24 February 2022
EMA/190958/2022
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Imbruvica

ibrutinib

Procedure no: EMEA/H/C/003791/P46/03

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Steps taken for the assessment

Description	Date
Start of procedure	27 Dec 2021
CHMP Rapporteur Assessment Report	31 Jan 2022
CHMP adoption of conclusions	24 Feb 2022

Table of contents

1. Introduction

On 9th December 2021, the MAH submitted a completed paediatric study for ibrutinib (Imbruvica), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study SPARKLE, 54179060LYM3003 is part of a clinical development program EMEA-001397-PIP03-14-M05 as PIP Study 3. This is the last study listed in the program.

A line listing of all the concerned studies is annexed.

2.2. Information on the pharmaceutical formulation used in the study

Ibrutinib was administrated as capsules or oral suspension.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- 54179060LYM3003 (LYM 3003), SPARKLE

2.3.2. Clinical study

54179060LYM3003, SPARKLE

Hereafter referred to as LYM3003.

Description

Study LYM3003 was a phase 3, 2-part, multicenter open-label study in paediatric and young adult patients with relapsed or refractory mature B-cell non-Hodgkin lymphoma.

A safety and PK run-in part (Part 1) was conducted before the randomized part (Part 2) of the study. All eligible subjects in Part 1 received ibrutinib in combination with CIT (investigator choice of RICE or RVICI). Enrolment began with children in the 2 older age groups (6-11, 12-17 years) to assess PK and safety data before allowing enrolment of children in the youngest age group (1-5 years).

In Part 2, subjects were randomized in a 2:1 ratio to receive ibrutinib in combination with CIT (investigator choice of RICE or RVICI) or CIT alone.

Methods

Study participants

The study population consisted of subjects with relapsed/refractory BL, BLL, Burkitt Leukaemia (B-AL), DLBCL, DLBCL not otherwise specified, primary mediastinal B-cell lymphoma (PMBCL) or other paediatric mature B-cell NHL. Subjects were required to have relapsed (and received only 1 prior line of therapy for Part 2 only) or have had disease that was primarily refractory to conventional therapy. Subjects in Part 1 were 1 to <18 years old. Subjects in Part 2 were 1 to 30 years old, inclusive, who had an initial diagnosis of mature B-cell NHL at <18 years of age.

Subjects were required to have at least 1 site of measurable disease defined as >1 cm in the longest diameter and >1 cm in the shortest diameter by radiological imaging, bone marrow (BM) involvement, or CSF with blastspresent. Subjects were to have a Lansky-Karnofsky score of≥50. Subjects were excluded, if they had an ongoing treatment with anticoagulants, had inherited or acquired bleeding disorders, prior exposure to ibrutinib; a diagnosis of post-transplant lymphoproliferative disease (PTLD); or an allogeneic bone marrow transplant within 6 months of start of treatment.

Treatments

Ibrutinib capsules (140 mg and 70 mg) and ibrutinib suspension (70 mg/mL single-dose and multi-dose) were used to meet the different dosing regimens and needs across the age groups in Study LYM3003.

Ibrutinib was dosed based on BSA:

Part 1: Ibrutinib up to a maximum dose of 329 mg/m^2 per day (equivalent to the maximum fixed dose of 560 mg per day in adults) was evaluated as add-on therapy to RICE or RVICI. The first 2 subjects enrolled in each age group (1-5 years, 6-11 years, and 12-17 years) were treated at a lower starting dose of 240 mg/m^2 (not to exceed 420 mg per day) for the first cycle (older children [6-17 years] were enrolled first before enrolling younger children [1-5 years]), followedby dose escalation to 329 mg/m^2 (not to exceed 560 mg per day) at the start of Cycle 2 as long as the exposure was within the target range and there were no safety concerns for the 2 subjects and for all subsequently enrolled subjects in that age group. If exposure in the 2 subjects was lower than or exceeded the target range, the dose for these subjects and for all other subjects in that age group was adjusted based on available exposure data.

Subjects were instructed to take ibrutinib orally once daily, starting at Cycle 1 Day 1. Subjects were recommended to take ibrutinib within 2 hours after a meal.

Part 2: Subjects were randomized in a 2:1 ratio to Treatment group A (daily dose of ibrutinib 329 mg/m^2 or 440 mg/m^2 [dose selected from Part 1]) by age groups, and RICE or RVICI

background therapy) or Treatment group B (RICE or RVICI background therapy only). Study treatment administration started on Cycle 1 Day 1 and ended on the last day of Cycle 3, unless the subject experienced unacceptable toxicity or disease progression. Cycles were 28 days long; however, if count recovery occurred quickly, cycles could be truncated to 21 days. As long as there was no disease progression after Cycle 1 or 2, a second and third cycle of therapy were given, respectively. Upon completion of 3 cycles of combination therapy, subjects randomized toibrutinib +CIT with a response of PR or better could continue on ibrutinib monotherapy at the same daily dose for (1) up to three 28-day cycles or until disease progression or unacceptable toxicity, or (2) up until initiating subsequent anti lymphoma therapy or a conditioning regimen forstem cell transplantation, whichever came first.

Subjects received ibrutinib in either a capsule (70 mg or 140 mg) or suspension formulation to be self-administered at home on each day of the cycle.

RICE or RVICI

Part 1 and Part 2: Subjects received ibrutinib in combination with background intravenous CIT (investigator choice of RICE or RVICI) for 3 treatment cycles. The RICE regimen was composed of rituximab 750 mg/m^2, ifosfamide 9 g/m^2, carboplatin 635 mg/m^2, etoposide 300 mg/m^2, and dexamethasone 100 mg/m^2. The RVICI regimen was composed of rituximab 750 mg/m^2, vincristine 1.6mg/m^2, idarubicin 20 mg/m^2, carboplatin 800 mg/m^2, ifosfamide 10 g/m^2,and dexamethasone 100 mg/m^2 (all doses represented as cumulative administered in 1 cycle). Forboth regimens, triple intrathecal therapy consisting of methotrexate, corticosteroid, and cytarabine was administered for central nervous system (CNS) prophylaxis in age-appropriate dosing. Subjects with CNS disease at study entry received additional doses of triple intrathecal therapy until CSF was clear of disease. Cycles were 28 days long but could be shortened to 21 days based on investigator's discretion.

Study treatment continued for 3 cycles, unless the subject experienced unacceptable toxicity or disease progression.

Objective/outcomes/endpoints

Run-in Part (Part 1)

Objectives	Endpoints
Primary	
• Confirm that the pharmacokinetics (PK) in pediatric subjects was consistent with that in adults	• Exposure (AUC) • CL/F, apparent (oral) volume of distribution (Vd/F), andderived measures of exposure such as C_{max} • Relationship between PK parameters and age or measure of body size
Secondary	
• Evaluate the safety and tolerability of ibrutinibin combination with RICE or RVICI background therapy in pediatric subjects with B-cell malignancies	• Safety parameters, including gastrointestinal effects, immune function, intensified cardiac monitoring (in particular, after previous anthracycline exposure)
• Assess anti-tumor activity of ibrutinib asadd-on to RICE or RVICI regimens	• Overall response (complete response [CR], including CR biopsy-negative [CRb] and unconfirmed CR [CRu]) and partial response [PR])

• Assess disease-specific biomarkers	• Phospho-BTK, as well as SYK, STAT3, caspase-3, BCL-Xl, and Ciap1 expression at baseline and during treatment • BCR/CD79B, CARD11, and MYD mutations • c-MYC, immunoglobulin, and T-cell receptor gene rearrangements at baseline
• Assess the pharmacodynamic response	• BTK occupancy
• Acceptability and palatability assessment of all ibrutinib formulations	• Visual analog scale score for palatability
Exploratory	
• Evaluate other response biomarkers	• Other biomarkers, as applicable
• Explore the exposure-response relationships	• Potential relationships between systemic exposure and response

Abbreviation's key: AUC: area under curve; BCL-Xl: B-cell lymphoma-extra-large; BCR: B-cell receptor; BTK: Bruton's tyrosine kinase; CARD11: Caspase Recruitment Domain Family Member 11; Ciap1: cellular inhibitor of apoptosis protein-1; CL/F: clearance
RICE: rituximab, ifosfamide, carboplatin, etoposide, and dexamethasone; RVICI: rituximab, vincristine, idarubicin, carboplatin, ifosfamide, and dexamethasone; STAT3: Signal transducer and activator of transcription 3; Vd/F: Volume of distribution
Source: p. 27 CSR Body

Randomized Part (Part 2)

Objectives	Endpoints
Primary	
• Assess efficacy (EFS) of ibrutinib in combinationwith RICE or RVICI background therapy compared to RICE or RVICI background therapyalone	• Difference in EFS between the 2 treatment groups (anevent is defined as the time from randomization to death, disease progression, or lack ofCR or PR after 3 cycles of treatment based on blinded independent event review)
Secondary	
• Evaluate the safety and tolerability of ibrutinib in combination with RICE or RVICI background therapy in pediatric subjects and young adults with B-cell malignancies	• Safety parameters, including gastrointestinal effects, immune function, intensified cardiac monitoring (in particular, after previous anthracycline exposure)
• Determine the ORR (overall response rate)	• The proportion of subjects who achieve CR,(including CRb and CRu) and PR
• Evaluate tumor volume reduction at Day 14	• Percent decrease in the sum of the products of the lesion diameters at Day 14
• Determine the number and proportion of subjectswho proceed to stem cell transplantation	• Number and proportion of subjects who proceed tostem cell transplantation
• Evaluate the time to response	• The time interval from the first dose of ibrutinib to the first documented response for those subjects who respond
• Measure the duration of response	• Duration calculated from the date of initial documentation of a response (CR or PR) to the dateoffirst documented evidence of progressive disease (PD) or death
• Evaluate long-term survival (EFS at 2 and 3 years)	• Proportion of subjects with EFS at 2 and 3 years
• Evaluate overall survival	• The duration from the date of randomization to thedate of the subject's death

• Assess disease-specific biomarkers	• Phosphor-BTK, as well as SYK, STAT3, caspase-3, BCL-Xl, and Ciap1 expression at baseline and during treatment • BCR/CD79B, CARD11, and MYD mutations • c-MYC, immunoglobulin, and T-cell receptor gene rearrangements at baseline
• Assess the pharmacodynamic response, if deemed appropriate based on Part 1 results	• BTK occupancy
• Assess the population PK of ibrutinib in pediatricsubjects and young adults	• Population PK parameters and derived systemic exposure to ibrutinib such as AUC • Relationship between PK parameters and age or measure of body size
• Acceptability and palatability assessment of all ibrutinib formulations	• Visual analog scale score for palatability
Exploratory	
• Evaluate other response biomarkers	• Other biomarkers, as applicable
• Explore the exposure-response relationships	• Potential relationships between systemic exposure and response

Abbreviation's key: AUC: area under curve; BCL-Xl: B-cell lymphoma-extra-large; BCR: B-cell receptor; BTK: Bruton's tyrosine kinase; CARD11: Caspase Recruitment Domain Family Member 11; Ciap1: cellular inhibitor of apoptosis protein-1; CL/F: clearance
CR: complete response; EFS: event-free survival; ORR: overall response rate; PR: partial response; RICE: rituximab, ifosfamide, carboplatin, etoposide, and dexamethasone; RVICI: rituximab, vincristine, idarubicin, carboplatin, ifosfamide, and dexamethasone; STAT3: Signal transducer and activator of transcription 3
Source: p. 28 CSR Body

Sample size

Since Part 1 was to confirm that the PK profile of ibrutinib plus CIT in paediatric subjects was consistent with adults, no formal sample size calculations were performed. The required number of subjects in Part 1 was based on PK results and clinical judgment.

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

Randomisation and blinding (masking)

Randomization was not applicable for Part 1 of the study.

Central randomization was implemented in Part 2 of this study. Subjects were randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule. The randomization was balanced by using randomly permuted blocks and was stratified by histologyand background therapy, then randomized in a 2:1 ratio to either Treatment group A (ibrutiniband RICE or RVICI background therapy) or Treatment group B (RICE or RVICI background therapy only).

Statistical Methods

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

estimates were provided. Comparisons between the 2 treatment groups in Part 2 was performed as follows: for the continuous variables representing change from baseline to a particular postbaseline timepoint, analysis of variance was used. For discrete variables, Chi-square test was used. For time-to-event variables, non-stratified log-rank test and non-stratified Cox proportion hazard model was used unless specified otherwise.

The primary endpoint of event-free survival (EFS) (events determined by IRC) was compared between treatment groups using a non-stratified log-rank test. The estimated median EFS along with its 90% CI for each treatment group are presented. The EFS curve is presented using the Kaplan-Meier method. The estimate of the HR between the 2 treatment groups and its associated 90% CI were computed using a non-stratified Cox proportional hazards model.

The secondary endpoints were OS, overall response rate (ORR), tumour volume reduction, time to response, DOR, and proportion of subjects who proceeded to stem cell transplantation. Overall survival was analysed using a non-stratified log-rank test. Survival time of living subjects was censored on the last date a subject was known to be alive or lost to follow-up. The survival curve, the median OS, and its 90% CI were estimated using the Kaplan-Meier product-limit method. The HR of ibrutinib+CIT relative to CIT alone and its associated 90% CI were calculated using a non-stratified Cox proportional hazards model. Overall response rate was computed as the proportion of IRC confirmed responders (best overall response of PR or better) for each treatment group and was compared between treatment group using a 2-sided chi-square test at the 10% level of significance. The relative risk of being a responder (ibrutinib+CIT versus CIT) was reported along with the associated 90% CI. The mean tumour volume reduction from baseline to Day 14 was compared between treatment groups using a 2-sided t-test at the 10% level of significance. The mean difference and its associated 90% CI were provided. Time to response was summarized for each treatment group using descriptive statistics. Duration of response and median time survival were summarized using the Kaplan-Meier product-limit method. The proportion of subjects who proceeded to stem cell transplantation was presented for each treatment group and compared between treatment groups using a 2-sided chi-square test at the 10% level of significance. Logistic regression analysis was also used to estimate the odds ratio of proceeding to transplant in ibrutinib +CIT versus CIT along with its 90% CI.

During Part 2, an external IDMC was used for periodic safety reviews. The pre-planned IA was conducted when 31 EFS events were reached. An external IDMC were to determine the appropriateness for early stopping using the nonbinding stopping rules as well as other efficacy and safety endpoints. The 1-sided p-value required for early stopping for futility was ≥0.367 and efficacy was ≤0.006 if there were 30 EFS events at the IA. This design employed the sequential testing approach as described by O'Brien and Fleming (O'Brien 1979) to preserve the Type-I error rate.

Results

Recruitment

The pre-planned IA of part 2 was conducted when 31 EFS events were reached. The IDMC recommended stopping enrolment as the futility boundary for early stopping was reached (1-sided p-value ≥0.341 based on observed 31 of 60 EFS events). Consequently, subject enrolment ceased. The study was closed after all remaining subjects had reached 1 year follow-up.

Baseline data

Part 1:

Demographic and Baseline Characteristics-Part 1; Safety Analysis Set (Study54179060LYM3003)

	Ibrutinib+RVICI	Ibrutinib+RICE	Total
Analysis set: Safety	10	11	21
Age (years)			
N	10	11	21
1 to 5	2 (20.0%)	2 (18.2%)	4 (19.0%)
6to 11	6(60.0%)	4 (36.4%)	10 (47.6%)
12 to 17	2 (20.0%)	5 (45.5%)	7 (33.3%)
>=18	0	0	0
Mean (SD)	8.3 (3.43)	10.5 (4.91)	9.4 (4.31)
Median	8.0	11.0	8.0
Range	(4; 15)	(3; 17)	(3; 17)
Sex			
N	10	11	21
Female	1 (10.0%)	3 (27.3%)	4 (19.0%)
Male	9 (90.0%)	8 (72.7%)	17 (81.0%)
Ethnicity			
N	10	11	21
Hispanic or Latino	0	2 (18.2%)	2 (9.5%)
Not Hispanic or Latino	9 (90.0%)	6(54.5%)	15 (71.4%)
Unknown	0	1 (9.1%)	1 (4.8%)
Not Reported	1 (10.0%)	2 (18.2%)	3 (14.3%)
Race			
N	10	11	21
White	10 (100.0%)	9 (81.8%)	19 (90.5%)
Black	0	0	0
Asian	0	1 (9.1%)	1 (4.8%)
American Indian or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Other	0	0	0
Unknown or not reported	0	1 (9.1%)	1 (4.8%)
Region			
N	10	11	21
Europe	10 (100.0%)	8 (72.7%)	18 (85.7%)
North America	0	1 (9.1%)	1 (4.8%)
Latin America	0	1 (9.1%)	1 (4.8%)
Asia	0	1 (9.1%)	1 (4.8%)
Weight (kg)			
N	10	11	21
Mean (SD)	29.06(13.506)	44.34 (27.965)	37.06(23.113)
Median	25.90	34.00	28.00
Range	(13.5; 57.0)	(15.0; 102.5)	(13.5; 102.5)
Height (cm)			
N	10	11	21
Mean (SD)	133.20 (24.197)	148.22 (29.936)	141.07 (27.760)
Median	136.00	142.00	140.00
Range	(100.0; 182.0)	(100.5; 192.0)	(100.0; 192.0)
BSA(m^2)			
N	10	11	21
Mean (SD)	1.04 (0.324)	1.33 (0.535)	1.19 (0.460)
Median	1.00	1.20	1.00
Range	(0.6; 1.7)	(0.6; 2.3)	(0.6; 2.3)

RICE: Iifosfamide, carboplatin, etoposide, and dexamethasone;
RVICI=rituximab, vincristine, ifosfamide, carboplatin, idarubicin, and dexamethasone

Note: Percentages are calculated with the number of subjects in the safety analysis set with non-missing values for that parameter as the denominator.

[TSIDEM01P1.RTF] [JNJ-54179060\54179060LYM3003\DBR_CSR\RE_CSR\PROD\TSIDEM01P1.SAS] 02AUG2021, 11:57

Source: Table 6 CSR Body

Baseline Disease Characteristics - Part 1 ; Safety Analysis Set (Study 54179060LYM3003)

	Ibrutinib+RVICI	Ibrutinib+RICE	Total
Analysis set: Safety	10	11	21
Time from initial diagnosis to enrollment (months)			
N	10	11	21
Mean (SD)	10.5 (6.22)	11.7 (10.94)	11.1 (8.81)
Median	8.2	7.0	7.2
Range	(5; 25)	(4; 37)	(4; 37)
Time from most recent relapse to enrollment (months)			
N	10	11	21
Mean (SD)	0.7 (0.95)	0.3 (0.21)	0.5 (0.68)
Median	0.3	0.3	0.3
Range	(0; 3)	(0; 1)	(0; 3)
Diagnosis at enrollment			
Type of Mature B cell NHL			
N	10	11	21
Burkitt-like lymphoma	1 (10.0%)	2 (18.2%)	3 (14.3%)
Burkitt Lymphoma	4 (40.0%)	4 (36.4%)	8 (38.1%)
Burkitt leukemia	3 (30.0%)	2 (18.2%)	5 (23.8%)
DLBCL	0	3 (27.3%)	3 (14.3%)
Primary mediastinal B-cell lymphoma	1 (10.0%)	0	1 (4.8%)
Other pediatric mature B-cell NHL	1 (10.0%)	0	1 (4.8%)
Extra Nodal Sites			
Central nervous system			

Table 7: Baseline Disease Characteristics - Part 1 ; Safety Analysis Set (Study 54179060LYM3003)

	Ibrutinib+RVICI	Ibrutinib+RICE	Total
N	10	11	21
Yes	1 (10.0%)	0	1 (4.8%)
No	9 (90.0%)	11 (100.0%)	20 (95.2%)
Bone marrow			
N	10	11	21
Yes	4 (40.0%)	3 (27.3%)	7 (33.3%)
No	6(60.0%)	8 (72.7%)	14 (66.7%)
Other			
N	10	11	21
Yes	9 (90.0%)	9 (81.8%)	18 (85.7%)
No	1 (10.0%)	2 (18.2%)	3 (14.3%)
Initial diagnosis			
Type of Mature B cell NHL			
N	10	11	21
Burkitt-like lymphoma	1 (10.0%)	2 (18.2%)	3 (14.3%)
Burkitt Lymphoma	3 (30.0%)	4 (36.4%)	7 (33.3%)
Burkitt leukemia	4 (40.0%)	2 (18.2%)	6(28.6%)
DLBCL	0	3 (27.3%)	3 (14.3%)
Primary mediastinal B-cell lymphoma	1 (10.0%)	0	1 (4.8%)
Other pediatric mature B-cell NHL	1 (10.0%)	0	1 (4.8%)
First relapse			
Type of Mature B cell NHL			
N	10	11	21
Burkitt-like lymphoma	1 (10.0%)	2 (18.2%)	3 (14.3%)
Burkitt Lymphoma	4 (40.0%)	4 (36.4%)	8 (38.1%)
Burkitt leukemia	3 (30.0%)	2 (18.2%)	5 (23.8%)
DLBCL	0	3 (27.3%)	3 (14.3%)
Primary mediastinal B-cell lymphoma	1 (10.0%)	0	1 (4.8%)
Other pediatric mature B-cell NHL	1 (10.0%)	0	1 (4.8%)
Second relapse			
Type of Mature B cell NHL			
N	6	1	7
Burkitt-like lymphoma	1 (10.0%)	0	1 (4.8%)
Burkitt Lymphoma	2 (20.0%)	1 (9.1%)	3 (14.3%)
Burkitt leukemia	1 (10.0%)	0	1 (4.8%)
DLBCL	0	0	0
Primary mediastinal B-cell lymphoma	1 (10.0%)	0	1 (4.8%)
Other pediatric mature B-cell NHL	1 (10.0%)	0	1 (4.8%)
Baseline lymphoma symptoms			
N	10	11	21
No	2 (20.0%)	6(54.5%)	8 (38.1%)
Yes	8 (80.0%)	5 (45.5%)	13 (61.9%)
At least one symptom	8	5	13
Recurrent fevers	0	1 (9.1%)	1 (4.8%)
Night sweats	0	1 (9.1%)	1 (4.8%)
Weight loss	1 (10.0%)	1 (9.1%)	2 (9.5%)
Physical discomfort due to enlarged lymph node	2 (20.0%)	2 (18.2%)	4 (19.0%)
Itching	0	2 (18.2%)	2 (9.5%)
Fatigue (severe and persistent)	4 (40.0%)	2 (18.2%)	6(28.6%)
Other	6(60.0%)	2 (18.2%)	8 (38.1%)
CSF cytologic evaluation			
N	10	11	21
CNS-Positive	3 (30.0%)	0	3 (14.3%)
CNS-Negative	7 (70.0%)	11 (100.0%)	18 (85.7%)
Lymphoma cells or Lymphoblasts			

N	10	11	21
Mean (SD)	16.0 (25.77)	13.1 (27.92)	14.5 (26.28)

	Ibrutinib+RVICI	Ibrutinib+RICE	Total
Median	3.8	0.0	0.0
Range	(0; 82)	(0; 80)	(0; 82)
Karnofsky performance status scale			
N	1	3	4
Mean (SD)	80.0 (-)	83.3 (20.82)	82.5 (17.08)
Median	80.0	90.0	85.0
Range	(80; 80)	(60; 100)	(60; 100)
Lansky performance status scale			
N	10	8	18
Mean (SD)	77.0 (13.37)	88.8 (15.53)	82.2 (15.17)
Median	75.0	95.0	85.0
Range	(60; 100)	(60; 100)	(60; 100)

Key : RICE=rituximab, ifosfamide, carboplatin, etoposide, and dexamethasone;
RVICI=rituximab, vincristine, ifosfamide, carboplatin, idarubicin, and dexamethasone
Note: Percentages are calculated with the number ofsubjects in the Safety analysis set with non-missing values for that parameter as the denominator.

[TSIDEM02P1.RTF] [JNJ-54179060\54179060LYM3003\DBR_CSR\RE_CSR\PROD\TSIDEM02P1.SAS] 01SEP2021, 14:26
Source: Table 7 CSR Body

Part 2:

Demographic and Baseline Characteristics-Part 2; Intent-to-treat Analysis Set (Study54179060LYM3003)

	Ibrutinib+CIT(RICE,RVICI)	CIT(RICE,RVICI)	Total
Analysis set: Intent-to-treat	35	16	51
Age (years)			
N	35	16	51
1 to 5	2 (5.7%)	2 (12.5%)	4 (7.8%)
6to 11	5 (14.3%)	2 (12.5%)	7 (13.7%)
12 to 17	23 (65.7%)	11 (68.8%)	34 (66.7%)
>=18	5 (14.3%)	1 (6.3%)	6(11.8%)
Mean (SD)	13.9 (3.94)	13.2 (4.37)	13.7 (4.05)
Median	15.0	14.5	15.0
Range	(5; 19)	(3; 18)	(3; 19)
Sex			
N	35	16	51
Female	12 (34.3%)	3 (18.8%)	15 (29.4%)
Male	23 (65.7%)	13 (81.3%)	36(70.6%)
Ethnicity			
N	35	16	51
Hispanic or Latino	2 (5.7%)	2 (12.5%)	4 (7.8%)
Not Hispanic or Latino	30 (85.7%)	14 (87.5%)	44 (86.3%)
Unknown	1 (2.9%)	0	1 (2.0%)
Not Reported	2 (5.7%)	0	2 (3.9%)
Race			
N	35	16	51
White	22 (62.9%)	8 (50.0%)	30 (58.8%)
Black	0	1 (6.3%)	1 (2.0%)
Asian	8 (22.9%)	6(37.5%)	14 (27.5%)
American Indian or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Other	2 (5.7%)	1 (6.3%)	3 (5.9%)

Table 25: Demographic and Baseline Characteristics-Part 2; Intent-to-treat Analysis Set (Study 54179060LYM3003)

	Ibrutinib+CIT(RICE,RVICI)	CIT(RICE,RVICI)	Total
Unknown or not reported	3 (8.6%)	0	3 (5.9%)
Region			
N	35	16	51
Europe	25 (71.4%)	9 (56.3%)	34 (66.7%)
North America	2 (5.7%)	0	2 (3.9%)
Latin America	1 (2.9%)	2 (12.5%)	3 (5.9%)
Asia	7 (20.0%)	5 (31.3%)	12 (23.5%)
Weight (kg)			
N	35	16	51
Mean (SD)	53.92 (19.680)	52.56(21.587)	53.49 (20.089)
Median	55.50	50.60	52.60
Range	(16.4; 93.5)	(17.1; 87.5)	(16.4; 93.5)
Height (cm)			
N	35	16	51
Mean (SD)	158.33 (19.722)	157.44 (25.041)	158.05 (21.279)
Median	163.00	163.50	163.00
Range	(103.0; 184.5)	(100.6; 188.3)	(100.6; 188.3)
BSA(m^2)			
N	35	16	51
Mean (SD)	1.52 (0.375)	1.50 (0.421)	1.51 (0.386)
Median	1.60	1.50	1.50
Range	(0.7; 2.1)	(0.7; 2.1)	(0.7; 2.1)

Key: CIT=chemoimmunotherapy; RICE=rituximab, ifosfamide, carboplatin, etoposide, and dexamethasone; RVICI=rituximab, vincristine, ifosfamide, carboplatin, idarubicin, and dexamethasone
Note: Percentages are calculated with the number ofsubjects in the intent-to-treat analysis set with non-missing values for
that parameter as the denominator.

[TSIDEM01P2.RTF] [JNJ-54179060\54179060LYM3003\DBR_CSR\RE_CSR\PROD\TSIDEM01P2.SAS] 02AUG2021, 11:57
Source: Table 25 CSR Body

Baseline Disease Characteristics-Part 2 ; Intent-to-treat Analysis Set (Study 54179060LYM3003)

	Ibrutinib+CIT(RICE,RVICI)	CIT(RICE,RVICI)	Total
Analysis set: Intent-to-treat	35	16	51
Time from initial diagnosis to randomization (months)			
N	35	16	51
Mean (SD)	12.2 (13.23)	9.8 (10.85)	11.5 (12.48)
Median	8.1	6.6	7.2
Range	(3; 69)	(2; 46)	(2; 69)
Time from most recent relapse to randomization (months)			
N	35	16	51
Mean (SD)	0.5 (0.39)	0.7 (0.99)	0.5 (0.64)
Median	0.3	0.3	0.3
Range	(0; 2)	(0; 4)	(0; 4)
Diagnosis at randomization			
Type ofMature B cell NHL			
N	35	16	51
Burkitt-like lymphoma	1 (2.9%)	1 (6.3%)	2 (3.9%)
Burkitt Lymphoma	12 (34.3%)	4 (25.0%)	16(31.4%)
Burkitt leukemia	4 (11.4%)	1 (6.3%)	5 (9.8%)
DLBCL	12 (34.3%)	8 (50.0%)	20 (39.2%)
Primary mediastinal B-cell lymphoma	6(17.1%)	0	6(11.8%)
Other pediatric mature B-cell NHL	0	2 (12.5%)	2 (3.9%)

Extra Nodal Sites			
Central nervous system			
N	35	16	51
Yes	1 (2.9%)	1 (6.3%)	2 (3.9%)
No	34 (97.1%)	15 (93.8%)	49 (96.1%)
Bone marrow			
N	35	16	51
Yes	7 (20.0%)	5 (31.3%)	12 (23.5%)
No	28 (80.0%)	11 (68.8%)	39 (76.5%)
Other			
N	35	16	51
Yes	21 (60.0%)	10 (62.5%)	31 (60.8%)
No	14 (40.0%)	6(37.5%)	20 (39.2%)
Initial diagnosis			
Type ofMature B cell NHL			
N	35	16	51
Burkitt-like lymphoma	1 (2.9%)	0	1 (2.0%)
Burkitt Lymphoma	10 (28.6%)	5 (31.3%)	15 (29.4%)
Burkitt leukemia	6(17.1%)	1 (6.3%)	7 (13.7%)
DLBCL	12 (34.3%)	8 (50.0%)	20 (39.2%)
Primary mediastinal B-cell lymphoma	6(17.1%)	0	6(11.8%)
Other pediatric mature B-cell NHL	0	2 (12.5%)	2 (3.9%)
First relapse			
Type ofMature B cell NHL			
N	35	16	51
Burkitt-like lymphoma	1 (2.9%)	1 (6.3%)	2 (3.9%)
Burkitt Lymphoma	12 (34.3%)	4 (25.0%)	16(31.4%)
Burkitt leukemia	4 (11.4%)	1 (6.3%)	5 (9.8%)
DLBCL	12 (34.3%)	8 (50.0%)	20 (39.2%)
Primary mediastinal B-cell lymphoma	6(17.1%)	0	6(11.8%)
Other pediatric mature B-cell NHL	0	2 (12.5%)	2 (3.9%)
Second relapse			
Type of Mature B cell NHL			
N	2	0	2
Burkitt-like lymphoma	0	0	0

Table 26: Baseline Disease Characteristics-Part 2 ; Intent-to-treat Analysis Set (Study54179060LYM3003)

	Ibrutinib+CIT(RICE,RVICI)	CIT(RICE,RVICI)	Total
Burkitt Lymphoma	1 (2.9%)	0	1 (2.0%)
Burkitt leukemia	0	0	0
DLBCL	1 (2.9%)	0	1 (2.0%)
Primary mediastinal B-cell lymphoma	0	0	0
Other pediatric mature B-cell NHL	0	0	0
Baseline lymphoma symptoms			
N	35	16	51
No	21 (60.0%)	11 (68.8%)	32 (62.7%)
Yes	14 (40.0%)	5 (31.3%)	19 (37.3%)
At least one symptom	14	5	19
Recurrent fevers	0	1 (6.3%)	1 (2.0%)
Night sweats	3 (8.6%)	0	3 (5.9%)
Weight loss	2 (5.7%)	0	2 (3.9%)
Physical discomfort due to enlarged lymph node	1 (2.9%)	0	1 (2.0%)
Itching	1 (2.9%)	1 (6.3%)	2 (3.9%)
Fatigue (severe and persistent)	4 (11.4%)	1 (6.3%)	5 (9.8%)
Other	7 (20.0%)	4 (25.0%)	11 (21.6%)
CSF cytologic evaluation			
N	35	16	51
CNS-Positive	5 (14.3%)	1 (6.3%)	6(11.8%)
CNS-Negative	30 (85.7%)	15 (93.8%)	45 (88.2%)
Lymphoma cells or Lymphoblasts			
N	35	15	50
Mean (SD)	8.4 (23.72)	2.9 (8.94)	6.8 (20.49)
Median	0.3	0.0	0.0
Range	(0; 100)	(0; 35)	(0; 100)
Karnofsky performance status scale			
N	17	8	25
Mean (SD)	90.0 (8.66)	85.0 (11.95)	88.4 (9.87)
Median	90.0	90.0	90.0
Range	(70; 100)	(60; 100)	(60; 100)
Lansky performance status scale			
N	18	9	27
Mean (SD)	81.7 (17.24)	80.0 (17.32)	81.1 (16.95)
Median	85.0	90.0	90.0
Range	(50; 100)	(60; 100)	(50; 100)

Key: CIT=chemoimmunotherapy; RICE=rituximab, ifosfamide, carboplatin, etoposide, and dexamethasone; RVICI=rituximab, vincristine, ifosfamide, carboplatin, idarubicin, and dexamethasone
Note: Percentages are calculated with the number of subjects in the intent-to-treat analysis set with non-missing values for that parameter as the denominator.

[TSIDEM02P2.RTF] [JNJ-54179060\54179060LYM3003\DBR_CSR\RE_CSR\PROD\TSIDEM02P2.SAS] 01SEP2021, 14:27
Source: Table 26 CSR Bod

Number analysed

PK Analysis Set: It included subjects in the ibrutinib group that received ibrutinib doses and had quantifiable plasma concentration of ibrutinib.

Efficacy Analysis Set: The intent-to-treat (ITT) Population consisted of all randomized subjects; subjects were analysed based on randomization, regardless of study agent received. The ITT population was used for all efficacy analyses, subject disposition and biomarker analyses. The primary efficacy analysis was based on the ITT population for data collected in the Part 2. For Part 1, efficacy was provided as a secondary endpoint.

Safety Analysis Set: The safety population consisted of all subjects who received at least 1 dose of treatment. The safety population was used for all safety analyses and subjects were analysed based on actual study agent received.

Efficacy results

Part 1:

Summary of Best Overall Response Rate (IRC Assessment)-Part 1; Safety Analysis Set(Study 54179060LYM3003)

	Ibrutinib+RVICI	Ibrutinib+RICE	Total
Analysis set: Safety	10	11	21
Patients with IRC data available	7 (70.0%)	11 (100.0%)	18 (85.7%)
Best Overall Response Rate(CR,CRb,CRu,PR)	5 (50.0%)	9 (81.8%)	14 (66.7%)
Best Overall Response, n (%)			
Complete Response (CR)	1 (10.0%)	4 (36.4%)	5 (23.8%)
Complete Response Biopsy-Negative (CRb)	0	0	0
Complete Response Unconfirmed (CRu)	0	0	0
Partial Response (PR)	4 (40.0%)	5 (45.5%)	9 (42.9%)
Minor Response (MR)	0	1 (9.1%)	1 (4.8%)
No Response (NR)	1 (10.0%)	0	1 (4.8%)
Progressive disease (PD)	1 (10.0%)	0	1 (4.8%)
No Evidence of disease (NED)	0	0	0
Unknown (UNK)/Missing	3 (30.0%)	1 (9.1%)	4 (19.0%)

Note: Overall response will only consider tumour assessment up to subsequent anticancer therapy. NR = Stable Disease.

[TEFORR01P1.RTF] [JNJ-54179060\54179060LYM3003\DBR_CSR\RE_CSR\PROD\TEFORR01P1.SAS] 02AUG2021, 11:57
Source: Table 12 CSR Body

Duration of response (IRC) was summarized for the subjects who achieved either CR (including CR_b and CR_u) or PR. Overall, the median DOR was 4.83 months (90% CI: 1.91, 35.55).

17 (81%) subjects were reported with an EFS event and the median EFS was 3.02 months (90% CI: 1.84,5.25) by IRC assessment.

Part 2:

Of the 51 subjects, 50 (98%) subjects received at least 1 dose of study treatment (35 [100%] subjects received ibrutinib+CIT [RICE, RVICI] and 15 [93.8%] subjects received CIT [RICE, RVICI]). One of the 16 subjects randomized to the CIT group withdrew consent following randomization and did not receive study treatment.

Table 1: Event-free survival (Non-stratified Analysis)-Primary Analysis, Independent Review Committee Data-Part 2; Intent-to-treat Analysis Set (Study 54179060LYM3003)

	Ibrutinib+CIT(RICE,RVICI)	CIT(RICE,RVICI)	Ibrutinib+CIT vs. CIT
Analysis set: Intent-to-treat	35	16	
EFS event	22 (62.9%)	12 (75.0%)	
Disease progression	14 (40.0%)	9 (56.3%)	
Death	6 (17.1%)	3 (18.8%)	
Non-Responder	2 (5.7%)	0	
Censored	13 (37.1%)	4 (25.0%)	
Event Free Survival			
25th percentile (90% CI)	2.76 (1.08, 3.48)	2.60 (1.05, 5.75)	
Median (90% CI)	6.05 (2.99, 8.84)	6.97 (2.60, 11.07)	
75th percentile (90% CI)	36.11 (8.71, NE)	11.07 (8.05, NE)	
Range	(0.5+, 37.7+)	(0.0+, 36.2+)	
6-month event-free rate (90% CI)	0.504 (0.352, 0.638)	0.533 (0.306, 0.716)	
12-month event-free rate (90% CI)	0.347 (0.213, 0.484)	0.160 (0.039, 0.354)	
18-month event-free rate (90% CI)	0.347 (0.213, 0.484)	0.160 (0.039, 0.354)	
24-month event-free rate (90% CI)	0.347 (0.213, 0.484)	0.160 (0.039, 0.354)	
30-month event-free rate (90% CI)	0.347 (0.213, 0.484)	0.160 (0.039, 0.354)	
36-month event-free rate (90% CI)	0.347 (0.213, 0.484)	0.160 (0.039, 0.354)	
Hazard ratio (90% CI)[a]			0.902 (0.499, 1.629)
p-value (1-sided)[b]			0.3869

Key: CIT=chemoimmunotherapy; RICE=rituximab, ifosfamide, carboplatin, etoposide, and dexamethasone; RVICI=rituximab, vincristine, ifosfamide, carboplatin, idarubicin, and dexamethasone
[a]Hazard ratio is from a non-stratified proportional hazards model. A hazard ratio < 1 favours Ibrutinib + CIT (RICE, RVICI).
[b]P-value is from a non-stratified log-rank test.
Note: + refers to survival time is a censored observation.
[TEFEFS01P2.RTF] [JNJ-54179060\54179060LYM3003\DBR_CSR\RE_CSR\PROD\TEFEFS01P2.SAS] 02AUG2021, 11:55

Source: Table 3 Clinical Overview

ORR

The best overall response of PR or better was observed in 68.6% subjects in the ibrutinib+CIT group and 81.3% subjects in the CIT group with an odds ratio (ibrutinib+CIT versus CIT) of 0.503 (90% CI: 0.150, 1.692); p=0.3465.

In the ibrutinib+CIT group, 6 (17.1%) subjects had a complete response (CR) (4 subjects had BL, 1 subject had DLBCL, and 1 subject had PMBCL at study entry) and 18 (51.4%) subjects had a PR (8 subjects had DLBCL, 4 subjects had B-AL, 3 subjects had BL, 2 subjects had PMBCL, and 1 subject had primary mediastinal [thymic] large B-cell lymphoma at study entry).

In the CIT group, 3 (18.8%) subjects had a CR (2 subjects had DLBCL and 1 subject had BL at study entry) and 10 (62.5%) subjects had a PR (5 subjects had DLBCL, 3 subjects had BL,1 subject had B-cell NHL, and 1 subject had high-grade B-cell lymphoma at study entry).

Overall Survival

A median OS of 14.13 months was observed for subjects in the ibrutinib+CIT group and 11.07 months for subjects in the CIT group. The HR (ibrutinib+CIT versus CIT) was 0.900 (90% CI: 0.472, 1.717); p=0.7888.

Duration of Response

The median DOR was 6.01 months (90% CI: 3.06, NE) in the ibrutinib+CIT group and 6.51 months (90% CI: 4.53, 10.64) in the CIT group.

Subjects Who Proceed to Stem Cell Transplantation

Overall, 16 (45.7%) subjects in ibrutinib+CIT group and 7 (43.8%) subjects in CIT group proceeded to the stem cell transplantation. Thirteen (37.1%) subjects with IRC assessed response of PR or better response proceeded to stem cell transplantations in the ibrutinib+CIT group and 7 (43.8%) subjects in the CIT group. The odds ratio (ibrutinib+CIT versus CIT) was 0.760 (90% CI: 0.277, 2.084) with a p-value of 0.7604.

Safety results

Part 1:

Subject Disposition - Part 1 ; Safety Analysis Set (Study 54179060LYM3003)

	Ibrutinib+RVICI	Ibrutinib+RICE	Total
Safety	10	11	21
Ibrutinib disposition			
Ongoing	0	0	0
Completed	4 (40.0%)	8 (72.7%)	12 (57.1%)
Completed Ibrutinib treatment	0	4 (36.4%)	4 (19.0%)
Bone Marrow Transplant	4 (40.0%)	4 (36.4%)	8 (38.1%)
Prematurely discontinued	6(60.0%)	3 (27.3%)	9 (42.9%)
Reasons for Premature Discontinuation			
Adverse event	0	0	0
Adverse event –COVID-19 Related	0	0	0
Death	3 (30.0%)	2 (18.2%)	5 (23.8%)
Death –COVID-19 Related	0	0	0
Lost to follow-up	0	0	0
Physician decision	1 (10.0%)	0	1 (4.8%)
Study terminated by Sponsor	0	0	0
Withdrawal ofconsent by subject,Parent or Guardian	0	0	0
Pregnancy	0	0	0
Progressive disease	2 (20.0%)	1 (9.1%)	3 (14.3%)
Other	0	0	0
Other -COVID-19 Related	0	0	0
Study disposition			
Ongoing	0	0	0
Study discontinued	10 (100.0%)	11 (100.0%)	21 (100.0%)
Reasons for Study Discontinuation			
Death	9 (90.0%)	4 (36.4%)	13 (61.9%)
Death –COVID-19 Related	0	0	0
Lost to follow-up	0	0	0
Physician decision	0	0	0
Study terminated by Sponsor	1 (10.0%)	6(54.5%)	7 (33.3%)
Withdrawal ofconsent by subject,Parent or Guardian	0	0	0
Pregnancy	0	0	0
Other	0	1 (9.1%)	1 (4.8%)
Other -COVID-19 Related	0	0	0

Key : RICE=rituximab, ifosfamide, carboplatin, etoposide, and dexamethasone;
RVICI=rituximab, vincristine, ifosfamide, carboplatin, idarubicin, and dexamethasone
Note : Percentages are calculated with the number ofSafety subjects in each treatment group as the denominators.

[TSIDS01P1.RTF] [JNJ-54179060\54179060LYM3003\DBR_CSR\RE_CSR\PROD\TSIDS01P1.SAS] 06OCT2021, 09:21

Source: Table 5 CSR Body

Twelve of 21 (57.1%) subjects completed treatment with ibrutinib. Treatment cycles were 28 days long, but could be shortened to 21 days, if count recovery occurs quickly and the investigator deems a subject ready to proceed with the next cycle of therapy. Most of the subjects (61.9%) received ≥3 cycles of ibrutinib including ibrutinib monotherapy after completion of CIT. The median treatment duration was 2.33 months (range: 0.2 to 5.7 months). A relative dose intensity of ≥90% was observed in 20 (95.2%) subjects.

All 21 subjects experienced at least 1 TEAE of Grade 3 or higher, of which TEAEs in 17 (81.0%) subjects considered to be related to ibrutinib by the investigator.

In the ibrutinib+RVICI group, the most common (≥30% of subjects) reported TEAEs by PT were anemia (90%); thrombocytopenia (80%); neutropenia (70%); diarrhea, hypokalemia (60% each); abdominal pain, nausea, vomiting, febrile neutropenia, hypoalbuminemia (50% each); sepsis, mucosal inflammation, hypertension (40% each); pyrexia, constipation, decreased appetite, hypocalcemia, and hypotension (30% each).

In the ibrutinib+RICE group, the most common (≥30% of subjects) reported TEAEs by PT were anemia, febrile neutropenia (72.7% each); nausea (63.6%); thrombocytopenia, neutropenia (54.5% each); vomiting, platelet count decreased, AST increased (45.5% each), diarrhea, and ALT increased (36.4% each).

Grade 3 or 4 TEAEs mainly occurred in the blood and lymphatic system disorders system organ class (100% of subjects each in the ibrutinib+RVICI and ibrutinib+RICE groups) and gastrointestinal disorders (ibrutinib+RVICI group: 90% and ibrutinib+RICE group: 90.9%).

Thirteen (61.9%) subjects died during the study (8 [38.1%] subjects died due to disease progression and 5 [23.8%] experienced TEAEs leading to death). All the TEAEs leading to death were considered as not related or doubtfully related to ibrutinib by the investigator.

Nineteen (90.5%) subjects experienced ≥Grade 3 treatment-emergent SAEs. The most common (≥30%) SAE observed across both treatment groups was febrile neutropenia. In the ibrutinib+RVICI group, the most common (≥30% of subjects) treatment-emergent SAEs were sepsis (4 of 10 [40%] subjects) and febrile neutropenia (3 of 10 [30%] subjects). In the ibrutinib+RICE group, the most common (≥30% of subjects) treatment-emergent SAE was febrile neutropenia, reported in 4 of 11 (36.4%) subjects. Seven (33.3%) subjects experienced treatment-emergent SAEs that were considered related to ibrutinib by the investigator.

No subject had a TEAE leading to treatment discontinuation of ibrutinib. One subject had ibrutinib dose-reductions due to TEAEs of ALT increased (Grade 3) and AST increased (Grade 2) in the ibrutinib+RICE group. These AEs were resolved after dose reduction of ibrutinib.

Seven subjects experienced TEAEs of major haemorrhage, all of which were Grade 3 or 4. Four major haemorrhage events occurred in 3 subjects (intestinal haemorrhage and melena [1 subject], epistaxis [1 subject], intracranial haemorrhage [1 subject]) were considered possibly related to ibrutinib by the investigator. All the 4 major haemorrhage events were reported in the ibrutinib+RVICI group. Subarachnoid haemorrhage was considered doubtfully related to ibrutinib by the investigator in the ibrutinib+RVICI group. The majority of the observed bleeds were confounded by other contributory risk factors including thrombocytopenia, CNS disease involvement, BK virus infection, sacral fracture, lumbar puncture and hypertension, which were assessed as not related to ibrutinib.

Eleven (52.4%) subjects experienced TEAEs of bleeding events (ibrutinib+RVICI group: 6 [60.0%] subjects and ibrutinib+RICE group: 5 [45.5%] subjects). In the ibrutinib+RVICI group, bleeding

events included epistaxis, hematemesis, haemorrhage intracranial, intestinal haemorrhage, melena, mouth haemorrhage, rectal haemorrhage, spinal cord hematoma, and subarachnoid haemorrhage (1 subject each). All the bleeding events were Grade 3 or 4 except Grade 1 or 2 bleeding events of mouth haemorrhage and rectal haemorrhage. In the ibrutinib+RICE group, bleeding events included epistaxis (2 subjects), melena, cystitis haemorrhagic, ecchymosis, and traumatic hematoma (1 subject each). All the bleeding events were Grade 1 or 2 except the bleeding events of Grade 3 or 4 melena and cystitis haemorrhagic.

Part 2:

Subject Disposition -Part 2; Intent-to-treat Analysis Set (Study 54179060LYM3003)

	Ibrutinib+CIT(RICE,RVICI)	CIT(RICE,RVICI)	Total
Intent-to-treat (ITT) [a]	35	16	51
Safety [b]	35 (100.0%)	15 (93.8%)	50 (98.0%)
Did not receive study drug	0	1 (6.3%)	1 (2.0%)
Ibrutinib disposition			
Ongoing	0	NA	0
Completed	19 (54.3%)	NA	19 (37.3%)
Completed Ibrutinib treatment	8 (22.9%)	NA	8 (15.7%)
Bone Marrow Transplant	11 (31.4%)	NA	11 (21.6%)
Prematurely discontinued	16(45.7%)	NA	16(31.4%)
Reasons for Premature Discontinuation			
Adverse event	1 (2.9%)	NA	1 (2.0%)
Adverse event –COVID-19 Related	0	NA	0
Death	3 (8.6%)	NA	3 (5.9%)
Death –COVID-19 Related	0	NA	0
Lost to follow-up	0	NA	0
Physician decision	3 (8.6%)	NA	3 (5.9%)
Study terminated by Sponsor	0	NA	0
Withdrawal of consent by subject, Parent or Guardian	3 (8.6%)	NA	3 (5.9%)
Pregnancy	0	NA	0
Progressive disease	6(17.1%)	NA	6(11.8%)
Other	0	NA	0
Other -COVID-19 Related	0	NA	0
CIT disposition			
Ongoing	0	0	0
Completed	19 (54.3%)	9 (56.3%)	28 (54.9%)
Completed CIT treatment	10 (28.6%)	8 (50.0%)	18 (35.3%)
Bone Marrow Transplant	9 (25.7%)	1 (6.3%)	10 (19.6%)
Prematurely discontinued	16(45.7%)	6(37.5%)	22 (43.1%)
Reasons for Premature Discontinuation			
Adverse event	2 (5.7%)	0	2 (3.9%)
Adverse event –COVID-19 Related	0	0	0
Death	3 (8.6%)	2 (12.5%)	5 (9.8%)
Death –COVID-19 Related	0	0	0
Lost to follow-up	0	0	0
Physician decision	3 (8.6%)	2 (12.5%)	5 (9.8%)
Study terminated by Sponsor	0	0	0
Withdrawal of consent by subject, Parent or Guardian	3 (8.6%)	0	3 (5.9%)
Pregnancy	0	0	0
Progressive disease	5 (14.3%)	2 (12.5%)	7 (13.7%)
Other	0	0	0
Other -COVID-19 Related	0	0	0
Study disposition			
Ongoing	0	0	0
Study discontinued	35 (100.0%)	16(100.0%)	51 (100.0%)
Reasons for Study Discontinuation			
Death	19 (54.3%)	10 (62.5%)	29 (56.9%)
Death –COVID-19 Related	0	0	0

Lost to follow-up	0	0	0
Physician decision	0	0	0
Study terminated by Sponsor	12 (34.3%)	4 (25.0%)	16(31.4%)
Withdrawal of consent by subject, Parent or Guardian	4 (11.4%)	2 (12.5%)	6(11.8%)
Pregnancy	0	0	0
Other	0	0	0

Table 24: Subject Disposition -Part 2; Intent-to-treat Analysis Set (Study 54179060LYM3003)

	Ibrutinib+CIT(RICE,RVICI)	CIT(RICE,RVICI)	Total
Other -COVID-19 Related	0	0	0

Key: CIT=chemoimmunotherapy; RICE=rituximab, ifosfamide, carboplatin, etoposide, and dexamethasone; RVICI=rituximab, vincristine, ifosfamide, carboplatin, idarubicin, and dexamethasone
Note: Percentages are calculated with the number ofintent-to-treat subjects in each treatment group as the denominators. [a]Intent-to-treat analysis set is defined as all subjects randomized into the study and classified according to assigned treatment group, regardless of the actual treatment received.
[b]Safety population includes all randomized subjects who receive at least one dose of Ibrutinib + CIT (RICE,RVICI) or CIT (RICE, RVICI) and classified to the treatment group according to their actual treatment received.
[TSIDS01P2.RTF] [JNJ-54179060\54179060LYM3003\DBR_CSR\RE_CSR\PROD\TSIDS01P2.SAS] 06OCT2021, 09:21
Source: Table 24 CRS Body

Of the 51 subjects, 41 subjects received RICE and 9 received RVICI as CIT.

Summaries of AEs and other safety data are based on 50 subjects who received at least 1 dose of treatment (35 subjects received ibrutinib+CIT [RICE, RVICI] and 15 subjects received CIT [RICE, RVICI]). Nineteen of 35 (54.3%) subjects completed treatment with ibrutinib and 28 of 51 (54.9%) completed CIT treatment. Eighteen (51.4%) subjects received ≥3 cycles of ibrutinib including ibrutinib monotherapy after completion of CIT. The median treatment duration was 2.23 months (range: 0.4 to 7.3 months). A relative dose intensity of ≥90% was observed in 35 (100%) subjects.

Adverse Events

All subjects experienced at least 1 TEAE of Grade 3 or higher in the ibrutinib+CIT and CIT groups. Grade 3 or higher TEAEs in 29 (82.9%) subjects in ibrutinib+CIT group were considered to be related to ibrutinib by the investigator.

In the ibrutinib+CIT group, the most common (>30% of subjects) reported TEAEs by PT were anaemia (82.9%); vomiting (71.4%); febrile neutropenia (68.6%), nausea (60%); thrombocytopenia (57.1%); headache (45.7%); neutropenia, pyrexia (40% each); abdominal pain, platelet count decreased (37.1%); hypokalaemia (34.3%); and neutrophil count decreased (34.3%).

In the CIT group, the most common (>30% of subjects) reported TEAEs by PT were anaemia (93.3%); neutrophil count decreased (60%); platelet count decreased (53.3%); febrile neutropenia, hypokalaemia (46.7% each); thrombocytopenia, neutropenia, white blood cell count decreased, ALT increased, pyrexia (40% each); aspartate aminotransferase increased, and hypomagnesemia (33.3% each).

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Twenty-nine (58.0%) subjects died during the study (ibrutinib+CIT group: 19 [54.3%]) subjects and CIT group: 10 [66.7%] subjects). Of the 29 subjects, 20 subjects died due to disease progression (ibrutinib+CIT group: 12 [34.3%] subjects and CIT group: 8 [53.3%] subjects), 6 subjects died due to AEs (ibrutinib+CIT group: 4 [11.4%] subjects and CIT group: 2 [13.3%] subjects), and 2 (5.7%) subjects died due to "other reasons" and 1 (2.9%) subject died due to an unknown reason in the ibrutinib+CIT group. Four subjects died due to TEAEs in the ibrutinib+CIT group (1 subject each with TEAEs of septic shock, pulmonary haemorrhage, pneumonia, and multiple organ dysfunction syndrome) and 2 subjects in the CIT group (1 subject each due to a TEAE of device related infection and sepsis).

Treatment-emergent SAEs were experienced by similar number of subjects (71.4% subjects in the ibrutinib+CIT group and 73.3% subjects in the CIT group) and all SAEs were ≥Grade 3. The most common (≥30%) SAE observed across both treatment groups was febrile neutropenia (ibrutinib+CIT group: 60.0% and CIT group: 40.4%). Eighteen (51.4%) subjects in the ibrutinib+CIT group experienced treatment-emergent SAEs that were considered related to ibrutinib by the investigator.

Four (11.4%) subjects had TEAEs leading to CIT discontinuation in the ibrutinib+CIT group, and in 1 of these 4 subjects, treatment with ibrutinib was discontinued due to SAE of Grade 4 febrile neutropenia. The other 3 subjects had discontinued CIT treatment due to Grade 4 febrile neutropenia, Grade 2 acute kidney injury, and Grade 2 methaemoglobinemia.

In the ibrutinib+CIT group, the TEAEs of thrombocytopenia (Grade 4 in 2 subjects), lower gastrointestinal haemorrhage (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.

Other Significant Adverse Events

In the ibrutinib+CIT group, 6 (17.1%) subjects experienced TEAEs of major haemorrhage. Five (14.3%) subjects had Grade 3 or 4 TEAEs of major haemorrhage and 1 subject had fatal (Grade 5) TEAE of pulmonary haemorrhage. One subject had 4 major haemorrhagic events of lower gastrointestinal haemorrhage, menorrhagia, pulmonary haemorrhage, and upper gastrointestinal haemorrhage. All the TEAEs of major haemorrhagic events in the subject were considered as possibly related to ibrutinib by the investigator except 2 of the 3 events of lower gastrointestinal haemorrhage and 2 events of upper gastrointestinal haemorrhage, which were considered as doubtfully related to ibrutinib by investigator. The other 5 subjects had major haemorrhagic events, which were considered as doubtfully related or not related to ibrutinib by the investigator except subdural haematoma and subdural haemorrhage, which were considered as possibly related to ibrutinib by the investigator.

In the CIT group, 1 (6.7%) subject experienced a TEAE of Grade 4 lower gastrointestinal haemorrhage. The TEAE was considered as very likely related to carboplatin and not related to other CIT by the investigator

In the ibrutinib+CIT group, 21 (60.0%) subjects experienced TEAEs of bleeding. Five (14.3%) subjects had Grade 3 or 4 TEAEs of bleeding events and 1 subject had fatal (Grade 5) TEAE of bleeding event. The most common (≥10% subjects) bleeding events were epistaxis (8 [22.9%] subjects) and haematuria (6 [17.1%]) In the CIT group, 2 (13.3%) subjects experienced TEAEs of bleeding. One subject had epistaxis and lower gastrointestinal haemorrhage and 1 subject had ecchymosis.

Laboratory and Other Safety Observations

No new safety signals were revealed from clinical laboratory and other safety observation data (physical examination, electrocardiogram, and echocardiography/ MUGA scan). Three subjects met laboratory criteria for Hy's Law in the ibrutinib+CIT group. All 3 subjects met the criteria in the context of septic shock or multiple organ failure and were not considered to be due to drug induced liver toxicity.

SmPC information

Currently, the Imbruvica SmPC states the following regarding paediatric use:

Section 4.2:

Paediatric population

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

Section 5.1:

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with IMBRUVICA in all subsets of the paediatric population in MCL, CLL and lymphoplasmacytic lymphoma (LPL) (for information on paediatric use, see section 4.2).

MAH Conclusion

The results of Part 1 supported the addition of ibrutinib to CIT and proceeding to Part 2 of the study. The study stopped enrolment in Part 2 due to futility as the 1-sided p-value for the primary endpoint, EFS, crossed the prespecified stopping boundary. There were no trends for differences for any subgroups in efficacy relative to the overall population. The primary endpoint of EFS superiority was not met and there was no additional benefit observed in EFS from adding ibrutinib to background CIT.

The observed AEs were consistent with the known safety profile of the individual agents and CIT, in addition to those expected in patients with the underlying disease of relapsed orrefractory mature B-cell NHL. No additional safety concerns were identified in this study during treatment with combinations of ibrutinib and CIT (RICE, RVICI). Based on the results of this study, the overall safety profile of ibrutinib+RVICI and ibrutinib+RICE is consistent with the known individual safety profiles of ibrutinib in adults, RVICI, and RICE.

2.3.3. Clinical pharmacology

Objectives

The primary objective of the PK analysis was to compare the exposure to ibrutinib in the paediatric population to the exposure observed in adults, corresponding to a median area under the concentration-time curve (AUC) of 509 ng.h/mL for a 560 mg daily dose.

Data

Subjects were sampled at pre-dose, 1, 2, 4, and 6 hours post-dose for multiple times over the course of the therapy, resulting in 1 to 3 rich PK (sub-)profiles for each individual. These sub-profiles were to

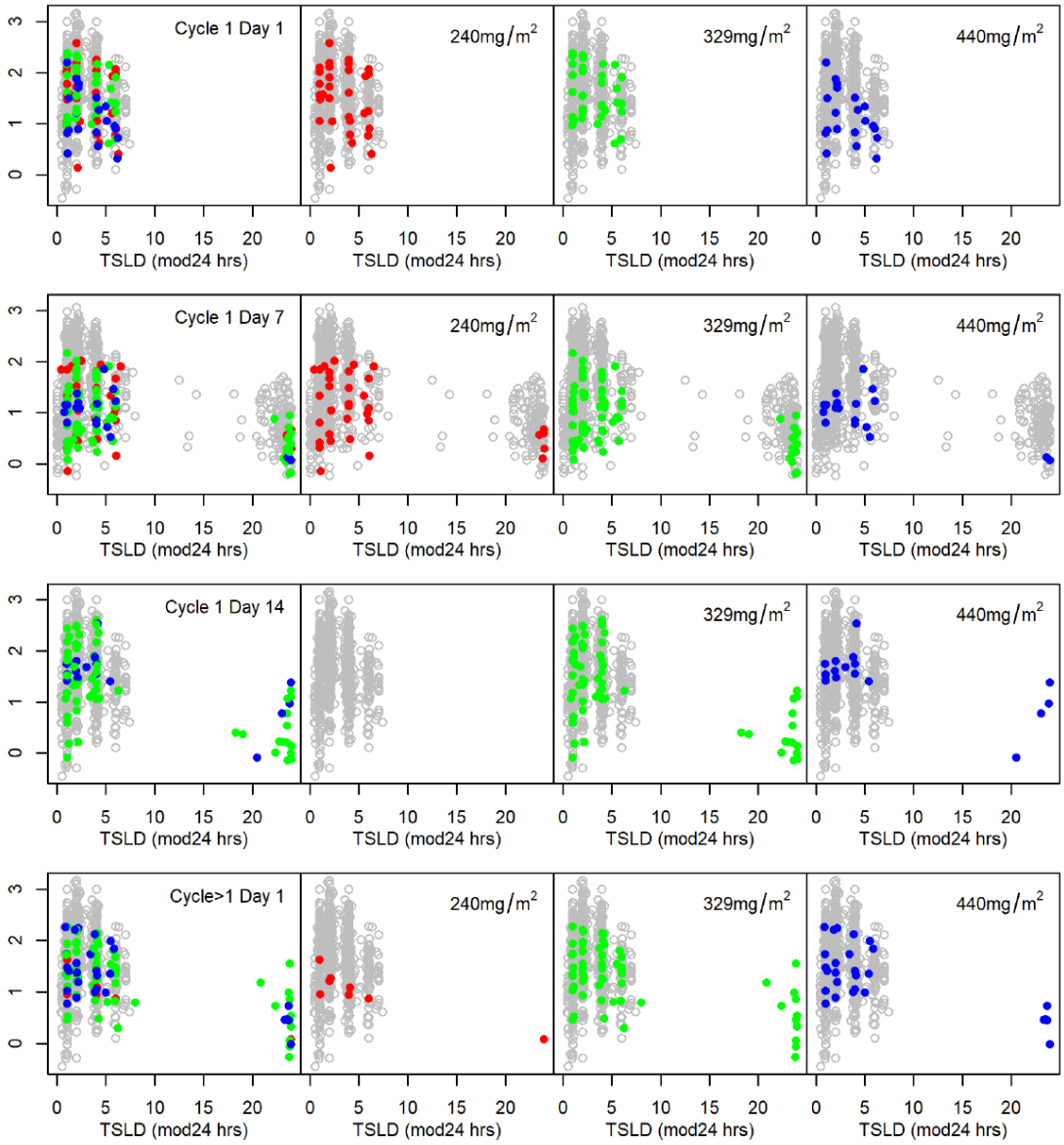
be taken at 4 possible occasions: Cycle 1 Day 1, Cycle 1 Day 7, Cycle 1 Day 14, and Day 1 of subsequent cycles (Cycle 2 or Cycle 3). This resulted in 1 to 3 rich PK profiles per subject. The relevant covariates in the PK dataset are summarized in Table 2.

Table 2 Demographic characteristics of the subjects involved in the pharmacokinetic assessment

Subjects	N	Sex	Age (years)	Weight (kg)	BSA (m^2)
Age Group 1 (1-5 yr)	6	5 M/1 F	4.3±0.8	17.1±3.1	0.7±0.1
Age Group 2 (6-11 yr)	13	12 M/1 F	7.8±1.5	28.7±8.3	1.0±0.2
Age Group 3 (12-17 yr)	28	16 M/12 F	14.8±1.7	58.4±16.5	1.6±0.3
Age Group 4 (18+ yr)	5	3 M/2 F	18.4±0.5	73.6±17.3	1.9±0.3

Abbreviations: BSA: body surface area, Yr: years

The pharmacokinetic analysis dataset consisted of 771 quantifiable ibrutinib plasma concentrations, observed across 52 subjects. All concentrations below the lowest quantifiable concentration or missing data were labeled as such in the concentration database. The PK results of Study LYM3003 were pooled for Part 1 and Part 2. The observed plasma concentrations in children are overlayed the analysed adult PK data in Figure 1.



PK=pharmacokinetic; TSLD=time since last dose.
Log10(Concentrations) are presented; Cycle >1 Day 1=Cycle 2 or Cycle 3, Day 1.
Filled circles: Part 2 Subjects; Crosses: Part 1 Subjects
Red: 240 mg/m^2; Green 329 mg/m^2; Blue 440 mg/m^2

Figure 1 Overlay plot of the observed concentration of previous adult population PK data (grey) and paediatric data (color-coded by dose) versus time since last dose by occasion.

Methods

The PopPK analysis was performed using non-linear mixed effects modelling in NONMEM. A PopPK model was developed using a PopPK model developed for adults, as a starting point. The adult PopPK model was a linear two-compartment model with an absorption lagtime.

A two-step approach was used to evaluate exposure in peadiatric subjects compared to adults. First, the paediatric PopPK model was fitted to the observed PK data for each subject, to obtain individual parameter estimates. Second, the individual parameters were used to derive (a) the AUC during each day with rich PK profiles (Cycle 1 Day 1, Cycle 1 Day 7, Cycle 1 Day 14 and Cycle>1 Day 1) and (b) the AUC at steady-state (AUCss) calculated as $AUC_{ss} = \frac{Dose \times CL}{F}$.

The target exposure in adults corresponded to a median AUC of 509 ng.h/mL, following an adult dose of 560 mg. The acceptable range for the median AUC in the paediatric population was set between 250 and 1500 ng.h/mL.

Model diagnostic methods were based on graphical evaluation of various goodness-of-fit plots. The relevant covariates weight, age, BSA and occasion were graphically evaluated by comparing individual parameters vs these covariates (η-plots).

Results

The developed paediatric PopPK model had the same structure as the adult model. Limited modifications compared to the adult PK model were applied. This included addition of inter-occasion variability (IOV) in relative bioavailability and an occasion-specific relative bioavailability of 0.496 for Cycle 1 Day 7 (the typical relative bioavailability was 1 at other occasions). Given the transient nature of the Day 7 covariate, no physiological cause for this deviation was explored.

No significant relation was found between variability individual PK parameters and the covariates weight, age and BSA in the paediatric population (which was based on graphical inspection of η vs covariate plots).

The presented data indicate that dosing regimens of 329 mg/m2 for children 12 years or older and 440 mg/m2/day for children below 12 years appear to result in overall comparable exposure to adults. The median individual AUCss values for 1-5 year olds assigned to 440 mg/m2, 6-11 year olds assigned to 440 mg/m2 and 12-17 year olds assigned to 329 mg/m2 were all within the acceptance limits of 250-1500 ng.h/mL (Table 3). Of note, predictions from Cycle 1 Day 7 were not included when calculating the median values in Table 3.

Table 3 Ibrutinib AUCss for different age groups assigned to 329 and 440 mg/m2/day

Age group	Ibrutinib dosing	Number of subjects	Median AUCss [IQR]
1-5	440 mg/m2	5	310 [238-357]
6-11	440 mg/m2	10	425 [206-564]
12-17	329 mg/m2	27	611 [262-828]

AUCss from Cycle 1 Day 7 were excluded from calculation of the median AUCss. AUCss is the indivually predicted AUC at steady state. Source: Table 2 in Attachment PK model summary, diagnostics and extended results in Clinical Study report 54179060LYM3003

SmPC information

Currently, the Imbruvica SmPC states the following regarding paediatric use:

Section 5.2:

Paediatric population

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

MAH conclusion

Based on the results of the pooled analysis (Part 1 and Part 2), the dosing regimens of 329 mg/m2 for children 12 years or older and 440 mg/m2/day for children below 12 years can be expected to provide comparable exposure as seen in adults.

2.3.4. Discussion on clinical aspects

In Study LYM300, ibrutinib in combination with RICE or RVICI demonstrated no additional efficacy in a two part Phase 3 including a PK-run in phase and a RCT in paediatric subjects with and young adult patients with relapsed or refractory mature B-cell non-Hodgkin lymphoma (NHL). At the interim analysis the IDMC recommended stopping enrolment as the futility boundary for early stopping was reached.

Clinical pharmacology

The MAH concludes that regimens of 329 mg/m2 for children 12 years or older and 440 mg/m2/day for children below 12 years can be expected to provide comparable exposure as seen in adults. Overall, the agency agrees that the presented PopPK analysis indicates this. However, limitations have been identified and relevant information is missing which would be needed to support the conclusion by the MAH.

Overall, the database is considered appropriate to allow support that exposures are comparable between children and adults, at the proposed ibrutinib dosing regimens. Of note, the youngest subject included in the study appears to be 3 years old (i.e. no 1 to 2 year old subjects were included). The PopPK analysis appears to be overall reasonable, however, not all relevant information was available upon the assessment to conclude the validity of the analysis. For instance, how body size was incorporated in the (e.g. using allometric scaling with fixed or estimated coefficients) is currently not clear. The report for the adult PopPK model from 2015 (report number EDMS-ERI-112451527) and the final model output for the final paediatric PopPK model were not found.

No relevant model misspecifications were evident based on the model diagnostics provided in Attachment PK model summary, diagnostics and extended results in Clinical Study report 54179060LYM3003. The individual plots (included in PK model summary, diagnostics and extended results in Clinical Study report 54179060LYM3003) is considered relevant, however, the typical model predictions (sometimes referred to as PRED within NONMEM) which can be considered an important part of this type of diagnostic plots, were not included. In addition, no visual predictive check (VPC) was provided, which is considered an important diagnostic plot for the analysis.

Comparing exposure based on individually predicted parameters (such as AUCss) is considered an acceptable approach. A clear justification for why the acceptance limits were set to 250-1500 ng.h/mL was not identified by the assessor. Summary of the relevant individual parameters and stratified on age groups were provided as part of PK model summary, diagnostics and extended results in Clinical Study report 54179060LYM3003.

In conclusion, the PopPK analysis and exposure comparison to adults appears to be overall reasonable. However, important aspects (final model output, adult PopPK report [report number EDMS-ERI-112451527], lines for typical model predictions [PRED] in the individual plots and VPCs) are missing from the provided documentation.

Efficacy and safety

In total 35 patients were randomised to ibrutinib + RICE/RVICI and 16 to RICE/RVICI. 22 (62.9%) subjects were reported with an EFS event in the ibrutinib + RICE/RVICI group compared to 12 (75.0%) subjects in the RICE/RVICI rendering a HR of 0.902 (90% CI 0.499, 1.629, p (1-sided) 0.3869). There was also no difference in ORR, DoR, OS or proportion of patients proceeding to SCT.

The safety results of Study LYM3003 were consistent with the known safety profile of ibrutinib and RICE/RVICI. Common TEAEs reported for patients treated with ibrutinib + RICE/RVICI were anaemia, vomiting, febrile neutropenia, thrombocytopenia, headache, neutropenia, pyrexia, abdominal pain, platelet count decreased, hypokalaemia and neutrophil count decreased. Four patients in the ibrutinib + RICE/RVICI group died due to AEs. 1 subject each with TEAEs of septic shock, pulmonary haemorrhage, pneumonia, and multiple organ dysfunction syndrome.

The safety data from the study does not give raise to new safety concerns.

3. Overall conclusion and recommendation

☒ **Fulfilled:**

In view of the available data regarding ibrutinib in combination with RICE or RVICI in paediatric patients with relapsed or refractory mature B-cell non-Hodgkin lymphoma the MAH should either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. This should be provided without any delay and ***no later than 60 days after the receipt*** of these conclusions.

- Section 4.2 should be updated by replacing the text 'No data are available' with a reference to section 5.1
- Section 5.1 of the SmPC should be updated with a brief description of the results of MS100070-0306 (number of patients, the diagnoses and that no responses were seen)
- Section 5.2 subsection 'Paediatric population' should be updated with information on comparability in PK exposure between children and adults. Note that additional information related to the PopPK analysis is required to support the MAH conclusion of comparable PK exposure in children vs adults, and this should be included in case a variation is submitted.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Clinical studies

Product Name: Imbruvica Active substance: Ibrutinib

Study title	Study number	Date of completion	Date of submission of final study report
Multi-Centre, randomized, controlled study to evaluate safety and efficacy of ibrutinib as add-on in paediatric patients with newly-diagnosed mature B cell lymphoma	PIP Study 4; PCI-32765PEDXXXX	Deleted in procedure EMEA-001397-PIP03-14-M05	n/a
Physiologically Based Pharmacokinetic (PBPK) Simulations of JNJ-54179060 (PCI-32765 or ibrutinib) in Paediatric Population	PIP Study 5; FK10755	22 December 2017	3 January 2018
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	PIP Study 3; 54179060LYM3003 (SPARKLE)	26 October 2021	9 December 2021