CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217003Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	Efficacy Supplements (SE5 and SE8), New NDA
Application Number(s)	NDA 205552 S-36, S-37, NDA 210563 S-12, S-13, NDA 217003
Priority or Standard	NDA 205552 S-36, NDA 210563 S-12, and NDA 217003 – Priority, NDA 205552 S-37 and NDA 210563 S-13 – Standard
Submit Date(s)	NDA 205552 S-36, S-37, NDA 217003: February 24, 2022 NDA 210563 S-12, S-13: April 1, 2022
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PDUFA Goal Date	NDA 205552 S-36, NDA 217003: August 24, 2022 NDA 210563 S-12: October 1, 2022 NDA 205552 S-37: December 24, 2022 NDA 210563 S-13: February 1, 2023
Division/Office	Division of Hematologic Malignancies I / Office of Oncologic Diseases
Review Completion Date	August 22, 2022
Established Name	Ibrutinib
(Proposed) Trade Name	IMBRUVICA
Pharmacologic Class	Kinase inhibitor
Applicant	Pharmacyclics LLC
Formulation(s)	NDA 205552 – capsules, NDA 210563 – tablets; NDA 217003 – oral suspension
Dosing Regimen	Patients 12 years and older: 420 mg, orally once daily Patients 1 to less than 12 years: 240 mg/m^2, orally once daily (up to a dose of 420 mg)
Applicant Proposed Indication(s)/Population(s)	For the treatment of adult and pediatric patients age 1 year and older with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of adult and pediatric patients age 1 year and older with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

ADR	adverse drug reaction
AE	adverse event
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AUC	area under the plasma concentration-time curve
BA	bioavailability
B-AL	Burkitt leukemia
BL	Burkitt lymphoma
BLA	biologics license application
BLL	Burkitt-like lymphoma
BORR	best overall response rate
BSA	body surface area
BTK	Bruton's tyrosine kinase
cGVHD	chronic graft-vs.-host disease
CI	confidence interval
CIT	chemoimmunotherapy
CLL	chronic lymphocytic leukemia
COVID-19	Coronavirus Disease 2019
CR	complete response
CRF	case report form
CSR	clinical study report
CYP	cytochrome P450
DBP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECP	extracorporeal photochemotherapy
EFS	event-free survival
ER	exposure-response
FDA	Food and Drug Administration
FFS	failure-Free Survival
FU	follow-up
GI	gastrointestinal
GMR	geometric mean ratio
HCT	hematopoietic cell transplantation
HLA	human leukocyte antigen
IB	Investigators Brochure

Ibr	ibrutinib
ICH	International Conference on Harmonization
IIV	inter-individual variability
ILD	interstitial lung disease
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITK	inducible T-cell kinase
ITT	intent to treat
KM	Kaplan-Meier
LTFU	long-term follow-up
Max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
MCL	mantle cell lymphoma
Min	minimum
mITT	modified intent to treat
NA	not applicable
NHL	non-Hodgkin lymphoma
NIH	National Institutes of Health
MZL	marginal zone lymphoma
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NCT	National Clinical Trial
NDA	new drug application
NE	not evaluable
OD	oral dose
ORR	overall response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
Pbo	placebo
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PK	pharmacokinetics
PMBCL	primary mediastinal B-cell lymphoma
PMR	postmarketing requirement
PPSR	proposed pediatric study request
PR	partial response
PRO	patient reported outcome
PT	preferred term

QL	quality of life
REMS	risk evaluation and mitigation strategy
RICE	rituximab, ifosfamide, carboplatin, etoposide, and dexamethasone
RPED	recommended pediatric equivalent dose
RR	response rate
R/R	relapsed/refractory
RVICI	rituximab, vincristine, idarubicin, carboplatin, ifosfamide, and dexamethasone
SAE	serious adverse event
SBP	systolic blood pressure
SDRC	Safety and Dosing Review Committee
SLL	small lymphocytic lymphoma
SMQ	standard MedDRA query
sNDA	supplemental New Drug Application
SOC	standard of care
TEAE	treatment emergent adverse event
TN	treatment-naïve
TSS	total summary score
TTR	time to response
US	United States
USPI	US Prescribing Information
WHO	World Health Organization
WM	Waldenstrom's macroglobulinemia
WR	Written Request

1. Executive Summary

1.1. Product Introduction

Drug Established Name:	Ibrutinib
Trade Name:	Imbruvica
Dosage Forms:	Capsules (70 mg and 140 mg), tablets (140 mg, 280 mg, 420 mg, and 560 mg), oral suspension (70 mg/mL)
Chemical Class:	Small molecule
Therapeutic Class:	Kinase inhibitor
Mechanism of Action:	Inhibitor of Bruton's tyrosine kinase (BTK)

Ibrutinib is an orally administered BTK inhibitor that is approved for adult patients with mantle cell lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, Waldenström's macroglobulinemia, marginal zone lymphoma, and chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy. The approval for adults with cGVHD after failure of one or more lines of systemic therapy was on August 8, 2017. Efficacy in adults with cGVHD was based on a single-arm trial in 42 adult patients with cGVHD after failure of first line corticosteroid therapy with an overall response rate (ORR) of 67% (complete response [CR] 21% and partial response [PR] 45%).

The Applicant now submits a supplementary New Drug Application (sNDA) to support an indication for the treatment of pediatric patients 1 year and older with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy. The supplement also included updated efficacy information for the adult study in cGVHD and the results of a study in pediatric patients with relapsed or refractory non-Hodgkin lymphoma (NHL). Concurrently, a new NDA was submitted to support the approval of the pediatric formulation, an oral suspension.

The submission was administratively split to the following:

- Capsules
  - NDA 205552/S-036: SE5 – pediatric previously treated cGVHD
  - NDA 205552/S-037: SE8 – adult previously treated cGVHD
  - NDA 205552/S-038: SE8 – pediatric relapsed/refractory NHL

- Tablets
  - NDA 210563/S-012: SE5 – pediatric previously treated cGVHD
  - NDA 210563/S-013: SE8 – adult previously treated cGVHD
  - NDA 205552/S-014: SE8 – pediatric relapsed/refractory NHL
- Oral Suspension
  - NDA 217003: original NDA

This review encompasses the multi-disciplinary assessment for NDA 205552 S-36 and 37, NDA 210563 S-12 and 13, and NDA 217003. Review of the submission for pediatric R/R NHL under NDA 205552 S-38 and NDA 210563 S-14 are provide in a separate review by the Division of Hematologic Malignancies 2.

The review team recommends approval of ibrutinib for the treatment of pediatric patients age 1 year and older with cGVHD after failure of one or more lines of systemic therapy. The recommendation is based on the ORR (CR+PR) through week 25 in Study PCYC-1146-IM (IMAGINE) and supported by extrapolation of efficacy from the approved adult indication.

The review team recommends approval of the supplemental information in adults with previously treated cGVHD to update the Lee Symptom Scale (LSS) information (Study PCYC-1129-CA). However, the updated efficacy information will not be included in labeling due to missing data.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The IMAGINE study (PCYC-1146-IM, NCT03790332) is an ongoing, open-label, dose finding, safety, and efficacy study of oral ibrutinib in pediatric and young adult patients with moderate or severe cGVHD. Eligible patients were ≥1 year old to <22 years old with either previously treated cGVHD after failing one or more prior therapies and treated with single agent ibrutinib (concomitant treatment with supportive care therapies for cGVHD was permitted) or newly diagnosed cGVHD treated with ibrutinib in combination with corticosteroids. Patients were excluded if single organ genitourinary involvement was the only manifestation of cGVHD. Patients age 12 years and older were treated with ibrutinib 420 mg orally once daily, and patients age 1 year to less than 12 years were treated with ibrutinib 240 mg/m2 orally once daily. All patients also received standard supportive care, including infection prophylaxis.

The study included 2 parts (Part A and B) conducted in parallel. Part A was a dose finding and safety study for patients ≥1 to <12 years old with previously treated moderate or severe cGVHD, and the recommended pediatric equivalent dose (RPED) was the dose that achieved approximately equivalent exposure to adult patients. Part B initially enrolled patients ≥12 to <22 years old with previously treated or newly diagnosed moderate or severe cGVHD. After determination of the RPED from Part A for patients ≥1 to <12 years, then Part B was expanded to include the entire age range of ≥1 years to <22 years.

The primary endpoints in Part A were pharmacokinetic (PK based on AUC) to determine the RPED of ibrutinib for use in pediatric subjects (age ≥ 1 to < 12 years) with cGVHD and in Part B were PK (AUC) and safety of ibrutinib in pediatric subjects (age ≥ 1 and < 22 years) with cGVHD. Additional secondary endpoints included safety, pharmacodynamics (BTK occupancy), overall response rate (ORR), duration of response (DOR), ORR at 24 weeks and ORR at 48 weeks. For efficacy, the FDA assessment relied on ORR through the Week 25 visit. FDA considered two definitions of duration of response: 1) time from response to progression, new systemic therapy, or death; and 2) time from response to new systemic therapy or death. There was no formal hypothesis testing for the efficacy endpoints in this study. Support of efficacy in pediatric patients was also provided by extrapolation of efficacy from the approved adult population.

The IMAGINE study enrolled 59 patients, including 47 patients with previously treated cGVHD and 12 patients with newly diagnosed cGVHD. The approval in pediatric patients (b) (4) with the 12 patients enrolled to this study in light of a failed trial in newly diagnosed cGVHD in adults and adolescents (see review below for details on Study INTEGRATE, PCYC-1140-IM, NCT02959944). Therefore, the analysis conducted by the FDA was primarily based on the 47 patients enrolled with previously treated cGVHD. In those 47 patients, the median age was 13 years (range, 1 to 19 years) with one patient ≥1 to <2 years, 20 patients ≥2 to <12 years, 23 patients ≥12 to <18 years, and 3 patients ≥18 to <22 years. The median time since cGVHD diagnosis was 16.1 months and the median number of prior cGVHD treatments was 2 (range, 1 to 12).

Using FDA-adjudicated responses in the 47 pediatric and young adult patients with previously treated cGVHD, the ORR by the Week 25 visit was 59.6% (95% CI: 44.3, 73.6). The median duration of response was 5.3 months (95% CI: 2.8, 8.8). The median time to new therapy or death was 14.8 months (95% CI: 4.6, not evaluable). A >7-point reduction in cGVHD LSS score by Week 25 visit was achieved by 50% (13/26) of patients aged 12 years and older.

The 60% ORR in pediatric patients with previously treated cGVHD with durable responses and a reduction in the LSS in adolescent patients are considered substantial evidence of effectiveness. On the basis of biology of treatment-refractory cGVHD and mechanism of action of ibrutinib, the efficacy
of ibrutinib for treatment of cGVHD can also be extrapolated from the study in adults to pediatric patients at ≥ 1 year as supportive evidence of effectiveness.

The currently approved indication for the treatment of adults with cGVHD after failure of one or more lines of systemic therapy was based on the results of Study 1129 (PCYC-1129-CA, NCT02195869). Review of the evidence to support effectiveness from Study 1129 was provided in Supplement 17. This submission included updated efficacy information from Study 1129 in 42 adult patients with additional follow up. However, a substantial proportion of the response assessments are incomplete or missing prohibiting FDA confirmation of response by any standard criteria. The patient reported outcomes measure based on the LSS was re-analyzed by at least a 7-point decrease in LSS through Week 25, to be consistent with LSS outcome in Study IMAGINE.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Chronic GVHD occurs in about 40% of patients after allogeneic hematopoietic stem cell transplantation (HSCT). Without treatment, cGVHD can cause severe multisystem tissue damage due to chronic inflammation and fibrosis, which can be fatal. Standard first-line treatment is steroids with or without a calcineurin inhibitor, depending on the severity of the disease. Almost half the patients require 3 or more lines of therapy, which include multiple types of immunosuppressive drugs used off-label. Ibrutinib is currently only approved in adults with previously treated cGVHD. Belumosudil and ruxolitinib are the only other drugs approved for treatment of previously treated cGVHD in adults and adolescents ≥12 years old. All approved treatments for cGVHD have relatively low complete remission rates and limited long-term disease control. There is a clear need for drugs for the treatment of cGVHD in pediatric patients.

Ibrutinib is an orally administered BTK inhibitor that is currently approved for adult patients with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy. Efficacy in adults with cGVHD was based on a single-arm trial in 42 adult patients with cGVHD after failure of first line corticosteroid therapy with an overall response rate (ORR) of 67% (complete response [CR] 21% and partial response [PR] 45%).

The IMAGINE Study (PCYC-1146-IM) was an open-label, dose finding, safety, and efficacy study of oral ibrutinib in pediatric and young adult patients with moderate or severe cGVHD. Patients age 12 years and older were treated with ibrutinib 420 mg orally once daily, and patients age 1 year to less than 12 years were treated with ibrutinib 240 mg/m2 orally once daily. In 47 patients with previously treated cGVHD enrolled, the ORR by Week 25 visit was 59.6% (95% CI: 44.3, 73.6). The median duration of response was 5.3 months (95% CI: 2.8, 8.8). The median time to new therapy or death was 14.8 months (95% CI: 4.6, not evaluable). A >7-point reduction in cGVHD LSS score by Week 25 visit was achieved by 50% (13/26) of patients aged 12 years and older. Additional supportive efficacy data was provided by extrapolation of efficacy from Study 1129 in adults.

Safety of ibrutinib in pediatric and young adult patients (age ≥1 to <22 years) was evaluated in the IMAGINE study in the 47 patients with previously treated cGVHD. Additional analyses included 12 patients with newly diagnosed cGVHD in the IMAGINE study and 3 patients with newly diagnosed cGVHD in the INTEGRATE study. In the 47 patients with previously treated cGVHD, ibrutinib was generally well tolerated with a median duration of exposure of 7.1 months (range, 0.2 to 25.9 months). Serious adverse reactions occurred in 64% of patients and fatal adverse reactions occurred in two patients, including sepsis and adult respiratory distress syndrome. The most common (≥20%) adverse reactions were anemia, musculoskeletal pain, pyrexia, diarrhea, pneumonia, abdominal pain, stomatitis, thrombocytopenia, and headache. The serious adverse reactions in the clinical trial were limited by the
prespecified dose modifications for toxicity and a safety monitoring plan as mitigation strategies.

In the overall pediatric and young adult population (N=62), no additional safety signals were identified. Generally, the safety profile was similar across the pediatric age range and between pediatric and adult populations. Exposure-response analyses showed no apparent E-R relationship between ibrutinib exposure and ORR in pediatric patients with cGVHD, and no clear E-R relationship for the adverse events of specific clinical interests (AESIs) including atrial fibrillation (any grade), hemorrhage (any grade or major), liver function test abnormalities (Grade ≥3), and neutropenia (Grade ≥3). The results from relative bioavailability study (Study PCI-32765CLL1015) showed that the suspension formulation (70 mg/mL) was bioequivalent to the capsule formulation based on the geometric mean ratio of AUC_{last} compared to the approved capsule formulation.

Given the observed response rate with durability, and with the mitigation strategies in place
in labeling, the clinical benefit of ibrutinib appears to outweigh the risks for adult and pediatric
patients ≥1 year with cGVHD after failure of one or more lines of systemic therapy. Additional information is needed to confirm safety with long-term use in pediatric patients regarding potential effects on growth and development, and this can be accomplished postmarketing with continued follow up on patients enrolled in the IMAGINE study.

Briefly, the INTEGRATE study (PCYC-1140-IM) study was a randomized, double-blind study of oral ibrutinib in combination with prednisone versus placebo in combination with prednisone in patients newly diagnosed cGVHD in adolescents ≥12 years and adults. The primary endpoint of the study was ORR at week 48. The FDA's preferred efficacy evaluation for the treatment of cGVHD is ORR through week 25. The study enrolled 193 patients (95 in ibrutinib with prednisone, 98 in placebo with prednisone),

including 2 patients <18 years (13 and 15 years old, respectively, both randomized to the ibrutinib with prednisone arm). The Applicant reported a negative result for the analysis of the primary efficacy endpoint of ORR at 48 weeks (41% vs 37%, p = 0.54). FDA adjudicated response of ORR by week 25 also showed no improvement in response rate with 73% for ibrutinib with prednisone arm vs 79% for placebo with prednisone. The data from the INTEGRATE [redacted] (b) (4) [redacted] In light of light of the failed trial in adults with newly diagnosed cGVHD, the 12 pediatric patients with newly diagnosed cGVHD enrolled in the IMAGINE study [redacted] (b) (4) in children.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• cGVHD occurs in about 40% of patients after allogeneic hematopoietic stem cell transplantation. • Without treatment, cGVHD can cause severe multisystem tissue damage due to chronic inflammation and fibrosis. • The complications of cGVHD can be fatal.	cGVHD in pediatric patients is a serious and life-threatening disease.
Current Treatment Options	• Standard first line treatment is steroids with or without a calcineurin inhibitor depending on the severity of the disease. • Ibrutinib is approved for treatment of cGVHD after 1 or more lines of therapy in adult patients. ORR occurred in 67%, and the median duration of response was less than 5 months. • Belumosudil is approved for treatment of cGVHD after failure of 2 or more lines of therapy in adult and pediatric patients 12 years and older. ORR occurred in 75%, and the median duration of response was less than 2 months. • Ruxolitinib is approved treatment of cGVHD after failure of one or two lines of systemic therapy in adult and pediatric patients 12	There is a need for effective treatments for cGVHD in pediatric patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	years and older. ORR occurred in 70%, and the median duration of response was 4.2 months.	
Benefit	• Study IMAGINE (PCYC-1146-IM) was an open-label study of ibrutinib for pediatric and young adult patients (≥1 to <22 years) with moderate to severe cGVHD. • In patients with previously treated cGVHD, the ORR by Week 25 visit was 59.6% (95% CI: 44.3, 73.6). • The median duration of response was 5.3 months (95% CI: 2.8, 8.8). • The median time to new therapy or death was 14.8 months (95% CI: 4.6, not evaluable). • A >7-point reduction in cGVHD LSS score by Week 25 visit was achieved by 50% (13/26) of patients age 12 years and older.	The endpoint of ORR by week 25 with durability supports the effectiveness of ibrutinib for cGVHD in pediatric patients. Efficacy is supported by extrapolation from the adult study for the same indication.
Risk and Risk Management	• There were two fatal adverse reactions, including sepsis and adult respiratory distress syndrome (ARDS). • An adverse reaction resulting in treatment discontinuation occurred in 23% and dose reduction in 19%. • The most common (≥20%) adverse reactions were anemia, musculoskeletal pain, pyrexia, diarrhea, pneumonia, abdominal pain, stomatitis, thrombocytopenia, and headache. • The safety of long-term use on growth and development in pediatric patients has not been established.	The safety profile of ibrutinib 420 mg orally once daily (≥12 years) and 240 mg/m2 orally once daily (≥1 to <12 years) appears tolerable. No specific toxicity signals were identified in pediatric patients with cGVHD.

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as			
			X	Patient reported outcome (PRO)	Section 8.1.1.1, Section 8.1.2.1, Section 8.1.3.1
			☐	Observer reported outcome (ObsRO)	
			☐	Clinician reported outcome (ClinRO)	
			☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	☐	Patient-focused drug development or other stakeholder meeting summary reports			
	☐	Observational survey studies designed to capture patient experience data			
	☐	Natural history studies			
	☐	Patient preference studies (e.g., submitted studies or scientific publications)			
	☐	Other: (Please specify)			
☐	Patient experience data that was not submitted in the application, but was considered in this review.				

X

Cross-Disciplinary Team Leader
Lori Ehrlich

2. Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Chronic graft-vs.-host disease (cGVHD) is a serious and life-threatening condition which represents an impediment to the otherwise curative potential of allogeneic hematopoietic cell transplantation (HCT) (Arai et al, 2011[2]; Pidala et al 2011[35]; Baird and Pavletic 2006[7]; Lee et al 2003[26]). It is the most common long-term complication following HCT, affecting 30% to 70% of subjects who survive past the first 100 days (Lee, 2010[28]) and is a leading cause of non-relapse mortality (Pidala et al, 2011[35]), with rates of 21% at 1 year and 31% at 5 years (Arora et al, 2011[4]). Pathologically, cGVHD is characterized by fibrosis and inflammation of affected organs (e.g., the skin, liver, gastrointestinal [GI] tract, and lung) (Shulman et al, 2006[40]). While cGVHD occurs in approximately 40% of allogeneic HCT recipients, reported incidence rates range from 6% to 80% depending upon the presence of risk factors and diagnostic criteria used (Filipovich et al, 2005[15]; Carlens et al, 1998[11]; Ochs et al, 1994[34]; Atkinson et al, 1990[5]).

Much of the literature on cGVHD has focused on its occurrence in adults (Jacobsohn 2010[23]). Although cGVHD is less common in children than in adults, pediatric patients nonetheless represent a meaningful proportion of the overall cGVHD population and have substantial morbidity and mortality associated with this disease (Baird et al, 2010[8]). The pathogenesis of cGVHD, although not yet fully understood, appears to be essentially the same in adult and pediatric patients. Recent information implicates the activity of both B cells and T cells in the generation of cGVHD (Sarantopoulos et al, 2015[37]; Allen et al, 2014[1]; Flynn et al, 2014[16]; Johnston et al, 2014[24]). First recognized in the adult cGVHD population, the involvement of T- and B-cells was confirmed in a biomarker study conducted in children with cGVHD (Fujii et al, 2008[17]; She et al, 2007[39]). The occurrence of cGVHD in children is of major importance especially since they potentially have an overall longer life expectancy following the complications of cGVHD (e.g., malnutrition, poor weight gain/linear growth, musculoskeletal deformities due to sclerotic skin changes and joint contractures) and its therapy (Baird et al, 2010[6]; Jacobsohn 2010[23]).

There are currently no approved therapies for children < 12 years of age with chronic GVHD, in the front line or relapsed/refractory setting. Current treatment approaches typically rely on a backbone of corticosteroids, if tolerated, in various combinations with other systemic immunosuppressants. The long-term effects of chronic steroid use are well-documented in children (Blanco et al, 2005[9]; Volmer et al, 2018[43]; Grennan and Wang, 2019[19]) and can have serious implications such as an increased risk of bone disease, obesity, diabetes, hypertension, cataracts, and other long-term effects that have the potential to affect children for decades following treatment (DeFeo et al, 2020[14]). Taken together with the risk of infections and other risks associated with corticosteroid use, as well as the limited efficacy that steroids provide in the R/R setting, alternative or steroid-sparing agents are desperately needed in this population. Due to lack of data, current practice is based on lower levels of evidence, typically generated in adults, as summarized in the current National Comprehensive Cancer Network (NCCN) guidelines (Saad et al, 2020[36]).

The FDA's Assessment:
FDA agrees with the Applicant's conclusion that chronic GVHD in pediatric patients is a serious, potentially life-threatening condition.

Biology of chronic GVHD:
cGVHD is a multisystem disorder that is manifested by both inflammatory and fibrosing features. Experimental models have implicated both the innate and adaptive immune systems in the etiology. The pathogenesis is thought to evolve from an acute inflammatory response to tissue injury early posttransplant which evolves into chronic inflammation and dysregulation of both T and B cells with subsequent aberrant tissue repair and fibrotic reaction (Cooke KR et al 2017). It has been hypothesized that the thymus plays a major role in the development of cGVHD, as it is responsible for the negative selection that limits expansion of alloreactive donor cells and pathogenic B cells. Although this has been cited as the basis for a lower incidence of cGVHD in children, who are more likely than adults to have a functioning thymus, there is no evidence that the natural history or response to treatment differs by age once cGVHD (and especially treatment-refractory cGVHD) occurs.

U.S. population of patients with chronic GVHD:

Table 1 below shows demographic and baseline patient characteristics of US Population Samples for patients with chronic GVHD based on US population reference of Bachier et al. 2019, and Bachier et al. 2021.

Table 1. Demographic and Baseline Patient Characteristics of US Population Sample

	Characteristics	cGVHD Patients n=5259
Age (years)	Median	58 Years
Sex	Female	42%
	Male	58%
Geographical Region	Midwest	24-28%
	Northeast	20-21%
	South	30-37%
	West	14-25%
Race	Native American	0%
	Hispanic	5%
	White	82%
	Asian	2%
	Black	6%
	Other	2%
	Unknown	3%
Number of lines of systemic therapy for cGVHD	One	95.7%
	Two	70.9%
	Three	46.8%
	Four or more	29.2%
Top Treatment Regimens within 12 months post-Diagnosis	Steroid Only	22.3 - 28.2%
	CNI Only	21.0 - 23.2%
	Steroid + CNI	9.6 - 13.4%
	mTOR inhibitors	5.4 - 8.6%
	Steroid + mTOR inhibitors	4.2 - 4.7%
	MMF	3.2 – 3.9%
	Steroid + MMF	3.5 – 3.8%
	ECP	2.3 -3.6%
	Steroid + ECP	2.3%
	Ibrutinib	0.5%
	Ruxolitinib	0.5 – 2.5%
	Other Regimen	15.7 -18.8%

Source: Reproduced based on the references of Bachier et al. 2019, and Bachier et al. 2021.
Abbreviations: CNI: calcineurin inhibitor; MMF: mycophenolate mofetil; ECP: extracorporeal photopheresis.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

The initial and current standard of care treatment for cGVHD is the prolonged administration of corticosteroids (Csanadi et al, 2019[12]). However, more than 50% of patients eventually relapse

or become refractory, requiring second-line treatment, for which there is no standard of care. The frequent morbidity associated with prolonged corticosteroid use has prompted the investigation of corticosteroid therapy in conjunction with other immunosuppressant agents (Gilman et al, 2012[18]; Martin et al, 2009[29]; Koc et al, 2002[26]; Arora et al, 2001[3]; Koc et al, 2000[25]; and Sullivan et al, 1988[42]). Agents such as cyclosporine, tacrolimus, sirolimus, and/or mycophenolate mofetil are often added to corticosteroid therapy in both frontline and second-line settings despite the lack of demonstrated efficacy (Martin et al, 2011[31]). Ruxolitinib, a protein kinase inhibitor, is approved for patients with cGVHD 12 years of age and older after failure of 1 or 2 lines of treatment and belumosidil is approved for patients with cGVHD 12 years and older who have already tried at least 2 other therapies for the disease.

Treatment of pediatric patients is based heavily on experience in adults, and often includes prednisone and/or a calcineurin inhibitor in the frontline setting (Baird et al, 2010[6]; Zecca et al, 2002[45]). Prospective studies of salvage therapies for cGVHD are scarce in children, and the use of salvage agents such as sirolimus, mycophenolate mofetil, pentostatin, or extracorporeal photochemotherapy (ECP) in pediatric patients is supported with limited data (Jacobson et al, 2009[22]; Baird et al, 2010[6]; Busca et al, 2000[10]; Messina et al, 2003[32]).

While cGVHD in adults and children share many similar clinical features, there are some differences. Due in part to children's longer life expectancy, prospective studies are needed in the pediatric setting to study the long-term impact of cGVHD therapies and associated effects on morbidity and mortality. Differences in biomarkers have been identified in pediatric vs adult cGVHD, although the significance of these in guiding the best therapeutic approach for children is not yet known (Schultz et al, 2020[38]; Subburaj et al, 2021[41]). The tools available to study new therapies, such as the 2014 NIH criteria, also require further refinement to apply consistently to young children (e.g., pulmonary function testing) (Cuvelier et al, 2019[13]).

Preclinical results have demonstrated a substantial therapeutic benefit of ibrutinib treatment in reducing the prolonged allo-immune effects of cGVHD in animal models and have supported investigation in clinical studies. The approval of ibrutinib in adult patients with cGVHD after failure of one or more lines of systemic therapy demonstrated that ibrutinib has robust clinical activity with a high response rate by National Institutes of Health (NIH) criteria as well as an overall favorable safety profile.

The FDA's Assessment:

Standard first-line treatment for cGVHD is steroids with or without a calcineurin inhibitor, depending on the severity of the disease. Almost half the patients require 3 or more lines of therapy, which include multiple types of immunosuppressive drugs used off-label. Ibrutinib, belumosudil and ruxolitinib are the only drugs approved for treatment of cGVHD, and they have relatively low complete remission rates and limited long-term disease control, and are approved for use in adult patients (ibrutinib), or in adult and pediatric patients 12 years and older. There is a clear need for treatment of cGVHD in pediatric patients.

Table 2 shows the drugs approved by FDA for treatment of cGVHD.

Table 2. Drugs Approved for Treatment of Chronic GVHD

Drug	Excerpted Indication
Ruxolitinib	For the treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (cGVHD) after failure of one or two lines of systemic therapy.
Belumosudil	For the treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least two prior lines of systemic therapy.
Ibrutinib	For the treatment of adult patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy.

Source: FDA review

Ibrutinib is currently approved for treatment of cGVHD after 1 or more lines of therapy in adult patients. The overall response rate (ORR) was 67%, and the median duration of response was less than 5 months (Miklos et al. 2017). Belumosudil is approved for treatment of cGVHD after failure of 2 or more lines of therapy in adult and pediatric patients 12 years and older. ORR was 75%, and the median duration of response was less than 2 months. Ruxolitinib is approved treatment of cGVHD after failure of one or two lines of systemic therapy in adult and pediatric patients 12 years and older. ORR was 70%, and the median duration of response was 4.2 months.

Table 3 shows the response rate and duration of response for the drugs approved by FDA for treatment of cGVHD.

Table 3. ORR and DOR of Drugs Approved for Treatment of Chronic GVHD

	Ruxolitinib		Belumosudil	Ibrutinib
Indicated Population	After failure of 1 or 2 lines of systemic therapy in adult and pediatric patients ≥ 12 years		After failure of at least 2 lines of systemic therapy in adult and pediatric patients ≥ 12 years	After failure of 1 or more lines of systemic therapy in adult patients
	Ruxolitinib	Best available therapy		
N	165	164	65	42
Overall Response (95% CI)	70% (63%, 77%)	57% (49%, 65%)	75% (63%, 85%)	67% (51%, 80%)
Complete Response	8%	5%	6%	21%
Partial Response	62%	52%	69%	45%
Duration of Response (95% CI)	4.2 months (3.2, 6.7)	2.1 months (1.6, 3.2)	1.9 months (1.2, 2.9)	
≥ 7-point decrease in the cGVHD LSS Score (95% CI)	40%* (32%, 48%)	29%* (22%, 36%)	52% (40%, 65%)	24% (10/42) of patients on at least 2 consecutive visits

Source: FDA analysis, see also USPI for ibrutinib, belumosudil, and ruxolitinib.
Note: *cGVHD Total Symptom Score.

The efficacy of ibrutinib, belumosudil, and ruxolitinib were based on NIH response criteria for cGVHD clinical trial, as defined by the 2014 NIH Consensus Development Project on Criteria for Clinical Trials in cGVHD (Lee et al 2015).

The National Comprehensive Cancer Network (NCCN) Guidelines suggested systemic agents for steroid-refractory chronic GVHD include abatacept, alemtuzumab, calcineurin inhibitors (e.g., tacrolimus, cyclosporine), etanercept, ECP, hydroxychloroquine, ibrutinib, imatinib, interleukin-2 (IL-2), low-dose methotrexate, MTOR inhibitors (e.g., sirolimus), mycophenolate mofetil, pentostatin, rituximab, or ruxolitinib (NCCN 2022). The guidelines indicate that there is insufficient evidence to recommend one systemic agent as preferred over another. There are no differences in the recommended treatments by patient age.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Pharmacyclics has received the following approvals for IMBRUVICA® (ibrutinib) for the treatment of adult patients:

- Accelerated approval for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy on 13 November 2013;
- Accelerated approval for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy on 12 February 2014;
- Full approval for the treatment of patients with CLL who have received at least one prior therapy, and approval for the treatment of patients with CLL with 17p deletion on 28 July 2014;
- Full approval for the treatment of patients with Waldenstrom's macroglobulinemia (WM) on 29 January 2015;
- Full approval for the treatment of patients with CLL on 04 March 2016;
- Full approval for the treatment of patients with CLL/small lymphocytic lymphoma (SLL), and dosing of IMBRUVICA with bendamustine and rituximab in patients with CLL/SLL; full approval for the treatment of patients with CLL/SLL with 17p deletion on 06 May 2016;
- Accelerated approval for the treatment of patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti CD20-based therapy on 18 January 2017;
- Full approval for cGVHD in adults after failure of one or more lines of systemic therapy on 02 August 2017;
- Full approval for the treatment of patients with WM, including new data on ibrutinib in combination with rituximab on 24 August 2018; and
- Full approval for ibrutinib in combination with obinutuzumab or chlorambucil in combination with obinutuzumab for patients with treatment naive CLL/ SLL on 25 January 2019.

The FDA's Assessment:
FDA agrees with the Applicant's statement.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

The clinical studies providing supportive safety data were designed taking into consideration applicable guidelines (i.e., International Council on Harmonization) as well as advice obtained from consultations with health authorities regarding clinical study design, statistical principles, selection of endpoints, and assessment of safety and efficacy.

Breakthrough Therapy Designation: On 22 June 2016, ibrutinib was granted Breakthrough Therapy Designation by the FDA as monotherapy for the treatment of patients with cGVHD after failure of 1 or more lines of systemic therapy.

Orphan Drug Designation: On 23 June 2016, ibrutinib was granted Orphan Drug Designation for the treatment of patients with cGVHD.

cGVHD Approval in Adult Patients: On 02 August 2017, ibrutinib received full approval by the FDA for the treatment of adult patients with cGVHD after failure of 1 or more lines of systemic therapy, based on clinical data from Study PCYC-1129-CA (hereafter referred to as Study 1129; N = 42), which demonstrated that ibrutinib treatment resulted in a high frequency of sustained responses in adult subjects with relapsed/refractory cGVHD; observed responses were associated with decreased corticosteroid use, an improvement in cGVHD symptoms, and an acceptable safety profile.

Other Regulatory Interaction(s) Relevant to the Proposed Application: On 25 May 2021, details of the planned sNDA were discussed in the pre-sNDA/NDA Meeting interaction, in which the FDA agreed to the Applicant's key proposals below:

- The sNDA is submitted in response to a pediatric written request; thereby would be eligibile for Priority Review and Pediatric Exclusivity determination at the time of sNDA submission.
- The approach to cross-reference relevant sections of the pediatric cGVHD sNDA for the oral suspension formulation NDA 217003.
- Presentation of safety and efficacy data by age subsets of 1 to < 6 years, 6 to < 12 years, and 12 to < 22 years of age.
- The clinically relevant endpoints in the submission and the proposed extrapolation in children.

- Separate presentation of safety data in the ISS and SCS for pediatric cGVHD and B-cell malignancy studies.
- Omission of certain previously requested variables from the dataset, including date of first treatment of acute GVHD and IRC reads.

A tabular summary of key FDA interactions specific to the cGVHD pediatric indication is provided in Table 4.

Table 4 Applicant – Tabular Summary of Regulatory Interactions with the FDA

Date	IND Number	Regulatory Interaction
26 May 2017	102688	Type B Meeting with FDA to discuss the scope of the Applicant's PPSR and proposed WR
20 November 2017	102688	Draft PPSR/WR submitted to FDA
13 February 2018	102688	FDA feedback on draft PPSR/WR submitted on 20 November 2017
14 March 2018	102688	Revised proposed PPSR/WR submission to FDA
18 May 2018	102688	FDA issued WR to investigate ibrutinib in the treatment of pediatric patients with cGVHD and mature B-cell -NHL
	102688	Proposed WR Amendment 1 submitted to FDA
	102688	FDA feedback on Proposed WR Amendment 1
27 August 2018	102688	Responses to "Inadequate Proposed Amendment to WR" communication dated 20 August 2018 submitted to FDA
31 August 2018	102688	Teleconference with FDA to discuss definition of upper age limit of pediatric population for the purposes of the WR
17 September 2018	102688	Updated WR (Amendment 1) submitted to FDA
13 December 2018	102688	FDA issued WR (Amendment 1), which included (1) revising the age requirement and minimum number of pediatric subjects to be enrolled in iNTEGRATE/PCYC-1140-IM and iMAGINE/PCYC-1146-IM, and (2) revising the number of pediatric subjects by age subset to be included in SPARKLE/LYM3003
31 July 2020	102688	Teleconference with FDA to discuss outcome of SPARKLE/LYM3003 Interim Analysis
10 August 2020	102688	Proposed WR Amendment 2 submitted to FDA
18 September 2020	102688	FDA issued WR Amendment 2, which included (1) a reduction in the minimum number of pediatric subjects < 18 years of age in SPARKLE/LYM3003 and (2) an agreement on early stoppage of the SPARKLE study due to futility
08 December 2020	147315	Submission of primary analysis CSR for iNTEGRATE/PCYC-1140-IM to FDA
25 May 2021	147315	Pre-sNDA/NDA teleconference held with FDA to discuss and reach agreement on the content of the proposed (1) sNDA to support a pediatric cGVHD indication and (2) NDA for a new multi-dose, oral suspension formulation for pediatric cGVHD subjects age ≥ 1 to < 12 years
08 December 2021	102688	Submission of final analysis CSR for SPARKLE/LYM3003
15 December 2021	147315	Submission of final analysis CSR for iNTEGRATE/PCYC-1140-IM to FDA

cGVHD = chronic graft vs. host disease; FDA = Food and Drug Administration (United States); NDA = new drug application; NHL = Non-Hodgkin lymphoma; PPSR = proposed pediatric study request; sNDA: supplemental new drug application; WR = written request

The FDA's Assessment:

At the 5/25/2021 Type B Pre-sNDA meeting, FDA advised the Applicant of the following:

1. Data from iMAGINE together with data from iNTEGRATE (b) (4) . Patients treated with ibrutinib with treatment naïve GVHD were co-administered corticosteroids which was shown in iNTEGRATE to not have a benefit compared to corticosteroids alone on response rate at 48 weeks in adults. (b) (4)

2. The Applicant proposed that best overall response rate per National Institutes of Health (NIH)-defined complete response (CR) or partial response (PR) was the primary efficacy endpoint for Study PCYC-1129-CA and a key secondary endpoint in iMAGINE; sustained response for 5 months was chosen for Studies PCYC-1129-CA and iMAGINE; Lee cGVHD Symptom Scale was employed for Study PCYC-1129-CA and for adolescents (age ≥ 12 years) in iMAGINE. FDA advised the Applicant that the inclusion of particular endpoints in the USPI will be a review issue. For each proposed endpoint, the submission should discuss support for extrapolation from the adult study and the clinical relevance in pediatric patients. The Agency also agrees that the Applicant may present justification for the value of the pediatric data independent of the adult data.

3. The Applicant proposed that Imbruvica will be indicated for the treatment of adult and pediatric patients aged 1 year or older. FDA advised that the approval for the younger age groups will depend on the number of patients treated and whether there were any differences in efficacy or toxicity between the groups.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Clinical data from PCYC-1146-IM were submitted to the Agency in support of a New Drug Application supplement NDA 205552 S-036 for ibrutinib proposed as treatment of adult and pediatric patients ages one year and older with chronic graft versus host disease, after failure of one or more lines of systemic therapy. The Applicant (Pharmacyclics LLC, an AbbVie Company) was inspected for oversight of Study PCYC-1146-IM.

Based on the inspection, Pharmacyclics LLC's oversight of the above study appeared adequate. The study data submitted to the Agency for assessment are considered acceptable in support of the proposed indication.

4.2. Product Quality

NDA 217003 was submitted to provide the CMC information for the oral suspension. CMC recommendation is approval of the oral suspension. No new CMC information was provided for capsules or tablets.

Pharmacology/Toxicology review:
The safety assessment regarding the ibrutinib oral suspension drug product has been evaluated from the pharmacology/toxicology perspective in a separate review under NDA 217003. The review includes the determination of the safety of the proposed specifications for impurities and excipients in the drug product. In particular, the safety of the levels of benzyl alcohol (b) (4) were assessed with regard to the maximum daily exposure (MDE) allowed in the pediatric population. Additionally, the acceptability of the levels of extractables and leachables from the container closure system [cap/cap liner, oral administration syringes, and press in bottle adapter (PIBA)] were evaluated based on the acceptable daily intake (ADI). The Agency concludes that the proposed specifications and MDE/ADI values are acceptable.

Clinical review:
In regard to the use of benzyl alcohol in the suspension, the FDA agrees that given that the amount of benzyl alcohol in the proposed oral solution is small, the oral route of administration, and that it will be rapidly metabolized, it is unlikely that benzyl alcohol will cause harm to a neonate, fetus in pregnancy, the child who is breastfeeding, or the female or male of reproductive potential.

4.3. Clinical Microbiology

NDA 217003 was submitted in support of the pediatric patients with cGVHD for ibrutinib oral suspension 70 mg/mL. The oral suspension formulation will allow pediatric cGVHD patients to receive the recommended pediatric equivalent dose of 240 mg/m^2 which is based on body surface area. The oral suspension utilizes the same ibrutinib drug substance that is used in the manufacture of the approved Imbruvica. The applicant provided results of microbiology testing of 10 batches, that showed < (b) (4) cfu/g of aerobic microbial count or yeast and molds. Also, testing for *Burkholderia cepacia complex* (in 6 batches) and *E.coli* in 10 batches was negative. The microbiology data provided by the Applicant are acceptable. See the CMC review of NDA 217003 for additional information.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5. Nonclinical Pharmacology/Toxicology

The Applicant's Position:

As communicated to and agreed with FDA in the pre-sNDA interactions (Table 4), no new data are provided on the nonclinical pharmacology/toxicology profile of ibrutinib in the current submission. Thus, the applicant has not provided any information for Section 5 of the Assessment Aid.

The FDA's Assessment:

The Agency concurs with the Applicant's statement that no new pharmacology/toxicology data for ibrutinib were submitted to the current supplement. A separate Pharmacology/Toxicology review for the safety assessment of the ibrutinib oral suspension drug product has been documented under NDA 217003.

6. Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

The Applicant submitted an efficacy supplement to support approval of the following new indication for ibrutinib: treatment of pediatric patients 1 year of age and older with cGVHD.

Efficacy and safety data to support this supplement application were derived from Studies PCYC-1146-IM and PCYC-1140-IM (see Section 7 for more details on these clinical trials). The proposed recommended dosage of ibrutinib is 240 mg/m2 once daily for patients with cGVHD 1 to < 12 years.

This clinical pharmacology review focused on the acceptability of the proposed dosing regimen and the age-appropriate suspension formulation. Population PK (PPK) analysis and exposure-response (E-R) analyses for safety and efficacy were included. The E-R for safety analysis showed that there was no apparent E-R relationship between ibrutinib exposure and ORR in pediatric patients with cGVHD. Similarly, there were no clear E-R relationship for the adverse events of specific clinical interests (AESIs) including atrial fibrillation (any grade), hemorrhage (any grade or major), liver function test abnormalities (Grade ≥3), and neutropenia (Grade ≥3).

The results from relative bioavailability study (Study PCI-32765CLL1015) showed that the suspension formulation (70 mg/mL) was bioequivalent to the capsule formulation based on the geometric mean ratio of AUClast (108.5%, 90% CI: 94.2, 124.9). Further, the magnitude of food-effect on ibrutinib exposure (Cmax and AUClast) was comparable for the suspension formulation and the approved capsule formulation.

The proposed recommended dosage of 240 mg/m2 QD in pediatric patients with cGVHD is acceptable based primarily on Study PCYC-1146-IM results (ORR following 240 mg/m2 QD ranged from 69 to 78% in pediatric patients aged >1 to 5 years, ≥6 to 12 years, and ≥12 to 17 years), which was comparable to the ORR observed in adult patients (ORR = 67%; 95% CI: 51, 80). Similarly, the safety profile did not show a clinically meaningful difference compared to the adult cGVHD patients (Study PCYC-1129-CA.

The Applicant's proposed dose-modification for cGVHD patients with hepatic impairment identified using total bilirubin values, and in the presence of concomitant CYP3A4 inhibitor in the revised USPI is also acceptable.

RECOMMENDATION
The Office of Clinical Pharmacology has reviewed the information and data submitted in this efficacy supplement. This efficacy supplement is approvable from a clinical pharmacology perspective.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

The clinical pharmacology of ibrutinib has been well characterized and summarized in previous submissions.

This Summary of Clinical Pharmacology supports a supplemental new drug application for ibrutinib to extend the existing cGVHD indication to pediatric patients ≥ 1 years of age. The dosing recommendation is based primarily on data from Study PCYC-1146-IM (hereafter referred to as Study 1146) in patients with cGVHD, which focused on a population ≥ 1 to < 22 years of age with cGVHD and showed that treatment with ibrutinib results in strong efficacy outcomes (Summary of Clinical Efficacy Module 2, Section 2.7.3 [R&D/21/0873]).

The pharmacokinetics (PK) and pharmacodynamic properties of ibrutinib were studied in Study 1146 and in a Phase 3 study in pediatric (≥ 12 years) and adult subjects with cGVHD. Data from these studies were included in a population PK analysis of integrated data from pediatric subjects and in an exposure-response (ER) analysis of efficacy and safety endpoints in the same pediatric population.

In addition, a Phase 1 study (PCI-32765CLL1015, hereafter named CLL1015) was conducted in healthy subjects to investigate the relative bioavailability of age-appropriate oral formulations of ibrutinib that were developed for the treatment of patients ≥ 1 to < 12 years of age.

The FDA's Assessment:
FDA agrees with the Applicant's position. Regarding the Applicant's PK and PD properties in the pediatric patient population, the Applicant's population PK report showed a trend for lower systemic exposures in pediatric patients aged < 12 years compared to the adolescent patients (≥ 12 years) and adult patients with cGVHD (See 19.4 for a detailed review of the Applicant's population PK report). Nevertheless, based on the absence of E-R relationships for safety and efficacy, and the comparable efficacy observed in patients < 6 years (73% ORR; 95% CI = 39, 94)

and patients, ≥6 years to <12 years old (69% ORR; 95% CI = 41, 89), the observed lower exposure in pediatric patients does not appear to have a clinical impact. A positive trend for TEAE leading to dose-reduction was observed in pediatric patients with increasing age; however, the rate of dose-reduction was lower in pediatric patients with cGVHD when compared to the adult patients (Table 5).

Table 5. PK parameters, Efficacy, and Safety of ibrutinib at steady-state in pediatric patients (Studies PCYC-1140-IM and PCYC-1146-IM) and adult patients (Study PCYC-1129-CA) with cGVHD

	Pediatric studies Study 1140-IM and Study 1146-IM			**Adult Study 1129-CA[a]**
Age (years)	<6 yrs	≥6 to <12 yrs	≥12 to <17 yrs	19 – 74 yrs
No. of patients	8	16	22	42
PK, mean (CV%)[b]: AUC_{ss}, (ng*h/mL)	315 (75%)	596 (64%)	1199 (56%)	1159 (50%)
Efficacy: ORR, % [95% CI]	73 [39, 94]	69 [41, 89]	78 [56, 93]	67 [51, 80]
Safety (N)	**11**	**16**	**23**	**42**
Grade ≥3 TEAE	64%	63%	65%	74%
Grade ≥3 serious TEAEs	55%	63%	65%	45%
Any grade hemorrhage/ bleeding	27%	31%	44%	26%
Any grade liver function test abnormalities	0%	0%	0%	2%
TEAE leading to dose reduction	0%	6%	30%	31%
TEAE leading to drug discontinuation	27%	13%	13%	38%

Source: Recreated from Applicant's submission. [a] Adult study data reported from Study report PCYC-1129-CA; [b] model predicted exposure without moderate/strong CYP3A inhibitors.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1 General Dosing

The Applicant's Position:

An age-appropriate oral suspension formulation of ibrutinib was developed for the treatment of patients ≥ 1 to <12 years of age, as summarized in the Summary of Biopharmaceutics Studies Module 2, Section 2.7.1. The existing capsule and tablet formulations of ibrutinib used for the treatment of adult patients are also intended for the treatment of patients ≥ 12 years of age.

Results from Study 1146, which focused on subjects ≥ 1 to < 22 years of age with cGVHD, showed that treatment with ibrutinib results in strong efficacy outcomes (overall response rate [ORR]). Pediatric subjects ≥ 1 to < 12 years of age were treated with ibrutinib at a dose of

240 mg/m^2 once daily (equivalent to the approved adult flat dose of 420 mg once daily) and subjects ≥ 12 to < 22 years of age were treated with the adult dose of 420 mg once daily (Summary of Clinical Pharmacology Module 2, Section 2.7.2.3.5.4). In Study 1146, 13 subjects from Part A and 15 subjects from Part B received the dose of 240 mg/m^2 once daily. The suspension was administered to 25 subjects < 12 years of age and 3 subjects aged 12 years and older.

Irrespective of the ibrutinib formulation (suspension, capsules, or tablets), a population PK analysis was conducted to characterize the PK of ibrutinib based on the integrated population of subjects ≥ 1 to < 22 years of age with cGVHD in Studies 1146 and 1140, and to compare the results with the PK observed in adult subjects with cGVHD in Study 1129. The integrated data from Studies 1146, 1140, and 1129 were used for the population PK analysis. The exposure-response (ER) relationships for efficacy and safety endpoints were also explored in the integrated population of subjects ≥ 1 to < 22 years of age from Studies 1146 and 1140.

No trends were observed in pediatric covariate (age, weight, and BSA) effects on model parameters that would require a dose adjustment in pediatric subjects. No covariates were identified that contributed to the observed PK variability. Based on simulations of the recommended pediatric dosing regimens of 240 mg/m^2 once daily in subjects ≥ 1 to < 12 years of age, and of 420 mg once daily in subjects ≥ 12 to < 22 years of age, exposures across the age ranges were within the target exposure range in adult subjects with cGVHD in Study 1129: geometric mean: 760 ng*h/mL (95% prediction interval: lower 2.5%, 134 ng*h/mL; upper 97.5%, 4300 ng*h/mL), with younger subjects having exposures within the lower range of the target exposure range. The exposure-efficacy analysis showed that the majority of pediatric subjects had a positive treatment outcome across the exposure range, suggesting that an efficacy plateau was reached in this population. No significant trends were observed in the ER relationships for clinical efficacy and safety endpoints. In logistic regression analyses for safety, no significant association occurred between any of the safety endpoints considered (atrial fibrillation [any grade], hemorrhage [any grade or major], liver function test abnormalities [Grade ≥ 3], and neutropenia [Grade ≥ 3]) and the exposure of ibrutinib ($AUC_{\tau,ss}$). This is consistent with results from Study 1129 in adult subjects, which demonstrated high ORR (67%) along with an acceptable safety profile in subjects with cGVHD who were treated with ibrutinib at a daily dose of 420 mg.

The mean BTK occupancy measured from evaluable subjects in Study 1146 ranged from 95.1% to 99.6%. This is consistent with the BTK occupancy observed in Study 1129, where mean BTK occupancy for ibrutinib at this dose level was 93.2%.

The ibrutinib doses of 240 mg/m^2 once daily for subjects ≥ 1 to < 12 years of age and 420 mg once daily for subjects ≥ 12 to < 22 years of age demonstrated a favorable benefit-risk profile in pediatric subjects in Study 1146 and were therefore chosen as the appropriate doses for the treatment of pediatric patients with cGVHD.

The FDA's Assessment:
FDA agrees with the Applicant's position that the adolescent and young adult patients treated with either suspension formulation or oral capsules of ibrutinib (Studies 1146 and 1140) showed comparable exposures to those in adult patients (Study 1129) with cGVHD, and the younger pediatric patients showed exposure in the lower range of ibrutinib exposure in the adult population. It should be noted that the observed steady-state AUC and C_{max} of ibrutinib in adult patients with cGVHD (Study 1129) were 1159 ± 583 ng*h/mL and 203 ng*h/mL (Source: Table 10 in Study report of Trial PCYC-1129-CA).

The E-R relationships for efficacy and most safety endpoints did not show any significant trends. However, as noted earlier, there was a positive trend for TEAEs leading to dose-reductions in the pediatric patients administered ibrutinib at 240 mg/m^2 QD with different age groups. As discussed in section 19.4.1, the Applicant's PopPK report appears adequate to describe the concentration-time profiles following oral administration of ibrutinib. In addition, the covariate analysis further confirmed that no dose adjustment would be required based on age, sex, body weight or BSA. Overall, FDA agrees with the Applicant's position that the recommended clinical doses for the pediatric patients with cGVHD are supported by available data.

6.2.2.2 Therapeutic Individualization

The Applicant's Position:

No change is proposed to the currently approved US Prescribing Information (USPI) based on intrinsic or extrinsic factors (IMBRUVICA® USPI, 2021).

The FDA's Assessment:
FDA does not agree with the Applicant's position above. The dose of ibrutinib for patients with cGVHD with hepatic impairment (defined by total bilirubin level >1.5 to 3 x upper limit of normal [ULN] [unless of non-hepatic origin or due to Gilbert's syndrome]) will be lowered by 67% (i.e., dose-modification from 420 mg or 240 mg/m^2 starting dose to 140 mg or 80 mg/m^2 for patients ≥ 12 years and 1 to < 12 years, respectively). The use of ibrutinib in adult and

pediatric patients with cGVHD and total bilirubin level > 3 x ULN (unless of non-hepatic origin or due to Gilbert's syndrome) will be avoided. The proposed dose-modification in the patients with hepatic impairment is based on the 3-fold higher exposure of ibrutinib observed at 420 mg QD in patients with moderate hepatic impairment defined by the NCI-ODWG criteria (See discussion in Section 6.3.2.3).

In addition, the dose of ibrutinib will be lowered by 33% (i.e., from 240 mg/m^2 to 160 mg/m^2) when administered with voriconazole for suspension at 9 mg/kg (up to 350 mg) twice daily dose and by 67% (i.e., from 240 mg/m^2 to 80 mg/m^2) when administered with posaconazole. This magnitude of dose-modification is proposed based on the target dose and exposure of voriconazole or posaconazole in the pediatric population. See additional discussion in Section 6.3.2.4 for details.

6.2.2.3 Outstanding Issues

The Applicant's Position:

None

The FDA's Assessment:
In general, FDA agrees that there are no outstanding issues regarding the approvability of the recommended dose of ibrutinib at 240 mg/m^2 QD (equivalent to 420 mg QD adult dose) in pediatric patients with cGVHD.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:

Population Pharmacokinetic (PK) Analysis

- The observed concentration-time data for ibrutinib in pediatric subjects and young adults (≥1 to < 22 years of age) with cGVHD were adequately described by a 2-compartment PK model with sequential zero- and first-order absorption and first-order elimination.
- No trends were observed in the effects of pediatric covariates (age, weight, and body surface area [BSA]) on model parameters in pediatric subjects. No covariates were identified that contributed to the observed pharmacokinetic (PK) variability. Age was not a contributing covariate to the observed PK variability, as shown in previous analyses, for the comparison between adolescents and adults.
- Based on simulations of the recommended dosing regimens of 240 mg/m^2 once daily in subjects ≥ 1 to < 12 years of age and 420 mg once daily in subjects ≥ 12 to < 22 years of age,

exposures across the age groups were within the target exposure range established in adult subjects with cGVHD (geometric mean [95% PI]: 760 [134 to 4300] ng*h/mL).

Exposure-response Analysis

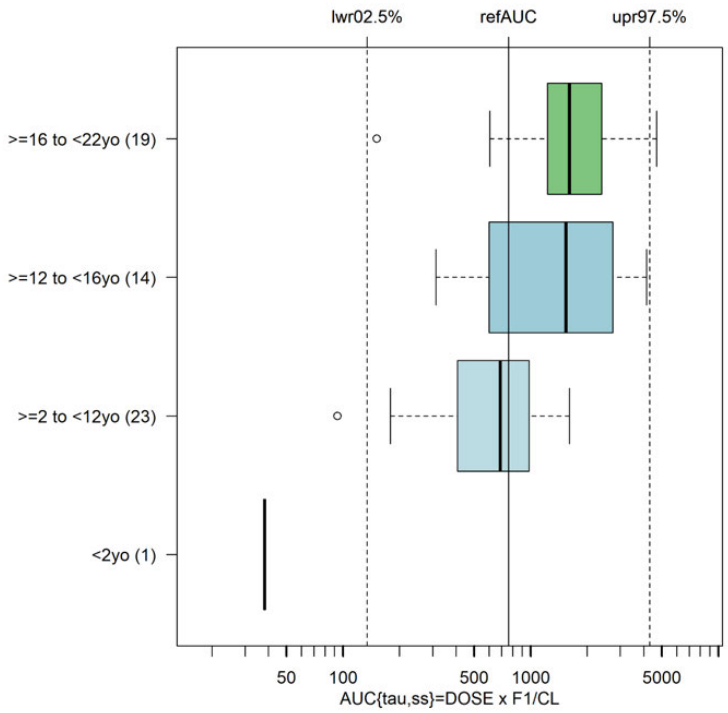
Exposure-efficacy Analysis

- In the exposure-response analysis of subjects ≥ 1 to < 22 years of age with cGVHD, the exposure-efficacy analysis showed that the majority of pediatric subjects had a positive treatment outcome (ORR) across the exposure range, suggesting that an efficacy plateau was reached for this population.
- Even though the population PK model suggests that the 240 mg/m^2 dosing in subjects ≥ 1 to < 12 years of age may have resulted in exposures in the lower range relative to adults, there is no indication of a corresponding unfavorable effect on efficacy outcome.

Exposure-safety Analysis

- In the ER analysis of subjects ≥ 1 to < 22 years of age with cGVHD, the exposure-safety analysis showed no significant relationship between the systemic exposure to ibrutinib (AUCτ,ss) and the selected safety endpoints (atrial fibrillation [any grade], hemorrhage [any grade or major], liver function test abnormalities [Grade ≥3], and neutropenia [Grade ≥3]) at the doses evaluated in pediatric subjects.
- This lack of a significant relationship was also observed for the adult population with cGVHD.

Figure 1 Applicant – Model-predicted Steady-state Exposures ($AUC_{\tau,ss}$) of the Prescribed Ibrutinib Dose



The FDA's Assessment:
Applicant's PPK and E-R for efficacy and safety analysis results appears acceptable.

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

Yes. Results from Study 1146, which focused on subjects ≥ 1 to < 22 years of age with cGVHD, showed that treatment with ibrutinib results in strong efficacy outcomes (ORR). Pediatric subjects ≥ 1 to < 12 years of age were treated with ibrutinib at a dose of 240 mg/m2 once daily (equivalent to the approved adult flat dose of 420 mg once daily) and subjects ≥ 12 to < 22 years of age were treated with the adult dose of 420 mg once daily (Summary of Clinical Pharmacology Module 2, Section 2.7.2.3.5.4). In Study 1146, 13 subjects from Part A and 15 subjects from Part B received the dose of 240 mg/m2 once daily. The suspension was administered to 25 subjects < 12 years of age and 3 subjects aged 12 years and older.

In the exposure-response analysis of subjects ≥ 1 to < 22 years of age with cGVHD, the exposure efficacy analysis showed that the majority of pediatric subjects had a positive treatment outcome (ORR) across the exposure range, suggesting that an efficacy plateau was reached for this population.

Results from Study 1129 in adult subjects demonstrated high ORR (67%) along with an acceptable safety profile in subjects with cGVHD who were treated with ibrutinib at a daily dose of 420 mg. In the same study, the mean BTK occupancy for ibrutinib at this dose level was 93.2%. The mean BTK occupancy measured from evaluable subjects in Study 1146 ranged from 95.1% to 99.6%, which was similar to the BTK occupancy observed in Study 1129.

The FDA's Assessment:

FDA agrees with the Applicant's position on the supportive evidence of the effectiveness of ibrutinib in pediatric patients ≤ 12 years with cGVHD at the proposed dosage of 240 mg/m^2 QD. E-R analyses for efficacy showed that there was no apparent E-R relationship between ibrutinib exposure and ORR in pediatric patients with cGVHD (age 2 to less than 18 years). The high BTK occupancy observed in both adult and pediatric patients with cGVHD suggested that the recommended dose of ibrutinib was able to nearly saturate the target.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's Position:

Yes, the proposed dosing regimen is appropriate for the patient population for which the indication is being sought. Specifically, the proposed dosing regimen for pediatric subjects with cGVHD age 1 to < 12 years is 240 mg/m^2 PO daily and for patients age 12 years and older, the proposed dosing regimen is 420 mg PO daily.

The FDA's Assessment:
FDA agrees with the Applicant's position.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The Applicant's Position:

No change is proposed to the currently approved USPI based on intrinsic patient factors (IMBRUVICA® USPI, 2021).

The FDA's Assessment:
The FDA does not agree with the Applicant's position. The currently approved USPI only provides recommendations for dose-modification for adult patients with hematologic malignancies based on HI using Child-Pugh scores. The dose-modification in the patients with cGVHD with hepatic impairment will be based on total bilirubin values and the HI designation per NCI-ODWG criteria.

Patients with cGVHD commonly experience hepatic dysfunction. However, ibrutinib-induced hepatotoxicity was not noted at the therapeutic doses. The pediatric studies (Studies 1146 and 1140) supporting the current submission allowed for dose-modification for HI based on total bilirubin values with no dose-modification indicated for total bilirubin elevation due to a non-hepatic cause (i.e., cGVHD-related or Gilbert's Syndrome). As shown in Table 6, the exposure (AUC_{ss} and C_{max}) of ibrutinib at different dose-levels (140, 280, and 420 mg) was similar for patients with mild HI and normal hepatic function. The impact of moderate HI on ibrutinib exposure was inconclusive given the limited clinical data. Nevertheless, at the recommended dose of 420 mg QD in patients ≥ 12 years of age (n = 1), there was ~3.3-fold increase in AUC_{ss} and ~3.4-fold increase in C_{max} in the patient with moderate HI compared to normal hepatic function.

Table 6. PK of ibrutinib by dose and hepatic function per NCI-ODWG criteria in adult and adolescent patients with cGVHD (Study 1146 and Study 1140)

PK parameter	140 mg			280 mg			420 mg		
	Normal	Mild	Moderate	Normal	Mild	Moderate	Normal	Mild	Moderate
N	10	3	3	23	18	2	64	37	1
AUC_{ss} (h*ng/mL)									
Geo. Mean	681.4	515.1	591.7	1297.7	1072.2	530.1	978.4	1073.1	3211.1
CV%	61.3	24.4	45.2	67.3	65.7	28.5	73.3	66.5	-
C_{max} (h*ng/mL)									
Geo. Mean	125.5	57	89.5	202.6	172.8	60.28	162.8	174.1	553.3
CV%	62.7	24	54.3	65.5	61.1	9.3	82.2	68.2	-

Source: Applicant's response to information request dated 15 June 2022

Similarly, the observed efficacy in patients with mild HI and normal hepatic function was numerically lower with overlapping 95% CI for patients enrolled Studies 1146 and 1129 with young adult and adult, respectively (Table 7). There were limited number of patients with moderate HI to interpret the impact of moderate HI on efficacy.

Table 7. Overall Response Rate by Hepatic Function per NCI-ODWG criteria in Ibrutinib Treated Patients ≥ 12 Years Old (Study 1146 and Study 1129)

	Study 1146			Study 1129		
	Normal	Mild HI	Moderate HI	Normal	Mild HI	Moderate HI
No of patients	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
	17	**13**	**2**	**29**	**13**	**0**
ORR (CR+PR) [95% CI]	15 (88.2) [63.6, 98.5]	10 (76.9) [46.2, 95]	2 (100) [15.8, 100]	21 (72.4) [52.8, 87.3]	8 (61.5) [31.6, 86.1]	NA
CR	1 (5.9)	0	0	11 (37.9)	2 (15.4)	NA
PR	14 (82.4)	10 (76.9)	2 (100)	20 (34.5)	6 (46.2)	NA

Source: Applicant's response to information request dated 15 June 2022

Overall, the recommended dose-reduction of ibrutinib by 67% (i.e., 420 mg to 140 mg for cGVHD patients ≥ 12 years of age and 240 mg/m^2 to 80 mg/m^2 for pediatric patients aged 1 to < 12 years) with total bilirubin level > 1.5 to 3 x ULN (unless of non-hepatic origin or due to Gilbert's syndrome) is acceptable. Further, ibrutinib administration in patients with total bilirubin level > 3 X ULN (unless of non-hepatic origin or due to Gilbert's syndrome) will be avoided.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant's Position:

No change is proposed to the currently approved USPI based on food-drug or drug-drug interactions (IMBRUVICA® USPI, 2021).

The FDA's Assessment:

Food Effect

FDA agrees with the Applicant's position. The observed magnitude of food-effect on ibrutinib exposure (C_{max} and AUC_{last}) for capsules and suspension was similar (Table 8). Therefore, the Applicant's approach to not change the proposed administration based on food-drug interactions is acceptable.

Table 8. The Relative Bioavailability of Ibrutinib for Suspension Formulation Under Fasting and Fed Conditions Compared to Capsule Formulation.

Formulation	PK Parameter	Fed/Fasted	Geo Mean	Ratio (%)	90% CI
Suspension [a] (560 mg)	C_{max} (ng/mL)	Fasted	19.04		
		Fed	74.48	391.3	(302.17 - 506.60)
	AUC_{last} (ng*h/mL)	Fasted	236.17		
		Fed	427.81	181.1	(155.56 - 210.94)
Capsules [a] (140 mg X 4)	C_{max} (ng/mL)	Fasted	29.57		
	AUC_{last} (ng*h/mL)	Fasted	217.73		
Capsules [b] (420 mg)	C_{max} (ng/mL)	Fasted	32.67		
		Fed	125.82	385.2	(332.23 - 446.51)
	AUC_{last} (ng*h/mL)	Fasted	260.17		
		Fed	462.42	177.7	(161.70 – 195.37)

a Source: Applicant's study report PCI-32765CLL1015 Tables TPKCONC01 and TPKCONC03
b Data obtained from adult approval review (NDA 205552)

Drug-Drug Interaction

FDA does not agree with the Applicant that no change is proposed to the currently approved USPI based on drug-drug interaction. In general, it is reasonable to use similar dose-reductions for pediatric patients and adult patients. However, the dose-adjustment for ibrutinib in the presence of Posaconazole or voriconazole should be evaluated according to the pediatric formulation and dosing regimens.

Both voriconazole and posaconazole are available in different formulations and routes of administration (oral or IV). Limited pediatric recommended dosage regimens are available for posaconazole (6 mg/kg up to a maximum of 300 mg QD maintenance dose via IV or 300 mg delayed-release oral suspension/tablet), which show similar exposures to that with 300 mg IV adult dose. Therefore, the proposed ibrutinib dose-modification for pediatric patients who require posaconazole follows the adult recommendations with concomitant 300 mg IV dosage (i.e., 67% dose-reduction). The maximum labeled oral dose of voriconazole in pediatric patients is 350 mg BID (~9 mg/kg maintenance dose via oral suspension/tablets), which is equivalent to 200 mg BID adult oral dosage. However, the IV doses of voriconazole (8 mg/kg BID) result in higher exposure as compared to the oral doses. Because voriconazole at adult doses > 200 mg BID acts as a strong CYP3A4 inhibitor and the dose-modification instruction for strong CYP3A4

(i.e., avoid concomitant use of ibrutinib) is applied, the dose modification for pediatric patients who are on concomitant medications with voriconazole should be adjusted based on voriconazole dose.

FDA recommended that the proposed USPI should clearly indicate the voriconazole dosage of 9 mg/kg BID via oral administration in pediatric patients to be consistent with the adult dose-modification for concomitant administration of voriconazole at 200 mg BID via oral administration.

7. Sources of Clinical Data

7.1. Table of Clinical Studies

The Applicant's Position

The current application includes efficacy data on ibrutinib in pediatric patients and young adults ≥ 1 to < 22 years of age with cGVHD from the following studies (Table 9):

- iMAGINE (PCYC-1146-IM): "Phase 1/2 dose finding, safety and efficacy study of ibrutinib in pediatric subjects with chronic graft versus host disease (cGVHD)." This study enrolled subjects who were ≥ 1 to < 22 years of age (59 ibrutinib-treated subjects age ≥ 1 to < 22 years, including 56 subjects who were ≥ 1 to < 18 years of age).
- iNTEGRATE (PCYC-1140-IM): "A randomized, double-blind, Phase 3 study of ibrutinib in combination with corticosteroids versus placebo in combination corticosteroids in subjects with new onset chronic graft versus host disease (cGVHD)." This study enrolled adult and adolescent subjects who were ≥ 12 years of age, including 94 ibrutinib-treated subjects (3 of whom were < 22 years of age and 2 of whom were < 18 years of age), and 96 placebo-treated subjects.

Efficacy and safety results from pooled analyses in the pediatric population (62 subjects ≥ 1 to < 22 years of age) from Studies 1146 and 1140 are supported by data generated in 131 ibrutinib-treated adult subjects from Study 1140 and Study 1129, the latter being the study supporting the current cGVHD indication in the USPI (IMBRUVICA (ibrutinib) [prescribing information] 2020) which is based on similarity of disease, treatment effects, and exposure-response relationships.

- PCYC-1129-CA: "A multicenter, open-label, Phase 1b/2 study of ibrutinib in steroid dependent or refractory chronic graft versus host disease". A total of 42 ibrutinib-treated subjects were included in the all-treated population , 2 of whom were < 22 years of age.

Safety data from B-cell NHL Study LYM3003 are presented with pooled data for 1,476 subjects from 10 pivotal studies in B-cell malignancies (the "B-cell malignancy label pool"), representing the approved indications of CLL/SLL, MCL, WM, and MZL. This information will be used to support Section 8.4 (Pediatric Use) in the USPI.

- 54179060LYM3003: "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". This study met the statistical boundary for futility; as a result, the Sponsor's inclusion of Study LYM3003 in the application is solely intended to provide information on safety and clinical pharmacology of ibrutinib in combination with RICE (i.e., rituximab, ifosamide, carboplatin, etoposide, and dexamethasone) or RVICI (i.e., rituximab, vincristine, ifosamide, carboplatin, idarubicin, and dexamethasone) chemoimmunotherapy in pediatric patients with mature B-cell NHL.

Data from Study 1146 will also support the use of an age-appropriate dosage form (i.e., a 70 mg/mL, ready to-use, multi-dose, oral suspension) developed for use in pediatric patients. Data supporting the development of the suspension formulation are provided in a separate application NDA 217003.

Table 9 Applicant – Listing of Clinical Trials Relevant to this sNDA

Trial Identity	NCT no.	Trial Design	Regimen/schedule/ route	Study Endpoints	Treatment Duration/ Follow-up	No. of subjects enrolled	Study Population	No. of Centers and Countries
Pivotal Controlled Trials Contributing Efficacy and Safety Data								
iMAGINE (PCYC-1146-IM)	NCT03790332	Open-label, multicenter, global, Phase 1/2, dose-finding, safety, and efficacy	Subjects ≥ 1 to < 12 yrs of age: starting dose ibrutinib 120 mg/m^2 PO QD for 14 days, then 240 mg/m^2 PO QD until RPED was determined. Subjects ≥ 12 yrs of age: adult fixed dose (420 mg PO QD) in Part B of the study. Formulations available (oral): 140 mg tablet, 70 mg capsule, and 70 mg/mL suspension. Prednisone was given orally at a starting dose of 1.0 mg/kg/day and tapered as tolerated over a target of 6 months (TN subjects only).	Part A: RPED of ibrutinib based on PK (AUC) and safety data, PD (BTK occupancy), safety and efficacy as for Part B; Part B: PK (AUC), safety, ORR, DOR, ORR 24 wks, ORR 48 wks, RR 24 wks, sustained response 20 wks, OS, growth & development, immune reconstitution.	Until cGVHD progression, initiation of another systemic treatment for cGVHD, progression or relapse of the underlying malignancy, or unacceptable toxicity.	59 (12 TN; 47 R/R);	Part A: subjects ≥ 1 to < 12 yrs of age (including at least 3 subjects aged 1 to < 6 years) with moderate or severe cGVHD after failure of 1 or more lines of systemic therapy (R/R). Part B: ≥1 to < 22 yrs of age with moderate or severe cGVHD after failure of 1 or more lines of systemic therapy (R/R) or with newly diagnosed moderate or severe cGVHD (TN).	29 sites in 12 countries

Trial Identity	NCT no.	Trial Design	Regimen/schedule/ route	Study Endpoints	Treatment Duration/ Follow-up	No. of subjects enrolled	Study Population	No. of Centers and Countries
iNTEGRATE (PCYC-1140-IM)	NCT02959944	Phase 3, multicenter, global, randomized, double-blind, placebo-controlled, safety and efficacy	Arm A (Ibr + Pred): ibrutinib 420 mg, PO QD until cGVHD progression, the initiation of another systemic treatment for cGVHD, or unacceptable toxicity, plus prednisone (1 mg/kg/day until successfully tapered) Formulations available (oral): ibrutinib 70 mg or 140 mg hard gelatin capsule Arm B (Pbo + Pred): Placebo hard gelatin capsules PO QD; Prednisolone oral tablet: starting dose of 1 mg/kg/day PO or 0.5 mg/kg/day PO continuously until unacceptable toxicity or until the subject was successfully tapered from the prednisone.	RR at 48 and 24 wks, DOR, proportion of subjects obtaining a steroid dose level less than 0.15 mg/kg/day at 24 weeks, time to withdrawal of all immunosupressants (except Ibr/Pbo), OS, Lee cGVHD Symptom Scale improvement, safety & tolerability, steroid-related morbidities	Until cGVHD progression, progression of underlying malignancy, initiation of another systemic treatment for cGVHD, or unacceptable toxicity	Arm A: Enrolled: 95 Arm B: Enrolled: 98	Subjects aged ≥ 12 years with treatment-naïve, moderate or severe cGVHD as defined by the 2014 NIH Consensus Development Project Criteria, with a history of allogeneic hematopoietic cell transplant, a need for systemic treatment with corticosteroids for cGVHD, and no previous systemic treatment for cGVHD (including ECP)	66 sites in 15 countries

Trial Identity	NCT no.	Trial Design	Regimen/schedule/ route	Study Endpoints	Treatment Duration/ Follow-up	No. of subjects enrolled	Study Population	No. of Centers and Countries
Supportive Study Contributing Efficacy Data Only								
PCYC-1129-CA	NCT02195869	Single-arm, open-label, conducted in 2 phases; Phase 1 included a modified 3 + 3 + 3 design to determine the RP2D	Phase 1b: ibrutinib capsules 420/mg PO QD (potential dose reduction[s] to 280 mg and 140 mg PO QD if DLTs detected). Phase 2: ibrutinib capsules administered at RP2D (420/mg PO QD) until PD, unacceptable toxicity, recurrence of underlying malignancy, withdrawal of consent, closure of the Phase 2 part of the study, or subject's cGVHD no longer required treatment.	DLTs, BORR, rate of sustained response for ≥ 5 months, DOR, corticosteroid requirement changes over time, rate of improvement in Lee cGVHD Symptom Scale, safety, FFS, photographic changes in skin and mucocutaneous manifestations, PK, PD, biomarkers.	Until PD, unacceptable toxicity, recurrence of underlying malignancy, withdrawal of consent for treatment by subject, or closure of the Phase 2 part of the study	45	Subjects with steroid-dependent or refractory cGVHD; with ≤ 3 prior therapeutic regimens for cGVHD; with either > 25% BSA NIH-defined criteria "erythematous rash" or > 4 total mouth score by NIH-defined criteria. Key exclusion criteria included known or suspected active acute GVHD.	10 sites in the US
Supportive Study Contributing Safety Data Only								
54179060LYM3003	NCT02703272	Randomized, Open-label, Safety and Efficacy Study in 2 parts	-Part 1 (safety and PK run-in): Ibr up to a max dose of 440 mg/m^2/day + CIT -Part 2 (randomized 2:1 ratio): Treatment group A (daily dose of Ibr 329 mg/m^2 or 440 mg/m^2 [dose	Part 1: PK, PD, safety, tolerability, anti-tumor activity, biomarkers, acceptability, palatability Part 2: efficacy (EFS, ORR, tumor vol reduction, TTR, no.	Treatment Phase: Combination therapy: Ibr + CIT (RICE or RVICI) for 3 cycles[d] Post-treatment Phase:	Part 1 (subjects 1 to < 18 years of age), n = 21[a] Part 2 (subjects 1 to 30	Subjects with relapsed/refractory BL, BLL, B-AL, DLBCL, DLBCL not otherwise specified, PMBCL, or other pediatric mature B-cell NHL.	94 sites in 21 countries

Trial Identity	NCT no.	Trial Design	Regimen/schedule/ route	Study Endpoints	Treatment Duration/ Follow-up	No. of subjects enrolled	Study Population	No. of Centers and Countries
			selected from Part 1]) by age groups + CIT, or treatment group B (CIT only).	subjects with stem cell transplantation, DOR, OS), safety, tolerability, biomarkers, PD, PK, acceptability, palatability	Monotherapy Ibr for 3 cycles[e] Survival FU: Post-treatment Phase: survival FU until death, LTFU, consent withdrawal, or study end, whichever occurred first	years of age), n = 51[b]		

AUC = area under the concentration-time curve; B-AL = Burkitt leukemia; BL = Burkitt lymphoma; BLL = Burkitt-like lymphoma; BORR = best overall cGVHD response rate; BSA = body surface area; BTK = Bruton's tyrosine kinase; cGVHD = chronic graft vs. host disease; CIT = chemoimmunotherapy; CR = complete response, DLBCL = diffuse large B-cell lymphoma; DLT = dose-limiting toxicity; DOR = duration of response; ECP = extracorporeal photopheresis; EFS = event-free survival; FU = follow-up; Ibr = ibrutinib; FTFU = lost-to-follow-up; NHL = Non-Hodgkin's Lymphoma; NIH = National Institutes of Health; ORR = overall response rate; OS = overall survival; PD = progressive disease or pharmacodynamics; Pbo = placebo; PK = pharmacokinetics; PMBCL = primary mediastinal B-cell lymphoma; PO = by mouth; PR = partial response; Pred = prednisone; QD = once daily; RICE = rituximab, ifosfamide, carboplatin, etoposide, and dexamethasone; RPED = recommended pediatric equivalent dose; RP2D = recommended Phase 2 dose; RR = response rate; RVICI = rituximab, vincristine, idarubicin, carboplatin, ifosfamide, and dexamethasone; R/R = relapsed/refractory; TN = treatment-naïve; yrs = years; TTR = time to response

a. Safety analysis set.

b. ITT population; 1 subject did not receive study drug.

c. Or indication for transplantation, or until PD or unacceptable toxicity.

d. Only subjects with response of PR or better. 3 cycles or until PD, unacceptable toxicity, or until initiation of subsequent antilymphoma therapy or a conditioning regimen for stem cell transplantation

e. Source: Module 5.2

The FDA's Assessment:
There are three clinical trials for cGVHD treatment indication. They differ by age for eligibility and whether cGVHD at study baseline was treatment-naive or had failed prior therapy.

Table 10 shows a brief overview of the three clinical trials relevant to cGVHD.

Table 10. Clinical Trials Relevant to cGVHD

Trial Identity	Trial Design	Study Population
PCYC-1129-CA	Single-arm, open-label: Phase 1b to determine the RP2D; Phase 2 at RP2D	*Adults* with *steroid-dependent or refractory* cGVHD; with ≤ 3 prior therapeutic regimens for cGVHD
iNTEGRATE (PCYC-1140-IM)	Phase 3, multicenter, randomized, double-blind, placebo-controlled, safety and efficacy	*Age ≥ 12 years* with *treatment-naïve*, moderate or severe cGVHD, a need for systemic treatment with steroids
iMAGINE (PCYC-1146-IM)	Open-label, multicenter, global, Phase 1/2, dose-finding, safety, and efficacy	**Part A**: ≥ 1 to < 12 yrs of age with moderate or severe cGVHD after failure ≥1 lines of therapy (R/R). **Part B**: *≥1 to < 22 yrs* of age with moderate or severe cGVHD *(R/R) or* with newly diagnosed cGVHD *(TN)*

Study 1129 was the trial that supported the original approval, and updated data were submitted to support a proposed labeling change in Supplement 037. Studies 1140 and 1146 are new data in Supplement 036.

The data from Study iMAGINE (PCYC-1146-IM) was used for the review of efficacy. The Clinical Study Report of Study 1146 in the sNDA and the Assessment Aid prepared by the Applicant were received on 02/24/2022. The review of efficacy used the data from the original sNDA submission and the additional information in the Applicant's responses to Information Requests.

Analyses by the clinical reviewers were performed using JMP 15.2.1 and JMP 16.0 (SAS Institute, Inc., Cary, NC).

8. Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. iMAGINE (PCYC-1146-IM)

Trial Design

The Applicant's Description:

Study 1146 was an open-label, multicenter, international, Phase 1/2 dose finding, safety, and efficacy study of oral ibrutinib in pediatric subjects with moderate or severe cGVHD (Study 1146 Primary analysis CSR Appendix 1 Protocol Amendment 2). The study was divided into 2 parts (Part A and B) conducted in parallel.

Part A: dose finding and safety study for subjects who were ≥ 1 to < 12 years of age with moderate or severe cGVHD after failure of 1 or more lines of systemic therapy. Intra-subject dose escalation was conducted to determine the RPED based on pharmacokinetics (PK) and safety data. Subjects received oral ibrutinib once daily, starting with a dose of 120 mg/m^2 (equivalent to approximately 50% of the adult cGVHD dose calculated using mg/m^2). The RPED was the dose that achieved approximately the equivalent exposure to that seen in adult subjects with cGVHD treated with 420 mg of ibrutinib daily. Once the RPED was established for subjects ≥ 1 to < 12 years (240 mg/m^2 once daily), enrollment of these subjects was allowed in Part B of the study. Subjects participating in Part A continued to receive daily ibrutinib at their current tolerated dose until the RPED was determined, at which time it could be adjusted to the RPED dose. A Safety and Dosing Review Committee (SDRC) was established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in the study and to evaluate pharmacokinetic data to determine the RPED.

Part B: started in parallel with Part A and was a PK, safety, and efficacy study that initially enrolled adolescent subjects who were ≥ 12 to < 22 years of age with moderate or severe cGVHD who failed 1 or more lines of systemic therapy, or with newly diagnosed moderate or severe cGVHD. Based on similarity of the elimination pathways with adult subjects, the adolescent subjects received the adult fixed dose of ibrutinib 420 mg orally daily (adjusted for hepatic impairment or concomitant CYP3A inhibitor use). Following establishment of the RPED

in subjects from Part A of the study, enrollment of subjects in Part B included subjects in the overall range of ≥ 1 to < 22 years of age. Subjects with newly diagnosed moderate or severe cGVHD received ibrutinib in addition to corticosteroids (prednisone at a starting dose of 1.0 mg/kg/day, or, if contraindicated [eg, poorly controlled diabetes mellitus, major mood disturbances], as low as 0.5 mg/kg/day) as first line therapy for cGVHD.

Ibrutinib was administered continuously until cGVHD progression, the initiation of another systemic treatment for cGVHD, progression or relapse of the underlying malignancy, or unacceptable toxicity. Prednisone was given continuously until unacceptable toxicity or until the subject was successfully tapered from prednisone.

The FDA's Assessment:
Study 1146 is a single-arm Phase 1/2 dose-escalation, dose-expansion study in pediatric and young adult patients 1 to <22 years old.

Eligibility was open to patients with previously treated cGVHD and to patients with treatment-naïve (TN) cGVHD.

Study Endpoints

The Applicant's Description:

The primary endpoints were: in Part A, PK (AUC) to determine the RPED of ibrutinib for use in pediatric subjects (age ≥ 1 to < 12 years) with cGVHD. In Part B, PK (AUC) and safety (treatment-emergent AEs and laboratory abnormalities) of ibrutinib in pediatric subjects (age ≥ 1 and < 22 years) with cGVHD.

The secondary endpoints were: In Part A, Safety, including treatment-emergent AEs, laboratory abnormalities and other safety endpoints; Pharmacodynamics (BTK occupancy); for those subjects continuing therapy after dose escalation (Part A Continuation Cohort), secondary endpoints were the same as outlined under Part B. In Part B, overall Response Rate (ORR), duration of response (DOR), ORR at 24 weeks, ORR at 48 weeks, response rate at 24 weeks, sustained response rate for at least 20 weeks, overall survival (OS), growth and development, immune reconstitution.

The exploratory endpoints were: pharmacodynamics (BTK and IL-2 Inducible T-cell Kinase [ITK] occupancy), response rate at 48 weeks, change in quality of life, as assessed by the pediatric stem cell QL questionnaire (PedsQLTM Stem Cell Transplant Module), improvement in Lee cGVHD Symptom Scale in subjects ≥ 12 years at enrollment, improvement in modified Lee cGVHD Symptom Scale in subjects ≥ 12 years at enrollment, sustained response rate for at least 32 weeks, Event-Free Survival (EFS, defined as: absence of progressive cGVHD, relapse of underlying malignancy, new subsequent cGVHD systemic immunosuppressive therapy, and death due to any cause), and Failure-Free Survival (FFS, defined as: absence of relapse of underlying malignancy, new subsequent cGVHD systemic immunosuppressive therapy, and death).

The FDA's Assessment:

FDA assessment of efficacy will rely on ORR through the Week 25 visit. FDA will consider two definitions of duration of response: 1) time from response to progression, new systemic therapy, or death; and 2) time from response to new systemic therapy or death. The definitions used by the FDA reviewers are shown in Table 11.

Table 11. Definitions of Efficacy Endpoints in FDA's Analyses

Endpoint	Definition
Overall Response at any visit through Week 25 visit	Complete response (CR) or partial response (PR) according to the 2014 NIH Response Criteria (Lee et al 2015) without institution of new systemic therapies.
Complete Response (CR)	CR is defined as fulfilling the CR criteria for all organs according to the 2014 NIH Response Criteria.
Partial Response (PR)	PR is defined as fulfilling the PR criterion in at least one organ without fulfilling a progression criterion for any other organ according to the 2014 NIH Response Criteria
Source: FDA analysis.	

Please also refer to comments below in the section about Statistical Analysis Plan.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The Applicant's planned analyses, including endpoints and analysis methods as presented in the Applicant's statistical analysis plan, were finalized prior to data transfer.

No formal hypothesis testing was performed. For the analysis of ORR, sustained response, ORR by 24 and 48 weeks, and improvement in Lee cGVHD Symptom Scale (including the modified scale), the rates and the 95% CIs using Clopper-Pearson's exact method were calculated. Duration of response, OS, EFS, and FFS were estimated by using Kaplan-Meier methodology. Response rate at 24 and 48 weeks was calculated. Time to first response (TTFR) was summarized desctiptively. Growth and development and immune reconstitution were summarized descriptively. Change in Quality of Life Peds Scale data were summarized; for subjects between 8-12 years old, summary statistics and mean change from baseline over time were provided for each of the subscale score and the total score per assessments by both parents and subjects. The sparse concentration data of ibrutinib were to be analyzed using population PK approach.

Safety data were summarized by prior treatment status (TN vs. R/R) and total based on the safety population (Part A and Part B combined). Adverse events were coded in accordance with the Medical Dictionary for Regulatory Activities (MedDRA). Severity of AEs were graded by the investigator according to the NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03.

The primary analysis for PK, safety and efficacy occurred after all subjects have had the opportunity to complete 24 weeks of treatment. A final analysis (including long-term developmental and immune reconstitution data) will occur after all subjects (from Part A and Part B) have had the opportunity to complete 60 months of follow-up.

The FDA's Assessment:

As the efficacy analysis in Study 1146 was exploratory, it did not have a primary efficacy endpoint or hypothesis testing. The results are being used to extend the age range using extrapolation from the efficacy in adult patients rather than to support a new indication.

The primary efficacy analysis was specified to occur when all subjects completed 24 weeks of treatment.

The Applicant's planned analysis set included patients with at least one response assessment, but the FDA analysis used all treated patients.

The Applicant defined overall response (OR) as CR or PR by 2014 NIH criteria prior to relapse or first subsequent therapy for cGVHD, using investigator response assessment, and OR by the Week 25 visit is one of the prespecified endpoints.

FDA used OR prior to first subsequent systemic therapy by Week 25 and adjudicated all responses.

Protocol Amendments

The Applicant's Description:

There were 2 global amendments to the protocol and 1 country-specific amendment (Australia) (Study 1146 Primary Analysis CSR Table 1). Substantive changes in Amendment 1 (17 September 2018) included advising clinical research sites of dose level changes based on PK or safety findings, and (once the RPED was determined) advising on the appropriate Part B dose for subjects under 12 years of age; clarifying the posaconazole dosing considerations that required ibrutinib dose adjustment for subjects under 12 years of age; clarifying the rationale for dosing in subjects with hepatic dysfunction; revising eligibility criteria regarding hepatic function in the dose escalation (Part A) cohort, and providing futher detail on the action to be taken with ibrutinib dosing for multiple recurrences of elevated bilirubin.

Substantive Amendment 2 (16 January 2020) changes included restricting enrollment to specific age groups and/or cGVHD subsets and stipulating total enrollment would be driven by pediatric regulatory commitments; adding an exclusion criteria for subjects at risk for allergy or hypersensitivity reaction to the investigational drug, including benzyl alcohol; adding new details on the risk of cerebrovascular accidents in accordance with the current version of investigator's brochure; and adding an option for decreased intensity of follow-up for subjects with durable response who were no longer taking ibrutinib.
Amendment 2.1 (Australia only, 20 April 2021) allowed subjects previously enrolled in Study 1140 to roll over to Study 1146 Part B for late effects surveillance only (not receiving study drug).

The FDA's Assessment:
FDA agrees with the Applicant's statement about Protocol Amendments.

8.1.1.1 Study Results

Compliance with Good Clinical Practices

The Applicant's Position:

Study 1146 was conducted in accordance with the principles of the Declaration of Helsinki and in compliance with Good Clinical Practice. The study was registered with ClinicalTrials.gov (NCT03790332).

Conduct of the study largely occurred during the COVID-19 pandemic, which was declared by the World Health Organization (WHO) in January 2020. Study-specific guidance was prepared in alignment with current regulatory guidances and requirements to ensure the safety of study subjects, relevant clinical staff, and Sponsor/vendor personnel as well as the continuity of key study-conduct activities at the affected sites (Study 1146 Primary Analysis CSR Appendix 25).

The FDA's Assessment:
FDA agrees with the Applicant's statement.

Financial Disclosure

Per protocol, completed financial-disclosure forms were to be obtained from the principal investigator as well as sub-investigators for this study (Study 1146 Primary Analysis CSR Appendix 1 Section 12.12). Refer to Section 19.2 of this document and Module 1.3.4 for further information.

The FDA's Assessment:
FDA agrees with the Applicant's statement.

Patient Disposition

The Applicant's Position:

A total of 59 subjects were enrolled (12 TN and 47 R/R) and received study drug (ibrutinib) and comprised the safety population used for safety analyses and all treated population used for efficacy analyses (Study 1146 Primary Analysis CSR Table 14.1.1). Fifty-six subjects (94.9%) in the safety population were < 18 years of age and comprised the pediatric population used for safety and efficacy summaries or listings. Subjects participated at 29 sites overall; 11 sites in North America, 8 sites in EU, and 10 sites in Asia/Pacific (Study 1146 Primary Analysis CSR Table 14.1.2).

For the primary analysis, the data extract was 02 August 2021. At the time of the data extract for the primary analysis, the median time on study was 20.4 months (range: 1.6+ to 31.7 months) for all subjects; 15.5 months (range: 1.9+ to 21.7 months) for TN subjects, and 20.6 months (range: 1.6+ to 31.7 months) for R/R subjects (Table 12).

Treatment was ongoing in 37.3% of subjects, and 44.1% of subjects were off treatment and in follow-up overall. For the 18.6% of subjects who were off study overall, the most common primary reason for study exit was death (10.2%). For the 62.7% of subjects who discontinued ibrutinib overall, the most common primary reasons (≥ 5% of subjects) were AE not related to progressive disease (13.6%), withdrawal of consent/assent for treatment by subject (13.6%), progressive disease - cGVHD (11.9%), investigator decision (6.8%), subject began treatment with another systemic therapy (including extracorporeal photopheresis) for cGVHD (6.8%), progression or relapse of the underlying disease that was the indication for transplantation (5.1%), and death (5.1%) (Study 1146 Primary Analysis CSR Table 14.1.4). For the 33.3% of TN subjects who discontinued prednisone, the most common primary reasons were progressive disease - cGVHD (8.3%), progression or relapse of the underlying disease that was the indication for the transplant (8.3%), withdrawal of consent/assent for treatment by subject (8.3%), and investigator decision (8.3%) (Study 1146 Primary Analysis CSR Table 14.1.5).

Table 12 Applicant – Study Disposition – Study 1146 (All Treated Population)

	TN (N=12)	R/R (N=47)	All (N=59)
Subject status, n (%)			
In treatment phase[a]	7 (58.3)	15 (31.9)	22 (37.3)
In follow-up	4 (33.3)	22 (46.8)	26 (44.1)
Off study	1 (8.3)	10 (21.3)	11 (18.6)
Primary reason for study exit, n (%)			
Withdrawal of consent/assent for follow up observation	0	5 (10.6)	5 (8.5)
Lost to follow-up	0	0	0
Death	1 (8.3)	5 (10.6)	6 (10.2)
Other	0	0	0
Time on study (months)[b]	12	47	59
Median (95% CI)	15.5 (10.8, 17.7)	20.6 (19.7, 22.1)	20.4 (18.7, 21.1)
Min, Max	1.9+, 21.7	1.6+, 31.7	1.6+, 31.7

cGVHD = chronic graft versus host disease; CI = confidence interval; R/R = relapsed/refractory; TN = treatment naive

a In treatment phase includes subjects still receiving ibrutinib or prednisone, including subjects who no longer need treatment for cGVHD.

b Time on study is based on the follow-up time of overall survival and median is estimated using the reverse Kaplan-Meier method. + indicates censored observation.

Source: Study 1146 Primary Analysis CSR Table 14.1.3

The FDA's Assessment:
FDA agrees with the Applicant's statement.

Protocol Violations/Deviations

The Applicant's Position:

One subject had an important protocol deviation regarding the study drug/diary (Study 1146 Primary Analysis CSR Appendix 14; the subject received an overdose of ibrutinib for approximately 6 days. On the first day, the subject took the first ibrutinib dose correctly in the hospital but then at home the subject took it incorrectly as 3 times per day, before the subject resumed the correct daily dose). There was no associated toxicity for this subject and this deviation did not affect the overall efficacy and safety results of the study.

The FDA's Assessment:
FDA agrees with the Applicant's statement.

Table of Demographic Characteristics

The Applicant's Position:

The demographic characteristics of the subjects in this study were generally representative of that of the target patient population. The median age was 13.0 years (range: 1 to 19 years); 27 subjects (45.8%) were 1 to < 12 years, 29 subjects (49.2%) were 12 to 17 years, and 3 subjects (5.1%) were ≥ 18 years (Table 13). In total, 71.2% of subjects were male, 47.5% of subjects were White, and 71.2% of subjects were located outside the US.

Table 13 Applicant – Subject Demographics – Study 1146 (All Treated Population)

	TN (N=12)	R/R (N=47)	All (N=59)
Age at enrollment (years)	12	47	59
Mean (standard deviation)	11.4 (5.43)	11.6 (5.06)	11.6 (5.09)
Median	11.5	13.0	13.0
Min, Max	3, 17	1, 19	1, 19
1-<12 years - n (%)	6 (50.0)	21 (44.7)	27 (45.8)
12-17 years - n (%)	6 (50.0)	23 (48.9)	29 (49.2)
≥18 years - n (%)	0	3 (6.4)	3 (5.1)
Gender - n (%)			
Male	9 (75.0)	33 (70.2)	42 (71.2)
Female	3 (25.0)	14 (29.8)	17 (28.8)
Race - n (%)			
American Indian or Alaska Native	0	0	0
Asian	1 (8.3)	13 (27.7)	14 (23.7)
Black or African American	0	4 (8.5)	4 (6.8)
Native Hawaiian or Other Pacific Islander	0	0	0
White	11 (91.7)	17 (36.2)	28 (47.5)
Multiple	0	5 (10.6)	5 (8.5)
Not Reported	0	8 (17.0)	8 (13.6)
Non-White	1 (8.3)	30 (63.8)	31 (52.5)
Ethnicity - n (%)			
Hispanic or Latino	1 (8.3)	7 (14.9)	8 (13.6)
Not Hispanic or Latino	11 (91.7)	33 (70.2)	44 (74.6)
Not Reported	0	7 (14.9)	7 (11.9)
Geographic Region - n (%)			
US	6 (50.0)	11 (23.4)	17 (28.8)
Non-US	6 (50.0)	36 (76.6)	42 (71.2)

R/R: relapsed/refractory; TN: treatment naive; US: United States

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

Source: Study 1146 Primary Analysis CSR Table 14.1.6

The FDA's Assessment:

FDA agrees with the Applicant's statement.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The Applicant's Position:

The median time from last transplant to initial cGVHD diagnosis was 8.15 months (Table 14). The median time from initial cGVHD diagnosis to enrollment was 12.42 months. A total of 12 subjects (20.3%) were TN and 47 subjects (79.7%) were R/R (Study 1146 Primary Analysis CSR Table 14.1.7). A total of 50.8% of subjects received their transplant from an unrelated donor (Study 1146 Primary Analysis CSR Table 14.1.8). The cell graft was human leukocyte antigen (HLA) matched between donor and recipient for 69.5% of subjects. The stem cell source was marrow for 50.8% of subjects.

At baseline, all subjects (100.0%) had a creatinine clearance > 60 mL/min and 47.5% of subjects had hepatic impairment based on National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) liver function classification (Table 14). A NIH global cGVHD severity grade of moderate was reported in 37.3% of subjects (TN 83.3%, R/R 25.5%) and severe in 62.7% (TN 16.7%, R/R 74.5%) of subjects. The most commonly involved organs were skin (81.4%), mouth (62.7%), and eye (57.6%) (Study 1146 Primary Analysis CSR Table 14.1.15.1). The median Karnofsky/Lansky score was 80.0, and 74.6% of subjects had a score ≥ 80 (Table 14). A history of acute GVHD was reported for 67.8% of subjects and a history of prophylactic GVHD treatment was reported for 93.2% of subjects (Study 1146 Primary Analysis CSR Table 14.1.7). The median number of prior cGVHD treatment regimens for the R/R subjects was 2.0 (range 1 to 12). At baseline, 76.3% of subjects were receiving systemic immunosuppressants (41.7% in the TN group and 85.1% in the R/R group).

Malignant underlying disease was reported as the indication for transplant for 64.4% of subjects (Table 14); most commonly acute myeloid leukemia (Study 1146 Primary Analysis CSR Table 14.1.9).

Table 14 Applicant – Baseline Characteristics – Study 1146 (All Treated Population)

	TN (N=12)	R/R (N=47)	All (N=59)
Creatinine Clearance (mL/min)			
n	12	47	59
Mean (standard deviation)	160.97 (52.096)	132.42 (50.021)	138.23 (51.318)
Median	151.13	116.19	119.68
Min, Max	104.0, 254.1	64.1, 290.6	64.1, 290.6
< 30 mL/min - n (%)	0	0	0
30 – 60 mL/min - n (%)	0	0	0
> 60 mL/min - n (%)	12 (100.0)	47 (100.0)	59 (100.0)
Hepatic impairment - n (%)[a]			
Yes	8 (66.7)	20 (42.6)	28 (47.5)
No	4 (33.3)	27 (57.4)	31 (52.5)
Number of Transplants Received - n (%)			
1	10 (83.3)	42 (89.4)	52 (88.1)
2	2 (16.7)	5 (10.6)	7 (11.9)
Number of Prior cGVHD Treatment Regimens			
n	0	47	47
Mean (standard deviation)	-	2.8 (2.58)	2.8 (2.58)
Median	-	2.0	2.0
Min, Max	-	1, 12	1, 12
Time from Last Transplant to Initial cGVHD Diagnosis in Months			
n	12	47	59
Mean (standard deviation)	7.77 (3.239)	11.18 (9.493)	10.49 (8.682)
Median	7.75	8.15	8.15
Min, Max	3.3, 12.9	2.8, 50.1	2.8, 50.1
Months from Initial cGVHD Diagnosis Date to Enrollment			
n	12	47	59
Mean (standard deviation)	8.52 (22.225)	28.54 (35.730)	24.47 (34.238)
Median	0.94	16.10	12.42
Min, Max	0.1, 77.8	0.2, 163.2	0.1, 163.2
NIH Global cGVHD Severity Grade - n (%)[b]			
Moderate	10 (83.3)	12 (25.5)	22 (37.3)
Severe	2 (16.7)	35 (74.5)	37 (62.7)
History of Acute GVHD - n (%)			
Yes	7 (58.3)	33 (70.2)	40 (67.8)
No	5 (41.7)	14 (29.8)	19 (32.2)

	TN (N=12)	R/R (N=47)	All (N=59)
Malignant Underlying Disease - n (%)			
Yes	8 (66.7)	30 (63.8)	38 (64.4)
No	4 (33.3)	17 (36.2)	21 (35.6)
Require Immediate Treatment with Prednisone during Screening - n (%)[c]			
Yes	4 (33.3)	0	4 (6.8)
No	8 (66.7)	0	8 (13.6)
Ongoing Use of Systemic Immunosuppressants - n (%)[d]			
Yes	5 (41.7)	40 (85.1)	45 (76.3)
No	7 (58.3)	7 (14.9)	14 (23.7)
Karnofsky/Lansky performance status[e]			
n	12	47	59
Mean	85.0 (10.87)	81.9 (13.45)	82.5 (12.94)
Median	90.0	80.0	80.0
Min, Max	70, 100	60, 100	60, 100
Score <80 - n (%)	3 (25.0)	12 (25.5)	15 (25.4)
Score ≥80 - n (%)	9 (75.0)	35 (74.5)	44 (74.6)

cGVHD: chronic graft versus host disease; GVHD: graft versus host disease; NCI ODWG: National Cancer Institute Organ Dysfunction Working Group; NIH: National Institutes of Health; R/R: relapsed/refractory; TN: treatment naive

N=number of subjects in the specified population. Percentages are calculated by 100*n/N.

a Based on NCI ODWG liver function classification.

b cGVHD staging per NIH Criteria.

c Only applies to treatment naive subjects.

d Immunosuppressants that were initiated for either treatment of or prophylaxis for acute GVHD.

e One subject who was 15 years old reported Karnofsky performance status.

Source: Study 1146 Primary Analysis CSR Table 14.1.7

The FDA's Assessment:

The efficacy of ibrutinib was evaluated in the Study PCYC-1146-IM (IMAGINE NCT03790332), an open-label, multi-center, single-arm trial of ibrutinib for treatment of pediatric and young adult patients age 1 year to less than 22 years with moderate or severe chronic GVHD as defined by NIH Consensus Criteria requiring additional therapy after failure of one or more prior lines of systemic therapy. Patients were excluded from the study if platelets were $< 30 \times 10^9$/L; absolute neutrophil count $< 1.0 \times 10^9$/L; AST or ALT > 3 × ULN; total bilirubin > 1.5 × ULN; estimated creatinine clearance < 30 mL/min; or presence of single organ genitourinary involvement as the only manifestation of chronic GVHD.

Since Study 1140, the randomized trial in adults and adolescents for first-line treatment of cGVHD, was negative (see Section 8.1.3 below), we focused our analysis of Study 1146 on only the 47 patients with recurrent or refractory cGVHD.

There were 47 patients with recurrent or refractory chronic GVHD treated with ibrutinib in the Study PCYC-1146-IM (IMAGINE). Patients age 12 years and older were treated with ibrutinib 420 mg orally once daily, and patients age 1 year to less than 12 years were treated with ibrutinib 240 mg/m^2 orally once daily. Concomitant treatment with supportive care therapies for chronic GVHD was permitted. Initiation of new systemic chronic GVHD therapy while on study was not permitted.

The median age was 13 years (range, 1 to 19 years), including patients in following groups: one patient 1 month to less than 2 years old, 20 patients 2 years to less than 12 years old, 19 patients 12 years to less than 17 years old, and 7 patients 17 years to less than 22 years old. 70.2% patients were male, and 36.2% were White. The median time since cGVHD diagnosis was 16.1 months, the median number of prior cGVHD treatments was 2 (range, 1 to 12 treatments). The majority of patients (87.2%) had at least 2 organs involved at baseline, with lung involvement at baseline in 48.9% of patients. The median daily corticosteroid dose (prednisone or prednisone equivalent) at baseline was 0.47 mg/kg/day, and 61% (19 of 31) of patients were receiving ongoing immunosuppressants in addition to systemic corticosteroids at baseline. Prophylaxis for infections was managed per institutional guidelines.

Demographics and baseline characteristics are summarized in Table 15.

Table 15. Demographics and Baseline Characteristics of Patients with Chronic GVHD in Study PCYC-1146-IM (IMAGINE)

	Recurrent/Refractory (N=47)
Age, Median, Years (minimum, maximum)	13 (1, 19)
1 month to < 2 Years, n (%)	1 (2.1)
2 Years to < 12 Years, n (%)	20 (42.6)
12 Years to < 17 Years, n (%)	19 (40.4)
17 Years and older, n (%)	7 (14.9)
Male, n (%)	33 (70.2)
Race, n (%)	
White	17 (36.2)

	Recurrent/Refractory (N=47)
Black	4 (8.5)
Other or Not Reported	26 (55.3)
Karnofsky/Lansky performance score of <80, n (%)	12 (25.5)
Median (range) time (months) from Chronic GVHD Diagnosis	16.1 (0.2, 163.2)
Median (range) Number of Prior Lines of Therapy	2 (1, 12)
Number of Prior Lines of Therapy, n (%)	
1	21 (44.7)
2	9 (19.1)
3	4 (8.5)
>3	13 (27.7)
Severe chronic GVHD, n (%)	35 (74.5)
Lung Involvement at Baseline, n (%)	23 (48.9)
≥ 2 Organs Involved, n (%)	41 (87.2)
≥ 4 Organs Involved, n (%)	22 (46.8)
Median (range) Lee Symptom Scale Score at baseline	19 (5.7, 56.8)
Median (range) Corticosteroid dose at baseline (PE/kg)[a]	0.47 (0.04, 2.68)
Source: FDA analysis [a] Prednisone equivalents/kilogram	

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Treatment Compliance

A total of 59 subjects were enrolled (12 TN and 47 R/R) and received study drug (ibrutinib). No formal treatment compliance measurements were performed. However, the median ibrutinib relative dose intensity (the actual dose received divided by the standard calculated dose during a set period) was 100.0% overall. The median ibrutinib treatment duration was 8.18 months

overall (range: 0.1 to 25.9 months); 9.71 months for TN subjects (range: 0.1 to 20.7 months), and 7.10 months (range: 0.2 to 25.9 months) for R/R subjects (Study 1146 Primary Analysis CSR Table 10). The ibrutinib dose was reduced due to an AE for 8.5% of subjects.

Concomitant Therapies

Overall, 54.2% of subjects took at least 1 concomitant systemic immunosuppressant medication other than prednisone; the most commonly taken (> 10% of subjects) by preferred term (PT) were mycophenolate mofetil (20.3%), cyclosporine (18.6%), and tacrolimus (18.6%) (Table 16).

Table 16 Applicant – Concomitant Systemic Immunosuppressant Medications Other Than Prednisone – Study 1146 (All Treated Population)

Pharmacological class Preferred term	TN (N=12) n (%)	R/R (N=47) n (%)	All (N=59) n (%)
Number of subjects taking at least 1 concomitant additional immunosuppressant medication	5 (41.7)	27 (57.4)	32 (54.2)
Corticosteroids for Systemic Use, Plain	0	3 (6.4)	3 (5.1)
Prednisolone	0	2 (4.3)	2 (3.4)
Methylprednisolone	0	1 (2.1)	1 (1.7)
Immunosuppressants	5 (41.7)	27 (57.4)	32 (54.2)
Mycophenolate mofetil	1 (8.3)	11 (23.4)	12 (20.3)
Cyclosporine	2 (16.7)	9 (19.1)	11 (18.6)
Tacrolimus	2 (16.7)	9 (19.1)	11 (18.6)
Sirolimus	0	4 (8.5)	4 (6.8)
Infliximab	0	1 (2.1)	1 (1.7)

R/R = relapsed/refractory; TN = treatment naive; WHO = World Health Organization

Medications are coded by WHO Drug dictionary and are considered concomitant if taken during the treatment emergent period.

Source: Study 1146 Primary Analysis CSR Table 14.1.12.4

Concomitant medications were used by 100.0% of subjects overall (Study 1146 Primary Analysis CSR Table 14.1.12.3). The most common concomitant medications by preferred term (≥ 30% of subjects) were sulfamethoxazole/trimethoprim (72.9%), paracetamol (47.5%), aciclovir (42.4%), azithromycin (37.3%), omeprazole (35.6%), ondansetron (32.2%), and phenoxymethylpenicillin (30.5%). Concomitant moderate/strong CYP3A inhibitors were used by 76.3% of subjects overall

(Study 1146 Primary Analysis CSR Table 14.1.12.5). Strong CYP3A inhibitors were used by 50.8% subjects; the most commonly used (> 20% of subjects) were posaconazole (25.4%) and voriconazole (25.4%). Moderate CYP3A inhibitors were used by 42.4% of subjects overall; the most commonly used (> 20% of subjects) was fluconazole (22.0%). A strong CYP3A inducer was used by 2 subjects (3.4%); 1 R/R subject used rifampicin and 1 R/R subject used carbamazepine (Study 1146 Primary Analysis CSR Table 14.1.12.6).

Rescue Mediation

Rescue medication was not a part of this study.

The FDA's Assessment:
FDA agrees with the Applicant's statement.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

The Applicant's Position:

There were no primary efficacy endpoints. Primary endpoints for the study were PK and safety parameters (Study 1146 Primary Analysis CSR Table 3).

The FDA's Assessment:
FDA agrees with the Applicant's statement.

Data Quality and Integrity

The Applicant's Position:

The data gathered and analyzed by study investigators were entered into an electronic database maintained by Pharmacyclics LLC. Study 1146 included site and remote monitoring performed by representatives of Pharmacyclics LLC or its designee. Pharmacyclics LLC was responsible for the detailed Trial Monitoring Plan, which defined and standardized all monitoring processes for the Clinical Research Associates/Site Monitors. On-site or remote periodic monitoring also occurred for specified critical variables per Trial Monitoring Plan. Sites

were provided with a case report form (CRF) instruction booklet. Data Management reviewed the data and queried sites as appropriate using edit checks and clinical review.

Information requested by the Office of Scientific Investigations (OSI) for this study is provided in Module 5.3.5.4. In general, no issues were identified with the quality or integrity of data from Study 1146 which could affect the efficacy findings.

The FDA's Assessment:

Table 17 shows a summary of the major efficacy review Issues identified in the Study 1146.

Table 17. Efficacy Issues in Study 1146

Issue	Impact	Solution
Discrepancy: FDA vs Investigator organ-based assessment	ORR, DOR	FDA adjudication of organ-based response by 2014 NIH
Discrepancy: FDA vs Applicant overall response assessment	ORR, DOR	FDA adjudication of overall response by 2014 NIH
Discrepancy: Subsequent anti-cGVHD new therapy or increase in steroids	ORR, DOR	FDA adjudication of subsequent therapy initiation
Inadequate Analysis: Pooling of heterogeneous data from different trials for efficacy	Integrated efficacy assessment	Efficacy assessment by separate trials

Source: FDA analysis

Regarding the Study PCYC-1146-IM data, FDA has completed adjudication of the elements required to determine the responses through the Week 25 visit and the duration of responses. The FDA adjudicated responses and dates were communicated with the Applicant who acknowledged all the adjudications.

The outcomes in FDA response adjudications were based on the 2014 NIH Consensus Conference criteria as published by Lee et al 2015, specifically with the following notes:

a. All available visits on study, including unscheduled visits, were used in the assessment.
b. The assessment for lung is based on Lung Score only when FEV1P is missing.
c. The assessment for joints requires both the Joint Score and photographic range of motion (P-ROM) scales.
d. The patient is not evaluable for response if any results for any organ assessments are missing.
e. The date of organ progression applies when there is progression in any individual

organ irrespective of response in other organs.

f. Increases in steroids to >= 0.9 PE/kg [prednisone equivalents/kilogram] is considered a new systemic therapy. (Przepiorka D, et al. 2022; Le RQ, et al. 2022.)

Table 18 shows there was about a 21% discordance rate in OR in the Study 1146 of 47 subjects with previously treated chronic GVHD, due to differences in either the date of subsequent therapy or in how the response criteria were applied. FDA has corresponded with the Applicant about the discordant cases, and FDA used the FDA-adjudicated results in labeling.

Table 18. Concordance between Applicant and FDA adjudicated results of ORR through Week 25 visit

	FDA's Response Adjudication		
Applicant's Response Adjudication	CR	PR	NR
CR	2	0	0
PR	0	21	5
NR	0	5	14

Source: FDA analysis

Efficacy Results – Secondary and other relevant endpoints

The Applicant's Position:

With a median time on study of 20.4 months overall (range: 1.6+ to 31.7 months) (N = 59); 15.5 months (range: 1.9+ to 21.7 months) for TN subjects (N = 12), and 20.6 months (range: 1.6+ to 31.7 months) for R/R subjects (N = 47) (Study 1146 Primary Analysis CSR Table 5), treatment with ibrutinib in subjects ≥ 1 to < 22 years of age with cGVHD across TN and R/R populations resulted in:

- A clinically meaningful ORR: 78.0% overall (95% CI: 65.3, 87.7); CR 8.5%, PR 69.5% (Study 1146 Primary Analysis CSR Table 11).
  - The ORR was 83.3% (95% CI: 51.6, 97.9) in TN subjects (CR 25.0%, PR 58.3%), and 76.6% (95% CI: 62.0, 87.7) in R/R subjects (CR 4.3%, PR 72.3%).
  - In the subgroup analyses, out of 11 subjects aged 1 to < 6 years, the ORR was 72.7% (95% CI: 39.0, 94.0); out of 16 subjects aged 6 to <12 years, the ORR was 68.8% (95% CI: 41.3, 89.0); and out of 32 subjects aged 12 to 19 years, the ORR was 84.4% (95% CI: 67.2, 94.7) (Study 1146 Primary Analysis CSR Table 12). ORR results were similar

in analyses by gender, race, geographic region, and NIH global severity grade subgroups.

- Of the 59 subjects with 24 weeks of follow up, the ORR was 64.4% overall (CR 5.1%, PR 59.3%) (Study 1146 Primary Analysis CSR Table 14.2.4.1).
    - Of the 10 TN subjects and 28 R/R subjects with 24 weeks of follow up, the ORR was 83.3% (CR 8.3%, PR 75.0%) in TN subjects and 59.6% (CR 4.3%, PR 55.3%) in R/R subjects.
- Of the 58 subjects with 48 weeks of follow up, the ORR was 74.1% overall (CR 6.9%, PR 67.2%) (Study 1146 Primary Analysis CSR Table 14.2.5.1).
    - Of the 10 TN subjects and 33 R/R subjects with 48 weeks of follow up, the ORR at 48 weeks was 83.3% (CR 25.0%, PR 58.3%) in TN subjects and 71.7% (CR 2.2%, PR 69.6%) in R/R subjects.

- Response rates at 24 weeks were 44.1% overall (CR 5.1%, PR 39.0%), 66.7% (CR 8.3%, PR 58.3%) in TN subjects, and 38.3% (CR 4.3%, PR 34.0%) in R/R subjects (Study 1146 Primary Analysis CSR Table 14.2.4.2).
- Majority of subjects with a sustained response: a sustained response for ≥ 20 weeks was achieved by 60.9% (95% CI: 45.4, 74.9) of subjects overall; by 70.0% (95% CI: 34.8, 93.3) of TN subjects and by 58.3% (95% CI: 40.8, 74.5) of R/R subjects (Study 1146 Primary Analysis CSR Table 14.2.2).
- Encouraging patient-reported outcomes:
    - The global ratings for well-being (total PedsQL score by Parent) for subjects > 2 and < 12 years old median score was 69.5 at baseline (range: 45.3, 93.8); 75.8 at Week 5 (range: 51.4, 93.3); 75.3 at Week 13 (range: 44.6, 93.6); and 71.8 at Week 25 (range: 48.1, 93.8) (Study 1146 Primary Analysis CSR Table 14.2.18.1); the mean parent-reported overall PedsQL scale score improved by 6.5 points at Week 5 and 3.9 points at Week 13.
    - Treatment was associated with an improvement in the Lee cGVHD Symptom Scale (subjects aged 12 years and older) summary score (defined as at least 7-point decrease at 2 consecutive visits) for 43.8% of subjects overall (50.0% of TN subjects and 42.3% of R/R subjects) (Study 1146 Primary Analysis CSR Table 14.2.14). Improvement (≥7 point decrease) in the Lee cGVHD Symptom Scale overall score at any time during the study were observed for 56.3% of subjects overall (83.3% of TN subjects and 50.0% of R/R subjects) (Study 1146 Primary Analysis CSR Table 14.2.10).
    - Treatment was associated with an improvement in the modified Lee cGVHD Symptom Scale summary score (defined as at least 6-point decrease at 2 consecutive visits) for 43.8% of subjects overall (50.0% of TN subjects and 42.3% of R/R subjects) (Study 1146 Primary Analysis CSR Table Table 14.2.16). Improvement (≥ 6-point decrease) in the modified Lee cGVHD Symptom Scale overall score at any time during the study was observed for 62.5% of subjects overall (100.0% of TN subjects and 53.8% of R/R subjects) (Study 1146 Primary Analysis CSR Table 14.2.12).

- The medians for DOR, OS, EFS, and FFS were not reached overall:
  - The median DOR was not reached overall. The KM point estimate of the DOR rate at 12 months was 58.4% and remained unchanged at 18 months (Study 1146 Primary Analysis CSR Table 13).
    - The median DOR was not reached in TN or R/R subjects. The KM point estimates of the DOR rate at 12 months were 60.0% in TN subjects and 57.6% in R/R subjects, respectively, and remained unchanged at 18 months.
  - The median OS was not reached overall; the KM point estimate at 12 months was 94.9% (Study 1146 Primary Analysis CSR Table 14).
    - The median OS was not reached in TN or R/R subjects; the KM point estimates at 12 months were 91.7% in TN subjects and 95.7% in R/R subjects.
  - The median EFS was 17.3 months (95% CI: 11.5, NE) overall; the KM point estimate at 12 months was 62.9% (Study 1146 Primary Analysis CSR Table 14.2.7).
    - The median EFS was not reached in the TN subjects and was 17.3 months (95% CI: 12.2, NE) in R/R subjects; the KM point estimates at 12 months was 50.0% TN subjects, and 66.5% in R/R subjects.
  - The median FFS was not reached overall; the KM point estimate at 12 months was 67.6% (Study 1146 Primary Analysis CSR Table 14.2.8).
    - The median FFS was not reached in TN or R/R subjects; the KM point estimates at 12 months was 58.3% in TN subjects and 70.0% in R/R subjects.

<u>The FDA's Assessment:</u>
The Applicant provided different number of subjects on Page 12 of Pediatric Study 1146 CSR: 59 subjects with 24 weeks of follow up, included 12 TN subjects and 47 R/R subjects with 24 weeks of follow up.

Data from the 12 TN pediatric patients from PCYC-1146-IM (IMAGINE) will be not sufficient (b) (4) , in light of the failed trial in adults in this setting (b) (4). Therefore, the responses in the 12 TN patients were not independently adjudicated by the FDA.

The efficacy of ibrutinib was based on overall response rate (ORR) through Week 25 visit where overall response included complete response or partial response according to the 2014 National Institutes of Health (NIH) Consensus Development Project Response Criteria. The ORR results are presented in Table 19 below for the 47 patients who received treatment for previously treated chronic GVHD in the PCYC-1146-IM (IMAGINE). The ORR was 59.6% (95% CI:

44.3, 73.6). The median time to first response was 0.9 month (range: 0.9, 6.1). The median follow-up time on study was 13.6 months (range, 2.6-25.0). The median duration of response, calculated from first response to progression, death, or new systemic therapies for chronic GVHD, was 5.3 months (95% CI: 2.8, 8.8). (The median time from first response to death or new systemic therapies for chronic GVHD was 14.8 months (95% CI: 4.6, not evaluable).

Table 19. Primary Efficacy Results for the patients with previously treated cGVHD[a] in the PCYC-1146-IM (IMAGINE).

	Relapsed / Refractory cGVHD (N=47)	
	Applicant Report	**FDA-Adjudicated**
ORR by Week 25	28 (59.6%)	28 (59.6%)
(95% CI)	-	(44.3, 73.6)
CR	2 (4.3%)	2 (4.3%)
PR	26 (55.3%)	26 (55.3%)
Median time to response (range)	-	0.9 months (0.9, 6.1)
Median DOR (95% CI)[b]	NE (range: 8.9, NE)	5.3 months (2.8, 8.8)
Median DUR (95% CI)[b]	-	14.8 months (4.6, NE)
Median follow-up of responders (range)	-	13.6 months (2.6, 25.0)
≥ 7-point decrease in LSS Score (95% CI)	14/26 (54%) (95% CI: 33, 73)	13/26 (50%) (95% CI: 30, 70)

Source: FDA analysis
Notes: CI = confidence interval; ORR = overall response rate
[a] Assessment based on 2014 NIH Consensus Development Project Response Criteria
[b] Based on all responders in the study

FDA identified 28 responders, for an ORR by week 25 of 59.6% with a lower 95% CI bound of 44%. There were only 2 patients with a CR.

The ORR was consistent across subgroups, and that analysis is in the following Table 20-Table 22. There was also no difference in ORR by whether the patient received the tablets vs the suspension formulation.

Reviewer comment: The Applicant provided data to support an exploratory analysis of the overall symptom bother in adolescent patients >12 years using the Lee Symptom Scale (LSS) with a 7-point decrease determined to be clinical benefit. The Division considered the Division of Clinical Outcome Assessments (DCOA) review which provided their view that the LSS is inadequate to support labeling claims. However, the LSS was included in support of efficacy in adult patients with cGVHD treated with ibrutinib. The LSS was designed to be assessed in adolescents or adults who can complete the survey independently, and the data presented in adolescents can be used to support efficacy evaluations in 26 patients on the IMAGINE study with previously treated cGVHD. The LSS has been used in support of efficacy evaluations in other approvals for cGVHD including ruxolitinib and belumosudil.

Table 20 shows that the FDA-adjudicated ORR (overall response rate) by Week 25 visit is consistent across subgroups by demographics in Study 1146.

Table 20. Study 1146 Efficacy Subgroup Analysis by Demographics

		CR+PR		
	N	**n**	**%**	**95% CI**
All	47	28	59.6%	(44.3, 73.6)
Age Group				
1 months to < 2 years	1	1	100%	3-100%
2 years to < 12 years	20	12	60%	36-81%
12 years to < 17 years	19	9	47%	24-71%
17 years and older	7	6	86%	42-100%
Sex				
Male	33	21	64%	45-80%
Female	14	7	50%	23-77%
Race				
White	17	10	59%	33-82%
Asian	13	7	54%	25-81%
Not Reported	8	3	38%	9-76%
Multiple	5	5	100%	48-100%
Black or African American	4	3	75%	19-99%
Ethnicity				
Hispanic Or Latino	7	5	71%	29-96%
Not Hispanic Or Latino	33	20	61%	42-77%
Not Reported	7	3	43%	10-82%

Geographic Region				
Non-US	36	23	64%	46-79%
US	11	5	45%	17-77%

Source: FDA Analysis

Table 21 shows that the FDA-adjudicated ORR (overall response rate) by Week 25 visit is consistent across subgroups by cGVHD Characteristics in Study 1146.

Table 21. Study 1146 Efficacy Subgroup Analysis by cGVHD Characteristics

		CR+PR		
	N	**n**	**%**	**95% CI**
All	47	28	59.6%	(44.3, 73.6)
Prior Lines of Therapy				
1	21	13	62%	38-82%
2	9	6	67%	30-93%
3	4	2	50%	7-93%
>3	13	7	54%	25-80%
cGVHD Severity at Baseline				
Moderate	12	8	67%	35-90%
Severe	35	20	57%	39-74%
Lung Involvement at Baseline				
N	24	14	58%	37-78%
Y	23	14	61%	38-80%
Total of Organ Involvement at Baseline				
1	6	3	50%	12-88%
2	8	5	63%	24-91%
3	11	8	73%	39-94%
4	11	7	64%	31-89%
5	8	3	38%	9-76%
6	3	2	67%	9-99%

Source: FDA Analysis

Table 22 shows that the FDA-adjudicated ORR (overall response rate) by Week 25 visit, is consistent across subgroups by ibrutinib formulations in Study 1146.

Table 22. Study 1146 Efficacy Subgroup Analysis by Ibrutinib Formulation

		CR+PR		
	N	n	%	95% CI
All	47	28	59.6%	(44.3, 73.6)
Ibrutinib Formulations				
Multiple*	4	2	50%	7-93%
Suspension	21	14	67%	43-85%
Tablet	22	12	55%	32-76%

Source: FDA Analysis
Notes: *The multiple formulation is when the patients received more than one formulation prior to week 25.

Dose/Dose Response

The Applicant's Position:

Population PK results including exposure-response analysis were reported in a population PK report provided in Study 1146 Primary Analysis CSR Appendix 21. See Section 6.2.1 for details.

The FDA's Assessment:
FDA agrees with the Applicant's statement.

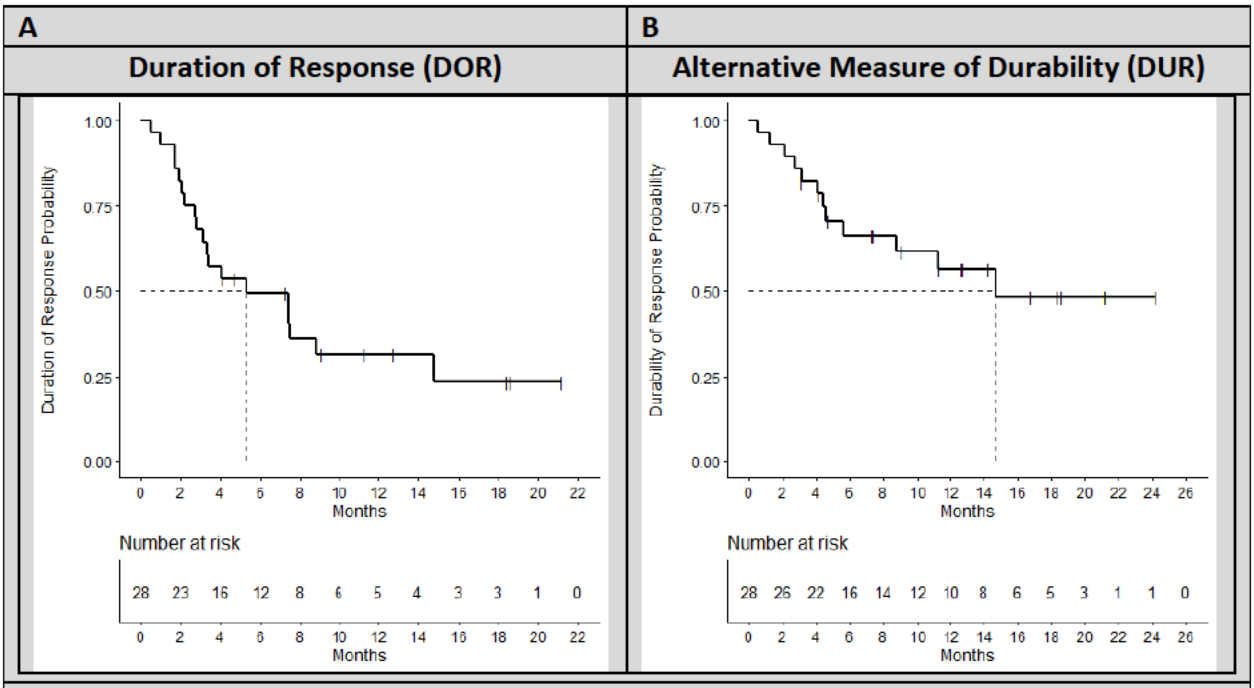
Durability of Response

The Applicant's Position:

The median DOR was not reached overall (see Efficacy Results – Secondary and other relevant endpoints).

The FDA's Assessment:
With a median follow-up time to last evaluation of 13.6 months (range, 2.6-25.0), the median DOR was 5.3 months (95% CI: 2.8, 8.8), observed 8.2 months (range, 1.4-22.1+). The median DUR (Alternative Measure of Durability, time to death or new therapy) was 14.8 months (95% CI: 4.6, NE), observed 8.3 months (range, 1.4-25.0+).

Figure 2 shows the duration of response (DOR) and alternative measure of durability (DUR) in the Study 1146.



Source: FDA Analysis

Figure 2. DOR (A) and DUR (B) in the Study 1146

Persistence of Effect

The Applicant's Position:

Time-to-event Analyses (i.e., OS, EFS, FFS)

With a median follow up of 20.4 months, the median OS and FFS were not reached overall; the median EFS was 17.3 months (95% CI: 11.5, NE) overall (see Efficacy Results – Secondary and other relevant endpoints).

Sustained Response Rate for at Least 32 Weeks

A sustained response for ≥ 32 weeks was achieved by 54.8% (95% CI: 38.7, 70.2) of subjects overall; by 60.0% (95% CI: 26.2, 87.8) of TN subjects and by 53.1% (95% CI: 34.7, 70.9) of R/R subjects (Study 1146 Primary Analysis CSR Table 14.2.3).

The FDA's Assessment:
See above for the FDA assessment for durability of response.

Efficacy Results – Secondary or exploratory Clinical Outcomes Assessment (COA) or Patient Reported Outcomes (PRO) endpoints

The Applicant's Position:

An improvement in the PedsQL (subjects > 2 and < 12 Years old) global ratings for well being (total PedsQL score by Parent) and an improvement in the Lee cGVHD Symptom Scale scores, as well as the modified Lee cGVHD Symptom Scale scores, indicate encouraging patient reported outcomes (see Efficacy Results – Secondary and other relevant endpoints).

The FDA's Assessment:
Total of 32 subjects in Study 1146 were 12 years and older; among the 32 subjects, only 26 subjects had previously treated cGVHD. (b) (4)

Among the 32 subjects who were 12 years and older, 56% (18/32) subjects had at least a 7-point decrease in Lee Symptom Scale overall summary score through Week 25 visit.

The analysis of the PRO data showed that ORR results were supported by exploratory analyses of patient-reported symptom bother which showed at least a 7-point decrease in Lee Symptom Scale overall summary score through Week 25 visit in 50% (13/26) (95% CI: 29.9, 70.1) of patients age 12 years and older with previously treated cGVHD.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

No additional analyses were conducted for this study.

The FDA's Assessment:
FDA agrees with the Applicant's statement.

8.1.2. iNTEGRATE (PCYC-1140-IM)

Trial Design

The Applicant's Description:

This was a Phase 3, multicenter, international, randomized, double-blind study of oral ibrutinib in combination with prednisone versus placebo in combination with prednisone in subjects with new onset, treatment-naïve, chronic GVHD (Study 1140 Primary Analysis CSR Revision 2 Appendix 1). Approximately 186 subjects with newly diagnosed moderate or severe cGVHD, as defined by the 2014 NIH Consensus Development Project Criteria, were to be randomized in a 1:1 ratio to receive either ibrutinib in combination with prednisone (Arm A) or placebo in combination with prednisone (Arm B). The randomization between arms was stratified according to age group (12 to < 22 years old vs. ≥ 22 years old), NIH Global Severity grade (moderate vs. severe), and ongoing use of systemic immunosuppressants that were initiated for either treatment of or prophylaxis for acute GVHD (aGVHD) (yes vs. no). It was expected that a minimum of 6 subjects in the adolescent group (≥12 and < 22 years of age) would be enrolled.

Ibrutinib (420 mg) or placebo (dose adjusted for cytochrome P450 [CYP] inhibitors or hepatic dysfunction as applicable) was given orally once daily continuously until cGVHD progression, progression of underlying malignancy, the initiation of another systemic treatment for cGVHD, or unacceptable toxicity. Ibrutinib/placebo could be withdrawn if cGVHD response was maintained after all immunosuppressants were withdrawn. Prednisone was administered orally at a starting dose of 1 mg/kg/day (or as low as 0.5 mg/kg/day if a subject could not tolerate higher doses) continuously until unacceptable toxicity or until the subject was successfully tapered from the prednisone.

Response was defined using the 2014 NIH Consensus Development Project Criteria and must have occurred in the absence of new systemic therapy for cGVHD, and in the absence of: progression of the underlying disease that was the indication for transplant, or post-transplant lymphoproliferative disease, or death. Progression of the underlying disease was defined using standard clinical criteria for the individual malignancy. All subjects had cGVHD response assessments performed during the ibrutinib/placebo treatment phase, and if applicable at the progressive disease visit, and end-of-treatment visit. Subjects who discontinued ibrutinib/placebo for reasons other than progressive cGVHD or progression of their underlying malignancy continued with response assessments. Subjects with cGVHD progression or progression of their underlying malignancy were followed for survival and the use of alternative cGVHD therapy. Chronic GVHD response determination was based on clinician assessment per

NIH Consensus Panel Response criteria. At the time of study closure by the sponsor, sites with active subjects without progressive disease who were still receiving ibrutinib treatment were given the option to roll over to a long-term extension study to continue ibrutinib treatment.

Data are summarized for subjects through the date of data cutoff for the final cumulative analysis (12 July 2021).

The FDA's Assessment:
Study 1140 is a randomized Phase 3 trial comparing ibrutinib plus steroids to steroids alone for treatment of 193 adults and children 12 years and older with treatment-naïve cGVHD.

Study Endpoints

For the primary analysis, the primary endpoint was the response rate at 48 weeks (ie, the proportion of responders [CR or PR] as assessed by investigators using the NIH Consensus Panel Chronic GVHD Activity Assessment [2014]) (Lee et al, 2015[28]). Secondary endpoints were: time to withdrawal of all corticosteroids for treatment of cGVHD; time to withdrawal of all immunosuppressants, including corticosteroids, for treatment of cGVHD (with the exception of ibrutinib/placebo); response rate at 24 weeks; improvement (at least 7 point decrease at 2 consecutive visits) in Lee cGVHD Symptom Scale score; proportion of subjects who achieved a corticosteroid dose level of less than 0.15 mg/kg/day at 24 weeks sustained for at least 30 days; OS; DOR; safety and tolerability of ibrutinib in combination with prednisone compared to prednisone in combination with placebo, and differences in corticosteroid-related morbidities (eg, hyperglycemia, hypertension). Post-hoc analyses were: event-free survival, and rate of relapse of underlying malignancy. Exploratory analyses were improvement in SF 36 patient reported outcome, and improvement in in Karnofsky Performance Scale score.

For the final analysis, all analyses performed for the primary analysis were repeated for the final analysis using the same method as for the primary analysis and included an updated analysis of OS with longer follow-up. In addition, as planned at the final analysis only, withdrawal of all systemic therapies for cGVHD (including ibrutinib/placebo) was assessed. New additional analyses for the final analysis were those based on the modified Lee cGVHD Symptom scale (a 5- or 6-point improvement on this 28-item scale is considered clinically meaningful (Teh et al, 2020[43]), and a summary of cardiac failure events. Analyses not specified

in the statistical analysis plan were those that summarized the impact of the COVID-19 pandemic on study visits.

The FDA's Assessment:
FDA agrees with the Applicant's statement about Study Endpoints.

The Applicant proposed primary endpoint of Study 1140 was OR at week 48. The FDA's preferred endpoints for efficacy evaluation of the treatment of cGVHD is OR through Week 25.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The primary and secondary endpoints were to be tested based on a serial gatekeeping testing procedure at the 2-sided significance level of 0.05. The analysis of the primary endpoint, response rate at 48 weeks, was performed using an unstratified chi-square test to compare the response rates between the 2 treatment arms at the 5% level of significance. Since statistical significance for the primary endpoint was not achieved (p = 0.5384), testing of the secondary endpoints was not performed and nominal p-values were reported. The chi-square test was also used in the analysis of response rate at 24 weeks, improvement in Lee Symptom Scale, and proportion of subjects who achieved reduction of corticosteroid dose level to less than 0.15 mg/kg/day (prednisone equivalent dose reduction to 0.15 mg/kg/day at 24 weeks sustained for at least 30 days). Gray's chi-square test (adjusting for competing risks) was used in the analysis of time to withdrawal of all corticosteroids, time to withdrawal of all immunosuppressants, and time to withdrawal of all systemic therapies for cGVHD (including ibrutinib/placebo) (Gray 1988[19]). Overall survival and duration of response were summarized using Kaplan-Meier estimates. Cardiac failure events were determined based on cardiac failure standard MedDRA query (SMQ; narrow) search.

Analysis of efficacy endpoints were conducted on the intent-to-treat (ITT) population, unless otherwise specified. Sensitivity analysis of the primary efficacy endpoint was conducted on the modified intent-to-treat (mITT) population which included all ITT subjects who did not have evidence of progression of underlying malignancy at or before randomization. The primary analysis of adverse events (AEs) was based on the ibrutinib/placebo treatment-emergent period (referred to as ibrutinib/placebo TEAEs). For completeness additional analyses were

performed to assess AEs that occurred while the subject was being treated with either component of the study treatment (ibrutinib/placebo and/or prednisone (referred to as study treatment AEs). For the primary analysis CSR and final analysis CSR addendum, AEs were coded by Medical Dictionary for Regulatory Affairs (MedDRA) Versions 22.1 and 24.0, respectively. Severity of AEs were graded by the investigator according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse (CTCAE) v4.03 for all hematologic and non-hematological AEs as well as all gradable laboratory abnormalities.

The FDA's Assessment:
FDA agrees with the Applicant's statement about the statistical analysis plan and amendments.

Protocol Amendments

The Applicant's Description:

There were 3 amendments to the protocol (Study 1140 Primary Analysis CSR Revision 2 Section 3.1.3). Substantive changes in Amendment 1 included revising inclusion criterion requirements for bilirubin and methods of birth control, dose modification guidance changes, and adding DOR as an exploratory objective and endpoint.

Substantive changes in Amendment 2 included revising study duration from "3 years" to "up to 7 years", per FDA request; revising the randomization stratification age group from 12 to <17 years old vs. ≥18 years old to 12 to <22 years old vs. ≥22 years old; and modifying several inclusion and exclusion criteria. Updated the dose modification guidelines for adverse reactions for subjects with hepatic impairment and for subjects using a CYP3A inhibitor; allowed prednisone to treat cGVHD to start prior to randomization if the clinical condition of the subject necessitated it; clarified restart of original blinded study therapy in the event of cGVHD worsening following ibrutinib/placebo withdrawal for those who previously responded and discontinued all other immunosuppressants; updated investigational product information to include 70 mg capsule for those needing dose reduction to the 70 mg dose; and revised DOR and Lee cGVHD Symptom Scale improvement from exploratory to secondary objectives/endpoints to address FDA comments; updated the study evaluation requirements; specified tapering for prednisone dose for flares; updated sample size determination to address FDA comments about secondary objectives and recommendations related to monitoring late effects in adolescents.

Substantive changes in Amendment 3 included revising the primary objective/primary endpoint from evaluating the efficacy based on response rate at 24 weeks, up to 48 weeks; evaluation of response rate at 24 weeks was added as a secondary objective/endpoint; adding that efficacy analyses were to be performed on the ITT population (all randomized subjects), rather than the mITT population; clarified that cGVHD flares were expected but if they occurred during response assessments, the clinician had discretion to re-evaluate response when flare had resolved or disease had progressed; revised expected length of follow-up for adolescents (<22 years of age at the time of randomization) from 5 years after randomization to up to 5 years after randomization; however, the study could close after the last subject below 18 years of age had exited the study if all other participating subjects had completed a minimum of 1 year of follow-up.

The FDA's Assessment:
FDA agrees with the Applicant's statement about protocol amendments. The primary endpoint of the Study PCYC-1140-IM was changed by the Applicant from ORR at 24 weeks to ORR at 48 weeks in the Protocol Amendment 3 dated 06 February 2019.

8.1.2.1 Study Results

Compliance with Good Clinical Practices

The Applicant's Position:

Study 1140 was conducted in accordance with the principles of the Declaration of Helsinki and in compliance with Good Clinical Practice. The study was registered with ClinicalTrials.gov (NCT 02959944).

As was the case with Study 1146, conduct of Study 1140 largely occurred during the COVID-19 pandemic, which resulted in the implementation of study-specific guidance for trial conduct during this period (Study 1140 CSR Addendum Appendix 25).

The FDA's Assessment:
FDA agrees with the Applicant's statement.

Financial Disclosure

The Applicant's Position:

Per protocol, completed financial-disclosure forms were to be obtained from the principal investigator as well as sub-investigators for this study (Study 1140 Primary Analysis CSR Revision 2 Appendix 1 Section 12.12). Refer to Refer to Section 19.2 of this document and Module 1.3.4 for further information.

The FDA's Assessment:
FDA agrees with the Applicant's statement.

Patient Disposition

The Applicant's Position:

A total of 193 subjects were randomized, 95 subjects to the Ibr+Pred arm and 98 subjects to the Pbo+Pred arm and comprised the ITT population (Study 1140 Final Analysis CSR Addendum Table 14.1.1.1). Of the 8 subjects aged < 22 years at the time of enrollment, 3 were randomized to the Ibr+Pred arm and 5 were randomized to the Pbo+Pred arm. Two subjects in the ITT population were < 18 years of age at the time of randomization and both were randomized to the Ibr+Pred arm. A total of 190 subjects (98.4%) in the ITT population received at least 1 dose of either ibrutinib or placebo, 94 subjects (98.9%) in the Ibr+Pred arm and 96 subjects (98.0%) in the Pbo+Pred arm and comprised the safety population.

For the final analysis, at the time of the data extract for the final analysis, the median time on study across both arms in the ITT population was 32.7 months (range: 0.03 to 47.2 months); 33.1 months (range: 0.59 to 47.2 months) for the Ibr+Pred arm and 32.5 months (range: 0.03 to 46.6 months) for the Pbo+Pred arm (Table 25).

Study drug disposition for ibrutinib and placebo is summarized in Table 23 and for prednisone in Table 24. Approximately twice the number of subjects discontinued prednisone in the Pbo + Pred arm (20 subjects [20.4%]) compared with subjects in the Ibr + Pred arm (10 subjects [10.5%]), due to subjects beginning treatment with another therapy for cGVHD.

Treatment-emergent AEs were reported as the primary reason for ibrutinib discontinuation for 19 subjects (20.2%) in the safety population in the Ibr+Pred arm; the most common events (≥ 2% of subjects) were atrial fibrillation and pneumonia (2.1% of subjects each [2 subjects each]). (Study 1140 Final Analysis CSR Addendum Table 14.3.1.13). Treatment-emergent AEs were reported as the primary reason for placebo discontinuation for 16 subjects (16.7%) in the safety population in the Pbo+Pred arm; the most common event (≥ 2% of subjects) was fatigue (2 subjects [2.1%]) (Study 1140 Final Analysis CSR Addendum Table 14.3.1.13).

Table 25 provides a summary of subjects' study disposition. In the Ibr+Pred arm, the most common (≥ 5.0% of subjects) primary reasons for discontinuation from the study were study terminated by Sponsor (60.0%), death (23.2%), withdrawal of consent for follow up observation (7.4%), and subject rolled over to the long-term follow-up study (6.3%). In the Pbo+Pred arm, the most common (≥ 5.0% of subjects) primary reasons for discontinuation from the study were study terminated by Sponsor (70.4%), death (21.4%), and withdrawal of consent for follow up observation (6.1%). Of the 8 subjects aged < 22 years at the time of enrollment, 4 subjects exited the study due to the study being terminated by the sponsor, 3 subjects died, and 1 subject was lost to follow up (Study 1140 Final Analysis CSR Addendum Listing 14.1.1.4).

Table 23 Applicant – Study Drug Disposition for Ibrutinib and Placebo – Study 1140 (Intent-to-Treat Population)

	Primary Analysis (Cumulatively up to 30 March 2020)			Final Analysis (Cumulatively up to 12 July 2021)		
	Ibr+Pred (N=95) n (%)	Pbo+Pred (N=98) n (%)	Total (N=193) n (%)	Ibr+Pred (N=95) n (%)	Pbo+Pred (N=98) n (%)	Total (N=193) n (%)
Study drug disposition						
Did not receive study drug[a]	1 (1.1)	2 (2.0)	3 (1.6)	1 (1.1)	2 (2.0)	3 (1.6)
Early study drug discontinuation	65 (68.4)	76 (77.6)	141 (73.1)	81 (85.3)	94 (95.9)	175 (90.7)
Subject still on treatment at study closure[b]	NA	NA	NA	13 (13.7)	2 (2.0)	15 (7.8)
Ongoing	29 (30.5)	20 (20.4)	49 (25.4)	NA	NA	NA
Primary reason for discontinuation of study drug						
Progressive disease – cGVHD	21 (22.1)	30 (30.6)	51 (26.4)	22 (23.2)	30 (30.6)	52 (26.9)
Adverse event NOT related to progressive disease	18 (18.9)	14 (14.3)	32 (16.6)	19 (20.0)	16 (16.3)	35 (18.1)
Investigator decision	11 (11.6)	12 (12.2)	23 (11.9)	22 (23.2)	26 (26.5)	48 (24.9)
Withdrawal of consent for treatment by subject	9 (9.5)	6 (6.1)	15 (7.8)	8 (8.4)	10 (10.2)	18 (9.3)
Subject began treatment with another therapy for cGVHD	2 (2.1)	7 (7.1)	9 (4.7)	2 (2.1)	6 (6.1)	8 (4.1)
Progression or relapse of the underlying disease	1 (1.1)	5 (5.1)	6 (3.1)	3 (3.2)	5 (5.1)	8 (4.1)
Death	3 (3.2)	2 (2.0)	5 (2.6)	4 (4.2)	1 (1.0)	5 (2.6)
Lost to follow-up	0	0	0	1 (1.1)	0	1 (0.5)

cGVHD: chronic graft vs. host disease; Ibr+Pred: ibrutinib and prednisone; NA: not applicable; Pbo+Pred: placebo and prednisone

N=number of subjects in the specified population. Percentages are calculated by 100*n/N.

a Reasons for not receiving study drug include hyperbilirubinemia, relapse of malignant disease, and withdrawal of consent.

b N = 15 subjects includes 6 subjects for whom study drug was on hold, 4 subjects who exited the study without rollover, and 5 subjects who rolled over on to the long-term follow-up study (data on-file).

Source: Study 1140 Final Analysis CSR Addendum Table 14.1.1.4.1; Study 1140 Primary Analysis CSR Revision 2 Table 7

Table 24 Applicant – Study Treatment Disposition for Prednisone – Study 1140 (Intent-to-Treat Population)

	Primary Analysis (Cumulatively up to 30 March 2020)			Final Analysis (Cumulatively up to 12 July 2021)		
	Ibr+Pred (N=95) n (%)	Pbo+Pred (N=98) n (%)	Total (N=193) n (%)	Ibr+Pred (N=95) n (%)	Pbo+Pred (N=98) n (%)	Total (N=193) n (%)
Study treatment disposition						
Did not receive study treatment[a]	1 (1.1)	2 (2.0)	3 (1.6)	1 (1.1)	2 (2.0)	3 (1.6)
Early study treatment discontinuation	52 (54.7)	63 (64.3)	115 (59.6)	81 (85.3)	87 (88.8)	168 (87.0)
Subject still on treatment at study closure	NA	NA	NA	13 (13.7)	9 (9.2)	22 (11.4)
Ongoing	42 (44.2)	33 (33.7)	75 (38.9)	NA	NA	NA
Primary reason for discontinuation of study treatment						
Progressive disease - cGVHD	13 (13.7)	21 (21.4)	34 (17.6)	17 (17.9)	21 (21.4)	38 (19.7)
Subject began treatment with another therapy for cGVHD	10 (10.5)	19 (19.4)	29 (15.0)	10 (10.5)	20 (20.4)	30 (15.5)
Investigator decision	8 (8.4)	8 (8.2)	16 (8.3)	30 (31.6)	27 (27.6)	57 (29.5)
Adverse event not related to progression of cGVHD	6 (6.3)	2 (2.0)	8 (4.1)	8 (8.4)	2 (2.0)	10 (5.2)
Withdrawal of consent for treatment by subject	8 (8.4)	5 (5.1)	13 (6.7)	8 (8.4)	7 (7.1)	15 (7.8)
Death	5 (5.3)	3 (3.1)	8 (4.1)	3 (3.2)	2 (2.0)	5 (2.6)
Progression or relapse of the underlying disease	2 (2.1)	5 (5.1)	7 (3.6)	3 (3.2)	8 (8.2)	11 (5.7)
Lost to follow-up	0	0	0	2 (2.1)	0	2 (1.0)

cGVHD: chronic graft vs. host disease; Ibr+Pred: ibrutinib and prednisone; NA: not applicable; ebo and prednisone

N=number of subjects in the specified population. Percentages are calculated by 100*n/N. Prednisone (or equivalent) administered as study treatment.

a Reasons for not receiving study drug include NOT eligible to start study drug prednisone is documented as CONMED, relapse of the malignant disease, and withdrawal of consent.

Source: Study 1140 Final Analysis CSR Addendum Table 14.1.1.4.2; Study 1140 Primary Analysis CSR Revision 2 Table 8

Table 25 Applicant – Study Disposition – Study 1140 (Intent-to-Treat Population)

	Final Analysis (Cumulatively up to 12 July 2021)		
	Ibr+Pred (N=95) n (%)	Pbo+Pred (N=98) n (%)	Total (N=193) n (%)
Subject Status			
Off study	95 (100.0)	98 (100.0)	193 (100.0)
Primary Reason for Study Exit			
Withdrawal of consent for follow up observation	7 (7.4)	6 (6.1)	13 (6.7)
Lost to follow-up	3 (3.2)	1 (1.0)	4 (2.1)
Study terminated by sponsor	57 (60.0)	69 (70.4)	126 (65.3)
Rollover to long-term follow-up study	6 (6.3)	0	6 (3.1)
Death	22 (23.2)	21 (21.4)	43 (22.3)
Other[a]	0	1 (1.0)	1 (0.5)
Time on study (months)[b]			
Median	33.1	32.5	32.7
Min, Max	0.59, 47.2	0.03, 46.6	0.03, 47.2

Ibr+Pred: ibrutinib and prednisone; Pbo+Pred: placebo and prednisone

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

a Other reasons include investigator decision.

b Time on study is based on the follow-up time of overall survival and median is estimated using the reverse Kaplan-Meier method.

Source: Study 1140 Final Analysis CSR Addendum Table 14.1.1.4

The FDA's Assessment:
FDA agrees with the Applicant's statement.

Protocol Violations/Deviations

The Applicant's Position:

In the primary analysis CSR, important protocol deviations were reported for 4 subjects (4.2%) in the Ibr+Pred arm and 1 subject (1.0%) in the Pbo+Pred arm, all of which were eligibility criteria deviations (Study 1140 Primary Analysis CSR Revision 2 Section 4.4). In the final analysis, 1 subject in the Ibr+Pred arm had an eligibility criteria deviation (Study 1140 Final Analysis CSR Addendum Section 4.4). In general, none of the important protocol deviations were likely to have affected the overall efficacy and safety findings of this study. There were no important

protocol deviations due to logistical restrictions resulting from the COVID-19 pandemic (Study 1140 Final Analysis CSR Addendum Section 4.4.1).

The FDA's Assessment:
FDA agrees with the Applicant's statement.

Table of Demographic Characteristics

The Applicant's Position:

Demographic characteristics were generally well balanced between treatment arms with the exception of a higher proportion of white subjects in the Pbo + Pred arm (Table 26).

Table 26 Applicant – Subject Demographics – Study 1140 (Intent-to-Treat Population)

	Ibr + Pred (N=95)	Pbo + Pred (N=98)	Total (N=193)
Age (Years)			
n	95	98	193
Mean (standard deviation)	50.0 (14.48)	51.1 (14.99)	50.6 (14.71)
Median	51.0	56.0	55.0
Min, Max	13, 72	18, 76	13, 76
Age groups - n (%)			
< 65 years	79 (83.2)	79 (80.6)	158 (81.9)
≥ 65 years	16 (16.8)	19 (19.4)	35 (18.1)
12 - 17 years	2 (2.1)	0	2 (1.0)
≥ 18 years	93 (97.9)	98 (100.0)	191 (99.0)
Gender - n (%)			
Male	61 (64.2)	65 (66.3)	126 (65.3)
Female	34 (35.8)	33 (33.7)	67 (34.7)
Race - n (%)			
American Indian or Alaska Native	1 (1.1)	0	1 (0.5)
Asian	27 (28.4)	19 (19.4)	46 (23.8)
Black or African American	6 (6.3)	4 (4.1)	10 (5.2)
Multiple	1 (1.1)	1 (1.0)	2 (1.0)
Native Hawaiian or Other Pacific Islander	1 (1.1)	0	1 (0.5)
Unknown	12 (12.6)	16 (16.3)	28 (14.5)
White	47 (49.5)	58 (59.2)	105 (54.4)
Ethnicity - n (%)			
Hispanic or Latino	5 (5.3)	2 (2.0)	7 (3.6)
Not Hispanic or Latino	78 (82.1)	78 (79.6)	156 (80.8)
Not reported	12 (12.6)	18 (18.4)	30 (15.5)
Geographic region - n (%)			
Non-US	56 (58.9)	58 (59.2)	114 (59.1)
US	39 (41.1)	40 (40.8)	79 (40.9)

Ibr+Pred: ibrutinib and prednisone; Pbo+Pred: placebo and prednisone; US: United States

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

Baseline is defined as the last measurement taken on or prior to first dose date of study drug or the date of randomization for non-treated subjects.

Source: Study 1140 Primary Analysis Revision 2 CSR Table 14.1.2.1

The FDA's Assessment:

Data from PCYC-1140-IM (INTEGRATE) will be not sufficient (b) (4) in light of the failed trial in adults in this setting. Study data was not independently verified.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The Applicant's Position:

Baseline characteristics were well balanced between arms (Table 27).

Table 27 Applicant – Summary of Baseline Characteristics – Study 1140 (Intent-to-Treat Population)

	Ibr+Pred (N=95)	Pbo+Pred (N=98)	Total (N=193)
Creatinine clearance (mL/min)			
Mean (standard deviation)	112.5 (50.76)	110.9 (53.41)	111.7 (52.00)
Median	99.0	100.2	100.2
Min, Max	37.8, 261.0	31.2, 364.8	31.2, 364.8
30 - 60 - n (%)	13 (13.7)	14 (14.3)	27 (14.0)
> 60 - n (%)	82 (86.3)	84 (85.7)	166 (86.0)
Hepatic impairment[a] - n (%)			
Yes	39 (41.1)	41 (41.8)	80 (41.5)
No	51 (53.7)	50 (51.0)	101 (52.3)
Missing	5 (5.3)	7 (7.1)	12 (6.2)
Time from transplant to cGVHD diagnosis (months)			
Mean (standard deviation)	11.2 (11.05)	11.7 (11.69)	11.4 (11.36)
Median	7.6	8.3	8.0
Min, Max	1.3, 72.9	3.1, 88.1	1.3, 88.1
Time from initial cGVHD diagnosis to randomization (months)			
Mean (standard deviation)	2.1 (5.07)	1.5 (3.31)	1.8 (4.27)
Median	0.4	0.4	0.4
Min, Max	0.0, 39.8	0.0, 25.7	0.0, 39.8
NIH global cGVHD severity grade[b] - n (%)			
Moderate	55 (57.9)	56 (57.1)	111 (57.5)
Severe	40 (42.1)	42 (42.9)	82 (42.5)
Prophylactic GVHD treatment - n (%)			
Yes	85 (89.5)	88 (89.8)	173 (89.6)
No	10 (10.5)	10 (10.2)	20 (10.4)
History of acute GVHD - n (%)			
Yes	50 (52.6)	55 (56.1)	105 (54.4)
No	45 (47.4)	43 (43.9)	88 (45.6)
Malignant underlying disease - n (%)			
Yes	94 (98.9)	96 (98.0)	190 (98.4)
No	1 (1.1)	2 (2.0)	3 (1.6)

	Ibr+Pred (N=95)	Pbo+Pred (N=98)	Total (N=193)
Ongoing use of systemic immunosuppressants[c] - n (%)			
Yes	50 (52.6)	56 (57.1)	106 (54.9)
No	45 (47.4)	42 (42.9)	87 (45.1)
Karnofsky Score[d]			
Mean (standard deviation)	83.7 (12.12)	84.1 (8.35)	83.9 (10.35)
Median	80.0	80.0	80.0
Min, Max	10.0, 100.0	60.0, 100.0	10.0, 100.0
Score < 80 - n (%)	12 (12.6)	11 (11.2)	23 (11.9)
Score ≥ 80 - n (%)	83 (87.4)	87 (88.8)	170 (88.1)

cGVHD: chronic graft vs. host disease; GVHD: graft vs. host disease; Ibr+Pred: ibrutinib and prednisone; NCI ODWG: National Cancer Institute organ dysfunction working group; NIH: National Institutes of Health; Pbo+Pred: placebo and prednisone

Baseline is defined as the last measurement taken on or prior to first dose date of study drug or the date of randomization for non-treated subjects or first study measurement, where applicable.

a Based on NCI ODWG liver function classification.

b cGVHD staging per NIH Criteria recorded in the clinical database.

c Immunosuppressants that were initiated for either treatment of acute GVHD or prophylaxis of GVHD as reported in the clinical database.

d Lansky scores were used for the 2 pediatric subjects.

Source: Study 1140 Primary Analysis CSR Revision 2 Table 14.1.2.2

The FDA's Assessment:

Data from PCYC-1140-IM (INTEGRATE) will be not sufficient (b) (4) in light of the failed trial in adults in this setting. Study data was not independently verified.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Treatment Compliance

No formal treatment compliance measurements were performed. However, at the final analysis, the median relative dose intensities (the actual dose received divided by the standard calculated dose during a set period) for ibrutinib and placebo were 100.0% and 99.2%, respectively (Study 1140 Final Analysis CSR Addendum Table 5).

Concomitant Medications

At the final analysis, the most common concomitant medications by therapeutic class (≥ 70% of subjects in either treatment arm) were, by Ibr+Pred vs. Pbo+Pred arms, antibacterials for systemic use (92.6% vs. 95.8%), antimycotics for systemic use (83.0% vs. 85.4%), antivirals for systemic use (92.6% vs. 94.8%), and drugs for acid related disorders (74.5% vs. 75.0%) (Study 1140 Final Analysis CSR Addendum Table 4). A total of 52.1% of subjects in the Ibr+Pred arm and 54.2% of subjects in the Pbo+Pred arm took at least 1 concomitant systemic immunosuppressant medication other than prednisone (Study 1140 Final Analysis CSR Addendum Table 14.1.4.4). Concomitant moderate/strong CYP3A inhibitors were used by 84.0% of subjects in the Ibr+Pred arm and 86.5% of subjects in the Pbo+Pred arm (Study 1140 Final Analysis CSR Addendum Table 14.1.4.5). Strong CYP3A inhibitors were used by 69.1% subjects in the Ibr+Pred arm, and 64.6% of subjects in the Pbo+Pred arm. A strong CYP3A inducer was used by 1 subject (1.1%) in the Ibr+Pred arm (phenytoin); no subjects in the Pbo+Pred arm used a strong CYP3A inducer (Study 1140 Final Analysis CSR Addendum Table 14.1.4.6). Anticoagulants were used by 11.7% and 17.7% of subjects in the Ibr+Pred and Pbo+Pred arms, respectively (Study Final Analysis 1140 CSR Addendum Table 14.1.4.7). Antiplatelets were used by 21.3% and 19.8% of subjects in the Ibr+Pred and Pbo+Pred arms, respectively.

The FDA's Assessment:
Data from PCYC-1140-IM (INTEGRATE) will be not sufficient (b) (4) in light of the failed trial in adults in this setting. Study data was not independently verified.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

The Applicant's Position:

In the primary analysis, the proportion of responders with a CR or PR at 48 weeks was 41.1% for the Ibr+Pred arm vs. 36.7% for the Pbo+Pred arm: p = 0.5384 (Table 28). The study did not meet its primary endpoint. Since statistical significance for the primary endpoint was not achieved, formal testing of the secondary endpoints was not performed and nominal p-values for the secondary endpoints were reported.

Table 28 Applicant – Response Rate at 48 Weeks – Study 1140 (Intent-to-Treat Population)

	Primary Analysis (Cumulatively up to 30 March 2020)			Final Analysis (Cumulatively up to 12 July 2021)		
	Ibr+Pred (N=95) n (%)	Pbo+Pred (N=98) n (%)	(Ibr+Pred) – (Pbo+Pred)	Ibr+Pred (N=95) n (%)	Pbo+Pred (N=98) n (%)	(Ibr+Pred) – (Pbo+Pred)
Response rate at 48 weeks (CR or PR)[a]						
n (%)	39 (41.1)	36 (36.7)		39 (41.1)	36 (36.7)	
Difference in rates (95% CI)[b]			0.043 (-0.094, 0.181)			0.043 (-0.094, 0.181)
p-Value[b]			0.5384			0.5384
Response at 48 weeks						
Complete response (CR)[c]	10 (10.5)	6 (6.1)		9 (9.5)	6 (6.1)	
Partial response (PR)	29 (30.5)	30 (30.6)		30 (31.6)	30 (30.6)	
Stable disease (standard deviation)	4 (4.2)	2 (2.0)		4 (4.2)	2 (2.0)	
Progressive disease	22 (23.2)	35 (35.7)		23 (24.2)	34 (34.7)	
Not evaluable due to cGVHD flare	1 (1.1)	2 (2.0)		1 (1.1)	3 (3.1)	
Death	7 (7.4)	1 (1.0)		7 (7.4)	1 (1.0)	
Subsequent therapy	14 (14.7)	14 (14.3)		12 (12.6)	14 (14.3)	
Relapse of underlying disease	2 (2.1)	6 (6.1)		2 (2.1)	5 (5.1)	
No responses available on or after Week 48[d]	6 (6.3)	2 (2.0)		7 (7.4)	3 (3.1)	

cGVHD: chronic graft vs. host disease; CI: confidence interval; CR: complete response; FU: follow up; Ibr+Pred: ibrutinib and prednisone; Pbo+Pred: placebo and prednisone; PR: partial response

a Response rate estimated using the crude proportion of responders. Responders are subjects who had response (PR or CR) at 48 weeks (study day 296-379) without starting any subsequent therapy for cGVHD or having evidence of relapse of underlying disease that was indication for transplant prior to response assessment at 48 weeks.

b Confidence interval is computed using normal approximation and p-value are computed using non-stratified Chi-Square test.

c For 1 subject in the Ibr+Pred treatment group, the change from "CR" in Primary Analysis to "PR" in the Final Analysis of Response at Weeks 24 and 48 was a data change resulting from a post-primary analysis data correction at site level.

d Subject discontinued study, withdrew consent for response FU prior to Week 48, or no response available on or after Week 48.

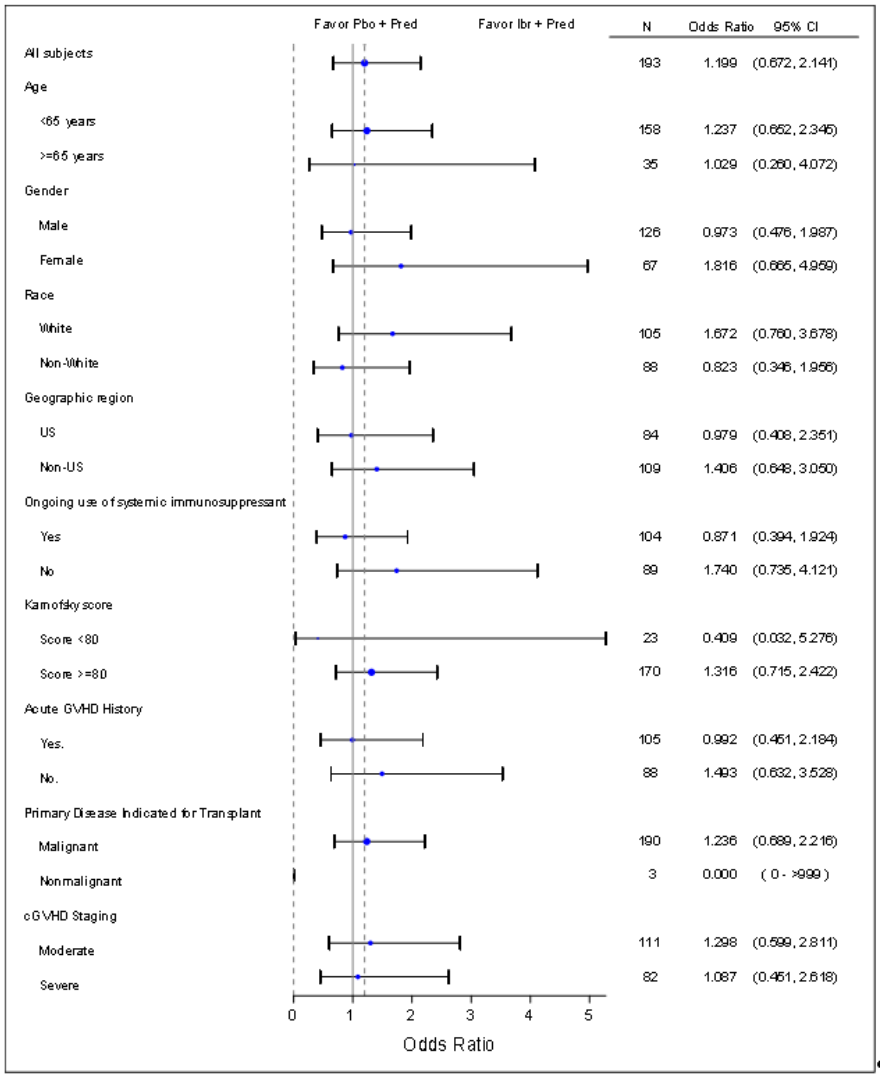
Source: Study Final Analysis 1140 CSR Addendum Table 14.2.1 and Study 1140 Primary Analysis CSR Revision 2 Table 20

A sensitivity analysis was conducted for the modified ITT (mITT) population, which included all ITT subjects who did not have evidence of progression of underlying malignancy at or before randomization; the proportion of responders with a CR or PR at 48 weeks was 41.1% for the Ibr+Pred arm vs. 37.1% for the Pbo+Pred arm: p = 0.5759 (Study 1140 Final Analysis CSR Addendum Table 14.2.1.1).

A review of subjects' Week 49 information (data on file) showed that COVID-19 did not have an impact on the primary endpoint of response rate at 48 weeks (Study Final Analysis 1140 CSR Addendum Section 3).

Subgroup analysis of the response rate at 48 weeks for the prespecified subgroups is presented in Figure 3.

Figure 3 Applicant – Forest Plot for Response Rate at 48 Weeks – Subgroup Analysis – Study 1140 (Intent-to-Treat Population)



sas-prod: BTK/PCYC-1140-IM/CSR_Final/Programs/f_eff_wk48_subgroup.sas merge Created on: 30AUG21:16:48:48

cGVHD: chronic graft vs. host disease; CI: confidence interval; Ibr+Pred: ibrutinib and prednisone; GVHD: graft vs. host disease; Pbo+Pred: placebo and prednisone; US: United States

Source: Study 1140 Final Analysis CSR addendum Figure 14.2.2

The FDA's Assessment:

The Applicant reported a negative result for the analysis of the primary efficacy endpoint of ORR at 48 weeks (41% vs 37%, p = 0.54).

Table 29 shows the negative results for the primary efficacy endpoint of ORR by Week 25 per Applicant-reported and per FDA-adjudicated responses.

Table 29. Negative Results of primary efficacy endpoint of OR by week 25

	Ibrutinib with prednisone (N=95)		Placebo with prednisone (N=98)	
Study 1140	N	%	N	%
Applicant reported Response by Week 25				
CR+PR	74	77.9%	82	83.7%
CR	16	16.8%	13	13.3%
PR	58	61.1%	69	70.4%
FDA Adjudicated Response by Week 25				
CR+PR	**69**	**72.6%**	**77**	**78.6%**
CR	11	11.6%	8	8.2%
PR	58	61.1%	69	70.4%

FDA re-analyzed the data using the accepted efficacy endpoint of OR by Week 25 visit using FDA-adjudicated responses, and we found a negative result for this endpoint as well, with ORR by Week 25 being 73% for ibrutinib+prednisone arm vs 79% for placebo+prednisone.

From this FDA concluded that the data from Study PCYC-1140-IM do not support (b) (4) of cGVHD.

Data Quality and Integrity

The Applicant's Position:

The data gathered and analyzed by study investigators were entered into an electronic database maintained by Pharmacyclics LLC. Study 1140 included site or remote monitoring performed by representatives of Pharmacyclics LLC or its designee. Pharmacyclics LLC was responsible for the detailed Trial Monitoring Plan, which defined and standardized all monitoring processes for the Clinical Research Associates/Site Monitors. On-site or remote periodic monitoring also occurred for specified critical variables per Trial Monitoring Plan. Sites were provided with a CRF instruction booklet. Data Management reviewed the data and queried sites as appropriate using edit checks and clinical review.

Information requested by the Office of Scientific Investigations (OSI) for Study 1140 is provided in Module 5.3.5.4. In general, no issues were identified with the quality or integrity of data from Study 1140 which could affect the efficacy findings.

The FDA's Assessment:
Data from PCYC-1140-IM (INTEGRATE) will be not sufficient (b) (4) in light of the failed trial in adults in this setting. Study data was not independently verified.

Efficacy Results – Secondary and other relevant endpoints

The Applicant's Position:

Secondary Efficacy Endpoints

- Forty-five subjects (47.4%) in the Ibr+Pred arm and 38 subjects (38.8%) in the Pbo+Pred arm had withdrawn from all corticosteroids. The nominal p-value comparing the cumulative incidence of time to withdrawal of all corticosteroids was p = 0.281 (Study 1140 Final Analysis CSR Addendum Table 9).
- Thirty-seven subjects (38.9%) in the Ibr+Pred arm and 30 subjects (30.6%) in the Pbo+Pred arm had withdrawn from all immunosuppressants including corticosteroids. The nominal p-value comparing the cumulative incidence of time to withdrawal of all immunosuppressants including corticosteroids was p = 0.216 (Study 1140 Final Analysis CSR Addendum Table 10).
- Seventeen subjects (17.9 %) in the Ibr+Pred arm and 8 subjects (8.2 %) in the Pbo+Pred arm had withdrawn from all immunosuppressants including corticosteroids and study treatment (ibrutinib/placebo). The nominal p-value comparing the cumulative incidence of time to withdrawal of all immunosuppressants including corticosteroids and study treatment was p = 0.030 (Study 1140 Final Analysis CSR Addendum Table 11).
- The proportion of responders with a CR or PR at 24 weeks was 47.4% for the Ibr+Pred arm and 54.1% for the Pbo+Pred arm; nominal p = 0.3510 (Study 1140 Final Analysis CSR Addendum Table 12).
- Treatment was associated with an improvement in the Lee cGVHD Symptom Scale summary score (defined as at least 7-point decrease at 2 consecutive visits) for 43.2% of subjects in the Ibr+Pred arm and 30.6% of subjects in the Pbo+Pred arm; nominal p = 0.0708 (Study 1140 Final Analysis CSR Addendum Table 13). An improvement associated with treatment in the modified Lee cGVHD Symptom Scale summary score, defined as a decrease of at least 5-points at 2 consecutive visits, was observed for 52.6% of subjects in the Ibr+Pred arm and 38.8% of subjects in the Pbo+Pred; nominal p = 0.0533; an improvement defined as a decrease of at least a 6-points at 2 consecutive visits, was observed for 48.4% of subjects in

the Ibr+Pred arm and 34.7% of subjects in the Pbo+Pred; nominal p = 0.0530 (Study 1140 Final Analysis CSR Addendum Table 14).

- A corticosteroid dose reduction to a level of less than 0.15 mg/kg/day at 24 weeks sustained for at least 30 days was observed for 41.1% of subjects in the Ibr+Pred arm and 45.9% of subjects in the Pbo+Pred arm; nominal p = 0.4955 (Study 1140 Final Analysis CSR Addendum Table 15).
- Overall survival (23 deaths in the Ibr+Pred arm; 22 deaths in the Pbo+Pred arm) was similar for both treatment arms: hazard ratio (HR): 1.061 (95% CI: 0.591, 1,904). The median OS was not reached for either arm (Study 1140 Final Analysis CSR Addendum Table 16).
- For subjects who had a response (subjects with a CR or PR at any time), the median DOR was 19.1 months (95% confidence interval [CI]: 7.4 months to not estimable) for the Ibr+Pred arm and 10.2 months (95% CI: 6.5 to 17.1 months) for the Pbo+Pred arm; nominal p = 0.1004 (Study 1140 Final Analysis CSR Addendum Table 17).

Post-hoc Analyses

- Median EFS was 15.0 months in the Ibr+Pred arm and 8.3 months in the Pbo+Pred arm (nominal p-value = 0.1091). The HR for EFS was 0.756 (95% CI: 0.535, 1.066) (Study 1140 Final Analysis CSR Addendum Table 18).
- The rate of relapse of the underlying malignancy in subjects who received at least 1 dose of study drug was 8.5% (8/94) in the Ibr+Pred arm vs. 12.5% (12/96) in the Pbo+Pred arm (Study 1140 Final Analysis CSR Addendum Table 19).

The FDA's Assessment:
Data from PCYC-1140-IM (INTEGRATE) will be not sufficient (b) (4) in light of the failed trial in adults in this setting. Study data was not independently verified.

Dose/Dose Response

The Applicant's Position:

There were no dose/dose response analyses in this study.

The FDA's Assessment:
Data from PCYC-1140-IM (INTEGRATE) will be not sufficient (b) (4) in light of the failed trial in adults in this setting. Study data was not independently verified.

Durability of Response

At the final analysis, the proportion of responders with a CR or PR at 24 weeks was 47.4% for the Ibr+Pred arm and 54.1% for the Pbo+Pred arm; nominal p = 0.3510 (see Efficacy Results – Secondary and other relevant endpoints for relevant data).

The FDA's Assessment:
Data from PCYC-1140-IM (INTEGRATE) will be not sufficient (b) (4) in light of the failed trial in adults in this setting. Study data was not independently verified.

Persistence of Effect

The Applicant's Position:

Time-to-event Analyses (i.e., OS, EFS)

See Efficacy Results – Secondary and other relevant endpoints for relevant data.

The FDA's Assessment:
Data from PCYC-1140-IM (INTEGRATE) (b) (4) in light of the failed trial in adults in this setting. Study data was not independently verified.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:

Improvement in the Lee cGVHD Symptom Scale summary score and Modified Lee cGVHD Symptom Scale summary score

See Efficacy Results – Secondary and other relevant endpoints for relevant data.

Improvement in Short Form Health Survey (SF-36) Patient Reported Outcome

At the final analysis, with the exception of higher general health norm-based scores in the Ibr+Pred arm, no differences were observed between the treatment arms in SF-36 scores

across the domains (Study Final Analysis 1140 CSR Addendum Table 14.2.12 and Figure 14.2.12).

Improvement in Karnofsky/Lansky Performance Scale Score

At the final analysis, no differences were observed between the treatment arms in Karnofsky/Lansky Performance Scale scores (Study 1140 Final Analysis CSR Addendum Table 14.2.13 and Figure 14.2.13).

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

No additional analyses were conducted for this study.

The FDA's Assessment:
Data from PCYC-1140-IM (INTEGRATE) will be not sufficient (b) (4) in light of the failed trial in adults in this setting. Study data was not independently verified.

8.1.3. PCYC-1129-CA

Trial Design

The Applicant's Description:

Study 1129 was a Phase 1b/2 open-label study designed to evaluate the safety and efficacy of ibrutinib in treating subjects with steroid dependent/refractory chronic GVHD. The study was a single-arm study conducted in 2 phases. Phase 1b evaluated the safety of a once daily dose of ibrutinib 420 mg, with the potential for subsequent dose reductions (to 280 mg and 140 mg) if dose-limiting toxicities (DLTs) were detected. Between 6-27 subjects were to be evaluated in depending on the frequency of DLTs and the need for dose reductions. A modified 3 + 3 + 3 design was used to determine the recommended Phase 2 dose (RP2D). All available safety and laboratory data were to be reviewed in a Dose Level Review Meeting by the Sponsor in conjunction with the study investigators. Once the RP2D was determined, Phase 2 commenced; subjects were given ibrutinib once daily at the RP2D along with their pre-existing

immunosuppressants for cGVHD and followed for signs of progression or resolution of cGVHD. Enrollment continued until approximately 40 subjects from both Phases 1b and 2 of the study received the RP2D. Subjects were treated until the occurrence of a DLT in the Phase 1b study or until disease progression, unacceptable toxicity, recurrence of underlying malignancy, withdrawal of consent, or closure of the Phase 2 part of the study. Data are summarized for subjects through the date of data cutoff for the final analysis (15 September 2017; data extraction date for the final cumulative analysis).

The FDA's Assessment:
Study 1129 was a Phase 1/2 study designed to test efficacy of ibrutinib in adult patients with recurrent or refractory cGVHD.

The Applicant submitted efficacy results updated from a data cut with an overall follow-up time of up to 37 months. This updated data in patients who have been followed since the original submission S017. There are no new patients for S-37, just the same 42 patients from the original submission S-17.

It's not clear whether all patients did have follow-up to Week 25 in the original submission S017 [Based on NDA 205552 S017 clinical review in 2017: 45% (19/42) patients had duration of treatment <3 months]. But this new S-37 included new data with follow-up to Week 25.
The new data from long-term follow-up included patients with an overall follow-up time of up to 37 months, with much longer duration of follow-up than that in the original submission S-17

Study Endpoints

The Applicant's Description:

In Phase 1b, the primary endpoint was safety and tolerability (DLTs). The primary efficacy endpoint for the study was best overall cGVHD response rate (BORR) according to the 2005 NIH Consensus Panel Response Criteria with modification. The secondary endpoints were rate of sustained response for at least 5 months, DOR, corticosteroid requirement changes over time, rate of improvement in Lee cGVHD Symptom Scale, and safety. The exploratory endpoints were FFS, photographic changes in skin and mucocutaneous manifestations, PK, biomarkers, and pharmacodynamic parameters.

The FDA's Assessment:
FDA agrees with the Applicant's statement.

Statistical Analysis Plan and Amendments

The Applicant's Description:

For the primary endpoint, the response rate and corresponding 95% confidence interval (CI) and p-value based on the exact binomial distribution were calculated. If the lower bound of the 95% CI of the response rate was ≥ 25%, the primary efficacy objective was achieved. Sustained responses were assessed based on the proportion (and 95% exact CI) of subjects who achieved an NIH-defined complete response (CR) or partial response (PR) that was sustained for at least 20 weeks (140 days). Time-to-event variables (eg, DOR and FFS) were assessed using Kaplan-Meier methodology to provide estimates of median time to event with 95% CIs when available. Changes in corticosteroid use were evaluated over time and based on the proportion of subjects who achieved 1 or more weeks where average daily steroid doses were < 0.15 mg/kg/day. In addition, the proportion of responders discontinuing corticosteroid therapy while in response was evaluated. For the rate of improvement in Lee cGVHD Symptom Scale, the proportion of subjects who had clinical meaningful improvement, defined as decreases of at least 7 points in Lee cGVHD Symptom Scale summary score, was summarized descriptively by overall and by 6 months for all subjects, responders, and non-responders. Descriptive summaries and/or listings were provided for DLTs (Phase 1b only), treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and other safety parameters including laboratory data. All other safety analyses, and all efficacy analyses, combined data from both study phases since the same dose and schedule (the RP2D) were used throughout the study.

The same statistical methods from the primary analysis were used for the final analysis with the following exceptions. Sustained response was analyzed at 2 additional time points, 32 weeks and 44 weeks. In addition to tabulation of the proportion of subjects with decreases of at least 7 points in Lee cGVHD Symptom Scale summary score (improvement), the proportion of subjects showing at least a 7 point decrease in Lee Symptom Scale overall score on at least 2 consecutive visits was tabulated. The categorization of cytochrome P450, family 3, subfamily A inhibitors was updated following the primary analysis, and data were tabulated by strength of the inhibitor (strong, moderate, weak, or other). The time period when study drug dosing was on hold because the physician felt the subject no longer needed systemic therapy for cGVHD

was excluded from the calculation of study drug exposure. Pharmacokinetic and biomarker results were reported in the primary analysis CSR.

The FDA's Assessment:
FDA agrees with the Applicant's statement.

Protocol Amendments

The Applicant's Description:

There were 2 amendments to the protocol. Amendment 1 key changes included updating the objectives of Phase 1b and Phase 2 parts of the study; updating sample size and statistical analysis section based on preliminary evidence of response; increasing screening phase period to 42 days and baseline time period for stable corticosteroid and immunosuppressive therapies prior to study entry; updating inclusion criteria; updating clinical safety language and risk section to match IB Version 8.0; amending protocol's response criteria with 2 modifications based on 2014 NIH criteria; addition of response assessment at Week 5. Amendment 2 changes included aligning language with that used in IB Version 9.0; updating enrollment number of subjects and study procedures to allow treatment of ≥18 months; adding inclusion of subjects with abnormal coagulation results unrelated to coagulopathy or bleeding disorders; and clarifying CYP3A language as it relates to ibrutinib dosing.

The FDA's Assessment:
FDA agrees with the Applicant's statement.

8.1.3.1 Study Results

Compliance with Good Clinical Practices

The Applicant's Position:

Study 1129 was conducted in accordance with the principles of the Declaration of Helsinki and in compliance with Good Clinical Practice. The study was registered with ClinicalTrials.gov (NCT02195869).

The FDA's Assessment:

FDA agrees with the Applicant's statement.

Financial Disclosure

The Applicant's Position:

Per protocol, completed financial-disclosure forms were to be obtained from the principal investigator as well as sub-investigators for this study (Study 1129 Primary Analysis CSR Appendix 1 Section 12.12). Refer to Section 19.2 of this document and Module 1.3.4 for further information.

The FDA's Assessment:
FDA agrees with the Applicant's statement.

Patient Disposition

The Applicant's Position:

At the time of the final analysis, all subjects had discontinued ibrutinib (Table 30). Unacceptable toxicity was the most common primary reason for discontinuation of study drug (35.7%). With longer follow up, the median (range) time on study increased from 13.9 months (0.5 to 24.9 months) to 25.6 months (0.5 to 36.7 months).

Table 30 Applicant – Disposition of Study Treatment – Study 1129 (All-Treated Population)

	Primary Analysis (Cumulatively up to 01 September 2016) (N=42)	Final Analysis (Cumulatively up to 15 September 2017) (N=42)
Study treatment phase disposition; n (%)		
Discontinued study drug	30 (71.4)	42 (100.0)
Ongoing	12 (28.6)	0
Primary reason for study drug discontinuation; n (%)		
cGVHD progression	5 (11.9)	5 (11.9)
Malignancy progression/relapse	2 (4.8)	2 (4.8)
Unacceptable toxicity	14 (33.3)	15 (35.7)
Withdrawal by subject	6 (14.3)	7 (16.7)
Physician decision	2 (4.8)	4 (9.5)
Study terminated by Sponsor	NA	7 (16.7)
Noncompliance with study drug	1 (2.4)	2 (4.8)
Time on study (months)[a]		
Median (95% CI)	13.90 (10.97, 16.59)	25.56 (21.19, 28.16)
Min, Max	0.53, 24.87	0.53, 36.70

cGVHD: chronic graft vs. host disease; CI: confidence interval; NA: not applicable

a Time on study was defined as the interval between the date of first dose of study drug and the study exit date. The reverse Kaplan-Meier method was used to estimate the median time on study with subjects who died being censored at death date.

Source: Study 1129 Final Analysis CSR Addendum Table 14.1.1.3 and Table 14.1.1.4; NDA205552/SN0181/Module 5.3.5.2/Study 1129 Primary Analysis CSR Table 5

The FDA's Assessment:
FDA agrees with the Applicant's statement.

Protocol Violations/Deviations

The Applicant's Position:

Five subjects (11.9%) had important protocol deviations (including 3 subjects with eligibility deviations and 2 with consent deviations) (NDA205552/SN0181/Module 5.3.5.2/Study 1129 Primary Analysis CSR Table 8). Based on Sponsor assessment, these deviations were unlikely to have affected the overall efficacy and safety results of the study.

The FDA's Assessment:
FDA agrees with the Applicant's statement.

Table of Demographic Characteristics

The Applicant's Position:

The demographic characteristics at baseline were generally reflective of the target population (Table 31). Approximately half of subjects (52.4%) were male. Most subjects were white (92.9%). The median age at baseline was 56.0 years (range: 19-74 years), and 83.3% of subjects were < 65 years of age.

Table 31 Applicant – Demographic Characteristics – Study 1129 (All-Treated Population)

	Total N=42
Age (years)	
Mean (SD)	50.5 (15.53)
Median	56.0
Min, Max	19, 74
<65 years	35 (83.3%)
≥65 years	7 (16.7%)
Gender, n (%)	
Male	22 (52.4)
Female	20 (47.6)
Race, n (%)	
Asian	1 (2.4)
Black or African American	1 (2.4)
White	39 (92.9)
Subject declined to answer/unknown	1 (2.4)
Ethnicity, n (%)	
Hispanic or Latino	2 (4.8)
Not Hispanic or Latino	40 (95.2)

SD: standard deviation

Source: NDA205552/SN0181/Module 5.3.5.2/Study 1129 Primary Analysis CSR Table 14.1.2.1

The FDA's Assessment:
FDA agrees with the Applicant's statement.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The Applicant's Position:

Key baseline characteristics are summarized in (Table 32). The majority of subjects (88.1%) had 2 or more organs involved at baseline, with the most commonly involved organs being mouth (85.7%), skin (81.0%), and gastrointestinal tract (GI) (33.3%) (NDA205552/SN0181/Module 5.3.5.2/Study 1129 Primary Analysis CSR Table 14.1.2.4). The majority of subjects (92.9%) had had only 1 transplant (NDA205552/SN0181/Module 5.3.5.2/Study 1129 Primary Analysis CSR Table 14.1.3.1). The median time from last transplant to enrollment in the study was 25.7 months. Most subjects had a history of non-myeloablative hematopoietic (stem) cell transplantation (HCT) (57.1%), and most subjects received their transplant from an unrelated donor (59.5%). For most subjects (88.1%), the cell graft was human leukocyte antigen (HLA) matched between donor and recipient. The source of stem cells for most subjects was peripheral blood (88.1%). The most common underlying malignancies leading to transplant were acute lymphocytic leukemia (16.7%), acute myeloid leukemia (AML) (16.7%), and chronic lymphocytic leukemia (16.7%) (NDA205552/SN0181/Module 5.3.5.2/Study 1129 Primary Analysis CSR Table 14.1.3.4).

Table 32 Applicant – Baseline Disease Characteristics – Study 1129 (All-Treated Population)

	Total N=42
Months from initial cGVHD diagnosis date to study entry	
Mean (SD)	18.0 (14.96)
Median	13.7
Min, Max	1.1, 63.2
Months from transplant to initial cGVHD diagnosis	
Mean (SD)	11.6 (14.39)
Median	7.6
Min, Max	1.5, 76.0
Karnofsky Performance Status Score, n (%)	
100	3 (7.1)
90	14 (33.3)
70 – 80	22 (52.4)
60	3 (7.1)
Number of prior cGVHD treatment regimens	
Mean (SD)	1.8 (0.73)
Median	2.0
Min, Max	1.0, 3.0
1	17 (40.5%)
2	18 (42.9%)
3	7 (16.7%)
Did subject receive extracorporeal photopheresis?	
Yes	11 (26.2%)
No	31 (73.8%)
Average daily steroid dose per weight (mg/kg/day)	
Mean (SD)	0.4 (0.27)
Median	0.3
Min, Max	0.1, 1.3

cGVHD: chronic graft vs. host disease; SD: standard deviation

NOTE: All subjects were taking prednisone at baseline. For subjects who were on steroids in addition to prednisone, the dose level after converting to prednisone was added to their dose of prednisone.

Source: NDA205552/SN0181/Module 5.3.5.2/Study 1129 Primary Analysis CSR Table 14.1.2.3

The FDA's Assessment:

FDA agrees with the Applicant's statement.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Treatment Compliance

No formal treatment compliance measurements were performed. However, based on the final analysis, the median relative dose intensity ([total cumulative dose actually taken / expected total cumulative dose in mg in the treatment phase]*100) was 94.38% (Study 1129 Final Analysis CSR Addendum Table 3).

Concomitant Medications

As of the final analysis, strong, moderate, mild, and other CYP3A inhibitors were used by 23.8%, 47.6%, 42.9%, and 0% of subjects, respectively. The most commonly used CYP3A inhibitors (≥ 10%) were fluconazole (42.9%), voriconazole (14.3%), and atorvastatin (11.9%) (Study 1129 Final Analysis CSR Addendum Table 14.1.5.4.1).

Rescue Medication

Rescue medication was not a part of this study.

The FDA's Assessment:
FDA agrees with the Applicant's statement.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

The Applicant's Position:

Efficacy analyses were performed using the All treated Population (N = 42), with the Response evaluable Population (N = 37) analyzed as supporting sensitivity analyses. Data from Phase 1b and Phase 2 were combined for the efficacy analyses because the subjects received the same dose and schedule of ibrutinib (the RP2D).

With longer follow-up, the results of the final analysis for BORR were consistent with the primary analysis (Table 33). Based on the final analysis, the BORR for the Response-evaluable Population was 78.4% (95% CI: 61.8, 90.2) (Study 1129 Final Analysis CSR Addendum Table 14.2.1.2). For 79.3% of responders, a response was documented at the first response assessment (Study 1129 Final Analysis CSR Addendum Table 14.2.3.3).

Table 33 Applicant – Best Overall Response Rate – Study 1129 (All-Treated Population)

	Primary Analysis (Cumulatively up to 01 September 2016) (N=42)	Final Analysis (Cumulatively up to 15 September 2017) (N=42)
Best overall response rate (CR or PR)		
n (%)[a]	28 (66.7)	29 (69.0)
95% CI[b]	50.5, 80.4	52.9, 82.4
p-value[c]	<0.0001	<0.0001
Best overall response, n (%)		
Complete response	9 (21.4)	13 (31.0)
Partial response	19 (45.2)	16 (38.1)
Stable disease	7 (16.7)	6 (14.3)
Progressive disease	2 (4.8)	2 (4.8)
Not evaluable/Unknown[d]	5 (11.9)	5 (11.9)

CI: confidence interval; CR: complete response; PR: partial response

a Response rate was estimated using the crude proportion of responders.

b The 95% CI was calculated using Clopper-Pearson's exact method.

c The one-sided p-value was calculated based on the null hypothesis of 25% response rate and exact binomial distribution.

d Subjects did not have any response assessment during the study.

Source: Study 1129 Final Analysis CSR Addendum Table 14.2.1.1; NDA205552/SN0181/Module 5.3.5.2/Study 1129 Primary Analysis CSR Table 11

Additional analyses related to the primary endpoint included organ response to treatment and BORR by subgroup. In the final analysis, for responders with 2 or more organs involved at baseline, 73.1% (19 of 26 subjects) had a response in 2 or more organs (Study 1129 Final Analysis CSR Addendum Table 5). For responders with 3 or more organs involved at baseline, 60.0% (6 of 10 subjects) had a response in 3 or more organs. For responders, the organ response rate for each organ analyzed was 66.7% or better (Study 1129 Final Analysis CSR Addendum Table 6). Due to the small number of subjects in the subgroups, no conclusions could be drawn for BORR for subgroups for the final analysis.

The FDA's Assessment:
A substantial proportion of the response assessments are incomplete or totally missing. This prohibits the reviewer's ability to confirm the response by any standard criteria.

See details below at section of Data Quality and Integrity.

Data Quality and Integrity

The Applicant's Position:

The data gathered and analyzed by study investigators were entered into an electronic database maintained by Pharmacyclics LLC. Study 1129 included site monitoring performed by representatives of Pharmacyclics LLC or its designee. Pharmacyclics LLC was responsible for the detailed Trial Monitoring Plan, which defined and standardized all monitoring processes for the Clinical Research Associates/Site Monitors. On-site periodic monitoring also occurred for specified critical variables per Trial Monitoring Plan. Sites were provided with a CRF instruction booklet. Data Management reviewed the data and queried sites as appropriate using edit checks and clinical review.

Information requested by the Office of Scientific Investigations (OSI) for Study 1129 is provided in Module 5.3.5.4. In general, no issues were identified with the quality or integrity of data from Study 1129 which could affect the efficacy findings.

The FDA's Assessment:
There are significant missing data regarding response assessments in the Study PCYC-1129-CA, using the 2005 or 2014 NIH Consensus Response Criteria. This prohibits the Agency's ability to confirm the response (Table 34).

Table 34. Study PCYC-1129-CA Missing Data Analysis

	Week											
	1	2	5	9	13	17	21	25	37	49	61	97
N Subjects	*43*	*41*	*36*	*29*	*23*	*18*	*19*	*16*	*12*	*10*	*9*	*2*
N Missing(XULN ALP)	0	0	**0**	0	**0**	0	0	**0**	0	0	0	1
N Missing(XULN ALT)	0	0	**0**	0	**0**	0	0	**0**	0	0	0	1
N Missing(XULN BILI)	0	0	**0**	0	**0**	0	0	**0**	0	0	0	1
N Missing(XULN PLAT)	0	0	**0**	1	**0**	0	0	**0**	0	0	0	1
N Missing(XASTRESC ERYTRASH)	6	41	**25**	26	**1**	18	19	**4**	1	0	2	1
N Missing(XASTRESC MOVESC)	8	41	**25**	26	**1**	18	19	**4**	1	0	2	1

N Missing(XASTRESC NONMOVSC)	7	41	**26**	26	**1**	18	19	**4**	1	0	2	1
N Missing(XASTRESC EYES)	40	41	29	28	18	18	19	8	6	4	2	1
N Missing(XASTRESC LEFTEYE)	41	41	**35**	29	**23**	18	19	**16**	12	10	9	2
N Missing(XASTRESC RIGHTEYE)	41	41	**35**	29	**23**	18	19	**16**	12	10	9	2
N Missing(XASTRESC MUCOSCOR)	6	41	**25**	26	**1**	18	19	**1**	1	0	0	1
N Missing(XASTRESC GIESOPHA)	6	41	**25**	26	**2**	18	19	**4**	1	0	2	1
N Missing(XASTRESC GILOWER)	6	41	**25**	26	**2**	18	19	**4**	1	0	2	1
N Missing(XASTRESC GPUPPER)	6	41	**25**	26	**2**	18	19	**4**	1	0	2	1
N Missing(XASTRESC LUNGS)	39	41	28	28	18	18	19	9	6	4	2	1
N Missing(XASTRESC LUNGFEV)	37	41	**36**	29	**20**	18	19	**14**	9	7	9	2
N Missing(XASTRESC SIBRDLCO)	35	41	**36**	28	**19**	18	19	**15**	9	8	9	2
N Missing(XASTRESC JF)	40	41	29	28	18	18	19	9	6	4	2	1
N Missing(XASTRESC WF)	40	41	30	29	19	18	19	9	6	4	2	1
N Missing(XASTRESC ELBOW)	40	41	30	29	19	18	19	9	6	4	2	1
N Missing(XASTRESC SHOULDER)	40	41	30	29	19	18	19	9	6	4	2	1
N Missing(XASTRESC FD)	40	41	30	29	19	18	19	9	6	4	2	1

Source: FDA analysis

Efficacy Results – Secondary and other relevant endpoints

The Applicant's Position:

Sustained response rate: at the time of the final analysis, the rate of sustained response for ≥ 20 weeks was 69.0% (95% CI: 49.2, 84.7) (20 of 29 responders) (Study 1129 Final Analysis CSR Addendum Table 14.2.2.1 and Figure 2). Eighteen of 29 responders (62.1%, 95% CI: 42.3, 79.3) had a sustained response for at least 32 weeks (Study 1129 Final Analysis CSR Addendum Table 14.2.3.2). Sixteen of 29 responders (55.2%, 95% CI: 35.7, 73.6) had a sustained response for at least 44 weeks (Study 1129 Final Analysis CSR Addendum Table 14.2.3.4).

Duration of response: at the time of the final analysis, median DOR for responders was not reached (range: 0.03+ to 33.87+) (Study 1129 Final Analysis CSR Addendum Table 7 and Figure 3). At the 30 month landmark, 75% (95% CI: 53.0, 88.3) of all responders remained alive and progression-free.

Changes in corticosteroid requirement over time: based on the results of the final analysis, the median steroid dose was reduced over time for the All treated Population (Study 1129 Final Analysis CSR Addendum Table 14.2.2.3.3 and Figure 4). Twenty-seven of 42 subjects (64.3%) had at least 1 week during the study where their average daily corticosteroid dose was < 0.15 mg/kg/day (Study 1129 Final Analysis CSR Addendum Table 14.2.2.3.4.3). Eight of 29 responders (27.6%) discontinued corticosteroid while in response (defined as stopping

systemic corticosteroid use for cGVHD for at least 28 days while in response to ibrutinib treatment) (Study 1129 Final Analysis CSR Addendum Listing 16.2.2.3.4.4).
Change in Lee Chronic Graft vs. Host Disease Symptom Scale Score: based on the final analysis, the overall improvement rate in Lee Chronic GVHD Symptom Scale total summary score was 42.9%; 58.6% for responders and 7.7% for non-responders (Study 1129 Final Analysis CSR Addendum Table 8). Based on the final analysis, the improvement rate in Lee Chronic GVHD Symptom Scale Score (decrease in score of at least 7 points) on at least 2 consecutive visits was 28.6% (Study 1129 Final Analysis CSR Addendum Table 9). Using data supporting the primary CSR, this improvement rate was 23.8%.
Failure-free survival: as of the final analysis, Kaplan-Meier point estimates for FFS at 24 months and 30 months were 38% and 27%, respectively (Study 1129 Final Analysis CSR Addendum Table 10 and Figure 5). The median FFS was 18.4 months
Biomarker analyses/pharmacodynamics: PD and biomarker assessments were reported in the Study 1129 Primary Analysis CSR (dated 06 January 2017), and there are no updates to provide in the Study 1129 Final Analysis CSR Addendum.

The FDA's Assessment:

1. For the Eye organ measures, the 2005 NIH recommendation was that "Eye response is measured by change in Schirmer's test" [Pavletic et al. 2006], while the 2014 NIH recommendation is that "Eye response is measured by change in NIH Eye Score" [Lee et al. 2015].

2. For the Study PCYC-1129-CA, the Applicant clarified that the eye response results were based on the NIH Eye Score in the 2014 NIH response criteria. The Applicant explained that the Schirmer's test of the 2005 NIH response criteria was not feasible for most investigators, and therefore was not reported in the Study PCYC-1129-CA, hence the perception of missing data in dataset XA.

3. The current ibrutinib USPI has a statement at Section 14.5, that "the responses were assessed by investigators using the 2005 National Institutes of Health (NIH) Consensus Panel Response Criteria with two modifications to align with the updated 2014 NIH Consensus Panel Response Criteria." It would be appropriate to clarify the ibrutinib USPI to specify the responses in (b) (4) .

4. The data for Study 1129 were not sufficient for analysis, with significant missing data.

Dose/Dose Response

The Applicant's Position:

Pharmacokinetic and biomarker results were reported in the Study 1129 Primary Analysis CSR (NDA205552/SN0181/Module 5.3.5.2/Study 1129 Primary Analysis CSR Section 5 and Appendix 9.4), and there are no updates to provide as of the final analysis.

The FDA's Assessment:
A substantial proportion of the response assessments are incomplete or totally missing. This prohibits the reviewer's ability to confirm the response by any standard criteria.

Durability of Response

The Applicant's Position:

Sustained Response Rate

For results of rate of sustained response for ≥ 20, ≥ 32 weeks, and ≥ 44 weeks, see Efficacy Results – Secondary and other relevant endpoints.

The FDA's Assessment:
A substantial proportion of the response assessments are incomplete or totally missing. This prohibits the reviewer's ability to confirm the response by any standard criteria.

Persistence of Effect

The Applicant's Position:

Time-to-event Analyses (i.e., DoR, FFS)

See Efficacy Results – Secondary and other relevant endpoints for relevant data.

The FDA's Assessment:
A substantial proportion of the response assessments are incomplete or totally missing. This prohibits the reviewer's ability to confirm the response by any standard criteria.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:

For results of the Lee Chronic Graft vs. Host Disease Symptom Scale Score, see Efficacy Results – Secondary and other relevant endpoints.

The FDA's Assessment:
From the CSR of Study 1129 and Applicant proposed labeling Section 14.5: "ORR results were supported by exploratory analyses of patient-reported symptom bother which showed at least a 7-point decrease in Lee Symptom Scale overall summary score in 2(b)(4)% (1(b)(4)/42) of patients on at least 2 consecutive visits."

The Applicant submitted PRO dataset on 3/24/2022 to show 33% (14/42) subjects with LSS improvement [with ≥ 7-point reduction from baseline in LSS through the Week 25 visit], as per the Investigator's assessment, but without clear information about LSS reporting compliance rate.

The Applicant also submitted updated LSS datasets on 6/27/2022 to show 24% (10/42) (95% CI: 12.1, 39.5) subjects with LSS improvement [with ≥ 7-point reduction from baseline in LSS through the Week 25 visit].

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

No additional analyses were conducted for this study.

The FDA's Assessment:
FDA agrees with the Applicant's statement.

8.1.4. Integrated Review of Effectiveness

The FDA's Assessment:
FDA does not agree with the Applicant's proposed plan to pool efficacy data across protocols.

FDA re-analyzed the data using the accepted efficacy endpoint of ORR by Week 25 visit using FDA-adjudicated responses in 47 patients who received treatment for previously treated chronic GVHD in the Study PCYC-1146-IM (IMAGINE).

Data from the 12 TN pediatric patients from PCYC-1146-IM (IMAGINE) and data from the 3 TN pediatric patients from PCYC-1140-IM (INTEGRATE) will be not sufficient (b) (4)

(b) (4) in light of the failed trial in adults in this setting (b) (4)

8.1.5. Assessment of Efficacy Across Trials

Primary Endpoints

The Applicant's Position:

The pediatric pool population (pediatric subjects with cGVHD, ≥ 1 to < 22 years of age) includes all subjects treated with ibrutinib using a target dose of 240 mg/m^2 once daily for subjects < 12 years of age (equivalent to the 420mg adult cGVHD dose, administered as tablets or suspension), and 420 mg once daily for subjects ≥ 12 years of age. It includes subjects with relapsed/refractory (R/R; treated with ibrutinib) and/or treatment-naïve (TN; treated with ibrutinib + prednisone) cGVHD:

- cGVHD pediatric pool (N = 62; including R/R and TN subjects ≥ 1 to < 22 years of age treated with ibrutinib from Study 1146 [n = 59] and Study 1140 [n = 3] combined).

This pediatric pool population was further divided into 2 populations for subjects with R/R or TN cGVHD:

- cGVHD R/R pediatric subjects (N = 47; including R/R subjects treated with ibrutinib from Study 1146)
- cGVHD TN pediatric pool (N = 15; including TN subjects ≥ 1 to < 22 years of age treated with ibrutinib from Study 1146 [n= 12] and Study 1140 [n = 3] combined).

Primary endpoints were different in each of the studies and are therefore not presented as primary or secondary endpoints for the pooled analysis presentation.

Efficacy results for all populations are summarized in Table 35 and further below.

Table 35 Applicant – Summary of Results of Efficacy Studies in Subjects with cGVHD

	Pediatric Pool[a]			Study 1146	Study 1129	Study 1140
Efficacy Endpoint	**TN**	**R/R**	**R/R + TN**	**All Ibr Treated**	**All Ibr Treated**	**All Ibr Treated**
Overall Response Rate (CR or PR)[b]	**N = 15**	**N = 47**	**N = 62**	**N = 59**	**N = 42**	**N = 94**
n (%)	13 (86.7)	36 (76.6)	49 (79.0)	46 (78.0)	29 (69.0)	74 (78.7)
95% CI	(59.5, 98.3)	(62.0, 87.7)	(66.8, 88.3)	(65.3, 87.7)	(52.9, 82.4)	(69.1, 86.5)
Overall Response Rate (CR or PR) by 24 weeks[b]	**N = 15**	**N = 47**	**N = 62**	**N = 59**	**N = 42**	**N = 94**
n (%)	13 (86.7%)	28 (59.6%)	41 (66.1%)	38 (64.4%)	27 (64.3%)	73 (77.7%)
95% CI	(59.5, 98.3)	(44.3, 73.6)	(53.0, 77.7)	(50.9, 76.4)	(48.0, 78.4)	(67.9, 85.6)
Response rate (CR or PR) at 24 weeks[b]	**N = 15**	**N = 47**	**N = 62**	**N = 59**	**N = 42**	**N = 94**
n (%)	9 (60.0%)	18 (38.3%)	27 (43.5%)	26 (44.1%)	19 (45.2%)	45 (47.9%)
95% CI	(32.3, 83.7)	(24.5, 53.6)	(31.0, 56.7)	(31.2, 57.6)	(29.8, 61.3)	(37.5, 58.4)
Overall Survival, median, months[c]	**N = 15**	**N = 47**	**N = 62**	**N = 59**	**N = 42**	**N = 94**
(95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (24.7, NE)	NE (NE, NE)
Range (min, max)	1.87, 30.00+	1.61, 31.24+	1.61, 31.24+	1.61, 31.24+	0.53+, 36.70+	0.59, 47.18+
Sustained Response Rate – at least 20 Weeks[b]	**N=13**	**N=36**	**N=49**	**N=46**	**N=29**	**N=74**
n (%)	8 (61.5)	21 (58.3)	29 (59.2)	28 (60.9)	20 (69.0)	47 (63.5)
95% CI	(31.6, 86.1)	(40.8, 74.5)	(44.2, 73.0)	(45.4, 74.9)	(49.2, 84.7)	(51.5, 74.4)

	Pediatric Pool[a]			Study 1146	Study 1129	Study 1140
Efficacy Endpoint	**TN**	**R/R**	**R/R + TN**	**All Ibr Treated**	**All Ibr Treated**	**All Ibr Treated**
Sustained Response Rate – at least 32 Weeks[b]	**N=13**	**N=32**	**N=45**	**N=42**	**N=29**	**N=74**
n (%)	6 (46.2)	17 (53.1)	23 (51.1)	23 (54.8)	18 (62.1)	43 (58.1)
95% CI	(19.2, 74.9)	(34.7, 70.9)	(35.8, 66.3)	(38.7, 70.2)	(42.3, 79.3)	(46.1, 69.5)
Lee cGVHD Symptom Scale, overall improvement rate[d]	**N=9**	**N-26**	**N=35**	**N=32**	**N=42**	**N=94**
n (%)	5 (55.6)	11 (42.3)	16 (45.7)	14 (43.8)	12 (28.6)	41 (43.6)
95% CI	(21.2, 86.3)	(36.9, 76.6)	(36.6, 71.2)	(37.7, 73.6)	(55.4, 84.3)	(45.8, 66.6)

CI = confidence interval; cGVHD = chronic graft vs. host disease; CR = complete response; PR = partial response; ORR = overall response rate; R/R = Relapse/Refractory; TN = Treatment naive

Note: N = number of subjects in the specified population, n = Number of responders (CR or PR). Percentages are calculated by 100*n/N.

Ibrutinib treated subjects from Studies 1146 and 1140 ≥ 1 to < 22 years of age.

Response rate was estimated using the crude proportion of responders. The 95% CI was calculated using Clopper-Pearson's exact method.

Estimated by Kaplan-Meier methodology.

Clinically meaningful improvement on Lee cGVHD symptom scale is defined as at least a 7-point decrease in Lee Symptom Scale overall. Improvement rate is estimated using the crude proportion of subjects ≥ 12 years of age with improvement. 95% CI is calculated using Clopper-Pearson's exact method.

Source: ISE (R&D/21/1343) Table 2.1, Table 2.2, Table 2.3, Table 2.4.1, Table 2.4.2, Table 2.8, Table 2.10

- **Overall Response Rate (ORR)** (SCE [R&D/21/0873] Table 7):
  - In the R/R + TN pediatric pool, the ORR per investigator assessment was 49/62 (79.0%) subjects (CI: 66.8, 88.3); 86.7% in TN subjects and 76.6% in R/R subjects.
  - The ORR was similar in males and females (77.8% and 82.4%), higher in white compared with non-white subjects (96.6% and 63.6%), similar in US and non-US regions (88.2% and 75.6%), and similar in subjects with moderate and severe cGVHD (76.0% and 81.1%) (SCE [R&D/21/0873] Table 8).

- In subgroup analyses by age, the ORR was similar across subjects aged 1 to < 6 years (72.7%), subjects aged 6 to < 12 years (68.8%), and subjects aged 12 to < 22 years (85.7%) (SCE [R&D/21/0873] Table 8).
- In Ibr-treated subjects in Studies 1146, 1129, and 1140, ORR ranged from 69.0% to 78.7%.
- In the R/R + TN pediatric pool, the best response was CR for 5/62 (8.1%) subjects. The best response was PR for 44/62 (71.0%) subjects.
- A total of 8.5%, 31.0%, and 25.5% of subjects achieved CR in Studies 1146, 1129, and 1140, respectively.

- **Duration of response (DOR)** (SCE [R&D/21/0873] Table 14):
  - In the R/R + TN pediatric pool, and in the individual studies, the median DOR was not achieved/not estimable; the KM estimate at 18 months was 62.4% (95% CI: 43.1, 76.8) in the pediatric pool, and 63.4%, 75.5%, and 67.1% in Studies 1146, 1129, and 1140, respectively.
- **Time to response** (SCE [R&D/21/0873] Table 16):
  - In subjects with R/R cGVHD who responded, the median time to first response was 5.93 weeks (range: 3.7 to 84.1 weeks) and the median time to best response was 11.57 weeks (range: 3.7 to 84.1 weeks).
- **Overall response rate (ORR) by 24 weeks** (SCE [R&D/21/0873] Table 9):
  - In the R/R + TN pediatric pool, the ORR per investigator assessment by 24 weeks was 41/62 (66.1%) subjects (CI: 53.0, 77.7.); 86.7% in TN subjects and 59.6% in R/R subjects.
  - In subgroup analyses by age, ORR by 24 weeks was similar across subjects aged 1 to < 6 years (63.6%), subjects aged 6 to < 12 years (68.8%), and for subjects aged 12 to < 22 years (65.7%) (SCE [R&D/21/0873] Table 20).
  - In Ibr-treated subjects in Studies 1146, 1129, and 1140, the ORR by 24 weeks ranged from 64.3% to 77.7%.
  - A total of 4.8% of subjects in the R/R + TN pediatric pool achieved CR by 24 weeks; in Studies 1146, 1129, and 1140, 5.1%, 9.5%, and 17.0% of subjects achieved CR at 24 weeks, respectively.
- **Overall response rate (ORR) by 48 weeks** (SCE [R&D/21/0873] Table 10):
  - In the R/R + TN pediatric pool, the ORR by 48 weeks was 46/61 (75.4%) subjects (CI: 62.7, 85.5); 86.7% in TN subjects and 71.7% in R/R subjects.
  - In subgroup analyses by age, ORR by 48 weeks was similar across subjects aged 1 to < 6 years (70.0%), subjects aged 6 to < 12 years (68.8%), and subjects aged 12 to < 22 years (80.0%) (SCE [R&D/21/0873] Table 20).

- In Ibr-treated subjects in Studies 1146, 1129, and 1140, the ORR by 48 weeks ranged from 69.0% to 77.7%.
- A total of 6.6% of subjects in the R/R + TN pediatric pool achieved CR by 48 weeks; in Studies 1146, 1129, and 1140, 6.9%, 11.9%, and 18.1% of subjects achieved CR by 48 weeks, respectively.

- **Response Rate (RR) at 24 weeks** (SCE [R&D/21/0873] Table 11):
  - In the R/R + TN pediatric pool, the response rate at 24 weeks was 27/62 (43.5%) subjects (CI: 31.0, 56.7); 60.0% in TN subjects and 38.3% in R/R subjects.
  - In Ibr-treated subjects in Studies 1146, 1129, and 1140, the response rate at 24 weeks ranged from 44.1% to 47.9%.
  - In subgroup analyses by age, the response rate at 24 weeks was similar across subjects aged 1 to < 6 years (45.5%), subjects aged 6 to < 12 years (50.0%), and subjects aged 12 to < 22 years (40.0%) (SCE [R&D/21/0873] Table 20).
  - A total of 4.8% of subjects in the R/R + TN pediatric pool achieved CR at 24 weeks; in Studies 1146, 1129, and 1140, 5.1%, 4.8%, and 10.6% of subjects achieved CR at 24 weeks, respectively.
- **Response Rate (RR) at 48 weeks** (SCE [R&D/21/0873] Table 12):
  - In the R/R + TN pediatric pool, the response rate at 48 weeks was 25/61 (41.0%) subjects (CI: 28.6, 54.3); 33.3% in TN subjects and 43.5% in R/R subjects.
  - In subgroup analyses by age, the response rate at 48 weeks was similar across subjects aged 1 to < 6 years (40.0%), subjects aged 6 to < 12 years (43.8%), and subjects aged 12 to < 22 years (40.0%) (SCE [R&D/21/0873] Table 20).
  - In Ibr-treated subjects in Studies 1146, 1129, and 1140, the response rate at 48 weeks ranged from 41.5% to 43.1%.
  - A total of 4.9% of subjects in the R/R + TN pediatric pool achieved CR at 48 weeks; in Studies 1146, 1129, and 1140, 5.2%, 4.8%, and 9.6% of subjects achieved CR at 48 weeks, respectively.
- **Sustained response rate for at least 20 weeks and 32 weeks** (SCE [R&D/21/0873] Table 13):
  - In the R/R + TN pediatric pool, for responders who achieved PR or better, the rate of sustained response (CR or PR) for at least 20 weeks was 29/49 (59.2%) subjects (95% CI: 44.2, 73.0); 61.5% in TN subjects and 58.3% in R/R subjects.
  - A total of 23/45 responders (51.1%, 95% CI: 35.8, 66.3) had a sustained response for at least 32 weeks; 46.2% in TN subjects and 53.1% in R/R subjects.
  - In subgroup analyses by age, the rate of sustained response for at least 20 weeks was 62.5% for subjects aged 1 to < 6 years, 72.7% for subjects aged 6 to < 12 years, and 53.3% for subjects aged 12 to < 22 years. The rate of sustained response for at least

32 weeks was 42.9% for subjects aged 1 to < 6 years, 72.7% for subjects aged 6 to < 12 years, and 44.4% for subjects aged 12 to < 22 years (SCE [R&D/21/0873] Table 20).

- **Improvement in the Lee cGVHD Symptom Scale score in subjects ≥ 12 years** (SCE [R&D/21/0873] Table 17):
  - In the R/R + TN pediatric pool, for subjects aged ≥ 12 years, the overall improvement rate in the Lee cGVHD Symptom Scale total summary score (decreasing at least 7 points at 2 consecutive visits with no disease progression, relapse of underlying disease or start of subsequent cGVHD treatment) was 16/35 subjects (45.7%; 95% CI: 36.6, 71.2); 55.6% in TN subjects and 42.3% in R/R subjects.
  - In Studies 1146, 1129, and 1140, the rate was 43.8%, 28.6%, and 43.6%, respectively.
- **Overall survival (OS)** (SCE [R&D/21/0873] Table 18):
  - In the R/R + TN pediatric pool, and in the individual studies, median OS was not achieved/not estimable; the KM estimate at 18 months was 90.0% (95% CI: 79.0, 95.4) in the R/R + TN pediatric pool, and 91.2%, 77.7%, and 83.8% in Studies 1146, 1129, and 1140, respectively

The FDA's Assessment:

FDA re-analyzed the data using the accepted efficacy endpoint of ORR by Week 25 visit using FDA-adjudicated responses in 47 patients who received treatment for previously treated chronic GVHD in the Study PCYC-1146-IM (IMAGINE).

Data from the 12 TN pediatric patients from PCYC-1146-IM (IMAGINE) and data from the 3 TN pediatric patients from PCYC-1140-IM (INTEGRATE) will be not sufficient (b) (4) in light of the failed trial in adults in this setting (b) (4)

Secondary and Other Endpoints

The Applicant's Position:

See above section Primary Endpoints for all pooled efficacy analysis results.

The FDA's Assessment:
FDA re-analyzed the data using the accepted efficacy endpoint of ORR by Week 25 visit using FDA-adjudicated responses in 47 patients who received treatment for previously treated chronic GVHD in the Study PCYC-1146-IM (IMAGINE).

Data from the 12 TN pediatric patients from PCYC-1146-IM (IMAGINE) and data from the 3 TN pediatric patients from PCYC-1140-IM (INTEGRATE) will be not sufficient (b) (4) in light of the failed trial in adults in this setting (b) (4)

Subpopulations

The Applicant's Position:

Overall response rate, response rate, and sustained response rate are summarized by age subgroup in Table 36.

Table 36 Applicant – Response Rates by Age Subgroup in Pediatric Pool Population in cGVHD Studies

	Pediatric Pool[a]											
	1 to < 6 years			6 to < 12 years			12 to < 22 years			Total		
Endpoint	N	Rate, n (%)	95% CI[b]	N	Rate, n (%)	95% CI[b]	N	Rate, n (%)	95% CI[b]	N	Rate, n (%)	95% CI[b]
ORR	11	8 (72.7)	(39.0, 94.0)	16	11 (68.8)	(41.3, 89.0)	35	30 (85.7)	(69.7, 95.2)	62	49 (79.0)	(66.8, 88.3)
ORR 24 weeks	11	7 (63.6)	(30.8, 89.1)	16	11 (68.8)	(41.3, 89.0)	35	23 (65.7)	(47.8, 80.9)	62	41 (66.1)	(53.0, 77.7)
ORR 48 weeks	10	7 (70.0)	(34.8, 93.3)	16	11 (68.8)	(41.3, 89.0)	35	28 (80.0)	(63.1, 91.6)	61	46 (75.4)	(62.7, 85.5)
Response rate 24 weeks	11	5 (45.5)	(16.7, 76.6)	16	8 (50.0)	(24.7, 75.3)	35	14 (40.0)	(23.9, 57.9)	62	27 (43.5)	(31.0, 56.7)
Response rate 48 weeks	10	4 (40.0)	(12.2, 73.8)	16	7 (43.8)	(19.8, 70.1)	35	14 (40.0)	(23.9, 57.9)	61	25 (41.0)	(28.6, 54.3)
Sustained Response Rate - ≥ 20 Weeks	8	5 (62.5)	(24.5, 91.5)	11	8 (72.7)	(39.0, 94.0)	30	16 (53.3)	(34.3, 71.7)	49	29 (59.2)	(44.2, 73.0)
Sustained Response Rate - ≥ 32 Weeks,	7	3 (42.9)	(9.9, 81.6)	11	8 (72.7)	(39.0, 94.0)	27	12 (44.4)	(25.5, 64.7)	45	23 (51.1)	(35.8, 66.3)

CI: confidence interval; ORR: overall response rate

Note: N = number of subjects in the specified population, n = Number of responders (CR or PR). Percentages are calculated by 100*n/N.

Ibrutinib treated subjects from Studies 1146 and 1140 ≥ 1 to < 22 years of age.

Source: ISE (R&D/21/1343) Table 2.11

The FDA's Assessment:
FDA re-analyzed the data using the accepted efficacy endpoint of ORR by Week 25 visit using FDA-adjudicated responses in 47 patients who received treatment for previously treated chronic GVHD in the Study PCYC-1146-IM (IMAGINE).

Data from the 12 TN pediatric patients from PCYC-1146-IM (IMAGINE) and data from the 3 TN pediatric patients from PCYC-1140-IM (INTEGRATE) will be not sufficient (b) (4) in light of the failed trial in adults in this setting (b) (4)

8.1.6. Integrated Assessment of Effectiveness

The Applicant's Position:

Efficacy results from pooled analyses in the pediatric population (≥ 1 to < 22 years of age) from Study 1146 and Study 1140, and data generated in adults from Study 1140 and Study 1129, indicate that treatment with ibrutinib demonstrates clinically meaningful benefit that is maintained after treatment completion in pediatric subjects with moderate to severe cGVHD, including in subjects with relapsed/refractory cGVHD.

The effectiveness of ibrutinib in pediatric subjects aged 1 year and older with cGVHD has been demonstrated based on the following evidence, which focused on a population ≥ 1 to < 22 years of age:

- Deep and durable responses:
  - Overall Response Rate (ORR): in the R/R + TN pediatric pool, the ORR per investigator assessment was 49/62 (79.0%) subjects (CI: 66.8, 88.3). In Ibr-treated subjects in Studies 1146, 1129, and 1140, ORR ranged from 69.0% to 78.7%. In the R/R + TN pediatric pool, the best response was CR for 5/62 (8.1%) subjects. The best response was PR for 44/62 (71.0%) subjects. A total of 8.5%, 31.0%, and 25.5% of subjects achieved CR in Studies 1146, 1129, and 1140, respectively. The ORR was 72.7% for subjects aged 1 to < 6 years, 68.8% for subjects aged 6 to < 12 years, and 85.7% for subjects aged 12 to < 22 years. The ORR was higher in white compared with non-white subjects, and similar across the sexes, US/non-US subjects, and moderate and severe cGVHD subgroups.
  - Overall response rate (ORR) by 24 weeks: in the R/R + TN pediatric pool, the ORR by 24 weeks was 41/62 (66.1%) subjects (CI: 53.0, 77.7.). In Ibr-treated subjects in

Studies 1146, 1129, and 1140, the ORR by 24 weeks ranged from 64.3% to 77.7%. A total of 4.8% of subjects in the R/R + TN pediatric pool achieved CR by 24 weeks; in Studies 1146, 1129, and 1140, 5.1%, 9.5%, and 17.0% of subjects achieved CR by 24 weeks, respectively. The ORR by 24 weeks was 63.6% for subjects aged 1 to < 6 years, 68.8% for subjects aged 6 to < 12 years, and 65.7% for subjects aged 12 to < 22 years.

- Overall response rate (ORR) by 48 weeks: in the R/R + TN pediatric pool, the ORR by 48 weeks was 46/61 (75.4%) subjects (CI: 62.7, 85.5). In Ibr-treated subjects in Studies 1146, 1129, and 1140, the ORR by 48 weeks ranged from 69.0% to 77.7%. A total of 6.6% of subjects in the R/R + TN pediatric pool achieved CR by 48 weeks; in Studies 1146, 1129, and 1140, 6.9%, 11.9%, and 18.1% of subjects achieved CR by 48 weeks, respectively. The ORR by 48 weeks was 70.0% for subjects aged 1 to < 6 years, 68.8% for subjects aged 6 to < 12 years, and 80.0% for subjects aged 12 to < 22 years.
- Response Rate (RR) at 24 weeks: in the R/R + TN pediatric pool, the response rate at 24 weeks was 27/62 (43.5%) subjects (CI: 31.0, 56.7). In Ibr-treated subjects in Studies 1146, 1129, and 1140, the response rate at 24 weeks ranged from 44.1% to 47.9%. A total of 4.8% of subjects in the R/R + TN pediatric pool achieved CR at 24 weeks; in Studies 1146, 1129, and 1140, 5.1%, 4.8%, and 10.6% of subjects achieved CR at 24 weeks, respectively. The response rate at 24 weeks was 45.5% for subjects aged 1 to < 6 years, 50.0% for subjects aged 6 to < 12 years, and 40.0% for subjects aged 12 to < 22 years.
- Response Rate (RR) at 48 weeks: n the R/R + TN pediatric pool, the response rate at 48 weeks was 25/61 (41.0%) subjects (CI: 28.6, 54.3). In Ibr-treated subjects in Studies 1146, 1129, and 1140, the response rate at 48 weeks ranged from 41.5% to 43.1%. A total of 4.9% of subjects in the R/R + TN pediatric pool achieved CR at 48 weeks; in Studies 1146, 1129, and 1140, 5.2%, 4.8%, and 9.6% of subjects achieved CR at 48 weeks, respectively. The response rate at 48 weeks was 40.0% for subjects aged 1 to < 6 years, 43.8% for subjects aged 6 to < 12 years, and 40.0% for subjects aged 12 to < 22 years.
- Duration of response (DOR): in the R/R + TN pediatric pool, and in the individual studies, the median DOR was not achieved/not estimable; the KM estimate at 18 months was 62.4% (95% CI: 43.1, 76.8) in the pediatric pool, and 63.4%, 75.5%, and 67.1% in Studies 1146, 1129, and 1140, respectively.

- <u>The responses were sustained; the majority of subjects had sustained responses:</u>
  - Sustained response rate for at least 20 weeks and 32 weeks: in the R/R + TN pediatric pool, for responders who achieved PR or better, the rate of sustained response (CR or PR) for at least 20 weeks was 29/49 (59.2%) subjects (95% CI: 44.2, 73.0) for responders. A total of 23/45 responders (51.1%, 95% CI: 35.8, 66.3) had a sustained response for at least 32 weeks. The rate of sustained response for at least 20 weeks was 62.5% for subjects aged 1 to < 6 years, 72.7% for subjects aged 6 to < 12 years,

and 53.3% for subjects aged 12 to < 22 years. The rate of sustained response for at least 32 weeks was 42.9% for subjects aged 1 to < 6 years, 72.7% for subjects aged 6 to < 12 years, and 44.4% for subjects aged 12 to < 22 years.

- Clinically meaningful patient-reported outcomes:
  - Improvement in the Lee cGVHD Symptom Scale score in subjects ≥12 years: in the R/R + TN pediatric pool, for subjects aged ≥ 12 years, the overall improvement rate in the Lee cGVHD Symptom Scale total summary score (decreasing at least 7 points at 2 consecutive visits with no disease progression, relapse of underlying disease or start of subsequent cGVHD treatment) was 16/35 subjects (45.7%; 95% CI: 36.6, 71.2). In Studies 1146, 1129, and 1140, the rate was 43.8%, 28.6%, and 43.6%, respectively.
- Other efficacy results (Overall Survival and Time To Response):
  - Overall survival (OS): In the R/R + TN pediatric pool, and in the individual studies, median OS was not achieved/not estimable; the KM estimate at 18 months was 90.0% (95% CI: 79.0, 95.4) in the R/R + TN pediatric pool, and 91.2%, 77.7%, and 83.8% in Studies 1146, 1129, and 1140, respectively.
  - Time to response: in subjects with R/R cGVHD who responded, the median time to first response was 5.93 weeks (range: 3.7 to 84.1 weeks) and the median time to best response was 11.57 weeks (range: 3.7 to 84.1 weeks).

Pooled data for key efficacy outcomes were consistent with those observed for pediatric subjects in Studies 1146 and 1140, as well as for adult subjects in Study 1129.

Study 1146 represents the largest prospective study objectively assessing the dosing, safety, and efficacy of any 2nd-line therapy in children with cGVHD. While there is not yet any published data on National Institutes of Health (NIH) response rates in children treated with standard-of-care therapy, the efficacy data from Study 1146 compare favorably with current data in adults (Miklos 2017[33]). Based on these results, ibrutinib represents a new, effective therapeutic option in the treatment of patients ≥ 1 to < 22 years of age with moderate to severe cGVHD who have failed 1 or more lines of systemic therapy.

These findings are supported by the efficacy results from Study 1129 (which included adult subjects with R/R cGVHD) and by the positive trends observed in Study 1140. While Study 1140 did not meet the primary efficacy endpoint (response rate at 48 weeks), several of the secondary endpoints showed trends favoring the ibrutinib + prednisone (Ibr + Pred) arm over the placebo + prednisone (Pbo + Pred) arm at the time of the primary analysis, particularly improvement in the Lee cGVHD Symptom Scale summary score, duration of response, as well as the post-hoc analysis of EFS. These trends were upheld with longer follow up at the final

analysis. A similar trend for improvement favoring the Ibr+Pred arm over the Pbo+Pred arm was also observed in the modified Lee cGVHD Symptom Scale summary score and withdrawal from all systemic therapies for cGVHD at the final analysis. Overall survival was similar for both treatment arms (the median OS was not reached for either arm).

The FDA's Assessment:

FDA does not agree with the applicant's proposed plan to pool efficacy data across protocols.

Data from the 12 TN pediatric patients from PCYC-1146-IM (IMAGINE) and data from the 3 TN pediatric patients from PCYC-1140-IM (INTEGRATE) will be not sufficient (b) (4) in light of the failed trial in adults in this setting (b) (4)

See efficacy analysis results in the Section 8.1.1.1 for Study PCYC-1146-IM.

FDA re-analyzed the data using the accepted efficacy endpoint of ORR by Week 25 visit using FDA-adjudicated responses in 47 patients who received treatment for previously treated chronic GVHD in the Study PCYC-1146-IM (IMAGINE).

The efficacy of IMBRUVICA was established based on overall response rate (ORR) through Week 25 where overall response included complete response or partial response according to the 2014 National Institutes of Health (NIH) Consensus Development Project Response Criteria. The efficacy results are shown in Table 37.

Table 37. Efficacy Results in Patients with Previously Treated cGVHD[a] in IMAGINE

	Total (N=47)
ORR by Week 25	28 (60%)
95% CI (%)	(44, 74)
Complete Response (CR)	2 (4%)
Partial Response (PR)	26 (55%)
Median Duration of Response, months (95% CI)[b]	5.3 (2.8, 8.8)

CI = confidence interval; ORR = overall response rate
[a] Assessment based on 2014 NIH Consensus Development Project Response Criteria
[b] Based on all responders in the study

Source: FDA analysis

The median time to first response was 0.9 month (range: 0.9, 6.1). The median duration of response, calculated from first response to progression, death, or new systemic therapies for

chronic GVHD, was 5.3 months (95% CI: 2.8, 8.8). The median time from first response to death or new systemic therapies for chronic GVHD was 14.8 months (95% CI: 4.6, not evaluable).

ORR results were supported by exploratory analyses of patient-reported symptom bother which showed at least a 7-point decrease in Lee Symptom Scale overall summary score through Week 25 in 50% (13/26) of patients age 12 years and older.

8.2. Review of Safety

The Applicant's Position:

Safety pediatric data from studies conducted in cGVHD and B-cell Non-Hodgkin's Lymphoma (NHL) are summarized to support safety updates to the USPI. Pooled safety data from 62 ibrutinib-treated pediatric subjects from Studies 1146 and 1140 (the "cGVHD Pediatric Pool") are presented side-by-side with pooled safety data from 131 ibrutinib-treated adult subjects from Studies 1140 and 1129 (the "cGVHD Adult Pool"), along with individual study data.

In addition, safety data from 71 subjects with B-cell NHL from Study LYM3003 are presented with pooled data for 1,476 subjects from 10 pivotal studies in B-cell malignancies (the "B-cell malignancy label pool.

The FDA's Assessment:
FDA acknowledges the Applicant's pooled data for safety (b) (4) pediatric patients with cGVHD with previously treated disease (Study 1146, N=47).

8.2.1. Safety Review Approach

The Applicant's Position:

Pooled safety data from 62 ibrutinib-treated pediatric subjects from Studies 1146 and 1140 (the "cGVHD Pediatric Pool") are presented side-by-side with pooled safety data from 131 ibrutinib-treated adult subjects from Studies 1140 and 1129 (the "cGVHD Adult Pool"), along with individual study data. Data analyses in the SCS are based on the safety population (i.e., subjects who received at least 1 dose of study treatment).

The review of safety is also based on safety data from SPARKLE (Study 54179060LYM3003; herein referred to as Study LYM3003) in the pediatric subjects population 1 to < 18 years (or up

to 30 years, if initial diagnosis of mature B-cell non-Hodgkin's Lymphoma (NHL) at < 18 years of age) with relapsed or refractory mature B cell NHL. Study LYM3003 met the statistical boundary for futility; as a result, the Sponsor's inclusion of Study LYM3003 in the proposed submission package is solely intended to provide information on safety and clinical pharmacology of ibrutinib in combination with chemoimmunotherapy (CIT) in pediatric subjects with mature B-cell NHL. Presentation of safety data from B-cell NHL Study LYM3003 (ibrutinib in combination with chemoimmunotherapy [CIT] vs. CIT alone), in addition to pooled data for 1,476 subjects from 10 pivotal studies in B-cell malignancies (the "B-cell malignancy label pool") representing the approved indications of CLL/SLL, MCL, Waldenstrom's macroglobulinemia (WM), and MZL, are presented for reference only. It should be noted that the subjects in the B-cell malignancy label pool did not receive intensive, multiagent CIT. This information will be used to (b) (4).

The FDA's Assessment:
FDA agrees with the Applicant's approach to safety data. As noted above, the FDA review is primarily based on the patients with previously treated cGVHD (N=47) in Study 1146. This study included patients up to age 22, and of those 47 patients, three were ≥18 years (one 18-year-old and two 19-year-old). The three adult patients were not excluded from the safety evaluation in pediatric patients. Additional analyses were performed by pediatric age group. In several sections, the FDA also reviewed the Applicant's "pediatric pool" data (n=62) that includes all patients <22 years old in Study 1146 and Study 1140 which included both treatment naïve patients and previously treated patients and commented on the results of the analysis.

The safety information in pediatric patients with NHL in SPARKLE in combination with chemo-immunotherapy is reviewed by the Division of Hematologic Malignancies 2 in NDA 205552 S-38 and NDA 210563 S-14.

8.2.2. Review of the Safety Database

Overall Exposure

The Applicant's Position:

In the cGVHD pediatric pool, the overall median ibrutinib treatment duration was 8.641 months (range: 0.07 to 25.89 months) (Table 38). The median relative dose intensity (the actual dose received divided by the standard calculated dose during a set period) was 99.778%. The median treatment duration in the cGVHD pediatric pool was similar to that in the cGVHD adult pool. In

the cGVHD adult pool, the overall median ibrutinib treatment duration was 5.027 months (range: 0.13 to 44.35 months). The median dose intensity was 99.588%.

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Table 38 Applicant – Study Drug Exposure – Ibrutinib/Placebo (All Treated Subjects)

	Pediatric Pool[a]			Adult Pool[b]	Study1146	Study 1129	Study1140	
	R/R (N=47)	TN (N=15)	R/R+TN (N=62)	(N=131)	(N=59)	(N=42)	Ibr+Pred (N=94)	Pbo+Pred (N=96)
Treatment duration (months)								
Mean (SD)	10.163 (8.2301)	9.377 (6.5813)	9.973 (7.8188)	10.067 (10.4045)	10.005 (7.9315)	9.057 (9.8250)	10.435 (10.4529)	9.487 (8.6321)
Median	7.097	9.199	8.641	5.027	8.181	4.370	5.437	6.357
Min, Max	0.23, 25.89	0.07, 20.67	0.07, 25.89	0.13, 44.35	0.07, 25.89	0.23, 36.67	0.13, 44.35	0.13, 36.14
< 6 Months	19 (40.4%)	5 (33.3%)	24 (38.7%)	71 (54.2%)	23 (39.0%)	25 (59.5%)	48 (51.1%)	46 (47.9%)
6 -< 12 Months	10 (21.3%)	5 (33.3%)	15 (24.2%)	15 (11.5%)	14 (23.7%)	5 (11.9%)	12 (12.8%)	22 (22.9%)
12 -< 18 Months	7 (14.9%)	4 (26.7%)	11 (17.7%)	16 (12.2%)	10 (16.9%)	2 (4.8%)	15 (16.0%)	8 (8.3%)
≥ 18 Months	11 (23.4%)	1 (6.7%)	12 (19.4%)	29 (22.1%)	12 (20.3%)	10 (23.8%)	19 (20.2%)	20 (20.8%)
Relative Dose Intensity (%) mg[c]								
Mean (SD)	100.289 (35.9879)	96.787 (11.1658)	99.442 (31.7420)	91.787 (15.7210)	100.426 (32.1365)	85.483 (18.2850)	93.941 (14.0762)	94.804 (13.0139)
Median	99.057	100.000	99.778	99.588	100.000	94.375	100.000	99.172
Min, Max	29.39, 221.54	65.26, 117.65	29.39, 221.54	37.85, 132.53	29.39, 221.54	39.61, 100.00	37.85, 132.53	46.96, 149.93

Ibr = ibrutinib; Max = maximum; Min = minimum; Pbo = placebo; Pred = Prednisone; R/R = relapse/refractory; R/R = relapsed refractory; SD = standard deviation; TN = treatment-naive

Note: The holding period was deducted from treatment duration for subjects who stopped all study treatment because of no longer needing treatment but later came back on treatment.

a Ibr treated subjects from 1140 and 1146 with age ≥ 1 < 22.

b Ibr treated subjects from 1129 and/or Ibr+Pred treated subjects from 1140 with age ≥ 22.

c Calculated by total received dose level / total intended dose level up to last dose date.

Source: ISS (R&D/21/1342) Table 1.5

The FDA's Assessment:
FDA agrees with drug exposure data of all treated patients. Median treatment duration was higher among pediatric patients compared to adults, and within the pediatric pool, in patients who were TN compared to patients with R/R disease. As to treatment exposure by age subgroups, the number of patients is too small to draw meaningful conclusion.

Relevant characteristics of the safety population:

The Applicant's Position:

In the cGVHD pediatric pool, the median age at baseline was 13 years (range: 1 to 20 years), and no subject was ≥ 22 years of age (Table 39). Overall, 72.6% were male, and 46.8% were white. In the cGVHD pediatric pool 24.2% of subjects were TN, and 75.8% of subjects were R/R. Overall, 59.7% of subjects had severe cGVHD, 74.2% of subjects had ongoing systemic immunosuppressant use, and 72.6% of subjects had Karnofsky/Lansky performance score of ≥ 80.

In the cGVHD adult pool, the median age at baseline was 55 years (range: 22 to 74 years), and all subjects were ≥ 22 years of age (Table 39). Overall, 61.1% were male and 62.6% were white. In the cGVHD adult pool, 69.5% of subjects were TN and 30.5% subjects were R/R. Overall, 30.5% of subjects had severe cGVHD, 48.9% of subjects had ongoing systemic immunosuppressant use, and 80.9 % of subjects had a Karnofsky performance score of ≥ 80.

Table 39 Applicant – Subject Key Demographics and Baseline Characteristics (Safety Population)

	Pediatric Pool[a]				Study 1146	Study 1129	Study 1140
	R/R	TN	R/R + TN	Adult Pool[b] (N=131)	All Ibr Treated	All Ibr Treated	Ibr + Pred
Parameter	**N = 47**	**N = 15**	**N = 62**		**N = 59**	**N = 42**	**N = 94**
Age at enrollment (years)							
Mean (SD)	11.6 (5.06)	12.3 (5.35)	11.8 (5.10)	51.6 (13.34)	11.6 (5.09)	50.5 (15.53)	50.3 (14.26)
Median	13.0	13.0	13.0	55	13.0	56.0	51.0
Min, Max	(1.0, 19.0)	(3.0, 20.0)	(1.0, 20.0)	(22.0, 74.0)	(1.0, 19.0)	(19.0, 74.0)	(13.0, 72.0)
Age Categories, n (%)							
1 – < 12	21 (44.7)	6 (40.0)	27 (43.5)	0 (0.0)	27 (45.8)	0 (0.0)	0 (0.0)
1 – < 6	8 (17.0)	3 (20.0)	11 (17.7)	0 (0.0)	11 (18.6)	0 (0.0)	0 (0.0)
6 – < 12	13 (27.7)	3 (20.0)	16 (25.8)	0 (0.0)	16 (27.1)	0 (0.0)	0 (0.0)
12 – < 22	26 (55.3)	9 (60.0)	35 (56.5)	0 (0.0)	32 (54.2)	2 (4.8)	3 (3.2)
≥ 22	0 (0.0)	0 (0.0)	0 (0.0)	131 (100.0)	0 (0.0)	40 (95.2)	91 (96.8)
Gender, n (%)							
Male	33 (70.2)	12 (80.0)	45 (72.6)	80 (61.1)	42 (71.2)	22 (52.4)	61 (64.9)
Female	14 (29.8)	3 (20.0)	17 (27.4)	51 (38.9)	17 (28.8)	20 (47.6)	33 (35.1)
Race, n (%)							
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	1 (1.1)
Asian	13 (27.7)	2 (13.3)	15 (24.2)	27 (20.6)	14 (23.7)	1 (2.4)	27 (28.7)
Black or African American	4 (8.5)	1 (6.7)	5 (8.1)	6 (4.6)	4 (6.8)	1 (2.4)	6 (6.4)

Parameter	Pediatric Pool[a] R/R N = 47	Pediatric Pool[a] TN N = 15	Pediatric Pool[a] R/R + TN N = 62	Adult Pool[b] (N=131)	Study 1146 All Ibr Treated N = 59	Study 1129 All Ibr Treated N = 42	Study 1140 Ibr + Pred N = 94
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	1 (1.1)
More than 1 race	5 (10.6)	0 (0.0)	5 (8.1)	1 (0.8)	5 (8.5)	0 (0.0)	1 (1.1)
Not reported	8 (17.0)	0 (0.0)	8 (12.9)	13 (9.9)	8 (13.6)	1 (2.4)	12 (12.8)
White	17 (36.2)	12 (80.0)	29 (46.8)	82 (62.6)	28 (47.5)	39 (92.9)	46 (48.9)
Non white	30 (63.8)	3 (20.0)	33 (53.2)	49 (37.4)	31 (52.5)	3 (7.1)	48 (51.1)
Geographic Region, n (%)							
US	11(23.4)	6 (40.0)	17 (27.4)	78 (59.5)	17 (28.8)	42 (100.0)	38 (40.4)
Non-US	36 (76.6)	9 (60.0)	45 (72.6)	53 (40.5)	42 (71.2)	0 (0.0)	56 (59.6)
Prior treatment status, n (%)							
Treatment-naïve	0 (0.0)	15 (100)	15 (24.2)	91 (69.5)	12 (20.3)	0 (0.0)	94 (100.0)
Relapsed/refractory	47 (100.0)	0 (0.0)	47 (75.8)	40 (30.5)	47 (79.7)	42 (100.0)	0 (0.0)
Ongoing use of systemic immunosuppressants[c], n (%)							
Yes	40 (85.1)	6 (40.0)	46 (74.2)	64 (48.9)	45 (76.3)	22 (52.4)	44 (46.8)
No	7 (14.9)	9 (60.0)	16 (25.8)	67 (51.1)	14 (23.7)	20 (47.6)	50 (53.2)
NIH global cGVHD severity grade[d], n (%)							
Moderate	12 (25.5)	13 (86.7)	25 (40.3)	51 (38.9)	22 (37.3)	NA	54 (57.4)
Severe	35 (74.5)	2 (13.3)	37 (59.7)	40 (30.5)	37 (62.7)	NA	40 (42.6)

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

	Pediatric Pool[a]				Study 1146	Study 1129	Study 1140
	R/R	TN	R/R + TN	Adult Pool[b] (N=131)	All Ibr Treated	All Ibr Treated	Ibr + Pred
Parameter	**N = 47**	**N = 15**	**N = 62**		**N = 59**	**N = 42**	**N = 94**
Karnofsky/Lansky performance status							
Mean	81.91 (13.455)	82.00 (12.071)	81.94 (13.037)	82.98 (11.549)	82.54 (12.945)	80.95 (10.777)	83.62 (11.900)
Median	80.00	80.00	80.00	80.00	80.00	80.00	80.00
Min, Max	60.0, 100.0	60.0, 100.0	60.0, 100.0	10.0, 100.0	60.0, 100.0	60.0, 100.0	10.0, 100.0
Score < 80, n (%)	12 (25.5)	5 (33.3)	17 (27.4)	25 (19.1)	15 (25.4)	13 (31.0)	14 (14.9)
Score ≥ 80, n (%)	35 (74.5)	10 (66.7)	45 (72.6)	106 (80.9)	44 (74.6)	29 (69.0)	80 (85.1)

Ibr = ibrutinib; cGVHD = chronic graft vs. host disease; Max = maximum; Min = minimum; NA = not applicable; NIH = National Institutes of Health; Pred = Prednisone; R/R = relapsed refractory; SD = standard deviation; TN = treatment-naive; US = United States

a Ibr treated subjects from 1140 and 1146 with age ≥ 1 to < 22.

b Ibr treated subjects from 1129 and/or Ibr+Pred treated subjects from 1140 with age ≥ 22

c Immunosuppressants that were initiated for either treatment of or prophylaxis for acute cGVHD

d cGVHD staging per NIH Criteria.

Source: ISS (R&D/21/1342) Table 1.3 and Table 1.4

The FDA's Assessment:
The FDA agrees with the demographic and baseline characteristics of the safety population. Of note, more Asian patients had previously treated disease compared to more White patients who were treatment naïve. As to the difference between pediatric and adult patients (excluding differences due to study design or inclusion criteria parameters), more patients in the pediatric group had severe cGVHD (60%) compared to the adults (31%) .

Adequacy of the safety database:

The Applicant's Position:

Given the established safety profile of ibrutinib as a single agent in several malignancies, including cGVHD in adults, and the considerable dataset for the studies in subjects with moderate or severe cGVHD after failure of 1 or more lines of systemic therapy, the safety database is adequate in assessing the benefit-risk profile of ibrutinib in the proposed indication.

The individual safety profile of ibrutinib as a single agents is well known; as of 12 November 2021, a total of (b) (4) subjects have received ibrutinib in the clinical program; based on (b) (4) milligrams distributed worldwide from launch to 31 October 2021, the estimated exposure to ibrutinib is (b) (4) person years.

For ibrutinib, the safety data obtained to date was based on its continuous administration until disease progression or unacceptable toxicity; as a consequence, considerable long-term safety data have been obtained. Safety data for 195 ibrutinib-treated subjects with cGVHD from Studies 1146, 1140, 1129 comprise a sizeable database from which safety data could be comprehensively analyzed.

The FDA's Assessment:
The FDA agrees that the safety database presented here is adequate to assess the risk-benefit profile for treatment of chronic GVHD in children.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

No issues relating to data integrity or quality were identified in Studies 1146, 1140, 1129, or LYM3003.

The FDA's Assessment:
The FDA agrees with the Applicant's statement.

Categorization of Adverse Event

The Applicant's Position:

The AE parameters used in the studies in this safety review are standard, and the search criteria applied to relevant safety observations is considered appropriate. The AE categorizations were based on the latest versions of the NCI-CTCAE and conformant with recognized cGVHD guidelines.

The AE severity was assessed according to the National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE) Version 4.03. In addition to TEAEs, serious AEs (SAEs), events of special interest, and other safety observations of relevance for the indicated population (with attention to those for which specific recommendations for management is made in product labeling) were evaluated.

For protocol-defined events of special interest for ibrutinib, treatment-emergent bleeding events were identified by hemorrhage (excluding laboratory terms) standardized Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) search. Major hemorrhage TEAEs were defined as Grade 3 or higher, or serious bleeding events, or central nervous system (CNS) hemorrhage of any grade identified by hemorrhage (excluding laboratory terms) SMQ search.

For the analysis of other safety observations relevant to ibrutinib therapy, aggregate ibrutinib safety data were reviewed. Important events outlined in the Pharmacovigilance plan, in addition to other events of potential clinical relevance, were selected as other safety observations. These events include cytopenic adverse events, infections including viral reactivation, atrial fibrillation, other cardiac arrhythmias (SMQ including ventricular tachyarrhythmias excluding atrial fibrillation), cardiac failure (narrow SMQ), other malignancies, hepatic disorders, interstitial lung disease (narrow SMQ), hypertension (narrow SMQ), ischemic stroke (narrow SMQ), and embryofetal toxicity.

The FDA's Assessment:
FDA agrees with the selection of adverse events of special interest.

Routine Clinical Tests

The Applicant's Position:

The laboratory-abnormality parameters used in the studies in this safety review are standard. The laboratory-abnormality categorization was based on the latest versions of the NCI-CTCAE and is conformant with recognized cGVHD guidelines.

Laboratory parameters were graded for toxicity using the NCI-CTCAE criteria.

The FDA's Assessment:
FDA agrees with the Applicant's statement.

8.2.4. Safety Results

Deaths

The Applicant's Position:

In the cGVHD pediatric pool, TEAEs resulting in death were reported for 3 (4.8%) subjects; these events included cardiac tamponade (1 [1.6%]), septic shock (1 [1.6%]), and acute respiratory distress syndrome (1[1.6%]) (Table 40). In the cGVHD adult pool, TEAEs resulting in death were reported for 15 (11.5%) subjects; these events included death (2 [1.5%]), pneumonia (2 [1.5%]), acute myeloid leukemia recurrent (2 [1.5%]), cardiac arrest (1 [0.8%]), cGVHD (1 [0.8%]), septic shock (1 [0.8%]), bronchopulmonary aspergillosis (1 [0.8%]), pneumonia fungal (1 [0.8%]), sepsis (1 [0.8%]), leukemia recurrent (1 [0.8%]), post-transplant lymphoproliferative disorder (1 [0.8%]), and ischemic stroke (1 [0.8%]).

Table 40 Applicant – TEAEs Resulting in Death by SOC and PT (Safety Population)

System Organ Class Preferred Term	Pediatric Pool[a] R/R (N=47)	Pediatric Pool[a] TN (N=15)	Pediatric Pool[a] R/R+TN (N=62)	Adult Pool[b] (N=131)
Subjects with any events n (%)	3 (6.4)	0 (0.0)	3 (4.8)	15 (11.5)
Cardiac disorders	1 (2.1)	0 (0.0)	1 (1.6)	1 (0.8)
Cardiac tamponade	1 (2.1)	0 (0.0)	1 (1.6)	0 (0.0)
Cardiac arrest	0 (0.0)	0.(0.0)	0 (0.0)	1 (0.8)
General disorders and administration site conditions	0 (0.0)	0.(0.0)	0 (0.0)	2 (1.5)
Death	0 (0.0)	0.(0.0)	0 (0.0)	2 (1.5)
Immune system disorders	0 (0.0)	0.(0.0)	0 (0.0)	1 (0.8)
Chronic graft versus host disease	0 (0.0)	0.(0.0)	0 (0.0)	1 (0.8)
Infections and infestations	1 (2.1)	0 (0.0)	1 (1.6)	6 (4.6)
Septic shock	1 (2.1)	0 (0.0)	1 (1.6)	1 (0.8)
Bronchopulmonary aspergillosis	0 (0.0)	0.(0.0)	0 (0.0)	1 (0.8)
Pneumonia	0 (0.0)	0.(0.0)	0 (0.0)	2 (1.5)
Pneumonia fungal	0 (0.0)	0.(0.0)	0 (0.0)	1 (0.8)
Sepsis	0 (0.0)	0.(0.0)	0 (0.0)	1 (0.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	0.(0.0)	0 (0.0)	4 (3.1)
Acute myeloid leukemia recurrent	0 (0.0)	0.(0.0)	0 (0.0)	2 (1.5)
Leukemia recurrent	0 (0.0)	0.(0.0)	0 (0.0)	1 (0.8)
Post-transplant lymphoproliferative disorder	0 (0.0)	0.(0.0)	0 (0.0)	1 (0.8)
Nervous system disorders	0 (0.0%)	0.(0.0)	0 (0.0)	1 (0.8)
Ischemic stroke	0 (0.0)	0.(0.0)	0 (0.0)	1 (0.8)
Respiratory, thoracic and mediastinal disorders	1 (2.1)	0 (0.0)	1 (1.6)	0 (0.0)

System Organ Class Preferred Term	Pediatric Pool[a] R/R (N=47)	 TN (N=15)	 R/R+TN (N=62)	Adult Pool[b] (N=131)
Acute respiratory distress syndrome	1 (2.1)	0 (0.0)	1 (1.6)	0 (0.0)

Ibr = ibrutinib; Pred = prednisone; PT = preferred term; R/R = relapsed refractory; SOC = system organ class; TEAE = treatment-emergent adverse event; TN = treatment-naive.

a Ibr treated subjects from 1140 and 1146 with age ≥ 1 to < 22.

b Ibr treated subjects from 1129 and/or Ibr+Pred treated subjects from 1140 with age ≥ 22.

Note: Events are sorted by system organ class alphabetically and decreasing frequency of preferred term in any grade of Pediatric Pool "R/R+TN" column.

Source: ISS (R&D/21/1342) Table 2.5

In Part 1 of Study LYM3003, fatal TEAEs were reported for 5 (23.8%) subjects: sepsis (2 [9.5%]), neutropenic sepsis (1 [4.8%]), multiple organ dysfunction syndrome (1 [4.8%]), and septic shock (1 [4.8%]) (Study LYM3003 CSR Table 19). In Part 2 (Ibr + CIT) of Study LYM3003, fatal TEAEs were reported for 4 (11.4%) subjects (ISS [R&D/21/1342] Table 6.5). These events included multiple organ dysfunction syndrome (1 subject), pneumonia (1 subject), septic shock (1 subject), and pulmonary hemorrhage (1 subject). In the B-cell malignancy label pool, fatal TEAEs were reported for 70 (4.7%) subjects; the most common events (≥ 3 subjects) were MCL (7 subjects [0.5%]), death (5 subjects [0.3%]), cardiac arrest, pneumonia, sepsis (4 subjects [0.3% each]), and multiple organ dysfunction syndrome (3 subjects [0.2%]) (ISS [R&D/21/1342] Table 6.5).

The FDA's Assessment:

FDA agrees with the data showing that 5 patients died among pediatric patients with previously treated disease: three from adverse events, one from cGVHD and one from underlying disease. The patients who died from AE included one event each of cardiac tamponade, septic shock, and acute respiratory distress syndrome (ARDS). Reviewing the medical history of the patient who died from cardiac tamponade, it seems likely that the death was due to progression or complications of bronchitis obliterans, a manifestation of chronic GVHD, and not due to

ibrutinib treatment. As such, in the FDA assessment only 2 patients died from adverse reactions due to ibrutinib.

FDA agrees that TEAEs resulting in death by SOC and PT are less frequent in pediatric compared to adult patients. The two TEAE related deaths in the pediatric pool patients were in patients with previously treated disease and none in patients who were treatment naïve.

Serious Adverse Events

The Applicant's Position:

In the cGVHD pediatric pool, serious TEAEs were reported for 66.1% of subjects; the most common event (> 3 subjects) was pyrexia (11 [17.7%]) (Table 41 and ISS [R&D/21/1342] Table 2.4.1). In the cGVHD adult pool, serious TEAEs were reported for 52.7% of subjects and the most common events (> 3 subjects) were pneumonia (12 [9.2%]), cellulitis (5 [3.8%]), influenza (4 [3.1%]), and septic shock (4 [3.1%]) %]) (Table 41 and ISS [R&D/21/1342] Table 2.4.1).

In the cGVHD pediatric pool, the rate for of serious TEAEs for the subset of subjects age ≥ 1 to < 6 years (54.5%) was lower (> 10% difference) compared with the subsets ≥ 6 to < 12 years and ≥ 12 to < 22 years (68.8% and 68.6%) (ISS [R&D/21/1342] Table 2.4.2) In the subset of subjects age ≥ 1 to < 6 years, the most common (≥ 3 subjects) event reported was pyrexia (3 [27.3%]) and no single PT (≥ 3 subjects) was reported for the ≥ 6 to < 12 year age subset.

In the subset of subjects age ≥ 12 to < 22 years, the most common (≥ 3 subjects) events were pyrexia (6 [17.1%]), pneumothorax (3 [8.6%]), and chronic graft versus host disease (3 [8.6%]) (ISS [R&D/21/1342] Table 2.4.2).

Table 41 Applicant – Serious TEAEs by PT with Overall Subject Incidence ≥2 Subjects in Any Grade of Pediatric Pool in R/R + TN Column

	Pediatric Pool[a]									Adult Pool[b] (N=131)		
	R/R (N=47)			TN (N=15)			R/R+TN (N=62)					
Preferred Term	Any Grade	Grade 3+4	Grade 5	Any Grade	Grade 3+4	Grade 5	Any Grade	Grade 3+4	Grade 5	Any Grade	Grade 3+4	Grade 5
Subjects with any event, n(%)	30 (63.8)	25 (53.2)	3 (6.4)	11 (73.3)	9 (60.0)	0	41 (66.1)	34 (54.8)	3 (4.8)	69 (52.7)	48 (36.6)	15 (11.5)
Pyrexia	7 (14.9)	5 (10.6)	0	4 (26.7)	0 (0.0)	0	11 (17.7)	5 (8.1)	0	2 (1.5)	1 (0.8)	0
Stomatitis	3 (6.4)	3 (6.4)	0	0	0 (0.0)	0	3(4.8)	3 (4.8)	0	0	0	0
Chronic graft versus host disease	1 (2.1)	1 (2.1)	0	2 (13.3)	2 (13.3)	0	3 (4.8)	3 (4.8)	0	2 (1.5)	1 (0.8)	1 (0.8)
Pneumothorax	3 (6.4)	3 (6.4)	0	0	0	0	3 (4.8)	3 (4.8)	0	1 (0.8)	0	0
Hypoxia	2 (4.3)	2 (4.3)	0	1 (6.7)	1 (6.7)	0	3 (4.8)	3 (4.8)	0	0	0	0
Abdominal pain	2 (4.3)	1 (2.1)	0	0	0	0	2 (3.2)	1 (1.6)	0	0	0	0
Nausea	2 (4.3)	2 (4.3)	0	0	0	0	2 (3.2)	2 (3.2)	0	0	0	0
Vomiting	1 (2.1)	1 (2.1)	0	1 (6.7)	0	0	2 (3.2)	1 (1.6)	0	1 (0.8)	1 (0.8)	0
Bacteraemia	0	0	0	2 (13.3)	2 (13.3)	0	2 (3.2)	2 (3.2)	0	2 (1.5)	2 (1.5)	0
Bronchitis	1 (2.1)	1 (2.1)	0	1 (6.7)	1 (6.7)	0	2 (3.2)	2 (3.2)	0	0	0	0
Device related infection	2 (4.3)	2 (4.3)	0	0	0	0	2 (3.2)	2 (3.2)	0	0	0	0
Influenza	2 (4.3)	1 (2.1)	0	0	0	0	2 (3.2)	1 (1.6)	0	4 (3.1)	4 (3.1)	0

	Pediatric Pool[a]									Adult Pool[b] (N=131)		
	R/R (N=47)			TN (N=15)			R/R+TN (N=62)					
Preferred Term	**Any Grade**	**Grade 3+4**	**Grade 5**	**Any Grade**	**Grade 3+4**	**Grade 5**	**Any Grade**	**Grade 3+4**	**Grade 5**	**Any Grade**	**Grade 3+4**	**Grade 5**
Lower respiratory tract infection	2 (4.3)	2 (4.3)	0	0	0	0	2 (3.2)	2 (3.2)	0	0	0	0
Pneumonia	2 (4.3)	1 (2.1)	0	0	0	0	2 (3.2)	1 (1.6)	0	12 (9.2)	10 (7.6)	2 (1.5)
Dyspnoea	1 (2.1)	1 (2.1)	0	1 (6.7)	1 (6.7)	0	2 (3.2)	2 (3.2)	0	2 (1.5)	1 (0.8)	0
Migraine	2 (4.3)	1 (2.1)	0	0	0	0	2 (3.2)	1 (1.6)	0	0	0	0
Toxicity to various agents	2 (4.3)	2 (4.3)	0	0	0	0	2 (3.2)	2 (3.2)	0	0	0	0

Ibr = ibrutinib; Pred = prednisone; PT=preferred term; R/R=relapse/refractory; TEAE=treatment-emergent adverse event; TN=treatment-naive

a Ibr treated subjects from 1140 and 1146 with age ≥ 1 to < 22

b Ibr treated subjects from 1129 and/or Ibr+Pred treated subjects from 1140 with age ≥ 22.

Events are sorted by decreasing frequency of preferred term in any grade of Pediatric Pool "R/R+TN" column.

Source: ISS (R&D/21/1342) Table 2.4.1

In Part 1 of Study LYM3003, serious TEAEs were reported for 19 (90.5%) subjects. The most common events (≥ 5% of subjects) were febrile neutropenia (7 [33.3%]), sepsis (5 [23.8%]) and neutropenia (3 [14.3%]) (Study LYM3003 CSR Attachment TSFAE03P1). In Part 2 (Ibr + CIT) of Study LYM3003, serious TEAEs were reported for 25 (71.4%) of subjects (ISS [R&D/21/1342] Table 6.4.1). The most common events (≥ 5% of subjects) were febrile neutropenia (21 [60.0%]), sepsis (5 [14.3%]), platelet count decreased (3 [8.6%]), septic shock (3 [8.6%]), pneumonia (3 [8.6%]), thrombocytopenia (3 [8.6%]), neutropenia (2 [5.7%]) and anemia (2 [5.7%]).

In the B-cell malignancy pool, excluding Study E1912, serious TEAEs were reported for 535 (36.2%) of subjects; the most common event (≥ 5% of subjects) was pneumonia (88 [6.0%]) (ISS (R&D/21/1342) Table 6.4.1).

The FDA's Assessment:
Considering the pediatric pool (N=62, <22 years old as defined by the Applicant) and using the OOD composite group terms (GT), SAE in >3 patients were pyrexia in 11 (18%) and pneumonia in 8 (13%) patients. All the SAE of pneumonia were in the patients with previously treated disease, and 6 of them had toxicity grading of ≥3. GT for pneumonia included: atypical pneumonia (1), lower respiratory tract infection (2), Pneumocystis jirovecii pneumonia (1), pneumonia (2), pneumonia mycoplasma (1), and pneumonia serratia (1). The FDA agrees with the rest of the results of Serious TEAEs by PT with overall subject incidence ≥2 in the pediatric pool in patients with previously treated disease + patients who were TN compared to adults**.** The incidence of SAE was similar between adults and pediatric patients.

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

In Study 1146, TEAEs leading to ibrutinib discontinuation occurred in 23.7% of subjects overall (25.0% of TN subjects and 23.4% of R/R subjects); the most common event (≥ 2 of subjects) overall was mouth hemorrhage (3.4%) (Study 1146 Primary Analysis CSR Table 14.3.7). In TN subjects, only chloroma, chronic myeloid leukemia recurrent and hemothorax were reported in 1 subject each (8.3%); in R/R subjects, the most common event (≥ 2 subjects) was mouth hemorrhage (4.3%). TEAEs reported as the primary reason for ibrutinib discontinuation occurred in 13.6% of subjects overall (8.3% of TN subjects and 14.9% of R/R subjects) (Study 1146 Primary Analysis CSR Table 14.3.8); the most common event (≥ 2 of subjects)

overall was mouth hemorrhage (3.4%). In TN subjects, the only event, hemothorax, was reported in 1 subject (8.3%); in R/R subjects, the most common event (≥ 2 subjects) was mouth hemorrhage (4.3%).

In Study 1140 as of the final analysis, TEAEs were reported as the primary reason for ibrutinib discontinuation for 19 subjects (20.2%) in the Ibr+Pred arm; the most common events (≥ 2% of subjects) were atrial fibrillation and pneumonia (2.1% of subjects each [2 subjects each]) (Study 1140 Final Analysis CSR Addendum Table 14.3.1.13). Treatment-emergent AEs were reported as the primary reason for placebo discontinuation for 16 subjects (16.7%) in the Pbo+Pred arm; the most common event (≥ 2% of subjects) was fatigue (2.1% [2 subjects]).

In Study 1129 as of the final analysis, 18 subjects (42.9%) had 1 or multiple TEAEs leading to discontinuation of study drug (Study Final Analysis 1129 CSR Addendum Table 14.3.2.1.2). Fatigue and pneumonia (4.8% each) were the most common TEAEs leading to discontinuation of study drug.

In Study LYM3003, in the ibrutinib+CIT group, 4 (11.4%) subjects had TEAEs leading to CIT discontinuation and in 1 of these 4 subjects, treatment with ibrutinib was discontinued (Study LYM3003 CSR Table 35, Attachment TSFAE05P2, and Appendix 19, LSFAE03P2): the subject had a SAE of Grade 4 febrile neutropenia leading to treatment discontinuation of ibrutinib and CIT (rituximab, vincristine, ifosfamide, carboplatin, and idarubicin). The febrile neutropenia was considered as possibly related to vincristine, ifosfamide and probably related to ibrutinib, rituximab, carboplatin, and idarubicin by the investigator.

The FDA's Assessment:
In this section the Applicant presents the data per protocol, rather than the pooled data. Reviewing Study 1146, the FDA agrees with the data of TEAE leading to drug permanent withdrawal. The FDA also agrees that the most common cause of study drug discontinuation (≥ 2 of subjects) was mouth hemorrhage (2/59, 3.4%).

Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:

In Study 1146, TEAEs leading to ibrutinib dose reduction occurred in 15.3% of subjects overall (0% of TN subjects and 19.1% of R/R subjects); the most common event (≥ 2 subjects) overall was stomatitis (3.4%) (Study 1146 Primary Analysis CSR Table 14.3.10). In TN subjects, there

were no events leading to ibrutinib dose reduction; in R/R subjects, the most common event (≥ 2 subjects) was stomatitis (4.3%).

In Study 1140 as of the final analysis, TEAEs leading to ibrutinib dose reduction were reported for 9.6% of subjects in the Ibr+Pred arm; the most common event (≥ 2% of subjects) was fatigue (2.1%) (Study 1140 Final Analysis CSR Addendum Table 14.3.1.9). TEAEs leading to placebo dose reduction were reported for 11.5% of subjects in the Pbo+Pred arm; the most common events (≥ 2% of subjects) were fatigue (2.1%), alanine aminotransferase increased (2.1%), and thrombocytopenia (2.1%).

In Study 1129 as of the final analysis, 14 subjects (33.3%) had TEAEs leading to dose reduction (Study 1129 Final Analysis CSR Addendum Table 14.3.2.1.3). The most common TEAEs leading to dose reduction were fatigue (14.3%) and diarrhea (4.8%).

In the ibrutinib+CIT group, the TEAEs of thrombocytopenia (Grade 4 in 2 subjects), lower gastrointestinal hemorrhage (Grade 4 in 1 subject), headache, febrile neutropenia (Grade 3 in 1 subject each), and weight decreased (Grade 2 in 1 subject) led to dose reductions for ibrutinib and systemic inflammatory response syndrome (Grade 4 in 1 subject) led to dose reduction for carboplatin (Study LYM3003 CSR Attachment TSFAE07P2). In the CIT group, 1 subject had dose-reduction for ifosfamide due to TEAE of encephalopathy (Grade 1).

The FDA's Assessment:
The FDA disagrees with the data on drug interruption and dose reduction. Considering Study 1146, dose interruption occurred in 22 (47%) of patients with R/R disease and dose reduction due to AE in 9 (19%) patients with R/R disease. None of the treatment naïve patients had dose reduction. The FDA agrees with the Applicant's assessment that the most common cause of dose reduction was stomatitis in 2 patients (4.3%). The other causes were in 1 patient each.

Significant Adverse Events

The Applicant's Position:

In the cGVHD pediatric pool (All [RR+TN] column) and adult pool, Grade 3 or higher TEAEs were reported for 66.0% and 71.0% of subjects, with no single PT being reported in > 10% of subjects (ISS [R&D/21/1342] Table 2.3). A summary of Grade 3 or higher TEAEs in Studies 1146, 1140, and 1129 is provided in ISS (R&D/21/1342) Table 2.3.

In the cGVHD pediatric pool, the rates for of Grade 3 or higher TEAEs were similar (< 10%) between all age subsets: ≥ 1 to < 6 years (63.6%), ≥ 6 to < 12 years (62.5%), and ≥ 12 to < 22 years (68.6%) (ISS [R&D/21/1342] Table 2.3.2).

In Part 1 of Study LYM3003, Grade 3 or higher TEAEs were reported for all 21 (100.0%) subjects. The most common events (> 20% of subjects) were anemia (16 [76.2%]), thrombocytopenia (14 [66.7%]), neutropenia (13 [61.9%]) febrile neutropenia (13 [61.9%]), platelet count decreased (7 [33.3%]), hypokalemia (7 [33.3%]), and sepsis (6 [28.6%]) (Study LYM3003 CSR Table 17). In Part 2 (Ibr + CIT) of Study LYM3003, Grade 3 or higher TEAEs were reported for 35 (100%) subjects (Mod5.3.5.3/ISS/Table 6.3.1). The most common events (> 20% of subjects) were anemia (27 [77.1%]), febrile neutropenia (24 [68.6%]), thrombocytopenia (19 [54.3%]) neutropenia (14 [40.0%]), platelet count decreased (13 [37.1%]), neutrophil count decreased (12 [34.3%]), hypokalemia (11 [31.4%]), leukopenia (9 [25.7%]), and white blood cell decreased (8 [22.9%]).

In the B-cell malignancy label pool, Grade 3 or higher TEAEs were reported for 1110 (75.2%) subjects (Mod5.3.5.3/ISS/Table 6.3.1). The most common event (≥ 10% of subjects) was neutropenia (292 [19.8%]).

The FDA's Assessment:
The FDA agrees with the data on significant adverse event of ibrutinib treatment of cGVHD.

Treatment Emergent Adverse Events and Adverse Reactions

The Applicant's Position:

Determination of adverse drug reactions (ADR) was based on meeting either of the following criteria:

- Treatment-emergent AEs reported in ≥ 10% of subjects in the cGVHD pediatric pool.
- Biological plausibility: based on the current biological and clinical knowledge of ibrutinib therapy (e.g., mechanism of action, pharmacological profile, or ADR for ibrutinib from other clinical trials).

The most common (≥ 20% of subjects) non-hematologic ADRs in the cGVHD pediatric pool were pyrexia (30.6%), diarrhea (25.8%), abdominal pain (as a grouped term, 24.2%), (Table 42). One ADR was fatal (sepsis [1.6%]). There was 1 newly identified ADR in the cGVHD pediatric pool that was not previously identified in earlier registrational studies (hypogammaglobulinemia [12.9%]). Hematologic ADRs Grade ≥ 3 (based on abnormal laboratory measurements) included anemia (3.2%) and neutropenia (6.5%) (Table 43).

Table 42 Applicant – Non-Hematologic Adverse Drug Reactions: Subject Incidence ≥ 10% in Any Grade in the cGVHD Pediatric Pool (N = 62)

System Organ Class ADR Term	Pediatric Pool[a]		
	Any Grade	Grade 3+	Grade 5
Subjects with any events	58 (93. 5)	29 (46.8)	1 (1.6)
Blood and lymphatic system disorders	20 (32.3)	10 (16.1)	0 (0.0)
Anemia*	8 (12.9)	2 (3.2)	0 (0.0)
Hypogammaglobulinemia*	8 (12.9)	1 (1.6)	0 (0.0)
Hypokalemia	8 (12.9)	4 (6.5)	0 (0.0)
Gastrointestinal disorders	38 (61.3)	12 (19.4)	0 (0.0)
Diarrhea	16 (25.8)	1 (1.6)	0 (0.0)
Abdominal pain*	15 (24.2)	2 (3.2)	0 (0.0)
Stomatitis*	12 (19.4)	4 (6.5)	0 (0.0)
Vomiting	11 (17.7)	1 (1.6)	0 (0.0)
Nausea	10 (16.1)	2 (3.2)	0 (0.0)
General disorders and administration site conditions	26 (41.9)	7 (11.3)	0 (0.0)
Pyrexia	19 (30.6)	5 (8.1)	0 (0.0)
Infections and infestations	33 (53.2)	15 (24.2)	1 (1.6)
Pneumonia*	11 (17.7)	6 (9.7)	0 (0.0)
Skin infection*	10 (16.1)	2 (3.2)	0 (0.0)
Sepsis*	7 (11.3)	6 (9.7)	1 (1.6)
Investigations	8 (12.9)	3 (4.8)	0 (0.0)
Alanine aminotransferase increased	7 (11.3)	3 (4.8)	0 (0.0)
Musculoskeletal and connective tissue disorders	17 (27.4)	2 (3.2)	0 (0.0)
Musculoskeletal pain*	9 (14.5)	1 (1.6)	0 (0.0)
Arthralgia	7 (11.3)	1 (1.6)	0 (0.0)
Nervous system disorders	9 (14.5)	0 (0.0)	0 (0.0)
Headache	9 (14.5)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	18 (29.0)	3 (4.8)	0 (0.0)
Cough	12 (19.4)	1 (1.6)	0 (0.0)
Skin and subcutaneous tissue disorders	24 (38.7)	1 (1.6)	0 (0.0)

System Organ Class ADR Term	Pediatric Pool[a]		
	Any Grade	Grade 3+	Grade 5
Bruising*	12 (19.4)	0 (0.0)	0 (0.0)
Rash*	12 (19.4)	1 (1.6)	0 (0.0)
Vascular disorders	17 (27.4)	2 (3.2)	0 (0.0)
Hemorrhage*	11 (17.7)	0 (0.0)	0 (0.0)

ADR=adverse drug reaction; cGVHD=chronic graft versus host disease; Ibr=ibrutinib; SOC= system organ class

* ADRs that required grouping of individual Preferred Terms.

a Ibr treated subjects from 1140 and 1146 with age ≥ 1 to < 22.

Notes: Subjects with multiple events for a given ADR term are counted once only for each ADR term.
Events are sorted by SOC alphabetically and decreasing frequency of preferred term in Any Grade column.

Source: ISS (R&D/21/1342) Table 3.1

Table 43 Applicant – Hematologic Laboratory Abnormalities[a]: cGVHD Pediatric Pool (N = 62)

ADR Term, n (%)	Any Grade	Grades 3 or 4	Grades 4
Anaemia	8 (12.9)	2 (3.2)	0 (0.0)
Neutropenia	4 (6.5)	4 (6.5)	0.(0.0)
Thrombocytopenia	4 (6.5)	0.(0.0)	0.(0.0)

ADR = adverse drug reaction; cGVHD=chronic graft versus host disease

Note: Abnormalities based on laboratory measurements and grading by common terminology criteria for adverse events (CTCAE) version 4.03.

Source: ISS (R&D/21/1342) Table 3.1

In the cGVHD pediatric pool, (9.7%) subjects discontinued ibrutinib due to ADRs as the primary reason, with the following ADRs most commonly reported (≥ 2 subjects): hemorrhage (3 subjects, 4.8 %), as a grouped term (ISS [R&D/21/1342] Table 3.1.1). Adverse drug reactions leading to ibrutinib dose reduction were reported for 11.3% of subjects, with stomatitis (3.2%, as a grouped term) as the most commonly reported ADR (ISS [R&D/21/1342] Table 3.1.2).

The proportion of subjects with any grade ADRs were similar (< 10% difference) in the cGVHD pediatric pool vs. cGVHD adult pool (ISS [R&D/21/1342] Table 3.2). The rates of individual ADR terms were also similar (< 10% difference) in the cGVHD pediatric pool vs. cGVHD adult pool

except for hypogammaglobulinemia (12.9% vs. 2.5%), abdominal pain (24.2% vs. 12.5%), bruising (19.4% vs. 40.0%), diarrhea (25.8% vs. 40.0%), fatigue (6.5% vs. 57.5%), dyspnea (4.8% vs. 17.5%), fall (0.0% vs. 15.0%), muscle spasm (6.5% vs. 32.5%), nausea (16.1% vs. 27.5%), gastroesophageal reflux disease (0.0% vs. 10.0%), pyrexia (30.6% vs. 20.0%), and upper respiratory tract infection (6.5% vs. 17.5%).

The types of adverse reactions observed in pediatric subjects with cGVHD receiving ibrutinib were consistent with those reported in adult subjects.

The FDA's Assessment:
As earlier noted, restricting the patient population to previously treated patients, and using the OOD and the Applicant's preferred group terms (see Appendix 19.5), the FDA analysis is shown in the Table below.

Table 44. Non-hematologic adverse reactions in ≥10% of patients with previously treated cGVHD

Body System Adverse Reaction	IMBRUVICA (N=47)	
	All Grades n (%)	Grade 3 or 4 n (%)
General disorders and administration site conditions		
Pyrexia	14 (30)	5 (11)
Gastrointestinal disorders		
Diarrhea	13 (28)	1 (2)
Abdominal pain*	11 (23)	2 (4)
Stomatitis*	11 (23)	4 (9)
Vomiting	9 (19)	1 (2)
Nausea	9 (19)	2 (4)
Infections and infestations		
Pneumonia*	11 (23)	6 (13)
Skin infection*	8 (17)	2 (4)
Sepsis*	5 (11)	4 (9)

Skin and subcutaneous tissue disorders		
Rash*	9 (19)	1 (2)
Pruritus	6 (13)	0
Petechiae	6 (13)	0
Respiratory, thoracic and mediastinal disorders		
Cough	9 (19)	1 (2)
Vascular disorders		
Hemorrhage*	8 (17)	0
Hypertension*	5 (11)	2 (4)
Nervous system disorders		
Headache	10 (21)	1 (2)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain*	14 (30)	1 (2)
Osteonecrosis	5 (11)	4 (9)
Blood and lymphatic system disorders		
Hypokalemia	7 (15)	3 (6)
Hypogammaglobulinemia*	5 (11)	0
Cardiac Disorders		
Sinus tachycardia	5 (11)	0
Investigations		
Alanine aminotransferase increased	5 (11)	1 (2)
* Grouped term		

Laboratory Findings

The Applicant's Position:

In the cGVHD pediatric pool, treatment-emergent Grade 3 + 4 decreases in hemoglobin, platelet count, and absolute neutrophil count (ANC) were observed for 10.2%, 3.4%, and 8.1%, of subjects, respectively (Table 45). In the cGVHD adult pool, decreases in these laboratory parameters were observed for 3.1%, 4.6%, and 4.6% of subjects, respectively.

Table 45 Applicant – Worst Post-Baseline Hematology Toxicity Grade (Safety Population)

Lab Parameter, n (%)	Abnormal Direction	Pediatric Pool [a] R/R (N=47) Any Grade	Pediatric Pool [a] R/R (N=47) Grade 3+4	Pediatric Pool [a] TN (N=15) Any Grade	Pediatric Pool [a] TN (N=15) Grade 3+4	Pediatric Pool [a] R/R+TN (N=62) Any Grade	Pediatric Pool [a] R/R+TN (N=62) Grade 3+4	Adult Pool [b] (N=131) Any Grade	Adult Pool [b] (N=131) Grade 3+4
Hemoglobin	Low	23 (48.9)	6 (12.8)	4 (33.3)	0 (0.0)	27 (45.8)	6 (10.2)	33 (25.2)	4 (3.1)
Platelets	Low	10 (21.3)	2 (4.3)	4 (33.3)	0 (0.0)	14 (23.7)	2 (3.4)	57 (43.5)	6 (4.6)
ANC	Low	6 (12.8)	3 (6.4)	6 (40.0)	2 (13.3)	12 (19.4)	5 (8.1)	14 (10.7)	6 (4.6)

ANC = absolute neutrophil count; CTCAE = Terminology Criteria for Adverse Events; Ibr = ibrutinib; Pred = prednisone; R/R = relapsed refractory; TN = treatment-naïve

a Ibr treated subjects from 1140 and 1146 with age ≥1 to < 22.

b Ibr treated subjects from 1129 and/or Ibr+Pred treated subjects from 1140 with age ≥ 22.

Notes: Toxicities were graded using CTCAE version 4.03.

Abnormalities worsened after first dose of study treatment up to 30 days after the last dose of study drug were included in this table.

Source: ISS (R&D/21/1342) Table 4.1

Changes in clinical chemistry parameters Grade 3 + 4 were comparable and consistent in both the pediatric and adult pools (Table 46).

Table 46 Applicant – Worst Post-Baseline Chemistry Toxicity Grade (Safety Population)

		Pediatric Pool [a]						Adult Pool[b] (N = 131)	
		R/R (N = 47)		TN (N = 15)		R/R+TN (N = 62)			
Lab Parameter, n(%)	Abnormal Direction	Any Grade	Grade 3+4	Any Grade	Grade 3+4	Any Grade	Grade 3+4	Any Grade	Grade 3+4
Alanine aminotransferase	High	10 (21.3)	3 (6.4)	8 (53.3)	4 (26.7)	18 (29.0)	7 (11.3)	43 (32.8)	5 (3.8)
Alkaline phosphatase	High	6 (12.8)	0 (0.0)	5 (33.3)	0 (0.0)	11 (17.7)	0 (0.0)	36 (27.5)	4 (3.1)
Aspartate aminotransferase	High	9 (19.1)	1 (2.1)	5 (33.3)	2 (13.3)	14 (22.6)	3 (4.8)	32(24.4)	3(2.3)
Bilirubin	High	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	1 (1.7)	0 (0.0)	18 (13.7)	1 (0.8)
Creatinine	High	20 (42.6)	1 (2.1)	6 (40.0)	0 (0.0)	26 (41.9)	1 (1.6)	28 (21.4)	1 (0.8)
Creatinine Clearance	Low	6 (12.8)	0 (0.0)	1 (8.3)	0 (0.0)	7 (11.9)	0 (0.0)	48 (36.6)	0 (0.0)
Corrected Calcium	High	4 (8.5)	0 (0.0)	0 (0.0)	0 (0.0)	4 (6.5)	0 (0.0)	1 (1.1)	0 (0.0)
	Low	5 (10.6)	0 (0.0)	1 (33.3)	0 (0.0)	6 (9.7)	0 (0.0)	14 (15.4)	1 (1.1)
Potassium	High	5 (10.6)	1 (2.1)	1 (6.7)	0 (0.0)	6 (9.7)	1 (1.6)	19 (14.5)	0 (0.0)
	Low	11 (23.4)	2 (4.3)	6 (40.0)	1 (6.7)	17 (27.4)	3 (4.8)	35 (26.7)	6 (4.6)
Magnesium	High	3 (6.4)	0 (0.0)	2 (16.7)	0 (0.0)	5 (8.5)	0 (0.0)	8 (6.1)	2 (1.5)
	Low	8 (17.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (13.6)	0 (0.0)	27 (20.6)	0 (0.0)
Sodium	High	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.4)	0 (0.0)	7 (5.3)	0 (0.0)
	Low	11(23.4)	0 (0.0)	1 (8.3)	0 (0.0)	12 (20.3)	0 (0.0)	17 (13.0)	6 (4.6)

Ibr = ibrutinib; Pred = prednisone; R/R = relapsed/refractory; TN = treatment-naive

a Ibr treated subjects from 1140 and 1146 with age ≥1 to < 22.

b Ibr treated subjects from 1129 and or Ibr+Pred treated subjects from 1140 with age ≥ 22.

Notes: All chemistry parameters were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 with the modification of creatinine, which was graded on CTCAE version 4.03 criteria for values increased above upper limit of normal range (ULN) only.

Abnormalities worsened after first dose of study treatment up to 30 days after the last dose of study treatment were included in this table.

Source: (ISS [R&D/21/1342] Table 4.2)

The FDA's Assessment:
The FDA agrees with results of worst post-baseline hematology toxicity trade that reflects toxicity of ibrutinib in patient on treatment. Comparing pediatric to adult patients, low hemoglobin was more common in pediatric patients, while low platelets was more common in adults. Altogether, grade 3-4 laboratory abnormalities were comparable between pediatric and adult patients.

Table 47. Hematologic Laboratory Abnormalities: cGVHD Previously Treated Pediatric Patients

	IMBRUVICA (N=47)	
	All Grades N (%)	Grade 3 or 4 N (%)
Anemia	23 (49)	6 (13)
Thrombocytopenia	10 (21)	2 (4)
Neutropenia	6 (13)	3 (6)

As to the chemistry, the FDA agrees with the analysis, except for discrepancy in blood creatinine where FDA analysis showed high creatinine level in only 4/47 patients in the previously treated group and in only 5/62 patients in the overall pediatric pool). None of the post baseline toxicity indicates a new safety signal in pediatric patients. The laboratory abnormalities are acceptable for this patient population.

Vital Signs

The Applicant's Position:

Vital signs were not recorded in Study 1146.

Vital signs were summarized for the ibrutinib/placebo treatment-emergent period in Study 1140. In the Ibr + Pred arm, median changes from baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP) were ≤ 9.0 mmHg and ≤ 8.0 mmHg, respectively, at time points with data available from 10 or more subjects (Study 1140 Final Analysis CSR Addendum Section 6.4). Hypertension TEAEs were reported for 10.6 % of subjects in the Ibr + Pred arm (Study 1140 Final Analysis CSR Addendum Section 6.2.5.3.4.6). No clinically meaningful changes were observed for other vital signs (heart rate, temperature, weight) (Study 1140 Final Analysis CSR Addendum Attachment 3 Table 14.3.6).

In the Pbo + Pred arm, median changes from baseline in SBP and DBP were ≤ 8.5 mmHg and ≤ 7.0 mmHg, respectively, at time points with data available from 10 or more subjects (Study 1140 Final Analysis CSR Addendum Section 6.4). Hypertension TEAEs were reported for 13.5% of subjects in the Pbo+Pred arm (Study 1140 Final Analysis CSR Addendum Section 6.2.5.3.4.6). No clinically meaningful changes were observed for other vital signs (heart rate, temperature, weight) (Study 1140 Final Analysis CSR Addendum Attachment 3 Table 14.3.6).

No clinically meaningful changes were observed for vital signs in Study 1129 (NDA205552/SN0181/Module 5.3.5.2/Study 1129 Primary Analysis CSR Attachment 3 Table 14.3.4.1).

In Study LYM3003, the vital sign abnormalities which were reported as TEAEs are presented in the Study LYM3003 CSR Section 11.2.1.1 (Table 36), Attachment TSFAE02P2, and Attachment TSFAE02AP2.

The FDA's Assessment:
The FDA agrees with the Applicant's statement. No data was recorded for the majority of the patients for which the indication is sought (previously treated cohort in Study 1146). Considering the low frequency of changes in the blood pressure, the FDA will require additional assessment.

Electrocardiograms (ECGs)

The Applicant's Position:

No ECG evaluation was performed in Studies 1146, 1140, or 1129.

In Study LYM3003, 4 of 35 (11.4%) subjects in the ibrutinib+CIT group had abnormal ECG findings and none of the findings were clinically significant (Study LYM3003 CSR Attachment TSFECG01P2).

The FDA's Assessment:
The FDA agrees with the Applicant's statement.

QT

The Applicant's Position:

No evaluation of QT interval was performed in Studies 1146, 1140, or 1129. In Study LYM3003, ECGs were performed; QT prolongation and other clinically significant ECG abnormalities were summarized and listed (see above Section Electrocardiograms).

The FDA's Assessment:
The FDA agrees with the Applicant's statement.

Immunogenicity

The Applicant's Position:

No evaluation of immunogenicity was performed in Studies 1146, 1140, 1129, or LYM3003.

The FDA's Assessment:
The FDA agrees with the Applicant's statement.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1 Hemorrhagic Events

The Applicant's Position:

In the cGVHD pediatric pool, bleeding TEAEs reported for 30.6% of subjects; the most common events (≥ 5% of subjects) were petechia (9.7%), contusion (8.1%), and epistaxis (8.1%), (ISS [R&D/21/1342] Table 2.7). There were no Grade 3 or higher bleeding TEAEs reported (ISS [R&D/21/1342] Table 2.1). Major hemorrhage TEAEs were reported for 1.6% of subjects; the event was hemothorax (ISS [R&D/21/1342] Table 2.6) and no Grade 3 or higher major hemorrhage TEAEs were reported for the cGVHD pediatric pool (ISS [R&D/21/1342] Table 2.6.1).

In the cGVHD adult pool, bleeding TEAEs were reported for 38.2% of subjects; the most common events (≥ 5% of subjects) were increased tendency to bruise (14.5%), contusion (9.9%), and epistaxis (6.9%)(ISS [R&D/21/1342] Table 2.7). Grade 3 or higher bleeding TEAEs were reported for 2.3% of subjects (ISS [R&D/21/1342] Table 2.1). Major hemorrhage TEAEs were reported for 2.3% of subjects; the events were hematuria (1.5%), and melena (0.8%) (ISS [R&D/21/1342] Table 2.6) which were Grade 3 or higher (ISS [R&D/21/1342] Table 2.6.1) and none were Grade 5.

A summary of bleeding TEAEs, and major hemorrhage TEAEs in Studies 1146, 1140, and 1129 are provided in (ISS [R&D/21/1342] Table 2.1, Table 2.7, Table 2.6, and Table 2.6.1) respectively.

In Study LYM3003 Part 1, 11 (52.4%) subjects experienced bleeding TEAEs and major hemorrhage TEAEs were reported for 7 (33.3%) subjects. All reported major hemorrhage events were Grade 3 or 4 and none of them were fatal (Study LYM3003CSR Table 20).

In Part 2 (Ibr + CIT) of Study LYM3003, bleeding TEAEs were reported for 21 (60.0%) subjects (ISS [R&D/21/1342] Table 6.7). Major hemorrhage TEAEs were reported for 6 (17.1%) subjects (ISS [R&D/21/1342] Table 6.6); all reported major hemorrhage events were Grade 3 and higher, including 1 (2.9%) Grade 5 major hemorrhage event (ISS [R&D/21/1342] Table 6.6.1).

In the B-cell malignancy label pool, bleeding TEAEs were reported for 676 (45.8%) of subjects (ISS [R&D/21/1342] Table 6.7), and major hemorrhage TEAEs were reported for 51 (3.5%) subjects (ISS [R&D/21/1342] Table 6.6). Grade 3 or higher major hemorrhage were reported for 40 (2.7%) subjects and 3 (0.2%) subjects had Grade 5 major hemorrhage (ISS [R&D/21/1342] Table 6.6.1).

8.2.5.2 Infections (Including Viral Reactivation)

In the cGVHD pediatric pool, TEAEs in the system organ class (SOC) "infections and infestations" were reported for 66.1% of subjects; the most common events (≥ 5% of subjects) were pneumonia (8.1%), oral candidiasis (6.5%), paronychia (6.5%) and upper respiratory tract infection (6.5%) (ISS [R&D/21/1342] Table 2.2). Grade 3+4 infection TEAEs were reported for 32.3% of subjects; the most common events (≥ 3% of subjects) were pneumonia (3.2%), bronchitis (3.2%), lower respiratory tract infection (3.2%), bacteremia (3.2%) and device related infection (3.2%) (ISS [R&D/21/1342] Table 2.2). Fatal infections were reported for 1 (1.6%) subject (ISS [R&D/21/1342] Table 2.5).

In the cGVHD adult pool, TEAEs in the system organ class (SOC) "infections and infestations" were reported for 72.5% of subjects; the most common events (≥ 5% of subjects) were upper respiratory tract infection (16.0%), and pneumonia (12.2%), influenza (7.6%), cellulitis (6.9%) and urinary tract infection (5.3%) (ISS [R&D/21/1342] Table 2.2). Grade 3+4 infection TEAEs were reported for 34.4% of subjects; the most common events (≥ 3% of subjects) were

pneumonia (8.4%), cellulitis (4.6%) and influenza (3.1%) (ISS [R&D/21/1342] Table 2.2). Fatal infections were reported for 6 (4.6%) subjects (ISS [R&D/21/1342] Table 2.5).

A summary of infection TEAEs in Studies 1146, 1140, and 1129 are provided in the ISS (R&D/21/1342) Table 2.2.

8.2.5.3 Other Malignancies

In the cGVHD pediatric pool, the reported rate for other malignancy TEAE was 1.6%; the event was non-skin cancer acute myeloid leukemia. There were no non-melanoma skin cancer or melanoma TEAEs reported (ISS [R&D/21/1342] Table 2.9).

In the cGVHD adult pool, the reported rate for other malignancy TEAE was 3.8% (1.5% non-melanoma skin cancer and 2.3% non-skin cancer). The non-melanoma skin cancer TEAEs were basal cell carcinoma (0.8%) and squamous cell carcinoma (1.5%) (ISS [R&D/21/1342] Table 2.9). Melanoma was not reported. The rate of non-skin cancer TEAEs was 2.3%; the events were adenocarcinoma of colon (0.8%), myelodysplastic syndrome (0.8%), and post-transplant lymphoproliferative disorder (0.8%).

A summary of other malignancy TEAEs in Studies 1146, 1140, and 1129 is provided in ISS (R&D/21/1342) Table 2.9.

Other malignancies were also analyzed through the entire study period (including beyond 30 days of the last dose) (ISS [R&D/21/1342] Table 2.9.1). For the cGVHD pediatric pool and the cGVHD adult pool, the rate of non-melanoma skin cancer and melanoma skin cancer during the entire study period were similar to the rates of other malignancies during the treatment-emergent period.

8.2.5.4 Interstitial Lung Disease

Interstitial lung disease (ILD) terms were determined based on ILD SMQ narrow search (ISS [R&D/21/1342] Table 2.10). In the cGVHD pediatric pool, ILD TEAEs were reported for 8.1% of subjects; the events were obliterative bronchiolitis (4.8%), bronchiolitis (1.6%), and pneumonitis (1.6%) (ISS [R&D/21/1342] Table 2.10). Grade 3 or higher ILD TEAEs were reported for 1.6% of subjects (ISS [R&D/21/1342] Table 2.10.1). In the cGVHD adult pool, ILD TEAEs were reported for 1.5% of subjects; the events were pneumonitis (0.8%) and pulmonary toxicity (0.8%) (ISS [R&D/21/1342] Table 2.10). Grade 3 or higher ILD TEAEs were not reported (ISS [R&D/21/1342] Table 2.10.1).

A summary of ILD TEAEs in Studies 1146, 1140, and 1129 is provided in ISS (R&D/21/1342) Table 2.10 and Table 2.10.1.

The FDA's Assessment:
The FDA agrees with the frequencies of hemorrhage, other malignancies, and interstitial lung disease in the pediatric pool.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:

Clinical outcome assessments (ie, patient-reported outcomes) were performed for Study 1146 (refer to Section 8.1.1.1), Study 1140 (refer to Section 8.1.2.1), and Study 1129 (refer to Section 8.1.3.1).

The FDA's Assessment:
The FDA agrees with the clinical outcome assessment. Also, refer to section 8.1.1. under "Efficacy Results – Secondary or exploratory Clinical Outcomes Assessment (COA) or Patient Reported Outcomes (PRO) endpoints" for more information.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:

Age

The overall rate of any grade ADRs reported for the subset of subjects age ≥ 1 to < 6 years was 81.8% (ISS [R&D/21/1342] Table 3.1.3). The most common ADRs (> 20% of subjects) reported were pyrexia (45.5%), diarrhea (27.3%), anemia (27.3%), and pruritis (36.4%). Grade 3 and higher ADRs were reported for 63.6% of subjects and Grade 5 ADRs reported for 1 (9.1%) subject in this age subset.

The rate of any grade ADRs reported in the subset of subjects age ≥ 6 to < 12 years was 87.5% (ISS [R&D/21/1342] Table 3.1.3). The most common ADRs (>20% of subjects) reported were

pyrexia (31.3%), sepsis (25.0%), diarrhea (25.0%), and cough (25.0%). Grade 3 and higher ADRs were reported for 43.8% of subjects and no Grade 5 ADRs were reported in this age subset.

The rate of any grade ADRs reported in the subset of subjects age ≥ 12 to < 22 years was 100.0% (ISS [R&D/21/1342] Table 3.1.3). The most common ADRs (>20% of subjects) reported were abdominal pain (28.6%), nausea (25.7%), diarrhea (25.7%), vomiting (25.7%), pyrexia (25.7%), stomatitis (22.9%), bruising (22.9%), musculoskeletal pain (22.9%), and rash (22.9%). Grade 3 and higher ADRs were reported for 42.9% of subjects and no Grade 5 ADRs were reported in this age subset.

Sex

The overall rate of any grade ADRs was similar (< 10% difference) in females (88.2%) vs. males (95.6%) (ISS [R&D/21/1342] Table 3.1.4). Overall, the individual ADRs rates were comparable between the two groups; however the following ADRs were higher (> 10%) in females compared to males; pneumonia (29.4% vs. 13.3%), anemia (23.5% vs. 8.9%), musculoskeletal pain, (23.5% vs. 11.1%), headache (23.5% vs. 11.1%), aspartate aminotransferase increased (17.6% vs. 6.7%), diarrhea (28.9% vs. 17.6%), and blood alkaline phosphatase increased (11.8% vs 0.0%), whereas males had higher rate (> 10%) of skin infection (20.0% vs. 5.9%), hypokalemia (17.8% vs. 0.0%), constipation (13.3% vs. 0.0%), interstitial lung disease (11.1% vs. 0.0%) and rash (22.2% vs. 11.8%).

A similar percentage (< 5% difference) of females vs. males experienced Grade 3 or 4 ADRs (47.1% vs. 46.7%) (ISS [R&D/21/1342] Table 3.1.4). Overall, individual Grade 3 and higher rates were comparable between the two groups; however, the following ADRs were higher (≥ 5% difference) in females vs. males: alanine aminotransferase increased (17.6% vs. 0.0%), aspartate aminotransferase increased (11.8% vs. 0.0%), anemia (11.8% vs. 0.0%), pyrexia (11.8% vs. 6.7%), diarrhea (5.9% vs. 0.0%), and influenza (5.9% vs. 0.0%), while sepsis (13.3% vs. 0.0%), hypokalemia (8.9% vs. 0.0%), and constipation (6.7% vs. 0.0%) were higher (> 5% difference) in males.

The FDA's Assessment:
In general, the FDA agrees with most of the subgroup demographic analysis. Small differences, as follows, may originate from different composites of preferred group terms. See updated Table of TEAE by age groups below.

Table 48. Common TEAE (>20%) by age group

	Age 1 to <6 years N=11 n (%)		Age 6 to <12 years N=16 n (%)		Age 12 to <18 years N=31 n (%)	
	All grade*	Grade 3-4	All grade*	Grade 3-4	All grade	Grade 3-4
Any AE	10 (90.9)	6 (54.5)	16 (100)	9 (56.3)	31 (100)	20 (64.5)
Musculoskeletal pain**	2 (18.2)	0	1 (6.3)	0	12 (38.7)	1 (3.2)
Abdominal pain**	2 (18.2)	0	3 (18.8)	0	9 (29)	2 (6.5)
Diarrhea	3 (27.3)	1 (9.1)	4 (25)	0	9 (29)	0
Pneumonia**	2 (18.2)	2 (18.2)	2 (12.5)	1 (6.3)	8 (25.8)	4 (12.9)
Pyrexia	5 (45.5)	2 (18.2)	5 (31.3)	0	8 (25.8)	3 (9.7)
Nausea	0	0	1 (6.3)	1 (6.3)	8 (25.8)	0
Vomiting	0	0	2 (12.5)	0	8 (25.8)	0
Rash**	1 (9.1)	0	3 (18.8)	0	8 (25.8)	1 (3.2)
Headache**	3 (27.3)	0	0	0	7 (22.6)	0
Hypogamma-globulinemia**	1 (9.1)	0	0	0	7 (22.6)	0
Cough	1 (9.1)	0	4 (25)	0	7 (22.6)	1 (3.2)
Stomatitis**	1 (9.1)	0	3 (18.8)	2 (12.5)	9 (29.0)	2 (6.5)
Hypoxia	3 (27.3)	3 (27.3)	1 (6.3)	0	1 (3.2)	1 (3.2)
Pruritus	4 (36.4)	0	0	0	2 (6.5)	0
Sepsis**	2 (18.2)	0	4 (25)	4 (25)	1 (3.2)	1 (3.2)
Anemia	3 (27.3)	2 (18.2)	1 (6.3)	0	4 (12.9)	0

* One patient had grade 5 toxicity
** Composite Grouped terms

In summary, there was no significant difference in the TEAE between the age subgroups. Moreover, the difference detected between the Applicant analysis and the FDA analysis are minor and do not change the safety profile of ibrutinib.

The subset analysis related of sex is acceptable, with minimal differences in the numbers. Those differences do not change the safety profile of ibrutinib.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:

No specific studies were performed along with Studies 1146, 1140 and 1129 to evaluate safety concerns.

The FDA's Assessment:
The FDA agrees that no specific safety studies were performed, and safety was evaluated in the aforementioned studies.

The Applicant performed a human factors (HF) validation study to support the use of the suspension formulation. In general, the FDA agrees with the results of the human factors (HF) validation study. Nevertheless, the FDA identified use-errors with critical tasks, that can be mitigated with the Instructions For Use (IFU) document with labeling revisions to lessen the risk for these use errors. The recommendations by the Division of Medical Error Prevention and Analysis 2 (DMEPA2) are listed in the Table 5 of their review and were submitted to the Applicant.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

In Study 1140 at the final analysis, the rate of relapse of the underlying malignancy in subjects who received at least 1 dose of study drug was 8.5% (8/94) in the Ibr+Pred arm vs. 12.5% (12/96) in the Pbo+Pred arm (Study 1140 Final Analysis CSR Addendum Table 19).

The FDA's Assessment:
The FDA agrees with the Applicant’s statement.

Human Reproduction and Pregnancy

The Applicant's Position:

No pregnancies were reported during the conduct of Studies 1146, 1140, and 1129.

The FDA's Assessment:
The FDA agrees with the Applicant’s statement

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

In Study 1146, long-term follow up for growth and development is ongoing. A final analysis including long-term development will occur after all subjects (from Part A and Part B) have had the opportunity to complete 60 months of follow-up.

The FDA's Assessment:
The FDA agrees with the Applicant's plan. The FDA is planning to issue PMR regarding long term effect of ibrutinib on growth and development. See Section 13 for PMR information.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

No reports of overdose were reported during the conduct of Studies 1140 and 1129. In Study 1146, there were 2 reports of accidental overdose related to ibrutinib for 2/59 (3.4%) subjects.

The FDA's Assessment:
The FDA agrees with the Applicant's statement. No outcome data was provided regarding AEs related to overdosage.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Results from the Periodic Benefit-Risk Evaluation Report (PBRER) for the period of 13 November 2020 to 12 November 2021 showed that safety data from marketed use of ibrutinib are consistent with the known profile of ibrutinib for the treatment of adults in the approved indications (SN0361/Mod5.3.6/PBRER). The benefit-risk profile for ibrutinib remains favourable as shown by clinically meaningful efficacy associated with an acceptable safety and tolerability profile.

Since the database lock of the last PBRER, changes were applied to the current Imbruvica USPI Warnings and Precautions Section 5.4 (which includes details on Cardiac Arrythmias and Cardiac Failure), to provide further guidance to healthcare professionals about monitoring and managing cardiac risks.

The FDA's Assessment:
The FDA agrees with the Applicant's statement.

During the November 13, 2020, to November 12, 2021, DSUR reporting period, the SARs of cardiac failure, cardiac failure congestive, ischemic stroke, and pneumonia legionella were newly considered as expected SARs and added to the reference safety information section of the Investigator's Brochure (IB) Edition 14. Eye hemorrhage was identified as a new adverse reaction in the postmarketing setting. This information was updated in the IB Edition 15. All those complications were reported in adults.

In addition, review of 120-Day safety update report for NDA 217003 from 6/24/2022 of Study PCYC-1146-IM confirms previous finding and does not show any significant changes compared to previously submitted data. During this reporting period, however, the incidence of dyspnea and pneumonia increased (≥ 5% of all subjects) compared to the reported rates for Study 1146 primary analysis: dyspnea (3.4% increased to 6.8%) and pneumonia (3.4% increased to 5.1%). These findings confirm our assessment earlier that pneumonia and respiratory complications should be highlighted.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

The International Birth Date of ibrutinib is 13 November 2013 based on first authorization in the US. Ibrutinib is authorized in 103 countries worldwide. Results from the Periodic Benefit-Risk Evaluation Report (PBRER), for the period of 13 November 2020 to 12 November 2021, showed that safety data from marketed use of ibrutinib are consistent with the known profile of ibrutinib for the treatment of adults in the approved indications (SN0361/Mod5.3.6/PBRER). Based on (b) (4) milligrams distributed worldwide from launch to 31 October 2021, the estimated exposure to ibrutinib is (b) (4) person years. Postmarketing experience continues to support the established positive benefit-risk profile of ibrutinib for the approved indications. A new dosage form (i.e., a 70 mg/mL, ready to-use, multi-dose, oral suspension) of ibrutinib has been developed to enable age-appropriate dosing for pediatric patients age ≥ 1 to < 12 years with cGVHD. This new formulation has not been approved or marketed yet. The current edition of the ibrutinib Investigator Brochure (IB) (version 15, 10 December 2021) displays all ADRs (serious and non-serious), including events that comprise grouped ADR terms, which were identified in the ibrutinib clinical trial program (IB Edition 15 Table 25) and the post-marketing setting (IB Edition 15 Table 26)

The FDA's Assessment:
The FDA agrees with the statement, for additional information on postmarketing data see comments on “Safety Concerns Identified Through Postmarket Experience”.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

The safety profile of TEAEs for the cGVHD pediatric pool was similar to that observed for the cGVHD adult pool.

- The rate of TEAEs reported was similar in the cGVHD pediatric pool (98.4%) and in the adult pool (99.2%): the most common TEAEs (≥ 20%) observed in the cGVHD pediatric pool were pyrexia (30.6%) and diarrhea (25.8%) whereas in the cGVHD adult pool, the most common TEAEs observed were fatigue (30.5%), diarrhea (23.7%), muscle spasms (22.9%), edema peripheral (22.9%), and insomnia (21.4%).
- The rate of Grade 3 and higher TEAEs was similar in both the cGVHD pediatric pool (66.1%) and the cGVHD adult pool (71.0%), with no single PT being reported for > 10% subjects in the cGVHD pediatric pool or the cGVHD adult pool.
- In the cGVHD pediatric pool, the rate of TEAEs resulting in death was lower (4.8% vs. 11.5%) whereas the rate of serious TEAEs was higher (66.1% vs. 52.7%) compared with the cGVHD adult pool.
- The rate of major hemorrhage TEAEs was similar in the cGVHD pediatric and cGVHD adult pools (1.6% vs. 2.3%).
- The rate of other malignancy TEAE was 1.6% in the cGVHD pediatric pool and 3.8% in the the cGVHD adult pool. Melanoma was not reported in either pool.
- In the cGVHD pediatric pool, the rates of TEAEs of any grade and Grade 3 and higher TEAEs were similar (< 10% difference) between the age subsets of ≥ 1 to < 6 years, ≥ 6 to < 12 years, and ≥ 12 to < 22 years. The rate of serious TEAEs was lower (> 10% difference) for the age subset ≥ 1 to < 6 years (54.5%) compared with the age subsets ≥ 6 to < 12 years and ≥ 12 to < 22 years (68.8% and 68.6%).

In Study LYM3003, the overall TEAE profiles in the Ibr + CIT and CIT arms were comparable and the reported TEAEs were consistent with the known safety profiles of ibrutinib and CIT, and no new or unexpected safety concerns were observed.

The observed safety profile in the cGVHD pediatric pool (pediatric subjects in Studies 1146 and 1140) was similar to that established in the cGVHD adult pool (adult subjects in Studies 1129

and 1140). No new or unexpected safety concerns were observed in cGVHD pediatric pool and the safety profile was generally consistent with the safety profile observed across other B-cell malignancies.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:
The statistical review of this application focused on the results of Study 1146 in patients with previously treated cGVHD, and LSS PRO outcomes of Study 1129. See details in the Section 8 above, and in the standalone Statistical Review Memo.

8.4. Conclusions and Recommendations

The FDA's Assessment:
In summary, for the efficacy assessment, the cGVHD response data for Study 1146 appear favorable for treatment of children with previously treated cGVHD. In 47 patients, the ORR was 60% (4.3% CR and 55.3% PR) with a duration of response of 5.3 months. This demonstration of activity of ibrutinib for the treatment of cGVHD is supported by the previously approved treatment of adult patients for the same indication. Results from Study 1129 in adults with previously treated cGVHD were previously reviewed, and updated response data with longer follow up were not sufficient for analysis for response. Study 1140 in adults and adolescents with treatment naïve cGVHD failed to meet the primary endpoint of ORR at 48 weeks or additional analysis of ORR by week 24, and do not support an indication in the frontline setting

Considering the safety data in pediatric patients with cGVHD, although all studies reported in the ISS were included in the safety analysis, only patients with previously treated disease were considered for the indication of ibrutinib in children with chronic GVHD. No new safety signals were identified compared to the adult approved indication; however, the frequencies of

pneumonia and respiratory complications were noted in increased frequency both in study reports and in the post marketing data.

Based on the data reviewed, our clinical review recommendation is to approve S-36 based on Study 1146 to extend the intended population of previously treated chronic GVHD to include children at least 1 year old. The clinical review recommendation is to maintain the previously approved data for the response rates for adult patients in the Study 1129 and to update patient-reported outcome of LSS improvement in the Study 1129. In addition, the data submitted supports the approval of the ibrutinib liquid formulation under NDA 217003.

X	X
Primary Clinical Reviewers Robert Le / Kamar Godder	Clinical Team Leader Lori Ehrlich

9. Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

This application was not discussed by an Advisory Committee.

10. Pediatrics

The Applicant's Position:

Please see Section 11 below for the proposed changes to the pediatric sections of the IMBRUVICA USPI.

The FDA's Assessment:

FDA issued a Written Request (WR) for the use of ibrutinib in children on May 18, 2018, that included 3 studies. The WR was amended twice with the final revised WR issued on September 9, 2020.

1. Study 1: PCYC-1140-IM, was a phase 3, multicenter, international, randomized, double-blind study of ibrutinib in combination with prednisone versus placebo in combination with prednisone in subjects with treatment-naïve (TN), chronic GVHD including subjects ≥ 12 years old
2. Study 2: PCYC-1146-IM was an open label, multicenter, phase 1/2 dose-finding, safety and efficacy study of ibrutinib in pediatric subjects ≥ 1 and < 22 years of age with cGVHD.
3. Study 3: 54179060LYM3003 was a randomized, open-label safety and efficacy study of ibrutinib in pediatric and young adult patients ages 1 to 30 years with relapsed or refractory mature B-cell non-Hodgkin lymphoma (NHL).

Study 1 was completed and had negative efficacy endpoints of overall response rate at week 25 and week 48. The primary analysis does not support the use of ibrutinib in first line-treatment of cGVHD in adults and adolescents.

Study 2 demonstrated efficacy in pediatric patients. Furthermore, considering the similarity in clinical manifestation and exposure-response data between pediatric and adult patients with chronic GVHD, efficacy was also based on extrapolation from clinical trial results in adults.

Study 3 was terminated early after a prespecified interim analysis of EFS that met futility stopping parameters.

The FDA agrees that the terms of the written request were met. The FDA acknowledges that the study endpoint for study 1 was changed from response rate at 24 weeks as stated in the written request to response rate at 48 weeks. The division did not object to this revision. It was concluded that the data from the studies included in the written request provide sufficient

pediatric data to make a conclusion about the product. See the pediatric exclusivity review document for details.

Review by the pediatric exclusivity board granted Pediatric Exclusivity.

11. Labeling Recommendations

The Applicant's Position:

The high-level changes proposed to the current IMBRUVICA USPI are summarized in the table below. All proposed changes are provided in the draft USPI included in this submission.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
Highlights	N/A	Per 21 CFR 201.57(d)(8), the HL of the USPI should not exceed ½ page; the HL for this USPI exceeds ½ page and a waiver for this requirement is acceptable.
1 Indication and Usage, Chronic Graft versus Host Disease	Added pediatric patients age 1 year and older to the already labeled indication for adults with previously treated chronic graft versus host disease (cGVHD).	FDA agreed.
2.1 Dosage and Administration – Recommended Dosage	• Included recommended dosing guidance for adolescent patients ≥ 12 years of age at the adult dosage of 420 mg PO daily. • Added guidance for dosing pediatric patients 1 to < 12 years of age based on body surface area (BSA), using capsules/tablets or oral suspension at the dosage of 240 mg/m2 PO daily. Added reference to Instructions for Use for administration of oral suspension.	FDA generally agreed with the proposed edits but made formatting changes to replace symbols with their intended meanings, remove all instances of trailing zeros in Table 1, and clarify that Table 1 applies to pediatric patients 1 to less than 12 years of age.
2.2 Dosage and Administration - Dosage Modifications for Adverse Reactions	• Updated dose modification table to include adolescent patients in the existing column for cGVHD. • Added a new column for dose modification for pediatric patients 1 to <12 based on BSA. • Added a table to list the capsule/tablet (mg) or oral suspension (mL) needed to achieve correct dose modifications based on BSA from 0.3 m^2 to 1.6 m^2	FDA generally agreed but made formatting changes as described above in section 2.1.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
2.3 Dosage and Administration - Dosage Modifications for Use with CYP3A Inhibitors	• Added adolescent patients 12 years and older to existing section for adults with cGVHD • Added new rows for recommended IMBRUVICA dosage when coadministered with specific CYP3A inhibitors in pediatric patients 1 to < 12 years of age with cGVHD	FDA generally agreed but made formatting changes as described above in section 2.1.
2.4 Dosage and Administration - Dosage Modifications for Use in Hepatic Impairment	• Added a new section describing recommended dosage for patients with cGVHD based on total bilirubin levels.	FDA generally agreed but made formatting changes as described above in section 2.1.
6 Adverse Reactions	• Added the most common adverse reactions (b) (4) and hematologic laboratory abnormalities (b) (4)	FDA modified the section to change the denominator to (b) (4) (b) (4) Additional edits were made to align with current labeling practice in OOD for the presentation of clinical trial adverse reaction data.
8.4 Use in Specific Populations – Pediatric Use	• Safe and effective use in pediatric and young adult patients with cGVHD is described with appropriate cross-reference to other sections of the label. • A section describing the lack of safety and effectiveness in pediatric patients with previously treated mature B-cell non-Hodgkin lymphoma was added.	FDA modified this section to align with recommendations in the *Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling* guidance, including limiting the data described to the regulatory definition of the pediatric age range which is from birth through less than 17 years of age. FDA modified the section describing the lack of safety and effectiveness in pediatric patients with mature B-cell non-Hodgkin lymphoma to note that the study was stopped for futility and that major hemorrhage and discontinuation of chemoimmunotherapy occurred more frequently in the ibrutinib plus chemoimmunotherapy arm compared to the chemoimmunotherapy arm

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
	• [redacted] (b) (4)	alone. FDA also removed the statement concerning pharmacokinetic data because that information is more appropriately described in section 12.3. FDA did not agree with [redacted] (b) (4) (b) (4)
8.6 Use in Specific Populations – Hepatic Impairment	• Updated to include information about dosing in patients with cGVHD based on total bilirubin levels	FDA agreed.
11 Description	Added ingredient list for the oral suspension.	FDA agreed.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
12.2 Clinical Pharmacology - Pharmacodynamics	• Added a section on the pharmacodynamics in patients with cGVHD.	FDA agreed with the addition of the pharmacodynamics section. (b) (4)
12.3 Clinical Pharmacology - Pharmacokinetics	• Added a description of the pooled population pharmacokinetic analysis in pediatric and young adult patients with cGVHD under Specific Populations.	FDA modified the description to include the geometric mean (%CV), steady state AUC and Cmax in patients in the age range 1 – less than 12 years and from 12 to less than 17 years.
14.5 Clinical Studies – Chronic Graft versus Host Disease	• (b) (4) . • Added new section for pediatric and young adult patients age 1 year and older with moderate or severe cGVHD from the IMAGINE (b) (4) .	FDA did not agree with the addition of (b) (4) . LSS results for Study 1129 were updated to results through week 25. FDA modified the new pediatric section to delete (b) (4)
16 How Supplied/Storage and Handling	• Added information specific to the oral suspension.	FDA agreed.
17 Patient Counseling Information	• Added recommendation to read and follow the Instructions for Use	FDA agreed.
Patient Information	• Updated to reflect new information specific to use of the oral suspension • Updated to include common side effects observed in children with cGVHD	FDA edited the PPI to align with edits made in the USPI.
Instructions for Use (new)	• Created a new IFU to guide patients or caregivers in proper preparation, administration, storage and disposal of the oral suspension	FDA modified the IFU to align with changes made to the USPI and PPI and to align with current practice for display of information in IFUs.

The FDA's Assessment:

FDA modified sections of the USPI, PPI, and IFU as described in the table above; see the USPI, PPI, and IFU attached to the approval letter for final labeling.

12. Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

A REMS is not needed for the safe use of ibrutinib in the proposed indication.

13. Postmarketing Requirements and Commitments

The FDA's Assessment:

Considering that cGVHD is a serious and life-threatening condition, the occurrence of cGVHD and its therapy in children is of major importance, since they potentially have an overall long life expectancy following recovery from the complications of cGVHD. In a recent retrospective review of 1260 pediatric patients who survived 2 years after hematopoietic stem cell transplant reported to the Center for International Blood and Marrow Transplant Research (CIBMTR), development of cGVHD was independently associated with any late effect (Lee et al, 2022). Nevertheless, the effect of treatment of cGVHD was never studied. Ibrutinib is given until resolution of cGVHD symptoms, which may be prolonged; however, the effect of ibrutinib on growth and development in children one year and older is unknown.

FDA is issuing a PMR regarding long term effect of ibrutinib, with the following rationale as follows:

The safety of ibrutinib was evaluated in a single arm study in pediatric patients with treatment-naïve and previously treated cGVHD (Study PCYC-1146-IM). The median duration of exposure was 5 months (range: 0.1 to 44.4 months). The safety issues in the single arm study includes anemia, musculoskeletal pain, pyrexia, diarrhea, pneumonia, abdominal pain, stomatitis, thrombocytopenia, and headache. The long-term effect of treatment with ibrutinib on growth and development in children one year and older is unknown. The goal of this PMR is to evaluate and provide data to assess the signals of serious risk on the safety of long-term administration, including the impact on growth and development of ibrutinib in pediatric patients with cGVHD.

The PMR is requesting to evaluate growth and development milestones, for 5 years from the initiation of ibrutinib.

14. Division Director (DHOT) (NME ONLY)

X

15. Division Director (OCP)

X

Brian Booth

16. Division Director (OB)

X _____

17. Division Director (Clinical)

X

R. Angelo de Claro

18. Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X _____

19. Appendices

19.1. References

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19.2. Financial Disclosure

Data: Financial Disclosure Forms have been collected for all investigators who participated in Studies 1146, 1140, 1129, and LYM3003. Refer to the table below.

The Applicant's Position:

The Applicant considers the design and conduct of Studies 1146, 1140, 1129, and LYM3003 to be adequate to minimize the risk of bias to the study results.

The FDA's Assessment:
FDA agrees with the Applicant's statement.

Covered Clinical Studies*: 1146, 1140, 1129, and LYM3003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1569		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 1		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: 1 Significant equity interest held by investigator in study: 2 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 for initial disclosure timepoint, 30 for interim disclosure timepoint		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

19.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position:

No new information is provided in the current submission.

The FDA's Assessment:
FDA agrees with the Applicant’s statement.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

The FDA's Assessment:

19.4.1. Summary of Applicant's Ibrutinib Population PK Analysis in Pediatric patients with Chronic Graft-Versus-Host Disease (cGVHD)

Population PK (PPK) analysis for Ibrutinib in Pediatric cGVHD was conducted based on sparse PK data using 252 plasma ibrutinib concentrations from 57 patients aged 1 to <22 years with cGVHD including 2 subjects from Study PCYC-1140 (ibrutinib treatment arm), 55 subjects from Study PCYC-1146. The dose used in the analysis were 240 mg/m^2 for subjects 1 to <12 years old and 420 mg fixed dose for subjects 12 to <22 years old via orally administered QD. The PPK analysis was initiated with a previously developed adult model for cGVHD as a starting point, which adequately captured the ibrutinib concentration versus time profiles in adult cGVHD from study PCYC-1129, PCYC-1140, PCYC-1146, and GVH3001. A brief overview of the studies included in the PPK analysis is listed in Table 49. Summary statistics of the continuous and categorical covariates in the respective age groups included in this population PK analysis are provided in Table 50. In addition, the demographic by age and sex is provided in Figure 4 and the administered doses of all subjects by age subgroup is provided in Figure 5.

Table 49. Overview of Studies Included in the Pediatric Population PK Analysis and ER Analysis

Study	Study Information	Dose and Regimen	Analytes and PK Sampling
PCYC-1146-IM (Study 1146) Ongoing	A Phase 1/2 dose finding, safety and efficacy study of ibrutinib in pediatric subjects (aged 1 to <22 years) with cGVHD	420 mg qd for subjects aged >12 years 240 mg/m^2 qd for subjects aged 1 to <12 years	**PK:** Day 7 Week 2 (predose, 1 h, 2 h, 4 h), Day 1 Week 3 (for Part B of the study only; predose, 1 h, 2 h, 4 h), Day 1 Week 5 (predose, 1 h, 2 h, 4 h) **ER with endpoints:** Efficacy: ORR (CR or PR) Safety: occurrence of Afib (any Grade), hemorrhage (any grade and major events), liver function tests abnormalities (Grade ≥3), neutropenia (Grade ≥3), diarrhea (Grade ≥2)
PCYC-1140-IM (Study 1140) Completed	A randomized, double-blind, Phase 3 study of ibrutinib in combination with corticosteroids versus placebo in combination with corticosteroids in subjects aged ≥12 years with new onset cGVHD	Ibrutinib (420 mg) or placebo qd Prednisone (1 mg/kg) qd	**PK:** Day 1 Week 2 and Day 1 Week 25 (predose, 1 h, 2 h, 4 h, 6 h) plus predose at different weeks **ER with endpoints:** Efficacy: CR, ORR Safety: occurrence of Afib (any grade), hemorrhage (any grade and major events), liver function tests abnormalities (Grade ≥3), neutropenia (Grade ≥3), diarrhea (Grade ≥2)

Afib=atrial fibrillation; cGVHD=chronic graft-versus-host disease; CR=complete response; ER=exposure-response; h=hour; ORR=overall response rate; PK=pharmacokinetic(s); PR=partial response; qd=once daily.

Source: Applicant's PopPK-ER cGVHD Pediatric report, Table 2.

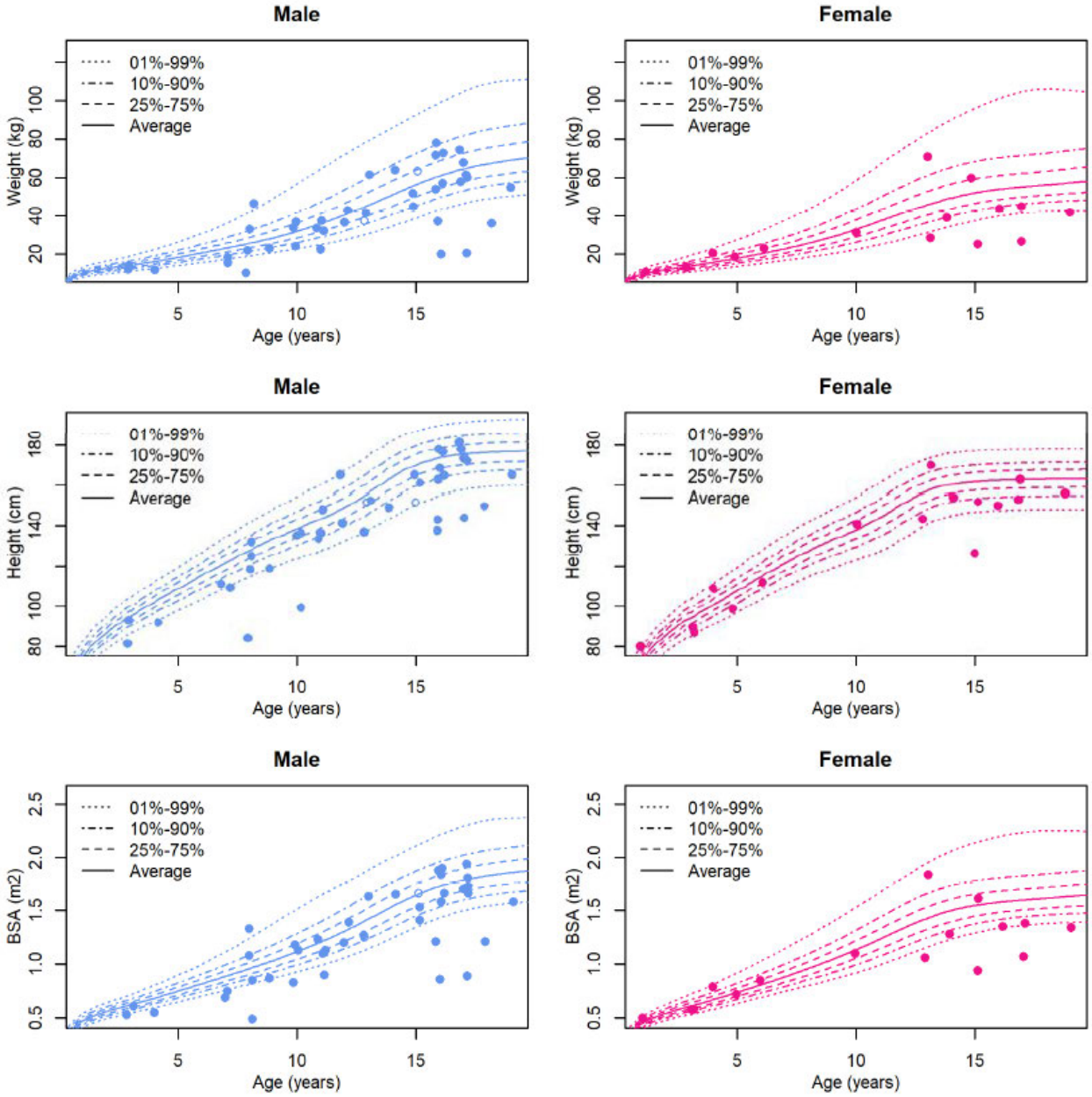
Table 50. Demographics of All Subjects Included in the Analyses

Study	Age Subgroup: Range (Years)	Subjects N	Subjects Cum.	Weight (kg) Mean (SD)	Weight (kg) Median [Range]	Age (Years) Mean (SD)	Age (Years) Median [Range]	BSA (m^2) Mean (SD)	BSA (m^2) Median [Range]
1140	12 to <16	2	2	50.4 (18.42)	50.4 [37.4-63.5]	14.0 (1.41)	14.0 [13.0-15.0]	1.5 (0.29)	1.5 [1.2-1.7]
1146	1[a] to <2	1	1	11.0 (NA)	11.0 [11.0-11.0]	1.0 (NA)	1.0 [1.0-1.0]	0.5 (NA)	0.5 [0.5-0.5]
	2 to <12	23	24	23.8 (9.98)	22.5 [10.3-46.6]	7.4 (2.95)	8.0 [3.0-11.0]	0.9 (0.25)	0.8 [0.5-1.3]
	12 to <16	12	36	47.3 (14.40)	44.0 [25.3-71.0]	13.7 (1.15)	13.5 [12.0-15.0]	1.4 (0.26)	1.4 [0.9-1.8]
	16 to <22	19	55	51.7 (18.02)	55.0 [20.0-78.1]	16.8 (0.96)	17.0 [16.0-19.0]	1.5 (0.34)	1.6 [0.9-1.9]
Pooled	1[a] to <2	1	1	11.0 (NA)	11.0 [11.0-11.0]	1.0 (NA)	1.0 [1.0-1.0]	0.5 (NA)	0.5 [0.5-0.5]
	2 to <12	23	24	23.8 (9.98)	22.5 [10.3-46.6]	7.4 (2.95)	8.0 [3.0-11.0]	0.9 (0.25)	0.8 [0.5-1.3]
	12 to <16	14	38	47.7 (14.24)	44.0 [25.3-71.0]	13.7 (1.14)	13.5 [12.0-15.0]	1.4 (0.26)	1.4 [0.9-1.8]
	16 to <22	19	57	51.7 (18.02)	55.0 [20.0-78.1]	16.8 (0.96)	17.0 [16.0-19.0]	1.5 (0.34)	1.6 [0.9-1.9]

BSA=body surface area; Cum.=cumulative count; NA=not applicable; SD=standard deviation.
[a] Months, not years.
Note: Age subgroup of 16 to <22 years includes 2 subjects >18 years old, both 19 years old.

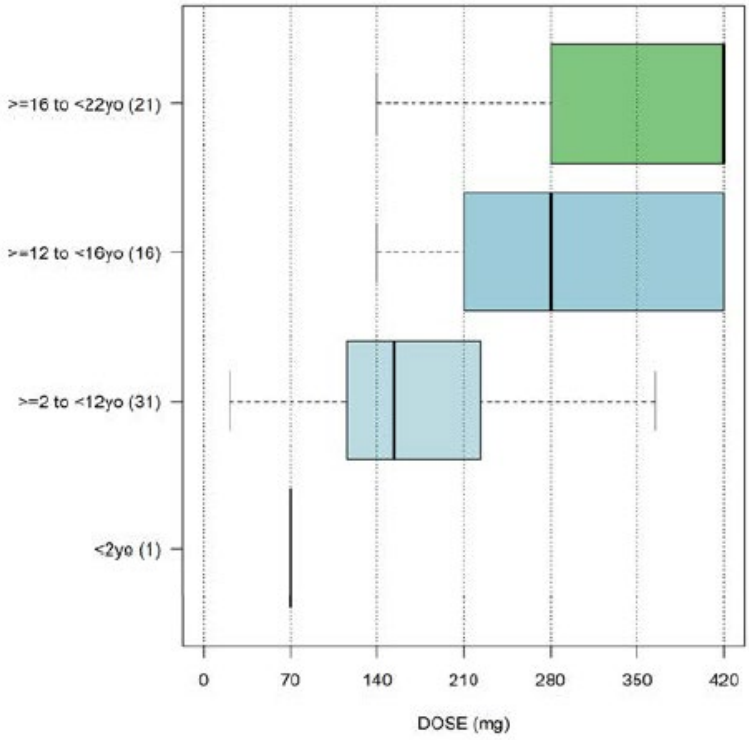
Source: Applicant's PopPK-ER cGVHD Pediatric report, Table 10.

Figure 4. Demographics of Studied Population (BSA, Height, Weight) by Age and Sex



Source: Applicant's PopPK-ER cGVHD Pediatric report, Figure 6.

Figure 5. Administered Doses in Studied Population by Age Subgroup



Source: Applicant's PopPK-ER cGVHD Pediatric report, Figure 7.

Similar to adult PPK model, the PK of ibrutinib in pediatric cGVHD patients was described by a 2-compartment PK model with sequential zero and first order absorption and first order elimination. The final PK model parameter estimates and the corresponding 95% confidence intervals (CIs) from bootstrap for ibrutinib are presented in Table 51. The goodness-of-fit plots for the final PK model are presented in Figure 6. The prediction corrected visual predictive check (pcVPC) based on all data (Figure 7) illustrated the prediction percentiles and corresponding 95% CI of simulated concentrations overlaid on the observed Ibrutinib concentrations and the corresponding 5th and 95th percentiles. The final popPK model was well validated with goodness-of-fit (GOF) plots and prediction-corrected visual predictive check (pcVPC).

The covariate analysis identified the fed status on F1 and D1, CYP3A inhibitors use and a "Japanese ethnicity effect" on F1 as statistically significant covariates. The estimates of apparent clearance and apparent volume of distribution at steady were generally similar across the age and BSA range (Figure 8). No significant relationship could be detected between the model parameters and the pediatric covariates including age (1-19 years old), body weight (BW, 10.3-78.1 kg), and body surface area (BSA, 0.5-1.9 m^2).

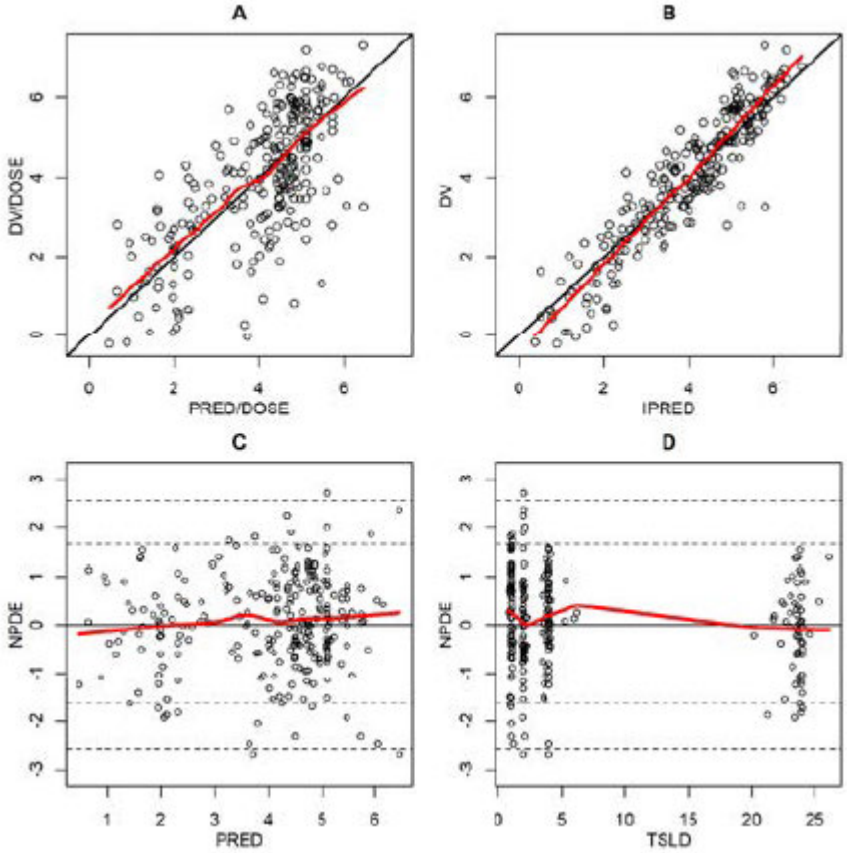
Table 51. PK Parameters of Ibrutinib from the Applicant's Final Pediatric PPK Model

Parameter	Population Estimate	%SEM	IIV (%CV) [shrinkage]	%SEM
CL/F (L/h)	1090 FIX	NA	0 FIX	NA
V2/F (L)	1340	14.9	112 [34%]	30.8
Q/F (L/h)	861	68.9	0 FIX	NA
V3/F (L)	4250	18	0 FIX	NA
k_a (1/h)	0.441 FIX	NA	0 FIX	NA
ALAG1 (h)	0.022	1.2	273 [75%]	1.7
D1 for fasted or mod fasted (h)	1.27 FIX	NA	0 FIX	NA
F1 for fed or mod fasted	2.81	21.2	86.9 [9.4%]	29.1
D1 for fed (h)	3.29	NA		
F1 for fasted	0.666	NA		
Effect of Moderate CYP3Ai on F1	1.86	17.9		
Effect of Strong CYP3Ai on F1	2.15	28.4		
Effect of Japanese on F1	2.67	26.3		
RUV(%)	78.4			

ALAG1=lag time before absorption process is started; CL/F=apparent (oral) plasma clearance; CV=coefficient of variation; CYP3Ai=cytochrome P450 3A inhibitor; D1=duration of zero-order input into gut compartment; F1=relative bioavailability; FIX=fixed in the model; mod fasted (modified fasted)=dose taken at least 30 minutes before a meal or at least 2 hours after a meal; h=hour; IIV=interindividual variability; ka=first-order absorption rate constant; NA=not available; Q/F=apparent intercompartmental flow; RUV=residual unexplained variability; SEM=relative standard error of the mean; V2/F=apparent volume of distribution of the central compartment; V3/F=apparent volume of distribution of the peripheral compartment.

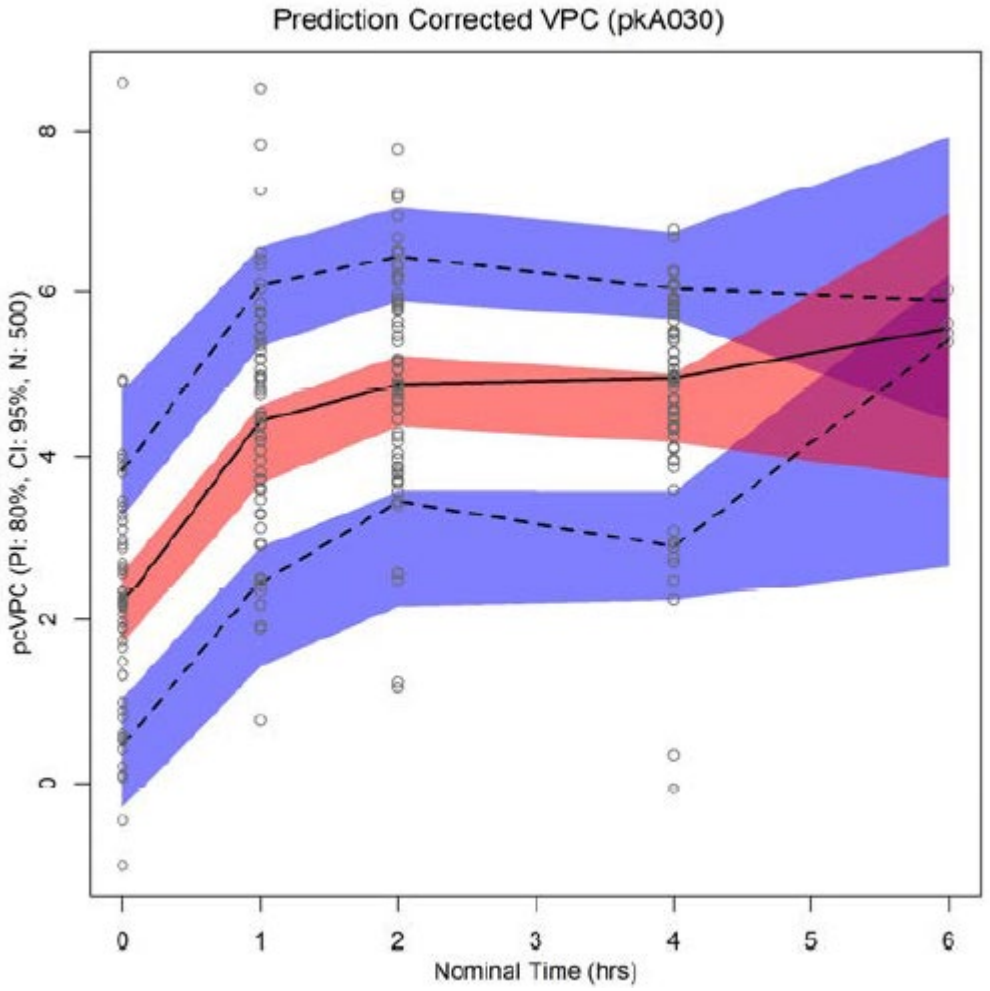
Source: Applicant's PopPK-ER cGVHD Pediatric report, Table 11.

Figure 6. Goodness-of-fit Plots for the Applicant's Final Population Pediatric PK Model for Ibrutinib



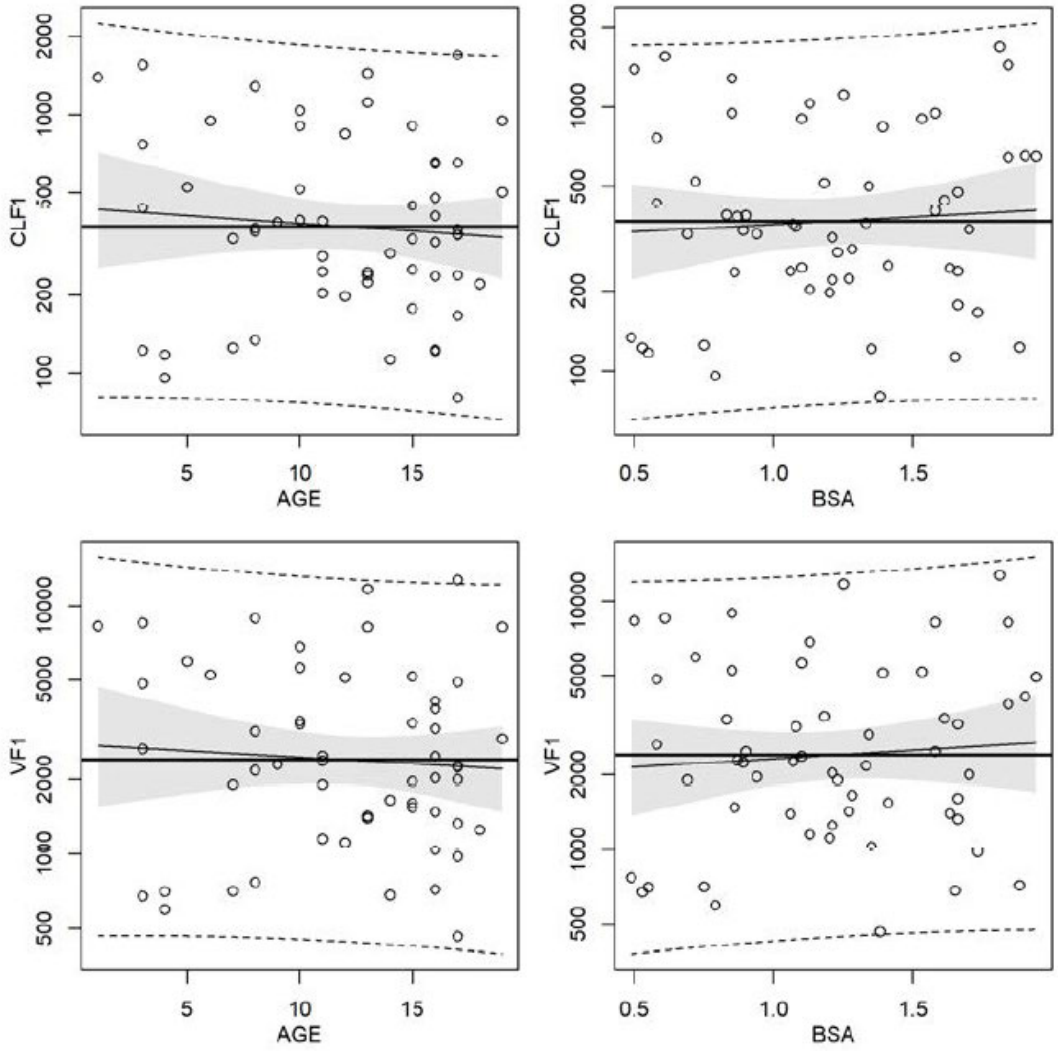
Source: Applicant's PopPK-ER cGVHD Pediatric report, Figure 23.

Figure 7. Visual Predictive Checks for the Final Model (Run PKA030)



Source: Applicant's PopPK-ER cGVHD Pediatric report, Figure 10.

Figure 8. Individual (Posthoc) Estimates of Apparent Clearance and Volume of Distribution Versus Age and BSA



BSA=body surface area; CLF1=apparent clearance; VF1=apparent volume of distribution.

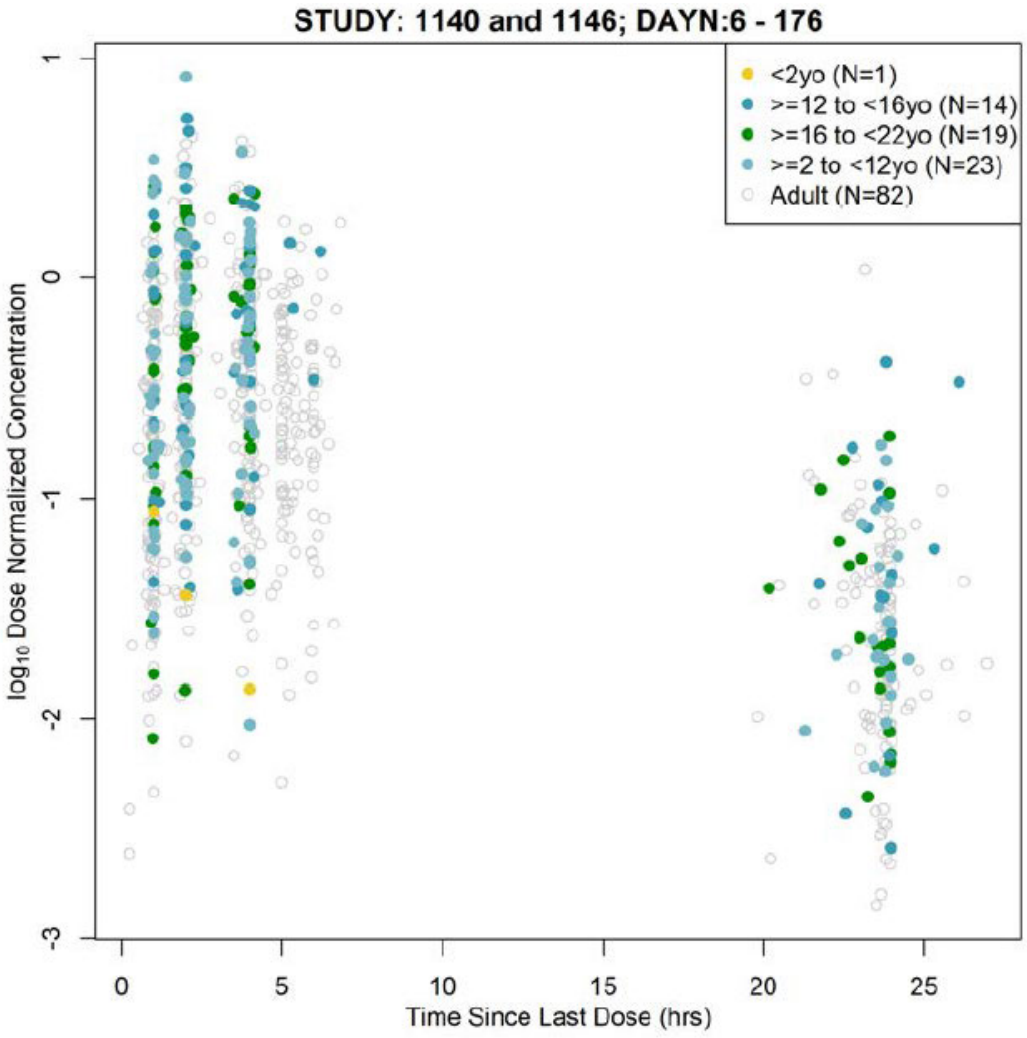
Source: Applicant's PopPK-ER cGVHD Pediatric report, Figure 1.

PK Exposure Matching using PPK Model

As shown in Figure 9, there is a good match between the dose-normalized concentrations observed in pediatric subjects compared with the concentrations observed in adults. Based on simulations of the recommended pediatric dosing regimens of 240 mg/m2 QD in subjects aged

1 to <12 years and of 420 mg QD in subjects aged 12 to <22 years, exposures across the age groups were generally within the target exposure range established in Study 1129 in adult subjects in the Figure 10.

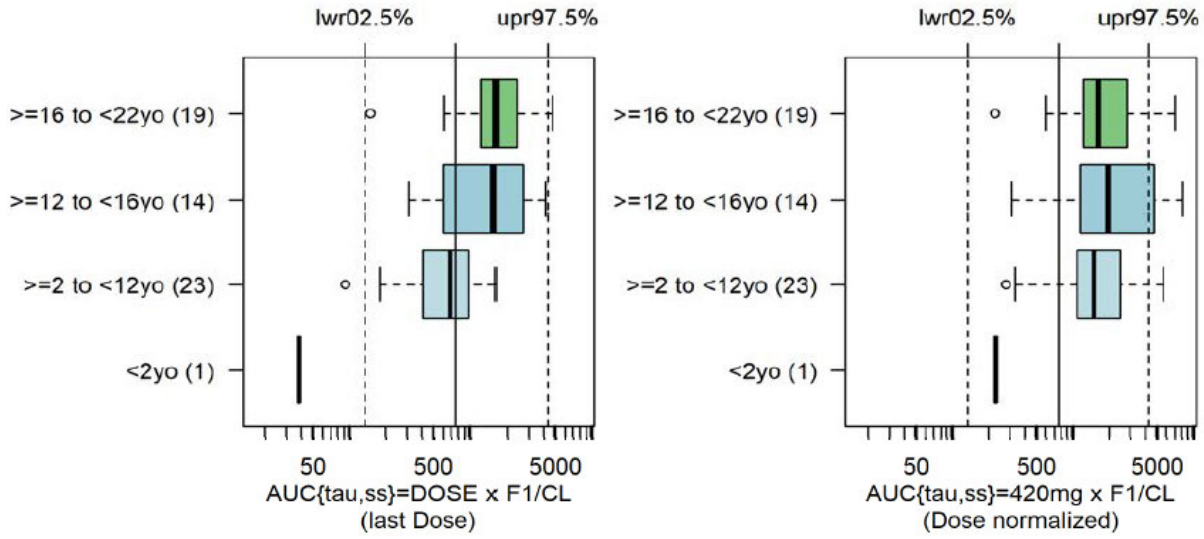
Figure 9. PK Exposure Graphical Matching with Dose-normalized Concentration-nominal Time Profile



hrs=hours; N=number of subjects; yo=years old.
Note: Overlay of observed dose-normalized concentrations.

Source: Applicant's PopPK-ER cGVHD Pediatric report, Figure 8.

Figure 10. PK Exposure Graphical Matching with Model-predicted AUCτ,ss



Source: Applicant's PopPK-ER cGVHD Pediatric report, Figure 11.

The FDA's Assessment:

In general, the Applicant's PPK models appears adequate to describe the concentration-time profiles of Ibrutinib in the cGVHD pediatric patients, following the oral administration of Ibrutinib with 240 mg/m^2 for subjects 1 to <12 years old and 420 mg fixed dose for subjects 12 to <22 years old. In the Applicant's ibrutinib PPK model, ETA shrinkage for F1 was reasonable (9.4%); ETA shrinkages for V2/F (34%) and ALAG1 (75%) were relatively large. There was no obvious bias in the parameter estimates for Ibrutinib. Therefore, the PK exposures of ibrutinib derived from the final PPK model are acceptable for exposure-response (E-R) analysis. Refer to Section 19.4.2 E-R analyses for safety and efficacy for more information.

In addition, the covariate analysis further confirmed the recommendation for no dose adjustment based on age, sex, body weight in the current labeling. Regarding the assessment of DDI effects, e.g., CYP3A4 inhibitor use in the current PPK analysis, the Applicant simply treated comedications as categorical covariates with the classifications as follows: 1) No CYP3A Inhibitor, 2) Moderate CYP3AInhibitor, or 3) StrongCYP3AInhibitor. This approach is not acceptable as the assessment of the impact of comedications on the PK of ibrutinib was not based on the actual dosing records for concomitant medications: e.g., dose level, dose frequency, formulation, route of administration, start and stop date and clock time, duration, dose modification, etc. The Applicant's PPK analysis appears to under-estimate the DDI effects as compared to the findings from the dedicated DDI studies and PBPK simulations. Of note,

there was no dedicated DDI study or PBPK simulations in pediatrics, and the PPK analysis for DDI in pediatric patients is not reliable due to the issues mentioned above. Without additional data, the dose adjustments for ibrutinib with the concomitant mild, moderate, and strong CYP3A inhibitors should in general follow the recommendations in the current labeling for adult patients.

Of note, based on the PPK simulations of the recommended pediatric dosing regimens of 240 mg/m^2 qd in subjects aged 1 to <12 years and of 420 mg qd in subjects aged 12 to <22 years, exposures across the age groups were within the target exposure range in adult subjects with cGVHD.

PPK Review Issues

Description of the Issue:
The Sponsor identified an issue in the NONMEM dataset of PCYC-1140-IM, and PCYC-1146-IM studies, used for the pediatric popPK/exposure-response: missing information on the fed/fasted status and/or comedication (ie. CYP3A inhibitors) at the time of administration for some patients led to a misspecification of the covariates between the time of administration and the first observation (approximately 1h post dose) in certain cases. This issue occurred while merging of the event and observation datasets to generate the NONMEM dataset used for this analysis. The SDTM dataset wasn't affected.

Impact Analysis:
The NONMEM dataset was updated to add the previously missing records on fed/fasting status and comedications and the analysis was rerun with the updated dataset. The results of the updated analysis show that there is no impact on the conclusions while there is a limited impact on the model parameters (see Table 52). There was a 5 to 10% difference in the estimated effect of comedication on the relative bioavailability of ibrutinib; the updated estimates were within the error margin of the reported values. The updated exposure estimates (AUC, C_{max}, C_{trough}) in the study population (in patients with and without moderate/strong CYP3A inhibitors) show little change after the updates compared to the previous values (see Table 53 and Table 54). There was no impact on the conclusions of the exposure-response analysis.

Table 52. Parameters of the Final Model – Updated Version

Parameter	Population Estimate	%SEM	IIV (%CV) [shrinkage]	%SEM
CL/F (L/h)	1090 FIX	NA	0 FIX	NA
V2/F (L)	1340 FIX	14.9	112 [34%]	30.8
Q/F (L/h)	861	68.9	0 FIX	NA
V3/F (L)	4250	18	0 FIX	NA
k_a (1/h)	.441 FIX	NA	0 FIX	NA
ALAG1 (h)	0.022	1.2	273 [75%]	1.7
D1 for fasted or mod fasted (h)	1.27 FIX	NA	0 FIX	NA
F1 for fed or mod fasted	2.81	21.2	86.9 [9.4%]	29.1
D1 for fed (h)	3.29	NA		
F1 for fasted	0.666	NA		
Effect of Moderate CYP3Ai on F1	1.86	17.9		
Effect of Strong CYP3Ai on F1	2.15	28.4		
Effect of Japanese on F1	2.67	26.3		
RUV(%)	79.0			

ALAG1=lag time before absorption process is started; CL/F=apparent (oral) plasma clearance; CV=coefficient of variation; CYP3Ai=cytochrome P450 3A inhibitor; D1=duration of zero-order input into gut compartment; F1=relative bioavailability; FIX=fixed in the model; mod fasted (modified fasted)=dose taken at least 30 minutes before a meal or at least 2 hours after a meal; h=hour; IIV=interindividual variability; ka=first-order absorption rate constant; NA=not available; Q/F=apparent intercompartmental flow; RUV=residual unexplained variability; SEM=relative standard error of the mean; V2/F=apparent volume of distribution of the central compartment; V3/F=apparent volume of distribution of the peripheral compartment.

Table 53. Summary Statistics for Observed PK Parameters by Age Subgroup – Old Version

Age Range (Years)	N	$AUC_{\tau,ss}$ (ng·h/mL)		C_{trough} (ng/mL)		C_{max} (ng/mL)	
		Mean (%CV)	Median [Range]	Mean (%CV)	Median [Range]	Mean (%CV)	Median [Range]
1 month to 2	1	38.2 (-)	38.2 [38.2-38.2]	0.234 (-)	0.234 [0.234-0.234]	6.49 (-)	6.49 [6.49-6.49]
2 to 12	23	737 (61%)	687 [93.5-1610]	5.55 (62%)	5.43 [0.534-11.8]	109 (70%)	76.8 [17.4-280]
12 to 16	14	1770 (69%)	1590 [313-4140]	14.4 (88%)	11.5 [1.87-46.9]	245 (67%)	185 [54.8-546]
16 to 21	19	1830 (61%)	1600 [151-4690]	12.9 (63%)	10.4 [2.04-29.2]	278 (65%)	234 [12.9-782]

$AUC_{\tau,ss}$=area under the plasma concentration-time curve during 24 hours after dosing at steady state; C_{max}=maximum concentration; C_{trough}=trough concentration; CV=coefficient of variation; N=number of subjects; PK=pharmacokinetic(s).
Notes: The units for the PK parameters are ng·h/mL for $AUC_{\tau,ss}$ and ng/mL for C_{trough} and C_{max}

Table 54. Summary Statistics for Observed PK Parameters by Age Subgroup – Updated Version

Age Range (Years)	N	$AUC_{\tau,ss}$ (ng·h/mL)		C_{trough} (ng/mL)		C_{max} (ng/mL)	
		Mean (%CV)	Median [Range]	Mean (%CV)	Median [Range]	Mean (%CV)	Median [Range]
1 month to 2	1	38 (-)	38 [38-38]	0.227 (-)	0.227 [0.227-0.227]	6.4 (-)	6.4 [6.4-6.4]
2 to 12	23	748 (61%)	686 [94.6-1630]	5.55 (62%)	5.46 [0.526-12.1]	110 (70%)	76.8 [17.4-280]
12 to 16	14	1770 (70%)	1490 [317-4160]	13.9 (88%)	11.6 [1.85-47]	245 (68%)	173 [55.1-554]
16 to 21	19	1860 (61%)	1640 [150-4760]	12.8 (63%)	10.5 [2.02-29.5]	279 (65%)	232 [12.8-785]

$AUC_{\tau,ss}$=area under the plasma concentration-time curve during 24 hours after dosing at steady state; C_{max}=maximum concentration; C_{trough}=trough concentration; CV=coefficient of variation; N=number of subjects; PK=pharmacokinetic(s).
Notes: The units for the PK parameters are ng·h/mL for $AUC_{\tau,ss}$ and ng/mL for C_{trough} and C_{max}.

The FDA's Assessment:

Based on the updated results dated 07/22/2022, there is no major impact on the overall data and PPK modeling and simulation results.

19.4.2. Summary of Applicant's Exposure-Response for Efficacy and Safety in Pediatric Patients with cGVHD

The pediatric ER efficacy and safety analyses were conducted in 53 cGVHD patients aged 1 to <22 years from Studies 1146, 1140, and 1129. A brief overview of the studies included in the ER analysis is listed in Table 49.

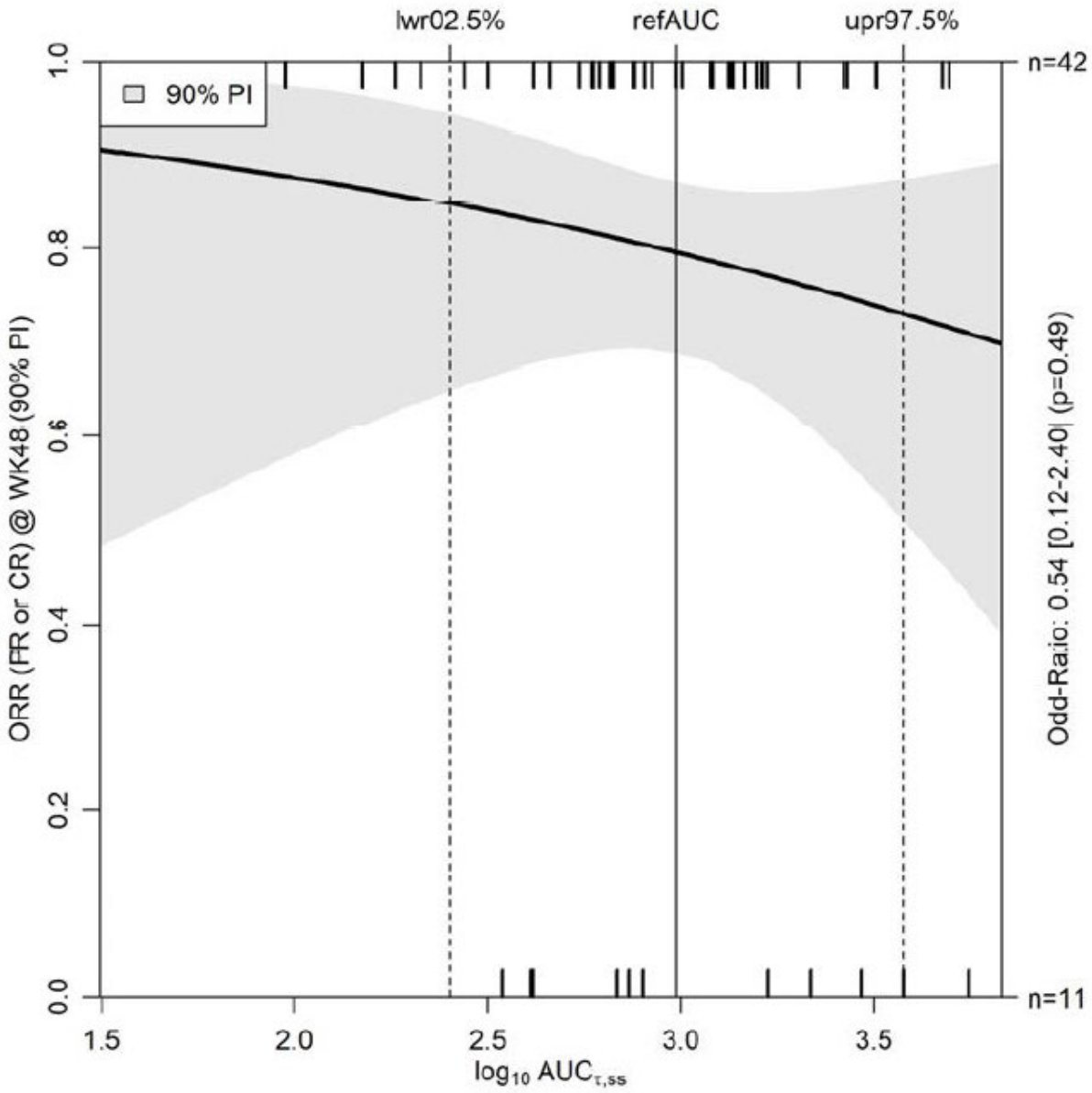
For the ER analysis for efficacy, the relationship between metrics of systemic exposure of ibrutinib and endpoints of clinical efficacy (ORR) was explored. The ORR at Week 48 was used in the analysis and was defined as the proportion of responders who had a response (PR or CR) at or prior to the Week 49 response assessment.

And ER for safety (hemorrhage (any grade and major events), Afib (any grade), liver function test abnormalities (Grade ≥3), and neutropenia (Grade ≥3)) was explored. For each safety endpoint, the proportion of subjects with the event was summarized by quartile of estimated area under the plasma concentration-time curve ($AUC_{\tau,ss}$) and graphically presented. In addition, the estimated $AUC_{\tau,ss}$ was summarized by the subject group with or without the event and graphically presented.

For the exposure-efficacy and exposure-safety analyses, a logistic regression analysis was conducted to assess any possible association between the metrics of ibrutinib systemic exposure and the endpoints of clinical efficacy and safety. The most significant metric of exposure for ibrutinib (among $AUC_{\tau,ss}$, C_{max}, and C_{trough}) was incorporated in the model separately.

For all efficacy and safety endpoints, a logistic regression was used to evaluate potential ER relationships based on the AUCτ,ss (Figure 11 and Figure 12). As none of the explored regressions showed a significant trend (i.e., all p-values were >0.05), the results are summarized in Table 55.

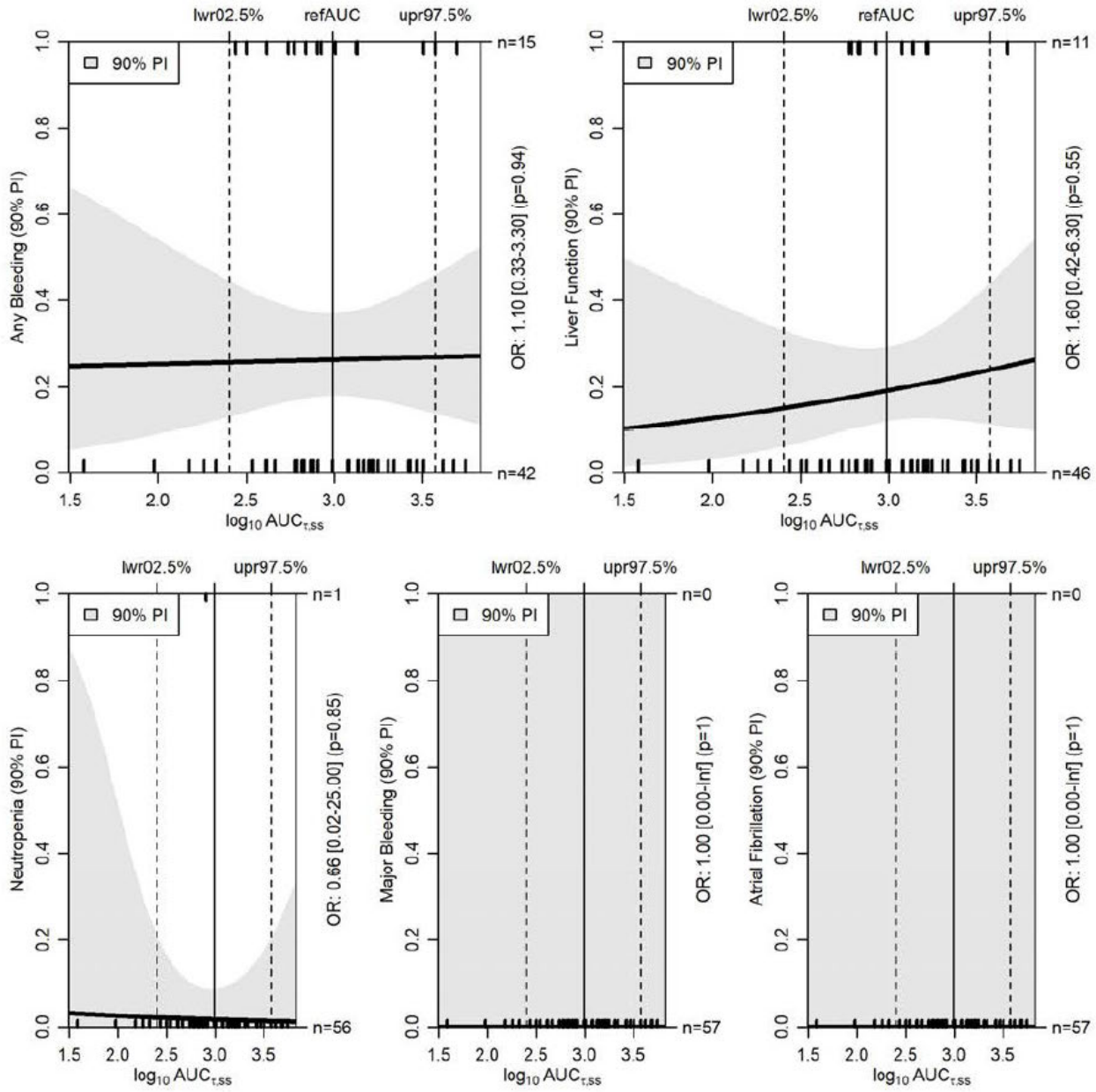
Figure 11. Exposure Efficacy Analysis for Positive Treatment Outcomes at Week 48



AUCτ,ss=area under the plasma concentration-time curve at steady state (maximum model-predicted AUC);CR=complete response; lwr=lower; n=number of subjects; ORR=overall response rate; PI=prediction interval; PR=partial response; upr=upper; WK=week. Note: Positive treatment outcome was defined as either a PR or CR.

Source: Applicant's PopPK-ER cGVHD Pediatric report, Figure 13.

Figure 12. Exposure Safety Analysis for the Defined Safety Endpoints



AE=adverse event (treatment-emergent); $AUC_{\tau,ss}$=area under the plasma concentration-time curve at steady state (maximum model-predicted AUC); lwr=lower; n=number of subjects; OR=odds ratio; PI=prediction interval; ref=reference; upr=upper.
Note: Logistic regression for the AE markers (any severity) versus no reported AE.

Source: Applicant's PopPK-ER cGVHD Pediatric report, Figure 14.

Table 55. Number of Responders (%) and Number of Subjects (%) Reporting TEAEs by Quartile

	Q1	Q2	Q3	Q4	None	N
Efficacy Endpoint						
ORR at 48 Weeks	10 (19%)	11 (21%)	12 (23%)	9 (17%)	11 (21%)	53[a]
Safety Endpoints						
Any bleeding	5 (9%)	4 (7%)	3 (5%)	3 (5%)	42 (74%)	57
Major bleeding	0 (0%)	0 (0%)	0 (0%)	0 (0%)	57 (100%)	57
Atrial fibrillation (any grade and major)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	57 (100%)	57
Neutropenia (Grade ≥3)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	56 (98%)	57
Liver Function (Grade ≥3)	1 (2%)	4 (7%)	5 (9%)	1 (2%)	46 (81%)	57

ORR=overall response rate; Qn=nth quartile interval (lower quartile=565.77, median=876.53, upper quartile=1593.4); TEAE=treatment-emergent adverse event.

[a] For a total of 53 subjects due to missing efficacy response in 4 subjects.

Source: Applicant's PopPK-ER cGVHD Pediatric report, Table 1.

The FDA's Assessment:

In general, applicant's E-R for safety and efficacy analysis appears acceptable. A flat E-R relationships between Ibrutinib PK exposures using updated PPK model and the efficacy and safety endpoints. The flat E-R relationships suggest that the effectiveness of Ibrutinib had already reached the plateau and E-R analysis can be limited due to relatively narrow exposure range at a dose level (420 mg) and 240 mg/m^2. The exposure-safety analysis showed that there was No clinically relevant exposure-response relationship between the systemic exposure (AUCτ,ss) to ibrutinib and the selected safety endpoints (hemorrhage, Afib, liver function test abnormalities, and neutropenia) in pediatric cGVHD patients. In addition, the current E-R analysis were generally in line with Adult cGVHD in the original submission.

The current E-R analyses further confirmed the appropriateness of the recommended ibrutinib dosing regimen for pediatric cGVHD from the safety and efficacy perspective.

19.4.3. Summary of Bioanalytical Method Validation and Performance

Plasma samples were analyzed for concentrations of ibrutinib via a validated liquid chromatography-tandem mass spectrometry method ((b) (4) which was the same bioanalytical method used in prior original and supplement NDA 205552 submissions. The bioanalytical method was adequately validated with a calibration range of 0.5 ng/mL to 250 ng/mL for both ibrutinib and PCI 45227 (dihydrodiol metabolite) and was demonstrated long-term storage stability for samples in the current trial. Table 56 summarizes the bioanalytical methods used for the respective studies supporting the current supplement submission.

Table 56. Summary of Bioanalytical Methods for Ibrutinib

Trial No.	Matrix	Bioanalytical Report	Bioanalytical method performance
PCYC-1146-IM	Plasma	690-R9766R1 (b) (4)	Method BTM-2201[a] (BTM-2201-R1) Lower limit of quantification (LLOQ): 0.5 ng/mL Calibrated Range: 0.5 to 250 ng/mL Intra-assay Precision (%CV): 5.7% to 9.7% Intra-assay Accuracy (% Diff): -5.1% to -2.4% Bench Top Stability: 6 hours at RT Long-term Stability: 756 days at -20 °C and 1059 days at -70 °C Free thaw stability: 3 freeze (-70 °C)/thaw (ice water bath or room temperature) cycles
PCYC-1140-IM		690R11132 (b) (4)	Method BTM-2201 (BTM-2201-R1) Lower limit of quantification (LLOQ): 0.5 ng/mL Calibrated Range: 0.5 to 250 ng/mL Intra-assay Precision (%CV): 5.1% to 11.0% Intra-assay Accuracy (% Diff): -7.7% to -0.3% Bench Top Stability: 6 hours at RT Long-term Stability: 1059 days at - 70 °C Free thaw stability: 3 freeze (-70 °C)/thaw (ice water bath or room temperature) cycles
PCI-32765CLL1006		JNJ-R3221 (b) (4)	Method BTM-1792-R0[b] • Ibrutinib Lower limit of quantification: 0.5 ng/mL Calibrated Range: 0.5 to 100 ng/mL Intra-assay Precision (%CV): 1.1% to 10.8% Inter-assay Precision (%CV): 3.5% to 7.6% Intra-assay Accuracy (% Diff): -13.6% to -2.7% Inter-assay Accuracy (%Diff): -8.0% to -3.3% Bench Top Stability: 6 hours at RT Long-term Stability: 700 days at -20 °C and 628 days at - 70 °C Free thaw stability: 3 freeze (-70 °C)/thaw (ice water bath or room temperature) cycles • PCI-45227 Lower limit of quantification: 0.5 ng/mL Calibrated Range: 0.5 to 100 ng/mL Intra-assay Precision (%CV): 0.8% to 8.2% Inter-assay Precision (%CV): 4.4% to 6.1% Intra-assay Accuracy (% Diff): -4.8% to 5.1% Inter-assay Accuracy (%Diff): -2.4% to 0.9% Bench Top Stability: 6 hours at RT

			Long-term Stability: 703 days at -20 °C and 628 days at - 70 °C Free thaw stability: 3 freeze (-70 °C)/thaw (ice water bath or room temperature) cycles

[a] Refers to both BRM-2201-R0 and BTM-2201-R1: Method BTM-2201-R0 was used for sample analysis performed for studied conducted under NDA 210563. It was later revised to Method BTM-2201-R1 and includes the preparation of the new QC concentration level (125/125 ng/mL).
[b] Previously reviewed under NDA 205552-Supplement 17. The report was updated with longer stability data.

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:
For the TEAE analysis of the application, the FDA used the OOD grouped terms together with the Applicant's group terms for MEDDRA 24.0 as follows:

Abdominal Pain	Abdominal pain, Abdominal pain upper
Acute Kidney Injury	Renal failure, Renal impairment
Hemorrhage	Gingival Bleeding, Hematuria, Lip haemorrhage, Mouth haemorrhage, Retinal haemorrhage, Spontaneous haemorrhage, Stoma site haemorrhage
Headache	Headache, Migraine
Hypogammaglobulinemia	Blood immunoglobulin G decreased, Hypogammaglobulinaemia
Musculoskeletal Pain	Arthralgia, Back pain, Bone pain, Musculoskeletal chest pain, Myalgia, Neck pain, Non-cardiac chest pain, Pain in extremity
Neutropenia	Neutrophil count decrease, Neutropenia
Pneumonia	Atypical pneumonia, Pneumocystis jirovecii pneumonia, Pneumonia, Lower respiratory tract infection, Pneumonia mycoplasmal, Pneumonia pseudomonal, Pneumonia serratia
Rash	Dermatitis atopic, Dermatitis acneiform, Eczema, Erythema, Rash erythematous, Rash macular, Rash maculo-papular, Urticaria
Sepsis	Bacteremia, Septic shock, Sphingomonas paucimobilis bacteraemia, Staphyloccocus sepsis, Streptoccocal bacteremia
Skin Infection	Cellulitis, Staphylococcal skin infection
Stomatitis	Aphthous ulcer, Mouth ulceration, Lip erosion, Oral mucosal erythema, Stomatitis
Thrombocytopenia	Platelet count decreased, Thrombocytopenia
Transaminase elevation	Alanine aminotransferase increased, Aspartate aminotransferase increased
Vomiting	Haematemesis, Vomiting

NDA 205552 S-36, S-37, NDA 210563 S-12, S-13, NDA 217003		

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Shwu-Luan Lee	OOD/DHOT	Sections: 4 and 5	Select one: ☑ Authored ☐ Approved
	Signature: Shwu-luan Lee -S		Digitally signed by Shwu-luan Lee -S Date: 2022.08.19 06:36:49 -04'00'	
Supervisory Pharmacologist	Brenda Gehrke	OOD/DHOT	Sections: 4 and 5	Select one: ☐ Authored ☑ Approved
	Signature: Brenda Gehrke -S		Digitally signed by Brenda Gehrke -S Date: 2022.08.19 09:26:27 -04'00'	
Clinical Pharmacology Reviewer	Ankit Shah	OCP/DCPI	Sections: 6, 19.4	Select one: ☑ Authored ☐ Approved
	Signature: Ankit B. Shah -S (Affiliate)		Digitally signed by Ankit B. Shah -S (Affiliate) Date: 2022.08.19 09:57:47 -04'00'	
Clinical Pharmacology Team Leader	Nan Zheng	OCP/DCPI	Sections: 6, 19.4	Select one: ☑ Authored ☐ Approved
	Signature: Nan Zheng -S		Digitally signed by Nan Zheng -S Date: 2022.08.19 10:22:31 -04'00'	
Clinical Pharmacology Division Director	Brian Booth	OCP/DCPI	Sections:	Select one: ☐ Authored ☐ Approved
	Signature: Brian P. Booth -S		Digitally signed by Brian P. Booth -S Date: 2022.08.22 09:31:39 -04'00'	
Pharmacometrics Reviewer	Yuzhuo Pan	OCP/DPM	Sections: 6, 19.4	Select one: ☑ Authored ☐ Approved
	Signature: Yuzhuo Pan -S		Digitally signed by Yuzhuo Pan -S Date: 2022.08.19 10:44:52 -04'00'	
Pharmacometrics Team Leader	Jiang Liu	OCP/DPM	Sections:	Select one: ☐ Authored ☐ Approved
	Signature: Jiang Liu -S		Digitally signed by Jiang Liu -S Date: 2022.08.19 13:32:42 -04'00'	
Clinical Reviewer	Robert Le	OOD/DHMI	Sections: 1, 2, 3, 4.3, 7, 8.1, 8.3, 8.4, 9, 11, 19.	Select one: ☑ Authored ☐ Approved
	Signature: Robert Q. Le -S		Digitally signed by Robert Q. Le -S Date: 2022.08.19 14:02:52 -04'00'	

Clinical Reviewer	Kamar Godder	OOD/DHMI	Sections:	**Select one:** ☐ Authored ☐ Approved
	Signature: Kamar Godder -S Digitally signed by Kamar Godder -S Date: 2022.08.19 14:34:50 -04'00'			
Clinical Team Leader	Lori Ehrlich	OOD/DHMI	Sections: All	**Select one:** ☑ Authored ☑ Approved
	Signature: Lori Ehrlich -S Digitally signed by Lori Ehrlich -S Date: 2022.08.22 15:47:48 -04'00'			
Associate Director for Labeling	Elizabeth Everhart	OOD	Sections:	**Select one:** ☑ Authored ☐ Approved
	Signature: Elizabeth E. Everhart -S Digitally signed by Elizabeth E. Everhart -S Date: 2022.08.19 13:38:23 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Lori Ehrlich	OOD/DHMI	Sections:	**Select one:** ☐ Authored ☐ Approved
	Signature: *{See appended electronic signature page}*			
Division Director (Clinical)	R. Angelo de Claro	OOD/DHMI	Sections:	**Select one:** ☐ Authored ☐ Approved
	Signature: *{See appended electronic signature page}*			

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PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	217003
Supporting document/s:	1 (eCTD sequence number 0001)
Applicant's letter date:	February 22, 2022
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Product:	Imbruvica (ibrutinib oral suspension)
Indication:	Pediatric patients with chronic Graft versus Host Disease (cGVHD)
Applicant:	Pharmacyclics LLC, an AbbVie Company
Review Division:	Division of Hematology Oncology Toxicology (DHOT) for Division of Hematologic Malignancies 1 (DHM1)
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1 Executive Summary

1.1 Introduction

The Applicant has submitted NDA 217003 for ibrutinib oral suspension (70 mg/mL) for the treatment of pediatric chronic Graft versus Host Disease (cGVHD) and is cross referencing the nonclinical study reports submitted for Imbruvica (ibrutinib) NDA 205552 (immediate release capsules). Pharmacology/Toxicology data used to support this current 505(b)(1) Type 3 NDA were previously reviewed under NDA 205552. To support the safety of the new ibrutinib oral suspension, the current application contains drug quality information submitted under Module 3 (mainly drug product) including safety information for the excipients and extractable and leachable compounds from the container closure system.

There are two commercially available Imbruvica (ibrutinib) oral formulations: immediate-release capsules (70 mg and 140 mg; NDA 205552) and immediate-release film-coated tablets (140 mg, 280 mg, 420 mg and 560 mg; NDA 210563). Both formulations are used for the indication for adult patients with cGVHD at the recommended dose of 420 mg once daily. Under the current NDA, the multidose suspension (70 mg/mL) was administered in the clinical pediatric cGVHD study (PCYC-1146-IM) and the same formulation is proposed for commercial use. The proposed commercial drug product is comprised of a multi-dose ibrutinib oral suspension, 70 mg/mL, in a 150 mL amber glass bottle co-packaged with two 3-mL oral dosing syringes in a carton. The proposed recommended pediatric equivalent dose (RPED) of 240 mg/m^2 is based on body surface area (BSA), with the maximum recommended ibrutinib dose of 420 mg per day (i.e., 6 mL of the oral suspension drug product).

1.2 Brief Discussion of Nonclinical Findings

Ibrutinib is a small-molecule inhibitor of Bruton Tyrosine Kinase (BTK). Ibrutinib forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. Nonclinical studies show that ibrutinib inhibits malignant B-cell proliferation and survival in vivo as well as cell migration and substrate adhesion in vitro.

There are no pharmacology/toxicology data submitted in this NDA. The safety assessment regarding the pediatric oral suspension drug product has been evaluated from the pharmacology/toxicology perspective. The proposed specifications of related substances (i.e., impurities), elemental impurities ((b) (4)), inactive ingredients (excipients), and (b) (4) have been reviewed. The drug substance (DS) and drug product (DP)-related safety assessments indicate that the levels of these components are in line with the ICH Q3 guideline. Special safety/risk assessments for the use of sucralose and benzyl alcohol in the indicated pediatric population (1-12 years old) conclude that the daily intake of these excipients is within the acceptable daily

intake (ADI) of 15 mg/kg/day and 4 mg/kg/day body weight, respectively, set by the European Panel on Food Additives and Flavorings (FAF). In addition, the safety of benzyl alcohol was substantiated via the review of scientific literature.

The sources of extractables and leachables (E&Ls) are mainly from manufacturing equipment, primary packaging components, and oral dosing syringes. In general, E&Ls impose safety concerns and may affect (b) (4) (b) (4) The risk assessments of the E&Ls associated with the container closure system, including the cap/cap liner, oral administration syringes, and press in bottle adapter (PIBA), were evaluated. The identified extractables with levels above an analytical evaluation threshold (AET; e.g., 1.5 µg/day according to the ICH M7 guidance) were subjected to the calculations for permissible daily exposure (PDE) and maximum daily exposure (MDE) levels. The toxicological risk assessment for extractables was based on the comparison between the MDE value of the extracted compounds and the calculated PDE value. The risk is expressed as the margin of safety, i.e., the fold of MDE value (µg/day)/PDE value (µg/day). The toxicological risk assessment revealed that the extracted organic compounds and elemental impurities found in the container closure system pose negligible risk to the patients as potential leachables. The interaction between container closure system components and the liquid drug product during administration could result in leaching of substances from the components, including the cap liner, PIBA and oral dosing syringes, into the dosage form. A similar toxicological risk assessment was conducted for the leachable compounds. Because no compounds above the AET were found (the MDE calculation indicated no detectable potential leachables), no PDE assessment was conducted. Based on the review of the risk assessment of the E&Ls, there are no Pharmacology/Toxicology concerns regarding E&Ls in the container closure system for the ibrutinib oral suspension drug product.

1.3 Recommendations

1.3.1 Approvability

There are no Pharmacology/Toxicology issues with NDA 217003; approval of the NDA is recommended.

1.3.2 Additional Non Clinical Recommendations

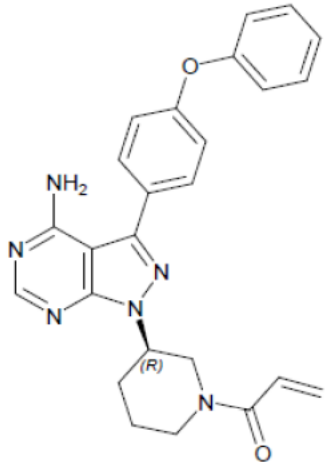
None

1.3.3 Labeling

The information for this ibrutinib oral suspension drug product is being added to the current Imbruvica (ibrutinib) label. With respect to the Pharmacology/Toxicology sections, appropriate modifications to support the current formulation and/or indication were made.

2 Drug Information

2.1 Drug

CAS Registry Number	936563-96-1
Generic Name	Ibrutinib
Code Name	PCI-32765; JNJ-54179060-AAA (free base); CRA-032765
Chemical Name	1-{(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl]piperidin-1-yl}prop-2-en-1-one
Molecular Formula/Molecular Weight	$C_{25}H_{24}N_6O_2$/440.5 g/mol
Structure or Biochemical Description	**Figure 1: Structure of Ibrutinib** 
Pharmacologic Class	Kinase inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMF

DMFs

- Submission contains Letters of Authorization for 3 Drug Master Files (DMFs): (b) (4) [redacted] (b) (4)

NDA 205552

- Cross referencing nonclinical study reports in Module 4 of NDA 205552
- Cross referencing drug substance information and location of device (oral dosing syringe) information (Module 2.3 of Imbruvica capsule NDA 205552)

The ibrutinib oral suspension, 70 mg/mL, utilizes the same commercial ibrutinib drug substance that is used in the manufacture of the approved Imbruvica capsules (70 mg

and 140 mg) and Imbruvica tablets (140 mg, 280 mg, 420 mg, and 560 mg). Therefore, this current application does not include the Module 3 sections for the drug substance.

2.3 Drug Formulation

The Applicant developed a liquid formulation (oral suspension) to allow once-daily oral dosing for pediatric patients ≥ 1 year to < 12 years of age, where dosing is based on body surface area (BSA). The pediatric formulation has been developed with the following key requirements: dose flexibility, acceptability for a pediatric population, palatability, stability, and bioavailability (BA).

Table 1: Composition of Ibrutinib Pediatric Oral Suspension 70 mg/mL

Component	Quality Standard	Function	Amount (mg/mL)
Ibrutinib	In-house	Drug Substance	70.00
Microcrystalline Cellulose and Carboxymethylcellulose Sodium	NF		(b) (4)
Hypromellose (b) (4)	USP		
Disodium Hydrogen Phosphate (b) (4)	USP		
Citric Acid Monohydrate	USP		
Sucralose	NF		
Benzyl Alcohol	NF		
Purified Water	USP		

(Table from the Applicant, Section 3.2.P.1)

For the pediatric population, an oral dosing syringe is designed for convenient and accurate administration of the drug product.

Table 2: Description of Oral Dosing Syringe

Description	Part	Material
Three mL oral dosing syringe with 0.1 mL graduation marks and numerical marking every 0.5 mL	Barrel	(b) (4) (clear)
	Plunger	(b) (4) (purple)

(Table from the Applicant, Section 3.2.P.1)

2.4 Comments on Excipients

Inactive ingredients (excipients) in the drug product

The Applicant summarized the levels of the excipients of the two oral suspension formulations (single-dose and multi-dose) used in the pediatric clinical studies and the

proposed commercial formulation. The table below contains the summary of the clinical formulation of the ibrutinib oral suspension.

Table 3: Clinical Formulation of Ibrutinib Oral Suspension (70 mg/mL)

Component	Function	Clinical Formulation (Single-Dose) [a] (mg/mL)	Clinical, Primary Stability, and Proposed Commercial Formulation (Multi-Dose) [b] (mg/mL)
Ibrutinib	Drug Substance	70.00	70.00
(b) (4)			(b) (4)
			(b) (4)

(Table from the Applicant)

Modifications: Single-dose versus multi-dose formulations

(b) (4)

(b) (4)

Justification of the proposed levels

Table 4: Inactive Ingredient Database (IID, FDA) versus Applicant's Approach

Excipient	Route	Maximum potency per unit dose (FDA IID)	MDE (FDA IID)	Applicant's Approach
Carboxymethylcellulose sodium	Oral solution Oral suspension		1080 mg 1000 mg	
Microcrystalline cellulose	Oral suspension		1200 mg	
Hypromellose	Oral solution		1382 mg	(b) (4)
Citric acid monohydrate*	Solution Suspension	0.2% w/v (=2 mg/mL, 12 mg for 6 mL)	165 mg 180 mg	
Disodium hydrogen phosphate (b) (4)		Not available in IID		
Sucralose	Oral suspension		264 mg	
Benzyl alcohol	Oral solution	50 mg/mL	100 mg	

	Oral suspension			(b) (4)

MDE=maximum daily exposure
ADI= acceptable daily intake; FAF= the European Panel on Food Additives and Flavorings; SCF= the European Scientific Committee on Food; JECFA= The Joint FAO/WHO Expert Committee on Food Additives
*In the commercial formulation, Citric acid monohydrate: at (b) (4) %w/v ((b) (4) mg/mL, (b) (4) mg for (b) (4) mL) would provide confirmed (b) (4)
*Disodium hydrogen phosphate: at (b) (4) %w/v ((b) (4) mg/mL, (b) (4) mg for (b) (4) mL) would provide confirmed (b) (4)
**The excipients with specified ADI values from the European Panel on Food Additives and Flavorings (FAF) include the (b) (4) (benzyl alcohol) and the (b) (4) (sucralose). The ADI values for benzyl alcohol and sucralose are 4 mg/kg body weight and 15 mg/kg body weight, respectively.

Microcrystalline cellulose and carboxymethylcellulose sodium
The proposed specification of (b) (4) mg/mL with a daily exposure of (b) (4) mg at the recommended dose 420 mg/day (6 mL of the oral suspension) is acceptable. The daily intake of the suspension agents is below the MDE (1000-1200 mg, FDA IID).

Hypromellose (also known as (b) (4)
According to the Applicant, (b) (4)
(b) (4)

- Assessment of the acceptance of the maximum daily exposure to (b) (4) based on FDA IID

(b) (4)

Table 5: FDA Inactive ingredient database (IID) of Hypromellose (Oral route)

Hypromellose (Grade)	Format	Viscosity (mPa.s)	Maximum potency per unit dose	Maximum Daily Exposure (MDE)
				(b) (4)

MDE: maximum daily exposure /maximum potency; mPa.s: millipascal second

- Safety/risk assessment

Partly due to viscosities, absorption through the gastrointestinal tract will be very low (b) (4)
(b) (4)
(b) (4) Hypromellose is a GRAS substance and widely used as an excipient in pharmaceuticals. The permissible daily exposure (PDE) levels derived from toxicology studies in animals range from 650 mg/day to 2500 mg/day (data not shown)

Conclusion:
The daily intake of Hypromellose of (b) (4) mg ((b) (4) % w/v, or (b) (4) mg/mL for 6 mL) based on the proposed specification of (b) (4) mg/mL is lower than the MDE values in the FDA IID. The safety of this excipient is also supported by clinical experience (safe up to 15 g/day to lower total cholesterol) and comprehensive nonclinical data (see above).

Sucralose
Based on the consideration of (b) (4) formulation, a (b) (4) amount of sucralose ((b) (4) mg/mL) was added to (b) (4) (b) (4) concern.

Maximum Sucralose Dosed to Indicated Pediatric Patients

Age (year)	Average weight (kg)	Ibrutinib dose (mg/day)	Daily suspension dose volume (mL)	Daily intake (mg/day)	Daily intake (mg/kg/day)
1	10	~240*	(b) (4)		
12	41	420			

*Ibrutinib dose= 240 mg/m^2/day (m^2= body surface area, BSA) for 1 year old, m^2: approximately 1.14

The daily intake of sucralose ((b) (4) mg/kg) is lower than the MDE limit (FDA IID) as well as the acceptable ADI value of 15 mg/kg body weight (per the European Panel on Food Additives and Flavorings (FAF)).

Benzyl alcohol
The lowest concentration of benzyl alcohol required to guarantee an (b) (4) (b) (4) is (b) (4) mg/mL; (b) (4) (b) (4) mg/mL benzyl alcohol was selected as the target concentration.

Maximum Benzyl Alcohol Dosed to Indicated Pediatric Patients

Age (year)	Average weight (kg)	Ibrutinib dose (mg/day)	Daily suspension dose volume (mL)	Daily intake (mg/day)	Daily intake (mg/kg/day)
1	10	~240*	(b) (4)		
12	41	420			

*Ibrutinib dose= 240 mg/m^2/day (m^2= body surface area, BSA) for 1 year old, m : approximately 1.14

- Assessment of the acceptance of the maximum daily exposure to benzyl alcohol: based on FDA IID:
  - Maximum potency per unit dose: 50 mg/mL (oral solution), approximately (b) (4) mg/day at the recommended dose of 420 mg/day.
  - MDE: 100 mg (oral suspension)

- Safety/risk assessments

Benzyl alcohol is an aromatic alcohol. In the body, benzyl alcohol is metabolized into benzoic acid. Benzyl alcohol, benzoic acid and its salts (i.e., sodium, calcium, magnesium, and potassium benzoate), and benzyl benzoate are reported to function as fragrance ingredients, pesticides, pH adjusters, preservatives, solvents, and/or viscosity decreasing agents in cosmetic products. For medicinal usages, benzyl alcohol is mainly used as an excipient in medicinal products that are administered intramuscularly (e.g.,

antibiotics, anti-inflammatory or antipsychotic medicines), or intravenously (such as anti-cancer drugs, heparins, or cardiovascular drugs).[1]

The main concerns associated with the use of benzyl alcohol is the risk of accumulation in newborn babies (pre-and full-term) due to metabolic immaturity. Intravenous benzyl alcohol 100-200 mg/kg/day has been linked to the "gasping syndrome" in several pre-term newborns with metabolic acidosis that resulted in deterioration of the neurological status, cardio-vascular failure and hematological anomalies.[2] However, the minimum amount of benzyl alcohol at which toxicity may occur is not known.

In a toxicology study in juvenile rats, benzyl alcohol was administered by oral gavage daily to groups of 10 male and 10 female rat pups from post natal day 22 for a period of 6 weeks.[3] The No Observed Adverse Effect Level (NOAEL) was determined to be 300 mg/kg/day (the human equivalent dose [HED] in adults is approximately 48.6 mg/kg/day). There are no juvenile animal toxicity studies related to long-term use. Additional toxicology data of benzyl alcohol in animals includes the following:[4]

- Oral acute toxicity in rats: LD_{50}= 1,610 mg/kg
- Oral repeat dose toxicity:
  Long-term studies: NOAEL >400 mg/kg/day (rats) and >200 mg/kg/day (mice)
- Reproductive and developmental toxicity: Not remarkable
- Genotoxicity: Benzyl alcohol and benzonates are not mutagenic or clastogenic (based on weight of evidence)
- Carcinogenicity: Equivocal outcomes in a study in B6C3F1 mice (n=50/sex, 100 or 200 mg/kg benzyl alcohol in corn oil, 5 days per week for 103 weeks): In the high-dose male mice, 3 out of 48 animals showed incidences of adenomas of the adrenal cortex
- Ocular toxicity: (b) (4)

Based on animal toxicity data, the SCF (Scientific Committee on Food) of the European Commission has determined the Acceptable Daily Intake (ADI) of benzyl alcohol, benzoic acid and benzonates to be 0-5 mg/kg. Young children (< 3 years old) may not be sufficiently mature to metabolize and eliminate benzyl alcohol as efficiently as adults. In 2019, the ADI was re-evaluated to be 4 mg/kg.

Conclusion:
The concentration of benzyl alcohol in the ibrutinib oral suspension is within the MDE limit of 100 mg and within the acceptable daily intake (ADI) of 4 mg/kg/day body weight

[1] The revision of the Annex of the European Commission guideline "Questions and answers on benzyl alcohol used as an excipient in medicinal products for human use" (EMA/CHMP/302620/2017; October 9, 2017)
[2] Gershanik et al., N Engl J Med, 307(22): 1384-1388, 1982.
[3] Foulon et al., The Toxicology 84: S1, Abstracts of the 44th annual Meeting & Toxexpo, New Orleans, Abstract 265, March 2005.
[4] (b) (4)

(per the European Panel on Food Additives and Flavorings (FAF) following the evaluation (evaluated by the European Scientific Committee on Food (SCF)).

2.5 Comments on Impurities/Degradants of Concern

Drug substance

The following is excerpted from the Applicant (Module 2, Section 2.3 Introduction):
"The drug substance (ibrutinib) used in the manufacturing of Ibrutinib Oral Suspension is identical to that used for the approved ibrutinib capsules and tablets. Hence, the CMC information for the drug substance is not presented in this NDA and instead, a cross-reference to the drug substance information in NDA 205552 is provided. For ease of review of the NDA for Ibrutinib Oral Suspension, a copy of the approved drug substance CTD sections 3.2.S.1 (General Information), 3.2.S.2.1 (Manufacturers), 3.2.S.4.1 (Specification) and 3.2.S.7.1 (Stability Summary and Conclusion) is provided in this submission. These sections will continue to be maintained through the capsule NDA (NDA 205552)."

Table 6: Specification of Drug Substance

Parameters	Test Method	Acceptance Criteria
Appearance	Visual examination	White to off-white solid
Identification [a]		
IR	DS-TMD-23064	Consistent with reference spectrum
LC Retention Time	DS-TMD-23058	Consistent with reference standard
Assay [b] by HPLC	DS-TMD-23058	(b) (4) % (w/w)
Chromatographic Purity Specified Impurities (b) (4) Any Unspecified Impurity Total impurities	DS-TMD-23133	Not more than (b) (4) % (w/w) Not more than (b) (4) % (w/w) Not more than % (w/w) Not more than % (w/w) Not more than % (w/w) Not more than (b) (4) % (w/w)
(b) (4)	DS-TMD-23153	Not more than (b) (4) % (w/w)
Related Impurity [a] (b) (4)	DS-TMD-23157	Not more than (b) (4) ppm
(b) (4)	DS-TMD-18226	Not more than (b) (4) ppm Not more than (b) (4) ppm Not more than ppm Not more than (b) (4) ppm Not more than ppm Not more than ppm Not more than (b) (4) ppm
Water Content	DS-TMD-23156	Not more than (b) (4) % (w/w)
Residue on Ignition/Sulphated Ash [a]	USP<281> or Ph. Eur. 2.4.14	Not more than (b) (4) % (w/w)
Particle Size D[v,0.9]	DS-TMD-22679 or 501.534	Not more than (b) (4) µm
(b) (4) Form by DSC	DS-TMD-23159	(b) (4)
(b) (4)		

(Table from the Applicant)

Drug product

The pediatric formulation should provide acceptable bioavailability. The single-dose suspension formulation was evaluated in a Phase 1 relative BA study (Study CLL1015) for PK, palatability, and relative BA as compared to the approved 140 mg capsule formulation. The recommended dose for the proposed pediatric cGVHD indication is 240 mg/m^2/day, based on the highest dose of 420 mg/day, i.e., approximately the dose for a pediatric patient with a body weight of 40 kg.

Impurities
Based on the Applicant's Amendment SD-001 (Section 3.2.P.5.1), the updated specifications for the impurities in the drug product (DP) are as follows:

Table 7: Specifications and Justifications (Drug Product Excipient and Impurities)

Test	Analytical Procedure (or equivalent)	Acceptance Criteria
Assay (UHPLC) Benzyl Alcohol		(b) (4) % LA (release) (b) (4) % LA (shelf-life)
Degradation Products (Ibrutinib) (UHPLC)		
(b) (4)		NMT (b) (4) % NMT % NMT %
Unspecified		NMT (b) (4) %
Total		NMT (b) (4) %

LA= Labeled amount; NMT=No more than
(Excerption of Table from the Applicant, Section 3.2.P.5.1)

The summary of the batch analysis for clinical and primary stability batches (Module 2, Section 2.3.P.5.4, Table 22) indicates the content of benzyl alcohol and degradation impurities are within the range of specification/acceptance criteria.

Degradant impurities:
Stability data for the ibrutinib oral suspension, 70 mg/mL, show that this drug product's degradation product profile is equivalent to that of ibrutinib drug substance. Therefore, there are no known degradation products unique to the drug product; however, the specifications/acceptance criteria for individual impurities are not the same as those for the drug substance. The table below is the summary of the evaluation of the proposed specifications/acceptance criteria for the drug substance and/or drug product impurities. The proposed specifications are acceptable.

Table 8: Summary of Drug Substance/Drug Product Impurities

Impurity (DS)/degradant (DP)	Acceptance criteria	Qualification
(b) (4)	(b) (4)	(b) (4)

The specification of up to NMT (b) (4) % for unspecified impurities is in line with the ICH Q3B guideline. The total degradation product specification is NMT (b) (4) %, and all the batches analyzed to date comply with the proposed specifications at release and during stability testing.

Elemental impurities

The Applicant considered all potential sources of elemental impurities in the components, the drug delivery system, container closure, and associated processes used in the production of the ibrutinib oral suspension. The risk assessment was based on the oral permitted daily exposure (PDE) for individual elemental impurities as described in the ICH Q3D guidance.

Components that were identified that could potentially introduce elemental impurities into the drug product are: (b) (4) Traces of the following elemental impurities were detected in these components: (b) (4) The assessment demonstrated that elemental impurity contributions from these components do not exceed the ICH Q3D control threshold level (i.e., less than 30% of the PDE) for the dosage regimen (420 mg/day, or 6 mL suspension) for ibrutinib oral suspension.

(b) (4) impurities

The assessment of the content of (b) (4) impurities indicated that the ibrutinib drug substance and the manufacturing process of the drug product are not at risk for the formation or introduction of (b) (4) impurities.

(b) (4)

Container Closure System

The drug product is comprised of multi-dose ibrutinib oral suspension, 70 mg/mL, in a 150 mL amber glass bottle co-packaged with two non-sterile reusable 3 mL oral dosing syringes in a carton. The sources of extractables and leachables (E&Ls) are mainly from manufacturing equipment, primary packaging components, and oral dosing syringes. The information for the extraction solvents and analytical methodologies to obtain the qualitative and quantitative profiles of the E&Ls are included in Section 3.2.P.2.4 of the submission (details not included in this review). In general, E&Ls impose safety concerns and may affect stability of the DP when these compounds mix and/or interact with the DP content.

The risk assessments for the E&Ls associated with the container closure system, including the cap/cap liner, oral administration syringes, and press in bottle adapter (PIBA), were evaluated and summarized in the following sections.

Pharmacology/Toxicology sent an information request (IR; April 28, 2022) to obtain detailed calculations of the MDE and PDE values, including the definition of the parameters and the source of pertinent toxicology data used to support the PDE derivation. The Applicant's response (May 9, 2022) provided adequate information for the review. Based on the information, the content of the summary tables of the MDE and PDE values and the margins of safety has been verified and concurred.

Assessments for Extractable compounds

For the controlled extraction study, an analytical evaluation threshold (AET) was calculated based on the safety concern threshold (SCT) of 1.5 microgram (µg) per day according to ICH M7, and for inorganic extractables, based on (b) (4) µg/day according to ICH Q3D [30% control threshold for the lowest permissible daily exposure (PDE)].

Table 9: Summary of AET of the Component of Container Closure System

Component	AET (µg/component)
PIBA	(b) (4)
Cap	
Oral dosing syringe	

The analytical sensitivity (i.e., quantification limits) of the methods employed for the extractable analysis was demonstrated to fulfill the AET criteria (data not shown).

Based on the identification and semi-quantification of all organic [volatiles (VOC), semi-volatiles (SVOC), and non-volatiles (NVOC)] and inorganic (elements) extractables above the AET, the MDE levels could be calculated.

$$\text{MDE}\left[\frac{\mu g}{\text{day}}\right] = \text{Extractable Amount}\ \left[\frac{\mu g}{\text{component}}\right] \times \text{Number of Articles}\ \left[\frac{\text{component}}{\text{day}}\right] \times \text{Surface Factor}$$

Number of Articles: Up to two oral dosing syringes can be used per day.
Surface Factor: Ratio of wetted/total surface area, based on CT scans and CAD drawings.

Where,

- Number of Articles

For Cap liner and PIBA Number of Articles (component/day) = number of components/container (1) x maximum daily dose (mL/day) / target container fill volume (mL/container), where maximum daily dose (mL/day) = 6 mL/day; target container fill volume (mL/container) = 120 mL
For Syringes Number of Articles (component/day) = 2

- Surface Factor

A simulation and controlled extraction study were performed on the primary packaging components (cap liner and PIBA) and the delivery device (oral dosing syringe). The components analyzed in the controlled extraction study were evaluated as whole pieces (cut to fit lab glassware), extracting from the full surface area. The surface area calculations were analyzed by Computerized Tomography (CT) Scan and evaluation of Computer Aided Design (CAD) drawings. The results from the controlled extraction study were multiplied by the ratio of wetted surface area to total surface area. The cap liner was not evaluated by CT scan but was assumed to be a maximum of 50% of the surface area in contact with drug product since only the inside, top and a portion of the inner top are available for wetting with the rest against the bottle neck. A factor of 0.5 is used in the calculations as Surface Factor for cap liner.

In general, the number of articles and the surface factor were (b) (4) and (b) (4) respectively, for the calculation of the MDE values for the compounds in the cap liner, PIBA and oral dosing syringe (summarized Appendix B, Applicant's response). The calculation of theMDE value of one compound, (b) (4) is shown in the table below as an example.

Compound	Extractable Amount (µg/component)	Number of Articles (components/day)*	Surface Factor	MDE Value [µg/day]
(b) (4)				

(Table from the Applicant)

Toxicological risk assessment

For extractable compounds with an MDE value above the TTC-based acceptable intake of 1.5 µg/day, a comparison of the compound-specific MDE level to its calculated PDE value was conducted. (b) (4)

(b) (4)

(b) (4)

Table 10: Toxicological Risk Assessment for Primary Package Components (Cap Liner)

Source	Compound	MDE Value [µg/day]	PDE Value [µg/day]	Margin of Safety
[redacted]				(b) (4)

a. Compound or elemental impurity observed in both primary package components and oral dosing syringes or observed in leachable simulation study. The Margin of safety is calculated based on the sum of the compound or elemental impurity observed in both primary package components and oral dosing syringes, or simulation study.

(Table from the Applicant)

The toxicological risk assessment revealed that the extracted organic compounds and elemental impurities listed in the table above pose negligible risk to the patients as potential leachables.

Table 11: Toxicological Risk Assessment for 3 mL Oral Dosing Syringe

Extractable	MDE Value [µg/day]	PDE Value [µg/day]	Margin of Safety
(b) (4)			

a. Compound or elemental impurity observed in both primary package components and dosing pipettes, or observed in leachable simulation study. The Margin of safety is calculated based on the sum of the compound or elemental impurity observed in both primary package components and dosing pipettes, or simulation study.
b. Treated as one category compounds and the sum was used for Margin of safety.
c. Treated as one category compounds and the sum was used for Margin of safety.
(Table from the Applicant)

Based upon the outcome of the toxicology risk assessment, the identified extractable compounds are expected to pose negligible risk to the patient as potential leachables.

Assessments for Leachable compounds

The interaction between the container closure system components and the liquid drug product during administration could result in leaching of substances from the components, including the cap liner, PIBA and oral dosing syringes, into the dosage form. To assess the potential safety risks to patients and potential compatibility risks for the drug product, a leachable simulation was conducted to analyze the interaction between the drug product and the container closure system components, especially the components that are in direct contact with the liquid drug product, including the cap liner, PIBA and oral dosing syringe.

Leachable simulation study

Samples of the cap liner, PIBA and dosing syringe were subjected to the leachable simulation study, where the samples were analyzed for VOC, SVOC and metals. Leachable compounds detected at MDE levels above the TTC of 1.5 µg/day were assessed regarding their toxicological risk to a patient by comparison of the compound-specific MDE level to its calculated PDE value. (b) (4) (b) (4) No leachable compounds above the TTC of 1.5 µg/day were found in the PIBA.

Table 12: Calculation of MDE Values of elemental Impurities (Leachable Simulation Study)

Leachable	Source	Leachable Amount (µg/mL)	Maximum Daily Dose (mL)	MDE Value (µg/day)*
(b) (4)				

* MDE (µg/day) = Leachable Amount (µg/mL) x Maximum Daily Dose (mL)

(Table from Appendix B, Applicant's response to IR)

Table 13: Leachable Simulation Results

Leachable	Source	MDE Value [µg/day]	PDE Value [µg/day]	Margin of Safety
(b) (4)				

a. Elemental impurity observed in both primary package components and dosing pipettes or observed in leachable simulation study. The Margin of safety is calculated based on the sum of elemental impurity observed in both primary package components and dosing pipettes, or simulation study.

The PDE calculations for the elemental impurities (Appendix A, Applicant's response) are reviewed and concurred.

(Table from the Applicant)

Based upon the outcome of the toxicology risk assessment, the simulation study results identified the extractable compounds, mainly the elemental impurities, would be expected to pose negligible risk to the patient as potential leachables.

Leachable assessment of the drug product manufacturing process and primary package
As with the extractable compound assessment, all drug product contact surfaces during manufacturing are considered low risk for leachables into the drug product, and thus, no leachable studies were conducted.

The analytical methods are mainly based on the nature of the drug product matrix, the identities and concentration levels of potential leachables and the required sensitivity based on the calculated AET. See descriptions of SCT, AET and pertinent regulatory guidances for the assessment of extractable compounds above. The dosing volume at the recommended dose of 420 mg/day is 6 mL.

$$\mathrm{AET_{SCT}} = \frac{\mathrm{SCT\ [\mu g]}}{\mathrm{Volume\ [mL]}} = \frac{1.5\ \mu g/day}{6.0\ mL/day} = 0.25\ \frac{\mu g}{mL}$$

SCT = Safety concern threshold; AET = Analytical evaluation threshold

All analytical techniques reveal a sufficient method sensitivity for the leachable analysis, as the limit of quantification (LOQ) is equal to the AET of 0.25 µg/mL.

The MDE calculation for the drug product is based on the highest leachable concentration (µg/mL) that was detected with the different analytical methods and a maximum daily administered volume of 6 mL.

$$\mathrm{MDE}\ \left[\frac{\mu g}{day}\right] = \mathrm{Leachable\ Concentration}\ \left[\frac{\mu g}{mL}\right] \times \mathrm{Daily\ Administered\ Volume}\ \left[\frac{mL}{day}\right]$$

Based on MDE values in three primary stability batches over a 6-month period, no detectable potential leachables (such as [redacted] (b) (4)) were detected in the drug product solution (data not shown). No other substances were detected above 1.5 µg/day.

The approach for a PDE-based toxicological risk assessment was used for the leachables, where the MDE level for each leachable compound or compound class was to be compared to their respective calculated PDE value based on a worst-case maximum daily dose. For leachable compounds with an MDE value above the TTC (1.5 µg/day), a comparison of the compound-specific MDE level to its calculated PDE value should be conducted. Because no compounds above the AET were found (the MDE calculation indicated no detectable potential leachables), no PDE assessment was conducted at this time.

Conclusion

Based on the proposed PDE and MDE values that are reviewed and concurred, all the extractable and leachable compounds identified pose negligible to minimal risk to the patient.

2.6 Proposed Clinical Population and Dosing Regimen

Proposed Indication: Treatment of adult and pediatric patients age 1 year and older with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy.

Route of Administration: oral

Dosing Regimen:
The recommended dosage of ibrutinib is 420 mg orally once daily for adult and adolescent patients age 12 years and older with cGVHD and 240 mg/m^2 orally once daily (equivalent to the approved adult flat dose of 420 mg once daily) for pediatric patients age ≥ 1 to < 12 years with cGVHD.

The proposed commercial formulation of ibrutinib for use in the pediatric population is a multidose oral suspension available in a strength of 70 mg/mL.

2.7 Regulatory Background

Ibrutinib has been well-studied and approved for multiple indications. The current NDA 217003 is a Type 3 NDA for the new pediatric oral suspension (70 mg/mL) to support the newly proposed pediatric cGVHD indication. The Applicant, Pharmacyclics LLC, is cross referencing their own clinical and nonclinical data, and drug substance information for Imbruvica (ibrutinib; NDA 205552).

3 Studies Submitted

3.1 Studies Reviewed

There is no Module 4 and therefore, no stand-alone nonclinical studies submitted to the current NDA.

3.2 Studies Not Reviewed

Not applicable

3.3 Previous Reviews Referenced

NDA 205552

Nonclinical supporting data
Pharmacology, pharmacokinetics/ADME/Toxicokinetics and toxicology studies of ibrutinib were reviewed under NDA 205552.

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/s/

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