Janssen Research & Development *

Clinical Protocol

A Randomized, Open-label, Safety and Efficacy Study of Ibrutinib in Pediatric and Young Adult Patients With Relapsed or Refractory Mature B-cell non-Hodgkin Lymphoma

Protocol 54179060LYM3003; Phase 3
Amendment 6

JNJ-54179060 (ibrutinib)

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This compound is being investigated in Phase 1, 2 and 3 clinical studies.

This study will be conducted under US Food & Drug Administration IND regulations (21 CFR Part 312).

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Prepared by: Janssen Research & Development, LLC
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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

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PROTOCOL AMENDMENTS

Protocol Version	Issue Date
Original Protocol	12 February 2016
Amendment 1	21 June 2016
Amendment 2	24 April 2017
Amendment 3	7 July 2017
Amendment 4	13 April 2018
Amendment 5	19 December 2019
Amendment 6	15 September 2020

Amendments are listed beginning with the most recent amendment.

Amendment 6 (15 September 2020)	
The overall reasons for the amendment: To report the outcome of the pre-planned interim analysis and clarify impact on further study conduct, including stopping new subject enrollment.	
Applicable Section(s)	Description of Change(s)
Rationale: To report the outcome and recommendations from the independent data monitoring committee (IDMC) following the interim analysis	
Synopsis, Overview of Study Design	Early stopping rules clarified
Rationale: To report survival follow up duration for subjects without progressive disease (PD)	
Synopsis, Efficacy Evaluations/ Endpoints	Survival follow up duration for subjects without PD clarified
Rationale: To report results of the interim analysis	
Synopsis, Statistical Methods	New text added to report the outcome of the pre-planned interim analysis. The IDMC recommended stopping new subject enrollment.
Rationale: Editorial amendment	
Synopsis, Table 2	Typographic error updated in Table 2, Time and Event Schedule. Check box added for pregnancy test at Cycle 1, Day 1. New footnote 'l' added; subsequent footnotes reordered.
Rationale: Editorial amendment	
Section 3.1 Overview of Study Design, Figure 1	Survival follow up duration for subjects without PD clarified
Rationale: Clarification of follow up duration for subjects with or without PD ≥ 3 years	
Section 9.1.4 Posttreatment Phase (Follow-Up)	Added requirement to follow up subjects without PD for survival status after the last efficacy assessment at 3 years. For subjects with PD after 3 years, the reason for progression will be entered in the case report form (CRF).
Rationale: To report results of the interim analysis	
Section 11.9.1 Results of IDMC review on 20 July 2020	New section added to report results of the pre-planned interim analysis. The IDMC recommended stopping new subject enrollment.
Rationale: To report results of the interim analysis	

Section 17.9.1 Study Completion/End of Study	New text added to report results of the pre-planned interim analysis.

Rationale: Minor editorial changes implemented across the protocol

Amendment 5 (19 December 2019)

The overall reasons for the amendment: To update safety information to align with the ibrutinib Investigator's Brochure (IB) to include information regarding cerebrovascular accidents as a new safety observation identified from the post-marketing setting, and to clarify that assessment of pulse/heart rate and blood pressure is expected until end of treatment

Applicable Section(s)	Description of Change(s)
Rationale: To update the safety for ibrutinib, including information on cerebrovascular accidents	
1.3.2.2 Efficacy/Safety Studies	Safety information on ibrutinib updated to align with the current IB
Rationale: To clarify that regular monitoring of pulse/heart rate and blood pressure is expected until end of treatment	
Table 2 and Table 3 Time and Events Schedules (row for "Heart rate and blood pressure" added; footnote added);	Pulse/heart rate and blood pressure assessments added Footnote d (Table 2) and footnote c (Table 3) added to clarify that vital sign assessments should be recorded in source documents but will not be routinely collected in the eCRF
9.8 Safety Evaluations	Vital signs description added to specify pulse/heart rate and blood pressure evaluation methods and timings, ie, at every protocol-specified visit until end of treatment
Rationale: To add an external link for examples of CYP3A inhibitors and inducers; to add additional dose reduction information for CYP3A co-administration	
Attachment 4 Instruction for Concomitant Medications to be Used With Precaution, Attachment 5 Inhibitors and Inducers of CYP3A	Inserted an additional link to FDA classification of CYP3A inhibitors and inducers in Attachment 4 and Attachment 5 Updated dose reduction description in Attachment 4
Attachment 1 Ibrutinib Dosing Guides, Attachment 2 Potential Dose for Younger Subjects	Added dosing tables for 330 mg/m^2, 220 mg/m^2, and 110 mg/m^2 (ie, dose reductions in patients starting at 440 mg/m^2) Moved dosing table for 440 mg/m^2 to Attachment 1; Attachment 2 deleted
Rationale: To improve clarity and accuracy throughout the protocol	
Table 1 and Table 2 Time and Events Schedules	Added a separate Time and Events Schedule for Part 2 of the study (Table 2); removed references to Part 2 as appropriate

Table 1, Table 3, Table 4, Table 5 Time and Events Schedules, Attachment 7 Blood Volume Tables	Added and/or edited headings and footnotes for clarity
3.1 Overview of Study Design	Clarified pharmacokinetic sampling to be obtained only for subjects receiving ibrutinib in combination with background therapy in Part 2
3.1 Overview of Study Design, 6.1 Study Treatment, 9.1.4 Posttreatment Phase (Follow-up)	Clarified subjects must have completed 3 cycles of treatment to be eligible to receive ibrutinib monotherapy
Figure 2 Schematic Overview of the Study (Part 2; Randomized Part), 4.1 Inclusion Criteria	Eligibility criteria updated to specify subjects were to have received only 1 prior line of therapy for inclusion in Part 2 of the study
6 Dosage and Administration	Added reference to Investigational Product Preparation Instruction for subjects requiring dosing through a feeding tube
6.1.2 Ibrutinib Administration	Clarified methods for dispensing ibrutinib by cycle
9.2.3 Lumbar Puncture	Provided additional information for lumbar puncture and cerebral spinal fluid collection
Table 9 International Pediatric non-Hodgkin lymphomas (NHL) Response Criteria	Updated to align with guidance
11.9 Interim Analysis	Replaced “external” with “independent” as a descriptor for the Data Monitoring Committee for consistency within the document.
14.3 Drug Accountability	Specified documentation on the drug accountability form applicable for study drug dispensed from central supply
15 Study-specific Materials	Revised bullet “Visual analog scale for palatability” to read “Visual analog for palatability and acceptability”
17.4 Source Documentation	Deleted bullet referencing history of nicotine use to be recorded into the CRF, as this was not collected for the study

Rationale: Minor editorial changes implemented across the protocol

Amendment 4 (13 April 2018)

The overall reason for the amendment: To amend the study population to subjects in first relapse only, to include the 70 mg/mL multi-dose formulation, to make the protocol consistent with updated safety information in the Investigator’s Brochure (IB; version 11, November 2017) by including ventricular arrhythmias and Hepatitis B reactivation as potential risks along with guidance for their management, and to clarify procedures/requirements for the concomitant administration of CYP-mediated medications and pharmacokinetic sampling in subjects who are not receiving ibrutinib.

Applicable Section(s)	Description of Change(s)
Rationale: Upon review of Part 1 data, subjects with >1 relapse were noted to have very short survival duration partially due to the nature of the disease but also due to toxicity of multiagent CIT. These high-risk subjects are heavily pretreated making them suboptimal candidates for intensive CIT and unable to achieve any meaningful exposure to ibrutinib therapy.	
Synopsis: Subject Population; Figure 1: Eligibility; Figure 2: Eligibility; 4.1. Inclusion Criteria; Criterion 3	Clarified that subjects must be in first recurrence or have disease that is primarily refractory to conventional therapy. Text indicating "or late(r)" recurrence deleted.
Rationale: To include information on the new 70 mg/mL multi-dose formulation.	
14.1.1. Physical Description; 14.1.4. Preparation, Handling, and Storage	Included information regarding the 70 mg/mL multi-dose suspension.
14.1.2. Packaging	Packaging details were added.
14.3. Drug Accountability	Used bottles added to list of potentially hazardous materials.
Rationale: To make the protocol consistent with updated safety information in the IB (Version 11, November 2017) and to align with company core data sheet (CCDS) updates.	
Table 1: Time and Events Schedule (Part 1 and Part 2), footnote "m"; 9.8. Safety Evaluations	Provided more specific guidance related to testing and monitoring of subjects with evidence of Hepatitis B core antibody positivity, and suggested consideration of prophylactic therapy consistent with local practice.
1.3.2.2. Efficacy/Safety Studies, Cardiac Arrhythmias	Updated background on cardiac arrhythmias to align with CCDS; as well as to add ventricular arrhythmias as a potential risk.
Rationale: To clarify the administration of CYP-mediated medications in subjects who are NOT receiving ibrutinib.	
6.1.2. Ibrutinib Administration; 6.2.2. Ibrutinib; 8.1. Permitted Medications and Supportive Therapies; 8.3. Concomitant Medications to be Avoided or to be Used with Caution	Text clarified to indicate restrictions for subjects receiving ibrutinib. There is no restriction in the administration of concomitant medications classified as CYP3A inhibitors/inducers in patients NOT receiving ibrutinib as there is no anticipated interaction.
Rationale: To minimize enrollment of subjects who may not derive clinical benefit from retreatment with ibrutinib after initial failure.	
4.2 Exclusion Criteria; Criterion 15	New exclusion criterion added to exclude subjects with previous exposure to ibrutinib.
Rationale: To align IV hydration requirements with accepted standard practice.	

Applicable Section(s)	Description of Change(s)
Table 4: Dose and Administration Table: RICE With or Without Ibrutinib	IV hydration requirements of 3,000 mL/m^2/day were clarified (ie, required on Days 1 through 5 of each treatment cycle).
Rationale: To understand the impact of ibrutinib on stem cell collection.	
Table 1: Time and Events Schedule (Part 1 and Part 2), Laboratory Assessments; Table 2: Time and Events Schedule: Posttreatment Phase for Subjects Continuing on Ibrutinib Monotherapy, Laboratory Assessments; Table 3: Time and Events Schedule: Posttreatment Phase for Subjects not Receiving Ibrutinib Monotherapy, Laboratory Assessments; 9.1.1. Overview	Text added to include cell count from stem collection for transplant, if applicable.

Applicable Section(s)	Description of Change(s)
Rationale: To avoid the use of language that may not translate as intended.	
Synopsis, Dosage and Administration; Table 1: Time and Events Schedule (Part 1 and Part 2), footnotes "f" and "n"; 1.3.2.2. Efficacy/Safety Studies; 4.3. Prohibitions and Restrictions: Criterion 1 and Criterion 4; 6.2.1. RICE/RVICI; 6.2.2. Ibrutinib; Table 7, Ibrutinib Dose Modifications; 8.3.1. Radiation Therapy; 9.3.1. Evaluations; 11.10. Study Evaluation Team (SET); Attachment 5	Text that previously read "hold or "held" has been revised to "temporarily stop" or "temporarily stopped"
Rationale: To increase clarity throughout the protocol.	
Synopsis, Dosage Administration; Table 4: Dose and Administration Table: RICE With or Without Ibrutinib, footnote "e" Table 5: Dose and Administration Table: RVICI With or Without Ibrutinib, footnote "d" 1.4. Background Chemoimmunotherapy 6.1. Study Treatment	Corticosteroids administered as part of the intrathecal (IT) regimen are not limited to hydrocortisone and prednisolone. Text identifying IT corticosteroid as hydrocortisone or prednisolone deleted.
Attachment 7	Footnote added to clarify that other corticosteroids may be administered as per local supply provided that the steroid equivalent dose is equal to the prednisolone dose.
Table 1: Time and Events Schedule (Part 1 and Part 2), Procedures: BSA	Footnote "d" added to clarify that BSA and dose should only be recalculated at Cycle 2 Day 1 and Cycle 3 Day 1 if there is >10% weight change from the weight used in the previous BSA calculation.
Table 2: Time and Events Schedule: Posttreatment Phase for Subjects Continuing on Ibrutinib Monotherapy, Procedures: BSA, Weight	Footnote "b" modified to clarify that BSA and dose should only be recalculated at Day 1 in Cycles 1-3 if there is >10% weight change from the weight used in the previous BSA calculation. Weight will continue to be obtained prior to dosing on Day 1 for each cycle of monotherapy.

Applicable Section(s)	Description of Change(s)
Table 1: Time and Events Schedule (Part 1 and Part 2), Procedures: Pathology and footnote "b"; 4.1 Inclusion Criteria; Criterion 2 9.1.2. Pretreatment (Screening) Phase	Clarified that the pathology report from the original NHL diagnosis or the pathology report at relapse, if available, is acceptable for the confirmation of diagnosis at study entry.
Table 1: Time and Events Schedule (Part 1 and Part 2), footnote "c"	Clarified that for biomarker studies no tumor tissue sample is required at the End of Treatment in the absence of progressive disease.
Table 1: Time and Events Schedule (Part 1 and Part 2), footnote "a"	Clarified which standard of care assessments can be used for the study if performed within 5 days of signing the ICF.
Table 1: Time and Events Schedule (Part 1 and Part 2), footnote "o"	For Part 2, clarified that assessments taken at 4 hour postdose are applicable for subjects receiving ibrutinib only. Instruction provided for sample collection in the event of post lumbar puncture bleeding.
Table 1, Time and Events Schedule, footnote "j"; 9.2.2. Bone Marrow/Lymph Node Assessment	Clarified that morphology and IHC or flow cytometry of the bone marrow aspirate and/or biopsy are required at screening for all subjects. If a subject has negative bone marrow results at screening, subsequent assessments at disease evaluation visits must include morphologic assessment of the bone marrow, while immunophenotyping is optional.
Table 4: RICE Dose and Administration footnote "d"	In Tables 4 and 5, clarified that the instruction for shortened infusion and stopping criteria for Mesna administration only applies to subjects who are receiving ibrutinib.
Table 5: RVICI Dose and Administration footnote "c"	In Table 5, clarified that the mesna and ifosfamide infusion may be given as per standard of care for subjects not receiving ibrutinib.
6.1. Study Treatment; 7.1. Ibrutinib Compliance	Text added to clarify that dietary intake should be reported on PK days.
8.1.2. Medications Permitted During Treatment	Clarified that a single dose of corticosteroid premedication is allowed prior to rituximab infusion and/or in response to infusion-related reactions. Clarified that non-azole antifungal prophylaxis is allowed for subjects on ibrutinib. Azole antifungals are allowed for subjects randomized to background therapy only
9.1.4. Posttreatment Phase (Follow-Up)	Text referring to Tables 2 and 3 added to clarify follow-up visit intervals.
9.2.1. Imaging Assessments	Clarified that all anatomical regions should be scanned at each timepoint irrespective of the site of disease.
9.3.1. Evaluations	Clarified that subjects must take ibrutinib for a minimum of 3 days prior to all pharmacokinetics timepoints after Cycle 1 Day 1. If ibrutinib is temporarily stopped on any pharmacokinetics sampling days, or within 3 days prior to pharmacokinetics sampling, the medical monitor should be contacted for guidance.
9.7. Palatability Assessment	Clarified that palatability refers to palatability of ibrutinib.

Applicable Section(s)	Description of Change(s)
Rationale: Alignment of text with recent protocol template changes.	
17.3. Subject Identification	Added '(as allowed by local regulations)' following 2 instances of 'date of birth'.
17.4. Source Documentation	Added sentence relating to source documentation in e-Source system.
17.11. Use of Information and Publication	Added the text in bold: 'key assessment parameters of the study will be used to determine a coordinating investigator **for the study'**. Revised the text beginning 'Authorship of publications...'
Rationale: Minor corrections and errors were addressed.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.
Table 4: Dose and Administration Table: RICE With or Without Ibrutinib, Table Title and footnote "d"	Title of tables revised to indicate that background therapies (RICE or RVICI) can be administered with or without ibrutinib. New text added in table and footnotes indicating that shortened infusion for mesna (RICE) and mesna and ifosfamide (RVICI) are for subjects receiving ibrutinib.
Table 5: Dose and Administration Table: RVICI With or Without Ibrutinib, Table Title and footnote "c"	
6.1.2. Ibrutinib Administration	Redundant statement "Ibrutinib is to be taken around the same time each day" removed from second paragraph.

Amendment 3 (7 July 2017)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: To amend the total number of pediatric subjects allowed to be enrolled in Part 1 from 12 subjects to approximately 24 subjects. The ibrutinib exposures have been lower than expected in the initial subjects enrolled in the 2 younger age groups (ages 1-5 and 6-11), and so additional data are required for more certainty surrounding dose confirmation in the younger subjects before opening Part 2 to these 2 younger age groups. There were no unexpected safety findings identified by the Study Evaluation Team (SET) who perform ongoing review of subjects treated with RVICI or RICE in combination with ibrutinib. Furthermore, dose escalations were performed as planned per protocol.

Applicable Section(s)	Description of Change(s)
Rationale: Ibrutinib exposures have been lower than expected in the 2 younger age groups (ages 1-5 and 6-11). Enrolling more subjects into Part 1 will allow for more confidence around the dosing in these younger subjects before opening Part 2 to these 2 younger age groups.	
Synopsis (Overview of Study Design); 3.1 Overview of Study Design; 3.2.2 Study Treatments; 5 Treatment Allocation and Blinding; 6.1 Study Treatment; 11.10 Study Evaluation Team (SET); Attachment 8 (Blood Volume Tables)	Revised the number of subjects to be enrolled into Part 1 (ie, from 12 to up to approximately 24 subjects). Clarified that at a minimum, the first 2 subjects in each age group will enroll into Part 1 before recruitment of children in that age group will begin in Part 2.
Rationale: To clarify testing procedures.	
Table 1 (Time and Events Schedule [Part 1 and Part 2])	Added footnote “e” to clarify timing of drug acceptability and palatability assessment.
Table 1 (Time and Events Schedule [Part 1 and Part 2] footnote “a”)	Clarified standard of care tests now include comorbidities documentation, and include viral serologies in baseline disease documentation.
Table 1 (Time and Events Schedule [Part 1 and Part 2] footnote “m”)	Clarified that if ibrutinib is held on any PK sampling days, or within 3 days prior to PK sampling, the medical monitor should be contacted for guidance. Removed the footnote “m” from individual time points and moved it to the assessment column to include the entire row of assessment.
Table 1 (Time and Events Schedule [Part 1 and Part 2] footnote “n” and corresponding table row)	Clarified timing of Part 2 biomarker blood samples for phospho-protein and molecular characterization, and BTK occupancy evaluations.
Table 2 (Time and Events Schedule: Posttreatment Phase for Subjects Continuing on Ibrutinib Monotherapy; footnote “h”)	Clarified that whole blood samples for phospho-protein and molecular characterization should be obtained at the End-of-Monotherapy Visit and at PD, and samples for BTK occupancy should be obtained if PD occurs during Cycles 1-3 of monotherapy or and the End-of-Monotherapy Visit.

Attachment 8 (Blood Volume Tables)	Added footnotes "f" and "g" for Part 1 and Part 2 respectively to indicate that subjects who enter monotherapy will have a tetanus and pneumococcal titer sample taken at End-of-Monotherapy Visit. Added footnotes "g" and "h" for Part 1 and Part 2 respectively to indicate that for the approximate total blood volume, an additional biomarker sample may be taken if PD occurs during a follow-up visit. Clarified footnote "f" for Part 2 to state that pharmacodynamic and biomarker samples may be collected in Cycle 2 or Cycle 3.
Rationale: To clarify timing of adverse event reporting or concomitant medication collection.	
Table 1 (Time and Events Schedule [Part 1 and Part 2]); 8 Prestudy and Concomitant Therapy; 9.8 Safety Evaluations; 12.3.1 All Adverse Events	Text was amended to indicate that adverse events and concomitant medication use will be collected for 30 days after the last dose, or until the start of subsequent antilymphoma therapy, whichever is earlier, unless related to study treatment.
Rationale: To clarify exclusion criteria for subjects who are pregnant, or breastfeeding, or planning to become pregnant while enrolled in this study.	
4.2 Exclusion Criteria 9	Added text to clarify that subjects who are pregnant, or breastfeeding, or planning to become pregnant while enrolled in this study or within at least 3 months after the last dose of ibrutinib or 1 year after the last dose of the background CIT, whichever is later, are to be excluded from the study.
Rationale: To clarify background chemotherapy doses.	
Synopsis (Dosage and Administration)	Added text to clarify that background chemoimmunotherapy dose values were cumulative.
Rationale: Corrected errors in Amendment 2.	
Table 1 (Time and Events Schedule [Part 1 and Part 2] plasma samples row, biomarker row and footnote "n")	Corrected timing of PK, protein binding, and biomarker assessments by adding an assessment at Cycle 1 Day 14.
Table 2 (Time and Events Schedule: Posttreatment Phase for Subjects Continuing on Ibrutinib Monotherapy)	Timing of limited physical exams was revised to align with the timing of disease evaluations for subjects in the Post-Treatment phase receiving monotherapy with ibrutinib. Assessments were added at 12, 24, and 36 months after Cycle 1 Day 1.
Section 15 Study-Specific Materials	Removed text "Diagnosis and subtyping report form", as this form is not applicable to the study.
Rationale: To clarify ibrutinib target dose and dose adjustment based on exposure data.	
Synopsis (Dosage and Administration); 3.2.2 Study Treatments; 6.1 Study Treatment	Added text to clarify target ibrutinib dose and dose adjustment are based on exposure data.
Rationale: To outline a higher dosing option in the event that drug exposures in the additional subjects enrolled into Part 1 prove to be too low.	
Attachment 2 (Potential Dose for Younger Subjects)	An additional table for suspension and capsule dosing in younger subjects under 12 years of age at 440 mg/m^2 was added.

Rationale: To provide sufficient blood sample for pharmacodynamic evaluation.	
9.1.1 Overview; Attachment 8 (Blood Volume Tables)	Increased blood volumes for pharmacodynamic samples for Part 1 and Part 2 from 4.0 mL to a range of 4.0 – 6.0 mL, and aligned blood sampling with the Time and Events Schedule. Added a new PK and biomarker sample at the End-of-Monotherapy Visit for Parts 1 and 2. These changes increased the approximate total blood volume in Parts 1 and 2 to a min/max of 139-230.5 mL and 131.4-222.9 mL, respectively.
Rationale: To comply with Janssen company standards.	
Title Page	Added Janssen Pharmaceutica NV to list of legal entities
Rationale: Minor errors were noted.	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

Amendment 2 (24 April 2017)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is to incorporate changes requested during Health Authority review.

Applicable Section(s)	Description of Change(s)
Rationale: Per a request received from a Health Authority, contraception language was changed to clarify length of time subjects should avoid pregnancy after the last dose of any study drug.	
Section 4.1 Inclusion Criteria (#10)	Clarified that study participants of childbearing potential must agree to remain on a highly effective birth control method from 1 year after the last dose of the background chemoimmunotherapy (instead of rituximab). Also added that women of child bearing potential must use highly effective contraceptive measures while taking IMBRUVICA. Those using hormonal methods of birth control must add a barrier method (eg, condom with spermicidal foam/gel/film/cream/suppository).
Section 4.2 Exclusion Criteria (#9)	The exclusion criteria were updated to clarify the minimum amount of time a subject should avoid becoming pregnant or breast feeding following the last dose of study drug.
Rationale: To align with the most recent ibrutinib protocol template language.	
Section 1.3.2.2 Efficacy/Safety Studies	The risks associated with ibrutinib use were updated; modified the following sections (Hematological and non-Hematological Adverse Events): cytopenias, lymphocytosis and leukostasis (sections are now separate), bleeding-related events, atrial fibrillation, diarrhea, infections, rash, tumor lysis syndrome, interstitial lung disease; and hypertension and non-melanoma skin cancer (new text added).

Attachment 4 (Instruction for Concomitant Medications to be Used With Precaution); Attachment 5 (Inhibitors and Inducers of CYP3A)	The web link for classification of commonly used inhibitors and inducers of CYP3A enzymes was corrected.
Attachment 5 (Inhibitors and Inducers of CYP3A)	The attachment was updated to reflect recent changes per the website.
Rationale: To exclude subjects with post-transplant lymphoproliferative disease since the pathogenesis of the disease is different from other mature B-cell non-Hodgkin lymphomas (NHLs).	
Section 4.2 Exclusion Criteria (added criterion #13)	Added exclusion criterion for subjects with a diagnosis of post-transplant lymphoproliferative disease (PTLD).
Rationale: To implement the Study Evaluation Team recommendation.	
Section 4.2 Exclusion Criteria (added criterion #14)	Added exclusion criterion for subjects who received an allogeneic bone marrow transplant within 6 months.
Rationale: To define the short axis diameter of an involved lymph node that enables a subject to be enrolled.	
Synopsis (Subject Population); Section 4.1 Inclusion Criteria (#4); Section 9.2.5.1 Evaluation of Measurable Disease	Subjects must have at least 1 site of measurable disease defined as >1 cm in the longest diameter **and >1 cm in the shortest diameter** by radiological imaging, bone marrow involvement, or cerebrospinal fluid with blasts present.
Rationale: Clarified follow-up visit requirement to ensure consistency with the study endpoint.	
Synopsis (Efficacy Evaluations/Endpoints); Table 1 (Time and Events Schedule [Part 1 and Part 2]) footnote "f"); Figure 1 (Schematic Overview of the Study [Part 1; Run-in Part]); Figure 2 (Schematic Overview of the Study [Part 2: Randomized Part]); Section 3.1 Overview of Study Design; Section 9.1.4 Posttreatment Phase (Follow-up)	**Changed statement:** Follow-up visits to assess disease progression will be required if study treatment is discontinued prior to PD (including subjects who go on to transplant) and will be completed as per **Table 2 and Table 3** until PD, the clinical cutoff for the primary endpoint, or **for** up to **3** years after the **date of Cycle 1 Day 1**, whichever occurs first.
Rationale: To clarify Posttreatment Phase evaluations.	
Table 2 (Time and Events Schedule [Posttreatment Phase for Subjects Continuing on Ibrutinib Monotherapy]); Table 3 (Time and Events Schedule [Posttreatment Phase for Subjects not Receiving Ibrutinib Monotherapy])	Table 2 and Table 3 were added to the protocol. The Posttreatment Phase was deleted from Table 1.
Figure 1 (Schematic Overview of the Study [Part 1; Run-in Part]); Figure 2 (Schematic Overview of the Study [Part 2: Randomized Part])	Text was clarified in the figures to align with updated protocol text.

Rationale: To monitor concomitant steroid dosing.	
Section 8.2 Prohibited Medications	Clarified that the medical monitor should be contacted if stress dose steroids are required.
Rationale: To recommend antimicrobial prophylaxis for subjects at risk for opportunistic infections and guide choice of antifungal prophylaxis.	
Section 8.1 Permitted Medications and Supportive Therapies; Section 8.1.2 Medications Permitted During Treatment	Added recommendation for antimicrobial prophylaxis in accordance with standard practice in subjects who are at increased risk for opportunistic infections. Added recommendation for use of non-azole antifungal prophylaxis with coverage for aspergillosis (eg, amphotericin B or echinocandins).
Rationale: Clarified language around mesna dosing in subjects without hematuria.	
Table 4 (Dose and Administration Table: RICE With Ibrutinib)	Removed "shortened infusion" from the dosing instructions for mesna in subjects without hematuria in footnote "d".
Rationale: Concomitant GCSF was added to the RVICI regimen as prophylaxis against neutropenia commonly associated with this regimen.	
Table 5 (Dose and Administration Table: RVICI With Ibrutinib [footnote "e" added); Section 8.1 Permitted Medications and Supportive Therapies	Added GCSF to Dose and Administration table with guidance on timing of administration (GCSF should be administered beginning on Day 12 and continued until ANC ≥500/μL on 2 occasions post-nadir).
Rationale: Changed ifosfamide infusion timing to align with mesna infusion timing.	
Table 5 (Dose and Administration Table: RVICI With Ibrutinib)	Text was changed: Ifosfamide 2 g/m^2/24 hr over 5 days (**administer as a shortened infusion per instructions in the footnote)**[c] (continuous infusion was removed).
Rationale: To clarify treatment modification guidelines for potential ibrutinib-drug related toxicity.	
Synopsis (Dosage and Administration); Section 6.2.2 Ibrutinib	Hematologic toxicities are expected with the background CIT therapies (RICE and RVICI). Therefore, clarified that treatment with ibrutinib should be held for any **unmanageable,** potentially study drug-related toxicity that is Grade ≥3 in severity.
Table 7 (Ibrutinib Dose Modifications)	Dose modifications were clarified.
Rationale: Blood volumes were aligned with the Time and Events Schedule (Table 1).	
Section 9.1.1 Overview; Attachment 7 (Blood Volume Tables)	Updated blood volumes for Cycle 1 (protein binding) in Attachment 7. The estimated maximum total volume of blood was also updated in Section 9.1.1.
Rationale: To indicate that bone marrow on Cycle 2 Day 1 is only to be obtained if clinically indicated.	
Synopsis (Efficacy Evaluations/Endpoints); Table 1 (Time and Events Schedule [Part 1 and Part 2] footnote "h"); Section 9.2.5 Efficacy Evaluations	Clarified timing of imaging, bone marrow assessments and CSF evaluations. Added instruction that bone marrow on Cycle 2 Day 1 is only to be obtained if clinically indicated.

Rationale: To add flow cytometry as an option to evaluate bone marrow specimens.	
Table 1 (Time and Events Schedule [Part 1 and Part 2] footnote "h")	Clarified that morphological examination and IHC or flow cytometry is required of all bone marrow specimens.
Rationale: To avoid the need for repeated imaging and radiation exposure if imaging was recently performed.	
Table 1 (Time and Events Schedule [Part 1 and Part 2] footnote "a"); Section 9.2.1 Imaging Assessments	Added: Imaging performed for standard of care up to 5 days prior to signing ICF may be used as baseline evaluations if they are of sufficient quality.
Rationale: To allow flexibility in the timing of procedures.	
Table 4 (Dose and Administration Table: RICE With Ibrutinib [footnote "e"]); Table 5 (Dose and Administration Table: RVICI With Ibrutinib [footnote "d"])	Clarified that intrathecal therapy may be administered not more than 24 hours before Day 1 of each cycle.
Table 1 (Time and Events Schedule [Part 1 and Part 2] footnotes "g" and "h"); Section 9.2.2 Bone Marrow/Lymph Node Assessment; Section 9.2.3 Lumbar Puncture	Clarified that lumbar puncture and bone marrow procedures may be performed the day prior to the start of a treatment cycle for logistical reasons as needed.
Rationale: To highlight that imaging performed on Cycle 1 Day 14 is exploratory and requires clinician discretion to determine if response assessment is consistent with PD.	
Section 9.1.3 Treatment Phase; Section 9.2.5 Efficacy Criteria	Clarified that imaging evaluations performed on Cycle 1 Day 14 are exploratory; if PD is indicated based on these scans, investigator discretion should be used to determine if the clinical evaluation is consistent with PD. If not, the subject may continue with study treatment until confirmation of PD or the subject meets other criteria for withdrawal.
Rationale: To require documentation of lymph node size on physical exam.	
Section 9.2.4 Physical Examination	Clarified that approximate measurement of palpable lymph nodes or masses should be provided.
Rationale: Clarification was provided regarding disease assessments in subjects with bone marrow only disease.	
Section 9.2.5 Efficacy Criteria	Clarified that for subjects with bone marrow disease and no nodal involvement, imaging is only required at screening.
Rationale: Missing laboratory evaluations (lymphoblasts, urea, serology panel, and tetanus and pneumococcal testing) were added in this section for consistency with the Time and Events Schedules.	
Section 9.8 Safety Evaluations	Lymphoblasts were added to the Hematology Panel, urea was added to the Serum Chemistry Panel, a Viral Serology Panel was added, and tetanus and pneumococcal antibody titers were added to the safety evaluations section of the protocol.
Rationale: Storage conditions for capsules and oral suspension were updated according to the most recent ibrutinib Investigator's Brochure (IB; Edition 10.2).	
Section 14.1.4 Preparation, Handling, and Storage	The storage conditions for ibrutinib 70 mg and 140 mg capsules, and oral suspension were updated for consistency with the current IB.

Rationale: Clarified the results of a recent drug-drug interaction (DDI) study of ibrutinib in combination with moderate CYP3A inhibitors.	
Attachment 4 (Instruction for Concomitant Medications to be Used With Precaution)	A DDI study in patients with B-cell malignancies (PCI-32765LYM1003) found that co-administration of ibrutinib with the moderate CYP3A inhibitors erythromycin and voriconazole, increased C_{max} by 3.4-fold and 6.7-fold and increased AUC by 3.0-fold and 5.7-fold, respectively.
Rationale: Clarifications or corrections were made to the protocol.	
Table 1 (Time and Events Schedule [Part 1 and Part 2])	Footnotes were clarified.
Table 1 (Time and Events Schedule [Part 1 and Part 2]); Section 3.2.6 Biomarker Collection	Timing of biomarker samples was specified.
Table 4 (Dose and Administration Table: RICE With Ibrutinib); Table 5 (Dose and Administration Table: RVICI With Ibrutinib)	The formulations of dexamethasone (IV or PO) were clarified.
Section 3.2.2 Study Treatments; Section 5 Treatment Allocation and Blinding; Section 6.1 Study Treatment	Text was clarified to indicate that for subjects being treated at the lower starting dose of 240 mg/m^2 during the first cycle, the maximum dose should not exceed a 420 mg/day equivalent dose. If the pharmacokinetic data are within the expected range and there are no safety concerns, at Cycle 2, dose escalation may not exceed a 560 mg/day equivalent dose.
Section 6.2.1 RICE/RVICI	Text was clarified to indicate hematologic parameters to be met before initiation of Cycles 2 and 3 due to a treatment delay.
Section 8.3.1 Radiation Therapy	Subjects should have (removed “other”) sites of measurable disease, other than those that were irradiated, that can be followed for response.
Reference 19	Citation corrected (authors and title were correct).
Attachment 1 (Ibrutinib Dosing Guides)	Column added to provide additional detail on actual dose to be administered for suspension formulation.

Amendment 1 (21 June 2016)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The overall reason for the amendment: The overall reason for the amendment is to incorporate changes requested during Health Authority review.

Applicable Section(s)	Description of Change(s)
Rationale: As requested by a Health Authority, enrollment will begin in the 2 older age groups (6-11 years, 12-17 years) before allowing enrollment of children in the youngest age group (1-5 years) to ensure adequate safety and pharmacokinetic data are available and it is deemed safe by the Study Evaluations Team (SET) to proceed in children 1-5 years of age.	
Synopsis (Overview of Study Design and Dosage and Administration); 1.5 Rationale for the Study; 3.1 Overview of Study Design; 3.2.2. Study Treatments; 5. Treatment Allocation and Blinding; 6.1. Study Treatment; 11.10 Study Evaluation Team	Clarified that subjects in the 2 older age groups (6-11 years, 12-17 years) will be enrolled and treated prior to opening enrollment to subjects in the younger age group (1-5 years). The SET will meet to decide on any changes to the starting dose for each age group and when enrollment may begin for the youngest age group.
Rationale: Clarification of screening requirements for subjects who enter the study with only bone marrow disease.	
Table 1 (Time and Events Schedule; footnote 'f'); 9.2.2. Bone Marrow/ Lymph Node Assessment	Subjects will be followed by bone marrow biopsy **and** aspirate. Radiographic images are required at screening but if no nodal disease is identified, subsequent imaging is not required.
Rationale: Clarification of procedures performed in follow-up phase.	
Table 1 (Time and Events Schedule; footnote 'h', 'i')	Added lumbar puncture and bone marrow aspirate and biopsy to follow-up phase, but qualified in footnotes "obtain if clinically indicated".
Rationale: Mesna will be administered as a shortened infusion rather than a bolus to allow the longest infusion time while still separating it from the ibrutinib dosing to avoid drug-drug interactions.	
Table 2 (Time and Events Schedule); Table 3 (Time and Events Schedule)	Revised mesna infusion to a "shortened infusion" instead of a "bolus". Added to footnotes 'c' and 'd' (Table 2) and footnote 'c' (Table 3) that mesna infusion should be stopped 3 hours prior to administering ibrutinib and should not be started for 6 hours after administering ibrutinib.

Applicable Section(s)	Description of Change(s)
Rationale: Correction made to pharmacokinetic sampling after Cycle 1**.** Windows were added to provide guidance for pharmacokinetic sample collection and whole blood sample collection for pharmacodynamics.	
Table 1 (Time and Events Schedule; footnotes 'l' and 'm'); 9.3.1. Evaluations	In Part 1, added that 'Subsequent samples will be collected predose and 1, 2, 4, and 6 hours postdose on Day 1 of Cycle 2 or Cycle 3 (not both). In Part 2 samples will be collected either on Day 7 or 8 of Cycle 1 (preferred), but if unable to be obtained during Cycle 1, can collect on Day 7 or 8 if Cycle 2 or 3. Collection windows provided for all postdose pharmacokinetic sample collection times in footnote 'l'. Collection window provided for 4-hour postdose collection of whole blood sample for pharmacodynamics analysis in footnote 'm'.
Rationale: Additions made to provide serologic evidence to support the exclusion criteria.	
Table 1 (Time and Events Schedule)	Added collection of HIV serologies and Hepatitis B and C serologies to be performed at screening to provide support for exclusion criterion #4. Added footnote 'q': A patient without a known history of these viral infections may be randomized if the serology results are not available at the time of the randomization. However, if the serology results return as positive, the medical monitor should be contacted immediately.
Rationale: Baseline assessment added to aid in interpretation of the same assessments collected during study follow-up.	
Table 1 (Time and Events Schedule)	Added tetanus and pneumococcal antibody titers at screening.
Rationale: Clarification on the timing for collection of sample for protein binding	
Table 1 (Time and Events Schedule, footnote 'l')	Sample for protein binding will be taken on Cycle 1 Day 1 (Part 1 only) and must be obtained prior to any ibrutinib exposure.
Rationale: Correction to number of cycles subjects will receive ibrutinib monotherapy in Posttreatment Phase	
Synopsis (Overview of Study Design); Table 1 (Time and Events Schedule); 6.1.2. Ibrutinib Administration	During the Posttreatment Phase subjects on ibrutinib with a response of PR or better will continue on ibrutinib monotherapy for ~~up to~~ three 28-day cycles.
Rationale: Clarification of the definitions of RICE and RVICI.	
Synopsis (Objectives, Endpoints, and Hypothesis); List of Abbreviations; 1.4. Background Chemotherapy	In this study RICE is defined as: rituximab, ifosfamide, carboplatin, etoposide **and dexamethasone;** and RVICI is defined as: rituximab, vincristine, ifosfamide, carboplatin, idarubicin, **and dexamethasone**. For clarity, statements to indicate this have been added to the protocol.
Rationale: Added description of results from a recent study of ibrutinib in combination with RICE	
1.3.2.2 Efficacy/Safety Studies	Results from a Phase 1 combination study of ibrutinib with RICE in subjects with relapsed or refractory DLBCL were summarized.

Applicable Section(s)	Description of Change(s)
Rationale: Definition of the term 'evaluable patient' was provided for clarity.	
3.1. Overview of Study Design	Subjects in Part 1 will be considered 'evaluable' if PK samples are obtained appropriately and lead to interpretable results.
Rationale: Revised language providing age at which a subject can provide informed consent, as this age varies by country.	
4.1. Inclusion Criteria; 9.1.2. Pretreatment (Screening) Phase	In inclusion criterion #8 'children <18' was deleted. Reference to <18 years of age changed to 'legal age of consent'.
Rationale: Clarification of biopsy requirements at screening.	
Table 1 (Time and Events Schedule; footnote 'o')	Clarified that the pathology report for the original NHL diagnosis should be sent to Janssen immediately after signing the ICF, and if that prior pathology report is not available, results of a fresh biopsy will be required for study entry.
4.1. Inclusion Criteria; 9.1.2. Pretreatment (Screening) Phase	Added to criterion #2 that if the pathology report for the original NHL diagnosis is not available, results of a fresh biopsy will be required for enrollment into the study.
Rationale: Change made as safety precaution to take into account the rituximab-half-life and 3-month cycle of sperm regeneration.	
4.1. Inclusion Criteria	In criterion #10, replaced last dose of 'study drug' with 'at least 3 months after the last dose of ibrutinib and 1 year after the last dose of rituximab, whichever is later'.
Rationale: Guidance for dosing of ibrutinib around the time of lumbar procedures added due to risk of bleeding.	
4.3. Prohibitions and Restrictions	For lumbar punctures, ibrutinib should be held for 24 hours before the procedure. If there is evidence of bleeding at the time of the lumbar puncture (ie, a "bloody tap") defined as > 500 RBC/μL on cell count, a platelet transfusion should be given. Consider giving a platelet transfusion if there is any other clinical sign of bleeding. If bleeding does occur, ibrutinib should be held and the medical monitor should be contacted. If there is no evidence of bleeding during or post-procedure, ibrutinib may be resumed.
Table 1 (Time and Events Schedule; footnote 'l'); 9.3.1. Evaluations	Added 'If a subject experiences bleeding with an lumbar puncture and needs to delay the dose of ibrutinib on Day 1 of the cycle, the Day 1 pharmacokinetic should be done after administration of CIT is complete (on Day 7 or 8) instead. If this occurs during Cycle 1, the Day 1 pharmacokinetic will be skipped altogether.'
Rationale: Change made for consistency with recent PIP modification.	
6.1.2. Ibrutinib Administration	Added recommendation to take ibrutinib within 2 hours after a meal.
Rationale: Change made to allow subjects to switch between capsule and suspension formulations as complications of treatment may lead to difficulty in swallowing capsules.	
6.1.2. Ibrutinib Administration	Changed statement that subjects cannot switch between formulations 'during the study' to 'on days when pharmacokinetic will be drawn'.

Applicable Section(s)	Description of Change(s)
Rationale: Change made for consistency with other studies in the ibrutinib program.	
8.2. Prohibited Medications; 8.3. Concomitant Medications to be Avoided or to be Used with Caution	Strong and moderate CYP3A inhibitors or inducers moved from prohibited medications to concomitant medications to be avoided or to be used with caution.
Rationale: Clarification of what is required to be centrally reviewed before a subject is removed from study therapy.	
8.4. Subsequent Antilymphoma Therapies	Text (indicated in bold type) added to the following sentence: Note that the medical monitor must be notified of the subject's suspected PD and **all** imaging, **bone marrow, and CSF analyses are** required to be centrally reviewed before a subject is removed from the study.
Rationale: Clarification of preferences for scanning options for imaging assessments provided.	
9.2.1. Imaging Assessments	Added a list of scanning options in decreasing order of preference.
Rationale: Clarification added regarding when CSF sampling should occur.	
9.2.3. Lumbar Puncture	Added 'Subsequent sampling in subjects with CNS-positive disease should **occur every 4 days +/- 1 day until CSF is cleared of lymphoma cells. For all subjects, CSF should** be obtained at the **start of each cycle and** following completion of CIT.'
Rationale: Clarification of tissues that can be used for biomarker analysis.	
Synopsis (Pharmacodynamic and Biomarker Evaluations); Table 1 (Time and Events Schedule, footnote 'b'); 9.6. Biomarkers	Added that if archived tissue is unavailable and a fresh lymph node biopsy cannot be obtained, bone marrow biopsy slides (when positive for disease) can be submitted. Added 'In the event that no archived tissue is available, the subject is too unstable to undergo a fresh biopsy, but it is expected that the biopsy may be feasible after beginning chemotherapy, a fresh lymph node biopsy is recommended to be obtained after debulking with the study treatment regimen in subjects with DLBCL only (cell of origin studies will not be affected by initiation of therapy).'
Rationale: To provide a lower acceptable age for subjects providing a palatability assessment	
9.7. Palatability Assessment	Children as young as 4 years old should have the capacity to assess palatability with the given scale. Clarified that the scale is a 5 point visual analog scale.
Rationale: Corrections made to protocol	
9.2.5.1 Evaluation of Measurable Disease	Deleted 'In addition, if more than 6 sites of disease are measurable, then these other sites of measurable disease may be included as assessable disease.'
9.8. Safety Evaluations	Clarified that pregnancy testing needs to be performed within 24 hours prior to the start of treatment.
Table 1 (Time and Events Schedule)	Lumbar puncture/CSF cytologic evaluation assessment added at Early withdrawal/ End of Treatment Visit.

Applicable Section(s)	Description of Change(s)
Rationale: Ibrutinib dosing guides revised to accommodate addition of a lower dose.	
Attachment 1 Ibrutinib Dosing Guides	Table added for suspension and capsule dosing at 120 mg/m^2.
Rationale: Blood volumes were updated in response to changes made to the protocol.	
9.1.1. Overview	Updated blood volumes in Attachment 7. Title changed to '**Estimated Maximum** Volume of Blood…'.
Rationale: Clarification on discontinuation of study treatment	
9.1.3. Treatment Phase	If a subject shows signs of progression on physical examination or laboratory assessment, the subject may continue study treatment until **PD is confirmed by the central IRC** ~~progression is confirmed by centrally assessed computed tomography (CT) scan~~.
Rationale: Clarification to efficacy criteria	
9.2.5. Efficacy Criteria	Added 'Imaging, bone marrow assessments and CSF evaluations are required at each disease assessment.'
Rationale: Clarification regarding when hematology and chemistry samples should be drawn.	
Table 1 (Time and Events Schedule; footnote 'j')	Change made to ensure blood samples are in accordance with the label and as per standard of care in this patient population.
Rationale: Minor clarifications were made in the protocol.	
Table 1 (Time and Events Schedule; footnote 'c')	Clarified that height is collected during disease evaluation visits in the Treatment and Post-treatment phases.
Table 1 (Time and Events Schedule; footnote 'h'); 9.2.3. Lumbar Puncture	Clarified that the lumbar puncture on Cycle 1 Day 1 can be used as the screening lumbar puncture only if collected prior to the administration of ibrutinib or background therapy.
Table 1 (Time and Events Schedule; footnote 'k')	Clarified that timing of serum or urine β-hCG will occur prior to treatment on Cycle 1 Day 1.
Table 1 (Time and Events Schedule; footnote 'm')	Clarified that whole blood samples for flow cytometry and molecular characterization will be collected during Part 1 and Part 2.
Table 1 (Time and Events Schedule; footnote 'n')	Clarified that testing performed per standard of care can be used for the study if performed within 5 days of signing the ICF.
Table 1 (Time and Events Schedule; footnote 'p')	Added that 'Subjects with hematology and chemistry laboratory results from End of Treatment do not need repeat hematology and chemistry testing on monotherapy Cycle 1 Day 1 if testing was performed within 1 week.'
3.2.6. Biomarker Collection	Added that analysis will be performed 'based on availability of tumor samples.'
6. Dosage and Administration	Added that the medical monitor should be contacted for advice on subjects who require dosing through a feeding tube.
6.1. Study Treatment	Clarified that ibrutinib will be supplied as capsules **or** as a suspension.
6.1.2. Ibrutinib Administration	Clarified that the volume of water that should be taken with the ibrutinib capsules or suspension is <u>10 mL/kg with a maximum of</u> 240 mL.
9.2.2. Bone Marrow/ Lymph Node Assessment	Removed reference to samples for biomarkers as it is redundant to information in Section 9.6.

Applicable Section(s)	Description of Change(s)
10.2 Discontinuation of Study Treatment	Clarified statement on study treatment discontinuation to be more definitive (ie, changed “should” to “will”).
Attachment 7 (new)	Blood volume tables moved from body of the protocol into new attachment (Attachment 7).
Rationale: Minor errors were noted	
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.

SYNOPSIS

A Randomized, Open-label, Safety and Efficacy Study of Ibrutinib in Pediatric and Young Adult Patients With Relapsed or Refractory Mature B-cell non-Hodgkin Lymphoma

Ibrutinib (IMBRUVICA®; PCI-32765; JNJ-54179060) is an orally-administered, covalently-binding small molecule Bruton's tyrosine kinase (BTK) inhibitor currently being co-developed by Janssen Research & Development, LLC and Pharmacyclics LLC for the treatment of B-cell malignancies.

OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

Run-in Part (Part 1):

Objectives	Endpoints
Primary	
• Confirm that the pharmacokinetics in pediatric subjects is consistent with that in adults	• Exposure (area under the plasma concentration-time curve [AUC]) • Apparent (oral) plasma clearance (CL/F), apparent (oral) volume of distribution (Vd/F), and derived measures of exposure such as maximum observed plasma concentration (C_{max}) • Relationship between pharmacokinetic parameters and age or measure of body size
Secondary	
• Evaluate the safety and tolerability of ibrutinib in combination with rituximab, ifosfamide, carboplatin, etoposide, and dexamethasone (RICE) or rituximab, vincristine, ifosfamide, carboplatin, idarubicin, and dexamethasone (RVICI) background therapy in pediatric subjects with B-cell malignancies	• Safety parameters, including gastrointestinal effects, immune function, intensified cardiac monitoring (in particular, after previous anthracycline exposure)
• Assess anti-tumor activity of ibrutinib as add-on to RICE or RVICI regimens	• Overall response (complete response [CR], including CR biopsy-negative [CR_b] and unconfirmed CR [CR_u]) and partial response [PR])
• Assess disease-specific biomarkers	• Phospho-BTK, as well as SYK, STAT3, caspase-3, BCL-xL, and cIAP1 expression at baseline and during treatment • B-cell receptor (BCR)/CD79B, CARD11, and MYD mutations • c-MYC, immunoglobulin, and T-cell receptor gene rearrangements at baseline
• Assess the pharmacodynamic response	• BTK occupancy
• Acceptability and palatability assessment of all ibrutinib formulations	• Visual analog scale score for palatability
Exploratory	
• Evaluate other response biomarkers	• Other biomarkers, as applicable
• Explore the exposure-response relationships	• Potential relationships between systemic exposure and response

Randomized Part (Part 2):

Objectives	Endpoints
Primary	
• Assess efficacy (event-free survival [EFS]) of ibrutinib in combination with RICE or RVICI background therapy compared to RICE or RVICI background therapy alone	• Difference in EFS between the 2 treatment groups (an event is defined as the time from randomization to death, disease progression, or lack of CR or PR after 3 cycles of treatment based on blinded independent event review)
Secondary	
• Evaluate the safety and tolerability of ibrutinib in combination with RICE or RVICI background therapy in pediatric subjects and young adults with B-cell malignancies	• Safety parameters, including gastrointestinal effects, immune function, intensified cardiac monitoring (in particular, after previous anthracycline exposure)
• Determine the overall response rate (ORR)	• The proportion of subjects who achieve CR, (including CR_b and CR_u) and PR
• Evaluate tumor volume reduction at Day 14	• Percent decrease in the sum of the products of the lesion diameters at Day 14
• Determine the number and proportion of subjects who proceed to stem cell transplantation	• Number and proportion of subjects who proceed to stem cell transplantation
• Evaluate the time to response	• The time interval from the first dose of ibrutinib to the first documented response for those subjects who respond
• Measure the duration of response	• Duration calculated from the date of initial documentation of a response (CR or PR) to the date of first documented evidence of progressive disease (PD) or death
• Evaluate long-term survival (EFS at 2 and 3 years)	• Proportion of subjects with EFS at 2 and 3 years
• Evaluate overall survival	• The duration from the date of randomization to the date of the subject's death
• Assess disease-specific biomarkers	• Phospho-BTK, as well as SYK, STAT3, caspase-3, BCL-xL, and cIAP1 expression at baseline and during treatment • BCR/CD79B, CARD11, and MYD mutations • c-MYC, immunoglobulin, and T-cell receptor gene rearrangements at baseline
• Assess the pharmacodynamic response, if deemed appropriate based on Part 1 results	• BTK occupancy
• Assess the population pharmacokinetics of ibrutinib in pediatric subjects and young adults	• Population pharmacokinetic parameters and derived systemic exposure to ibrutinib such as AUC • Relationship between pharmacokinetic parameters and age or measure of body size
• Acceptability and palatability assessment of all ibrutinib formulations	• Visual analog scale score for palatability
Exploratory	
• Evaluate other response biomarkers	• Other biomarkers, as applicable
• Explore the exposure-response relationships	• Potential relationships between systemic exposure and response

Hypothesis: The addition of ibrutinib to a salvage chemoimmunotherapy (CIT) regimen will extend EFS compared to CIT alone in pediatric and young adult subjects with relapsed or refractory mature B-cell non-Hodgkin lymphoma (NHL).

OVERVIEW OF STUDY DESIGN

This is a 2-part, multicenter study. A safety and pharmacokinetic run-in part (Part 1) will be conducted before starting the randomized part (Part 2) of the study. Part 2 is a randomized, open-label, Phase 3 study to compare the safety and efficacy of ibrutinib in combination with CIT (RICE or RVICI) versus CIT alone in children and young adult subjects with relapsed or refractory mature B-cell NHL. All subjects in Part 1 will receive ibrutinib in combination with CIT (investigator choice of RICE or RVICI); 6 to approximately 24 pediatric subjects (1 to <18 years) will be enrolled to allow confirmation of the dose regimen. Enrollment will begin with children in the 2 older age groups (6-11, 12-17 years) to assess pharmacokinetic and safety data before allowing enrollment of children in the youngest age group (1-5 years). The SET will meet to decide on any changes to the starting dose for each age group, and when enrollment may begin for the youngest age group. At a minimum, the first 2 subjects in each age group will enroll into Part 1 before recruitment of children in that age group will begin in Part 2. In Part 2, approximately 72 additional subjects will be randomized in a 2:1 ratio to receive ibrutinib in combination with CIT (investigator choice of RICE or RVICI) or CIT alone; at least 40 subjects are targeted to be of age 1 to <18 years and at least 10 of the 40 subjects are targeted to be age <11 years. Subjects will be stratified by histology (Burkitt lymphoma [BL]/Burkitt leukemia [B-AL] versus other) and by background therapy (RICE versus RVICI). Pharmacokinetic samples will be obtained during Part 2 of the study to characterize the pharmacokinetics in pediatric subjects.

Part 1 and Part 2 of the study will be conducted in 3 phases: a Pretreatment (Screening) Phase, a Treatment Phase, and a Posttreatment Phase. The Treatment Phase will extend from enrollment/randomization until 1 of the following: 1) completion of 3 cycles of therapy, 2) transplantation, if clinically indicated, or 3) disease progression, whichever comes first. Subjects will begin the Posttreatment Phase after completion of combination therapy. During the Posttreatment Phase, subjects on ibrutinib with a response of PR or better and have completed 3 cycles of combination treatment will continue on ibrutinib monotherapy for three 28-day cycles as described below (see Dosage and Administration). All subjects will be followed to assess disease progression as described below (see Efficacy Evaluations/Endpoints). The Posttreatment Phase will continue until death, loss to follow up, consent withdrawal, or study end, whichever occurs first. The end of study is defined as when approximately 60 EFS events have occurred in Part 2 (death, disease progression, or lack of CR or PR after 3 cycles of treatment based on blinded independent event review), or the sponsor terminates the study, whichever comes first. Study enrollment may be stopped upon recommendation from the IDMC at the interim analysis based on early stopping rules.

SUBJECT POPULATION

The study population will include subjects with relapsed/refractory BL, Burkitt-like lymphoma, B-AL, diffuse large B-cell lymphoma (DLBCL), DLBCL not otherwise specified, or other pediatric mature B-cell NHL. Subjects should be in first recurrence and have received only one prior line of therapy or have disease that is primarily refractory to conventional therapy. Subjects in Part 1 will be 1 to <18 years old. Subjects in Part 2 will be 1 to 30 years old, inclusive, who had an initial diagnosis of mature B-cell NHL at <18 years of age. Subjects must have at least 1 site of measurable disease defined as >1 cm in the longest diameter and >1 cm in the shortest diameter by radiological imaging, bone marrow involvement, or cerebrospinal fluid with blasts present. Subjects will have a Lansky-Karnofsky score of ≥50.

DOSAGE AND ADMINISTRATION

Ibrutinib at a target dose of 329 mg/m^2 per day (estimated equivalent to the maximum fixed dose of 560 mg per day in adults) is being evaluated as add-on therapy to RICE or RVICI. The first 2 subjects in each of the older groups (6-11 years and 12-17 years) will be started on the estimated 420-mg equivalent dose (240 mg/m^2). The first 2 subjects in the younger age group (1-5 years) will be started on the 420-mg equivalent dose (240 mg/m^2) or lower, as deemed appropriate by the SET following assessment of pharmacokinetic and safety in the 2 older age groups. If there are no safety concerns and exposure (AUC) in Cycle 1 does not exceed the target range, the dose will be increased from Cycle 2 onward for these

2 subjects and for all subsequently enrolled subjects in that age group. However, if exposure (AUC) in the first 2 subjects in a given age group at the 420-mg equivalent is lower than or exceeds the target range set, the dose for these subjects and other subjects in that age group may be adjusted as appropriate based on available exposure data.

Subjects in Part 1 will receive ibrutinib in combination with background CIT (investigator choice of RICE or RVICI) for 3 treatment cycles. Subjects in Part 2 will be randomized in a 2:1 ratio to receive either ibrutinib in combination with CIT (RICE or RVICI) or CIT alone, for 3 treatment cycles. The RICE regimen is comprised of cumulative doses as follows: rituximab 750 mg/m^2, ifosfamide 9 g/m^2, carboplatin 635 mg/m^2, etoposide 300 mg/m^2, and dexamethasone 100 mg/m^2. The RVICI regimen is comprised of cumulative doses as follows: rituximab 750 mg/m^2, vincristine 1.6 mg/m^2, idarubicin 20 mg/m^2, carboplatin 800 mg/m^2, ifosfamide 10 g/m^2, and dexamethasone 100 mg/m^2 (all doses represented as total administered in 1 cycle). For both regimens, triple intrathecal therapy consisting of methotrexate, corticosteroid, and cytarabine will be administered for central nervous system prophylaxis in age-appropriate dosing. Subjects with central nervous system disease will receive additional doses of triple intrathecal therapy. Cycles will be 28 days long, but may be shortened to 21 days. Study treatment will continue for 3 cycles, unless the subject experiences unacceptable toxicity or disease progression. Upon completion of 3 cycles of combination therapy, subjects randomized to ibrutinib having a response of PR or better will continue on ibrutinib monotherapy at the same daily dose for three 28-day cycles or until disease progression or unacceptable toxicity, or up until initiating subsequent antilymphoma therapy or a conditioning regimen for stem cell transplantation, whichever comes first.

Subjects who discontinue any component of CIT without disease progression will continue ibrutinib and remaining CIT components until 3 cycles are completed. If ibrutinib is discontinued for any reason, any remaining study treatment (RICE/RVICI) may continue. Ibrutinib should be temporarily stopped for any unmanageable, potentially study drug-related toxicity that is Grade ≥3 in severity until recovery to Grade ≤1 or baseline.

EFFICACY EVALUATIONS/ENDPOINTS

Assessment of tumor response and disease progression will be according to the International Pediatric NHL Response Criteria. Disease evaluations (imaging, CSF, and bone marrow evaluations) will be performed at baseline, Cycle 1 Day 14 (imaging only), beginning of Cycle 2 (CSF evaluation; only perform bone marrow if clinically indicated), beginning of Cycle 3 (imaging, CSF and bone marrow), and the End-of-Treatment visit (imaging, CSF and bone marrow). During the Posttreatment Phase, all subjects who are without PD including those subjects who discontinue study treatment prior to PD will have efficacy assessments until PD, the clinical cutoff for the primary endpoint, or for up to 3 years after the date of Cycle 1 Day 1, whichever occurs first. After that, evaluations may be performed as clinically indicated (at the discretion of the investigator). Subjects who have not progressed by the last efficacy assessment at 3 years should continue to be followed up for survival status. If PD is assessed after 3 years, the date and reason for progression will be entered in the CRF.

PHARMACOKINETIC EVALUATIONS

Population pharmacokinetics will be performed during Part 1 using a sparse sampling approach. Additional sparse pharmacokinetic samples will be collected during Part 2 to expand the pediatric pharmacokinetic dataset. Pharmacokinetic parameters and exposure information of ibrutinib will be derived using population pharmacokinetic modeling. Individual- as well as population-predicted pharmacokinetic parameters will include CL/F, V_d/F, and metrics of systemic exposure such as AUC and C_{max}, as the data allow. The relationships between pharmacokinetics and response (pharmacodynamics, clinical, or safety endpoints) will also be explored as the data allow. The impact of age or body size on the pharmacokinetic parameters will also be investigated.

PHARMACODYNAMIC AND BIOMARKER EVALUATIONS

Biomarkers will be assessed to characterize the pharmacodynamic profile and to identify markers of response to ibrutinib. Biomarkers will be analyzed in tumor tissue or bone marrow biopsy (if positive for disease), and blood samples.

SAFETY EVALUATIONS

Regular periodic medical evaluations will be conducted including adverse event monitoring, physical examination, weight evolution, vital signs, concomitant medication usage, and performance status evaluation. Hematology and serum chemistry tests will be performed at regular intervals. A baseline and end-of-treatment electrocardiogram (ECG) and left ventricular ejection fraction measurement by multiple-gated acquisition scan (MUGA) or echocardiography is required in all subjects. Further echocardiography/MUGA and ECG are required after each cycle in the RVICI treatment group only. Data will also be collected on new malignant tumors occurring during study treatment and during any protocol-specified follow-up periods.

STATISTICAL METHODS

Approximately 72 subjects will be randomized in Part 2. The sample size calculation for the randomized part (Part 2) is based on the assumption of 100% improvement (hazard ratio = 0.5) in median EFS in subjects receiving ibrutinib plus CIT (RICE or RVICI) compared with CIT (RICE or RVICI) (10 months versus 5 months). Utilizing a 2:1 randomization, Part 2 will enroll approximately 72 subjects (approximately 48 subjects treated with ibrutinib [and RICE or RVICI background therapy]). Based on 60 events for the 2 treatment groups, this study will have at least 80% power, given a 1-sided alpha of 0.05. An accrual rate of 1.44 subjects per month will result in a study duration of approximately 4.2 years. One interim analysis will be conducted when approximately 30 EFS events are reached in Part 2 (expected to be 32 months after the first subject is randomized). An independent Data Monitoring Committee will review safety data periodically and the data from the interim analysis.

Outcome of IDMC review on 20 July 2020

The pre-planned interim analysis was conducted to determine the appropriateness for early stopping using the nonbinding stopping rules, in addition to a review of the efficacy and safety of patients in Part 2 of this study. As the futility boundary for early stopping was reached (31 of 60 EFS events), the IDMC recommended stopping enrollment. Consequently, new patient enrollment has ceased. No new safety concerns were identified. Follow-up of the ongoing patients will continue until the sponsor decides to stop the study.

The primary efficacy endpoint is EFS, which is defined as the time interval from randomization to death, disease progression, or lack of CR or PR after 3 cycles of treatment based on blinded independent event review by an Independent Review Committee, whichever occurs first. The efficacy analysis will be based on the intent-to-treat population, which is defined as all subjects randomized in Part 2 who will be analyzed as randomized. For the primary efficacy analysis, EFS will be compared between treatment groups using a non-stratified log-rank test. The estimate of the hazard ratio between the 2 treatment groups and its associated 90% confidence interval will be computed based on the non-stratified Cox proportional hazards model.

TIME AND EVENTS SCHEDULE

Table 1: Time and Events Schedule (Part 1 Only)

	Pretreatment Phase	Treatment Phase					
	Screening[a] Up to 14 days before administration of study drug	Cycle 1, Day 1	Cycle 1, Day 7 or 8	Cycle 1, Day 14 (±1 day)	Cycle 2, Day 1	Cycle 3, Day 1	Early withdrawal/ End-of-Treatment visit
Procedures							
Informed consent	X						
Pathology report from original NHL diagnosis or at relapse, if available[b]	X						
Formalin-fixed, paraffin-embedded archival biopsy tissue, or fresh lymph node biopsy or bone marrow slides for biomarker studies[c]	X						X[c]
Inclusion/Exclusion criteria confirmed/met	X						
Demographics/Medical history	X						
Complete physical examination including lymph node measurements	X						X
Limited physical examination including lymph node measurements with lymphoma symptoms reviewed		X		X	X	X	
Age-appropriate performance status	X						X
Weight	X	X			X	X	X
Height	X	X			X	X	X
BSA (See Attachment 3)		X			X[d]	X[d]	
ECG	X				X[e]	X[e]	X
Echocardiogram or MUGA	X				X[e]	X[e]	X
Concomitant medications/procedures	Adverse events and concomitant medications to be collected from signing of the ICF and up until 30 days after the last dose of study treatment or until the start of subsequent antilymphoma therapy, if earlier.						
Adverse events							
Drug acceptability and palatability assessment (Visual analog scale); for subjects on ibrutinib only[f]		X				X	
Disease Evaluations							
Disease evaluation (CT/MRI)[g] (see Section 9.2.1)	X			X		X[h]	X[h]
Lumbar puncture/CSF cytologic evaluation	X	X[i]			X[i]	X[i]	X[i]
Bone marrow aspirate and/or biopsy	X[j]				X[j]	X[j]	X[j]

	Pretreatment Phase	Treatment Phase					
	Screening[a] Up to 14 days before administration of study drug	Cycle 1, Day 1	Cycle 1, Day 7 or 8	Cycle 1, Day 14 (±1 day)	Cycle 2, Day 1	Cycle 3, Day 1	Early withdrawal/ End-of-Treatment visit
Laboratory Assessments							
Hematology (see Section 9.8)	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X
Clinical chemistry (see Section 9.8)	X[k]	X[k]	X[k]	X[k]	X[k]	X[k]	X
Serum or urine β-hCG pregnancy test (for young women with childbearing potential)	X	X[l]			X	X	
HIV serologies, Hepatitis B and C serologies[m]	X						
Tetanus and pneumococcal antibody titers	X						
Plasma samples for PK and protein binding (subjects on ibrutinib only)[n]		X	X	X	X	X	
Biomarker blood samples for phospho-protein and molecular characterization and BTK occupancy evaluations [o]		X	X	X	X	X	X
Cell count from stem cell collection for transplant (if applicable; See Section 9.1.1.)		←----------X----------→					

β-hCG=beta-human chorionic gonadotropin; BM=bone marrow; BSA=body surface area; BTK=Bruton's tyrosine kinase; CIT=chemoimmunotherapy; CNS=central nervous system; CSF=cerebrospinal fluid; CT=computed tomography; ECG=electrocardiogram; h=hour(s); HIV=human immunodeficiency virus; ICF=informed consent form; IHC=immunohistochemistry; MRI=magnetic resonance imaging; MUGA=multiple-gated acquisition scan; NHL=non-Hodgkin lymphoma; PD=progressive disease; PK=pharmacokinetics; RVICI=rituximab, vincristine, ifosfamide, carboplatin, idarubicin, and dexamethasone; yrs=years.

a. Standard of care testing to document comorbidities and baseline disease, with the exception of tetanus and pneumococcal titers, hematology, and chemistry, can be counted as screening assessments for the study if performed within 5 days of signing ICF. Procedures must have been performed according to protocol requirements and imaging must meet the Imaging Acquisition Guidelines standards.

b. Pathology report for the original NHL diagnosis or at relapse, if available, should be sent to the Janssen medical monitor immediately after signing the ICF. If the prior pathology report is not available, then a pathology report from a fresh biopsy will be required for study entry.

c. Formalin-fixed paraffin-embedded tumor tissue (mandatory at Screening) collected for biomarker studies only. A fresh lymph node biopsy should be collected at Screening or prior to Cycle 1 and at the time of PD (even if not previously collected), if feasible, where local regulations/shipping logistics permit. If archival tissue is unavailable and a fresh lymph node biopsy cannot be obtained, bone marrow slides (when positive for disease) can be submitted at screening and at the time of PD. No tumor tissue is required at the end of treatment in the absence of progressive disease.

d. BSA and dose should only be recalculated if there is >10% weight change from the weight used in the previous BSA calculation**.**

e. Echocardiography/MUGA and ECG required at the end of each cycle (within 3 days prior to the next cycle) in RVICI treatment group only; otherwise, obtain at Screening and End-of-Treatment only.

f. If ibrutinib is temporarily stopped on C1D1 or C3D1, the assessment should be taken with the first dose of ibrutinib in each respective cycle.
g. Positron emission tomography scan at baseline recommended but not mandatory. Subjects entering study with only BM disease should be followed by BM biopsy and/or aspirate. In these subjects, radiographic images are required at screening but if no nodal disease is identified, subsequent imaging is not required.
h. Scans may be performed up to 3 days prior to Cycle 3 Day 1. Scans may be done ± 3 days of End-of-Treatment visit. Disease evaluations that show PD can be used as end-of-treatment evaluations. Additional disease evaluations may be obtained at discretion of investigator to confirm clinical response or PD.
i. Lumbar puncture in conjunction with triple intrathecal therapy for CNS treatment per the Dosage and Administration tables (Table 5 and Table 6) may be performed the day prior to the start of a treatment cycle for logistical reasons. Lumbar puncture on Cycle 1 Day 1 can be used as the screening lumbar puncture only if collected prior to the administration of any ibrutinib or background therapy. Disease evaluations that show PD can be used as end-of-treatment evaluations.
j. Bone marrow at Cycle 2 Day 1 only if clinically indicated. Morphological examination and IHC or flow cytometry is required of all bone marrow specimens at screening for all subjects. If bone marrow results at screening are negative, subsequent assessments must include morphologic assessment of the bone marrow, while immunophenotyping is optional. Procedure may be performed 1 day prior to the start of a treatment cycle for logistical reasons. If marrow is empty (lack of count recovery), repeat marrow should be obtained prior to initiating next cycle. Refer to protocol Section 9.2.2 for details regarding bone marrow testing. Disease evaluations that show PD can be used as end-of-treatment evaluations.
k. Must be taken on day of or day prior to dosing, provided results are available before study drug is given. Hematology and chemistry should be done at Screening and on Cycle 1 Day 1 and weekly thereafter in Cycle 1. For Cycle 2 and Cycle 3, hematology and chemistry should be done on Day 1 and between Days 14 to 21.
l. Required within 24 hours prior to treatment on Cycle 1 Day 1.
m. Hepatitis B serologic testing should include HBsAg, HBcAb, and HBsAb. A subject without a known history of these viral infections may be randomized if the serology results are not available at the time of the randomization. However, if the serology results return as positive, the medical monitor should be contacted immediately, and the guidance provided in Section 9.8 should be followed.
n. On days of PK sample collection, ibrutinib should be taken within 2 hours after a meal. If ibrutinib is temporarily stopped on any PK sampling days, or within 3 days prior to PK sampling, the medical monitor should be contacted for guidance.
In Cycle 1, samples collected predose and at 1 (window 45-75 minutes), 2 (window 1.5-2.5 hours), 4 (window 3.5-5 hours), and 6 hours (window 5-8 hours) postdose on Day 1 and on Day 7 or 8 (per investigator choice). Subsequent samples will be collected predose and 1, 2, 4, and 6 hours postdose on Day 1 of Cycle 2 or Cycle 3 (not both). If a subject experiences bleeding with a lumbar puncture and needs to delay the dose of ibrutinib on Day 1 of the cycle, the Day 1 PK should be done after administration of CIT is complete (on Day 7 or 8) instead. If this occurs during Cycle 1, the Day 1 PK will be skipped altogether. The sample for protein binding will be taken on Cycle 1 Day 1 and must be obtained prior to any ibrutinib exposure.
o. Whole blood sample taken predose and at 4 hours postdose (window 3.5-6h, to coincide with the 4h PK sample) on Day 1 and Day 7 or 8 of Cycle 1 (same day and time as PK samples), predose on Cycle 2 Day 1 or Cycle 3 Day 1, and at PD or the End-of-Treatment visit. If a subject experiences bleeding with a lumbar puncture and needs to delay the dose of ibrutinib on Day 1 of the cycle, a predose and 4h sample should be done after administration of CIT is complete (on Day 7 or 8) instead (same as PK samples). If this occurs during Cycle 1, a predose sample must also be obtained prior to any treatment on Day 1 and prior to ibrutinib exposure.

Table 2: Time and Events Schedule (Part 2)

	Pretreatment Phase	Treatment Phase				
	Screening[a] Up to 14 days before administration of study drug	Cycle 1, Day 1	Cycle 1, Day 14 (±1 day)	Cycle 2, Day 1	Cycle 3, Day 1	Early withdrawal/ End-of-Treatment visit
Procedures						
Informed consent	X					
Pathology report from original NHL diagnosis or at relapse, if available[b]	X					
Formalin-fixed, paraffin-embedded archival biopsy tissue, or fresh lymph node biopsy or bone marrow biopsy slides for biomarker studies[c]	X					X[c]
Inclusion/Exclusion criteria confirmed/met	X[a]					
Demographics/Medical history	X[a]					
Complete physical examination including lymph node measurements	X[a]					X
Limited physical examination including lymph node measurements with lymphoma symptoms reviewed		X	X	X	X	
Age-appropriate performance status	X[a]					X
Weight	X[a]	X		X	X	X
Height	X[a]	X		X	X	X
Vital signs[d]	Pulse/heart rate and blood pressure are expected in all protocol-specified visits					
BSA (See Attachment 3)		X		X[e]	X[e]	
ECG	X[a]			X[f]	X[f]	X
Echocardiogram or MUGA	X[a]			X[f]	X[f]	X
Concomitant medications/procedures Adverse events	Adverse events and concomitant medications to be collected from signing of the ICF and up until 30 days after the last dose of study treatment or until the start of subsequent antilymphoma therapy, if earlier.					
Drug acceptability and palatability assessment (Visual analog scale); for subjects on ibrutinib only[g]		X			X	
Disease Evaluations						
Disease evaluation (CT/MRI)[h] (see Section 9.2.1)	X[a]		X		X[i]	X[i]
Lumbar puncture/CSF cytologic evaluation	X[a]	X[j]		X[j]	X[j]	X[j]
Bone marrow aspirate and/or biopsy	X[k]			X[k]	X[k]	X[k]

	Pretreatment Phase	Treatment Phase				
	Screening[a] Up to 14 days before administration of study drug	Cycle 1, Day 1	Cycle 1, Day 14 (±1 day)	Cycle 2, Day 1	Cycle 3, Day 1	Early withdrawal/ End-of-Treatment visit
Laboratory Assessments						
Hematology (see Section 9.8)	X[m]	←----------X[m]----------→				
Clinical chemistry (see Section 9.8)	X[m]	←----------X[m]----------→				
Serum or urine β-hCG pregnancy test (for young women with childbearing potential)	X[a]	X[l]		X[n]	X[n]	
HIV serologies, Hepatitis B and C serologies[o]	X[a]					
Tetanus and pneumococcal antibody titers	X[a]					
Plasma samples for PK and protein binding (subjects on ibrutinib only)[p]			X[p]			
Biomarker blood samples for phospho-protein and molecular characterization and BTK occupancy evaluations[q]		X	X[q]		X	X
Cell count from stem cell collection for transplant (if applicable; See Section 9.1.1.)		←----------X----------→				

β-hCG=beta-human chorionic gonadotropin; BM=bone marrow; BSA=body surface area; BTK=Bruton's tyrosine kinase; CIT=chemoimmunotherapy; CNS=central nervous system; CSF=cerebrospinal fluid; CT=computed tomography; ECG=electrocardiogram; h=hour(s); HIV=human immunodeficiency virus; ICF=informed consent form; IHC=immunohistochemistry; MRI=magnetic resonance imaging; MUGA=multiple-gated acquisition scan; NHL=non-Hodgkin lymphoma; PD=progressive disease; PK=pharmacokinetics; RVICI=rituximab, vincristine, ifosfamide, carboplatin, idarubicin, and dexamethasone; yrs=years.

a. Standard of care testing to document comorbidities and baseline disease, with the exception of tetanus and pneumococcal titers, hematology, and chemistry, can be counted as screening assessments for the study if performed within 5 days of signing ICF. Procedures must have been performed according to protocol requirements and imaging must meet the Imaging Acquisition Guidelines standards.

b. Pathology report for the original NHL diagnosis or at relapse, if available, should be sent to the Janssen medical monitor immediately after signing the ICF. If the prior pathology report is not available, then a pathology report from a fresh biopsy will be required for study entry.

c. Formalin-fixed paraffin-embedded tumor tissue (mandatory at Screening) collected for biomarker studies only. A fresh lymph node biopsy should be collected at Screening or prior to Cycle 1 and at the time of PD (even if not previously collected), if feasible, where local regulations/shipping logistics permit. If archival tissue is unavailable and a fresh lymph node biopsy cannot be obtained, bone marrow slides (when positive for disease) can be submitted at screening and at the time of PD. No tumor tissue is required at the end of treatment in the absence of progressive disease.

d. These assessments should be recorded in source documents but will not be routinely collected in the eCRF. Clinically significant abnormalities should be recorded as adverse events and reported in the eCRF.

e. BSA and dose should only be recalculated if there is >10% weight change from the weight used in the previous BSA calculation**.**

f. Echocardiography/MUGA and ECG required at the end of each cycle (within 3 days prior to the next cycle) in RVICI treatment group only; otherwise, obtain at Screening and End-of-Treatment only.

g. If ibrutinib is temporarily stopped on C1D1 or C3D1, the assessment should be taken with the first dose of ibrutinib in each respective cycle.

h. Positron emission tomography scan at baseline recommended but not mandatory. Subjects entering study with only BM disease should be followed by BM biopsy and/or aspirate. In these subjects, radiographic images are required at screening but if no nodal disease is identified, subsequent imaging is not required.

i. Scans may be performed up to 3 days prior to Cycle 3 Day 1. Scans may be done ± 3 days of End-of-Treatment visit. Disease evaluations that show PD can be used as end-of-treatment evaluations. Additional disease evaluations may be obtained at discretion of investigator to confirm clinical response or PD.

j. Lumbar puncture in conjunction with triple intrathecal therapy for CNS treatment per the Dosage and Administration tables (Table 5 and Table 6) may be performed the day prior to the start of a treatment cycle for logistical reasons. Lumbar puncture on Cycle 1 Day 1 can be used as the screening lumbar puncture only if collected prior to the administration of any ibrutinib or background therapy. Disease evaluations that show PD can be used as end-of-treatment evaluations.

k. Bone marrow at Cycle 2 Day 1 only if clinically indicated. Morphological examination and IHC or flow cytometry is required of all bone marrow specimens at screening for all subjects. If bone marrow results at screening are negative, subsequent assessments must include morphologic assessment of the bone marrow, while immunophenotyping is optional. Procedure may be performed 1 day prior to the start of a treatment cycle for logistical reasons. If marrow is empty (lack of count recovery), repeat marrow should be obtained prior to initiating next cycle. Refer to protocol Section 9.2.2 for details regarding bone marrow testing. Disease evaluations that show PD can be used as end-of-treatment evaluations.

l. Required within 24 hours prior to treatment on Cycle 1 Day 1

m. Must be taken on day of or day prior to dosing, provided results are available before ibrutinib or background therapy is given. Hematology and chemistry should be done at Screening and on Cycle 1 Day 1 and weekly thereafter in Cycle 1. For Cycle 2 and Cycle 3, hematology and chemistry should be done on Day 1 and between Days 14 to 21.

n. Required within 24 hours prior to treatment on Cycle 2 Day 1 and Cycle 3 Day 1.

o. Hepatitis B serologic testing should include HBsAg, HBcAb, and HBsAb. A subject without a known history of these viral infections may be randomized if the serology results are not available at the time of the randomization. However, if the serology results return as positive, the medical monitor should be contacted immediately, and the guidance provided in Section 9.8 should be followed.

p. PK Sampling: On day of PK sample collection, ibrutinib should be taken within 2 hours after a meal. If ibrutinib is temporarily stopped on any PK sampling days, or within 3 days prior to PK sampling, the medical monitor should be contacted for guidance. PK samples are only collected from subjects randomized to ibrutinib with background CIT. If randomized to background CIT only, no PK samples are required to be collected.
Subjects randomized to ibrutinib and background CIT: 4 samples collected from each subject. Samples collected either at C1D14 (preference) or at C2D1, not both timepoints. Sample collected at predose; 1 (window 45-75 minutes), 2 (window 1.5-2.5 hours), and 4 hours (window 3.5-6 hours) postdose. If sample unable to be obtained at C1D14 (eg, due to a temporary stop of ibrutinib) sample can be collected on C2D1.

q. Biomarker Samples: Whole blood sample must be taken C1D1 predose and at 4 hours postdose (window 3.5-6 hours), and at C1D14 OR C2D1 (same day as the PK samples) predose and 4 hours postdose (samples collected either at C1D14 [preference] or at C2D1, not both timepoints). **Note: The 4-hour postdose samples are only required for patients randomized to take ibrutinib**. Whole blood sample taken also at predose on C3D1, and at PD or the End-of-Treatment visit. If a subject experiences bleeding with a lumbar puncture and needs to delay the dose of ibrutinib on Day 1 of the cycle, a predose and 4h sample should be done after administration of CIT is complete (on Day 14) instead. If this occurs during Cycle 1, a predose sample must also be obtained prior to any treatment on Day 1 and prior to ibrutinib exposure.

Table 3: Time and Events Schedule: Posttreatment Phase for Subjects Continuing on Ibrutinib Monotherapy

Posttreatment Phase for subjects continuing on **ibrutinib monotherapy** (randomized to ibrutinib and achieved response of PR or better)								
	Monotherapy (Day 1 of Cycles 1-3, 28-day cycles)	End-of-Mono-therapy visit (±7days)	9 months after C1D1[a] (±7days)	12 months after C1D1[a] (±7days)	18 months after C1D1[a] (±7days)	24 months after C1D1[a] (±7days)	30 months after C1D1[a] (±7days)	36 months after C1D1[a] (±7days)
Procedures								
Complete physical examination including lymph node measurements		X						
Limited physical examination including lymph node measurements with lymphoma symptoms reviewed	X		X	X	X	X	X	X
Age-appropriate performance status	X	X						
Weight[b]	X							
Height		X	X	X	X	X	X	X
Vital signs[c]	X	X						
BSA[b]	X							
ECG[d]		X						
Concomitant medications/procedures	X		Adverse events and concomitant medications will be reported until 30 days following the last dose of study treatment.					
Adverse events	X							
Survival	←——X (after PD, contact by visit or telephone q4wks)——→							
Disease Evaluations [e]								
Disease evaluation (CT/MRI) (see Section 9.2.1)		X		X		X		X
Lumbar puncture/CSF cytologic evaluation		X[f]		X[f]		X[f]		X[f]
Bone marrow aspirate and/or biopsy		X[f]		X[f]		X[f]		X[f]
Laboratory Assessments								
Hematology (see Section 9.8)	X[g]	X						
Clinical chemistry (see Section 9.8)	X[g]	X						
Serum or urine β-hCG pregnancy test (for young women with childbearing potential)	X[h]							
Tetanus and pneumococcal antibody titers		X						
Biomarker fresh tumor biopsy and blood samples for phospho-protein and molecular characterization and BTK occupancy evaluations[i]		X	←——X (at the time of PD)——→					
Cell count from stem cell collection for transplant (if applicable; See Section 9.1.1.)	←——X——→							

β-hCG=beta-human chorionic gonadotropin; BSA=body surface area, C1D1=Cycle 1 Day 1; CSF=cerebrospinal fluid; CT=computed tomography; ECG=electrocardiogram; MRI=magnetic resonance imaging; PD=progressive disease; q4wks=every 4 weeks.

a. C1D1 of original combination treatment phase.
b. Weight is required prior to dosing on Day 1 for each cycle of monotherapy. BSA and dose should only be recalculated if there is >10% weight change from the weight used in the previous BSA calculation.
c. These assessments should be recorded in source documents but will not be routinely collected in the eCRF. Clinically significant abnormalities should be recorded as AEs and reported in the eCRF.
d. To be performed at End-of-Monotherapy Visit only if not performed within previous 30 days.
e. Disease assessments may be repeated as clinically indicated to confirm response or progression.
f. Obtain only if clinically indicated.
g. Laboratory results from End-of-Treatment do not need to be repeated on monotherapy Cycle 1 Day 1 if testing was performed within 1 week.
h. Required within 24 hours prior to treatment on monotherapy Cycle 1 Day 1 and monthly thereafter.
i. Whole blood samples for phospho- protein and molecular characterization should be obtained at the End-of-Monotherapy Visit and at PD. Whole blood sample for pharmacodynamic analysis (BTK occupancy) should be obtained if PD occurs during Cycles 1-3 of monotherapy or at the End-of-Monotherapy Visit. A fresh lymph node biopsy should be collected at PD (even if not previously collected), if feasible, where local regulations/shipping logistics permit. If a fresh lymph node biopsy cannot be obtained, bone marrow slides (when positive for disease at PD) can be submitted.

Table 4: Time and Events Schedule: Posttreatment Phase for Subjects not Receiving Ibrutinib Monotherapy

Posttreatment Phase for subjects **NOT receiving ibrutinib monotherapy**							
	6 months after C1D1[a] (±7days)	9 months after C1D1[a] (±7days)	12 months after C1D1[a] (±7days)	18 months after C1D1[a] (±7days)	24 months after C1D1[a] (±7days)	30 months after C1D1[a] (±7days)	36 months after C1D1[a] (±7days)
Procedures							
Limited physical examination including lymph node measurements with lymphoma symptoms reviewed	X	X	X	X	X	X	X
Height	X	X	X	X	X	X	X
Survival	←——X (after PD, contact by visit or telephone q4wks)——→						
Disease Evaluations[b]							
Disease evaluation (CT/MRI) (see Section 9.2.1)	X		X		X		X
Lumbar puncture/CSF cytologic evaluation	X[c]		X[c]		X[c]		X[c]
Bone marrow aspirate and/or biopsy	X[c]		X[c]		X[c]		X[c]
Laboratory Assessments							
Tetanus and pneumococcal antibody titers	X						
Fresh tumor biopsy and blood samples for biomarker evaluations[d]	←——X (at the time of PD)——→						
Cell count from stem cell collection for transplant (if applicable; See Section 9.1.1.)	←——X——→						

C1D1=Cycle 1 Day 1; CSF=cerebrospinal fluid; CT=computed tomography; ECG=electrocardiogram; MRI=magnetic resonance imaging; PD=progressive disease; q4wks=every 4 weeks.

a. C1D1 of treatment phase.

b. Disease assessments may be repeated as clinically indicated to confirm response or progression.

c. Obtain only if clinically indicated.

d. Whole blood samples for phospho- protein and molecular characterization should be obtained at PD. A fresh lymph node biopsy should be collected at PD (even if not previously collected), if feasible, where local regulations/shipping logistics permit. If a fresh lymph node biopsy cannot be obtained, bone marrow slides (when positive for disease at PD) can be submitted.

Table 5: Dose and Administration Table: RICE With or Without Ibrutinib

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Days10-28[a]
Ibrutinib 329 mg/m^2 [b]	X [c]	X	X	X	X	X	X	X	X	X
Rituximab 375 mg/m^2	X		X							
Ifosfamide 3 g/m^2 over 2 hrs[c]			X	X	X					
Carboplatin 635 mg/m^2 over 1 hr			X							
Etoposide 100 mg/m^2 over 1 hr			X	X	X					
Mesna 600 mg/m^2 with ifosfamide and at 3, 6, 9, and 12 hrs after the start of each dose[c]			X	X	X					
Mesna 3,000 mg/m^2/day (administer as a shortened infusion per instructions in footnote for subjects receiving ibrutinib) [d]			X	X	X	X	X	X	X	
Dexamethasone 20 mg/m^2/day in 3 divided doses (IV or PO)					X	X	X	X	X	
IV hydration 3,000 mL/m^2/day	X	X	X	X	X					
Triple intrathecal therapy [e]	X				X[e]				X[e]	

CNS=central nervous system; hr(s)=hour(s); IV=intravenous; PO=orally; RICE=rituximab, ifosfamide, carboplatin, etoposide, and dexamethasone.
Note: See Pharmacy Manual/study Site Investigational Product Manual for calculation of ibrutinib dose.

a. If count recovery occurs quickly, cycles can be shortened to a minimum of 21 days.
b. Up to a maximum dose of 560 mg per day. See Attachment 1 for ibrutinib dosing guides.
c. Ibrutinib to be administered early in the day. To avoid a drug-drug interaction, mesna infusion should be stopped 3 hours prior to administering ibrutinib and not started for 6 hours after administering ibrutinib. Since mesna is given first with ifosfamide, ifosfamide dosing should also be separated accordingly from ibrutinib.
d. Administer mesna as a continuous infusion instead of intermittent dosing only in subjects with hematuria. For subjects receiving ibrutinib, to avoid a drug-drug interaction, mesna infusion should be stopped 3 hours prior to administering ibrutinib and not started for 6 hours after administering ibrutinib.
e. If CNS-negative, triple intrathecal therapy (methotrexate, corticosteroid, and cytarabine) should be administered on the first day of each cycle. If CNS-positive, administer every 4 ± 1 days until cerebrospinal fluid is cleared of blasts. Intrathecal rituximab is not permitted. Intrathecal therapy may be administered not more than 24 hours before Day 1 of each cycle.

Table 6: Dose and Administration Table: RVICI With or Without Ibrutinib

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Days 10-28[a]
Ibrutinib 329 mg/m^2 [b]	X [c]	X	X	X	X	X	X	X	X	X
Rituximab 375 mg/m^2	X		X							
Vincristine 0.4 mg/m^2/24 hr continuous infusion over 4 days			X	X	X	X				
Idarubicin 10 mg/m^2 over 4 hrs			X	X						
Carboplatin 200 mg/m^2/24 hr continuous infusion over 4 days			X	X	X	X				
Ifosfamide 2 g/m^2/24 hr over 5 days (administer as a shortened infusion per instructions in the footnote for subjects receiving ibrutinib) [c]			X	X	X	X	X			
Mesna 500 mg/m^2 bolus			X							
Mesna 3,000 mg/m^2/day (administer as a shortened infusion per instructions in the footnote for subjects receiving ibrutinib) [c]			X	X	X	X	X	X	X	
Dexamethasone 20 mg/m^2/day in 3 divided doses (IV or PO)					X	X	X	X	X	
IV hydration 3,000 mL/m^2/day	X	X	X	X	X	X	X	X	X	
Triple intrathecal therapy [d]	X				X				X	
GCSF										X [e]

ANC=absolute neutrophil count; CNS=central nervous system; hr(s)=hour(s); GCSF=granulocyte colony-stimulating factor; IV=intravenous; PO=orally; RVICI=rituximab, vincristine, ifosfamide, carboplatin, idarubicin, and dexamethasone.

Note: See Pharmacy Manual/study Site Investigational Product Manual for calculation of ibrutinib dose.

a. If count recovery occurs quickly, cycles can be shortened to a minimum of 21 days.

b. Up to a maximum dose of 560 mg per day. See Attachment 1 for ibrutinib dosing guides.

c. Ibrutinib to be administered early in the day. For subjects receiving ibrutinib, to avoid a drug-drug interaction, mesna infusion should be stopped 3 hours prior to administering ibrutinib and not started for 6 hours after administering the dose. Since mesna is given first with ifosfamide, ifosfamide dosing should also be separated accordingly from ibrutinib. For subjects not receiving ibrutinib, the mesna and ifosfamide infusion may be given as per standard of care.

d. If CNS-negative, triple intrathecal therapy (methotrexate, corticosteroid, and cytarabine) should be administered on the first day of each cycle. Intrathecal therapy may be administered not more than 24 hours before Day 1 of each cycle. If CNS-positive, administer every 4 ± 1 days until cerebrospinal fluid is cleared of blasts. Intrathecal rituximab is not permitted.

e. GCSF should be administered beginning Day 12 and continued until ANC ≥500/μL on 2 occasions post-nadir.

ABBREVIATIONS

ANC	absolute neutrophil count
AUC	area under the plasma concentration-time curve
B-AL	Burkitt leukemia
B-ALL	B-cell acute lymphoblastic leukemia
BCR	B-cell receptor
β-hCG	beta-human chorionic gonadotropin
BL	Burkitt lymphoma
BLL	Burkitt-like lymphoma
BSA	body surface area
BTK	Bruton's tyrosine kinase
CIT	chemoimmunotherapy
CL/F	apparent (oral) plasma clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CR	complete response
CR_b	complete response biopsy-negative
CRF	case report form
CR_u	unconfirmed complete response
CSF	cerebrospinal fluid
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eDC	electronic data capture
EFS	event-free survival
EICNHL	European Intergroup Collaboration for Childhood non-Hodgkin Lymphoma
EMA	European Medicines Agency
GCB	germinal center B-cell like
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
ILD	interstitial lung disease
IRB	Institutional Review Board
IRC	Independent Review Committee
ITT	intent-to-treat
IWRS	interactive web response system
LVEF	left ventricular ejection fraction
MCL	mantle cell lymphoma
MRI	magnetic resonance imaging
MUGA	multiple-gated acquisition (scan)
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
ORR	overall response rate
PBPK	physiologically-based pharmacokinetic
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
P-gp	P-glycoprotein
PQC	Product Quality Complaint
PR	partial response
PTLD	post-transplant lymphoproliferative disease

RICE	rituximab, ifosfamide, carboplatin, etoposide, and dexamethasone
RVICI	rituximab, vincristine, ifosfamide, carboplatin, idarubicin, and dexamethasone
SET	Study Evaluation Team
SF	shortening fraction
SJS	Stevens-Johnson Syndrome
SLL	small lymphocytic lymphoma
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
Vd/F	apparent (oral) volume of distribution

1. INTRODUCTION

Ibrutinib (IMBRUVICA®; PCI-32765; JNJ-54179060) is an orally-administered, covalently-binding, small molecule Bruton's tyrosine kinase (BTK) inhibitor currently co-developed by Janssen Research & Development, LLC and Pharmacyclics LLC for the treatment of B-cell malignancies. For the most comprehensive nonclinical and clinical information regarding ibrutinib, refer to the latest version of the Investigator's Brochure and Addenda for ibrutinib and the ibrutinib package insert. 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. Mature B-cell Non-Hodgkin Lymphoma

In children, mature B-cell non-Hodgkin lymphomas (NHLs) occur rarely; the most common types are Burkitt lymphoma (BL) and diffuse large B-cell lymphoma (DLBCL).[24,29] Although these are aggressive lymphomas that are fatal in weeks to months if untreated,[8] the cure rate in children with BL and DLBCL is between 85% to 90% after initial treatment.[25,33] Given this high cure rate, the incidence of relapsed or refractory BL and DLBCL within the broader pediatric population of NHL is very small.[2,4,6,13,31,35,41] Relapse of pediatric BL most commonly occurs within 6 months of the end of treatment and has a poor prognosis.[26] A review of children with mature B-cell NHL who relapsed or progressed following treatment with frontline pediatric B-cell NHL protocols had survival rates of less than 20%; however, these data were not summarized by the individual subtypes of BL or DLBCL.[3,7,34] Despite the reported overall response rate (ORR) of over 50% in most of these series, the overall mortality of this population is high and the 1- and 2-year event-free survival (EFS) rates are approximately 40% and 20%, respectively. Long-term survival beyond 2 years is poor, with only 10% to 20% of these patients surviving,[3,13,15,18] underscoring the unmet medical need in this patient population.

1.2. Current Methods of Treatment of Previously-Treated Mature B-cell Non-Hodgkin Lymphoma

Due to the low number of pediatric patients who relapse and the aggressive nature of the disease at the time of relapse, few studies have been conducted that have established a standard of care regimen in the relapsed or refractory setting. In both pediatric and adult patients in the relapsed and refractory setting, therapy may include a stem cell transplantation.[1,5,14,40]

The most recent study in relapsed or refractory BL and DLBCL was a pilot Phase 2 study (Study ANHL0121) conducted by the Children's Oncology Group that assessed the toxicity and efficacy of ifosfamide, carboplatin, and etoposide (ICE) combined with rituximab in children and adolescents with recurrent or refractory B-cell (CD20+) NHL and mature B-cell acute lymphoblastic leukemia ALL (B-ALL).[15] In this study, rituximab, ifosfamide, carboplatin, and etoposide (RICE) was established as an acceptable salvage induction regimen for patients who had been previously treated with a risk-adapted dose-intense chemotherapy regimen. An ORR of 60% was achieved (14 BL/mature B-ALL, 6 DLBCL evaluable subjects). The complete response (CR) rate was 64% and 50% among subjects with BL/B-ALL and DLBCL, respectively.

Similar to other salvage regimens, almost all subjects treated with the RICE regimen had severe myelosuppression that was reversible. Infections were frequently seen, but clinically manageable. No subjects died from infection. Rituximab-related infusion reactions occurred 15% of the time infusions were administered. Following completion of therapy, 6 subjects were able to proceed to consolidation with high-dose therapy and stem cell rescue. However, despite the 60% ORR, 40% (8/20) of subjects failed therapy and had a poor outcome (median survival of 2.5 months from study entry); among the subjects who responded, long-term survival (>24 months) was 15% (ie, 2/14 BL/B-ALL and 1/6 DLBCL). The high mortality rate in the relapsed/refractory population supports the unmet medical need to develop new and effective therapies for this pediatric population.[3,13,15,16,18,19,32]

Historically, RICE has been the most commonly used treatment regimen for DLBCL and BL in the relapsed/refractory pediatric population. However, among members of the European Intergroup Collaboration for Childhood non-Hodgkin Lymphoma (EICNHL), an alternative treatment regimen (the rituximab, vincristine, ifosfamide, carboplatin, idarubicin, and dexamethasone [RVICI] regimen) is being increasingly used in BL patients.[15,42]

1.3. Ibrutinib

1.3.1. Nonclinical Studies

Pharmacologic Profile

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.[30] Ibrutinib inhibited the proliferation of cell lines derived from patients with DLBCL, with a median effective concentration of 1 or 2 nM.

Toxicology

General toxicity studies in rats and dogs have identified lymphoid tissues (lymphoid depletion) and the gastrointestinal tract (soft feces/diarrhea, with or without inflammation) as the target organs with potential relevance to human safety. Results from an immunotoxicity assessment of ibrutinib in rats were consistent with the expected pharmacology of the drug and included dose-associated decreases in B-lymphocyte numbers, lymphoid depletion in the white pulp of the spleen and decreased immunoglobulin responses to keyhole limpet hemocyanin immunization. Cardiovascular assessments in dog safety pharmacology and toxicity studies identified decreased heart rate and prolonged PR intervals related to ibrutinib administration as a relevant finding.

Pharmacokinetics and Metabolism

After oral administration, ibrutinib showed rapid absorption and high plasma clearance in nonclinical species. Excretion of ibrutinib-related radioactivity occurred principally via feces. In human plasma, 97.3% of ibrutinib and 91.0% of the major dihydrodiol metabolite PCI-45227 was bound to protein.

In vitro nonclinical data show that ibrutinib is metabolized primarily by cytochrome P450 (CYP)3A. Ibrutinib is a weak reversible inhibitor toward CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 and does not display time-dependent CYP450 inhibition. The dihydrodiol metabolite of ibrutinib is a weak inhibitor toward CYP2B6, CYP2C8, CYP2C9, and CYP2D6. Both ibrutinib and the dihydrodiol metabolite are at most weak inducers of CYP450 isoenzymes in vitro.

1.3.2. Clinical Studies

1.3.2.1. Human Pharmacokinetics

The pharmacokinetics of ibrutinib has been assessed in subjects with B-cell malignancies as well as in healthy subjects. Pharmacokinetic assessments in subjects with B-cell malignancies were typically done in elderly subjects (median 67 years; range, 30-87). In all studies, both parent ibrutinib and metabolite PCI-45227 were quantified. The on-target effects of metabolite PCI-45227 are not considered clinically relevant. The pharmacokinetic profile of ibrutinib does not significantly differ for patients with different B-cell malignancies.

Extensive pharmacokinetic sampling and evaluation have been performed in approximately 250 subjects receiving ibrutinib across 5 clinical studies: PCYC-04753, PCYC-1102-CA, PCYC-1104-CA, PCYC-1106-CA, and PCYC-1109-CA. Results are briefly summarized below:

Following oral administration of ibrutinib at doses ranging from 1.25 to 12.5 mg/kg/day, area under the plasma concentration-time curve (AUC) values for ibrutinib increased with increasing dose, but with considerable overlap in values. The coefficient of variation for the AUC ranged from 60% to 107% across 3 studies (Studies PCYC-04753, PCYC-1102-CA, and PCYC-1109-CA). The mean half-life of ibrutinib across 4 clinical studies ranged from 4.3 to 8.9 hours, with a median time of maximum concentration of 2 hours. Ibrutinib pharmacokinetics in adults could be accurately predicted using a physiologically-based pharmacokinetic (PBPK) model, which was also successfully used to predict the magnitude of interactions with CYP3A inhibitors and inducers.

A population pharmacokinetics model was developed based on the data of 9 clinical Phase 1 to 3 studies in subjects with hematological malignancies (N=1,202, mainly chronic lymphocytic leukemia [CLL] and mantle cell lymphoma [MCL]). The population pharmacokinetics model was a linear 2-compartment pharmacokinetics model with sequential zero to first order absorption and first order elimination. Ibrutinib pharmacokinetics were dose-proportional and time-independent, absorption was rapid, apparent oral plasma clearance (CL/F) and oral volume of distribution at steady-state were approximately 1,100 L/h and 9,000 L, respectively. The pharmacokinetics model included a significant effect of food on relative bioavailability (F1, decreased when ibrutinib was given in overnight fasting condition versus the meal condition used in the clinical studies [ibrutinib taken at least 30 minutes before eating or at least 2 hours after a meal] and after a high-fat meal) and duration of the zero order absorption process (D1, increased when ibrutinib was given after a high-fat meal). The model also included the effect of the co-administration of moderate and strong CYP3A inhibitors, which caused a significant increase of F1 (and thus, of the systemic exposure to ibrutinib). Also, increasing age was

associated with a significant, though minor, increase in ibrutinib systemic exposure. None of the other examined covariates (including sex, subject pretreatment, and clinical chemistry data, such as calculated creatinine clearance, baseline liver enzymes, and total bilirubin) had a significant effect on pharmacokinetic parameters.

In a food effect study (Study PCI-32765CLL1001), AUC of ibrutinib approximately doubled when 420 mg was given 30 minutes before, 30 minutes after, or 2 hours after a high-fat breakfast, in comparison with the fasted condition. The effect on maximum observed plasma concentration (C_{max}) ranged from 2- to 4-fold, with the maximal effect observed when ibrutinib was administered 2 hours after the meal. This latter condition was chosen to determine the effect of food on the suspension formulation developed for administration to pediatric patients (Study PCI-32765CLL1015). Preliminary data showed a similar food effect as for the capsule formulation. The relative bioavailability of the suspension in comparison with the capsule (560 mg) was similar for AUC and was approximately 35% lower for C_{max}.

In a mass-balance study (Study PCI-32765CLL1004) in 6 men administered ibrutinib as a 140-mg solution admixed with ^{14}C-ibrutinib, approximately 90% of radioactivity was excreted within 168 hours after administration, with less than 10% accounted for in urine and the remainder in feces. A negligible fraction was excreted as unchanged drug.

Pharmacokinetic and Pharmacodynamic Relationships

Ibrutinib binds covalently and irreversibly to Cys-481 near the BTK active site and inhibits the enzymatic activity of purified BTK with a half maximal inhibitory concentration of 0.39 nM. In Study PCYC-04753, the BTK active-site occupancy by ibrutinib was measured. Bruton's tyrosine kinase remained fully occupied by ibrutinib (≥90% occupancy) for at least 24 hours in all subjects receiving 2.5 to 12.5 mg/kg/day and for the 560 mg continuous dosing cohorts. Although ibrutinib is rapidly eliminated from the plasma after oral administration, once daily dosing with ibrutinib is adequate to sustain maximal pharmacodynamic activity for 24 hours post-dosing.

Based on the available data, ibrutinib exposures were not significantly related to tumor response. This may be due to the limited number of subjects exposed to low doses of ibrutinib; only few of the examined subjects showed ibrutinib exposures lower than the AUC required for providing 90% BTK engagement. The mean steady-state AUC in the adult population after a daily dose of 560 mg (953 ng.h/mL) is on the flat part of the exposure-response curve and deemed sufficient to achieve >90% BTK engagement in the large majority of subjects. The occurrence of bleeding and infections (irrespective of the severity and causal relationship to the ibrutinib treatment) did not highlight a significant or meaningful relationship with ibrutinib systemic exposure.

Drug-drug Interaction Study

Study PCI-32765CLL1002 was an open-label study with a drug-drug interaction cohort of 18 healthy men, in which ibrutinib was administered alone at a 120 mg dose or in combination with ketoconazole at a 40 mg dose. Results demonstrated that ketoconazole, a strong CYP3A inhibitor, increased ibrutinib exposure by 29- and 24-fold, respectively. Guidance on concomitant use of ibrutinib with CYP3A inhibitors or inducers is provided in Attachment 4.

1.3.2.2. Efficacy/Safety Studies

Burkitt Lymphoma

No clinical data on the use of ibrutinib in BL are available. Burkitt cell line experiments demonstrate that ibrutinib significantly induces a dose-dependent decrease in cell proliferation in both rituximab-sensitive and rituximab-resistant cell lines. In addition, a significant decrease in phospho-BTK expression was demonstrated in the presence of ibrutinib when compared to control. When cells lines were exposed to a combination of ibrutinib and dexamethasone, cell proliferation decreased significantly following 5 days of treatment.[28]

In BL xenografted mice, a significant decrease in tumor burden was observed at Days 20 and 25 compared to control. Additionally, ibrutinib-treated mice demonstrated prolonged survival when compared to control mice with a median survival post-ibrutinib therapy of 31.5, 37.5, and 22.5 days, respectively, when compared to control (24 days). These results indicate that ibrutinib may serve as an adjuvant therapy for BL.[21]

Diffuse Large B-cell Lymphoma

Three early phase studies have been completed and a Phase 3 registration study in adults is ongoing. The 3 completed studies are summarized in Table 7. Efficacy results from Studies PCYC-04753 and PCYC-1106-CA demonstrate that ibrutinib has robust activity as a single agent in subjects with relapsed or refractory DLBCL, with possible lower response rates in subjects with the germinal center B-cell (GCB) subtype.

Table 7: Completed Efficacy Studies of Ibrutinib in DLBCL

Study Number/Design	Study Population	Ibrutinib Dosing Schedule	Outcome
PCYC-04753: First-in-human, open-label, nonrandomized, multicenter, dose escalation study	Recurrent NHL	1.25-12.5 mg/kg for 28 consecutive days in a 35-day cycle; or 8.3 mg/kg/day (continuous); or 560 mg/day (continuous)	• Full BTK occupancy (>95%) achieved at doses ≥2.5 mg/kg/day (12.5 mg/kg/day highest dose cohort evaluated). MTD not established. • 5/15 (33%) subjects with DLBCL had objective responses (2 CRs, 3 PRs). • Median time on treatment: 8 weeks (range: 2 to 98 weeks). • Median PFS: 2.5 months (range: 0.7 to 4.6 months). • Median follow-up: 3.5 months (range: 0.8 to 22.5 months).
PCYC-1106-CA: Open-label, parallel-cohort, nonrandomized, multicenter study	Relapsed or refractory DLBCL	560 mg/day (continuous)	• ORR: 24% (60 subjects). • Median time on study: 3.9 months. • ABC subtype, ORR: 41% (10/25 subjects; CR: 17%, PR: 24%). • GCB subtype, ORR: 5%. • Ibrutinib showed preferential activity in the non-GCB DLBCL subtype.
PCI-32765DBL1002: Open-label, nonrandomized, multicenter, dose-escalation study	Newly diagnosed CD20-positive B-cell NHL including DLBCL, FL, and MCL	280, 420, or 560 mg/day (continuous), + R-CHOP	• Demonstrated tolerability and efficacy of ibrutinib (560 mg) in combination with R-CHOP. • ORR (DLBCL, MCL, and FL): 85.7%, 100.0%, 95.2%, and 93.8% in the 280 mg, 420 mg, 560 mg, and combined dose cohorts. • 18 subjects (7 GCB, 2 non-GCB) with DLBCL at 560 mg ibrutinib+R-CHOP: 100.0% ORR (15 CRs, 3 PRs).

ABC=activated B-cell like DLBCL; BTK=Bruton's tyrosine kinase; CR=complete response; DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; GCB=germinal center B-cell like; MCL=mantle cell lymphoma; MTD=maximum tolerated dose; NHL=non-Hodgkin lymphoma; non-GCB=non-germinal center B-cell like; ORR=overall response rate; PFS=progression-free survival; PR=partial response; R-CHOP=rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

A Phase 1 study was conducted to evaluate ibrutinib in combination with RICE in adult subjects with relapsed or refractory DLBCL. A standard 3 + 3 dose escalation schedule for ibrutinib, 420 mg, 560 mg, and 840 mg, was administered on Days 1 to 21 with RICE for 3 cycles. There were no dose limiting toxicities observed up to 840 mg daily in combination with RICE. Per computed tomography (CT), 1 CR, 6 PRs, and 4 subjects with stable disease were reported. Per positron emission tomography (PET), 4 subjects achieved a CR and 7 remained PET avid at the end of treatment.[37]

Clinical Safety of Ibrutinib

For the most comprehensive clinical safety information, please refer to the latest version of the ibrutinib Investigator's Brochure and Addenda.

Hematological Adverse Events

Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib. Monitor complete blood counts monthly.

Lymphocytosis

Upon initiation of single-agent treatment with ibrutinib, a reversible increase in lymphocyte counts (ie, ≥50% increase from baseline and an absolute count >5,000/mcL), often associated with reduction of lymphadenopathy, has been observed in most subjects (66%) with CLL/small lymphocytic lymphoma (SLL). This effect has also been observed in some subjects (35%) with MCL treated with ibrutinib. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease (PD) in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first month of ibrutinib therapy and typically resolves within a median of 8 weeks in subjects with MCL and 14 weeks in subjects with CLL/SLL (range, 0.1 to 104 weeks). This pharmacodynamic effect was less prominent or not observed in other indications.

Leukostasis

There were isolated cases of leukostasis reported in subjects treated with ibrutinib. A high number of circulating lymphocytes (>400,000/mcL) may confer increased risk. These subjects should be closely monitored. Administer supportive care including hydration and/or cytoreduction as indicated. Ibrutinib may be temporarily stopped, and medical monitor should be contacted.

Non-Hematological Adverse Events

Bleeding-related Events

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

In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed. Use of either anticoagulant or antiplatelet agents concomitantly with ibrutinib increases the risk of major bleeding. A higher risk for major bleeding was observed with anticoagulant than with antiplatelet agents. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with ibrutinib. See Attachment 4 for guidance on concomitant use of anticoagulants, antiplatelet therapy, and/or supplements. See Section 4.3 for guidance on ibrutinib management with surgeries or procedures.

Subjects with congenital bleeding diathesis have not been studied.

Subjects in the current study will be monitored closely for bleeding (see Section 12.3.3).

Cardiac Arrhythmias

Atrial fibrillation, atrial flutter, and cases of ventricular tachyarrhythmia including some fatal events, have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmia. Periodically monitor subjects clinically for cardiac arrhythmia. Subjects who develop arrhythmic symptoms (eg, palpitations, lightheadedness, syncope, chest discomfort or new onset of dyspnea) should be evaluated clinically and, if indicated, have an electrocardiogram (ECG) performed. For cardiac arrhythmias which persist, consider the risks and benefits of ibrutinib treatment and follow the dose modification guidelines.

Cerebrovascular Accidents

Although causality has not been established, cases of cerebrovascular accident, transient ischemic attack, and ischemic stroke including fatalities have been reported with the use of ibrutinib in the post-marketing setting, with and without concomitant atrial fibrillation and/or hypertension. Regular monitoring and appropriate treatment of conditions that can contribute to the occurrence of these events is recommended.

Diarrhea

Diarrhea is the most frequently reported non-hematologic adverse event 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 antidiarrheals and antiemetics. Subjects should be monitored carefully for gastrointestinal adverse events and cautioned to maintain fluid intake to avoid dehydration. Medical evaluation should be made to rule out other etiologies such as *Clostridium difficile* or other infectious agents. Should symptoms be severe or prolonged, follow the protocol dose modification guidelines. Refer to Section 6.2.

Infections

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects treated with ibrutinib therapy. Some of these infections have been associated with hospitalization and death. Consider prophylaxis according to standard of care in subjects who are at increased risk for opportunistic infections (see Section 8.1). Although causality has not been established, cases of progressive multifocal leukoencephalopathy and Hepatitis B reactivation have occurred in subjects treated with ibrutinib. Subjects should be monitored for signs and symptoms (fever, chills, weakness, confusion, vomiting, and jaundice) and appropriate therapy should be instituted as indicated.

Rash

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 1112. Most rashes were mild to moderate in severity. Isolated cases of severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) have been reported in subjects treated with ibrutinib. Subjects should be closely monitored for signs

and symptoms suggestive of SCAR including SJS. Subjects receiving ibrutinib should be observed closely for rashes and treated symptomatically, including interruption of the suspected agent as appropriate. In addition, hypersensitivity-related events erythema, urticaria, angioedema have been reported.

Hypertension

Hypertension has occurred in subjects treated with ibrutinib. Regularly monitor blood pressure in subjects treated with ibrutinib and initiate or adjust antihypertensive medication throughout treatment with ibrutinib as appropriate.

Tumor Lysis Syndrome

Tumor lysis syndrome has been reported with ibrutinib therapy. Subjects at risk of tumor lysis syndrome are those with-high tumor burden prior to treatment. Monitor subjects closely and take appropriate precautions.

Interstitial Lung Disease

Cases of interstitial lung disease (ILD) have been reported in subjects treated with ibrutinib. Monitor subjects for pulmonary symptoms indicative of ILD. If symptoms develop, follow the protocol dose modification guidelines (see Section 6.2.2). If symptoms persist, consider the risks and benefits of ibrutinib treatment and follow the dose modification guidelines (see Section 6.2.2).

Non-melanoma Skin Cancer

Non-melanoma skin cancers have occurred in subjects treated with ibrutinib. Monitor subjects for the appearance of non-melanoma skin cancer.

1.4. Background Chemoimmunotherapy

Ibrutinib is being evaluated as add-on therapy to RICE or RVICI (see Table 5 and Table 6, respectively, for doses). In this study, dexamethasone was added to RICE to align with the dexamethasone given as part of RVICI. In a Children's Oncology Group study of children with NHL in the relapsed/refractory setting, RICE led to a 60% ORR.[15] The RVICI regimen has demonstrated a 63% 4-year survival.[42] For both regimens, triple intrathecal therapy consisting of methotrexate, corticosteroid, and cytarabine will be administered for central nervous system (CNS) prophylaxis in age-appropriate dosing (see Attachment 6). Subjects with CNS disease will receive additional doses of triple intrathecal therapy as per the Time and Events Schedule (Table 5 and Table 6). For further information regarding background therapy, please refer to the local prescribing information.

1.5. Rationale for the Study

As described above, long-term survival for patients with relapsed or refractory BL and DLBCL is poor, with only 10% to 20% of these patients surviving beyond 2 years,[3,13,15,18] underscoring the unmet medical need in this patient population. Ibrutinib is an oral agent with an acceptable safety profile and novel mechanism of action. The drug inhibits the B-cell receptor pathway via

BTK inhibition, thereby overcoming the B-cell receptor (BCR) and chemokine-controlled retention of malignant B cells in their supportive microenvironments. It has been shown to disrupt the pathogenesis of several B-cell malignancies. Therefore, the addition of ibrutinib to a salvage regimen like RICE/RVICI may provide some advantages for the pediatric population given its non-overlapping mechanism of action and toxicity profile. Although there is no clinical pediatric experience with ibrutinib, translational models demonstrate activity of ibrutinib in BL and DLBCL. Clinical data also demonstrate the safety and activity of ibrutinib in adult subjects with relapsed DLBCL. No effect of the R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) on ibrutinib pharmacokinetics was observed, nor did ibrutinib affect the pharmacokinetics of vincristine, also a CYP3A substrate. Therefore, an open-label study of ibrutinib in combination with RICE/RVICI in pediatric subjects with relapsed or refractory BL or DLBCL is planned. The available safety and pharmacokinetic information combined with the unmet medical need support foregoing a stepwise approach and support starting treatment using the body surface area (BSA)-derived equivalent of the 560 mg ibrutinib dose used in adults with lymphomas. In the 2 older age groups (6-11 years, 12-17 years), the first 2 evaluable subjects in each age group will start treatment with the equivalent of 420 mg, followed by up-titration to the 560-mg equivalent guided by safety and pharmacokinetic evaluation. In the youngest age group (1-5 years), the first 2 evaluable subjects will start treatment with the equivalent of 420 mg or lower as deemed appropriate by the Study Evaluation Team (SET) following assessment of pharmacokinetic and safety in the 2 older age groups.

2. OBJECTIVES, ENDPOINTS, AND HYPOTHESIS

2.1. Objectives and Endpoints

2.1.1. Run-in Part (Part 1)

Objectives	Endpoints
Primary	
• Confirm that the pharmacokinetics in pediatric subjects is consistent with that in adults	• Exposure (AUC) • CL/F, apparent (oral) volume of distribution (Vd/F), and derived measures of exposure such as C_{max} • Relationship between pharmacokinetic parameters and age or measure of body size
Secondary	
• Evaluate the safety and tolerability of ibrutinib in combination with RICE or RVICI background therapy in pediatric subjects with B-cell malignancies	• Safety parameters, including gastrointestinal effects, immune function, intensified cardiac monitoring (in particular, after previous anthracycline exposure)
• Assess anti-tumor activity of ibrutinib as add-on to RICE or RVICI regimens	• Overall response (CR, including CR biopsy-negative [CR_b] and unconfirmed CR [CR_u]) and partial response [PR])
• Assess disease-specific biomarkers	• Phospho-BTK, as well as SYK, STAT3, caspase-3, BCL-xL, and cIAP1 expression at baseline and during treatment • BCR/CD79B, CARD11, and MYD mutations • c-MYC, immunoglobulin, and T-cell receptor gene rearrangements at baseline
• Assess the pharmacodynamic response	• BTK occupancy
• Acceptability and palatability assessment of all ibrutinib formulations	• Visual analog scale score for palatability
Exploratory	
• Evaluate other response biomarkers	• Other biomarkers, as applicable
• Explore the exposure-response relationships	• Potential relationships between systemic exposure and response

2.1.2. Randomized Part (Part 2)

Objectives	Endpoints
Primary	
• Assess efficacy (EFS) of ibrutinib in combination with RICE or RVICI background therapy compared to RICE or RVICI background therapy alone	• Difference in EFS between the 2 treatment groups (an event is defined as the time from randomization to death, disease progression, or lack of CR or PR after 3 cycles of treatment based on blinded independent event review)
Secondary	
• Evaluate the safety and tolerability of ibrutinib in combination with RICE or RVICI background therapy in pediatric subjects and young adults with B-cell malignancies	• Safety parameters, including gastrointestinal effects, immune function, intensified cardiac monitoring (in particular, after previous anthracycline exposure)
• Determine the ORR	• The proportion of subjects who achieve CR, (including CR_b and CR_u) and PR
• Evaluate tumor volume reduction at Day 14	• Percent decrease in the sum of the products of the lesion diameters at Day 14
• Determine the number and proportion of subjects who proceed to stem cell transplantation	• Number and proportion of subjects who proceed to stem cell transplantation
• Evaluate the time to response	• The time interval from the first dose of ibrutinib to the first documented response for those subjects who respond
• Measure the duration of response	• Duration calculated from the date of initial documentation of a response (CR or PR) to the date of first documented evidence of PD or death
• Evaluate long-term survival (EFS at 2 and 3 years)	• Proportion of subjects with EFS at 2 and 3 years
• Evaluate overall survival	• The duration from the date of randomization to the date of the subject's death
• Assess disease-specific biomarkers	• Phosphor-BTK, as well as SYK, STAT3, caspase-3, BCL-xL, and cIAP1 expression at baseline and during treatment • BCR/CD79B, CARD11, and MYD mutations • c-MYC, immunoglobulin, and T-cell receptor gene rearrangements at baseline
• Assess the pharmacodynamic response, if deemed appropriate based on Part 1 results	• BTK occupancy
• Assess the population pharmacokinetics of ibrutinib in pediatric subjects and young adults	• Population pharmacokinetic parameters and derived systemic exposure to ibrutinib such as AUC • Relationship between pharmacokinetic parameters and age or measure of body size
• Acceptability and palatability assessment of all ibrutinib formulations	• Visual analog scale score for palatability
Exploratory	
• Evaluate other response biomarkers	• Other biomarkers, as applicable
• Explore the exposure-response relationships	• Potential relationships between systemic exposure and response

Refer to Section 9, Study Evaluations, for evaluations related to endpoints.

2.2. Hypothesis

The addition of ibrutinib to a salvage chemoimmunotherapy (CIT) regimen will extend EFS compared to CIT alone in pediatric and young adult subjects with relapsed or refractory mature B-cell NHL.

3. STUDY DESIGN AND RATIONALE

3.1. Overview of Study Design

This is a 2-part multicenter study. A safety and pharmacokinetic run-in part (Part 1) will be conducted before starting the randomized part (Part 2) of the study. Part 2 is a randomized, open-label, Phase 3 study to compare the safety and efficacy of ibrutinib in combination with CIT (RICE or RVICI) versus CIT alone in children and young adult subjects with relapsed or refractory mature B-cell NHL. Subjects who are 1 to 30 years old at the time of relapse (but with primary NHL diagnosis at age of <18 years old) will be eligible.

Due to the expected similarity among subjects in each cohort in pharmacokinetics, the rarity of the patient population, and expected tolerability of ibrutinib, a safety and pharmacokinetic run-in part (Part 1) will be conducted before starting the randomized part (Part 2) of the study. The safety and tolerability of the ibrutinib dose initially proposed based on modeling and simulation will be confirmed clinically during the run-in part (Part 1) of the study. The data generated during Part 1 will be used to confirm or adapt the dose prior to starting Part 2, by taking into account observed exposures in combination with the predicted exposures using the PBPK modeling. Interim pharmacokinetic and, if feasible, pharmacodynamic assessments will be conducted in order to monitor if predictions are correct (ie, ensure drug exposure is consistent with the equivalent adult dose of 560 mg). If exposure is within the approximate range observed in adult subjects treated at 560 mg/day adult steady-state exposure (median, 830 ng.h/mL; range, 250 to 1,500 ng.h/mL), then no dose adjustment will be required, provided there are no safety concerns. If exposure is not within the adult steady-state exposure range, then dose adjustments will be considered. A SET will review safety and pharmacokinetic data during the SET meetings (see Section 11.10). Safety will be assessed by evaluating the number of dose reductions and dose interruptions among the subjects treated in Part 1. Enrollment will begin with children in the 2 older age groups (6-11, 12-17 years) to assess pharmacokinetic and safety data before allowing enrollment of children in the youngest age group (1-5 years). The SET will meet to decide on any changes to the starting dose for each age group, and when enrollment may begin for the youngest age group. If dose adjustment requires a higher dose to be evaluated in the run-in part (Part 1), then the highest adult dose of 560 mg once daily will not be exceeded in children.

In Part 1, a minimum of 6 and up to approximately 24 pediatric subjects (1 to <18 years) evaluable for pharmacokinetic assessment will be enrolled. Subjects in Part 1 will be considered "evaluable" if pharmacokinetic samples are obtained appropriately and lead to interpretable results. Based on the disease characteristics, it is expected that a range of ages will be represented. Safety and tolerability of ibrutinib in combination with RICE or RVICI will be assessed. If dose adjustment is required due to pharmacokinetic assessments or safety concerns, enrollment will be expanded to include additional subjects until dose adjustments are no longer needed for any age group. At a minimum, the first 2 subjects in each age group will enroll into Part 1 before recruitment of children in that age group will begin in Part 2. For each of the CIT regimens (RICE or RVICI), at least 3 subjects must receive that regimen in Part 1 with no toxicities of concern identified before randomization on that regimen can begin in Part 2.

In Part 2, approximately 72 subjects will be randomized in a 2:1 ratio to receive ibrutinib in combination with CIT (investigator choice of RICE or RVICI) or CIT alone. Among the approximately 72 subjects enrolled in Part 2, at least 40 subjects are targeted to be age 1 to <18 years, and at least 10 of the 40 subjects are targeted to be age <11 years. Subjects will be stratified by histology (BL/Burkitt leukemia [B-AL] versus "other") and by background therapy (RICE versus RVICI). Pharmacokinetic samples will be obtained from those subjects randomized to ibrutinib in combination with RICE or RVICI during Part 2 of the study to characterize the pharmacokinetics in pediatric subjects.

Part 1 and Part 2 of the study will be conducted in 3 phases: a Pretreatment (Screening) Phase, a Treatment Phase, and a Posttreatment Phase. Before any study-related procedure can be performed, each subject or his/her legally-acceptable representative must sign an informed consent form (ICF). In addition, an assent form must be signed by children capable of understanding the nature of the study, if applicable according to local regulations. The Screening Phase will occur within 14 days before administration of study drug, during which the subject's eligibility and baseline characteristics will be determined.

The Treatment Phase will extend from enrollment (in Part 1) or randomization (in Part 2) until 1 of the following: 1) completion of 3 cycles of therapy, 2) transplantation, if clinically indicated, or 3) PD, whichever comes first. Cycles will be 28 days long; however, if count recovery occurs quickly and the investigator deems a subject ready to proceed with the next cycle of therapy, cycles can be shortened to as few as 21 days. As long as there is no disease progression after Cycle 1 or 2, a second and third cycle of therapy will be given, respectively. All subjects will receive background therapy with RICE or RVICI during the Treatment Phase.

The investigator will evaluate sites of disease by radiological imaging, physical examination, or other procedures as necessary, including but not limited to review of hematology, clinical chemistry, and lumbar puncture results. Assessment of tumor response and progression will be according to the International Pediatric NHL Response Criteria. The primary efficacy analysis of EFS will be based on assessment by an Independent Review Committee (IRC). At each site visit, subjects will undergo safety evaluations. Safety evaluations will include adverse event monitoring, physical examinations, concomitant medication usage, and clinical laboratory parameters. Population pharmacokinetics will be performed during Part 1 using a sparse sampling approach. Additional sparse pharmacokinetic samples will be collected during Part 2 to expand the pediatric pharmacokinetic dataset. Blood samples will be obtained for pharmacodynamic assessments (BTK occupancy) and for protein binding (Part 1 only).

Subjects will begin the Posttreatment Phase after completion of combination therapy. During the Posttreatment Phase, subjects on ibrutinib having a response of PR or better and have completed 3 cycles of combination treatment will continue on ibrutinib monotherapy at the same daily dose for three 28-day cycles, or until disease progression or unacceptable toxicity, or up until initiating subsequent antilymphoma therapy or a conditioning regimen for stem cell transplantation, whichever comes first. Follow-up visits to assess disease progression will be required if study treatment is discontinued prior to PD (including subjects who go on to transplant) and will be completed as per Table 3 and Table 4 until PD, the clinical cutoff for the

primary endpoint, or for up to 3 years after the date of Cycle 1 Day 1, whichever occurs first. After that, evaluations may be performed as clinically indicated at the discretion of the investigator. Subjects who have not progressed by the last efficacy assessment at 3 years should continue to be followed for survival status. Subjects who discontinue study treatment for reasons other than disease progression must continue to have disease evaluations according to the Time and Events Schedules (Table 1, Table 2, Table 3, and Table 4). The Posttreatment Phase will continue until death, loss to follow-up, consent withdrawal, or study end, whichever occurs first. The end of study is defined as when approximately 60 EFS events have occurred in Part 2 (death, disease progression, or lack of CR or PR after 3 cycles of treatment based on blinded independent event review), or the sponsor terminates the study, whichever comes first. Study enrollment may be stopped early upon recommendation from the IDMC at the interim analysis based on early stopping rules.

During the randomized part of the study, an independent Data Monitoring Committee (DMC) will convene for ongoing, real-time review of safety and make recommendations (refer to Section 11.8, Independent Data Monitoring Committee, for details). One interim analysis will be conducted when approximately 30 EFS events are reached (approximately 32 months after the first subject is enrolled). The DMC will determine the appropriateness for early stopping using the nonbinding stopping rules as well as other efficacy and safety endpoints (see Section 11.8). A diagram of the study design for Part 1 and Part 2 is provided in Figure 1 and Figure 2, respectively.

Figure 1: Schematic Overview of the Study (Part 1; Run-in Part)

SCREENING

Eligibility:

- Male or female age 1 to <18 years old.
- Relapsed/refractory BL, BLL, Burkitt leukemia (ie, B-AL), DLBCL, DLBCL NOS, or other pediatric mature B-cell NHL. No diagnosis of PTLD.
- No allogeneic bone marrow transplant within 6 months of treatment start.
- In first recurrence or have disease that is primarily refractory to conventional therapy.
- Lansky-Karnofsky score of ≥50.
- No ongoing anticoagulation with Vitamin K antagonists and no inherited or acquired bleeding disorders.
- No clinically significant arrhythmia, complex congenital heart disease, or LVEF <50% or SF ≤28%.

↓

TREATMENT PHASE

Treatment:
Combination therapy: Ibrutinib + CIT (RICE or RVICI) until 3 cycles are completed, transplantation is indicated, or until PD or unacceptable toxicity

Response Assessment:
Response assessments will be done at Disease Evaluation 1 which includes Cycle 1 Day 14 (imaging only) and start of Cycle 2 BM (if clinically indicated) and CSF, Disease Evaluation 2 beginning of Cycle 3 and at Disease Evaluation 3 at the EoT.

↓

POSTTREATMENT PHASE

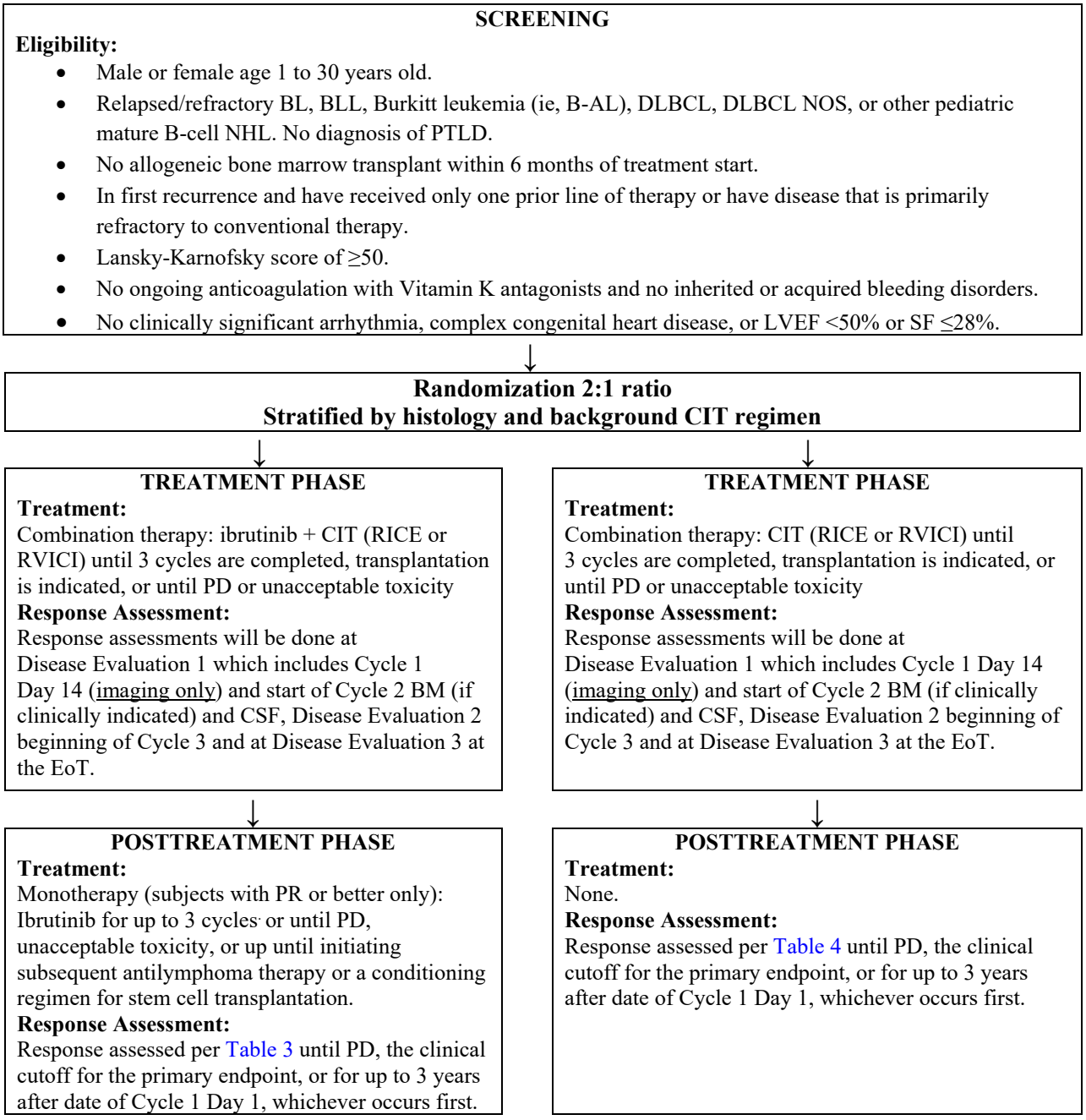
Treatment:
Monotherapy (subjects with PR or better only): Ibrutinib for 3 cycles, or until PD, unacceptable toxicity, or up until initiating subsequent antilymphoma therapy or a conditioning regimen for stem cell transplantation

Response Assessment:
Response assessed by CT, MRI and/or PET, CSF and BM evaluations.
For subjects on ibrutinib monotherapy: evaluations per Table 3 until PD, the clinical cutoff for the primary endpoint, or for up to 3 years after date of Cycle 1 Day 1, whichever occurs first.

Survival Follow-up:
The Posttreatment Phase will continue until death, loss to follow-up, consent withdrawal, or study end, whichever occurs first.

B-AL=mature B-cell acute lymphoblastic leukemia; BL=Burkitt lymphoma; BLL=Burkitt-like lymphoma; BM=bone marrow; CIT=chemoimmunotherapy; CSF=cerebrospinal fluid; CT=computed tomography; DLBCL=diffuse large B-cell lymphoma; EoT =End of Therapy; LVEF=left ventricular ejection fraction; MRI=magnetic resonance imaging; NHL=non-Hodgkin lymphoma; NOS=not otherwise specified; PD=progressive disease; PET=positron emission tomography; PR=partial response; PTLD=post-transplant lymphoproliferative disease; RICE=rituximab, ifosfamide, carboplatin, etoposide, and dexamethasone; RVICI=rituximab, vincristine, ifosfamide, carboplatin, idarubicin, and dexamethasone; SF=shortening fraction.

Figure 2: Schematic Overview of the Study (Part 2; Randomized Part)



B-AL=mature B-cell acute lymphoblastic leukemia; BL=Burkitt lymphoma; BLL=Burkitt-like lymphoma; BM=bone marrow; CIT=chemoimmunotherapy; CSF=cerebrospinal fluid; DLBCL=diffuse large B-cell lymphoma; EoT=End of Therapy; LVEF=left ventricular ejection fraction; NHL=non-Hodgkin lymphoma; NOS=not otherwise specified; PD=progressive disease; RICE=rituximab, ifosfamide, carboplatin, etoposide, and dexamethasone; PTLD=post-transplant lymphoproliferative disease; RVICI=rituximab, vincristine, ifosfamide, carboplatin, idarubicin, and dexamethasone; SF=shortening fraction.

3.2. Study Design Rationale

This is a Phase 3, randomized, open-label, controlled study evaluating the addition of ibrutinib to the standard of care for children and young adults with relapsed/refractory mature B-cell NHL. This is a registration study designed to support global regulatory applications. The study will recruit subjects globally and is adequately powered to demonstrate improved efficacy of the addition of ibrutinib to the standard of care treatment.

Randomization will be used to minimize bias in the assignment of subjects to treatment groups, to increase the likelihood that known and unknown subject attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons between treatment groups. Subjects will be stratified by histology and background therapy. The study is not blinded; however, the determination of response by the IRC is blinded.

3.2.1. Study Population

Although there is no clinical pediatric experience with ibrutinib, translational models demonstrate activity of ibrutinib in BL and DLBCL. Clinical data also demonstrate the safety and activity of ibrutinib in adult subjects with relapsed DLBCL.

Enrollment will be targeted toward children aged 1 to <18 years. However, for sites that treat young adult populations, subjects between 18 and 30 years of age may be enrolled if the initial diagnosis of NHL occurred before 18 years of age.

3.2.2. Study Treatments

The target dose of 329 mg/m^2 daily dose of ibrutinib (up to a maximum of 560 mg per day) was selected as the recommended dose based on normalization per BSA relative to a 1.7 m^2 adult. Enrollment will begin with children in the 2 older age groups (6-11 years, 12-17 years) to assess pharmacokinetics and safety data before allowing enrollment of children in the youngest age group (1-5 years). For the first 2 subjects enrolled per age group (1-5 years, 6-11 years, and 12-17 years) in the study, a lower starting dose of 240 mg/m^2 for the first cycle (up to a maximum of 420 mg per day), which is equivalent to the lower therapeutic dose of ibrutinib (adult dose of 420 mg normalized per 1.7 m^2, rounded down from 247 mg/m^2), was selected to confirm exposure and safety, particularly in the younger age groups (see Section 6.1 for dose escalation details). Metabolic clearance of ibrutinib is almost exclusively mediated by CYP3A, which is known to reach adult expression levels at around 1 year of age,[9] and characterized by blood flow limited clearance and high first pass metabolism, resulting in low oral bioavailability. Exposure predictions across the range of pediatric ages have been performed by adapting the adult PBPK model for ibrutinib. Based on the adult dose of 560 mg, the BSA-derived equivalent dose of 329 mg/m^2 with a maximum dose of 560 mg per day is expected to result in comparable systemic exposures (within 1.4-fold [40% higher] using either the adapted adult PBPK model or allometric scaling) in children aged 6 years and older, but higher exposures in children 1 to 5 years of age (up to approximately 2.3-fold at 12 months of age using the adapted adult PBPK model). Given the safety margins with ibrutinib, the starting dose of 240 mg/m^2 in pediatric

subjects and the intra-subject escalation is considered adequate for Phase 1. Dose escalation will occur at the start of Cycle 2 as long as all pharmacokinetic assessments are within the expected range and there are no safety concerns. This approach to dosing will occur for the first 2 subjects in each age group during Part 1, and the age cohorts will only be allowed to enroll into Part 2 after approval by the SET. The intensified pharmacokinetic schedule will occur for all subjects in Part 1. Dosing confirmation will be performed as a Phase 1b run-in. Data from the run-in will be used to verify that exposure is equivalent to that in adults. However, if exposure (AUC) in the first 2 subjects in a given age group at the 420-mg equivalent dose is below or exceeds the target range set, the dose for these subjects and all other subjects in that age group will be adjusted as appropriate based on available exposure data.

The comparator in this study, CIT, is the standard of care for DLBCL and BL in children. Historically, RICE has been the most commonly used treatment regimen for DLBCL and BL in the relapsed/refractory population. However, among members of the EICNHL, an alternative treatment regimen (RVICI) is being increasingly used in BL patients.[42]

3.2.3. Study Assessments

The primary endpoint, EFS, has served as the basis for regulatory approval in DLBCL and represents a clinically meaningful improvement attributable to treatment in this subject population.

3.2.4. Pharmacodynamic Analysis

The pharmacodynamic activity of ibrutinib in the presence of CIT (RICE or RVICI) may be assessed by determining the percentage of probe occupancy of the BTK receptor at the timepoints listed in the Time and Events Schedule (Table 1, Table 2, and Table 3), according to the conditions specified in Section 9.4. Previous studies of single-agent ibrutinib have shown that greater than 90% receptor occupancy occurs within 4 hours of treatment; however, in combination with other agents the time of full occupancy may be different, and this will be compared to the previous studies. Therefore, monitoring for pharmacodynamic effects following combination treatment could provide an estimate of target engagement (BTK occupancy).

3.2.5. Pharmacokinetic Analysis

The assessment of pharmacokinetics is important to extrapolate both safety and efficacy from adults to this patient population. The study includes a sparse pharmacokinetic sampling strategy for population pharmacokinetic purposes, which will serve as a means to derive the individual subject's ibrutinib exposure. In addition to determination of subject-covariates that influence the pharmacokinetics of the drug, this may provide supportive evidence for the efficacy and safety analyses, help in deriving dosing regimens not directly studied in clinical studies, and identify at-risk subjects who require a dose-adaptation.

3.2.6. Biomarker Collection

As a part of the biomarker collection, tumor (from archived tumor tissue or biopsies collected during Screening) and blood will be evaluated to identify markers predictive of response to ibrutinib. Analyses for mechanistic features including expression of certain characteristic genes,

and also for identification of cell of origin subtype (non-GCB or GCB; for DLBCL subjects only) will be performed based on availability of tumor samples. Tumor response in the non-GCB cohort will be compared to that observed in other studies in DLBCL (Study PCI-32765DBL3001). If feasible, tumor samples obtained at progression may be subjected to sequence analysis and compared to identify novel mutations/genetic lesions that correlate with primary resistance or response, or with acquired resistance during therapy. Subjects with resistant mutations can be excluded or targeted for other combination therapy in future biomarker-driven studies. Regional or local regulations could sometimes limit sample availability for somatic genome analysis. However, if regions allow, samples from other cells, such as T-cells, will be banked and analyzed later as sequencing controls and to evaluate T-cell receptor gene rearrangements. Other proteomic assays to confirm drug mechanism of action will be performed in these samples. Secreted proteins may be analyzed in these samples to examine the effects of treatment on protein expression. The volume and frequency of blood samples will be limited to minimize undue stress to the children in this pediatric study.

4. SUBJECT POPULATION

Screening for eligible subjects will be performed within 14 days before administration of the study drug. The inclusion and exclusion criteria for enrolling subjects in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the medical monitor and resolve any issues before enrolling a subject in the study. Waivers are not allowed.

For a discussion of the statistical considerations of subject selection, refer to Section 11.2, Sample Size Determination. The last assessment/evaluation or laboratory result obtained prior to randomization will be used to determine eligibility.

4.1. Inclusion Criteria

Each potential subject must satisfy all of the following criteria to be enrolled in the study.

1. 1 to <18 years of age (Part 1 only), or 1 to 30 years of age, inclusive, if initial diagnosis of mature B-cell NHL occurred at <18 years of age (Part 2 only)
2. Criterion modified per amendment 1

   2.1 Criterion modified per amendment 4

   2.2 Relapsed/refractory BL, Burkitt-like lymphoma (BLL), Burkitt leukemia (ie, B-AL) with FAB3 morphology or presence of surface immunoglobulin by flow cytometry, DLBCL, DLBCL not otherwise specified (NOS), or other pediatric mature B-cell NHL

   NOTE: Must have pathology report for the original NHL diagnosis or from the time of relapse (if available). If these pathology reports are not available, the pathology results of a fresh biopsy will be required for enrollment into the study.

3. Criterion modified per amendment 4

   3.1 Criterion modified per amendment 5

   3.2 Must be in first recurrence and have received only one prior line of therapy or have disease that is primarily refractory to conventional therapy

4. Criterion modified per amendment 2

   4.1 Must have at least 1 of the following:

   a) 1 site of measurable disease >1 cm in the longest diameter and >1 cm in the shortest diameter by radiological imaging

   b) bone marrow involvement

   c) cerebrospinal fluid with blasts present

5. Lansky-Karnofsky score of ≥50

6. Adequate organ function defined as follows:

   a) Absolute neutrophil count (ANC) ≥500 cells/µL. Growth factor support per institutional guidelines is permitted during the Screening and Treatment phases.

   b) Platelets ≥50,000 cells/µL. Subjects with thrombocytopenia due to bone marrow infiltration are eligible if platelets are ≥25,000 cells/µL. Transfusion support is permitted during the Screening and Treatment phases.

   c) Alanine aminotransferase ≤3 x upper limit of normal (ULN)

   d) Aspartate aminotransferase ≤3 x ULN

   e) Total bilirubin <1.5 x ULN, except in subjects with Gilbert syndrome or in subjects in whom the bilirubin rise is of non-hepatic origin

   f) Serum creatinine <2 x ULN for age or glomerular filtration rate >30 mL/min/1.73 m^2 by the CKiD Schwartz equation[38]

7. Must have recovered from the acute toxic effects of prior chemotherapy, immunotherapy, or radiotherapy, in the opinion of the investigator, prior to entering this study; and hematologic toxicities must meet the above criteria

8. Criterion modified per amendment 1

   8.1 ICF must be signed by legally authorized representative or by the subject if at legal age of consent indicating understanding of the purpose of, and procedures required for, the study and willingness to participate in the study. Assent is also required of children capable of understanding the nature of the study per country-specific or site-specific standards as described in Section 16.2.3, Informed Consent and Assent Form.

9. Adolescent women/young women of childbearing potential must have a negative highly sensitive serum or urine β-human chorionic gonadotropin (β-hCG) pregnancy test at Screening before enrollment/randomization. Adolescent/young women who are pregnant or breastfeeding are ineligible for this study.

10. Criterion modified per amendment 1

10.1 Criterion modified per amendment 2

10.2 Adolescents/young women of childbearing potential must be practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agree to remain on a highly effective method throughout the study and for at least 3 months after the last dose of ibrutinib and 1 year after the last dose of the background CIT, whichever is later.

Examples of highly effective contraceptives include

- user-independent methods:
  implantable progestogen-only hormone contraception associated with inhibition of ovulation; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); vasectomized partner; sexual abstinence (*sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject*).
- user-dependent methods:
  combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, and transdermal; progestogen-only hormone contraception associated with inhibition of ovulation: oral and injectable; a barrier method of contraception (eg, condom with spermicidal foam/gel/film/cream/suppository).

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method.

Women of child bearing potential must use highly effective contraceptive measures while taking IMBRUVICA. Those using hormonal methods of birth control must add a barrier method (eg, condom with spermicidal foam/gel/film/cream/suppository).

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active,) a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

11. During the study and for a minimum of 1 spermatogenesis cycle (defined as approximately 90 days) after receiving the last dose of study drug, in addition to the user-independent highly effective method of contraception, a man

    - who is sexually active with a woman of childbearing potential must agree to use a barrier method of contraception (eg, condom with spermicidal foam/gel/film/cream/suppository)
    - who is sexually active with a woman who is pregnant must use a condom
    - must agree not to donate sperm

12. Must be willing and able to adhere to the prohibitions and restrictions specified in this protocol

4.2. Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study.

1. Ongoing anticoagulation treatment with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon), or ongoing treatment with agents known to be strong CYP3A4/5 inhibitors, or has taken any disallowed therapies as noted in Section 8.2, Prohibited Medications, before the planned first dose of study drug

2. Inherited or acquired bleeding disorders

3. Clinically significant arrhythmias, complex congenital heart disease, or left ventricular ejection fraction (LVEF) <50% or shortening fraction (SF) ≤28%

4. Known history of human immunodeficiency virus (HIV) or active Hepatitis B or C virus

5. Any condition that could interfere with the absorption or metabolism of ibrutinib including malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel

6. Known allergies, hypersensitivity, or intolerance to ibrutinib or its excipients (refer to Investigator's Brochure)

7. Known allergy, hypersensitivity, or intolerance to any of the backbone CIT

8. Received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 30 days before the planned first dose of study drug, or is currently being treated in an investigational study

9. Criterion modified per amendment 2:

    9.1 Criterion modified per amendment 3

    9.2 Pregnant, or breastfeeding, or planning to become pregnant while enrolled in this study or within at least 3 months after the last dose of ibrutinib or 1 year after the last dose of the background CIT, whichever is later

10. Plans to father a child while enrolled in this study or within 3 months after the last dose of study drug

11. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments

12. Had major surgery (eg, requiring general anesthesia) within 4 weeks before enrollment/randomization, or has not fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study or within 4 weeks after the last dose of study drug administration. Lumbar puncture, bone marrow aspiration/biopsy, or placement of central venous access device are not considered major procedures.

13. Criterion added per amendment 2:

    13.1 A diagnosis of post-transplant lymphoproliferative disease (PTLD)

14. Criterion added per amendment 2:

    14.1 Patients who are within 6 months of an allogeneic bone marrow transplant

15. Criterion added per amendment 4

    15.1 Subjects who have had prior exposure to ibrutinib

NOTE: Investigators should ensure that all study enrollment criteria have been met at Screening. If a subject's clinical status changes (including any available laboratory results or receipt of additional medical records) after Screening but before the first dose of study drug is given such that he or she no longer meets all eligibility criteria, then the subject should be excluded from participation in the study. Section 17.4, Source Documentation, describes the required documentation to support meeting the enrollment criteria.

4.3. Prohibitions and Restrictions

Potential subjects must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. Criterion modified per amendment 4

   1.1 Concurrent radiation with ibrutinib is prohibited. Ibrutinib must be temporarily stopped for 3 days post-radiation

2. Refer to Section 8, Prestudy And Concomitant Therapy, for details regarding prohibited and restricted therapy during the study

3. Agree to follow the contraceptive requirements as noted in the inclusion criteria

4. Criterion modified per amendment 4

   4.1 The following guidance should be applied during the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib:

   - For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be temporarily stopped at least 7 days prior to the intervention and should be temporarily stopped at least 7 days after the procedure, and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.

   - For procedures such as a central line placement, needle biopsy, thoracentesis, or paracentesis ibrutinib should be temporarily stopped for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to temporarily stop ibrutinib.

   - For lumbar punctures, ibrutinib should be temporarily stopped for 24 hours before the procedure. If there is evidence of bleeding at the time of the lumbar puncture (ie, a “bloody tap”) defined as > 500 RBC/μL on cell count, a platelet transfusion should be given. Consider giving a platelet transfusion if there is any other clinical sign of bleeding. If bleeding does occur, ibrutinib should be temporarily stopped and the medical monitor should be contacted. If there is no evidence of bleeding during or post-procedure, ibrutinib may be resumed.

   For emergency procedures, ibrutinib should be temporarily stopped after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

5. TREATMENT ALLOCATION AND BLINDING

Treatment Allocation

Enrollment in Part 1

All subjects enrolled in Part 1 will receive ibrutinib and RICE or RVICI background therapy. A minimum of 6 subjects are needed in order to proceed to the randomized portion of the study. Three subjects are required in the RICE group and 3 in the RVICI group. If 6 subjects are enrolled and the majority receives RICE, Part 2 randomization will be opened for RICE only and RVICI randomization will only open after 3 subjects have completed Part 1 with this background therapy. If dose adjustments are required based on pharmacokinetic analyses, enrollment will be expanded before proceeding to the randomized portion of the study. The first 2 subjects enrolled in each age group (1-5 years, 6-11 years, and 12-17 years) will be treated at a lower starting dose of 240 mg/m^2 (not to exceed 420 mg) for the first cycle (older children [6-17 years] will be enrolled first before enrolling younger children [1-5 years]), followed by dose escalation at the start of Cycle 2 as long as all pharmacokinetic assessments are within the expected range and there are no safety concerns.

Procedures for Randomization and Stratification (Part 2 Only)

Central randomization will be implemented in Part 2 of this study. Subjects will be randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks and will be stratified by histology and background therapy, then randomized in a 2:1 ratio to either Treatment Arm A (ibrutinib and RICE or RVICI background therapy) or Treatment Arm B (RICE or RVICI background therapy only). The interactive web response system (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug kit for the subject. The requestor must use his or her own user identification and personal identification number when contacting the IWRS, and will then provide the relevant subject details to uniquely identify the subject.

Blinding

As this is an open-label study, blinding procedures are not applicable.

6. DOSAGE AND ADMINISTRATION

For the purposes of this study, ‘study drug’ refers to ibrutinib and ‘study treatment’ refers to ibrutinib and CIT. The dosages for background CIT are described in Table 5 and Table 6. A dosing guide for ibrutinib is provided in Attachment 1. For subjects who require dosing through a feeding tube please refer to the Investigational Product Preparation Instruction (IPPI) for information on compatible tubes. All dosing information must be recorded in the Dosage Administration page of the case report form (CRF).

6.1. Study Treatment

Ibrutinib will be administered at a target dose of 329 mg/m^2 per day (up to a maximum of 560 mg per day). The first 2 subjects in each age group (1-5 years, 6-11 years, and 12-17 years) will be started on the 420-mg equivalent dose (240 mg/m^2). For subjects being treated at the 240 mg/m^2 dose level, the maximum dose should not exceed a total of 420 mg per day. If there are no safety concerns and exposure (AUC) in Cycle 1 does not exceed the target range, the dose will be increased from Cycle 2 onward for these 2 subjects and for all subsequently enrolled subjects in that age group. However, if exposure (AUC) in these 2 subjects at the 420-mg equivalent is lower than or exceeds the target range set, the dose for these subjects and all other subjects in that age group will be adjusted as appropriate based on available exposure data. Enrollment will begin with children in the 2 older age groups (6-11, 12-17 years) to assess pharmacokinetic and safety data before allowing enrollment of children in the lowest age group (1-5 years). The SET will meet to decide on any changes to the starting dose for each age group, and when enrollment may begin for the youngest age group. At a minimum, the first 2 subjects in each age group will be enrolled into Part 1 before children in that age group will be enrolled into Part 2.

This approach to dosing will occur for the first 2 subjects in each age group. The intensified pharmacokinetic schedule will occur for all subjects in Part 1 (regardless of age).

All subjects will receive background CIT, which is investigator's choice of either RICE or RVICI. For both regimens, triple intrathecal therapy consisting of methotrexate, corticosteroid, and cytarabine will be administered for CNS prophylaxis in age-appropriate dosing (see Attachment 6). Subjects with CNS disease will receive additional doses of triple intrathecal therapy as per the Time and Events Schedule (Table 5 and Table 6). Dosages and schedule of study treatments for RICE and RVICI are described in Table 5 and Table 6, respectively.

Subjects will be randomized in a 2:1 ratio to Treatment Arm A (ibrutinib 329 mg/m^2 or other dose as determined in Part 1, and RICE or RVICI background therapy) or Treatment Arm B (RICE or RVICI background therapy only). Study treatment administration begins on Cycle 1 Day 1 and ends on the last day of Cycle 3, unless the subject experiences unacceptable toxicity or disease progression. Cycles will be 28 days long; however, if count recovery occurs quickly, cycles can be truncated to as few as 21 days. As long as there is no disease progression after Cycle 1 or 2, a second and third cycle of therapy will be given, respectively. Upon completion of 3 cycles of combination therapy, subjects randomized to ibrutinib having a response of PR or better will continue on ibrutinib monotherapy at the same daily dose for three 28-day cycles or until disease progression or unacceptable toxicity, or up until initiating subsequent antilymphoma therapy or a conditioning regimen for stem cell transplantation, whichever comes first.

Ibrutinib will be supplied as capsules or as a suspension and will be self-administered at home on each day of each cycle. Study-site personnel will instruct subjects on how to store ibrutinib for at-home use as indicated for this protocol. Subjects randomized to ibrutinib will be asked to keep a log of medication administration and report dietary intake on PK days.

The amount (in mg) of all study treatment to be administered will be determined by BSA (Attachment 3). Dosing guides for capsule and suspension administration are provided in Attachment 1. If a subject experiences a >10% change in weight from the weight used in the previous BSA calculation, then the BSA and dose should be recalculated.

6.1.1. RICE/RVICI Administration

Investigators should refer to the local prescribing information for storage and handling, and detailed instructions on the administration of rituximab, ifosfamide, carboplatin, etoposide, vincristine, idarubicin, and dexamethasone. Rituximab biosimilar drugs are not permitted in this study. All intravenous drugs should be administered at the dosages and schedule outlined in Table 5 and Table 6. Refer also to the Pharmacy Manual/study Site Investigational Product Manual.

6.1.2. Ibrutinib Administration

Subjects will be instructed to take ibrutinib orally once daily, starting at Cycle 1, Day 1. Study medication will be taken around the same time each day. It is recommended to take ibrutinib within 2 hours after a meal.

Subjects may receive ibrutinib in either a capsule (70 mg or 140 mg) or suspension formulation (see Section 14.1 for a description of the study drug and Attachment 1 for ibrutinib dosing guides). Subjects may not switch between formulations on days when pharmacokinetics will be drawn (ie, for each subject, the same formulation given on the first day pharmacokinetic samples are taken [capsule or suspension] should be given on all days when pharmacokinetic samples will be drawn thereafter). Further instructions regarding the administration of study medication are provided in the Pharmacy Manual/study Site Investigational Product Manual. Capsules and suspension should be taken with approximately 10 mL/kg with a maximum of 240 mL of water. The capsules should be swallowed whole and should not be opened, broken, or chewed.

Subjects taking ibrutinib should avoid consuming food and beverages containing grapefruit or Seville oranges for the duration of the study due to CYP3A inhibition. Subjects taking ibrutinib should refrain from taking the study drug on the morning of study visits designated for pharmacokinetic sampling until seen at the site (see Section 9.3.1). On days of pharmacokinetic sample collection (see Table 1 and Table 2), ibrutinib should be taken within 2 hours after a meal.

If a dose of study drug is missed, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra doses to make up the missed dose.

Ibrutinib (capsules or suspension) will be dispensed on Day 1 of each treatment cycle, with sufficient study drug to cover dosing for the entire cycle. Regardless of remaining capsules or suspension at the end of a treatment cycle, a new IWRS dispensing transaction should occur at the start of each new cycle and new bottle(s) of ibrutinib capsules or suspension dispensed for the subject's new cycle.

During the Posttreatment Phase, for subjects continuing on monotherapy, ibrutinib will be dispensed per cycle for three 28-day cycles. Unused study drug dispensed during previous visits must be returned and drug accountability records will be updated. Returned study drug must be discarded and may not be re-used in this study or outside the study. Study staff will instruct subjects on how to store study drug for at-home use as indicated for this protocol. Storage instructions are provided in the study Site Investigational Product Manual.

6.2. Dose Modifications and Dose Delay

6.2.1. RICE/RVICI

Management of toxicities and any dose modifications with rituximab, ifosfamide, carboplatin, etoposide, vincristine, idarubicin, and dexamethasone should be done in accordance with the respective product labels or institutional guidance. Refer to the product labels and institutional guidance for complete details on expected adverse events for each component of RICE/RVICI.

The start of a new cycle may be delayed on a weekly basis until recovery of toxicity to a level allowing continuation of therapy. A subject whose cycle is delayed should be assessed at least weekly for resolution of toxicity. If toxicity persists after a 2-week cycle delay that is related to 1 specific drug (eg, vincristine, carboplatin, etc.), the responsible drug should continue to be temporarily stopped and the new cycle should be started with the remaining drugs. If RICE/RVICI chemotherapy is delayed, treatment with ibrutinib should be continued during the delay phase.

Subjects who discontinue any component of RICE/RVICI chemotherapy without disease progression may continue the remaining components and ibrutinib until 3 cycles are completed, disease progression, or unacceptable toxicity, whichever occurs first. If there is a delay in the start of a new cycle of more than 3 weeks due to insufficient recovery from toxicity (with all drugs temporarily stopped), the case should be discussed with the medical monitor before reinitiating therapy. However, the start of a new cycle after more than a 3-week delay (with all drugs temporarily stopped) may occur if there is clear clinical benefit and only after approval by the sponsor. Cycles 2 and 3 may be initiated, at the discretion of the investigator, after the following parameters are met:

- Platelet count ≥50,000 cells/µL (prior platelet transfusion is allowed)
- Hemoglobin ≥8 g/dL (≥4.96 mmol/L) (prior red blood cell transfusion or recombinant human erythropoietin use is allowed)
- ANC ≥500 cells/µL (growth factor use is allowed, eg, granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor)

6.2.2. Ibrutinib

Treatment with ibrutinib should be temporarily stopped for any unmanageable, potentially study drug-related toxicity that is Grade ≥3 in severity. Hematologic toxicities are expected with RICE and RVICI and it may not be feasible to determine any relationship to ibrutinib. If the hematologic toxicities are not manageable, ibrutinib should be temporarily stopped, however, if

the cytopenias can be managed with transfusion and/or growth factor support and there are no unmanageable secondary complications from these cytopenias (eg, serious infection, significant bleeding) ibrutinib may be continued, at the discretion of the investigator. Ibrutinib may be temporarily stopped for a maximum of 21 consecutive days unless reviewed and approved by the sponsor. Ibrutinib should be discontinued permanently in the event of a toxicity lasting more than 21 days. If ibrutinib is delayed or temporarily stopped, any remaining study treatment (ie, rituximab, ifosfamide, carboplatin, etoposide, vincristine, idarubicin, and dexamethasone) may be continued.

The actions in Table 8 below should be taken for the following drug-related toxicities. Changes must be recorded in the Drug Accountability Records and Dosage Administration page of the electronic CRF.

- Grade 3 or greater febrile neutropenia
- Grade 4 neutropenia (ANC <0.5 x 10^9/L [ie, <500/mm^3]) for >14 days (after completion of CIT)
- Grade 3 thrombocytopenia (platelets <50 x 10^9/L [ie, <50,000/mm^3]) in the presence of significant bleeding (ie, ≥Grade 2 bleeding)
- Grade 4 thrombocytopenia (platelets <25 x 10^9/L [ie, <25,000/mm^3])
- Grade 3 or greater non-hematological toxicity

Table 8: Ibrutinib Dose Modifications

Occurrence of the Same Adverse Event	Action
First	Temporarily stop study drug until recovery to Grade ≤1 or baseline; may restart at original dose level
Second	Temporarily stop study drug until recovery to Grade ≤1 or baseline; restart at 25% decrease in dose (ie, 1 dose level lower)[a]
Third	Temporarily stop study drug until recovery to Grade ≤1 or baseline; restart at 50% decrease in dose (ie, 1 dose level lower)[a]
Fourth	Discontinue study drug

a. Consult the sponsor for calculation of the reduced dose to be administered, if needed.

Refer to Attachment 1 for BSA-based dosing/rounding. Refer to Attachment 4 for instructions on dose modifications or temporary stop during concomitant administration of CYP3A inhibitors or inducers for subjects taking ibrutinib. Refer to Section 4.3 for guidance on dose delays during the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving study drug.

7. TREATMENT COMPLIANCE

Upon termination of the study, or at the request of the sponsor or its designee, the pharmacist must return the study drug to the sponsor or its designee, after all drug supplies have been accounted for, unless it is destroyed at the site as agreed upon by both the sponsor and the site.

Instructions regarding accountability for study drug are provided in the study Site Investigational Product Manual.

7.1. Ibrutinib Compliance

The study drug (ibrutinib) is to be prescribed only by the principal investigator or a qualified physician listed as a subinvestigator on required forms. Records should be kept on the study drug accountability record provided by the sponsor or its designee. Dispensing of the study drug (ibrutinib) must be recorded in the subject's source documents. Ibrutinib may not be used for any purpose other than that outlined in this protocol, including other human studies, animal investigations, or in vitro testing.

The IWRS will be used to assign centrally supplied study treatment kits for each subject. The investigator or the site pharmacist will maintain a log of all ibrutinib dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study. Subjects/caregivers will be provided with a diary card to record intake at home. Site personnel are to instruct the subject to bring the diary card and any unused ibrutinib to the site at the beginning of each treatment cycle to check ibrutinib dosing compliance.

Instructions for proper self-administration and ibrutinib storage conditions will be provided. Precautions associated with the use of ibrutinib and prohibited concomitant medications will be reviewed. Site staff will provide additional instruction to re-educate any subject who is not compliant with the ibrutinib schedule. Subjects will be asked to keep a log of ibrutinib administration and report dietary intake on PK days.

7.2. RICE/RVICI Compliance

Background therapy with RICE/RVICI will be provided by qualified study-site personnel and each administration will be recorded in the electronic CRF. The site pharmacist will maintain a log of all drug vials prepared for infusion and administration. Drug supplies, if provided by the sponsor, for each subject will be inventoried and accounted for throughout the study. The infusion will be administered according to the approved prescribing information or approved institutional guidelines.

8. PRESTUDY AND CONCOMITANT THERAPY

Systemic use of the following concomitant medications will be collected in the electronic CRF and recorded in the source documents beginning with signing of the ICF to 30 days after the last dose of the last study treatment or until the start of subsequent antilymphoma therapy (whichever is earlier): growth factors, transfusions, anti-infectives (antibacterials, antivirals, and antimycotics), steroids, anti-arrhythmics and other cardiac supportive therapy, anti-epileptics, psychoanaleptics, and any anticancer therapy (including radiation). Concomitant therapies administered at the time of, and used in the treatment of a serious adverse event, should be recorded. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

8.1. Permitted Medications and Supportive Therapies

Concomitant medications for medical conditions other than NHL are permitted. Usage of antimicrobial prophylaxis in accordance with standard practice is permitted and should be considered in subjects who are at increased risk for opportunistic infections. Non-azole antifungal prophylaxis with coverage for aspergillosis is recommended (eg, amphotericin B or echinocandins). The use of growth factors is permitted in this study, but should be used according to institutional, provincial, or other guidelines (eg, American Society of Clinical Oncology) and according to the investigators site standard for use of growth factors during treatment of NHL with standard RICE/RVICI chemotherapy. The use of granulocyte colony stimulatory factor (GCSF) should be used with the RVICI regimen beginning on Day 12 and continued until ANC ≥500/µL on 2 occasions post-nadir (Table 6). Supportive therapies, other than anticancer treatment, needed for the management of subjects enrolled in this study are permitted with restrictions for corticosteroids (see Section 8.2).

8.1.1. Medications Permitted Prior to Study Treatment

Corticosteroids to control symptoms of lymphoma are permitted prior to enrollment/randomization (40 mg/m^2/day prednisone or equivalent) for a maximum of 10 days. If pretreatment corticosteroids exceed 40 mg/m^2/day of prednisone or equivalent, please consult the medical monitor. If steroids are administered, they should be given after the baseline imaging assessment, baseline laboratory assessments, and baseline performance status assessment. Steroids must be recorded on the electronic CRF. Treatment with steroids should be discontinued upon beginning the Treatment Phase.

8.1.2. Medications Permitted During Treatment

The following supportive therapies are recommended:

- Histamine 2 (H_2) blocker or proton pump inhibitors for peptic ulcer prophylaxis
- 5-HT_3 antagonists or equivalent antiemetics
- Uric acid-lowering agents:

  Subjects with more than 1 of the factors listed below are considered to be at increased risk of tumor lysis syndrome and should be considered for hydration and treatment with a uric acid-lowering agent as well as for frequent monitoring of tumor lysis-associated signs and symptoms, including blood chemistry. Uric acid-lowering agents may include xanthine oxidase inhibitor allopurinol or Uloric® [febuxostat] with or without rasburicase per the drug product package inserts.

  – Serum creatinine ≥1.5 x ULN or calculated creatinine clearance <60 mL/min
  – Uric acid ≥450 µmol/L or 7.5 mg/dL
  – Bulky disease (eg, lymph node >10 cm or massive splenomegaly)
  – Elevated lactic acid dehydrogenase >2 x ULN
- Premedication with acetaminophen or equivalent, and diphenhydramine (or an antihistamine of investigator's choice).

- Loperamide for the treatment of diarrhea, starting at the time of the first watery stool. Infectious diarrhea should be ruled out prior to initiation of loperamide. The loperamide dose regimen should be according to standard practice.
- Blood product transfusions (including but not limited to platelets, red blood cells, and immunoglobulins), and growth factors, as required.
- Prophylactic treatment for pneumocystis carinii pneumonia, oral candidiasis and Herpes simplex virus infections according to local standards.
- Non-azole antifungal prophylaxis with coverage for aspergillosis (eg, amphotericin B or echinocandins) for subjects on ibrutinib. Azole antifungals are allowed for subjects randomized to background therapy only.
- A single dose of corticosteroids given as premedication prior to rituximab infusions and/or in response to infusion-related reactions.

8.2. Prohibited Medications

The following medications and supportive therapies are prohibited during the Treatment Phase:

- Any anticancer agent other than the outlined CIT regimen
- Systemic corticosteroids above that given for CIT chemotherapy and anti-emetic use (prednisone not more than 4 to 5 mg/m^2/day or its equivalent is allowed for the treatment of adrenal insufficiency or other medical reason that is not cancer related). If stress dose steroids are required, the medical monitor should be informed.
- Any experimental agents other than ibrutinib

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

8.3. Concomitant Medications to be Avoided or to be Used with Caution

Attachment 4 provides instructions for medications to be avoided or used with precaution in subjects taking ibrutinib, including strong and moderate CYP3A inhibitors or inducers, and a list of these medications is provided in Attachment 5. Numerous antibiotics, antivirals, antifungals, antiepileptic, and cardiac medications are included in this list. Supplements such as fish oil and vitamin E preparations should be avoided.

8.3.1. Radiation Therapy

Radiation therapy must not be given concurrently with ibrutinib. Ibrutinib should be temporarily stopped for 3 days after the last radiation treatment. Subjects should have sites of measurable disease, other than those that were irradiated, that can be followed for response. If a subject's disease progresses while on study and the subject requires radiation therapy, disease assessment evaluations should be obtained prior to initiating radiation.

8.4. Subsequent Antilymphoma Therapies

Administration of subsequent antilymphoma therapy is not allowed until:

- Confirmed residual disease after completion of at least 3 cycles of study treatment, or
- PD (or relapse after CR) any time during treatment as established according to the criteria described in Section 9.2.5.2, Response Categories.

Note that the medical monitor must be notified of the subject's suspected PD and all imaging, bone marrow, and cerebrospinal fluid (CSF) disease analyses are required to be centrally reviewed before a subject is removed from study therapy. Subjects who have not progressed while on therapy and who receive subsequent therapy for NHL will continue to be followed until PD. For any subsequent antilymphoma therapy, the start date, end date, and best response should be documented in the appropriate section of the electronic CRF.

9. STUDY EVALUATIONS

9.1. Study Procedures

9.1.1. Overview

The study is divided into 3 phases: a Pretreatment (Screening) Phase, a Treatment Phase, and a Posttreatment Phase. The Time and Events Schedule summarizes the frequency and timing of efficacy, pharmacokinetic, pharmacodynamic, biomarker, and safety measurements applicable to this study (Table 1, Table 2, Table 3, and Table 4).

The estimated maximum blood volume collected from each subject for the entire study duration is approximately 139.0 to 230.5 mL in Part 1, and 131.4 to 222.9 mL in Part 2, including samples drawn for safety, pharmacokinetics, pharmacodynamics, biomarkers, protein binding (Part 1 only), and pregnancy testing (when urine is not available for testing; young women of childbearing potential only) (see Attachment 7). Blood volumes drawn should not exceed local or institutional standards.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples but should not exceed allowable daily blood volume limits per local standards.

If at any time, a subject undergoes stem cell harvest in preparation for a stem cell transplant, the total cell count collected should be recorded in the eCRF.

9.1.2. Pretreatment (Screening) Phase

All subjects, or their legally-acceptable representatives, must sign an ICF prior to the conduct of any study-related procedures. Where applicable, subjects below the age of legal consent should sign an assent form prior to the conduct of any study-related procedures. During this phase, eligibility criteria will be reviewed and a complete clinical evaluation performed as specified in the Time and Events Schedule (Table 1 and Table 2). The pathology report for the original diagnosis of NHL or at the time of relapse, if available, will be used to confirm diagnosis. If that pathology report is not available, the results of a fresh biopsy will be required for enrollment into

the study. The results of laboratory tests noted in the inclusion criteria must be within the limits specified prior to enrollment/randomization; testing may be repeated for this purpose. The last result obtained prior to start of study treatment will be used to determine eligibility. Assessments performed as part of the subject's routine clinical evaluation and not specifically for this study need not be repeated after signed informed consent has been obtained provided that assessments fulfill the study requirements and are performed within the specified timeframe prior to randomization (Table 1 and Table 2). Echocardiography or multiple-gated acquisition scan (MUGA) is mandatory at Screening, and for subjects treated with RVICI background therapy, it is also mandatory after each cycle (before treatment on Day 1 of Cycle 2 and Cycle 3). Echocardiography or MUGA may be repeated if clinically indicated during the study (using same modality) either at an assessment visit or at an unscheduled visit.

Retesting for Eligibility

Limited retesting of abnormal Screening values that lead to exclusion are allowed only once using an unscheduled visit during the Screening period (to reassess eligibility). If a subject does not meet all inclusion and exclusion criteria (is a screen failure) but at some point in the future is expected to meet the subject eligibility criteria, the subject may be rescreened on 1 occasion only. Subjects who are rescreened will be assigned a new subject number, undergo the informed consent process, and then restart a new screening phase.

9.1.3. Treatment Phase

The Treatment Phase will begin at enrollment (for Part 1) or randomization (for Part 2) and will continue until discontinuation of combination study treatment (ie, ibrutinib + CIT or CIT alone) due to disease progression, initiation of subsequent antilymphoma therapy, unacceptable toxicity, withdrawal, CR, or completion of study treatment after Cycle 3. The last measurements taken on Cycle 1 Day 1 before administration of study treatment or at Screening (whichever value was last) will be defined as the baseline values for safety assessment and treatment decision. Laboratory values obtained prior to Cycle 1 Day 1 should be repeated if they were collected more than 5 days prior to the start of ibrutinib treatment. These values should be consistent with the values in the inclusion and exclusion criteria (Sections 4.1 and 4.2, respectively) in order for the subject to receive treatment.

A symptom-directed physical exam (including lymphoma B-symptoms) and laboratory testing will be conducted. Adverse events and changes to concomitant medications will be recorded. Subjects will be evaluated throughout this phase for possible toxicities. Dose modifications will be made as according to criteria described in the protocol (see Section 6.2).

All subjects will visit the study site on Day 1 of Cycle 1 during the Treatment Phase. Clinical evaluations and laboratory studies may be repeated more frequently, if clinically indicated. When all evaluations have been completed, and it has been determined that the subject may continue treatment, CIT will be administered intravenously and sufficient study drug will be dispensed for self-administration. The subject should refrain from taking the study drug on the morning of study visits designated for pharmacokinetic sampling until seen at the site. If a subject shows signs of progression on physical examination or laboratory assessment, the subject may continue

study treatment until PD is confirmed by the central IRC. If PD is diagnosed, then the subject will discontinue study treatment, complete the End-of-Treatment visit within 30 days after the last dose of the last study treatment, and enter the Posttreatment Phase. Imaging evaluations performed on Cycle 1 Day 14 are exploratory; therefore, if PD is indicated based on these scans, investigator discretion should be used to determine if the clinical evaluation is consistent with PD. If not, the subject may continue with study treatment until confirmation of PD or the subject meets other criteria for withdrawal. If CR is confirmed at the end of 2 cycles of treatment, then the subject is eligible to proceed to stem cell transplantation.

End-of-Treatment Visit

Subjects who discontinue the last study treatment due to progression, adverse event, or other reasons and enter the Posttreatment Phase should have the End-of-Treatment visit completed before starting any subsequent antilymphoma therapy. If a subject is unable to return to the site for the End-of-Treatment visit, the subject should be contacted to collect adverse events that occur within 30 days after the last dose of the last study treatment. Additional information on reporting adverse events may be found in Section 12.

If the subject requires subsequent antilymphoma therapy in the interim period following the last dose of study treatment and the End-of-Treatment visit, then this visit should be completed earlier, ie, just prior to initiation of subsequent antilymphoma therapy. Refer to the Time and Events Schedule for a complete list of procedures to be performed (Table 1, Table 2, Table 3, and Table 4).

9.1.4. Posttreatment Phase (Follow-Up)

After the completion of the End-of-Treatment procedures, all subjects will enter a Posttreatment Phase. During the Posttreatment Phase, subjects randomized to ibrutinib having a response of PR or better after 3 cycles of combination treatment will continue on ibrutinib monotherapy at the same daily dose for three 28-day cycles or until disease progression or unacceptable toxicity, or up until initiating subsequent antilymphoma therapy or a conditioning regimen for stem cell transplantation, whichever occurs first.

For subjects who enter the Posttreatment Phase without disease progression, follow-up visits to assess disease progression will be completed as per Table 3 and Table 4 until PD, the clinical cutoff for the primary endpoint, or for up to 3 years after the date of Cycle 1 Day 1, whichever occurs first. After that, evaluations may be performed as clinically indicated at the discretion of the investigator. After the last protocol efficacy assessment at 3 years, subjects without PD will be followed for survival status as per the standard routine of care of the investigator site. If PD is assessed after 3 years, the date and reason for progression will be entered in the CRF. Additionally, if the investigator becomes aware of the subject death, the date of death will be entered in the CRF.

The interval between follow-up visits should be maintained as outlined in the Times and Events Schedules (Table 3 and Table 4); if a visit occurs earlier or later than the scheduled visit date, then the next visit date should be rescheduled to maintain the required interval from the previous

visit. At any visit, if there is clinical evidence or suspicion of PD, then appropriate testing must be performed to document progression (See Section 9.2.1).

Investigators may re-contact the subject to obtain long-term follow-up information regarding the subject's safety or survival status as noted in the ICF (refer to Section 16.2.3, Informed Consent and Assent Form). Survival follow-up (physician visit or telephone contact) will be required every 4 weeks for all subjects following PD until death or study end, whichever occurs first. The interval between post-PD survival follow-up visits should be maintained at 4 weeks; if a visit occurs earlier or later than the scheduled visit date, then the next visit date should be rescheduled to maintain the required interval from the previous visit.

At the time of PD or if residual disease is present upon completion of 3 cycles, the subject is considered eligible to receive subsequent antilymphoma therapy. Subsequent antilymphoma therapy will be recorded in the electronic CRF. Subjects with residual disease who receive subsequent antilymphoma therapy will be followed until PD, end of the study, or death. Investigators should maintain adequate contact with the subject to obtain follow-up information on safety and survival status. Where allowed by local law, public records may be used to document death. Any new malignancy reported during the posttreatment follow-up phase will be recorded in the CRF (Section 12.3.4).

9.1.5. Clinical Cutoffs

Two clinical cutoffs are planned. The first clinical cutoff will occur when approximately 30 EFS events have been observed in Part 2 of the study. The second clinical cutoff will occur when approximately 60 EFS events have been observed in Part 2 of the study. The interim analysis and final analysis of the primary endpoint EFS will take place at these 2 clinical cutoffs, respectively.

9.2. Efficacy Evaluations

9.2.1. Imaging Assessments

Magnetic resonance imaging (MRI) or CT scan with intravenous contrast of the neck, chest, abdomen and pelvis, and, if indicated, CNS, with or without a PET scan, should be used to evaluate sites of disease as specified in the Time and Events Schedule (Table 1, Table 2, Table 3, and Table 4). Each region is to be scanned regardless of the presence/absence of disease in a given area. The same modality used at baseline should be obtained at subsequent disease evaluations. Positron emission tomography scan at baseline is recommended but not mandatory. If disease is PET avid upon Screening, PET should be repeated at subsequent evaluations. Imaging performed for standard of care up to 5 days prior to signing ICF may be used as baseline evaluations if they are of sufficient quality. Brain MRI and lumbar puncture may be required in subjects with CNS-positive disease, as clinically indicated. Evaluation of other sites of disease may be performed by radiological imaging, physical examination, or other procedures as necessary, and should be performed throughout the study using the same method of assessment per subject.

The following are scanning options in decreasing order of preference:

1. Neck-Chest-Abdomen-Pelvis CT with IV-contrast administration
2. Chest CT without IV-contrast administration **and** Neck-Abdomen-Pelvis MRI with gadolinium IV contrast, only if iodine contrast media is medically contraindicated at any time during the study
3. Neck-Chest-Abdomen-Pelvis MRI with IV contrast, only if CT IV contrast media is medically contraindicated at any time during the study and chest CT cannot be performed
4. Neck-Chest-Abdomen-Pelvis CT without IV contrast, only under exceptional circumstances if MRI cannot be performed

9.2.2. Bone Marrow/ Lymph Node Assessment

A subject may enter the study with only bone marrow disease. If this happens, then the subject will be followed by a bone marrow biopsy and/or aspirate for disease evaluations. Radiographic images are required at screening in these subjects but if no nodal disease is identified, subsequent imaging is not required. The timepoints for bone marrow evaluations are outlined in Table 1, Table 2, Table 3, and Table 4. Morphological examination and IHC or flow cytometry is required of all bone marrow specimens at screening for all subjects. If bone marrow results at screening are negative, subsequent assessments must include morphologic assessment of the bone marrow, while immunophenotyping is optional. Bone marrow procedures may be performed the day prior to the start of a treatment cycle for logistical reasons as needed.

9.2.3. Lumbar Puncture

Cerebral spinal fluid should be obtained at Screening in order to diagnose CNS-status at study entry. Lumbar puncture on Cycle 1 Day 1 can be used as the screening lumbar puncture only if collected prior to administration of ibrutinib or background therapy. For all subjects, CSF should be obtained at the start of each cycle and following completion of study treatment. Lumbar punctures may be performed the day prior to the start of a treatment cycle for logistical reasons as needed. In addition, CSF sampling in subjects with CNS-positive disease at baseline should occur every 4 days ±1 day until CSF is cleared of lymphoma cells.

9.2.4. Physical Examination

During the Screening, Treatment Phase, and Posttreatment Phase (see Time and Events Schedule for procedures, (Table 1, Table 2, Table 3, and Table 4), subjects should have a physical examination to evaluate the presence of palpable lymph nodes, tumor masses, or spleen and liver enlargement. Approximate measurement of palpable lymph nodes or masses should be provided. Symptom-directed questions will be asked to evaluate for the presence of B-symptoms.

9.2.5. Efficacy Criteria

All efficacy assessments must continue until disease progression (even if subsequent antilymphoma therapy is started), withdrawal of consent from study participation, or clinical cutoff for the primary analysis. The Sponsor Medical Monitor is to be notified within 24 hours for subjects who have disease progression and central assessment will ensue. Imaging, bone marrow assessments and CSF evaluations are required at Screening, Cycle 3 Day 1, and at End of Treatment. CSF evaluation is also required at Cycle 2 Day 1, but bone marrow is only

required at this time point if clinically indicated. Subjects without nodal disease (ie, subjects with bone marrow only disease) only require imaging at Screening. Imaging evaluations performed on Cycle 1 Day 14 are exploratory; if PD is indicated based on these scans, investigator discretion should be used to determine if the clinical evaluation is consistent with progressive disease. If not, the subject may continue with study treatment until confirmation of PD or the subject meets other criteria for withdrawal.

9.2.5.1. Evaluation of Measurable Disease

Subjects with nodal disease must have at least 1 measurable lymph node >1 cm in the longest diameter and >1 cm in the shortest diameter detected by CT scan or MRI in order to participate in this study. Measurable sites of disease are defined as lymph nodes, lymph node masses, or extranodal sites of lymphoma/leukemia. In the absence of nodal disease, the presence of blasts in the cerebrospinal fluid or >25% blasts in the bone marrow will be sufficient for measurable disease.

Up to 6 of the most representative nodal or extranodal masses should be selected for measurement in 2 perpendicular dimensions. In addition, the selection of these lesions should be from as disparate regions of the body as possible. Additional lesions that are present but not included in the assessment should be added as non-target lesions and followed throughout the study. The longest diameter of the spleen and liver will be assessed at Screening and at all subsequent disease evaluations.

All other sites of disease will be considered assessable. Assessable disease includes objective evidence of disease that is identified by radiological imaging, physical examination, or other procedures as necessary including bone marrow aspiration/biopsy or peripheral blood counts. Examples of assessable disease include bone lesions; mucosal lesions in the gastrointestinal tract; effusions; pleural, peritoneal, or bowel wall thickening; disease limited to bone marrow; and groups of lymph nodes that are not measurable but are thought to represent lymphoma.

9.2.5.2. Response Categories

Assessment of tumor response and progression will be according to the International Pediatric NHL Response Criteria (Table 9 and Table 10).[36] Disease response will be evaluated by radiological imaging, physical examination, or other procedures as necessary, including but not limited to review of hematology, clinical chemistry, and lumbar puncture results. Disease evaluations, for the purpose of the study result analyses, will be reviewed by an IRC blinded to study treatment information and independent of investigators and personnel who are involved in conduct of the study. As part of the central review, radiographic evaluations will be assessed by an independent radiologist and relevant clinical data will be assessed by an independent oncologist. Detailed procedures will be described in a separate charter.

Table 9: International Pediatric NHL Response Criteria

Criterion	Definition
CR	Disappearance of all disease (3 designations)
CR	CT or MRI reveals no residual disease or new lesions Resected residual mass that is pathologically (morphologically) negative for disease (detection of disease with more sensitive techniques described as supporting data [Table 10]) BM and CSF morphologically free of disease (detection of disease with more sensitive techniques described as supporting data [Table 10]) with no new lesions by imaging examination
CR_b	Residual mass has no morphologic evidence of disease from limited or core biopsy (detection of disease with more sensitive techniques described as supporting data), with no new lesions by imaging examination BM and CSF morphologically free of disease (detection of disease with more sensitive techniques described as supporting data [Table 10]) No new or PD elsewhere
CR_u	Residual mass is negative by FDG-PET; no new lesions by imaging examination BM and CSF morphologically free of disease (detection of disease with more sensitive techniques described as supporting data [Table 10]) No new or PD elsewhere
PR	50% decrease in SPD on CT or MRI; FDG-PET may be positive (Deauville score or 4 or 5 with reduced lesional uptake compared with baseline); no new or PD; morphologic evidence of disease may be present in BM or CSF if present at diagnosis (detection of disease with more sensitive techniques described as supporting data [Table 10]); however, there should be 50% reduction in percentage of lymphoma cells
MR	Decrease in SPD >25% but <50% on CT or MRI; no new or PD; morphologic evidence of disease may be present in BM or CSF if present at diagnosis (detection of disease with more sensitive techniques described as supporting data [Table 10]); however, there should be 25% to 50% reduction in percentage of lymphoma cells
NR	For those who do not meet CR, PR, MR, or PD criteria
PD	For those with >25% increase in SPD of residual lesions (calculated from nadir) on CT or MRI, Deauville score 4 or 5 on FDG-PET with increase in lesional uptake from baseline, documentation of new lesions or development of new morphologic evidence of disease in BM or CSF

BM=bone marrow; CR=complete response; CR_b=complete response biopsy-negative; CR_u=complete response unconfirmed; CSF=cerebrospinal fluid; CT=computed tomography; FDG=[18F]fluorodeoxyglucose; MR=minor response; MRI=magnetic resonance imaging; NHL=non-Hodgkin lymphoma; NR=no response; PD=progressive disease; PET=positron emission tomography; PR=partial response; SPD=sum of the products of the lesion diameters.

Table 10: Supporting International Pediatric NHL Response Criteria Data

Supporting Information	Definition
BM Involvement	Currently defined by morphologic evidence of lymphoma cells; this applies to any histologic subtype; type and degree of BM involvement should be specified[a]
BMm	BM positive by morphology (specify percentage of lymphoma cells)
BMi	BM positive by immunophenotypic methods (histochemical or flow cytometric analysis; specify percentage of lymphoma cells)
BMc	BM positive by cytogenetic or FISH analysis (specify percentage of lymphoma cells)
BMmol	BM positive by molecular techniques
CNS Involvement	
CSF status	CSF positivity is based on morphologic evidence of lymphoma cells; CSF should be considered positive when any number of blasts is detected; CSF may be unknown; as with BM, type of CSF involvement should be described whenever possible
CSFm	CSF positive by morphology (specify No. of blasts/µL)
CSFi	CSF positive by immunophenotype methods (histochemical or flow cytometric analysis; specify percentage of lymphoma cells)
CSFc	CSF positive by cytogenetic or FISH analysis (specify percentage of lymphoma cells)
CSFmol	CSF positive by molecular techniques
RM	
RMm	Tumor detected by standard morphologic evaluation
RMi	Tumor detected by immunophenotypic methods (immunohistochemical or flow cytometric analysis)
RMc	Tumor detected by cytogenetic or FISH analysis
RMmol	Tumor detected by molecular techniques

BM=bone marrow; CNS=central nervous system; CSF=cerebrospinal fluid; FISH=fluorescent in situ hybridization; NHL=non-Hodgkin lymphoma; PB=peripheral blood; RM=residual mass.

a. Same approach should be used for PB involvement (ie, PBm, PBi, PBc, PBmol).

9.3. Pharmacokinetics

Plasma samples will be used to evaluate the pharmacokinetics of ibrutinib. Plasma collected for pharmacokinetic analyses may additionally be used to evaluate safety or efficacy aspects that address concerns arising during or after the study period. Genetic analyses will not be performed on these samples.

9.3.1. Evaluations

During Part 1, venous blood samples of approximately 0.6 mL will be collected for measurement of plasma concentrations of ibrutinib and the PCI-45227 metabolite using a sparse sampling approach (1 sample predose, and 4 samples at 1, 2, 4, and 6 hours postdose on Day 1 and on Day 7 **or** 8 of Cycle 1). Subsequent samples will be collected predose and 1, 2, 4, and 6 hours postdose on Day 1 of Cycle 2 or Cycle 3 (not both). Sample time windows are provided in Table 1 (Time and Events Schedule). If a subject experiences bleeding with a lumbar puncture and needs to delay the dose of ibrutinib on Day 1 of the cycle, the “Day 1” pharmacokinetic sampling should be done after administration of CIT is complete (on Day 7 or 8) instead. If this occurs during Cycle 1, the Day 1 pharmacokinetic assessment for that day will be skipped altogether.

During Part 2, sparse pharmacokinetic samples will be collected from subjects randomized to receive ibrutinib to expand the pediatric pharmacokinetic dataset. Four samples will be collected from each subject. Samples will be collected at the following timepoints: samples collected at predose; 1 (window 45-75 minutes), 2 (window 1.5-2.5 hours), and 4 hours (window 3.5-6 hours) postdose, either on Cycle 1 Day 14 (preferred), but if unable to be obtained during Cycle 1 (eg, due to a temporary stop of ibrutinib) can be collected on Cycle 2 Day 1. Please note that subjects must take ibrutinib for a minimum of 3 days prior to all pharmacokinetics timepoints after Cycle 1 Day 1 for pharmacokinetics to be valid. If ibrutinib is temporarily stopped on any pharmacokinetics sampling days, or within 3 days prior to pharmacokinetics sampling, the medical monitor should be contacted for guidance.

Additional information about the collection, handling, and shipment of biological samples can be found in the Laboratory Manual.

Subjects should refrain from taking the study drug on the morning of study visits designated for pharmacokinetic sampling until instructed to do so at the site. Subjects should not receive red blood cell transfusions during the period of pharmacokinetic sampling, beginning 1 hour before the first sample collection. On days of pharmacokinetic sample collection (see Table 1 and Table 2), ibrutinib should be taken within 2 hours after a meal. The times of the meals before and after dosing, as well as any vomiting up to 4 hours after ibrutinib administration, are to be recorded on the laboratory requisition form. The investigator or designee will supervise administration of the study treatment and record the exact time of study treatment administration. Samples and information on subjects' feeding state will only be collected from subjects treated with ibrutinib.

9.3.2. Analytical Procedures

Plasma samples will be analyzed to determine concentrations of ibrutinib and the metabolite PCI-45227 using a validated, specific, and sensitive liquid chromatography/tandem mass spectrometry (LC-MS/MS) method by or under the supervision of the sponsor. If required, some plasma samples may be analyzed to document the presence of circulating metabolites using a qualified research method.

9.3.3. Pharmacokinetic Parameters

Based on the individual plasma concentration-time data obtained in Part 1, using the actual dose taken and the actual sampling times, pharmacokinetic parameters and metrics of exposure of ibrutinib will be derived using population pharmacokinetic modeling (nonlinear mixed effects modeling). The population model developed in adults may be used. Individual as well as population-predicted pharmacokinetic parameters will include CL/F and V_d/F. Metrics of systemic exposure to ibrutinib (AUC) will also be estimated. The effect of age or body size (weight, BSA) on pharmacokinetics parameters will be evaluated. The effect of other baseline covariates (eg, creatinine clearance, race) on pharmacokinetic parameters may also be explored, as considered relevant.

Plasma concentration-time data obtained in Part 2 will be used to expand the pediatric pharmacokinetic dataset and further refine the model, as required. The details of the pharmacokinetic assessments will be described in a dedicated analysis plan. Metabolite data will be only summarized using descriptive statistics (not derived using population pharmacokinetic modeling).

9.4. Pharmacodynamic Evaluations

Blood samples will be collected for pharmacodynamic assessments (BTK occupancy) according to the Time and Events Schedule (Table 1, Table 2, and Table 3).

9.5. Pharmacokinetic/Pharmacodynamic Evaluations

Model-derived exposure parameters may be subjected to further analyses to explore the correlations between ibrutinib exposure and relevant clinical or biomarker information. Results will be presented in a separate report.

9.6. Biomarkers

Archived formalin-fixed paraffin-embedded tumor or fresh lymph node biopsy (if collection is feasible and where local regulations and shipping logistics permit) will be used for biomarker evaluations at Screening and at the time of disease progression. If archived tissue is unavailable and a fresh lymph node biopsy cannot be obtained, bone marrow biopsy slides (when positive for disease) can be used.

In the event that no archived tissue is available, the subject is too unstable to undergo a fresh biopsy, but it is expected that the biopsy may be feasible after beginning chemotherapy, a fresh lymph node biopsy is recommended to be obtained after debulking with the study treatment regimen in subjects with DLBCL only (cell of origin studies will not be affected by initiation of therapy). Blood samples for biomarker evaluations, as described in Section 3.2.6, will be collected according to the Time and Events Schedule (Table 1, Table 2, Table 3, and Table 4).

Stopping Analysis

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and may be deferred or not performed if, during or at the end of the study, it becomes clear that the analysis will have no scientific value or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments will be based on justification and intended utility of the data.

Additional Collections

If it is determined at any time before study completion that additional material is needed from a formalin-fixed, paraffin-embedded tumor sample for the successful completion of the protocol-specified analyses, the sponsor may request that additional material be retrieved from existing samples. Also, based on emerging scientific evidence, the sponsor may request additional material from previously collected tumor samples during or after study completion for

a retrospective analysis. In this case, such analyses would be specific to research related to the study drug or diseases being investigated.

9.7. Palatability Assessment

Palatability of ibrutinib will be measured using a visual analog scale adapted from published literature.[22,23,39] The scale is a 5-point visual analog scale incorporating a facial hedonic scale designed to span pediatric ages and levels of subject comprehension. Children as young as 4 years should have the developmental capacity to assess palatability using this scale. Assessments will be obtained during the study Treatment Phase as specified in the Time and Events Schedule (Table 1 and Table 2).

9.8. Safety Evaluations

All subjects who receive at least 1 dose of treatment will be considered evaluable for safety. The SET will monitor subject safety during the dose-confirmation part of the study. Part 2 of the study will be monitored by an independent DMC (details are provided in Section 11.8, Independent Data Monitoring Committee). Subjects will be assessed by physical examination, weight evolution, and performance status evaluation. Hematology and clinical chemistry tests will be performed at regular intervals as specified in the Time and Events Schedule. The study will include the following evaluations of safety and tolerability according to the timepoints provided in the Time and Events Schedule (Table 1, Table 2, Table 3, and Table 4).

Adverse Events

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally-acceptable representative) from the time of signed consent until 30 days after the last dose of study drug (including ibrutinib monotherapy) or until the start of a subsequent systemic antineoplastic therapy, if earlier, unless the subject has withdrawn consent for study participation. Adverse events occurring after 30 days following the last dose of study treatment should also be reported if considered related to study treatment. Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the CRF. Any clinically significant abnormalities persisting at the End-of-Treatment visit/early withdrawal will be followed by the investigator until resolution or until a clinically stable endpoint is reached. All Grade 3 or 4 adverse events considered related to study drug must be followed until recovery to ≤Grade 1 or baseline, deemed irreversible, or until end of study.

All adverse events will be recorded with the details of the duration and the severity of each episode, action taken with respect to the study drug, investigator’s evaluation of its relationship to the study drug (ie, not related, doubtful, possibly, probably, very likely related), and the subjects’ outcome. All serious adverse events (life-threatening, results in death, results in or prolongs hospitalization, or results in persistent disability/incapacity, congenital anomaly/birth defect, suspected transmission of any infectious agent, or medically important) must be reported to the sponsor within 24 hours. Progressive disease of NHL should not be reported as an adverse event, but instead, the clinical diagnosis that is associated with disease progression is to be reported.

Adverse Events of Special Interest

Major hemorrhage has been identified as an adverse event of special interest and will require enhanced reporting and data collection (see Section 12.3.3, Adverse Events of Special Interest, for details).

Clinical Laboratory Tests

Blood samples for serum chemistry and hematology will be collected. Samples for required laboratory tests may be collected on the day of or day before dosing. For Day 1 Cycle 1 only, clinical laboratory tests do not need to be repeated if the Screening tests were performed within 5 days prior to the first dose of study treatment, with the exception of pregnancy testing which needs to be performed within 24 hours prior to the start of treatment per cycle.

The investigator must review the local laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. For example, laboratory abnormalities leading to an action regarding any study treatment (dose change, temporary stop, delay of the start of a cycle or permanent stop) or the start of concomitant therapy should be reported. For each laboratory abnormality reported as an adverse event, the following laboratory values should be reported in the laboratory section of the electronic CRF: the value indicative of the onset of each toxicity grade; the most abnormal value observed during the adverse event, and the value supporting recovery to Grade ≤1 or to baseline values. The following tests will be performed by the local laboratory at the timepoints shown in the Time and Events Schedule (Table 1, Table 2, Table 3, and Table 4):

- Hematology Panel

  -hemoglobin
  -platelet count
  -white blood cell count
  -absolute neutrophil count
  -absolute lymphocyte count
  -lymphoblasts (also called blasts) if applicable

- Serum Chemistry Panel

  -sodium
  -potassium
  -blood urea nitrogen or urea
  -creatinine
  -aspartate aminotransferase
  -albumin
  -alkaline phosphatase
  -total bilirubin
  -lactic acid dehydrogenase
  -uric acid
  -alanine aminotransferase

- Viral Serology Panel

  -HBsAg
  -HBsAb
  -HBcAb
  -Hepatitis C
  -HIV

If Hepatitis B core antibody is positive, Hepatitis B DNA by polymerase chain reaction (PCR) needs to be performed and confirmed as negative to continue with study participation. Subjects should be monitored for viral reactivation by liver enzymes and Hepatitis B PCR when appropriate and prophylactic antiviral medication should be considered per local practice.

- Tetanus and pneumococcal antibody titers (central laboratory)
- Serum or urine pregnancy testing for young women of childbearing potential only

Electrocardiogram/Echocardiography/MUGA Scan

Baseline LVEF/SF must be assessed by MUGA or echocardiogram and demonstrate LVEF ≥50% or SF >28% for subjects to be eligible and may be repeated throughout the study, protocol directed or when clinically indicated. When the examination is repeated, the same modality should be used. Echocardiography/MUGA and 12-lead ECGs will be obtained for all subjects at the timepoints specified in the Time and Events Schedule (Table 1, Table 2, and Table 3). Additional cardiovascular assessments should be performed as clinically appropriate to ensure subject safety.

During the collection of ECGs, subjects should be in a quiet setting without distractions (eg, television, cell phones). Subjects should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling is scheduled for the same timepoint as ECG recording, the ECG should be performed before the blood draw.

Vital Signs

Assessment of pulse/heart rate and blood pressure is expected at every protocol-specified visit from screening until end of treatment. Blood pressure and pulse/heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones). Clinically significant abnormalities should be recorded as adverse events. If an abnormal heart rhythm is suspected, further investigation (ECG and/or Holter monitor) is required per investigator's discretion.

Body Surface Area

Calculation of BSA (Attachment 3) at Cycle 1 Day 1 is required for CIT and ibrutinib dosing. The BSA should be recalculated if a subject experiences a >10% change in weight from the weight used in the most recent BSA calculation. Weight will be collected as specified in the Time and Events Schedule (Table 1, Table 2, and Table 3).

Physical Examination

Complete physical examination will be performed at Screening. The Screening physical examination will include, at a minimum, the general appearance of the subject, height and weight, examination of the skin, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Directed physical examination

(includes all organ systems that were previously abnormal or involved with disease and documentation of any clinically relevant abnormalities in any organ) will be performed at the timepoints specified in the Time and Events Schedule (Table 1, Table 2, Table 3, and Table 4). Lymphoma symptoms reported at Screening should be reviewed and recorded during the directed physical examination.

9.9. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form. Refer to the Time and Events Schedule for the timing and frequency of all sample collections (Table 1, Table 2, Table 3, and Table 4). Instructions for the collection, handling, storage, and shipment of samples are found in the Laboratory Manual that will be provided.

Any volume of blood collected must be consistent with the recommendations of the European Medicines Agency (EMA) for study-related blood loss.[12] In pediatric populations this should be no more than 3% of the total blood volume during a 4-week period and not more than 1% of total blood volume at a single timepoint. At a total blood volume estimated at 80 to 90 mL/kg body weight this equals 2.4 to 2.7 mL of blood per kilogram of body weight every 4 weeks or 0.8 to 0.9 mL per kilogram at any one time. It is the responsibility of the investigator to comply with these guidelines and to prioritize study blood collection as follows:

1. Safety laboratory studies (hematology and serum chemistry) that are study-related and not part of routine care
2. Pharmacokinetic samples
3. Pharmacodynamic samples
4. Biomarker samples

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

10.1. Completion

A subject will be considered to have completed the study if he or she has died before the end of the study, has not been lost to follow-up, or has not withdrawn consent before the end of study.

10.2. Discontinuation of Study Treatment/Withdrawal from the Study

Subjects who discontinue any component of CIT without disease progression will continue study drug (ibrutinib) and remaining components until 3 cycles are completed followed by ibrutinib monotherapy in case of response (PR or better), or until disease progression, or unacceptable toxicity, or until initiating subsequent antilymphoma therapy or a conditioning regimen for stem cell transplant, or for a maximum of three 28-day cycles, whichever occurs first. If study drug is discontinued for any reason, any remaining study treatment (CIT) may continue. Investigators are encouraged to keep a subject experiencing clinical benefit (ie, PR, CR, MR, or NR) in the study unless significant toxicity puts the subject at risk or routine noncompliance puts the study outcomes at risk.

Discontinuation of Study Treatment

A subject will not be automatically withdrawn from the study if they have to discontinue treatment before the end of the treatment regimen. A subject's study treatment will be discontinued if:

- The subject experiences disease progression or relapse
- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the subject to discontinue study treatment
- The subject becomes pregnant
- The subject or legally authorized representative refuses further treatment
- The criteria for discontinuation of study treatment described in Section 6.2 are met
- A serious protocol violation has occurred, as determined by the principal investigator or the sponsor

If a subject discontinues study treatment for any reason before the end of the Treatment Phase, end-of-treatment and posttreatment assessments should be obtained and scheduled assessments should be continued.

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
- Sponsor discontinues the study

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. Study drug assigned to the withdrawn subject may not be assigned to another subject. Subjects who withdraw will not be replaced. If a subject withdraws from the study, end-of-treatment and posttreatment assessments should be obtained, if possible.

10.3. Withdrawal From the Use of Research Samples

Withdrawal From the Use of Samples in Future Research

The subject may withdraw consent for use of samples for research (refer to Section 16.2.5, Long-Term Retention of Samples for Additional Future Research). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the ICF.

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.

All statistical testing will be performed using a 2-sided test at the 10% level of significance, unless otherwise noted. Confidence intervals will be presented as 2-sided 90% confidence intervals. Summary statistics for continuous variables include mean, standard deviation, median, minimum, and maximum unless otherwise specified. Categorical data will be presented as frequencies and percentages.

11.1. Subject Information

The intent-to-treat (ITT) Population will consist of all randomized subjects where subjects will be analyzed based on randomization, regardless of study drug received. The ITT population will be used for all efficacy analyses. The primary efficacy analysis is based on the ITT population for data collected in the Part 2. Efficacy for Part 1 will be provided as a secondary endpoint for Part 1.

The Safety population will consist of all subjects who received at least 1 dose of treatment. The safety population will be used for all safety analyses and subjects will be analyzed based on actual study drug received.

Summaries (demographics and baseline characteristics, safety) will be presented for Part 1 and Part 2 of the study. Analyses of disposition, demographic, baseline disease characteristics, and prior and concomitant therapy will be conducted on the ITT population. Analyses on treatment compliance and extent of exposure will be conducted on the Safety population. No statistical testing is planned.

Unless otherwise specified, all continuous endpoints will be summarized using descriptive statistics, which will include the number of subjects with a valid measurement (n), mean, standard deviation, median, minimum, and maximum. All categorical endpoints will be summarized using frequencies and percentages. Percentages will be calculated by dividing the number of subjects with the characteristic of interest by the number of subjects in the analysis population or the evaluable population.

11.2. Sample Size Determination

Approximately 72 subjects will be randomized in Part 2. The sample size calculation for the randomized part (Part 2) is based on the assumption of 100% improvement (hazard ratio = 0.5) in median EFS in subjects receiving ibrutinib plus CIT (RICE or RVICI) compared with CIT (RICE or RVICI) (10 months versus 5 months). Utilizing a 2:1 randomization, this study will enroll approximately 72 subjects (approximately 48 subjects treated with ibrutinib [and RICE or RVICI background therapy]) during Part 2. Based on a total of 60 events for the 2 treatment groups, this study will have at least 80% power, given a 1-sided alpha of 0.05. An accrual rate of 1.44 subjects per month will result in a study duration of approximately 4.2 years.

11.3. Efficacy Analyses

Descriptive statistics and subject listings will be used to summarize the data. For continuous variables, the number of observations, means, standard deviations, medians, and ranges will be used. For discrete variables, frequency will be provided. For time-to-event variables, Kaplan-Meier estimates will be provided.

Comparisons between the 2 treatment arms in Part 2 will be performed as follows: for the continuous variables representing change from baseline to a particular postbaseline timepoint, analysis of variance will be used. For discrete variables, Chi-square test will be used. For time-to-event variables, non-stratified log-rank test and non-stratified Cox proportion hazard model will be used unless specified otherwise. All tests will be conducted at 2-sided test at the 10% level of significance and 90% confidence intervals will be provided, unless otherwise stated.

11.3.1. Primary Endpoint

The primary efficacy endpoint is EFS in Part 2, which is defined as the time interval from randomization to death, disease progression, or lack of CR or PR after 3 cycles of treatment, based on blinded independent event review by the IRC, whichever occurs first. The process and conventions of the IRC will be detailed in a separate IRC charter.

The analysis of the primary endpoint (EFS) will be based on the ITT population. For the primary efficacy analysis, EFS will be compared between treatment groups using a non-stratified log-rank test. The Kaplan-Meier method will be used to estimate the distribution functions of EFS for each treatment group. The number of events, subjects censored, the estimate of medians, and 90% confidence interval for the medians will be presented. The plot of EFS using the Kaplan-Meier method will be presented. The estimate of the hazard ratio between the 2 treatment groups and its associated 90% confidence interval will be computed based on the non-stratified Cox proportional hazards model.

11.3.2. Secondary Endpoints

Secondary endpoints in Part 1 (Section 2.1.1) will be provided as listings. In Part 2, tumor volume reduction at Day 14, ORR, time to response, duration of response, overall survival, and number (%) of subjects who proceed to stem cell transplantation will be summarized. Other secondary endpoints will be provided as listings.

Overall survival is defined as the duration from the date of enrollment (in Part 1) or randomization (in Part 2) to the date of the subject's death. Overall survival will be analyzed using the non-stratified log-rank test for treatment comparison in Part 2. The overall survival distribution and median overall survival with its 90% confidence interval will be estimated using the Kaplan-Meier product-limit method. The hazard ratio for ibrutinib+CIT relative to CIT alone and its associated 90% confidence interval will be calculated based on the non-stratified Cox proportional hazards model. Exploratory analysis using the Cox proportional hazards model with and without the covariates, as well as exploratory analysis on the effect of subsequent antilymphoma therapy on overall survival, will be performed as appropriate.

11.4. Pharmacokinetic Analyses

Population pharmacokinetic analysis of ibrutinib plasma concentration-time data from sparse samplings will be performed using nonlinear mixed effects modeling. All concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. Concentrations below the lower quantifiable concentration will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the study report.

A cutoff date for pharmacokinetic samples to be analyzed will be defined at the time of interim analysis, if required. Samples collected before this date will be analyzed for ibrutinib and included in the population pharmacokinetic analysis. Samples collected after the cutoff date will be analyzed at a later date, and may be included in a population pharmacokinetic re-analysis when they become available after database lock.

Data will be listed for all subjects with available plasma concentrations per treatment group. Subjects will be excluded from the pharmacokinetic analysis if their data do not allow for accurate assessment of pharmacokinetics (eg, incomplete administration of the study drug; missing information of dosing and sampling times; concentration data not sufficient for pharmacokinetic parameter calculation). Descriptive statistics, including arithmetic mean, standard deviation, coefficient of variation, median, minimum, and maximum will be calculated for all individual ibrutinib and the PCI-45227 metabolite concentrations by dose (as applicable) and timepoints.

Pharmacokinetic analysis should allow achievement of, with at least 80% power, a 95% confidence interval within 60% and 140% of the geometric mean estimates of CL/F and V_d/F in the age group from 2 to less than 11 years. Mean or median plasma ibrutinib concentration-time profiles will be plotted after the first dose of study drug, and individual plasma concentration-time profiles may also be plotted. Details of the analysis will be provided in a population pharmacokinetic analysis plan and results of the population pharmacokinetic analysis will be presented in a separate report.

11.5. Pharmacodynamic Analyses and Biomarker Analyses

Biomarker analyses will be conducted on the ITT population. Changes in biomarkers over time will be summarized by treatment group. Summary statistics will be provided as appropriate. Based on resulting data, additional analyses may be performed. The results of the biomarkers analyses will be presented in a separate report.

11.6. Pharmacokinetic-Pharmacodynamic Analysis

The relationship between ibrutinib metrics of systemic exposure and relevant pharmacological (BTK engagement) and clinically (efficacy or safety-related) relevant endpoints will be explored graphically.

11.7. Safety Analyses

All safety analyses will be based on the safety population and will be performed by the treatment actually received. Safety parameters to be evaluated are the incidence, intensity, and type of adverse events, clinically significant changes in the subject's physical examination findings and clinical laboratory results by treatment arms. Exposure to investigational product and reasons for discontinuation of study treatment will be tabulated.

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). All reported adverse events will be included in the analysis.

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, and occur during treatment or within 30 days following the last dose of study treatment, or any adverse event that is considered study treatment-related regardless of the start date of the event. The number and percent of subjects with treatment-emergent adverse events will be summarized according to intensity using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (Version 4.03), drug relationship, and outcome. For each adverse event, the percentage of subjects who experience at least 1 occurrence of the given event will be summarized by treatment group. In addition, comparisons between treatment groups will be provided if appropriate. 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 of hematology, coagulation, and serum chemistry up to 30 days after last dose of study treatment or the End-of-Treatment visit date, whichever is later, will be reported in International System of Units. 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 timepoint. 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 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.

Electrocardiogram (ECG)

The effects on cardiovascular variables will be evaluated by means of descriptive statistics and frequency tabulations. These tables will include observed values and changes from baseline values (the initial ECG will be used as baseline).

Physical Examination

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

11.8. Independent Data Monitoring Committee

An independent DMC will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study and review the interim analysis results. The DMC will consist of at least 2 medical experts in the relevant therapeutic area and at least 1 statistician. The DMC responsibilities, authorities, and procedures will be documented in its charter.

The committee will meet periodically to review interim data. After the review, the DMC will make recommendations regarding the continuation of the study. The details will be provided in a separate DMC charter. At the interim analysis, the DMC may recommend stopping the study for either futility or efficacy, if the pre-specified stopping boundary is crossed (Section 11.9).

11.9. Interim Analysis

During Part 2, an independent DMC will be used for ongoing, real-time review of safety and will conduct an interim analysis. The pre-planned interim analysis will be conducted when approximately 30 EFS events are reached. An independent DMC will determine the appropriateness for early stopping using the nonbinding stopping rules (Table 11) as well as other efficacy and safety endpoints. The 1-sided p-value required for early stopping for futility is ≥0.367 and efficacy is ≤0.006 if there are 30 EFS events at the interim analysis. This design employs the sequential testing approach as described by O'Brien and Fleming (1979)[27] to preserve the Type–I error rate. The interim analysis will also include a pharmacokinetic assessment using the available data at the time.

Table 11: Stopping Boundaries (N=72 subjects, 2 Analyses)

Analysis Number	EFS events	Approximate Time	Number of Subjects	Cumulative Error		Stopping Boundary			
				Alpha	Beta	p-value (1-sided)		Observed Hazard Ratio	
				Efficacy	Futility	Efficacy	Futility	Efficacy	Futility
Interim	30 (50%)	32 months	46	0.006	0.07	≤0.006	≥0.367	<0.378	≥0.878
Final	60 (100%)	50 months	72	0.050	0.2	≤0.048	--------	<0.632	--------

EFS=event-free survival.

11.9.1. Outcome of IDMC review on 20 July 2020

The pre-planned interim analysis was conducted per the specifications outlined in Section 11.9 to determine the appropriateness for early stopping using the nonbinding stopping rules, in addition to a review of the efficacy and safety of patients in Part 2 of this study. As the futility boundary for early stopping was reached (31 of 60 EFS events), the IDMC recommended stopping enrollment. Consequently, new patient enrollment has ceased. No new safety concerns were identified. Follow-up of the ongoing patients will continue per guidance in Section 9.1.3 and Section 9.1.4, until the sponsor decides to stop the study.

11.10. Study Evaluation Team (SET)

A SET composed of study investigators and internal sponsor team members will convene (for all subjects in Part 1) to evaluate the safety of ibrutinib in combination with CIT to determine if the dose is appropriate, and when enrollment may start in the youngest age group. Safety review by the SET will include non-hematologic toxicities that required temporarily stopping study treatment for more than 10 days or cardiac rhythm abnormalities in those subjects receiving RVICI.

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.

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 European Union 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 1 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), other than PD of NHL. Progressive disease of NHL should not be reported as a serious and unexpected adverse event.

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 as an expected adverse event in the Investigator's Brochure. For background CIT (RICE or RVICI), the expectedness of an adverse event will be determined by whether or not it is listed in the package insert for each component study treatment drug.

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 will be made using the NCI-CTCAE, Version 4.03. 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 ibrutinib or any of the components of background CIT
- Suspected abuse/misuse of ibrutinib or any of the components of background CIT
- Accidental or occupational exposure to ibrutinib or any of the components of background CIT
- Medication error involving ibrutinib (with or without subject/patient exposure to ibrutinib, eg, name confusion) or any of the components of background CIT
- Exposure to ibrutinib from breastfeeding
- Pregnancy

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

12.3.1. All Adverse Events

All adverse events and special reporting situations, whether serious or nonserious, will be reported from the time a signed and dated ICF is obtained until 30 days following the last dose of study treatment or until the start of a subsequent systemic antineoplastic therapy, if earlier, unless the subject has withdrawn consent for study participation. Adverse events reported after 30 days following the last dose of study treatment should also be reported if considered related to study treatment. All Grade 3 or Grade 4 adverse events considered related to study treatment must be followed until recovery to baseline or Grade ≤1 or until no further improvement is expected. Cardiac adverse events of Grade 2 or higher will be followed until improvement to baseline or Grade ≤1 or no further improvement is expected. Any unresolved events will be followed for a maximum of 6 months.

Serious adverse events, including those spontaneously reported to the investigator during treatment or 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. All adverse events of special interest, as defined in Section 12.3.3, related to bleeding or resulting in bleeding complications must be followed until recovery or until there is no further improvement. Progressive disease should not be reported as an adverse event, but instead symptoms/clinical signs of disease progression may be reported, which then should be attributed to PD.

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. All records will need to capture the details of the duration and the severity of each episode, the action taken with respect to the study treatment, investigator's evaluation of its relationship to the study treatment, and the subject outcome. 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.

The subject must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number

- Statement, in the local language(s), that the subject is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical staff only)
- Site number
- Subject number

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, which must be completed and signed 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 made 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 should be reported as a serious adverse event (medically important). 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. A standard procedure for protocol therapy administration will not be

reported as a serious adverse event. Hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as a serious adverse event.

- The administration of blood or platelet transfusion. Hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable serious adverse event.
- A procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling, pharmacokinetic, or biomarker blood sampling). Hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.
- Prolonged hospitalization for technical, practical, or social reasons in the absence of an adverse event.

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 should be reported if they fulfill the serious adverse event definition (refer to Section 12.1.1, Adverse Event Definitions and Classifications).

12.3.3. Adverse Events of Special Interest

Specific adverse events or groups of adverse events will be followed as part of standard safety monitoring activities by the sponsor. These events should be reported to the sponsor within 24 hours of awareness irrespective of seriousness (ie, serious and nonserious adverse events) following the procedure described above for serious adverse events and will require enhanced data collection.

Major Hemorrhage

Major hemorrhage is defined as:

- Any treatment-emergent hemorrhagic adverse event of Grade 3 or higher.*
- Any treatment-emergent serious adverse event of bleeding of any grade.
- Any treatment-emergent CNS hemorrhage/hematoma of any grade.

**All hemorrhagic adverse events requiring a transfusion of red blood cells should be reported as a Grade 3 or higher adverse events per NCI-CTCAE.*

12.3.4. Other Malignancies

In addition to all routine adverse event reporting; all new malignant tumors, including solid tumors, skin malignancies, and hematologic malignancies; are to be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

12.3.5. Pregnancy

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 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.

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

For the purposes of this study, ‘study drug’ refers to ibrutinib.

14.1. Study Drug - Ibrutinib

14.1.1. Physical Description

The following formulations will be used in this study:

- Ibrutinib capsules, 140 mg
- Ibrutinib capsules, 70 mg

- Ibrutinib suspension, 70 mg/mL Single Dose
- Ibrutinib suspension, 70 mg/mL Multi-Dose

Ibrutinib capsules, 70 mg are hard gelatin capsules that contain 70 mg of ibrutinib. Ibrutinib oral suspension is supplied as a 70 mg/mL for use in this study. All excipients in all formulations are compendia and are commonly used in oral formulations. Refer to the Investigator's Brochure for capsule, single-dose vial, and multi-dose bottle suspension formulations. The 140-mg ibrutinib capsule, 70-mg ibrutinib capsule, and 70-mg/mL ibrutinib oral suspension will be dosed to meet the different dosing regimens and age groups. The study drug will be manufactured and provided under the responsibility of the sponsor.

14.1.2. Packaging

Ibrutinib capsules, 140 mg and 70 mg, will be packaged in opaque high-density polyethylene bottles with child-resistance closures. Ibrutinib single-dose oral suspension, 70 mg/mL, will be packaged in Type I amber glass vials with rubber stopper and aluminum seal. Ibrutinib multi-dose oral suspension, 70 mg/mL, will be packaged in Type III amber glass bottles with dosing adaptor and child resistant screw cap.

All study drugs will be packaged in individual subject kits with labels bearing the appropriate label text as required by governing regulatory agencies.

14.1.3. Labeling

Study drug labels will contain information to meet the applicable regulatory requirements.

14.1.4. Preparation, Handling, and Storage

Refer to the Pharmacy Manual/study Site Investigational Product Manual for additional guidance on study drug preparation, handling, and storage.

Ibrutinib capsules, 140 mg, should be stored according to the storage conditions indicated on the label. The recommended storage condition for ibrutinib capsules is 15°C to 25°C (59°F to 77°F) with excursions permitted to 30°C (86°F).

Ibrutinib capsules, 70 mg, should be stored according to the storage conditions indicated on the label. The recommended storage condition for this drug product is 15°C to 25°C (59°F to 77°F) with excursions permitted to 30°C (86°F). Current stability data indicate that the capsules will be stable for the duration of the clinical study under the labeled storage conditions. Study staff will instruct subjects on how to store medication for at-home use as indicated for this protocol.

Ibrutinib oral suspension, 70 mg/mL (both single and multi-dose), should be stored according to the storage conditions indicated on the label. The recommended storage condition for this drug product is 2°C to 8°C (35.6°F to 46.4°F). Once opened, the multi-dose drug bottle should be stored at 15°C to 25°C (59°F to 77°F). Current stability data indicate that the suspension will be stable for the duration of the clinical study under the labeled storage conditions. Study staff will instruct subjects on how to store medication for at-home use as indicated for this protocol.

14.2. Background Therapy (RICE or RVICI)

Rituximab, ifosfamide, carboplatin, etoposide, Mesna, dexamethasone, vincristine, and idarubicin labels will contain information to meet the applicable regulatory requirements. Rituximab, ifosfamide, carboplatin, etoposide, Mesna, dexamethasone, vincristine, and idarubicin must be prepared in an aseptic manner according to local standards for handling cytotoxic/cytostatic drugs. Refer to the rituximab, ifosfamide, carboplatin, etoposide, Mesna, dexamethasone, vincristine, and idarubicin local prescribing information or the Pharmacy Manual/study Site Investigational Product Manual for further instructions on preparation, handling, and storage.

14.3. Drug Accountability

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The dispensing of study drug (ibrutinib) to the subject, and the return of study drug from the subject (if applicable), must be documented in the drug accountability records. Subjects, or their legally-acceptable representatives where applicable, must be instructed to return all original containers, whether empty or containing study drug. For study drug supplied centrally, the CIT (RICE or RVICI) administered to the subject must be documented on the drug accountability form. All study treatment will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug, and study drug returned by the subject, must be available for verification by the sponsor's study-site monitor during on-site monitoring visits. The return to the sponsor of unused study drug, or used returned study drug for destruction, will be documented on the drug return form. When the study site is an authorized destruction unit and study drug supplies are destroyed on-site, this must also be documented on the drug return form.

Potentially hazardous materials such as used ampules, needles, syringes, bottles, and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes. 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. Returned study drug must not be dispensed again, even to the same subject. Study drug may not be relabeled or reassigned for use by other subjects. The investigator agrees neither to dispense the study drug from, nor store it at, any site other than the study sites agreed upon with the sponsor.

15. STUDY-SPECIFIC MATERIALS

The investigator will be provided with the following supplies:

- Study protocol
- Ibrutinib Investigator's Brochure

- Ibrutinib study drug diary
- International Pediatric NHL Response Criteria[36]
- Pharmacy Manual/study Site Investigational Product Manual
- Laboratory Manual
- NCI-CTCAE, Version 4.03
- Visual analog scale for palatability and acceptability
- IWRS Manual and supplies
- Electronic Data Capture (eDC) Manual and electronic CRF Completion Guidelines
- Sample ICF
- Subject information materials

16. ETHICAL ASPECTS

16.1. Study-Specific Design Considerations

This is a randomized, open-label, multicenter Phase 3 study to compare the safety and efficacy of ibrutinib in combination with CIT (RICE or RVICI) versus CIT alone in subjects with relapsed or refractory BL/B-AL and DLBCL, in subjects 1 to 30 years of age at the time of relapse. All subjects will receive background therapy with RICE or RVICI, recommended by an advisory board of key opinion leaders in pediatric oncology (see Section 3.2.2).

All participating subjects will receive full supportive care and will be followed closely for safety and efficacy throughout the study. Efficacy assessments will occur according to the internationally accepted International Pediatric NHL Response Criteria.[36] Safety assessments will occur through regular clinic visits including laboratory analyses. An independent DMC will be established to review the safety and efficacy of the treatment combination and make recommendations as to the future conduct of the study.

Potential subjects will be fully informed 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.

When referring to the signing of the ICF, the terms legal guardian and legally-acceptable representative refer to the legally appointed guardian of the child with authority to authorize participation in research. For each subject, his or her parent(s) (preferably both parents, if available) or a legally-acceptable representative(s), as required by local regulations, must give written consent (permission) according to local requirements after the nature of the study has been fully explained and before the performance of any study-related assessments. Assent must

be obtained from children (minors) capable of understanding the nature of the study; please refer to local regulations. For the purposes of this study, all references to subjects who have provided consent (and assent, as applicable) refers to the subjects and his or her parent(s) or the subject's legal guardian(s) or legally-acceptable representative(s) who have provided consent according to this process. Minors who assent to a study and later withdraw that assent will not be maintained in the study against their will, even if their parents still want them to participate.

The volume of blood collected will be consistent the recommendations of the EMA for study-related blood loss.[12] Sample volumes will be adjusted according to standards for pediatric subjects.

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)
- Investigator's Brochure (or equivalent information) and amendments/addenda
- Sponsor-approved subject recruiting materials
- Information on compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- 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
- If applicable, new or revised subject recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to subjects for participation in the study, if applicable
- New edition(s) of the Investigator's Brochure and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- 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
- Deviations from or changes to the protocol to eliminate immediate hazards to the subjects
- 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 least once a year, the IEC/IRB will be asked to review and reapprove this study, where required. At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

16.2.3. Informed Consent and Assent Form

Each subject (or a legally-acceptable representative) must give written consent/assent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) and assent form that is/are 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/assent 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 or their legally-acceptable representatives 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. Subjects will be told that alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that the investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject or legally-acceptable representative is authorizing such access, which includes permission to obtain information about his or her survival status. It also denotes that the subject agrees to allow his or her study physician to re-contact the subject for the purpose of obtaining consent/assent for additional safety evaluations, if needed. The physician may also re-contact the subject for the purpose of obtaining consent to collect information about his or her survival status.

The subject or legally-acceptable representative 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/assent should be appropriately recorded by means of either the subject's or his or her legally-acceptable representative's personally dated signature. After having obtained the consent/assent, a copy of the ICF must be given to the subject.

If the subject or legally-acceptable representative is unable to read or write, an impartial witness should be present for the entire informed consent/assent process (which includes reading and explaining all written information) and should personally date and sign the ICF after the oral consent/assent of the subject or legally-acceptable representative is obtained.

Children (minors) or subjects who are unable to comprehend the information provided can be enrolled only after obtaining consent of a legally-acceptable representative. Assent must be obtained from children (minors) capable of understanding the nature of the study; please refer to local regulations. Written assent should be obtained from subjects who are able to write. A separate assent form written in language the subject can understand should be developed for adolescents. After having obtained the assent, a copy of the assent form must be given to the subject, and to the subject's parent or, if applicable, legally-acceptable representative.

When prior consent/assent of the subject is not possible and the subject's legally-acceptable representative is not available, enrollment procedures should be described in the protocol with documented approval/favorable opinion by the IEC/IRB to protect the rights, safety, and well-being of the subject and to ensure compliance with applicable regulatory requirements. The

subject or legally-acceptable representative must be informed about the study as soon as possible and give consent to continue.

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/assent obtained from the subject (or his or her legally-acceptable representative) includes explicit consent/assent 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/assent 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.

Exploratory biomarker research is not conducted under standards appropriate for the return of data to subjects. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to subjects or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

16.2.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand ibrutinib, to understand NHL, to understand differential drug responders, and to develop tests/assays related to ibrutinib and NHL. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Subjects may withdraw consent for sample storage for research (refer to Section 10.3).

16.2.6. Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly

addressed as a specific ethical consideration in Section 16.1, Study-Specific Design Considerations.

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 IRB/IEC (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 in each respective country, if applicable. A study may 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 shipment of study drug 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 if applicable, 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
- Signed and dated statement of investigator (eg, Form FDA 1572), 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

The following documents must be provided to the sponsor before enrollment of the first subject:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

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 (as allowed by local regulations). In cases where the subject is not randomized into the study, the date seen and date of birth (as allowed by local regulations) 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:

- Race
- Height and weight
- Details of physical examination

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. An e-Source system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If e-Source is utilized, references made to the CRF in the protocol include the e-Source system but information collected through e-Source 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 data relating to the study must be recorded in CRF. 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. Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the subject's source documents. Data must be entered into the CRF in English. The CRF must be completed as soon as possible after a subject visit and the forms should be available for review at the next scheduled monitoring visit. 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 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, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review CRFs 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 use a combination of monitoring techniques (central, remote or on-site monitoring) to monitor this study. 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. Central monitoring will take place for data identified by the sponsor as requiring central review.

17.9. Study Completion/Termination

17.9.1. Study Completion/End of Study

The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the Clinical Trial Agreement.

On 20 July 2020, the IDMC conducted a pre-planned review of the interim analysis data for efficacy and safety. The IDMC recommended stopping enrollment into the study as ibrutinib in combination with CIT did not demonstrate additive efficacy. No new safety concerns were identified. Consequently, new patient enrollment has ceased. Ongoing patients may continue study treatment, as appropriate according to the investigator's medical judgement, and will be followed up as per time and events schedule Table 2. Patients who have completed treatment will continue to be followed up as per time and events schedule in Table 4 or until the sponsor decides to stop the study.

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
- Discontinuation of further study drug development

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 exploratory biomarker 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 for the study. Results of exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report. 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 (ICMJE) 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. For multicenter study designs and substudy approaches, 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 ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for the important intellectual content; and given final approval of the version to the published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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. Andion M, Molina B, Gonzalez-Vicent M, et al. High-dose busulfan and cyclophosphamide as a conditioning regimen for autologous peripheral blood stem cell transplantation in childhood non-Hodgkin lymphoma patients: a long-term follow-up study. J Pediatr Hematol Oncol. 2011;33:e89-e91.
2. Anoop P, Sankpal S, Stiller C, et al. Outcome of childhood relapsed or refractory mature B-cell non-Hodgkin lymphoma and acute lymphoblastic leukemia. Leuk Lymphoma. 2012;53:1882-1888.
3. Atra A, Gerrard M, Hobson R, Imeson JD, Hann IM, Pinkerton CR. Outcome of relapsed or refractory childhood B-cell acute lymphoblastic leukemia and B-cell non-Hodgkin's lymphoma treated with the UKCCSG 9003/9002 protocols. Br J Hematol. 2001;112:965-968.
4. Attarbaschi A, Dworzak M, Steiner M, et al. Outcome of children with primary resistant or relapsed non-Hodgkin lymphoma and mature B-cell leukemia after intensive first-line treatment: A population-based analysis of the Austrian Cooperative Study Group. Pediatr Blood Cancer. 2005;44:70-76.
5. Bradley MD, Cairo MS. Stem cell transplantation for pediatric lymphoma: past, present, and future. Bone Marrow Transplantation. 2008;41:149-158.
6. Burkhardt B, Zimmerman M, Ochlies I, et al. The impact of age and gender on biology, clinical features and treatment outcome of non-Hodgkin lymphoma in childhood adolescence. Br J Haematol. 2005;131:39-49.
7. Cairo MS, Gerrard M, Sposto R, et al. Results of a randomized international study of high risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia in children and adolescents. Blood. 2007;109:2736-2743.
8. Cultrera JL, Dalia SM. Diffuse large B-cell lymphoma: current strategies and future directions. Cancer Control. 2012;19:204-213.
9. De Wildt SN, Kearns GL, Leeder JS, van den Anker JN. Cytochrome P450 3A: Ontogeny and drug disposition. Clin Pharmacokinet. 1999;37:485-505.
10. Department of Medicine Clinical Pharmacology Drug Interactions Flockhart Table. Available at http://medicine.iupui.edu/clinpharm/ddis/main-table. Accessed 14 December 2019.
11. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Available at: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers. Accessed 18 December 2019.
12. EMA. Ethical considerations for clinical trials on medicinal products with the paediatric population. 2008. Available at: http://ec.europa.eu/health/files/eudralex/vol-10/ethical_considerations_en.pdf. Accessed 8 February 2016.
13. Fujita N, Mori T, Mitsui T, Inada H, Horibe K, Tsurusawa M. for the Lymphoma Committee of the Japanese Pediatric Leukemia/Lymphoma Study Group. The role of hematopoietic stem cell transplantation with relapsed or primary refractory childhood B-cell non-Hodgkin lymphoma and mature B-cell leukemia: a retrospective analysis of enrolled cases in Japan. Pediatr Blood Cancer. 2008;51:188-192.
14. Giulino-Roth L, Ricafort R, Kernan NA, et al. Ten-year follow-up of pediatric patients with non-Hodgkin lymphoma treated with allogeneic or autologous stem cell transplantation. Pediatr Blood Cancer. 2013;60:2018-2024.
15. Griffin TC, Weitzman S, Weinstein H, et al. A study of rituximab and ifosfamide, carboplatin, and etoposide chemotherapy in children with recurrent/refractory B-cell (CD20+) non-Hodgkin lymphoma and mature B-cell acute lymphoblastic leukemia: a report from the Children's Oncology Group. Pediatr Blood Cancer. 2009;52:177-181.
16. Harris RE, Termuhlen AM, Smith LM, et al. Autologous peripheral blood stem cell transplantation in children with refractory or relapsed lymphoma: results of Children's Oncology Group study A5962. Biol Blood Marrow Transplant. 2011;17:249-258.
17. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In Evaluation of chemotherapeutic agents. Edited by MacLeod CM. New York: Columbia University Press; 1949:191-205.
18. Kobrinsky NL, Sposto R, Shah NR, et al. Outcomes of treatment of children and adolescents with recurrent non-Hodgkin's lymphoma and Hodgkin's disease with dexamethasone, etoposide, cisplatin, cytarabine, and L-asparaginase, maintenance chemotherapy, and transplantation: Children's Cancer Group study CCG-5912. J Clin Oncol. 2001;19:2390-2396.

19. Kung FH, Harris MB, Krischer JP. Ifosfamide/carboplatin/etoposide (ICE), an effective salvaging therapy for recurrent malignant non-Hodgkin lymphoma of childhood: A Pediatric Oncology Group phase II study. Med Pediatr Oncol. 1999;32:225–226.
20. Lansky SB, List MA, Lansky LL, Ritter-Sterr C, Miller DR. The measurement of performance in childhood cancer patients. Cancer. 1987:1;60:1651-1656.
21. Lee S, Yin C, O'Connell T, et al. Ibrutinib significantly improves survival in a human Burkitt lymphoma (BL) xenograft NSG mouse model: Ibrutinib may be a potential adjuvant agent in the treatment of BL. AACR; Cancer Res. 2015;75(15 Suppl):Abstract 2608. doi: 10.1158/1538-7445.AM2105-2608.
22. Matsui D, Barron A, Rieder MJ. Assessment of the palatability of antistaphylococcal antibiotics in pediatric volunteers. Ann Pharmacother. 1996;30(6):586-588.
23. Matsui D, Lim R, Tschen T, Rieder MJ. Assessment of the palatability of beta-lactamase-resistant antibiotics in children. Arch Pediatr Adolesc Med. 1997;151(6):599-602.
24. Mbulaiteye SM, Biggar RJ, Bhatia K, Linet MS, Devesa SS. Sporadic childhood Burkitt lymphoma incidence in the United States during 1992-2005. Peadiatr Blood Cancer. 2009;53:366-370.
25. Miles RR, Arnold S, Cairo MS. Risk factors and treatment of childhood and adolescent Burkitt lymphoma/leukemia. Br J Haematol. 2012;156:1-14.
26. Molyneux EM, Rochford R, Griffin B, et al. Burkitt's lymphoma. Lancet. 2012;379:1234–1244.
27. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics. 1979;35:549-556.
28. O'Connell T, Yin C, Ayello J, et al. Ibrutinib significantly alters cell proliferation and programmed cell death in Burkitt lymphoma (BL) cell lines: ibrutinib may be a potential adjuvant agent in the treatment of BL. American Society of Hematology Meeting on Lymphoma Biology. Colorado Springs, Colorado, August 10-13, 2014 (poster).
29. Orphanet, 2010. Burkitt Lymphoma. Available at: http://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=3747&Disease_Disease_Search_diseaseGroup=burkitt&Disease_Disease_Search_diseaseType=Pat&Disease(s)%20concerned=Burkitt-lymphoma&title=Burkitt-lymphoma&search=Disease_Search_Simple. Accessed 3 September 2014.
30. Pan Z, Scheerens H, Li SJ, et al. Discovery of selective irreversible inhibitors for Bruton's tyrosine kinase. Chem Med Chem. 2007;2:58-61.
31. Patte C, Auperin A, Gerrard M, et al. Results of the randomized international FAB/LMB96 trial for intermediate risk B-cell non-Hodgkin lymphoma in children and adolescents: it is possible to reduce treatment for the early responding patients. Blood. 2007;109:2773-2780.
32. Philip T, Hartmann O, Pinkerton R, et al. Curability of relapsed childhood B-cell non-Hodgkin lymphoma after intensive first line therapy: a report from the Societe Francaise d'Oncologie Pediatrique. Blood. 1993;81:2003-2006.
33. Reiter A. Diagnosis and treatment of childhood non-Hodgkin lymphoma. Hematol. 2007;285-296.
34. Reiter A, Klapper W. Recent advances in the understanding and management of diffuse large B-cell lymphoma in children. Br J Haematol. 2008;142-347.
35. Salzburg J, Burkhardt B, Zimmermann M, et al. Prevalence, clinical pattern, and outcome of CNS involvement in childhood and adolescent non-Hodgkin's lymphoma differ by non-Hodgkin's lymphoma subtype: A Berlin-Frankfurt-Munster group report. J Clin Oncol. 2007;25:3915-3922.
36. Sandlund JT, Guillerman RP, Perkins SL, et al. International Pediatric Non-Hodgkin Lymphoma Response Criteria. J Clin Oncol. 2015;33:2106-2111.
37. Sauter, C, Verwys, S, McCall, et al. Phase 2 Study of Ibrutinib with Rituximab, Ifosamide, Carboplatin, and Etoposide for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. American Society for Clinical Oncology. Annual Meeting 2016. NCI-CTEP #9588.
38. Schwartz GJ, Munoz A, Schneider MF, et al. New equations to estimate GFR in children with CKD. J Am Soc Nephrol. 2009;20:629–637.
39. Sjövall J, Fogh A, Huitfeldt B, Karlsson G, Nylén O. Methods for evaluating the taste of paediatric formulations in children: a comparison between the facial hedonic method and the patients' own spontaneous verbal judgement. Eur J Pediatr. 1984;141(4):243-247.
40. Tilly H, Dreyling. Diffuse large B-cell non-Hodgkin's lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21(Suppl 5):v172–v174.

41. Tsurusawa M, Mori T, Kikuchi A, et al. Improved treatment results of children with B-cell non-Hodgkin lymphoma: a report from the Japanese Pediatric Leukemia/Lymphoma Study Group B-NHL03 study. Pediatr Blood Cancer. 2014;61:1215–1221.
42. Woessmann W, Zimmermann M, Burkhardt B, et al. Relapsed or refractory Burkitt lymphoma in children and adolescents after BFM-type first-line therapy - A BFM Group Report. 2014 (poster).

Attachment 1: Ibrutinib Dosing Guides

Suspension and Capsule Dosing 329 mg/m^2 (Full Dose Equivalent; 560 mg/1.7 m^2)

Body Surface Area (m^2)		Target Dose (mg)	Suspension (70 mg/mL) Volume to be Administered (mL)	Actual Dose to Administer by Suspension (mg)	# 70 mg Capsules[a,b]	Actual Dose to Administer by Capsule (mg)
From	To					
0.30	0.34	98.8	1.4	98	-	-
0.35	0.39	115.3	1.6	112	-	-
0.40	0.44	131.8	1.9	133	-	-
0.45	0.49	148.2	2.1	147	-	-
0.50	0.54	164.7	2.4	168	-	-
0.55	0.59	181.2	2.6	182	-	-
0.60	0.64	197.6	2.8	196	3	210
0.65	0.69	214.1	3.1	217	3	210
0.70	0.74	230.6	3.3	231	3	210
0.75	0.79	247.1	3.5	245	4	280
0.80	0.84	263.5	3.8	266	4	280
0.85	0.89	280.0	4.0	280	4	280
0.90	0.94	296.5	4.2	294	4	280
0.95	0.99	312.9	4.5	315	4	280
1.00	1.04	329.4	4.7	329	5	350
1.05	1.09	345.9	4.9	343	5	350
1.10	1.14	362.4	5.2	364	5	350
1.15	1.19	378.8	5.4	378	5	350
1.20	1.24	395.3	5.6	392	6	420
1.25	1.29	411.8	5.9	413	6	420
1.30	1.34	428.2	6.1	427	6	420
1.35	1.39	444.7	6.4	448	6	420
1.40	1.44	461.2	6.6	462	7	490
1.45	1.49	477.6	6.8	476	7	490
1.50	1.54	494.1	7.1	497	7	490
1.55	1.59	510.6	7.3	511	7	490
1.60	1.64	527.1	7.5	525	8	560
1.65	1.69	543.5	7.8	546	8	560
1.70 and higher		560.0	8.0	560	8	560

a. Rounded to nearest 70 mg capsule.
b. For older children, one 140-mg capsule may be substituted for each two 70-mg capsules.

Suspension and Capsule Dosing for the 240 mg/m^2 Dose (Full Dose Equivalent; 420 mg/1.7 m^2)

Body Surface Area (m^2)		Target Dose (mg)	Suspension (70 mg/mL) Volume to be Administered (mL)	Actual Dose to Administer by Suspension (mg)	# 70 mg Capsules[a,b]	Actual Dose to Administer by Capsule (mg)
From	To					
0.30	0.34	72.0	1.0	70	-	-
0.35	0.39	84.0	1.2	84	-	-
0.40	0.44	96.0	1.4	98	-	-
0.45	0.49	108.0	1.5	105	-	-
0.50	0.54	120.0	1.7	119	-	-
0.55	0.59	132.0	1.9	133	-	-
0.60	0.64	144.0	2.1	147	2	140
0.65	0.69	156.0	2.2	154	2	140
0.70	0.74	168.0	2.4	168	2	140
0.75	0.79	180.0	2.6	182	3	210
0.80	0.84	192.0	2.7	189	3	210
0.85	0.89	204.0	2.9	203	3	210
0.90	0.94	216.0	3.1	217	3	210
0.95	0.99	228.0	3.3	231	3	210
1.00	1.04	240.0	3.4	238	3	210
1.05	1.09	252.0	3.6	252	4	280
1.10	1.14	264.0	3.8	266	4	280
1.15	1.19	276.0	3.9	273	4	280
1.20	1.24	288.0	4.1	287	4	280
1.25	1.29	300.0	4.3	301	4	280
1.30	1.34	312.0	4.5	315	4	280
1.35	1.39	324.0	4.6	322	5	350
1.40	1.44	336.0	4.8	336	5	350
1.45	1.49	348.0	5.0	350	5	350
1.50	1.54	360.0	5.1	357	5	350
1.55	1.59	372.0	5.3	371	5	350
1.60	1.64	384.0	5.5	385	5	350
1.65	1.69	396.0	5.7	399	6	420
1.70	1.74	408.0	5.8	406	6	420
1.75 and higher		420.0	6.0	420	6	420

a. Rounded to nearest 70 mg capsule.
b. For older children, one 140-mg capsule may be substituted for each two 70-mg capsules.

Suspension and Capsule Dosing 160 mg/m^2 (Full Dose Equivalent; 280 mg/1.7 m^2)

Body Surface Area (m^2)		Target Dose (mg)	Suspension (70 mg/mL) Volume to be Administered (mL)	Actual Dose to Administer by Suspension (mg)	# 70 mg Capsules[a,b]	Actual Dose to Administer by Capsule (mg)
From	To					
0.30	0.34	48.0	0.7	49	-	-
0.35	0.39	56.0	0.8	56	-	-
0.40	0.44	64.0	0.9	63	-	-
0.45	0.49	72.0	1.0	70	-	-
0.50	0.54	80.0	1.1	77	-	-
0.55	0.59	88.0	1.3	91	-	-
0.60	0.64	96.0	1.4	98	-	-
0.65	0.69	104.0	1.5	105	-	-
0.70	0.74	112.0	1.6	112	-	-
0.75	0.79	120.0	1.7	119	2	140
0.80	0.84	128.0	1.8	126	2	140
0.85	0.89	136.0	1.9	133	2	140
0.90	0.94	144.0	2.1	147	2	140
0.95	0.99	152.0	2.2	154	2	140
1.00	1.04	160.0	2.3	161	2	140
1.05	1.09	168.0	2.4	168	2	140
1.10	1.14	176.0	2.5	175	3	210
1.15	1.19	184.0	2.6	182	3	210
1.20	1.24	192.0	2.7	189	3	210
1.25	1.29	200.0	2.9	203	3	210
1.30	1.34	208.0	3.0	210	3	210
1.35	1.39	216.0	3.1	217	3	210
1.40	1.44	224.0	3.2	224	3	210
1.45	1.49	232.0	3.3	231	3	210
1.50	1.54	240.0	3.4	238	3	210
1.55	1.59	248.0	3.5	245	4	280
1.60	1.64	256.0	3.7	259	4	280
1.65	1.69	264.0	3.8	266	4	280
1.70	1.74	272.0	3.9	273	4	280
1.75 or higher		280.0	4.0	280	4	280

a Rounded to nearest 70 mg capsule.
b For older children, one 140-mg capsule may be substituted for each two 70-mg capsules.

Suspension and Capsule Dosing 120 mg/m^2 (Full Dose Equivalent; 210 mg/1.7 m^2)

Body Surface Area (m^2)		Target Dose (mg)	Suspension (70 mg/mL) Volume to be Administered (mL)	Actual Dose to Administer by Suspension (mg)	# 70 mg Capsules[a,b]	Actual Dose to Administer by Capsule (mg)
From	To					
0.30	0.34	36.0	0.5	35	-	-
0.35	0.39	42.0	0.6	42	-	-
0.40	0.44	48.0	0.7	49	-	-
0.45	0.49	54.0	0.8	56	-	-
0.50	0.54	60.0	0.9	63	-	-
0.55	0.59	66.0	0.9	63	-	-
0.60	0.64	72.0	1.0	70	-	-
0.65	0.69	78.0	1.1	77	-	-
0.70	0.74	84.0	1.2	84	-	-
0.75	0.79	90.0	1.3	91	-	-
0.80	0.84	96.0	1.4	98	-	-
0.85	0.89	102.0	1.5	105	-	-
0.90	0.94	108.0	1.5	105	-	-
0.95	0.99	114.0	1.6	112	-	-
1.00	1.04	120.0	1.7	119	2	140
1.05	1.09	126.0	1.8	126	2	140
1.10	1.14	132.0	1.9	133	2	140
1.15	1.19	138.0	2.0	140	2	140
1.20	1.24	144.0	2.1	147	2	140
1.25	1.29	150.0	2.1	147	2	140
1.30	1.34	156.0	2.2	154	2	140
1.35	1.39	162.0	2.3	161	2	140
1.40	1.44	168.0	2.4	168	2	140
1.45	1.49	174.0	2.5	175	2	140
1.50	1.54	180.0	2.6	182	3	210
1.55	1.59	186.0	2.7	189	3	210
1.60	1.64	192.0	2.7	189	3	210
1.65	1.69	198.0	2.8	196	3	210
1.70	1.74	204.0	2.9	203	3	210
1.75 or higher		210.0	3.0	210	3	210

a. Rounded to nearest 70 mg capsule.
b. For older children, one 140-mg capsule may be substituted for each two 70-mg capsules.

Suspension and Capsule Dosing 80 mg/m^2 (Full Dose Equivalent; 140 mg/1.7 m^2)

Body Surface Area (m^2)		Target Dose (mg)	Suspension (70 mg/mL) Volume to be Administered (mL)	Actual Dose to Administer by Suspension (mg)	# 70 mg Capsules[a,b]	Actual Dose to Administer by Capsule (mg)
From	To					
0.30	0.34	24.0	0.3	21	-	-
0.35	0.39	28.0	0.4	28	-	-
0.40	0.44	32.0	0.5	35	-	-
0.45	0.49	36.0	0.5	35	-	-
0.50	0.54	40.0	0.6	42	-	-
0.55	0.59	44.0	0.6	42	-	-
0.60	0.64	48.0	0.7	49	-	-
0.65	0.69	52.0	0.7	49	-	-
0.70	0.74	56.0	0.8	56	-	-
0.75	0.79	60.0	0.9	63	-	-
0.80	0.84	64.0	0.9	63	-	-
0.85	0.89	68.0	1.0	70	-	-
0.90	0.94	72.0	1.0	70	-	-
0.95	0.99	76.0	1.1	77	-	-
1.00	1.04	80.0	1.1	77	-	-
1.05	1.09	84.0	1.2	84	-	-
1.10	1.14	88.0	1.3	91	-	-
1.15	1.19	92.0	1.3	91	-	-
1.20	1.24	96.0	1.4	98	-	-
1.25	1.29	100.0	1.4	98	-	-
1.30	1.34	104.0	1.5	105	-	-
1.35	1.39	108.0	1.5	105	-	-
1.40	1.44	112.0	1.6	112	2	140
1.45	1.49	116.0	1.7	119	2	140
1.50	1.54	120.0	1.7	119	2	140
1.55	1.59	124.0	1.8	126	2	140
1.60	1.64	128.0	1.8	126	2	140
1.65	1.69	132.0	1.9	133	2	140
1.70	1.74	136.0	1.9	133	2	140
1.75 and higher		140.0	2.0	140	2	140

a. Rounded to nearest 70 mg capsule.
b. For older children, one 140-mg capsule may be substituted for each two 70-mg capsules.

Suspension and Capsule Ibrutinib Dosing 440 mg/m^2 (Full Dose Equivalent; 748 mg/1.7 m^2)

NOTE: only to be used in subjects under 12 years of age-dose administered will not exceed 560 mg

Body Surface Area (m^2)		Target Dose (mg)	Suspension (70 mg/mL) Volume to be Administered (mL)	Actual Dose to Administer by Suspension (mg)	# 70 mg Capsules[a,b]	Actual Dose to Administer by Capsule (mg)
From	To					
0.30	0.34	132	1.9	133	-	-
0.35	0.39	154	2.2	154	-	-
0.40	0.44	176	2.5	175	-	-
0.45	0.49	198	2.8	196	-	-
0.50	0.54	220	3.1	217	-	-
0.55	0.59	242	3.5	245	3	210
0.60	0.64	264	3.8	266	4	280
0.65	0.69	286	4.1	287	4	280
0.70	0.74	308	4.4	308	4	280
0.75	0.79	330	4.7	329	5	350
0.80	0.84	352	5.0	350	5	350
0.85	0.89	374	5.3	371	5	350
0.90	0.94	396	5.7	399	6	420
0.95	0.99	418	6.0	420	6	420
1.00	1.04	440	6.3	441	6	420
1.05	1.09	462	6.6	462	7	490
1.10	1.14	484	6.9	483	7	490
1.15	1.19	506	7.2	504	7	490
1.20	1.24	528	7.5	525	8	560
1.25	1.29	550	7.9	553	8	560
1.30	1.34	560	8.0	560	8	560
1.35	1.39	560	8.0	560	8	560
1.40	1.44	560	8.0	560	8	560
1.45	1.49	560	8.0	560	8	560
1.50	1.54	560	8.0	560	8	560
1.55	1.59	560	8.0	560	8	560
1.60	1.64	560	8.0	560	8	560
1.65	1.69	560	8.0	560	8	560
1.70 and higher		560	8.0	560	8	560

a. Rounded to nearest 70 mg capsule.
b. For older children, one 140-mg capsule may be substituted for each two 70-mg capsules.

Suspension and Capsule Dosing 330 mg/m^2 (Full Dose Equivalent; 561 mg/1.7 m^2)

Body Surface Area (m^2)		Target Dose (mg)	Suspension (70 mg/mL) Volume to be Administered (mL)	Actual Dose to Administer by Suspension (mg)	# 70 mg Capsules[a,b]	Actual Dose to Administer by Capsule (mg)
From	To					
0.30	0.34	99.0	1.4	98	-	-
0.35	0.39	115.5	1.7	119	-	-
0.40	0.44	132.0	1.9	133	-	-
0.45	0.49	148.5	2.1	147	-	-
0.50	0.54	165.0	2.4	168	-	-
0.55	0.59	181.5	2.6	182	-	-
0.60	0.64	198.0	2.8	196	3	210
0.65	0.69	214.5	3.1	217	3	210
0.70	0.74	231.0	3.3	231	3	210
0.75	0.79	247.5	3.5	245	3	210
0.80	0.84	264.0	3.8	266	4	280
0.85	0.89	280.5	4.0	280	4	280
0.90	0.94	297.0	4.2	294	4	280
0.95	0.99	313.5	4.5	315	4	280
1.00	1.04	330.0	4.7	329	5	350
1.05	1.09	346.5	5.0	350	5	350
1.10	1.14	363.0	5.2	364	5	350
1.15	1.19	379.5	5.4	378	5	350
1.20	1.24	396.0	5.7	399	6	420
1.25	1.29	412.5	5.9	413	6	420
1.30	1.34	429.0	6.1	427	6	420
1.35	1.39	445.5	6.4	448	6	420
1.40	1.44	462.0	6.6	462	7	490
1.45	1.49	478.5	6.8	476	7	490
1.50	1.54	495.0	7.1	497	7	490
1.55	1.59	511.5	7.3	511	7	490
1.60	1.64	528.0	7.5	525	8	560
1.65	1.69	544.5	7.8	546	8	560
1.70 and higher		560.0	8.0	560	8	560

a. Rounded to nearest 70 mg capsule.
b. For older children, one 140-mg capsule may be substituted for each two 70-mg capsules.

Suspension and Capsule Dosing 220 mg/m^2 (Full Dose Equivalent; 374 mg/1.7 m^2)

Body Surface Area (m^2)		Target Dose (mg)	Suspension (70 mg/mL) Volume to be Administered (mL)	Actual Dose to Administer by Suspension (mg)	# 70 mg Capsules[a,b]	Actual Dose to Administer by Capsule (mg)
From	To					
0.30	0.34	66.0	0.9	63	-	-
0.35	0.39	77.0	1.1	77	-	-
0.40	0.44	88.0	1.3	91	-	-
0.45	0.49	99.0	1.4	98	-	-
0.50	0.54	110.0	1.6	112	-	-
0.55	0.59	121.0	1.7	119	-	-
0.60	0.64	132.0	1.9	133	2	140
0.65	0.69	143.0	2.0	140	2	140
0.70	0.74	154.0	2.2	154	2	140
0.75	0.79	165.0	2.4	168	2	140
0.80	0.84	176.0	2.5	175	3	210
0.85	0.89	187.0	2.7	189	3	210
0.90	0.94	198.0	2.8	196	3	210
0.95	0.99	209.0	3.0	210	3	210
1.00	1.04	220.0	3.1	217	3	210
1.05	1.09	231.0	3.3	231	3	210
1.10	1.14	242.0	3.5	245	3	210
1.15	1.19	253.0	3.6	252	4	280
1.20	1.24	264.0	3.8	266	4	280
1.25	1.29	275.0	3.9	273	4	280
1.30	1.34	286.0	4.1	287	4	280
1.35	1.39	297.0	4.2	294	4	280
1.40	1.44	308.0	4.4	308	4	280
1.45	1.49	319.0	4.6	322	5	350
1.50	1.54	330.0	4.7	329	5	350
1.55	1.59	341.0	4.9	343	5	350
1.60	1.64	352.0	5.0	350	5	350
1.65	1.69	363.0	5.2	364	5	350
1.70	1.74	374.0	5.3	371	5	350
1.75 and higher		385.0	5.5	385	6	420

a. Rounded to nearest 70 mg capsule.
b. For older children, one 140-mg capsule may be substituted for each two 70-mg capsules.

Suspension and Capsule Dosing 110 mg/m^2 (Full Dose Equivalent; 187 mg/1.7 m^2)

Body Surface Area (m^2)		Target Dose (mg)	Suspension (70 mg/mL) Volume to be Administered (mL)	Actual Dose to Administer by Suspension (mg)	# 70 mg Capsules[a,b]	Actual Dose to Administer by Capsule (mg)
From	To					
0.30	0.34	33.0	0.5	35	-	-
0.35	0.39	38.5	0.6	42	-	-
0.40	0.44	44.0	0.6	42	-	-
0.45	0.49	49.5	0.7	49	-	-
0.50	0.54	55.0	0.8	56	-	-
0.55	0.59	60.5	0.9	63	-	-
0.60	0.64	66.0	0.9	63	1	70
0.65	0.69	71.5	1.0	70	1	70
0.70	0.74	77.0	1.1	77	1	70
0.75	0.79	82.5	1.2	84	1	70
0.80	0.84	88.0	1.3	91	1	70
0.85	0.89	93.5	1.3	91	1	70
0.90	0.94	99.0	1.4	98	1	70
0.95	0.99	104.5	1.5	105	1	70
1.00	1.04	110.0	1.6	112	2	140
1.05	1.09	115.5	1.7	119	2	140
1.10	1.14	121.0	1.7	119	2	140
1.15	1.19	126.5	1.8	126	2	140
1.20	1.24	132.0	1.9	133	2	140
1.25	1.29	137.5	2.0	140	2	140
1.30	1.34	143.0	2.0	140	2	140
1.35	1.39	148.5	2.1	147	2	140
1.40	1.44	154.0	2.2	154	2	140
1.45	1.49	159.5	2.3	161	2	140
1.50	1.54	165.0	2.4	168	2	140
1.55	1.59	170.5	2.4	168	2	140
1.60	1.64	176.0	2.5	175	3	210
1.65	1.69	181.5	2.6	182	3	210
1.70	1.74	187.0	2.7	189	3	210
1.75 and higher		192.5	2.8	196	3	210

a. Rounded to nearest 70 mg capsule.
b. For older children, one 140-mg capsule may be substituted for each two 70-mg capsules.

Attachment 2: Lansky-Karnofsky Performance Status

Karnofsky Scale[a] (recipient age ≥16 years)	Lansky Scale[b] (recipient age <16 years)
100: Normal, no complaints, no evidence of disease	100: Fully active, normal
90: Able to carry on normal activity. Minor signs or symptoms of disease.	90: Minor restriction with strenuous physical activity
80: Normal activity with effort. Some signs or symptoms of disease.	80: Active, but gets tired more quickly
70: Cares for self, unable to carry on normal activity or to do active work	70: Both greater restrictions of, and less time spent in, active play
60: Requires occasional assistance but is able to care for most of personal needs	60: Up and around, but minimal active play; keeps busy with quieter activities
50: Requires considerable assistance and frequent medical care	50: Lying around much of the day, but gets dressed; no active play; participates in all quiet play and activities
40: Disabled, requires special care and assistance	40: Mostly in bed; participates in quiet activities
30: Severely disabled, hospitalization indicated, although death not imminent	30: Stuck in bed; needs help even for quiet play
20: Hospitalization necessary. Very sick, active supportive treatment necessary.	20: Often sleeping; play is entirely limited to very passive activities
10: Moribund, fatal process progressing rapidly	10: Does not play or get out of bed to play
0: Dead	0: Unresponsive

a. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents in cancer. In Evaluation of chemotherapeutic agents. Edited by MacLeod CM. New York: Columbia University Press; 1949:191-205.[17]
b. Lansky SB, List MA, Lansky LL, Ritter-Sterr C, Miller DR. The measurement of performance in childhood cancer patients. *Cancer*. 1987 Oct 1;60(7):1651-1656.[20]

Attachment 3: Body Surface Area Calculation

BSA should be calculated using a standard nomogram. An example nomogram follows:

$$\text{BSA} = \sqrt{\frac{Ht(inches) \times Wt(lbs)}{3131}}$$

or

$$\text{BSA} = \sqrt{\frac{Ht(cm) \times Wt(kg)}{3600}}$$

Attachment 4: Instruction for Concomitant Medications to be Used With Precaution

Ibrutinib is metabolized primarily by CYP3A. Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. Co-administration of ketoconazole, a strong CYP3A inhibitor, in 18 healthy subjects increased dose normalized exposure, C_{max} and AUC0-last, of ibrutinib by 29- and 24-fold, respectively. A DDI study in patients with B-cell malignancies (PCI-32765LYM1003) found that co-administration of ibrutinib with the moderate CYP3A inhibitors erythromycin and voriconazole, increased C_{max} by 3.4-fold and 6.7-fold and increased AUC by 3.0-fold and 5.7-fold, respectively. Clinical safety data in 66 subjects treated with moderate (n=47) or strong CYP3A inhibitors (n=19) did not reveal meaningful increases in toxicities. Strong inhibitors of CYP3A (eg, ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, telithromycin, itraconazole, nefazadone, and cobicistat) and moderate inhibitors (eg, voriconazole, erythromycin, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, fluconazole, fosamprenavir, imatinib, verapamil, amiodarone, dronedarone) should be avoided. If the benefit outweighs the risk and a strong CYP3A inhibitor must be used, reduce the ibrutinib dose by 75% (140 mg/1.7 m^2 rounded down to 80 mg/m^2 for starting dose of 329 mg/m^2 or to 110 mg/m^2 for dose of 440 mg/m^2) or stop treatment temporarily (for 7 days or less). If a moderate CYP3A inhibitor must be used, reduce ibrutinib by 75% (140 mg/1.7 m^2 rounded down to 80 mg/m^2 for starting dose of 329 mg/m^2 or to 110 mg/m^2 for dose of 440 mg/m^2) for the duration of the inhibitor use. No dose adjustment is required in combination with mild inhibitors. Monitor the subject closely for toxicity and follow dose modification guidance as needed. Avoid grapefruit and Seville oranges during ibrutinib treatment, as these contain moderate inhibitors of CYP3A.

Co-administration of ibrutinib with strong inducers of CYP3A decreases ibrutinib plasma concentrations by up to 90%. Avoid concomitant use of strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

Examples of inhibitors, inducers, and substrates can be found in Attachment 5 and at https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers[11] and http://medicine.iupui.edu/clinpharm/ddis/main-table/.[10]

Drugs That May Have Their Plasma Concentrations Altered by Ibrutinib

In vitro studies indicated that ibrutinib is a weak reversible inhibitor toward CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 and does not display time-dependent CYP450 inhibition. The dihydrodiol metabolite of ibrutinib is a weak inhibitor toward CYP2B6, CYP2C8, CYP2C9, and CYP2D6. Both ibrutinib and the dihydrodiol metabolite are at most weak inducers of CYP450 isoenzymes in vitro. Therefore, it is unlikely that ibrutinib has any clinically relevant drug-drug interactions with drugs that may be metabolized by the CYP450 enzymes.

In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp) nor other major transporters, except OCT2. The dihydrodiol metabolite and other metabolites are P-gp substrates. Ibrutinib is a mild inhibitor of P-gp and breast cancer resistance protein (BCRP). Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp and BCRP after a therapeutic dose. There are no clinical data available. To minimize the potential for an interaction in the gastrointestinal tract, narrow therapeutic range P-gp or BCRP substrates such as digoxin or methotrexate should be taken at least 6 hours before or after ibrutinib. Ibrutinib may also inhibit BCRP systemically and increase the exposure of drugs that undergo BCRP-mediated hepatic efflux, such as rosuvastatin.

Concomitant Use of Ibrutinib and Antiplatelet Agents and Anticoagulants

Warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function may increase the risk of bleeding. Subjects with congenital bleeding diathesis have not been studied. Ibrutinib should be temporarily stopped at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.

Subjects requiring the initiation of therapeutic anticoagulation therapy (other than warfarin or a vitamin K antagonist) during the course of the study should be discussed with the sponsor's medical monitor.

Attachment 5: Inhibitors and Inducers of CYP3A

The table below shows the classification of commonly used inhibitors and inducers of CYP3A enzymes. Further information can be found at the following websites:
https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers[11]
http://medicine.iupui.edu/clinpharm/ddis/main-table/.[10]

Inhibitors of CYP3A	Inducers of CYP3A
Strong inhibitors:	carbamazepine
Boceprevir	barbiturates
Clarithromycin	efavirenz
Cobicistat	glucocorticoids
Indinavir	modafinil
Itraconazole	nevirapine
Ketoconazole	oxcarbarzepine
Mibefradil	phenobarbital
Nefazodonene	phenytoin
Nelfinavir	pioglitazone
posaconazole [a]	rifabutin
Ritonavir	rifampin
Saquinavir	St. John's Wort
Suboxone	troglitazone
Telaprevir	
Telithromycin	
Troleandomycin	
Moderate inhibitors:	
Amiodarone	
Amprenavir	
Aprepitant	
Atazanavir	
Ciprofloxacin	
Crizotinib	
Darunavir	
diltiazem	
Dronedarone	
Erythromycin	
Fluconazole	
Fosamprenavir	
grapefruit juice	
Seville orange juice	
Verapamil	
voriconazole [a]	
Amiodarone	
Weak inhibitors:	
Cimetidine	
Fluvoxamine	
All other inhibitors:	
Chloramphenicol	
Delaviridine	
diethyl-dithiocarbamate	
Gestodene	
Mifepristone	
Norfloxacin	
Norfluoxetine	
star fruit	

[a] Classification based on internal data.

Attachment 6: Intrathecal Drug Doses by Age

	Intrathecal Drug Doses (mg)			
Age (years)	Methotrexate	Hydrocortisone*	Prednisolone*	Cytarabine
<1	8	8	4	15
≥1 to <2	10	10	6	20
≥2 to <3	12	12	8	25
≥3	15	15	10	30

*Other corticosteroids may be administered as per local supply provided that the steroid equivalent dose is equal to the prednisolone dose above.

Attachment 7: Blood Volume Tables

Estimated Maximum Volume of Blood to be Collected From all Subjects in Part 1, by Study Phase and Treatment Cycle

Type of Sample[a,b]	Volume per Sample	No. of Samples per Subject	Approximate Total Volume of Blood[c]
Screening			
Safety			
Hematology	2.5 – 5.0 mL	1	2.5 – 5.0 mL
Serum chemistry	2.5 – 5.0 mL	1	2.5 – 5.0 mL
Serum β-hCG pregnancy tests[d]	2.5 mL	1	2.5 mL
HIV, Hepatitis B, C serologies	2.5 – 5.0 mL	1	2.5 – 5.0 mL
Tetanus, pneumococcal titers	2.5 – 5.0 mL	1	2.5 – 5.0 mL
Cycle 1			
Safety			
Hematology	2.5 – 5.0 mL	4	10.0 – 20.0 mL
Serum chemistry	2.5 – 5.0 mL	4	10.0 – 20.0 mL
Serum β-hCG pregnancy tests[d]	2.5 mL	1	2.5 mL
Pharmacokinetic samples	0.6 mL	10	6.0 mL
Pharmacodynamic samples	4.0 – 6.0 mL	4	16.0 – 24.0 mL
Biomarker samples	1.2 mL	2	2.4 mL
Protein binding	1.0 mL	1	1.0 mL
Cycle 2			
Safety			
Hematology	2.5 – 5.0 mL	2	5.0 – 10.0 mL
Serum chemistry	2.5 – 5.0 mL	2	5.0 – 10.0 mL
Serum β-hCG pregnancy tests[d]	2.5 mL	1	2.5 mL
Pharmacokinetic samples	0.6 mL	5[e]	3.0 mL
Pharmacodynamic samples	4.0 – 6.0 mL	1[e]	4.0 – 6.0 mL
Biomarker samples	1.2 mL	1[e]	1.2 mL
Cycle 3			
Safety			
Hematology	2.5 – 5.0 mL	2	5.0 – 10.0 mL
Serum chemistry	2.5 – 5.0 mL	2	5.0 –10.0 mL
Serum β-hCG pregnancy tests[d]	2.5 mL	1	2.5 mL
End-of-Treatment Visit			
Safety			
Hematology	2.5 – 5.0 mL	1	2.5 – 5.0 mL
Serum chemistry	2.5 – 5.0 mL	1	2.5 – 5.0 mL
Pharmacodynamic samples	4.0 – 6.0 mL	1	4.0 – 6.0 mL
Biomarker samples	1.2 mL	1	1.2 mL
First Follow-up Assessment			
Safety			
Tetanus, pneumococcal titers[f]	2.5 – 5.0 mL	1	2.5 – 5.0 mL
Monotherapy Cycle 1-3 (if applicable)			
Safety			
Hematology	2.5 – 5.0 mL	3	7.5 – 15.0 mL
Serum chemistry	2.5 – 5.0 mL	3	7.5 – 15.0 mL
Serum β-hCG pregnancy tests[d]	2.5 mL	3	7.5 mL
End-of-Monotherapy Visit (if applicable)			
Safety			
Hematology	2.5 – 5.0 mL	1	2.5 – 5.0 mL
Serum chemistry	2.5 – 5.0 mL	1	2.5 – 5.0 mL
Pharmacodynamic samples	4.0 – 6.0 mL	1	4.0 – 6.0 mL
Biomarker samples	1.2 mL	1	1.2 mL
Approximate Total[g]			**139.0 - 230.5 mL**

β-hCG=beta-human chorionic gonadotropin; HIV=human immunodeficiency virus.
a. Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.
b. Sample volumes will be adjusted according to standards for pediatric subjects.
c. Calculated as number of samples multiplied by amount of blood per sample.
d. Serum pregnancy test to be performed only if urine is unavailable.
e. These samples may be collected in Cycle 2 or Cycle 3, but not both.
f. Subjects who enter monotherapy will have sample taken at End-of-Monotherapy Visit
g. An additional biomarker sample may be taken if PD occurs during a follow-up visit
Note: An indwelling intravenous cannula may be used for blood sample collection.

Estimated Maximum Volume of Blood to be Collected From Each Subject in Part 2, by Study Phase and Treatment Cycle

Type of Sample[a,b]	Volume per Sample	No. of Samples per Subject	Approximate Total Volume of Blood[c]
Screening			
Safety			
Hematology	2.5 – 5.0 mL	1	2.5 – 5.0 mL
Serum chemistry	2.5 – 5.0 mL	1	2.5 – 5.0 mL
Serum β-hCG pregnancy tests[d]	2.5 mL	1	2.5 mL
HIV, Hepatitis B, C serologies	2.5 – 5.0 mL	1	2.5 – 5.0 mL
Tetanus, pneumococcal titers	2.5 – 5.0 mL	1	2.5 – 5.0 mL
Cycle 1			
Safety			
Hematology	2.5 – 5.0 mL	4	10.0 – 20.0 mL
Serum chemistry	2.5 – 5.0 mL	4	10.0 – 20.0 mL
Serum β-hCG pregnancy tests[d]	2.5 mL	1	2.5 mL
Pharmacokinetic samples	0.6 mL	4[e]	2.4 mL
Pharmacodynamic samples	4.0 – 6.0 mL	4	16.0 – 24.0 mL
Biomarker samples	1.2 mL	2	2.4 mL
Cycle 2			
Safety			
Hematology	2.5 – 5.0 mL	2	5.0 –10.0 mL
Serum chemistry	2.5 – 5.0 mL	2	5.0 –10.0 mL
Serum β-hCG pregnancy tests[d]	2.5 mL	1	2.5 mL
Cycle 3			
Safety			
Hematology	2.5 – 5.0 mL	2	5.0 –10.0 mL
Serum chemistry	2.5 – 5.0 mL	2	5.0 –10.0 mL
Serum β-hCG pregnancy tests[d]	2.5 mL	1	2.5 mL
Pharmacodynamic samples	4.0 – 6.0 mL	1[f]	4.0 – 6.0 mL
Biomarker samples	1.2 mL	1[f]	1.2 mL
End-of-Treatment Visit			
Safety			
Hematology	2.5 – 5.0 mL	1	2.5 – 5.0 mL
Serum chemistry	2.5 – 5.0 mL	1	2.5 – 5.0 mL
Pharmacodynamic samples	4.0 – 6.0 mL	1	4.0 – 6.0 mL
Biomarker samples	1.2 mL	1	1.2 mL
First Follow-up Assessment			
Safety			
Tetanus, pneumococcal titers[g]	2.5 – 5.0 mL	1	2.5 – 5.0 mL
Monotherapy Cycle 1-3 (if applicable)			
Safety			
Hematology	2.5 – 5.0 mL	3	7.5 – 15.0 mL
Serum chemistry	2.5 – 5.0 mL	3	7.5 – 15.0 mL
Serum β-hCG pregnancy tests[d]	2.5 mL	3	7.5 mL
End-of-Monotherapy Visit (if applicable)			
Safety			
Hematology	2.5 – 5.0 mL	1	2.5 – 5.0 mL
Serum chemistry	2.5 – 5.0 mL	1	2.5 – 5.0 mL
Pharmacodynamic samples	4.0 – 6.0 mL	1	4.0 – 6.0 mL
Biomarker samples	1.2 mL	1	1.2 mL
Approximate Total[h]			**131.4 – 222.9 mL**

β-hCG=beta-human chorionic gonadotropin; HIV=human immunodeficiency virus.

a. Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.
b. Sample volumes will be adjusted according to standards for pediatric subjects.
c. Calculated as number of samples multiplied by amount of blood per sample.
d. Serum pregnancy test to be performed only if urine is unavailable.
e. The 4 pharmacokinetic samples are collected on a single day in Cycle 1 (on Day 14) OR Cycle 2 Day 1.
f. These pharmacodynamic and biomarker samples may be collected in Cycle 1 (on Day 14) OR Cycle 2 or Cycle 3 (predose only).
g. Subjects who enter monotherapy will have sample taken at End-of-Monotherapy Visit
h. An additional biomarker sample may be taken if PD occurs during a follow-up visit

Note: An indwelling intravenous cannula may be used for blood sample collection.

INVESTIGATOR AGREEMENT

JNJ-54179060 (ibrutinib)
Clinical Protocol 54179060LYM3003 Amendment 6

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 intervention, 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): Sanjay Deshpande MD

Institution: Janssen Research & Development

Signature: PPD Date: 21-SEP-2020

(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.