determine if any new or ongoing drug-related AEs or any SAEs regardless of relationship to Imbruvica™ exist. The sponsor will evaluate any safety information that is spontaneously reported by a participating physician beyond the time frame specified in the protocol.

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events will be followed by the investigator as specified in Section 12, Adverse Event Reporting.

Clinical Laboratory Tests

Blood samples for hematology and coagulation profile will be collected as per protocol. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. The laboratory reports must be filed with the source documents.

The following tests will be performed by the local laboratory

- Hematology Panel

  -hemoglobin
  -hematocrit
  -red blood cell (RBC) count
  -white blood cell (WBC) count with differential
  -platelet count
  [-percent reticulocytes]
  -absolute lymphocyte count (ALC)
  -coagulation (PT, INR and aPTT)

  Note: A WBC evaluation may include any abnormal cells, which will then be reported by the laboratory. A RBC evaluation may include abnormalities in the RBC count, RBC parameters, or RBC morphology, which will then be reported by the laboratory.
  In addition, any other abnormal cells in a blood smear will also be reported.

Physical examination and Vital Signs

Physical examination and vital sign parameters will be documented at the participating site. Physical examination and vital sign parameters will include blood pressure, pulse rate, respiratory rate, body temperature, and weight.

9.3. Sample Collection and Handling

The sponsor will provide reimbursement for specific investigations to be conducted as listed in TIME AND EVENTS SCHEDULE. The sample collection and handling procedures for these investigations, conducted if any, must be performed as per the guidelines prescribed by the local laboratory practice.

The actual date of sample collection must be recorded in the CRF or laboratory requisition form.

10. SUBJECT COMPLETION/DISCONTINUATION OF STUDY TREATMENT/ WITHDRAWAL FROM THE STUDY

10.1. Completion

The study will be considered completed with the EOS within the study for the last patient participating in the study. A subject will be considered to have completed the study if he or she has completed the telephonic assessments at month 13.

Last completed assessment of subjects who prematurely discontinue study treatment for any reason before completion of this phase IV study will be considered for analysis.

The sponsor reserves the right to close a participating site for data collection or to terminate the study at any time for any reason at the sole discretion of the sponsor. A participating site is considered closed when all required documents and study specific supplies have been collected and a site closure assessment has been performed.

The participating physician may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a participating site by the sponsor or participating physician may include but are not limited to:

- Failure of the participating physician to comply with the protocol, requirements of the IRB or local health authorities, or the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of subjects by the participating physician.

10.2. Discontinuation of Study Treatment/Withdrawal from the Study

Withdrawal From the Study

A subject will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- [Death]

If a subject discontinues study drug and withdraws from the study before the end of the study duration, [end-of-treatment] [and] [posttreatment] assessments should be obtained.

If a subject is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a subject withdraws before completing the study, the reason for withdrawal is to be documented in the CRF and in the source document. Subjects who withdraw will not be replaced. If a subject withdraws from the study before the end of the the study duration, end-of-treatment and post treatment assessments should be obtained.

11. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

11.1. Subject Information

For all subjects who receive at least 1 dose of study drug descriptive statistics will be provided.

11.2. Sample Size Determination

The primary objective of this study is to estimate the incidence of AEs in Indian subjects under actual conditions of use of Imbruvica™. A sample size of 75 subjects is as per the recommendations of Subject Expert Committee (Oncology & Haematology) made in its 70th meeting held on 23rd May 2018 at Central Drugs Standard Control Organization HQ, New Delhi communicated vide F.N. 12-10/2017-DC (Pt-Johnson-snd).

11.3. Efficacy Analyses

Statistical analyses will be performed by or under the authority of the sponsor. A general description of the planned statistical methods to be used to analyze the data collected in this study is presented in the following subsections. Additional details will be provided in the statistical analysis plan.

No formal hypothesis testing will be conducted for this study. Data will be summarized using descriptive statistics. Continuous variables will be summarized using descriptive statistics, which will include the number of subjects, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using frequencies and percentages, as appropriate. Exploratory endpoints will be summarized using descriptive statistics.

11.4. Safety Analyses

Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are adverse events with onset during the treatment phase or that are a consequence of a pre-existing condition that has worsened since baseline. All reported adverse events will be included in the analysis. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group.

Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an adverse event, or who experience a severe or a serious adverse event.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Reference ranges and markedly abnormal results (specified in the Statistical Analysis Plan) will be used in the summary of laboratory data. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the changes from baseline. Changes from baseline results will be presented in pre- versus

posttreatment cross-tabulations (with classes for below, within, and above normal ranges). [Frequency tabulations of the abnormalities will be made. A listing of subjects with any laboratory results outside the reference ranges will be provided. A listing of subjects with any markedly abnormal laboratory results will also be provided.

Parameters with predefined National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) toxicity grades will be summarized. Change from baseline to the worst adverse event grade experienced by the subject during the study will be provided as shift tables.

Vital Signs

Descriptive statistics of temperature, pulse/heart rate, respiratory rate, and blood pressure (systolic and diastolic values) and changes from baseline will be summarized at each scheduled time point. The percentage of subjects with values beyond clinically important limits will be summarized.

Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

Physical Examination

Descriptive statistics of changes from baseline will be summarized at each scheduled time point.

Physical examination findings will be summarized at each scheduled time point. Descriptive statistics will be calculated at baseline and for observed values and changes from baseline at each scheduled time point. Frequency tabulations of the abnormalities will be made.

12. ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events or serious adverse events. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about adverse event occurrence.

Solicited Adverse Events

Solicited adverse events are predefined local and systemic events for which the subject is specifically questioned and which are noted by subjects in their diary.

Unsolicited Adverse Events

Unsolicited adverse events are all adverse events for which the subject is specifically not questioned in the subject diary.

12.1. Definitions

12.1.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to Section 12.3.1. All Adverse Events, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

If a serious and unexpected adverse event occurs for which there is evidence suggesting a causal relationship between the study drug and the event (eg, death from anaphylaxis), the event must be reported as a serious and unexpected suspected adverse reaction even if it is a component of the study endpoint (eg, all-cause mortality).

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For ibrutinib, the expectedness of an adverse event will be determined by whether or not it is listed in the prescribing information.

Adverse Event Associated With the Use of the Drug

An adverse event is considered associated with the use of the drug if the attribution is possible, probable, or very likely by the definitions listed in Section 12.1.2, Attribution Definitions.

12.1.2. Attribution Definitions

Not Related

An adverse event that is not related to the use of the drug.

Doubtful

An adverse event for which an alternative explanation is more likely, eg, concomitant drug(s), concomitant disease(s), or the relationship in time suggests that a causal relationship is unlikely.

Possible

An adverse event that might be due to the use of the drug. An alternative explanation, eg, concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be excluded.

Probable

An adverse event that might be due to the use of the drug. The relationship in time is suggestive (eg, confirmed by dechallenge). An alternative explanation is less likely, eg, concomitant drug(s), concomitant disease(s).

Very Likely

An adverse event that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, eg, concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (eg, it is confirmed by dechallenge and rechallenge).

12.1.3. Severity Criteria

An assessment of severity grade for non-haematological AEs will be made using the NCI-CTCAE Version 4, which includes following descriptors[20]:

- Grade 1 Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Grade 2 Moderate: minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL.
- Grade 3 Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4 Life-threatening: consequences urgent intervention indicated.
- Grade 5 Death related to AE.

Hematologic toxicity will be also assessed by the IWCLL 2008 criteria for grading hematologic toxicity in CLL studies.[16]

For AEs that are not included in the NCI-CTCAE & IWCLL 2008 criteria, an assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

12.2. Special Reporting Situations

Safety events of interest on ibrutinib that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study drug
- Suspected abuse/misuse of the study drug
- Accidental or occupational exposure to the study drug
- Any failure of expected pharmacologic action (ie, lack of effect) of the study drug
- Unexpected therapeutic or clinical benefit from use of the study drug
- Medication error involving a sponsor product (with or without subject/patient exposure to the study drug, eg, name confusion)
- Exposure to a sponsor study drug from breastfeeding

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

12.3. Procedures

In this phase IV clinical study, Imbruvica™ is the Janssen product under study.

The sponsor will provide appropriate pharmacovigilance training to the participating site personnel. The sponsor assumes responsibility for appropriate reporting of (serious) AEs and significant safety information originating from the data collected for Janssen medicinal products to the regulatory authorities. All collected AEs will be summarized in the final study report.

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product safety issues and/or quality issues are listed on the contact information page(s), which is/are provided separately.

Sponsor's Contact Details:
Local Safety Officer
Janssen Pharmaceuticals India
Johnson & Johnson Private Limited, India.
501, Arena Space, 8th Floor,
Behind Majas Bus Depot,
Off. J.V. Link Road, Jogeshwari (East),
Mumbai 400060, India.
Telephone: +91 22 6664 6629
Fax: +91 22 6671 8204
Email: drugsafe@its.jnj.com

12.3.1. All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the subject's last study-related procedure, which may include contact for follow-up of safety. Serious adverse events, including those spontaneously reported to the investigator within 30 days after the last dose of study drug, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

Progression of CLL/MCL will not be considered as an AE. All events that meet the definition of a serious adverse event will be reported as serious adverse events, regardless of whether they are protocol-specific assessments. Signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition as per timelines. Disease progression is defined as per iwCLL 2008 criteria for CLL and revised response criteria for malignant lymphoma:2007 for MCL.

All adverse events, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology. (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

12.3.2. Serious Adverse Events

All serious adverse events occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the CRF, which must be completed and reviewed by a physician from the study site, and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be transmitted electronically or by facsimile (fax).

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event. Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a subject's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.
- For convenience the investigator may choose to hospitalize the subject for the duration of the treatment period.

- Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition (refer to Section 12.1.1, Adverse Event Definitions and Classifications).

12.3.3. Pregnancy

Based on findings in animals, Ibrutinib may cause foetal harm when administered to pregnant women. All initial reports of pregnancy in female subjects or partners of male subjects must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form. Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male subjects included in the study will be reported as noted above.

12.4. Contacting Sponsor Regarding Safety

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

13. PRODUCT QUALITY COMPLAINT HANDLING

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or package integrity. A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of subjects, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

13.1. Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

If the defect is combined with a serious adverse event, the study-site personnel must report the PQC to the sponsor according to the serious adverse event reporting timelines (refer to Section 12.3.2, Serious Adverse Events). A sample of the suspected product should be maintained for further investigation if requested by the sponsor.

13.2. Contacting Sponsor Regarding Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding product quality issues are listed in the Contact Information page(s), which will be provided as a separate document.

14. STUDY DRUG INFORMATION

14.1. Physical Description of Study Drug(s)

IMBRUVICA™ each capsule contains 140 mg of ibrutinib. White opaque, size 0, hard gelatin capsule marked with “ibr 140 mg” in black ink. Refer to the prescribing information or a list of excipients.

14.2. Packaging

IMBRUVICA TM capsules are supplied in a white HDPE bottle with a child resistant closure. Each HDPE bottle with a polypropylene closure contains 90 or 120 hard capsules.
Commercial stocks of IMBRUVICA™ affixed with additional investigational labels (to meet local regulatory requirements) will be provided by the sponsor to clinical trial subject from the existing distribution channel as per the mentioned duration in the study protocol.

14.3. Labeling

Commercial stocks of IMBRUVICA ™ supplied to the subjects will be affixed with additional investigational labels (to meet local regulatory requirements).

Keep out of the sight and reach of children.

14.4. Drug Accountability

Study drug must be handled in strict accordance with the protocol. Study drug returned by the subject must be available for verification by the sponsor's study site monitor during on-site monitoring visits.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study

15. STUDY-SPECIFIC MATERIAL

The investigator will be provided with the following supplies:

- Package Insert for imbruvica ™
- NCI-CTCAE Version 4
- Sample ICF
- CRF & CRF completion guidelines
- PRO questionnaires
  - Quality of Life by EORTC QLQ C-30 instrument (European Organization for Research and Treatment of Cancer Quality of Life Questionnaires Core 30)
  - Fatigue by FACIT Fatigue instrument (Functional Assessment of Chronic Illness Therapy Fatigue)

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

Potential subjects will be fully informed, prior to data collection, of the risks and requirements of the study and, during the study. Subjects will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only subjects who are fully able to understand the risks, benefits, and potential adverse events of the study, and provide their consent voluntarily will be enrolled.

16.2. Regulatory Ethics Compliance

16.2.1. Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

16.2.2. Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the subjects)
- Latest local prescribing information

- Information on compensation for study-related injuries or payment to subjects for participation in the study.
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for subjects
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and subject compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to subjects
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- Latest local prescribing information
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study drug
- New information that may adversely affect the safety of the subjects or the conduct of the study
- Report of deaths of subjects under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for subjects, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At the end of the study, the investigator will notify the IEC/IRB about the study completion

16.2.3. Informed Consent

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The ICF must be signed before performance of any study-related activity. The ICF that is used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the subject can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential subjects the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the subject will receive for the treatment of his or her disease.

The subject will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the subject's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the subject.

16.2.4. Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The subject has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

17. ADMINISTRATIVE REQUIREMENTS

17.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the subjects, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involves only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

17.2. Regulatory Documentation

17.2.1. Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities if applicable. The study will not be initiated until all local regulatory requirements are met.

17.2.2. Required Prestudy Documentation

The following documents must be provided to the sponsor before site initiation to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and subject compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.

- Regulatory authority approval or notification, if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

17.3. Subject Identification, Enrollment, and Screening Logs

The investigator agrees to complete a subject identification and enrollment log to permit easy identification of each subject during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The subject identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure subject confidentiality, no copy will be made. All reports and communications relating to the study will identify subjects by subject identification and date of birth. Since this a non-randomized study, the date seen and date of birth will be used.

The investigator must also complete a subject screening log, which reports on all subjects who were seen to determine eligibility for inclusion in the study.

17.4. Source Documentation

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: subject identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; drug receipt/dispensing/return records; study drug administration information; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The following data will be recorded directly into the CRF and will be considered source data

- Blood pressure and pulse/heart rate
- Height and weight
- Details of physical examination

- PRO (Patient Reported Outcomes)

The minimum source documentation requirements for Section 4.1, Inclusion Criteria and Section 4.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by subject interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

If the electronic source system is utilized, references made to the CRF in the protocol include the electronic source system but information collected through the electronic source system may not be limited to that found in the CRF. Data in this system may be considered source documentation.

17.5. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each subject in electronic format. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an electronic CRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor

All subjective measurements (e.g., FACIT Fatigue instrument, EORTC-QLQ-C30) will be completed by the same individual who made the initial baseline determinations whenever possible

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

17.6. Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, and periodic monitoring visits by the sponsor Written instructions will be provided for collection, handling, storage, and shipment of samples.

The sponsor will review CRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

17.7. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

17.8. Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary. The monitor will record dates of the visits in a study site visit log that will be kept at the study site. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the CRF with the source documents (eg, hospital/clinic/physician's office medical records).

The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the CRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will

be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Treatment

The study is considered completed with the last visit assessment for the last participating patient in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final patient visit assessment at that participating site, in the time frame specified in the Clinical Trial Agreement.

17.9.2. Study Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator

17.10. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Subject privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a

regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

17.11. Use of Information and Publication

All information, including but not limited to information regarding ibrutinib or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study, and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of ibrutinib, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Study subject identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. Secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 12 months of the availability of the final data (tables, listings, graphs), or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines

on authorship, such as those described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, which state that the named authors must have made a significant contribution to the design of the study or analysis and interpretation of the data, provided critical review of the paper, and given final approval of the final version.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law.

• REFERENCES

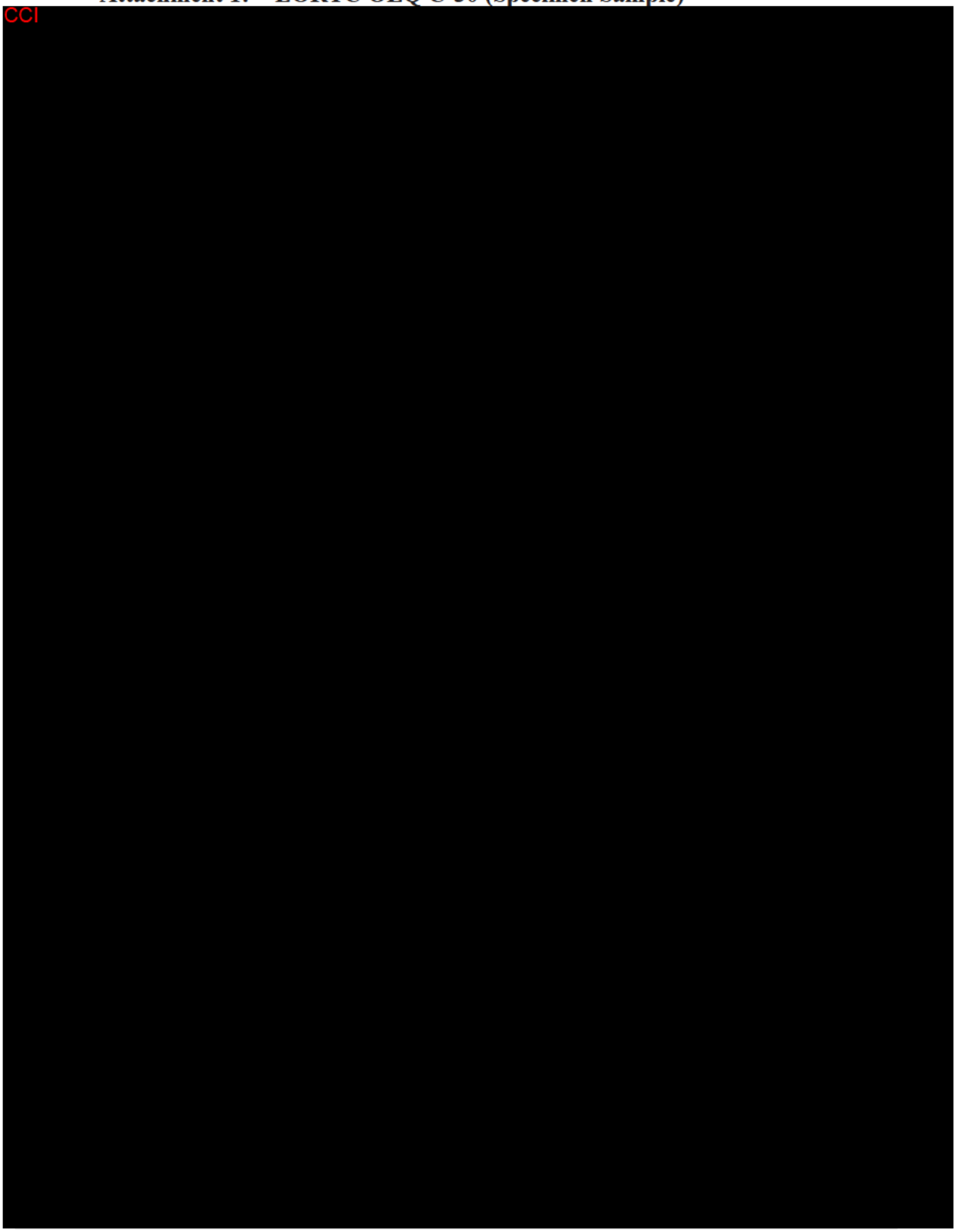
1. Pan Z, Scheerens H, Li S-J, et al. Discovery of Selective Irreversible Inhibitors for Bruton's Tyrosine Kinase. *ChemMedChem*. 2007;2(1):58-61. doi:10.1002/cmdc.200600221.
2. Honigberg LA, Smith AM, Sirisawad M, et al. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. *Proc Natl Acad Sci*. 2010;107(29):13075-13080. doi:10.1073/pnas.1004594107.
3. Herman SEM, Gordon AL, Hertlein E, et al. Bruton tyrosine kinase represents a promising therapeutic target for treatment of chronic lymphocytic leukemia and is effectively targeted by PCI-32765. *Blood*. 2011;117(23):6287-6296. doi:10.1182/blood-2011-01-328484.
4. National Cancer Registry Programme, Indian Council of Medical Research. *Consolidated Report of Hospital Based Cancer Registries 2007-2011- An Assessment of Burden and Care of Cancer Pateints*. Bengaluru, India.: National Center for Disease Informatics and Research; 2013:361. http://www.ncrpindia.org/ALL_NCRP_REPORTS/HBCR_REPORT_2007_2011/index.htm. Accessed January 10, 2015.
5. Advani RH, Buggy JJ, Sharman JP, et al. Bruton Tyrosine Kinase Inhibitor Ibrutinib (PCI-32765) Has Significant Activity in Patients With Relapsed/Refractory B-Cell Malignancies. *J Clin Oncol*. 2013;31(1):88-94. doi:10 1200/JCO.2012.42.7906.
6. Byrd JC, Furman RR, Coutre SE, et al. Targeting BTK with Ibrutinib in Relapsed Chronic Lymphocytic Leukemia. *N Engl J Med*. 2013;369(1):32-42. doi:10.1056/NEJMoa1215637.
7. Wang ML, Rule S, Martin P, et al. Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma. *N Engl J Med*. 2013;369(6):507-516. doi:10.1056/NEJMoa1306220.
8. Jaglowski SM, Jones JA, Flynn JM, et al. A phase Ib/II study evaluating activity and tolerability of BTK inhibitor PCI-32765 and ofatumumab in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and related diseases. *ASCO Meet Abstr*. 2012;30(15_suppl):6508.
9. Brown JR, Barrientos JC, Barr PM, et al. The Bruton tyrosine kinase inhibitor ibrutinib with chemoimmunotherapy in patients with chronic lymphocytic leukemia. *Blood*. 2015;125(19):2915-2922. doi:10.1182/blood-2014-09-585869.
10. Jaglowski SM, Jones JA, Nagar V, et al. Safety and activity of BTK inhibitor ibrutinib combined with ofatumumab in chronic lymphocytic leukemia: a phase 1b/2 study. *Blood*. 2015;126(7):842-850. doi:10.1182/blood-2014-12-617522.
11. Gujral S, Agarwal A, Gota V, et al. A clinicopathologic study of mantle cell lymphoma in a single center study in India. *Indian J Pathol Microbiol*. 2008;51(3):315. doi:10.4103/0377-4929.42503.
12. Naresh KN, Agarwal B, Nathwani BN, et al. Use of the World Health Organization (WHO) Classification of Non-Hodgkin's Lymphoma in Mumbai, India: A Review of 200 Consecutive Cases by a Panel of Five Expert Hematopathologists. *Leuk Lymphoma*. 2004;45(8):1569-1577. doi:10.1080/10428190410001683679.
13. Nimmagadda RV, Digumarti R, Nair R, et al. Histopathological pattern of lymphomas and clinical presentation and outcomes of diffuse large B cell lymphoma: A multicenter registry based study from India. *Indian J Med Paediatr Oncol*. 2013;34(4):299. doi:10.4103/0971-5851 125250.
14. de Jong J, Skee D, Murphy J, et al. Effect of CYP3A perpetrators on ibrutinib exposure in healthy participants. *Pharmacol Res Perspect*. 2015;3(4). doi:10.1002/prp2.156.
15. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia. *N Engl J Med*. 2014;371(3):213-223. doi:10.1056/NEJMoa1400376.
16. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines. *Blood*. 2008;111(12):5446-5456. doi:10.1182/blood-2007-06-093906.
17. Hallek M. Response Assessment in Chronic Lymphocytic Leukemia Treated with Novel Agents Causing an Increase of Peripheral Blood Lymphocytes. June 2012. http://www.bloodjournal.org/content/111/12/5446.e-letters?sso-checked=true#response-assessment-in-chronic-lymphocytic-leukemia-treated-with-novel-agents-causing-an-increase-of-peripheral-blood-lymphocytes. Accessed November 20, 2015.
18. Hallek M. Clarification Of iwCLL Criteria For A Partial Response To Therapy. November 2013. http://www.bloodjournal.org/content/111/12/5446 e-letters?sso-checked=true#clarification-of-iwcll-criteria-for-a-partial-response-to-therapy. Accessed November 20, 2015.
19. Cheson BD, Pfistner B, Juweid ME, et al. Revised Response Criteria for Malignant Lymphoma. *J Clin Oncol*. 2007;25(5):579-586. doi:10.1200/JCO.2006.09.2403.
20. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events v4.03. June 2010. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

21. Perry S, Kowalski TL, Chang C-H. Quality of life assessment in women with breast cancer: benefits, acceptability and utilization. *Health Qual Life Outcomes*. 2007;5:24. doi:10.1186/1477-7525-5-24.
22. Fayers P, Aaronson N, on behalf of the EORTC Quality of Life Group. *The EORTC QLQ-C30 Scoring Manual*. European Organisation for Research and Treatment of Cancer, Brussels; 2001.
23. Doorduijn J, Buijt I, van der Holt B, Steijaert M, Uyl-de Groot C, Sonneveld P. Self-reported quality of life in elderly patients with aggressive non-Hodgkin's lymphoma treated with CHOP chemotherapy. *Eur J Haematol*. 2005;75(2):116-123. doi:10 1111/j.1600-0609 2005.00438.x.
24. Holzner B, Kemmler G, Kopp M, Nguyen-Van-Tam D, Sperner-Unterweger B, Greil R. Quality of life of patients with chronic lymphocytic leukemia: results of a longitudinal investigation over 1 yr. *Eur J Haematol*. 2004;72(6):381-389. doi:10.1111/j.1600-0609 2004.00233.x.
25. Cella D, Lai J, Chang C-H, Peterman A, Slavin M. Fatigue in cancer patients compared with fatigue in the general United States population. *Cancer*. 2002;94(2):528-538. doi:10.1002/cncr.10245.
26. Fleiss JL, Levin B, Paik MC. Statistical Inference for a Single Proportion. In: *Statistical Methods for Rates and Proportions*. 3rd ed. Wiley Series in Probability and Statistics. Hoboken, New Jersey: John Wiley & Sons, Inc.; 2003:Page No 25.
27. *Imbruvica™ (Ibrutinib 140 Mg Capsules) [Prescribing Information]*. India: Johnson & Johnson Private Limited; 2015.

- **ATTACHMENTS**

Attachment 1: EORTC QLQ C-30 (Specimen Sample)

CCI



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CCI

[redacted]

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○ **Attachment 2: Functional Assessment of Chronic Illness Therapy-Fatigue**

FACIT Fatigue Scale (Version 4)

CCI [redacted]

CCI [redacted]

CCI

[redacted]

English (Universal) 16 November 2007

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Attachment 3: Dose Modifications for Adverse Reactions

Imbruvica™ therapy should be withheld for any new onset or worsening Grade 2 cardiac failure, Grade ⩾ 3 non hematological toxicities, Grade 3 or greater neutropenia with infection or fever, or Grade 4 hematological toxicities.

Once the symptoms of the toxicity have resolved to Grade 1 or baseline (recovery), resume IMBRUVICA therapy at the recommended dose as per the tables below.

Table 1: Recommended dose modifications for events of cardiac failure or cardiac arrhythmias:

Events	Toxicity occurrence	MCL/MZL dose modification after recovery Starting Dose 560 mg/day	CLL/SLL/WM/cGVHD dose modification after recovery Starting Dose 420 mg/day
Grade 2 cardiac failure	First	Restart at 420 mg daily	Restart at 280 mg daily
	Second	Restart at 280 mg daily	Restart at 140 mg daily
	Third	Discontinue Imbruvica™	
Grade 3 cardiac arrhythmias	First	Restart at 420 mg daily†	Restart at 280 mg daily†
	Second	Discontinue Imbruvica™	
Grade 3 or 4 cardiac failure Grade 4 cardiac arrhythmias	First	Discontinue Imbruvica™	

† Evaluate the benefit-risk before resuming treatment.

Table 2: Recommended dose modifications for non-cardiac events:

Events	Toxicity occurrence	MCL/MZL dose modification after recovery Starting Dose 560 mg/day	CLL/SLL/WM/cGVHD dose modification after recovery Starting Dose 420 mg/day
Grade 3 or 4 non-hematological toxicities	First*	Restart at 560 mg daily	Restart at 420 mg daily
	Second	Restart at 420 mg daily	Restart at 280 mg daily
Grade 3 or 4 neutropenia with infection or fever	Third	Restart at 280 mg daily	Restart at 140 mg daily
Grade 4 hematological toxicities	Fourth	Discontinue Imbruvica™	

*When resuming treatment, restart at the same or lower dose based on benefit-risk evaluation. If the toxicity reoccurs, reduce daily dose by 140 mg.

Summary of updated dosage modification recommendations:

- For patients experiencing Grade 2 cardiac failure, resume Imbruvica™ treatment at a lower dose (i.e., reduce daily dose by 140 mg).
- For patients experiencing Grade 3 cardiac arrhythmias, evaluate the benefit-risk, and if resuming Imbruvica™ treatment, re-start at a lower dose (i.e., reduce daily dose by 140 mg).

- For patients experiencing Grade 3 or 4 cardiac failure or Grade 4 cardiac arrhythmias, discontinue Imbruvica™ at first occurrence.
- For patients experiencing Grade 3 or 4 non-cardiac events, when resuming Imbruvica™ treatment, evaluate benefit-risk and re-start at the same or lower dose (i.e., reduce daily dose by 140 mg).

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Johnson & Johnson Private Limited

Signature: PPD PPD Date: 20 October 2022

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.