CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210563Orig1s000
210563Orig2s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review	
NDA	NDA 210563 (SDN 001, eCTD 001)
Type/Category	Original submission
Submission Date	09/12/2017
PDUFA	02/28/2018
Brand Name	IMBRUVICA®
Generic name	Ibrutinib
Formulation and Strength	Tablets 140 mg, 280 mg, 420 mg and 560 mg
Route of Administration	Oral
Applicant	Pharmacyclics LLC
Approved Indications	Treatment of patients with: • Mantle cell lymphoma (MCL) who have received at least one prior therapy; • Chronic lymphocytic leukemia (CLL)/Small lymphocytic lymphoma (SLL); • CLL/SLL with 17p deletion; • Waldenström's macroglobulinemia (WM); • Marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy. • Chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy
Approved Dosing Regimen	MCL and MZL: 560 mg taken orally once daily CLL/SLL, WM and cGVHD: 420 mg taken orally once daily
OCP Divisions	Division of Clinical Pharmacology V (DCPV)
OND Division	Division of Hematology Products (DHP)
OCP Primary Reviewer	Liang Li, Ph.D.
OCP Team Leader	Olanrewaju Okusanya, Pharm.D.; M.S.

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1. EXECUTIVE SUMMARY

Ibrutinib (IMBRUVICA®) is approved for the treatment of several B-cell malignancies and chronic graft versus host disease (cGVHD). In the current submission, the Applicant seeks the approval of a new tablet formulation at dose strengths of 140 mg, 280 mg, 420 mg, and 560 mg.

The Applicant submitted the study results of a relative bioavailability (BA) trial, a food effect trial, and two pivotal bioequivalence (BE) trials to support the to-be-marketed tablet formulation in 4 different strengths of 140 mg, 280 mg, 420 mg, and 560 mg for ibrutinib.

The review primarily focuses on:

1) the bioequivalence between ibrutinib to-be-marketed tablets and current available capsules;
2) food effect on to-be-marketed tablets.

The AUC of the to-be-marketed tablet was BE to that of the reference capsule at 140 mg and 560 mg dose strength. Although the C_{max} of the to-be-marketed tablet was 10.2% lower at 140 mg and 27.7% lower at 560 mg as compared to the reference capsule formulation, such difference in C_{max} is not expected to translate clinically meaningful impact on the effectiveness of ibrutinib. The food effect was generally comparable between tablet and capsule formulations. Overall, no clinically meaningful difference is expected between the reference capsule formulation and the to-be-marketed tablet formulation of ibrutinib.

1.1. Recommendations

The Office of Clinical Pharmacology has reviewed the information submitted. The to-be-marketed tablet formulation at dose strengths of 140 mg, 280 mg, 420 mg, and 560 mg is considered approvable from a clinical pharmacology perspective. Dosing guidelines regarding food timings for ibrutinib tablets should follow the same recommendation for the ibrutinib capsules in the current labeling, i.e., there are no restrictions for food consumption when taking ibrutinib tablets or capsules.

1.2. Post-Marketing Requirements and Commitments

There are no post-marketing requirements or commitments.

Signatures:

Liang Li, Ph.D.	**Olanrewaju Okusanya, Pharm.D.; M.S.**
Clinical Pharmacology Reviewer	Acting Clinical Pharmacology Team Leader
Division of Clinical Pharmacology V	Division of Clinical Pharmacology V

Cc: DHP: RPM – K Miller; MO – M Merino; MTL – T Wroblewski

DCPV: DDD – B Booth; DD – NA Rahman

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1. Pharmacology and Clinical Pharmacokinetics

Ibrutinib is a small molecule inhibitor of Bruton's tyrosine kinase (BTK). IMBRUVICA® (ibrutinib) has been approved for the treatment of patients with MCL or MZL at a recommended dose of 560 mg once daily (QD) and patients with CLL/SLL, WM or cGVHD at a recommended dose of 420 mg QD. For brevity, only information related to the current submission is summarized in **Table 1**.

Table 1: Summary of the Geometric Mean Ratios and 90% Confidence Intervals of the Ibrutinib PK Parameters from a Food Effect Trial and Two Pivotal Bioequivalence Trials.

Test vs. Reference formulaton	GMR (90% CI)		
	C_{max}	AUC_{last}	AUC_{inf}
1 x 560-mg tablet vs. 4 x 140-mg capsules	72.3% (67.6%, 77.3%)	97.9% (94.3%, 101.7%)	95.7% (91.5%, 100.0%)
1 x 140-mg tablet vs. 1 x 140-mg capsule	89.8% (84.2%, 95.7%)	107.2% (103.8%, 110.8%)	106.8% (103.4%, 110.4%)
1 x 560-mg tablet under fed condition vs. fasted condition	447.8% (369.5%, 542.6%)	197.2% (172.6%, 225.4%)	188.4% (164.5%, 215.7%)

2.2. Dosing and Therapeutic Individualization

2.2.1. General dosing

The recommended ibrutinib dose is 560 mg for the treatment of patients with MCL or MZL, and 420 mg for the treatment of patients with CLL/SLL, WM or cGVHD administered orally once daily as a monotherapy with or without food. No new dosing recommendations are provided for this new formulation.

2.2.2. Therapeutic individualization

There is no additional data to support therapeutic individualization in this NDA submission.

2.3. Outstanding Issues

There are no outstanding issues at this time.

2.4. Summary of Labeling Recommendations

The ibrutinib tablet formulations at four strengths of 140 mg, 280 mg, 420 mg and 560 mg have been updated in the labeling.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1.Overview of the Product and Regulatory Background

Ibrutinib received FDA approvals for the following indications:

- 11/13/2013: Accelerated approval for the treatment of patients with MCL who have received at least one prior therapy;
- 02/12/2014: Accelerated approval for the treatment of patients with CLL who have received at least one prior therapy;
- 07/28/2014: 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;
- 01/29/2017: Full approval for the treatment of patients with WM;
- 03/04/2016: Full approval for the treatment of patients with CLL;
- 05/06/2016: Full approval for the treatment of patients with CLL/SLL, and dosing of ibrutinib with bendamustine and rituximab in patients with CLL/SLL; full approval for the treatment of patients with CLL/SLL with 17p deletion;
- 01/18/2017: Accelerated approval for the treatment of patients with MZL who require systemic therapy and have received at least one prior anti-CD20-based therapy;
- 08/02/2017: Full approval for the treatment of patients with cGVHD.

In this new NDA submission, the Applicant submitted results of the relative BA trial, the food effect trial, and two pivotal BE trials to support the to-be-marketed tablet formulation in 4 different strengths of 140 mg, 280 mg, 420 mg, and 560 mg for ibrutinib:

- Trial 54179060CLL1018 (hereafter referred to as CLL1018): A Single-Dose, Open-Label, Randomized, 4-way Crossover Study to Assess the Relative Bioavailability of Four Ibrutinib Tablet Formulations in Healthy Adult Subjects Compared to the Imbruvica Capsule
- Trial 54179060CLL1019 (hereafter referred to as CLL1019): Open-Label, Randomized, 2-way-Crossover Study to Determine the Effect of Food on the Pharmacokinetics of Ibrutinib Administered as 560-mg Tablet
- Trial 54179060CLL1021 (hereafter referred to as CLL1021): A Single-Dose, Open-Label, Randomized, Replicate Crossover Study in Healthy Adult Subjects to Assess the Bioequivalence of an Ibrutinib 560-mg Tablet Compared to Four IMBRUVICA 140 mg Capsules
- Trial 54179060CLL1022 (hereafter referred to as CLL1022): A Single-Dose, Open-Label, Randomized, Replicate Crossover Study in Healthy Adult Subjects to Assess the Bioequivalence of an Ibrutinib 140-mg Tablet Compared to the IMBRUVICA 140-mg Capsule

3.2.General Pharmacological and Pharmacokinetic Characteristics

Please refer to the IMBRUVICA® labeling and the clinical pharmacology review in the original (DARRTS ID: 3400137) and supplement (DARRTS ID: 3529464, 3688592, 3887396, 3887396, 3948695, 4028014 and 4123064) NDA 205552 submissions regarding the detailed PK characteristics of ibrutinib.

3.3.Clinical Pharmacology Questions

For brevity, only questions related to the current submission are addressed below. For additional information, please refer to the clinical pharmacology reviews for the original and supplement NDA205552 submissions.

3.3.1. *Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?*

BE assessment

The to-be-marketed formulation will be a new film-coated immediate-release tablet dosage form of ibrutinib in four strengths (140 mg, 280 mg, 420 mg and 560 mg) manufactured jointly by Catalent CTS, LLC and AbbVie Inc. The manufacturing process for the to-be-marketed formulation was developed at (b) (4), and transferred to the commercial manufacturing site Catalent, Kansas City, MO and later from Catalent to the second commercial site AbbVie, North Chicago, IL. Formulations from Catalent were used in the two BE trials. The Applicant claimed that process development studies performed at Catalent and AbbVie have demonstrated that the manufacturing process is suitable for the manufacture of commercial batches using the established manufacturing process parameters.

In the relative BA Trial CLL1018, four different experimental 560-mg tablet formulations (b) (4) (b) (4) were selected for evaluation against the commercial 140-mg capsule in healthy subjects under fasted conditions at a single dose of 560 mg (**Table 2**). Results from the trial demonstrated that exposures for Formulation D were closest to the reference capsule formulation as evidenced by a GMR (90% CI) of the test to the reference of 91.8% (74.6%, 112.8%) for C_{max}, 106.6% (94.4%, 120.5%) for AUC_{last}, and 110.2% (94.9%, 128.0%) for $AUC_{0\text{-}inf}$. As such, Formulation D was selected for evaluation in the food effect trial and two pivotal BE trials in healthy subjects.

Table 2: Identity of Study Ibrutinib Formulations.

Test Treatment	Formulation	Process	Strength	Lot Number
A	(b) (4)	Hard gelatin capsule (b) (4) (b) (4)	140 mg	L0409196A
B		Tablet: (b) (4)	560 mg	HG-15G049
C		Tablet	560 mg	HG-15G047
D		Tablet	560 mg	1507071A
E		Tablet	560 mg	1507072A
(b) (4)				

Source: Table 1 from Clinical Study Report 54179060CLL1018.

Two formal BE trials CLL1021 and CLL1022 were performed to compare the PK of the to-be-marketed tablet to the reference capsule at the lowest strength of 140 mg and the highest strength of 560 mg in healthy subjects under fasted conditions.

In Trial CLL1021, the GMR (90% CI) of one 560-mg to-be-marketed tablet (test) vs. four 140-mg ibrutinib capsules (reference) was 97.9% (94.3% - 102%) for AUC_{last} and 95.7% (91.5% - 100%) for $AUC_{0\text{-}inf}$ (**Table 3**). The 90% CIs of the GMR for both AUC_{last} and AUC_{inf} fell completely within the 80.0% to 125.0% BE limits. However, the GMR (90% CI) between two treatments for C_{max} was 72.3% (67.6% - 77.3%), with the 90% CI of the GMR falling well below the 80.0% BE lower boundary limit.

Table 3: Summary of the Statistical Analysis of the Ibrutinib PK Parameters After Single Administration as Four 140-mg Oral Capsule of IMBRUVICA® or as one Single 560-mg Oral Tablet Under Fasted Conditions.

Pharmacokinetic Parameter[d]	Geometric mean		Geometric Mean Ratio, (%)	90% CI[c], (%)	Intra-subject CV, (%)	
	Treatment A 4 x 140-mg oral IMBRUVICA® capsules (reference)	Treatment B 1 x 560-mg oral tablet (test)			Treatment A (reference)	Treatment B (test)
N[a]	101[b]	102[b]				
C_{max} (ng/mL)	40.9	29.5	72.26	67.60 - 77.25	31.9	42.1
AUC_{last} (ng.h/mL)	330	323	97.93	94.27 - 101.73	21.7	23.4
AUC_{∞} (ng.h/mL)	359	343	95.65	91.50 - 100.00	22.4	22.6

Abbreviations: AUClast = area under the concentration-time curve (AUC) from time 0 to the time of the last measurable (non-below quantification limit [non-BQL] concentration), calculated by linear-linear trapezoidal summation; AUC∞ = AUC from time 0 to infinity, calculated as AUClast + Clast/λz, where Clast is the last observed measurable (non BQL) concentration; Cmax = maximum observed analyte concentration; N = number of subjects; CI = confidence interval; CV = coefficient of variation.

a: Number of subjects who had at least 1 observation

b: N = 86 for AUC∞ (reference); N = 87 for AUC∞ (test)

c: 90% confidence intervals

d: PK parameters are the arithmetic mean of the 2 obtained observations

Source: Applicant's Table 4 from Clinical Study Report 54179060CLL1021.

In Trial CLL1022, the GMR (90% CI) of 140-mg to-be-marketed tablet (test) vs. 140-mg ibrutinib capsule (reference) was 89.8% (84.2% - 95.6%) for C_{max}, 107.2% (103.8% - 110.8%) for AUC_{last} and 106.8% (103.4% - 110.4%) for $AUC_{0\text{-}inf}$ (**Table 4**). The 90% CIs of the GMR fell completely within the 80.0% to 125.0% BE limits.

Table 4: Summary of the Statistical Analysis of the Ibrutinib PK Parameters After Single Administration as a 140-mg Oral Capsule of IMBRUVICA® or as a 140-mg Oral Tablet Under Fasted Conditions.

Pharmacokinetic Parameter[d]	Geometric mean		Geometric Mean Ratio, (%)	90% CI[c], (%)	Intra-subject CV, (%)	
	Treatment A 140-mg oral IMBRUVICA® capsule (reference)	Treatment B 140-mg oral tablet (test)			Treatment A (reference)	Treatment B (test)
N[a]	102[b]	102				
C_{max} (ng/mL)	12.8	11.5	89.76	84.22 – 95.66	35.2	38.7
AUC_{last} (ng.h/mL)	93.2	99.9	107.20	103.76 – 110.75	18.9	21.0
AUC_{∞} (ng.h/mL)	96.8	103	106.84	103.40 – 110.40	18.0	20.6

Abbreviations: AUC_{last} = area under the plasma concentration-time curve (AUC) from time 0 to the time of the last measurable (non-below quantification limit [non-BQL] concentration), calculated by linear-linear trapezoidal summation; AUC_{∞} = AUC from time 0 to infinity, calculated as $AUC_{last} + C_{last}/\lambda_z$, where C_{last} is the last observed measurable (non BQL) concentration; C_{max} = maximum observed analyte concentration; N = number of subjects; CI = confidence interval; CV = coefficient of variation.

[a] Number of subjects who had at least 1 observation

[b] N =101 for AUC_{∞}

[c] 90% confidence intervals

[d] PK parameters are the arithmetic mean of the 2 obtained observations

Source: Applicant's Table 4 from Clinical Study Report 54179060CLL1022.

In both Trial CLL1021 and CLL1022, ibrutinib 140-mg and 560-mg tablets were associated with an acceptable safety profile after single dose administration in healthy subjects. There were no deaths or serious adverse events reported in both trials. The observed safety findings in the trials were consistent with the known safety profile of ibrutinib under NDA 205552 and no new or unanticipated safety concerns were identified.

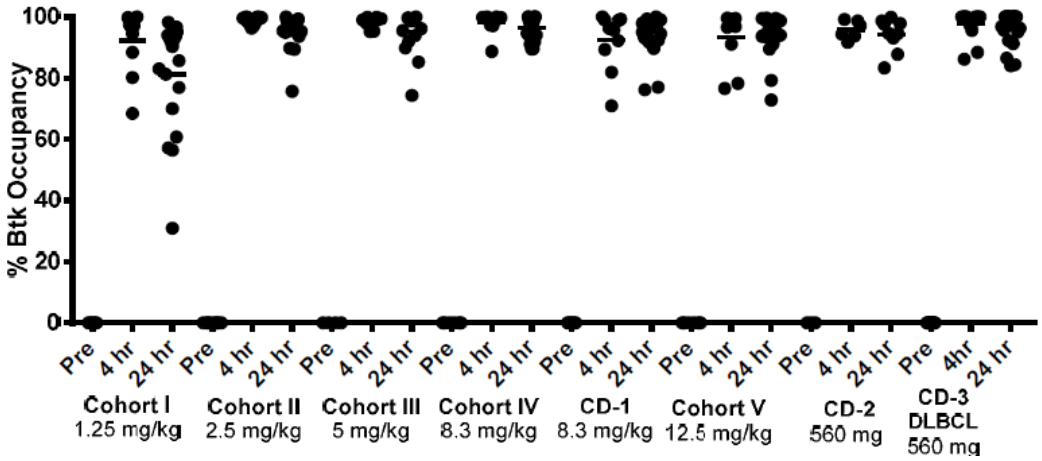
Clinical Relevance of C_{max}

Although a mean 27.7% lower C_{max} was observed for the 560-mg tablet compared to four 140 mg capsules in Trial CLL1021, this difference in C_{max} is not expected to translate clinically meaningful impact on the effectiveness of ibrutinib because of the following reasons:

- Maximum BTK occupancy achieved at doses 2.5 mg/kg and above

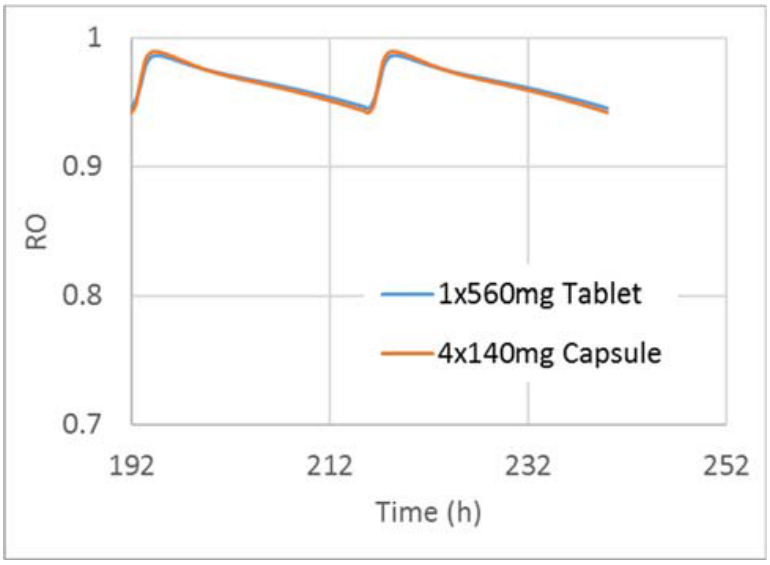
The dose-response relationship for BTK occupancy (**Figure 1**) in the Phase 1 dose escalation Trial PCYC-04753 showed that maximum BTK occupancy was achieved at doses of ≥ 2.5 mg/kg (≥ 175 mg for patients with an average weight of 70 kg). In addition, as shown in **Figure 2,** the predicted steady-state BTK receptor occupancy versus time profiles for the 560-mg to-be-marketed tablet overlapped with that for the 560 mg (4 x 140-mg) capsule, with nearly identical BTK receptor occupancy of 96% for the tablet formulation and 97% for the capsule formulation at the peak concentrations.

Figure 1: BTK Occupancy of > 90% at Doses ≥ 2.5 mg/kg in Trial 04753.



Source: Applicant's Figure 10 from Clinical Study Report PCYC-04753.

Figure 2: Predicted BTK Occupancy at Steady State after Administration of one 560-mg to-be-marketed Tablet and Four 140-mg Capsules Once Daily.



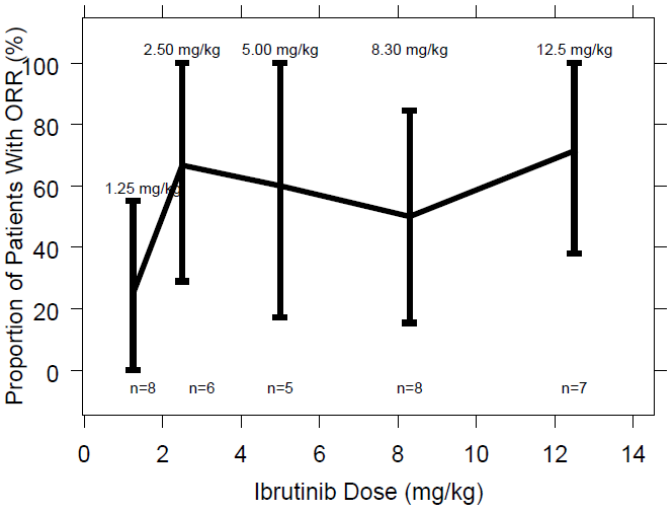
Source: Applicant's Figure 2 from Summary of Clinical Pharmacology Studies.

- Flat dose- and exposure-response relationship for clinical response at doses 2.5 mg/kg and above

The flat dose-response relationship for clinical primary efficacy endpoint, overall response rate (ORR), was achieved at doses of ≥ 2.5 mg/kg (≥ 175 mg for patients with an average weight of 70 kg) in the Phase 1 dose escalation Trial PCYC-04753 (**Figure 3**). The exposure-response relationships between ibrutinib C_{max} and ORR were also found flat across 4 quartiles ranging from lowest to highest C_{max} in patients with CLL at the recommended dose of 420 mg once daily (**Figure 4**) and in patients with MCL at the recommended

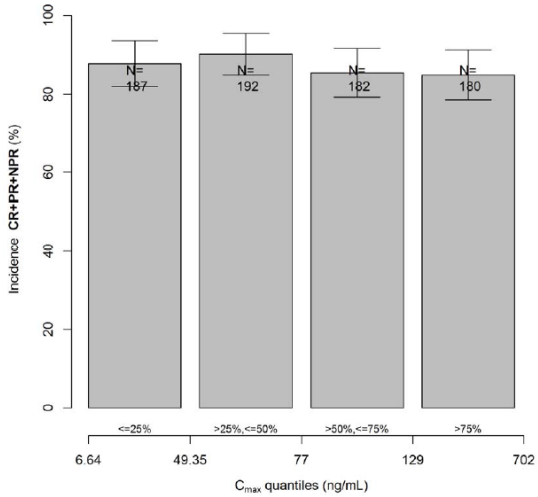
dose of 560 mg once daily (**Figure 5**). This suggests that small differences in C_{max} between the two formulations are not expected to have a significant impact on efficacy.

Figure 3: Dose-response Relationship for ORR in Phase 1 Dose Escalation Trial PCYC-04753.



Source: Reviewer's Figure 4 from Clinical Pharmacology Review for Original NDA 205552 (Reference ID: 3400137).

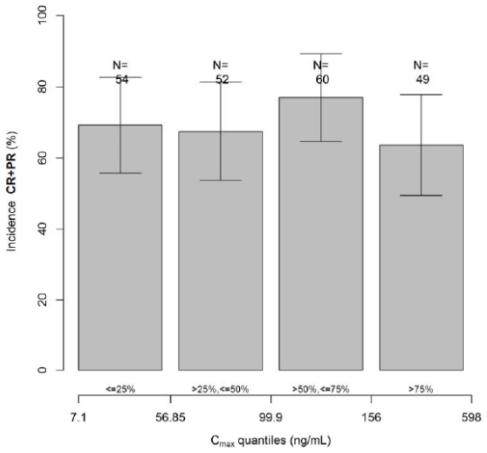
Figure 4: Bar Chart (±99% CIs) of Overall Response Rate in Patients with CLL (Trials 1102, 1112, 1115, 1117, CLL3001, 04753 in NDA205552) Classified by Ibrutinib $C_{max,ss}$ Quartile.



CLL=chronic lymphocytic leukemia; CI=confidence interval; $C_{max,ss}$=maximal ibrutinib concentration at steady-state; CR=complete response (includes CR with incomplete blood count recovery); N=number of subjects with overall response rate; NPR=nodal partial response; PR=partial response (includes PR with lymphocytosis). Note: The total number of subjects treated with ibrutinib with pharmacokinetic and overall response rate data across included studies was 820.

Source: Applicant's Figure 4 from Summary of Clinical Pharmacology Studies.

Figure 5: Bar Chart (±99% CIs) of Overall Response Rate in Patients with CLL (Trials 1104, MCL2001, MCL3001, 04753 in NDA205552) Classified by Ibrutinib $C_{max,ss}$ Quartile.



CI=confidence interval; $C_{max,ss}$=maximal ibrutinib concentration at steady-state; CR=complete response; MCL=mantle cell lymphoma; N=number of subjects with overall response rate; PR=partial response.
Note: The total number of subjects treated with ibrutinib with pharmacokinetic and overall response rate data across included studies was 300.

Source: Applicant's Figure 5 from Summary of Clinical Pharmacology Studies.

- Comparable C_{max} for 560-mg tablet and four 140-mg capsules under fed conditions

Although ibrutinib is recommended taken regardless of food, it is unlikely administered repeatedly under fully fasted conditions (fasting overnight and until 4 hours after ibrutinib administration) in a real clinical setting. The food effect Trial, CLL1019, demonstrated that the effect of food was more pronounced on C_{max} for the tablet with the GMR of fed vs. fasted of 4.5 compared to the capsule with a GMR of 3.1 (**Section 3.3.2**). These differences in food effect between the tablet and capsule formulaton translate to a 2% difference in C_{max} under fed conditions between the 2 formulations based on the cross-study comparision of the food effect GMRs for C_{max} for tablet (Trial CLL1019) and for capsule (Trial CLL1001 under NDA 205552). As such, the difference in C_{max} observed between the tablet and capsule formulations when ibrutinib is given fasted is not expected when given with food.

- Comparable C_{trough} for 560-mg tablet vs. four 140-mg capsules

The GMR (90% CI) of trough concentrations (C_{trough}) for 560-mg tablet vs four 140-mg capsules after single dose administration in Trial CLL1021 was estimated to be 108.8% (101.7%, 116.2%). This indicates that the tablet formulation would produce comparable ibrutinib trough concentrations as the capsule formulation, and hence is expected to maintain a similar minimum BTK occupancy compared to the capsule formulation.

3.3.2. *Are there clinically relevant food-drug interactions for the to-be-marketed formulation and what is the appropriate management strategy?*

Yes. high-fat, high-caloric breakfast had statistically significant interaction with the to-be-marketed 560-mg tablet based on the assessment in Trial CLL1019. As shown in **Table 5,** administration of a single dose

of 560-mg tablet with a high-fat, high-caloric meal resulted in 4.5-fold higher in C_{max}, 1.9-fold to 2.0-fold higher in AUC compared to administration under fasted condition. This fold change in exposure is generally consistent with the 2-fold to 4-fold higher C_{max} and 2-fold higher AUC observed with food with the capsule formulation in Trial CLL1001 under NDA 205552.

Table 5: Summary of the Statistical Analysis of the Pharmacokinetic Parameters of Ibrutinib After Single Administration of Ibrutinib as a Single 560-mg Oral Tablet of Under Fasted and Fed Conditions.

Pharmacokinetic Parameter	Geometric mean		Geometric Mean Ratio, %	90% CI[b], %	Intra-subject CV, %
	Treatment A 1 x 560-mg oral tablet of ibrutinib Fasted (reference)	Treatment B 1 x 560-mg oral tablet of ibrutinib Fed (test)			
N	24[a]	23			
C_{max} (ng/mL)	33.6	151	447.78	(369.54 – 542.59)	39.39
AUC_{last} (ng.h/mL)	313	617	197.24	(172.63 – 225.37)	26.77
AUC_{∞} (ng.h/mL)	331	623	188.37	(164.53 – 215.67)	26.51

[a] N=23 for AUC_{∞}
[b] 90% confidence intervals

Source: Applicant's Table 6 from Clinical Study Report CLL1019.

The safety results from Trial CLL1019 confirmed that ibrutinib 560-mg tablet under fed condition had an acceptable tolerability profile in healthy subjects. No new or unanticipated safety signals were identified. Therefore, dosing guidelines regarding food timings for ibrutinib tablet formulations should follow the same recommendation for the capsule formulation in the current labeling, i.e., there are no restrictions for food consumption when taking ibrutinib tablets or capsules.

4. APPENDICES

4.1.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 6** is a summary of bioanalytical report and corresponding bioanalytical method performance for Trial CLL1018, CLL1019, CLL1021 and CLL1022.

Table 6: Summary of Bioanalytical Methods for Ibrutinib.

Trial No.	Matrix	Bioanalytical Report	Bioanalytical method performance
54179060CLL1018 54179060CLL1019 54179060CLL1021 54179060CLL1022	Plasma	JNJ-R5932 (b) (4)	Method BTM-2201-R0 Lower limit of quantification: 0.5 ng/mL Calibrated Range: 0.5 to 250 ng/mL Intra-assay Precision (%CV): 4.1% to 5.8% Intra-assay Accuracy (% Diff): -11.2% to -0.9% Bench Top Stability: 6 hours at RT Long-term Stability: 328 days at -20 °C and -70 °C Free thaw stability: 3 freeze (-70 °C)/thaw (ice water bath or room temperature) cycles

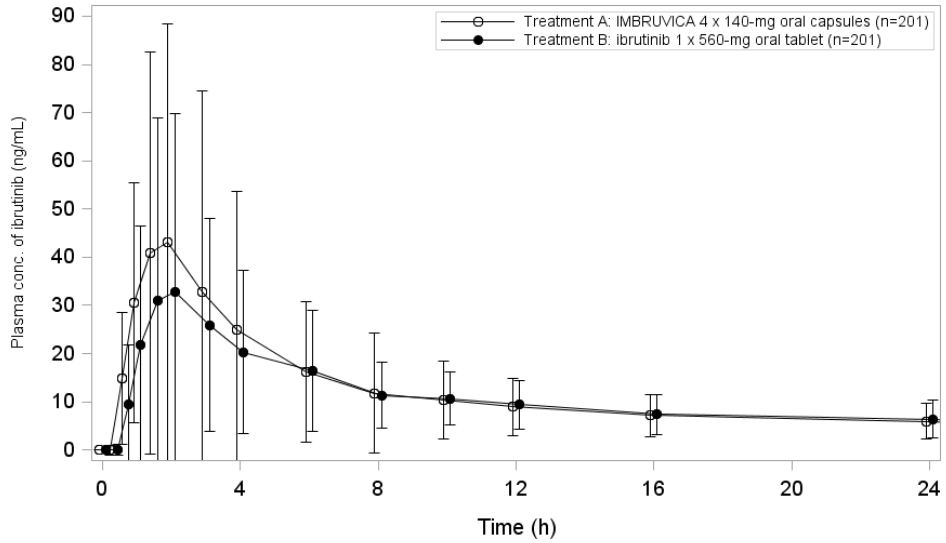
4.2.Clinical PK and/or PD Assessments

The current submission provided PK data of ibrutinib in healthy subjects after single administration of ibrutinib as four 140-mg capsules or as one single 560-mg to-be-marketed tablet under fasted condition in Trial 1021, as a 140-mg capsules or as a 140-mg to-be-marketed tablet under fasted condition in Trial 1022, and as a single 560-mg to-be-marketed tablet under fasted and fed conditions.

4.2.1. Trial 1021

The mean plasma concentration-time profiles of ibrutinib for both treatments in Trial 1021 are presented in **Figure 6**, and the summary list of key PK parameters is presented in **Table 7**. Compared to the IMBRUVICA® capsules (reference), oral administration of the 560-mg to-be-marketed tablet (test) resulted in lower peak plasma concentrations. Mean C_{max} values were 38.3 ng/mL for the test formulation and 51.9 ng/mL for the reference formulation. Mean AUC_{last}, AUC_{inf}, apparent terminal half-life ($t_{1/2}$), and median t_{max} values were comparable for both treatments.

Figure 6: Mean Plasma Concentration-Time Profiles of Ibrutinib After Single Administration of Ibrutinib as Four 140-mg Capsules of IMBRUVICA® or as one Single 560-mg to-be-marketed Tablet Under Fasted Conditions.



Source: Applicant's Figure 2 from Clinical Study Report CLL1021.

Table 7: Pharmacokinetic Results of Ibrutinib After Single Administration of Ibrutinib as Four 140-mg Capsules of IMBRUVICA® or as One Single 560-mg Oral Tablet Under Fasted Condition.

Pharmacokinetics of ibrutinib (mean±SD, t_{max}: median (range)	**Treatment A** **4 x 140-mg oral IMBRUVICA® capsules (reference)**	**Treatment B** **1 x 560-mg oral tablet (test)**
n	201[a]	201[b]
C_{max} (ng/mL)	51.9±46.8	38.3±38.5
t_{max} (h)	2.00 (0.68 – 10.00)	2.00 (0.67 – 30.00)
AUC_{last} (ng.h/mL)	381±244	358±190
AUC_{∞} (ng.h/mL)	432±261	395±202
$t_{1/2term}$ (h)	7.5±3.9	7.5±4.0

Abbreviations: AUClast = area under the concentration-time curve (AUC) from time 0 to the time of the last measurable (non-below quantification limit [non-BQL] concentration), calculated by linear-linear trapezoidal summation; AUC∞ = AUC from time 0 to infinity, calculated as AUClast + Clast/λz, where Clast is the last observed measurable (non BQL) concentration; Cmax = maximum observed analyte concentration; n = number of individual profiles, with 100 and 99 subjects contributing 2 profiles for Treatments A and B, respectively; SD = standard deviation; tmax = the actual sampling time to reach the maximum observed analyte concentration; t1/2term = apparent terminal elimination half-life, defined as 0.693/λz.

a: n=152 for AUC∞ and n=155 for t1/2term;

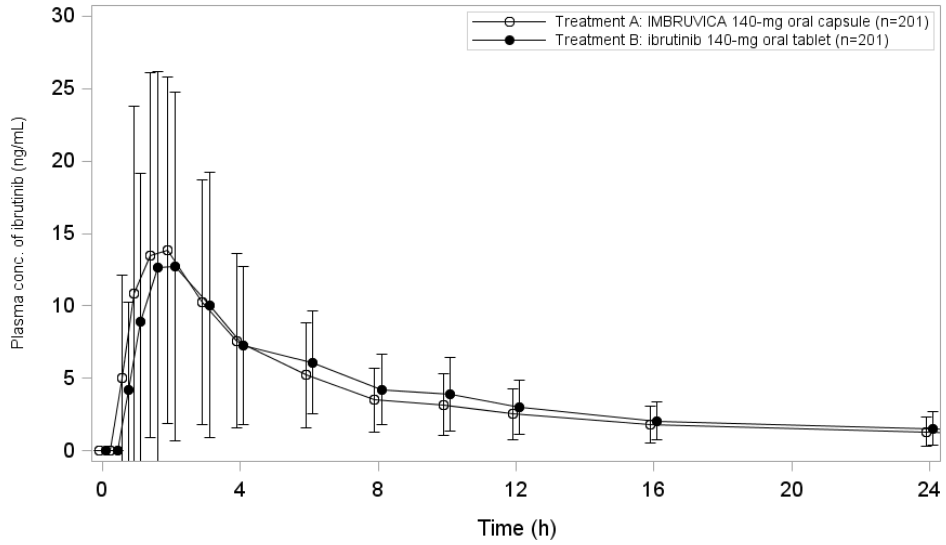
b: n= 200 for tmax, n=152 for AUC∞ and n=154 for t1/2term

Source: Applicant's Table 3 from Clinical Study Report CLL1021.

4.2.2. Trial 1022

The mean plasma concentration-time profiles of ibrutinib for both treatments in Trial 1022 are presented in **Figure 7**. The ibrutinib plasma concentrations declined in parallel for both treatments. The summary list of key PK parameters is presented in **Table 8.** Oral administration of the 140-mg to-be-marketed tablet (test) resulted in comparable mean C_{max}, AUC_{last}, AUC_{inf}, apparent terminal half-life ($t_{1/2}$), and median t_{max} values compared to the IMBRUVICA 140-mg capsule (reference).

Figure 7: Mean Plasma Concentration-Time Profiles of Ibrutinib After Single Administration of Ibrutinib as a 140-mg Capsules of IMBRUVICA® or as a 140-mg to-be-marketed Tablet Under Fasted Conditions.



Source: Applicant's Figure 2 from Clinical Study Report CLL1022.

Table 8: Pharmacokinetic Results of Ibrutinib After Single Administration of Ibrutinib as a 140-mg Capsules of IMBRUVICA® or as a 140-mg Oral Tablet Under Fasted Condition.

Pharmacokinetics of ibrutinib (mean±SD, t_{max} median (range)	**Treatment A** **4 x 140-mg oral IMBRUVICA® capsules (reference)**	**Treatment B** **1 x 560-mg oral tablet (test)**
n	201[a]	201[b]
C_{max} (ng/mL)	51.9±46.8	38.3±38.5
t_{max} (h)	2.00 (0.68 – 10.00)	2.00 (0.67 – 30.00)
AUC_{last} (ng.h/mL)	381±244	358±190
AUC_{∞} (ng.h/mL)	432±261	395±202
$t_{1/2term}$ (h)	7.5±3.9	7.5±4.0

Abbreviations: AUClast = area under the concentration-time curve (AUC) from time 0 to the time of the last measurable (non-below quantification limit [non-BQL] concentration), calculated by linear-linear trapezoidal summation; AUC∞ = AUC from time 0 to infinity, calculated as AUClast + Clast/λz, where Clast is the last observed measurable (non BQL) concentration; Cmax = maximum observed analyte concentration; n = number of individual profiles, with 100 and 99 subjects contributing 2 profiles for Treatments A and B, respectively; SD = standard deviation; tmax = the actual sampling time to reach the maximum observed analyte concentration; t1/2term = apparent terminal elimination half-life, defined as 0.693/λz.

a: n=152 for AUC∞ and n=155 for t1/2term;

b: n= 200 for tmax, n=152 for AUC∞ and n=154 for t1/2term

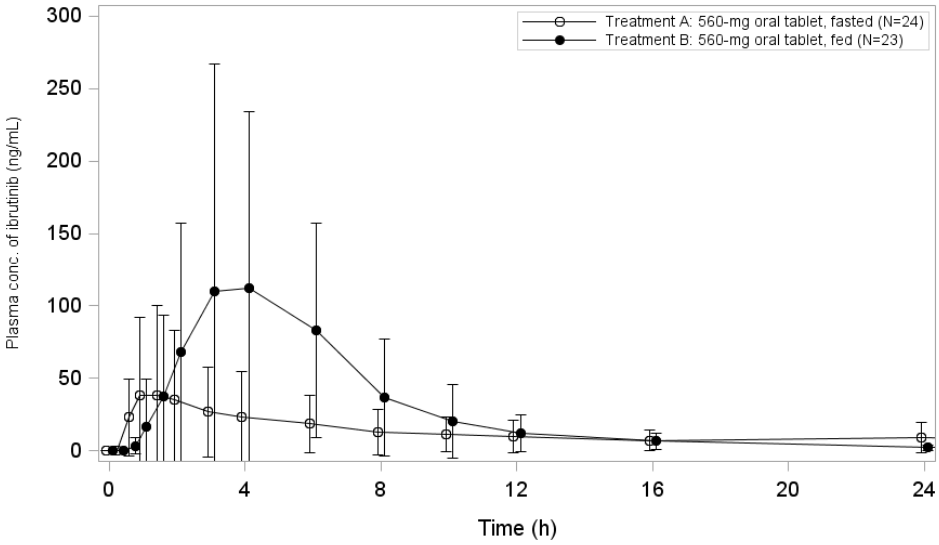
Source: Applicant's Table 3 from Clinical Study Report CLL1022.

4.2.3. Trial 1019

The mean plasma concentration-time profiles of ibrutinib for both treatments in Trial 1019 are presented in **Figure 8**. The mean PK profiles showed that the peak plasma concentration occurred later but was higher under fed compared to fasted condition, with maximum peak levels achieved at 4 and 1 hour, respectively. The summary list of key PK parameters is presented in **Table 9.** Compared to a single 560-mg to-be-marketed tablet under fasted condition, oral administration under fed conditions resulted in higher peak plasma concentrations (183 ng/mL vs. 49.0 ng/mL), longer median t_{max} (4 hr vs. 1.3 hr), higher

AUC_{last} (743 ng·h/mL vs. 426 ng·h/mL), higher AUC_{inf} (750 ng·h/mL vs. 460 ng·h/mL), and slightly shorter mean $t_{1/2}$ (6.4 hr vs. 8.4 hr).

Figure 8: Mean Plasma Concentration-Time Profiles of Ibrutinib After Single Administration of Ibrutinib as a Single 560-mg to-be-marketed Tablet Under Fasted and Fed Conditions.



Source: Applicant's Figure 1 from Clinical Study Report CLL1019.

Table 9: Pharmacokinetic Results of Ibrutinib After Single Administration of Ibrutinib as a Single 560-mg to-be-marketed Tablet Under Fasted and Fed Conditions.

Pharmacokinetics of ibrutinib (mean ± SD, t_{max}: median [range])	Treatment A 1 x 560-mg oral tablet of ibrutinib Fasted (reference)	Treatment B 1 x 560-mg oral tablet of ibrutinib Fed (test)
N	24[a]	23
C_{max} (ng/mL)	49.0 ± 60.6	183 ± 147
t_{max} (h)	1.25 (0.65 – 6.00)	4.00 (1.50 – 6.00)
AUC_{last} (ng.h/mL)	426 ± 456	743 ± 559
AUC_{∞} (ng.h/mL)	460 ± 470	750 ± 560
$t_{1/2term}$ (h)	8.4 ± 2.3	6.4 ± 2.2

[a] N=23 for AUC_{∞} and $t_{1/2term}$

Source: Applicant's Table 5 from Clinical Study Report CLL1019.

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/s/

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01/12/2018

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01/16/2018