CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205858Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology NDA Review	
Number	NDA 205-858 (\\CDSESUB1\evsprod\NDA205858\) NDA 206-545 (\\CDSESUB1\evsprod\NDA206545\)
Type/Category	NME, Original
Brand (generic) Name	Zydelig (idelalisib)
Proposed Indication	Refractory indolent non-Hodgkin lymphoma Relapsed chronic lymphocytic leukemia
Dosage Form	100 mg and 150 mg tablets
Route of Administration	Oral
Dosing Regimen and Strength	150 mg twice daily (BID)
Applicant	Gilead Sciences
OCP Division	DCPV
OND Division	DHP
Submission Dates	September 11, 2013 December 2, 2013

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1 EXECUTIVE SUMMARY

Idelalisib inhibits adenosine-5'-triphosphate (ATP) binding to the catalytic domain of phosphatidylinositide 3-kinase delta (PI3Kδ). The proposed indications are for the treatment of relapsed chronic lymphocytic leukemia (CLL, NDA 206-545) and refractory indolent mature B cell non-Hodgkin's lymphoma (NHL, NDA 205-858) at a dose of 150 mg BID without regard to food. The review addressed four key questions.

1. *Is the proposed starting dose of 150 mg BID reasonable?* Yes. The maximum administered dose (MAD) was 350 mg BID and no maximum tolerated dose (MTD) was identified in the dose escalation phase. No exposure-response (E-R) relationships were observed for the primary endpoints in the NHL (101-09) and CLL (312-0116) trials and for selected safety endpoints, except for diarrhea in the NHL population. In these trials most patients administered a dose of 150 mg BID achieved minimal concentrations (C_{tau}) greater than the in vitro EC_{90} for PI3Kδ inhibition. A lower starting dose is not recommended, because the E-R relationship with tumor size in the dose finding study (101-02) suggests that the lowest exposure is associated with less clinical activity. A higher starting dose is not recommended as idelalisib is associated with hepatotoxicity and higher exposures were associated with a greater incidence of diarrhea.
2. *What is an appropriate dose for patients taking acid-reducing agents (ARA)?* No dose adjustment is needed for patients taking ARA. Idelalisib demonstrates pH dependent solubility and the estimated gastric concentration exceeds the solubility at pH associated with ARA. A comparative analysis between patients with and without ARA in the NHL and CLL trials showed similar exposure and clinical efficacy. A higher incidence of rash and diarrhea was demonstrated, mainly in patients taking proton pump inhibitors (PPI). Overlapping toxicities are likely responsible for the increased incidence of adverse events.
3. *What is an appropriate dose for patients with baseline hepatic impairment?* No dose adjustment is needed for patients with baseline hepatic impairment. Mean exposure to idelalisib was increased up to 1.7-fold in subjects with baseline hepatic impairment, defined as AST or ALT or total bilirubin levels greater than the upper limits of normal (ULN) in an independent study. No difference in exposure or safety was observed for patients with baseline hepatic impairment in the NHL trial compared to patients without baseline hepatic impairment. Only one patient with baseline hepatic impairment was enrolled in the CLL trial. No E-R relationship was demonstrated for most safety endpoints in the NHL and CLL trials.
4. *What is an appropriate dose for patients taking a strong CYP3A inhibitor or inducer?*
    a. No dose adjustment is needed for patients taking strong CYP3A inhibitors with idelalisib. Although mean exposure to idelalisib was increased 1.8-fold in subjects taking a strong CYP3A inhibitor, no E-R relationship was demonstrated for most safety endpoints in the NHL and CLL trials.
    b. The coadministration of strong CYP3A inducers with idelalisib should be avoided. Mean exposure to idelalisib was decreased 75% in subjects taking a strong CYP3A inducer.

1.1 RECOMMENDATIONS

This NDA is acceptable from a clinical pharmacology perspective.

Decision	Acceptable to OCP?			Comment
Overall	Yes ×	No	NA	
Evidence of Effectiveness†	Yes ×	No	NA	
Proposed dose for general population	Yes ×	No	NA	
Proposed dose selection for others	Yes ×	No	NA	
Pivotal BE	Yes ×	No	NA	
Labeling	Yes ×	No	NA	

†This decision is from a clinical pharmacology perspective only. The overall safety and effectiveness determination is made by the Clinical reviewer.

1.2 PHASE 4 REQUIREMENTS AND COMMITMENTS

1.2.1 Post Marketing Requirements

None.

1.2.2 Post Marketing Commitments

None.

Signatures:

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1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Idelalisib inhibits ATP binding to the catalytic domain of PI3Kδ. The proposed indications are for the treatment of relapsed CLL (NDA 206-545) and refractory indolent B-cell NHL (NDA 205-858) at a dose of 150 mg BID without regard to food.

Gilead conducted an open-label trial to evaluate idelalisib as monotherapy in refractory NHL (101-09) and a randomized, double-blind, placebo-controlled trial to evaluate idelalisib in combination with rituximab in relapsed CLL (312-0116). No E-R relationships were observed for selected safety endpoints, except for grade ≥ 3 diarrhea in the NHL population or the primary efficacy endpoints in these trials. The proposed starting dose appears reasonable based on available safety and efficacy data.

Idelalisib exposure increased in a less than dose proportional manner with doses up to 350 mg in fasted conditions; it demonstrates dose-dependent absorption. The median T_{max} was observed at 1.5 h (0.5, 6 h) under fasted conditions. The administration of a single 400 mg dose of idelalisib with a high-fat meal resulted in a 1.4-fold increase in AUC. Idelalisib should be administered without regard to food. In the NHL and CLL trials, idelalisib was administered without regard to food.

Idelalisib is metabolized to its major metabolite GS-563117 via aldehyde oxidase (~70% contribution) and CYP3A4 (~30%). GS-563117 is inactive against PI3Kδ in vitro. Rifampin decreased idelalisib AUC by 75%. Idelalisib should not be coadministered with strong CYP3A inducers. Ketoconazole increased idelalisib AUC by 1.8-fold. No dose adjustment is recommended for patients taking strong CYP3A inhibitors with idelalisib.

Idelalisib or its metabolite inhibited CYP3A, CYP2C19, P-glycoprotein (P-gp), OATP1B1 and OATP1B3 in vitro. Idelalisib increased midazolam AUC by 5.4-fold; therefore, idelalisib should not be coadministered with sensitive CYP3A substrates. No changes in exposure to rosuvastatin (OAT1B1 and OATP1B3) or digoxin (P-gp) were observed. More diarrhea and rash were observed in patients taking idelalisib with proton pump inhibitors (PPI) (CYP2C19). Overlapping toxicities or a CYP-mediated drug interaction could be responsible for the additional adverse events.

Approximately 78% and 14% of the radioactivity was excreted in feces and urine, respectively following a single 150 mg oral dose of [^{14}C]-labeled idelalisib. GS-563117 accounted for most of the radioactivity in plasma (62%), urine (49%) and feces (44%). The AUC increased up to 1.7-fold in subjects with ALT or AST or bilirubin greater than the ULN compared to healthy subjects. No dose adjustment is the recommended for patients with baseline hepatic impairment. No difference in exposure or safety was found in patients with baseline hepatic impairment enrolled in the NHL trial. Only one patient with baseline hepatic impairment was enrolled in the CLL trial. No dose adjustment is needed for patients with creatinine clearance (CLcr) ≥ 15 mL/min, since the exposure was only increased 1.3-fold in patients with CLcr 15 to 29 mL/min.

2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

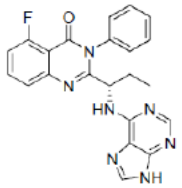
2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Idelalisib is a kinase inhibitor with a molecular weight of 415 grams per mole. The chemical structure is shown in **Figure 1**. (b) (4)

The drug product will be available as 100 mg and 150 mg tablets.

The molecular weight of the major metabolite GS-563117 is 431 grams per mole.

Figure 1. Chemical structure of idelalisib



Solubility

The pKa values are 1.6, 3.4, and 9.8. Idelalisib demonstrates pH dependent solubility; the solubility decreases with increasing pH (at ambient temperatures and at 37》C, **Table 1**). The solubility in stimulated gastric fluid (**Table 2**) is less than the clinical dose of 150 mg divided by 250 mL (equal to 0.6 mg/mL). This data suggests that drugs that elevate the gastric pH to a pH of 6 or higher, such as PPI and histamine 2 receptor antagonists (H2RA), could decrease the bioavailability and clinical activity of idelalisib.

Table 1. Idelalisib demonstrates pH dependent solubility at 37》C

pH	Solubility (mg/mL)	USP/Ph. Eur. Solubility Description
7.7[a]	< 0.10	Practically insoluble
1.2[b]	1.1	Slightly soluble

a Water
b 0.01 N HCl

Source: Table 3, 3.2.S.1.3 General Properties

Table 2. Idelalisib demonstrates poor solubility in stimulated intestinal fluid

Simulated Intestinal Fluids	Idelalisib Form	Solubility (mg/mL)
Fasted (pH 6.5)[a]	I	0.08
	II	0.08
Fed (pH 6.5)[b]	I	0.20
	II	0.19

a Water at pH 6.5 buffered with 0.05 M sodium phosphates; 3 mM total bile salts (1.5 mM sodium glycocholate and 1.5 mM sodium taurocholate); 0.75 mM lecithin; ionic strength at 150 mM by NaCl.
b Water at pH 6.5 buffered with 0.05 M sodium phosphates; 15 mM total bile salts (7.5 mM sodium glycocholate and 7.5 mM sodium taurocholate); 3.75 mM lecithin; ionic strength at 150 mM by NaCl.

Source: Table 8, 3.2.P.2.1

Gilead completed an exploratory analysis to assess the effects of acid reducing agents (ARA) on the PK, safety and efficacy of idelalisib (Sequence 020). It was assumed that lower exposure would be observed at neutral pH; however, the observed C_{tau} and the population PK parameters (**Table 3**) for patients in the NHL (101-09) and CLL (312-0116) trials were similar in patients taking idelalisib with or without an ARA. Patients were included in the "with acid reducers" category if the patient was receiving an ARA during any pre-dose sampling time (observed) or ≥ 50% of the time that coincided with PK sampling (population).

It was predicted that the incidence of adverse events or clinical activity would decrease secondary to reduced bioavailability. A higher incidence of grade 3 or 4 diarrhea/colitis (no ARA, 6.3% vs. yes ARA, 14.4%) and rash (2.1% vs. 4.5%) was observed in patients taking idelalisib with an ARA (n=95). The incidence of grade 3 or 4 ALT/AST was lower for patients taking ARA (20% vs. 12%). The increased incidence of diarrhea or rash could be caused by overlapping adverse events or a CYP-mediated drug interaction as described in *Section 2.4.2.3.* The ORR observed in NHL trial [55% (90% CI: 42, 69) vs. 58% (90% CI: 46, 70)] and the PFS observed in CLL trial [HR 0.08 (95% CI: 0.02 vs. 0.37) vs. HR 0.23 (95% CI: 0.13, 0.42)] is similar in patients receiving idelalisib with or without ARA.

In conclusion, ARA do affect tolerability, but do not affect the PK or efficacy of idelalisib.

Table 3. Summary of population predicted pharmacokinetic parameters in patients taking idelalisib with and without acid-reducing agents

	Study 101-09 (N = 121)		Study 312-0116 (N = 102)	
	With Acid Reducers (N = 35)	Without Acid Reducers (N = 86)	With Acid Reducers (N = 62)	Without Acid Reducers (N = 40)
$AUC_{0\text{-}24h}$ (ng*h/mL)				
Mean (SD)	21085.9 (6111.06)	20443.9 (6406.43)	20852.6 (8016.50)	23491.9 (9573.55)
Median	20405.4	19870.2	18307.8	21110.1
Min, Max	11492.5, 36491.9	4698.9, 39724.1	6926.2, 44211.3	9136.3, 57983.3
%CV	29.0	31.3	38.4	40.8
C_{trough} (ng/mL)				
Mean (SD)	336 (156.32)	329.5 (174.26)	378.0 (233.10)	406.0 (317.33)
Median	294.0	294.2	322.2	296.3
Min, Max	91.6, 742.5	43.5, 815.5	16.0, 1069.7	98.3, 1628.0
%CV	46.5	52.9	61.7	78.2
C_{max} (ng/mL)				
Mean (SD)	1965.7 (563.35)	1928.9 (581.57)	1834.0 (755.53)	2193.9 (648.64)
Median	1803.5	1904.7	1823.2	2185.4
Min, Max	898.6, 3223.4	272.4, 3509.3	437.0, 4577.6	823.8, 4027.2
%CV	28.7	30.1	41.2	29.6

SD: Standard deviation

Source: Tables 1-2 and 2-2

Source: Efficacy Amendment, Sequence 020

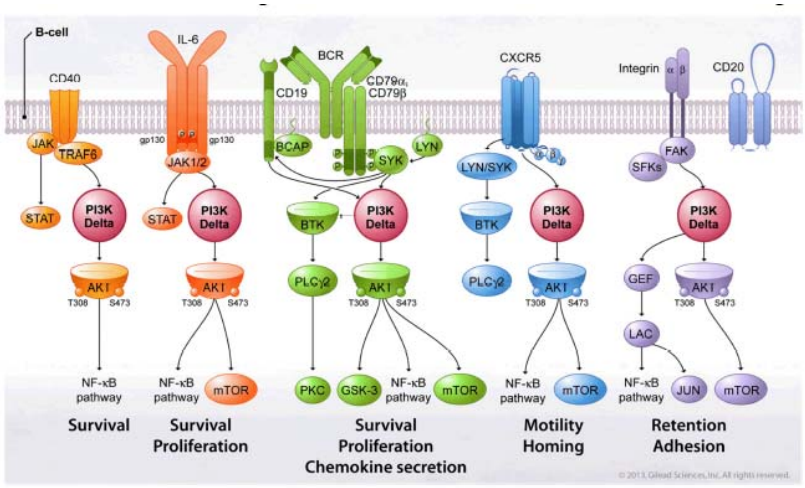
2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Mechanism of Action

Idelalisib inhibits ATP binding to the catalytic domain of PI3Kδ, resulting in the inhibition of the phosphorylation of the key lipid second messenger phosphatidylinositol (PIP) and Akt (**Figure 2**). Idelalisib did not inhibit other various PI3K isoforms (**Table 4**). It also did not significantly interact with or inhibit other kinases based on results from broad panels of kinases and receptors.

Idelalisib inhibited PI3Kδ signaling as determined by evaluating pAkt and pS6RP in cell lines and by measuring pAkt levels in primary tumor samples. Idelalisib also induced apoptosis or reduced proliferation in malignant B cells, including cell lines and primary samples.

Figure 2. Proposed downstream effects of PI3Kδ



Source: Nonclinical Overview

Table 4. Activity of idelalisib in in vitro assays

PI3K Isoform	Cell-based Assay and Stimulus	EC_{50} (nM)	Cell-based Delta Selectivity (fold)
PI3Kδ	Human Basophil- and Anti- FcεRI	8.9	1
PI3Kα	Murine Embryonic Fibroblast and PDGF	> 10,000 [a]	1,124
PI3Kβ	Murine Embryonic Fibroblast and LPA	1,419 [a]	159
PI3Kγ	Human Basophil and fMLP	2,500 [a]	281
Human Whole Blood Cell Assays			
PI3Kδ	Basophil- and Anti-FcεRI	39[a]	1
PI3Kγ	Basophil and fMLP	2833[a]	70
Human Lymphocyte Proliferation Assays			
PI3Kδ	B-lymphocyte and Anti-IgM	6	1
PI3Kδ	T-lymphocyte and Anti-CD3ε	973	160

fMLP = formyl-Met-Leu-Phe; LPA = lysophosphatidic acid; PDGF = platelet derived growth factor

a geometric mean

Source: Studies DR-4001, PC-312-2006, PC-312-2009

Source: Nonclinical Overview

GS-563117 is a major circulating metabolite, but it is inactive against all PI3K isoforms. GS-563117 did not significantly interact with a panel of kinases except Ste20-like kinase (SLK) and

lymphocyte-oriented kinase (LOK) (CAL007-01-p-00001). GS-563117 inhibited LOK and SLK phosphotransferase activity at concentrations achieved in patients at the proposed dose. The functions of LOK and SLK are not well characterized, but inhibiting SLK by erlotinib contributes to the development of dermatologic toxicity [PMID: 21606217]. Therefore, the interaction of GS-563117 with SLK could contribute to the development of rash associated with idelalisib.

Proposed Indications

The proposed indications are for relapsed CLL (NDA 206-545) and refractory indolent mature B cell NHL (NDA 205-858). The proposed indication for NHL will be modified to relapsed follicular lymphoma (FL) and small lymphocytic leukemia (SLL) based on the study population as described below.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dose is 150 mg BID by mouth without regard to food.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Clinical Pharmacology Studies

The clinical pharmacology program is comprised of 17 clinical trials as described in **Table 5**. This program is supported by additional studies conducted using human biomaterials and in animals.

Table 5. Description of clinical pharmacology studies

Study No.	Assessment	Dosage and Administration	N
Studies in healthy subjects			
101-01	Single- and multiple-dose	17 mg, 50 mg, 125 mg, 250 mg, or 400 mg QD OR 50 mg, 100 mg or 200 mg BID	48
101-05	Food effect, Drug interaction	400 mg	12
101-06	Bioavailability, Bioequivalence	100 mg	15
313-0111	Mass balance	150 mg	8
313-0117	QT/QTc Interval	150 mg or 400 mg	48
313-0126	Single-dose	150 mg	20
313-0130	Drug interaction	150 mg OR 150 mg BID	24
339-0101	Multiple-dose	100 mg or 150 mg BID with GS-3373 200 mg BID	24
Studies in patients with hematological malignancies			
101-02	Multiple-dose	50 mg, 100 mg, 150 mg, 200 mg or 350 mg BID OR 150 mg BID × 21 days OR 150 mg or 300 mg QD	191
101-07	Multiple-dose	50 mg, 75 mg, 100 mg or 150 mg BID with B, R, R+B, O, F, E, P, C or R+C[1]	226
101-08	Multiple-dose	150 mg BID with R[1]	64
101-09	Multiple-dose	75 mg, 100 mg or 150 mg BID	125
101-11	Multiple-dose	75 mg, 100 mg, 150 mg, 200 mg or 300 mg BID	25
312-0116	Multiple-dose	150 mg BID or placebo with R[1]	225

Studies in other populations			
101-04	Multiple dose	100 mg BID x 7 days	41
313-0112	Hepatic impairment	150 mg	32
313-0118	Renal impairment	150 mg	12

[1] B = bendamustine, R = rituximab, O = ofatumumab, F= fludarabine, E = everolimus, P = bortezomib or C= chlorambucil

Clinical Studies

Indolent Non-Hodgkin's Lymphoma

The proposed indication is based on the results of an open-label trial that evaluated the efficacy and safety of idelalisib 150 mg BID administered without regard to food as monotherapy in 125 patients with refractory indolent B-cell NHL (101-09). NHL includes many subtypes. The patients enrolled into this trial were diagnosed with FL (58%), SLL (22%), lymphoplasmacytic lymphoma or Waldenström macroglobulinemia (8%), or marginal zone lymphoma (12%). The ORR was 56% (95% CI: 47%, 65%) and the median duration of response was 12.5 months. Median exposure was 6.6 months (0.6, 23.9). Thirty patients (24%) discontinued idelalisib due to an adverse event. The results of this trial are supported by two open label trials: Study 101-02 and 101-07 (**Table 6**). The labeled indication will be limited to FL and SLL.

Table 6. Description of clinical studies supporting the non-Hodgkin lymphoma trial

Study No.	Study Design	Endpoint[1]
101-02	Sixty-four (64) patients with relapsed or refractory NHL received idelalisib at one of eight doses.	The ORR was 47% (95% CI: 34 to 60) with a median duration of response of 18 months (95% CI: 11 to 32). Median exposure was 3.8 months (0.3, 41).
101-07	Eighty (80) patients with relapsed or refractory NHL received idelalisib at one of 4 doses in combination with chemotherapy and/or immunotherapy.	The ORR was 81% (95% CI: 71 to 89) and the median duration of response was not reached. Median exposure was 10.1 months (0.5, 33).

[1] As reported by Gilead

Chronic Lymphocytic Leukemia

The proposed indication is based on the results of a single randomized, double-blind, placebo-controlled trial that evaluated the efficacy and safety of idelalisib in combination with rituximab for relapsed CLL (312-0116). Two hundred twenty (220) patients were randomized 1:1 to receive rituximab at a dose of 375 mg/m^2 on day 1 (week 0) and then at dose of 500 mg/m^2 intravenously on days 15, 29, 43, 57, 85, 113 and 141 (8 doses) in combination with idelalisib 150 mg BID or placebo to be taken without regard to food continuously. Randomization was stratified by17p deletion or TP53 mutation status, immunoglobulin heavy chain variable region (IgHV) mutation status, and prior therapy with an anti-CD20 therapeutic monoclonal antibody. A description of these genetic alterations can be found in *Section 2.3.2.9.* The median number of prior therapies was 3 and 96% of patients had received prior anti-CD20 monoclonal antibodies. The median time from diagnosis was ~8 years.

The trial was stopped for efficacy following the first pre-specified interim analysis. The median PFS was 5.5 (3.8, 7.1) months for patients receiving placebo, but was not reached for patients receiving idelalisib (HR 0.18, 95% CI: 0.10, 0.32) [second interim analysis]. The median duration of exposure was 5.0 months (0.3, 16 months). Ten percent of patients discontinued idelalisib due to an adverse event compared to 12% of patients who discontinued placebo. The

results of this trial are supported by three open label trials: Study 101-02, 101-07 and 101-08 (**Table 7**).

Table 7. Description of clinical studies supporting the chronic lymphocytic leukemia trial

Study No.	Study Design	Endpoint[1]
101-02	Fifty-four (54) 54 patients with relapsed or refractory CLL received idelalisib at one of eight doses. 17p deletion or TP53 mutation was identified in 24% of patients and an IgHV mutation was identified in 9% of patients.	The ORR was 72% (95% CI 58, 84) with a median duration of response of 16 months (95% CI 4.6, 41). Median exposure was 8.8 months (0.2, 49).
101-07	Eighty-five (85) patients with relapsed or refractory CLL received idelalisib at one of 4 doses in combination with chemotherapy and/or immunotherapy.	The ORR was 84% with a median duration of response of 24 months. Median exposure was 10.3 months (0.3, 34).
101-08	Sixty-four (64) subjects with previously untreated CLL received idelalisib at a dose of 150 mg BID in combination with rituximab at a dose of 375 mg/m^2 once weekly. 17p deletion or TP53 mutation was identified in 14% of patients and an IgHV mutation was identified in 42% of patients.	The ORR was 97% and the median duration of response has not been reached. Median exposure was 14.5 months (0.8, 31 months).

[1]As reported by Gilead

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

For the NHL trial, the primary endpoint was ORR, defined as the proportion of patients who achieved a complete response (CR) or partial response (PR) based on the Revised Response Criteria for Malignant Lymphoma. The primary analysis was based on evaluation by an independent review committee (IRC).

For the CLL trial, the primary endpoint was PFS defined as the interval from randomization to the earlier of the first documentation of definitive progressive disease or death from any cause. The primary analysis was based on evaluation by an IRC.

Both PFS and ORR are described as surrogate endpoints that can support accelerated or regular approval, but the adequacy of these endpoints to support approval is highly dependent upon other factors, such as effect size, effect duration, and benefits of other available therapy (FDA Guidance for Industry, *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics*).

For the clinical pharmacology studies, PK parameters were estimated using non-compartmental (NCA) or population analysis. The geometric mean ratio (GMR) and 90% confidence intervals (CI) were determined for comparative studies.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess PK parameters and exposure response relationships?

Yes. Idelalisib and its major metabolite GS-563117 were appropriately identified and measured in human samples to adequately assess the PK of these compounds (*Section 2.6*). GS-563117 is a major metabolite, since it accounts for 62% of the total radioactivity quantified in plasma (313-

0111).

2.2.4 Exposure-response

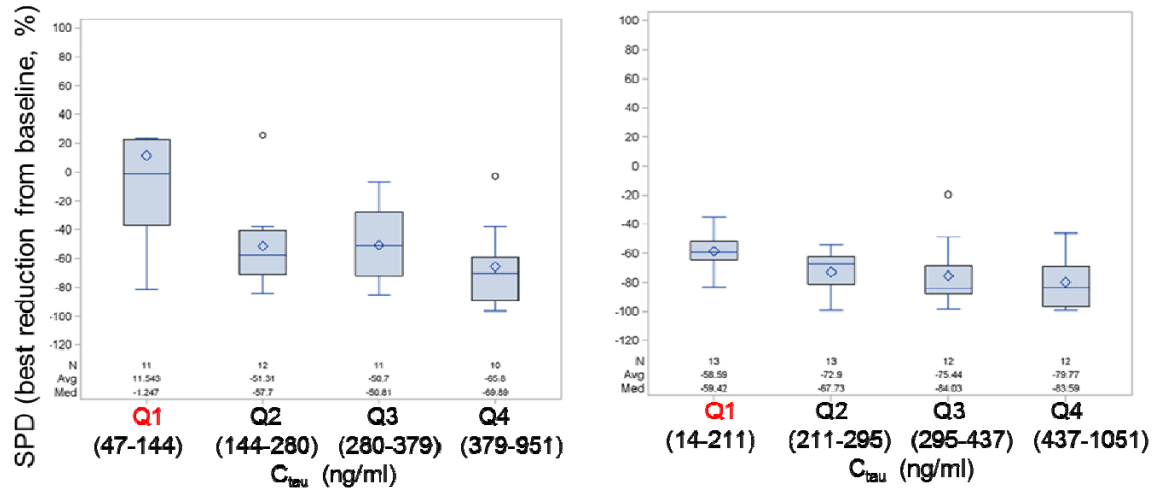
2.2.4.1 *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?*

No E-R was observed for the primary endpoints in the NHL and CLL trials. The dose is relatively well tolerated based on a number of dose reductions or discontinuations due to adverse events and median time to the first dose reduction. Furthermore, a maximum tolerated dose (MTD) was not identified in the dose escalation phase of the dose finding trial and the maximum administered dose (MAD) is 2.3 times higher than the proposed dose. Gilead supported dose selection based on an E-R relationship observed in the dose finding study (101-02); the E-R relationship suggests that patients with C_{tau} in the lowest quartile had a smaller reduction in tumor size. At the proposed dose of 150 mg BID, the C_{tau} exceeded the EC_{90} for PI3Kδ inhibition in vitro for most patients in the efficacy trials. Overall, the dose appears reasonable based on the available safety and efficacy data.

Dose Selection

Gilead conducted a dose finding trial in patients with selected, relapsed or refractory hematological malignancies receiving idelalisib as monotherapy once or twice daily in a fasted state (101-02). Tumor responses as assessed by changes in tumor size were evaluated and the relationship of the predicted exposures based on population PK modeling to activity was assessed (**Figure 3**). Gilead supported their dose selection of 150 mg BID based on the observations that the dose achieved concentrations within the third quartile (Q3). The median best reduction in tumor size (SPD) reached a plateau at Q3 and the C_{tau} associated with Q3 exceeds the EC_{90} (~125 ng/mL or 301 nM; PC-312-2009) for PI3Kδ inhibition in vitro. No relationship was observed for other activity endpoints.

Figure 3. Exposure-response relationship in dose finding trial in indolent non-Hodgkin lymphoma (left) and chronic lymphocytic leukemia (right)

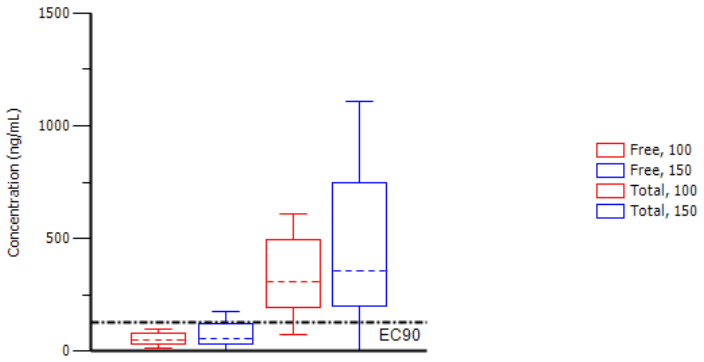


Source: Pharmacometrics Review

Figure 4 illustrates the median C_{tau} from the dose finding study (101-02) following administration of idelalisib 100 mg BID (n=22) and 150 mg BID (n=37) on day 28. Most

patients achieved C_{tau} values that exceeded the EC_{90} (100 mg, 91% and 150 mg, 87%). The C_{tau} values were highly variable and some patients did not maintain plasma concentrations that exceeded the EC_{90} during the dosing interval. In the NHL and CLL trials, the percentage of patients who achieved C_{tau} values that exceeds the PI3Kδ inhibition EC_{90} was greater than 85% on day 28.

Figure 4. Median minimal plasma concentrations observed on day 28 after continuous twice daily dosing of idelalisib at doses of 100 mg (red) and 150 mg (blue) (n=59)



Source: Data from pk1101.xpt

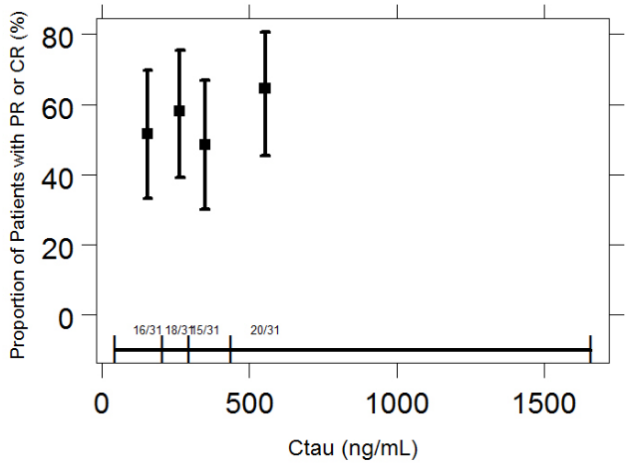
Peripheral blood mononuclear cells (PBMC) were screened for levels of pAkt by flow cytometry. Inhibition of constitutive pAktT308 was noted at the dose levels of idelalisib of 100 mg and 150 mg BID. On days 8 and 28, constitutive phosphorylation of Akt in cells from patients with CLL was reduced to the background level of healthy subjects.

A MTD was not defined, because no dose limiting toxicities were observed during the initial dose finding. The median duration of exposure for all doses was 3.7 months (0, 15). The median duration of exposure was slightly less at 2.9 months (0, 14) for patients taking idelalisib at the proposed clinical dose.

Indolent Non-Hodgkin Lymphoma

E-R analyses were conducted to assess the relationship between individual exposure estimated from population PK modeling and the primary endpoint of ORR in the NHL trial. No E-R relationships were observed between the ORR and C_{tau} (**Figure 5**). The percentage of patients who achieved a C_{tau} that exceeds the EC_{50} and EC_{90} for PI3Kδ inhibition was 100% and 85% on day 28, respectively.

Figure 5. No exposure-response relationship for indolent non-Hodgkin lymphoma

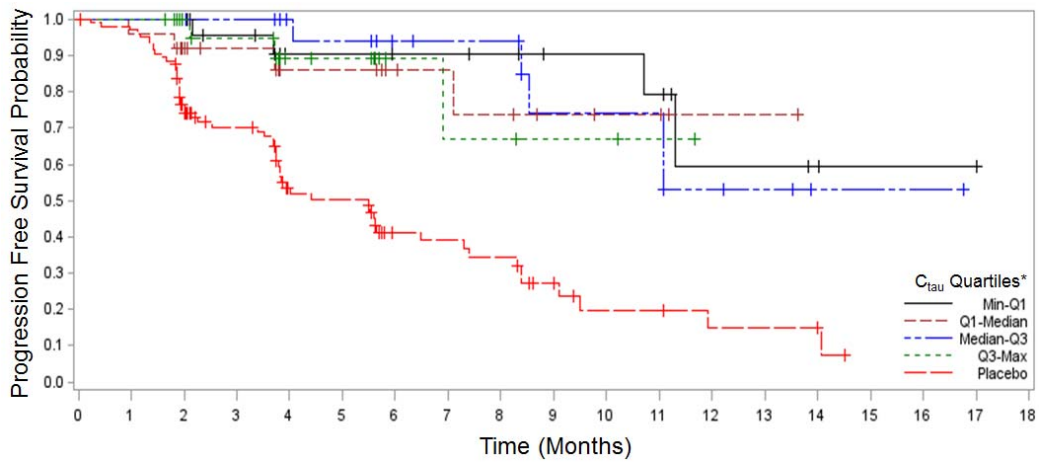


Source: Pharmacometrics Review

Chronic Lymphocytic Leukemia

E-R analyses were conducted to assess the relationship between individual exposures derived from population PK modeling and the primary endpoint of PFS in the CLL trial. No E-R relationship was observed between PFS and C_{tau} (**Figure 6**). Overall, the idelalisib C_{tau} quartile groups were uniformly beneficial relative to placebo and there was no specific threshold of plasma concentrations in patients receiving idelalisib that was associated with achieving a significantly better response. The percentage of patients who achieved C_{tau} that exceeds the EC_{50} and EC_{90} for PI3Kδ inhibition was 100% and 93% on day 28, respectively.

Figure 6. No exposure-response relationship for patients with chronic lymphocytic leukemia



Source: Pharmacometrics Review

2.2.4.2 *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?*

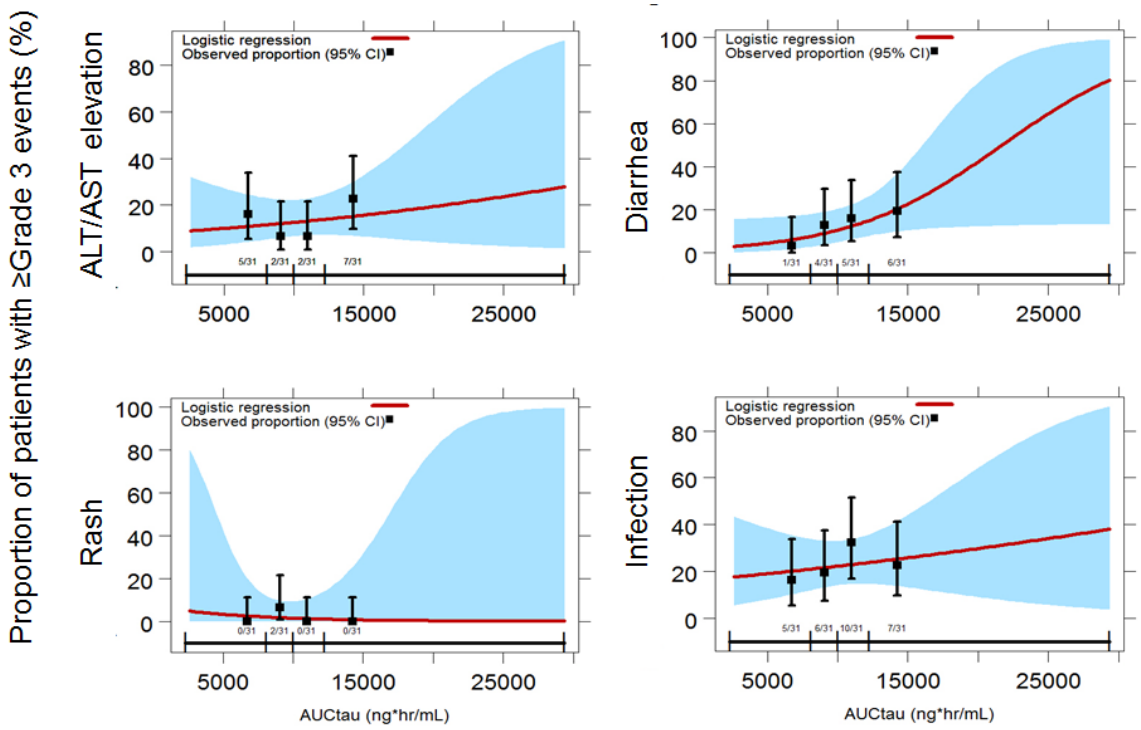
No E-R relationships between idelalisib or GS-563117 exposure and the selected safety endpoints were identified, except for a positive slope for grade ≥ 3 diarrhea in the NHL population. Relatively limited patients required a dose reduction or discontinued idelalisib for

adverse events. These data support the labeling recommendations regarding food and for patients taking strong CYP3A inhibitors and with baseline hepatic impairment as described below.

Monotherapy

The E-R relationship for selected safety endpoints of idelalisib and GS-563117 was evaluated in patients with hematologic malignancies who received idelalisib as monotherapy in the NHL trial using logistic regression analysis with exposures derived from population PK modeling. Safety parameters that were evaluated included grade ≥ 3 AST or ALT laboratory abnormalities and grade ≥ 3 neutropenia, diarrhea, skin rash, and infection. No E-R relationships were identified for these selected safety endpoints, except that there was a positive slope with statistically significant relationship of grade ≥ 3 diarrhea for idelalisib (**Figure 7**). The proposed labeling includes dose modifications for grade ≥ 3 diarrhea. Overall, there was no specific threshold of plasma concentrations in patients receiving idelalisib that was associated with a greater risk of experiencing any of these adverse events.

Figure 7. No exposure-response relationship selected safety endpoints except diarrhea in indolent non-Hodgkin lymphoma

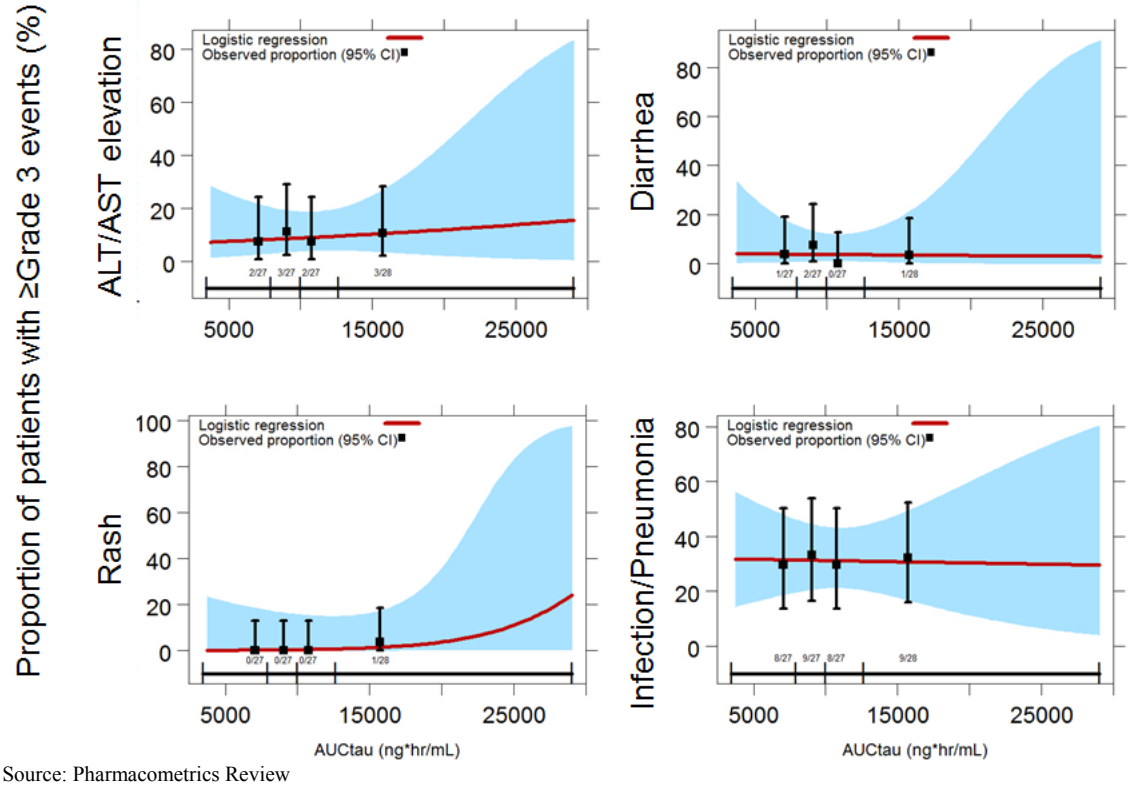


Source: Pharmacometrics Review

Combination

E-R relationships for selected safety endpoints were also evaluated in patients with relapsed CLL who received idelalisib in combination with rituximab as part of the CLL trial using logistic regression analysis with exposures derived from population PK modeling. Safety parameters that were evaluated included grade ≥ 3 AST or ALT laboratory abnormalities and grade ≥ 3 diarrhea, rash, and infection. No E-R relationships were observed for these selected safety endpoints and idelalisib or GS-365117 exposure in this trial (**Figure 8**).

Figure 8. No exposure-response relationship for selected safety endpoints in chronic lymphocytic leukemia



Source: Pharmacometrics Review

Dose modifications

The proposed labeling lists dose modifications for grade 3 or 4 AST or ALT laboratory abnormalities, diarrhea and (b) (4) Idelalisib can be continued at a dose of 100 mg BID once these events have resolved (defined as grade ≤ 1).

Dose reductions were permitted in the NHL and CLL trials.

Forty-two patients (34%) enrolled in the NHL trial had dose reductions from the starting dose; 40 patients had their dose reduced to 100 mg BID and two patients had their dose reduced to 75 mg BID. Of the 40 patients who had their dose reduced to 100 mg BID, seven patients had their dose further reduced to 75 mg BID. The adverse events most frequently associated with dose reduction were increased ALT and increased AST, followed by diarrhea, neutropenia, colitis, and rash. Fifteen patients had dose reductions for laboratory abnormalities that were not reported separately as an adverse event. The median duration of exposure was 6.6 months (0.6, 24). The median time to the first dose reduction was 82 days (17 – 504 days) after starting idelalisib.

Sixteen patients (14.5%) enrolled in the CLL trial who received idelalisib + rituximab were dose reduced to 100 mg BID. Median duration of exposure was 5 months (0.3, 16). The median time to the first dose reduction was 114 days (21 - 343 days) after starting idelalisib.

2.2.4.3 *Does this drug prolong the QT or QTc interval?*

Idelalisib 150 mg and 400 mg did not prolong the QT/QTc interval as stated in the overall summary of findings in the QT-IRT review.

Nonclinical data

The IC_{50} for the hERG potassium current was estimated to be greater than 50 μM (BHR00004). No effects on electrocardiograms (ECGs) were observed in dogs treated with doses up to 20 mg/kg. The no observed adverse effect level (NOAEL) is 20 mg/kg (BHR00041).

Clinical data

A partially-blinded, randomized, placebo- and positive-controlled crossover study was conducted in 46 healthy volunteers to evaluate the effect of idelalisib on the QT/QTc interval (313-0117). The volunteers received idelalisib 400 mg, idelalisib 150 mg (with placebo), placebo and moxifloxacin 400 mg with a washout period of 10 days between treatments. The treatment sequence was randomly assigned. Idelalisib was given with a standard meal (defined as 2 slices white bread toast, 1 tsp low-fat margarine, 1 tbsp jelly, 8 oz. apple juice and 8 oz. whole milk). Refer to *Section 2.5* for discussion regarding the effect of food on the PK of idelalisib. PK samples were collected to measure idelalisib in the plasma up to 48 h after each dose of idelalisib or placebo. Time-matched 12-lead ECGs were monitored up to 24 h after each treatment using a Holter monitor. The exposure following a dose of 150 mg was comparable to exposure observed in other studies conducted in healthy volunteers (**Table 8**).

Table 8. Pharmacokinetic parameters of idelalisib observed in thorough QT study

Parameter	150 mg	400 mg
C_{max} (ng/mL)	1,927 (26%)	3,134 (16%)
AUC_{inf} (ng•h/mL)	8,393 (29%)	19,072 (28%)

No significant QTc prolongation of idelalisib at doses of 150 mg or 400 mg was detected. The largest upper bounds of the two-sided 90% CI for the mean differences between idelalisib (150 mg and 400 mg) and placebo were below 10 msec.

No concentration-response relationship was found, but relatively few events were identified. No absolute QTc interval > 480 msec and no changes in baseline QTc interval > 60 msec were observed in volunteers taking idelalisib.

2.2.4.4 *Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and is there any unresolved dosing or administration issue?*

Yes. At this time, there are no unresolved dosing or administration issues.

2.2.5 What are the PK characteristics of the drug?

2.2.5.1 *What are the single dose and multiple dose PK parameters?*

Idelalisib demonstrates non-linear PK with no accumulation observed following multiple doses.

Study 101-01

Sixty-four (64) healthy men received placebo or idelalisib as monotherapy at one of eight doses: 17 mg, 50 mg, 125 mg, 250 mg, or 400 mg once (single dose) or 50 mg, 100 mg or 200 mg BID for seven days (multiple dose). The morning dose was administered without food after an overnight fast. For multiple dose cohorts, the evening dose was administered 12 h after the morning dose and at least 2 h after a meal. PK samples were collected up to 72 h for single dose cohorts and up to 12 h on day 1 and up to 72 h on day 7 for multiple dose cohorts. **Table 9** lists

the PK parameters of idelalisib after administration of 50 mg, 100 mg and 200 mg BID.

Table 9. Geometric mean (coefficient of variation (CV), %) pharmacokinetic parameters for idelalisib in healthy volunteers

Parameter		Day 1	Day 7
C_{max} (ng/mL)	50 mg (n=6)	598 (29%)	737 (29%)
	100 mg (n=6)	1,425 (30%)	1,832 (16%)
	200 mg (n=6)	1,769 (27%)	1,710 (34%)
AUC (ng•h/mL) [1]	50 mg (n=6)	2,301 (36%)	3,378 (31%)
	100 mg (n=6)	4,547 (17%)	7,709 (20%)
	200 mg (n=6)	8,110 (36%)	8,650 (36%)
$t_{½}$ (h)	50 mg (n=6)	3.0 (33%)	8.1 (30%)
	100 mg (n=6)	3.3 (30%)	5.5 (40%)
	200 mg (n=6)	3.5 (43%)	10.7 (37%)

[1] day 1 AUC_{inf} and day 7 $AUC_{0\text{-}12h}$

2.2.5.2 *How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?*

The population apparent oral clearance (CL/F) is ~30% higher in healthy volunteers compared to patients with cancer, suggesting that the exposure will be higher in patients with cancer compared to healthy volunteers taking the same dosage. Limited data is available to permit cross study comparison, but the available data suggests that exposure is higher in patients with cancer. The reason for the exposure differences is unknown. Possible explanations include reduced distribution of the idelalisib to the liver or reduced metabolism of idelalisib by hepatic enzymes secondary to reductions in expression of transport proteins or enzymes in patients with cancer. These changes could reduce hepatobiliary elimination and subsequently, idelalisib clearance.

Cross Study

Gilead completed a trial in 191 patients with select hematological malignancies (101-02). The PK sampling was inadequate to characterize the PK, because serial PK samples were only collected up to 8 h following the dose on days 1 and 28. **Table 10** lists the maximal plasma concentrations (C_{max}) at a dose of 50 mg and 100 mg BID on day 1 for idelalisib in healthy volunteers and patients with hematological malignancies.

Table 10. Comparative pharmacokinetics of idelalisib in healthy volunteers and patients with selected relapsed or refractory hematologic malignancies

Parameter	Healthy Volunteer Study 101-01		Patients Study 101-02	
	50 mg (n=6)	100 mg (n=6)	50 mg (n=16)	100 mg (n=25)
C_{max} (ng/mL)	598 (29%)	1,425 (30%)	881 (47%)	1,757 (45%)

Population
The population median (2.5th, 97.5th quartiles) CL/F is 32% higher in healthy volunteers (n=98; 19.7 (18.4, 21.3)) compared to patients (n= 638; 14.9 (14.4, 15.5)).

2.2.5.3 *What are the characteristics of drug absorption?*

The absolute bioavailability of idelalisib was not evaluated in humans. The relative bioavailability of different formulations is discussed in *Section 2.5.2.*

The median t_{max} was 1.5 h (0.5, 6 h) after a dose of idelalisib under fasted conditions on days 1 and 28 in patients with hematological malignancies (n=188, 101-02).

2.2.5.4 *What are the characteristics of drug distribution?*

The population estimated apparent central volume of distribution (Vc/F) of idelalisib and GS-563117 was 23 L and 7.5 L, respectively. Idelalisib is greater than 84% bound and GS-563117 was greater than 88% bound to human plasma proteins with no concentration dependence. Idelalisib and its metabolites are predominantly distributed to plasma.

Protein Binding
In human plasma, idelalisib had an average free fraction of 16% and GS-563117 had a free fraction of 12% (AD-313-2009).

The mean free fraction is lower in plasma collected from humans administered idelalisib compared to the free fraction measured in human plasma in vitro. The free fraction increases with hepatic impairment. These differences are not likely clinically relevant. Total exposure should be independent of protein binding, because idelalisib is administered orally and eliminated primarily by the liver (Benet and Hoener. Clin Pharmacol Ther 2002). **Table 11** lists the mean free fraction of idelalisib and GS-563117 in plasma measured post dose (hepatic impairment, 3 h and renal impairment, at time of maximal concentration) (313-0112 and 313-0118).

Table 11. Comparative mean (StD) free fraction of idelalisib and GS-563117 in healthy volunteers and subjects with organ impairment

Parameter	Idelalisib	GS-563117
Study 313-0112		
Healthy Volunteer	6.7 % (1.5%)	1.3% (0.6%)
Moderate Hepatic Impairment	7.6% (1.7%)	1.7% (0.6%)
Severe Hepatic Impairment	11.0% (3.5%)	3.6% (2.0%)
Study 313-0118		
Healthy Volunteer	6.0% (1.3%)	1.2% (0.5%)
Severe Renal Impairment	6.2% (1.5%)	1.2% (0.6%)

Partitioning
Idelalisib and its metabolites are predominantly distributed to plasma.

- In human blood, the blood to plasma ratios for idelalisib and GS-563117 were similar at 0.7 and 0.6, respectively (AD-313-2014).
- The mean whole blood-to-plasma concentration ratio of [^{14}C]-radioactivity ranged from 0.4 to 0.6 up to 48 h post dose. The mean whole blood-to-plasma AUC_{inf} ratio was ~ 0.5 (313-0111).

Transporters

Idelalisib and its metabolite undergo secretory transport. Idelalisib is a substrate of P-glycoprotein (P-gp; MDR1, ABCB1) and Breast Cancer Resistant Protein (BCRP; ABCG2) (400571, OPT-2010-124). Its metabolite GS-563117 is also a substrate of P-gp and BCRP (AD-312-2006).

Idelalisib is not a substrate of organic anion transporting polypeptide (OATP) 1B1 (SLCO1B1), OATP1B3 (SLCO1B3), organic anion transporter (OAT) 1 (SLC22A6), OAT3 (SLC22A8) or organic cation transporter (OCT) 2 (SLC22A2) (OPT-2010-124). GS-563117 is not a substrate of OATP1B1 and OATP1B3 (AD-312-2010). Gilead did not determine if GS-563117 is a substrate of OAT1, OAT3 and OCT1.

2.2.5.5 *Does the mass balance study suggest renal or hepatic as the major route of elimination?*

Hepatobiliary is the major route of elimination. Gilead conducted a study in patients with impaired hepatic and renal function as described in *Section 2.3.2.*

Clinical Studies

A single study was conducted in 8 healthy men who received a mixture of both unlabeled and [^{14}C]-labeled (specific activity: 134 μCi/mg, ≥ 98% purity) idelalisib 150 mg with a standard breakfast (313-0111). The percent of the radioactive dose recovered from feces and urine was 78% ± 3.9% and 14% ± 2.9%, respectively. Study 101-05 also indicates that hepatic elimination is the major route of elimination. Gilead conducted a study in subjects with impaired hepatic function as described in *Section 2.3.2.6.*

Nonclinical Studies

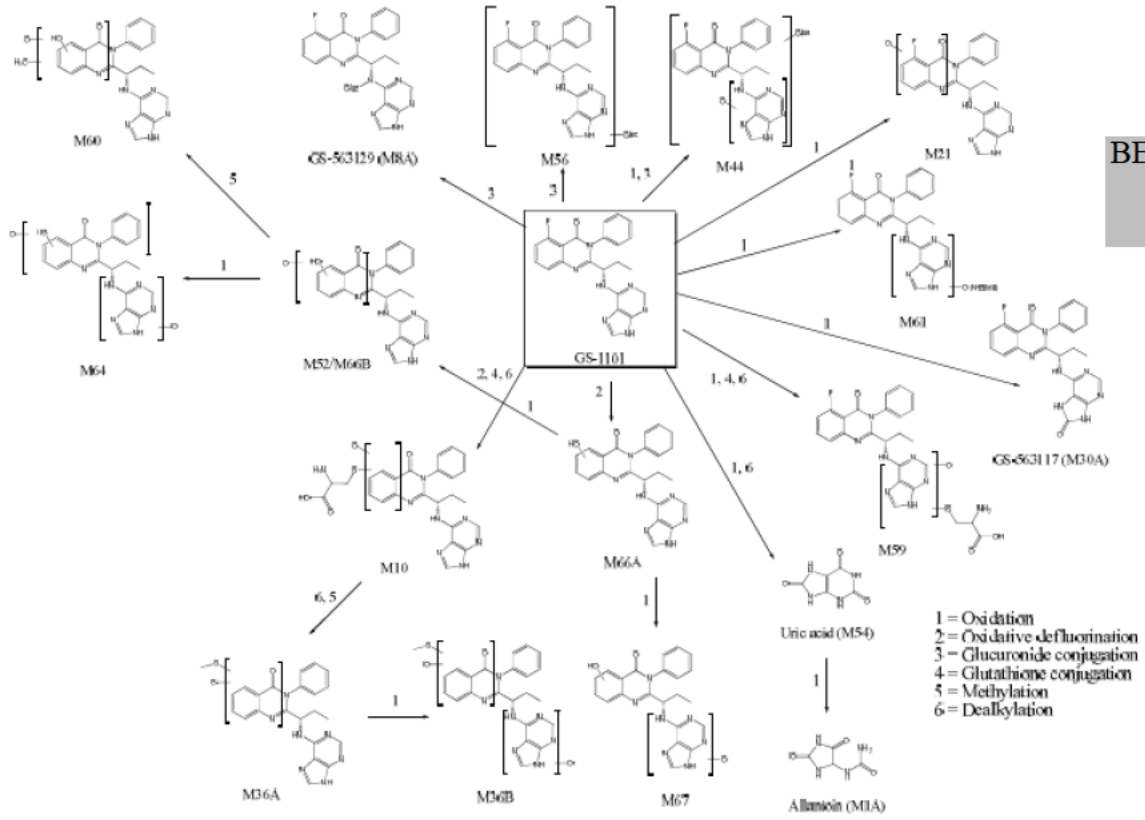
Following oral administration of [^{14}C]-idelalisib to rats and dogs, radiation was excreted primarily via the hepatobiliary route (AD-313-2003 and AD-313-2001). By 168 h post dose, the mean recovery of radioactivity in rats was 3.4% in the urine and 89% in the feces, and in dogs 6.5% in the urine and 88% in the feces. In bile duct-cannulated animals, the majority of the administered dose was recovered in the bile (64% in rats and 72% in dogs). These data suggest that idelalisib undergoes biliary secretion. A PK study in patients with renal impairment should be conducted, because idelalisib is intended for chronic use and renal impairment can inhibit some pathways of drug metabolism and transport. Gilead conducted a study in subjects with impaired renal function as described in *Section 2.3.2.5.*

2.2.5.6 *What are the characteristics of drug metabolism?*

Idelalisib (GS-1101) undergoes metabolism by aldehyde oxidase (~70%) and CYP3A4 (~30%) to form its major metabolite GS-563117 (AD-312-2023, 794306). GS-563117 accounts for 62% of the radioactivity quantified in the plasma. Therefore, the metabolism by aldehyde oxidase accounts for ~43% of the overall metabolism of idelalisib and CYP3A4 accounts for ~19%. GS-563117 also accounts for 49% of the radioactivity in the urine and 44% of the radioactivity in the feces. **Figure 9** illustrates the potential metabolic pathways for idelalisib.

Other metabolic pathways include glucuronide conjugation with involvement of UGT1A4 (AD-312-2022). The mass balance study suggests that the glucuronidated metabolites account for about 7% of the radioactivity in urine (M44 and M8A) and about 3% of the radioactivity in the feces (M56). Thus, glucuronidation accounts for ~3% of overall metabolism.

Figure 9. Proposed metabolism of idelalisib and its metabolites in humans



Source: Figure 10-8, Final Study Report, GS-US-313-0111

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2.2.5.7 *What are the characteristics of drug excretion?*

The population estimated CL/F of idelalisib was 14.9 L/hr for a patient with cancer and 19.7 L/hr for a healthy volunteer. The population estimated elimination half-life was 8.2 h.

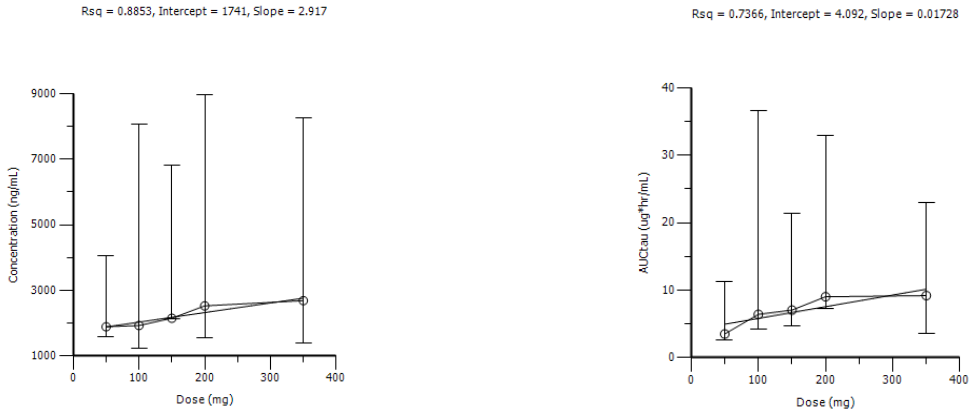
The population estimated CL/F for GS-563117 was estimated to be 4.4 L/hr for a patient with cancer and 6.7 L/hr for a healthy volunteer. The population estimated elimination half-life is 11.6 h.

The median CL/F and elimination half-life could not be estimated for patients enrolled into dose finding trial (101-02) as the sampling time was only up to 8 h post dose.

2.2.5.8 *Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?*

The mean idelalisib C_{max} and AUC_{0-6h} demonstrated less than dose proportional increases in exposure following multiple doses (day 28) (**Figure 10**) (101-02). Nonlinear PK was anticipated based on limited solubility and subsequent dose-dependent absorption.

Figure 10. Mean maximal concentrations (left) and area under the curve (right) 50 mg BID to 350 mg BID for patients with hematological malignancies (101-02)



Source: Data from pp.xpt (101-02)

2.2.5.9 *How do the PK parameters change with time following chronic dosing?*

No accumulation was identified based on a comparison of the C_{max} observed following a single dose (day 1; n = 144) and multiple-dose (day 28; n = 120) (101-02). No comparison of AUC values on day 28 to day 1 could be made, as PK sampling was not sufficient to adequately estimate the AUC_{inf} on day 1 and $AUC_{0\text{-}12h}$ on day 28.

2.2.5.10 *What is the inter- and intra-subject variability of the PK parameters in volunteers and patients and what are the responsible covariates?*

The inter- and intra-subject variability is not available for volunteers and patients separately. A population PK model that incorporated data from 736 patients and volunteers estimates the inter-individual variability in CL/F to be 38% and in Vc/F to be 85%. Intra-individual variability in plasma idelalisib concentrations was 53%. None of the covariates tested had a clinically meaningful impact on exposure to idelalisib.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

Body weight and hepatic impairment influence exposure to idelalisib. Body weight was maintained in the final population PK model, but body weight has no clinically meaningful effect on exposure. Exposure is significantly increased in subjects with hepatic impairment, but no E-R was observed for selected safety endpoints with the exception of diarrhea in the NHL population. No dose modifications are recommended based on body weight or in patients with baseline hepatic impairment. The remaining covariates assessed in the population PK model had no impact on exposure, including age, race, gender, background therapies, baseline serum creatinine, and CLcr.

2.3.2 Based upon what is known about E-R relationships and their variability, what dosage regimen adjustments, if any, are recommended for each group?

2.3.2.1 *Elderly*

None. Age as a continuous or categorical variable had no apparent influence on the PK of idelalisib. The population analysis included a reasonable number of elderly subjects. Two-hundred thirty-nine (239) subjects (32.5%) between 65 to 75 years and 91 subjects (12.4%) > 75 years were included.

2.3.2.2 *Pediatric*

Gilead requested a waiver from conducting pediatric studies with idelalisib in patients < 18 years of age with NHL per the FDCA Section 505B(a)(4)(A). Subsequently, FL, CLL/SLL, lymphoplasmacytic lymphoma with or without Waldenstrom's macroglobulinemia, marginal zone lymphoma (extranodal, nodal and splenic) have orphan designation (September 26, 2013 or October 15, 2013) and are exempt from Pediatric Research Equity Act (PREA).

CLL has orphan designation (August 25, 2011) and is exempt from PREA.

2.3.2.3 *Gender*

None. Women had ~9-12% higher C_{tau} and AUC as compared to men, which is explained by the fact that women have a lower body weight (mean body weight: 66 kg for women and 84 kg for men). Body weight was a statistically significant covariate in the population PK analysis. This difference in PK is well within the bioequivalence range and is not considered clinically meaningful; thus, gender has no apparent influence on the PK of idelalisib. A reasonable number of men and women were included in the population analysis. Seventy percent of subjects included in the analysis were men. Male preponderance is observed for NHL and CLL, but the higher number of men in the population PK is influenced by studies conducted in healthy men.

2.3.2.4 *Race/Ethnicity*

None. Race had no apparent influence on the PK of idelalisib or GS-563117.

Independent Study

The PK of idelalisib at a dose of 150 mg was compared in Japanese and Caucasian volunteers (313-0126). Idelalisib was administered in the morning with a standard breakfast. The C_{max} is higher in Japanese volunteers compared to Caucasian volunteers; however, these differences are not clinically meaningful (**Table 12**).

Table 12. Pharmacokinetics of idelalisib in Japanese and Caucasian volunteers

IDELA PK Parameter	Mean (%CV)		% GLSM Ratio (90% CI)
	Japanese (N = 10)	Caucasian (N = 10)	
C_{max} (ng/mL)	2535.0 (32.4)	1947.0 (22.6)	127.85 (103.92, 157.30)
T_{max} (h)[a]	1.25 (1.00, 2.50)	2.75 (1.50, 3.00)	—
$t_{1/2}$ (h)[a]	8.42 (5.63, 10.64)	10.04 (5.32, 17.39)	—
AUC_{0-last} (ng•h/mL)	9674.1 (27.4)	8194.7 (37.9)	122.46 (95.28, 157.39)
AUC_{inf} (ng•h/mL)	9828.3 (26.7)	8324.6 (37.8)	122.62 (95.54, 157.39)

a Median (Q1, Q3)

Note: Below limit of quantitation was treated as 0 for summary purposes and was treated as missing for natural log transformation.

Source: Final Study Report, Study GS-US-313-0126

Population Evaluation

Race was not a statistically significant covariate of CL/F or central Vc/F in the population PK analysis. Race was segregated into Whites and non-Whites. Non-Whites compromised only a small fraction of the population (13%) included in the analysis as expected. White Americans have the highest incidence rate of NHL and CLL, followed by Hispanics/Latinos and African Americans.

2.3.2.5 *Renal Impairment*

No dose adjustment is needed for patients with CLcr ≥ 15 mL/min, based on an independent study conducted in subjects with severe renal impairment.

Independent Study

An open-label adaptive study was conducted to compare the safety and PK of idelalisib in 6 subjects with impaired renal function to that of 6 healthy volunteers (313-0118). Each volunteer was matched for age, gender, and BMI. Subjects with severe (cohort one: CLcr 15 to 29 mL/min) renal impairment were enrolled into the study. Subjects with mild (cohort three: CLcr 60 to 79 mL/min) or moderate (cohort two: CLcr 30 to 59 mL/min) renal impairment were not enrolled based on the data available from the first cohort. Renal function was categorized based on estimated CLcr using the Cockcroft-Gault equation. Idelalisib was administered at dose of 150 mg in the morning with a standard meal.

The GMR indicates that the exposure in subjects with severe renal impairment is higher as compared to healthy volunteers, but the relative difference is not statistically significant (**Table 13**). No dose adjustment is recommended for patients with CLcr ≥ 15 mL/min.

Table 13. Pharmacokinetics of idelalisib in severe renal impairment

Parameter	C_{max} (ng/mL) (mean (CV%))		AUC_{inf} (ng•h/mL) (mean (CV%))	
Population	**Normal (n=6)**	**Severe (n=6)**	**Normal (n=6)**	**Severe (n=6)**
Idelalisib	2,533 (27)	2,678 (28)	11,782 (20)	15,672 (37)
	GMR 1.05 (77, 1.43)		GMR 1.27 (0.92, 1.76)	

Source: Final Study Report, GS-US-313-0118

Population Evaluation

Baseline serum creatinine as a continuous or categorical variable had no apparent influence on the PK of idelalisib. The analysis included an adequate number of individuals with varying degrees of renal function. Patients with mild impairment (CLcr 60-89 mL/min) accounted for 35% of the population, while moderate impairment (CLcr 30-59 mL/min) accounted for 17%. Severe impairment (CLcr 15-29 mL/min) accounted for only 1% of the population.

2.3.2.6 *Hepatic Impairment*

No dose adjustment is recommended for patients with baseline hepatic function. The exposure to idelalisib is higher in subjects with baseline hepatic impairment and the median exposure exceeds the median exposure estimated for the MAD (101-02), but no E-R relationship was identified for selected safety endpoints except for diarrhea in the NHL population. No differences in safety or exposure were observed for patients with baseline hepatic impairment compared to patients without baseline hepatic impairment in the NHL trial (101-09). Only one patient with baseline hepatic impairment was enrolled in the CLL trial (312-0116). Since no dose

modification is being recommended, the labeling will state that patients with baseline hepatic impairment will need to be closely monitored for serious adverse events. Health care providers will be instructed to follow the dose modifications outlined in the labeling for adverse events.

Independent Study

An open-label adaptive study was conducted to compare the safety and PK of idelalisib of subjects with impaired hepatic function to that of healthy volunteers (313-0112). Each volunteer was matched for age, gender, and BMI. Subjects with moderate (cohort one: Child Pugh class B) and severe (cohort two: Child Pugh class A) hepatic impairment were enrolled into the study. Subjects with mild hepatic impairment were not enrolled based on the data available from the other cohorts. Idelalisib was administered at a dose of 150 mg in the morning with a standard meal. Only 12 healthy volunteers were enrolled to match 10 subjects with moderate hepatic impairment and 10 subjects with severe hepatic impairment. PK samples were collected up to 120 h. The median laboratory values were AST 67 (14, 198) IU/L, ALT 40 (9, 100) IU/L and total bilirubin 36 (3, 100) mg/dL in patients with hepatic impairment.

The AUC of idelalisib is higher in subjects with moderate and severe hepatic impairment with similar changes observed in both groups using Child-Pugh criteria or NCI Organ Dysfunction Working Group (ODWG) criteria (**Table 14**). No changes were observed in C_{max} in subjects with hepatic impairment. As hepatic impairment increases exposure regardless of the degree of impairment, the AUC was compared for subjects with hepatic impairment defined as AST or ALT or bilirubin greater than the ULN to subjects without hepatic impairment. The AUC increased 1.7-fold (90% CI: 1.47, 2.06) in patients with AST greater than the ULN. The AUC increased 1.4-fold in patients with ALT (90% CI: 1.15, 1.80) and total bilirubin (90% CI: 1.13, 1.74) greater than the ULN.

Table 14. Comparative mean (CV%) pharmacokinetics of idelalisib in moderate and severe hepatic impairment

Hepatic Function	C_{max} (ng/mL)	AUC_{inf} (ng•h/mL)
Child-Pugh criteria		
Normal (n=12)	2,111 (26%)	10,047 (29%)
Moderate (n=10)	2,008 (20%)	16,700 (29%)
	GMR 0.96 (0.78, 1.18)	GMR 1.66 (1.31, 2.09)
Severe (n=10)	1,833 (35%)	16,544 (35%)
	GMR 0.84 (0.368, 1.04)	GMR 1.62 (1.28, 2.04)
NCI ODWG criteria		
Healthy (n=14)	2,095 (24%)	10,209 (27%)
Mild (n=7)	2,061 (19%)	17,718 (24%)
	GMR 0.99 (0.79, 1.24)	GMR 1.75 (1.38, 2.22)
Moderate (n=8)	1,787 (38%)	15,732 (34%)
	GMR 0.82 (0.66, 1.02)	GMR 1.50 (1.20, 1.89)
Severe (n=3)	1,893 (32%)	20,063 (34%)
	GMR 0.89 (0.65, 1.21)	GMR 1.94 (1.40, 2.70)

Source: Data from pp.xpt (study 112)

Collectively, these data suggest that patients with baseline hepatic impairment will have increased exposure to idelalisib; however, the median exposure was not higher for patients with baseline hepatic impairment compared to patients without baseline hepatic impairment enrolled

in the NHL trial (101-09). Only one patient with baseline hepatic impairment was enrolled into the CLL trial (312-0116).

Population Evaluation
Baseline AST and ALT as a continuous or categorical variable had no apparent influence on the PK of idelalisib. Greater than 94% of subjects included in these evaluations had AST and ALT ≤ 40 IU/L, suggesting that the population analyses is unlikely to identify a difference if present.

2.3.2.7 *What pregnancy and lactation use information is there in the application?*

PK studies in pregnant or nursing animals were not conducted. It is not known whether idelalisib is excreted in human milk.

Idelalisib will be pregnancy category D.

2.3.2.8 *Body Weight*

None. Baseline body weight was maintained in the final population PK analysis for idelalisib, but body weight had minimal effect on the population estimated CL/F. Body weight influenced CL/F by 10% or less with extreme weights of 53 kg (5^{th} percentile) or 112 kg (95^{th} percentile) compared to a typical body weight of 75 kg.

2.3.2.9 *Genetics*

Chronic Lymphocytic Leukemia
Chromosomal abnormalities involving chromosomes 11, 12, 13, and 17 and single gene mutations (herein collectively referred as genetic alterations) are common in CLL [PMID: 12040431]. Several of these genetic alterations, along with immunophenotypic features, have been associated with prognosis in retrospective and prospective studies (**Table 15**). The current clinical practice guidelines (NCCN) state that determination of 12 trisomy, 11q deletion, 13q deletion, 17p deletion (defined as > 10% positive cells), IgHV mutation status (defined as > 2% somatic mutation), CD38 (defined as ≥ 30% positive cells), ZAP-70 (defined as ≥ 20% positive cells) and TP53 sequencing provides useful prognostic information.

Table 15. Common genetic alterations observed in chronic lymphocytic leukemia

Genetic Change	Incidence	Median Survival
11q deletion[1]	16%	7 years
Trisomy 12[1]	18%	9 years
13q deletion[1]	55%	11 years
17p deletion[1]	7%	3 years
TP53 mutation[2]	8% (4% without 17p del)	2 years
IgHV(3-21) mutation positive[3]	55%	24 years
Normal Karotype[1]	18%	9 years

[1] PMID: 1136261, 17008705; [2] PMID: 20697090; [3] PMID: 10477713, 10477712, 11733578, 12149225

In the CLL trial, patients were allocated using a fixed-block centralized randomization within 8 strata defined by 3 stratification factors: (1) 17p deletion or p53 mutation (either vs. neither or indeterminate); (2) IgHV mutation (mutated vs. unmutated or indeterminate) and (3) any prior therapy with an anti-CD20 antibody (yes vs. no). The third stratification was excluded prior to unblinding for the first interim analysis, as most patients had received prior anti-CD20 therapy. Peripheral blood was collected at the screening and end-of-treatment visits using (a) FISH to

detect 11q deletion, 17p deletion and 12 trisomy, (b) DNA alteration analysis to assess TP53 and IgHV (IgHV3-21) and (c) flow cytometry to assess CD5, CD10, CD11C, CD19, CD20, CD23, CD38, CD45, light chains and ZAP-70.

17p deletion was detected using the Vysis CLL FISH probe kit (510(k), July 21, 2011). The kit uses FISH DNA probe technology to determine deletion status of probe targets for locus-specific identifier TP53 (17p), ATM (11q), 13q34 (13q) and D13S319 (13q), as well as D12Z3 alpha satellite (trisomy 12) in peripheral blood specimens from untreated patients with B-cell CLL. The FISH analysis was evaluated in at least 200 cells. Results were reported as abnormal if > 7% of the evaluated cells showed abnormal signal pattern for loss of 17p. This definition is not consistent with the published literature (> 20% of cells) or the current clinical practice guidelines (> 10% of cells).

TP53 was determined by Sanger sequencing of exons 5 to 9. About 95% of TP53 mutations for CLL reside in this region [PMID 11180073]. Results were reported as positive or negative for the detection of a mutation.

IgVH mutation was determined using a PCR-based assay to detect a monoclonal rearrangement followed by sequence analysis to determine the specific family and mutation frequency. Results were reported as mutated, unmutated, or failure. If mutations were detected at a level of 2% or higher, then the result was interpreted as mutated. This definition is consistent with current clinical practice guidelines.

Only the incidence of 17p deletion, TP53 and IgHV mutation status were provided in this application. The incidence differs than the incidence reported in the published literature. It is not clear whether differences in assay methodology or cutoff led to differences in the population Gilead characterized as 17p deletion positive. The differences could also be due to differences in patient populations, including prior treatment.

(b) (4)

Source: Applicant proposed labeling

Transaminitis

An exploratory genome-wide association study (GWAS) to search for common genetic variants and whole exome sequencing to identify rare functional genetic variations were conducted using DNA samples collected from 191 patients enrolled in the dose finding study (101-02) to identify possible predictors of liver injury. Gilead stated that there were no clear genetic variants predictive of liver injury after correction for multiple hypotheses testing. The incidence of hepatic injury or abnormal liver function tests was not reported for the genomic population, but AST or ALT elevations was reported in 19% and 18% of patients in Study 101-02, respectively.

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

Coadministration with a strong CYP3A inhibitor and a strong CYP3A inducer influenced the PK of idelalisib. It is recommended to avoid the coadministration of strong CYP3A inducers with idelalisib. Rifampin decreased idelalisib exposure by 75% and simulation indicates a 300 mg dose of idelalisib with rifampin cannot provide comparable exposure to a single 150 mg dose of idelalisib administered without an inducer. The labeling will state that strong CYP3A4 inducers should not be coadministered with idelalisib.

No dose modification is recommended for patients taking a strong CYP3A inhibitor with idelalisib. Although the exposure to idelalisib is higher in subjects taking strong CYP3A inhibitors compared to subjects not taking an inhibitor, no E-R relationship was identified for selected safety endpoints except for diarrhea in the NHL population. Patients taking strong CYP3A inhibitors will need to be closely monitored for serious adverse events associated with

idelalisib. Health care providers will be instructed to follow the dose modifications outlined in the labeling for adverse events.

2.4.2 What are the drug-drug interactions?

2.4.2.1 *Is there an in vitro basis to suspect in vivo drug-drug interactions?*

Yes, as idelalisib is metabolized by CYP3A4 and UGT1A4 and it inhibits CYP3A, CYP2C8, CYP2C9, and CYP2C19. Idelalisib or GS563117 is a substrate or inhibitor of several transporters, as well.

2.4.2.2 *Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?*

Idelalisib (GS-1101) undergoes metabolism by CYP3A4 (~19% of its overall metabolism) (AD-312-2023, 794306). Genetic differences will likely have no effect on idelalisib metabolism.

Inhibition

An open-label, crossover study was conducted in 12 healthy men to assess the effects of ketoconazole on the PK of idelalisib (101-05). One volunteer did not complete the study after experiencing increased transaminases, musculoskeletal pain and increased creatinine kinase. Ketoconazole is a strong CYP3A4 and P-gp inhibitor. Ketoconazole 400 mg was administered orally once daily for 4 days (days 1 to 4). Subjects were instructed to fast for 2 h after ketoconazole dosing on days 1 to 3. On day 4, idelalisib 400 mg was also administered in a fasted state (midnight until 4 h post dose). PK sampling occurred up to 48 h post dose. Concomitant administration of ketoconazole increased idelalisib AUC by 1.8-fold (**Table 16**).

Table 16. Effect of ketoconazole on the pharmacokinetics of idelalisib

IDELA PK Parameter	GLSM		GLSM Ratio (Test/Reference)		
	IDELA + Ketoconazole (Test)	IDELA (Reference)	Estimate	90% CI	
				Lower	Upper
C_{max} (ng/mL)	4450	3550	1.26	1.04	1.51
AUC_{0-last} (ng•h/mL)	28,000	15,300	1.83	1.60	2.09
AUC_{inf} (ng•h/mL)	28,500	15,900	1.79	1.57	2.04

Source: Final Study Report, 101-05, Table 6

Induction

An open label, fixed sequence study was conducted in 12 healthy volunteers to evaluate the effect of rifampin on the PK of idelalisib (313-0130). Rifampin was administered at a dose for 600 mg daily for eight days (days 11 to 18) in the fasted state. Idelalisib at a dose of 150 mg was administered on day 18, 2 h after a dose of rifampin with a standard meal.

Concomitant rifampin reduced idelalisib C_{max} by 58% and AUC by 75% (**Table 17**). Because idelalisib has dose dependent absorption, comparing exposures across different doses is difficult. To address this difficulty, the final population PK model of idelalisib which accounts for dose-dependent absorption, was used to predict concentrations of idelalisib at 300 mg given in combination with rifampin. The simulation suggests that a higher dose of idelalisib when administered with a strong CYP3A inducer is not likely to achieve exposure that is comparable to that of a 150 mg dose of idelalisib administered without a strong CYP3A inducer (**Figure 12**).

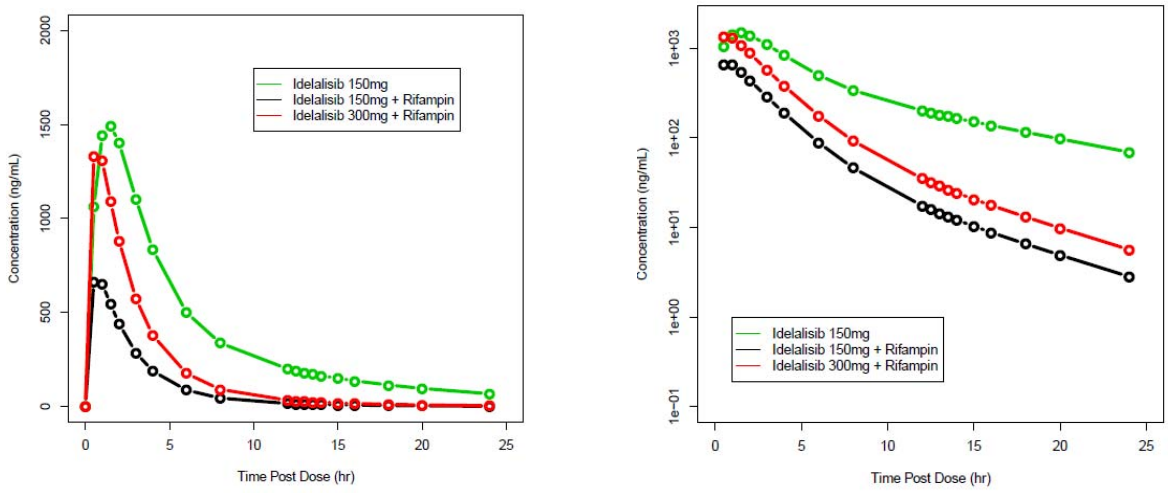
Table 17. Effect of rifampin on the pharmacokinetics of idelalisib

IDELA PK Parameter	Mean (%CV)		% GLSM Ratio (90% CI)
	IDELA Alone (N = 12)	IDELA + Rifampin 600 mg Once Daily (N = 11)	
C_{max} (ng/mL)	2151.67 (23.6)	932.55 (41.3)	42 (36, 49)
T_{max} (h)[a]	1.75 (1.25, 2.00)	1.50 (1.00, 2.00)	—
$t_{1/2}$ (h)[a]	5.75 (4.26, 6.43)	1.76 (1.02, 3.30)	—
AUC_{0-last} (ng•h/mL)	9363.0 (36.5)	2263.5 (40.0)	25 (23, 27)
AUC_{inf} (ng•h/mL)	9599.2 (37.0)	2293.5 (39.6)	25 (23, 27)

a Median (Q1, Q3)

Source: Final Study Report, GS-US-313-0130

Figure 12. Simulated concentration-time profile for idelalisib with and without rifampin at different doses on linear scale (left) and log-linear scale (right)



2.4.2.3 *Is the drug an inhibitor and/or an inducer of enzymes?*

Idelalisib or its metabolite strongly inhibits CYP3A substrate in humans. The exposure to a sensitive CYP3A substrate increased greater than 5-fold. The labeling will state that the coadministration of sensitive CYP3A substrates should be avoided with idelalisib.

Idelalisib and its metabolite are also likely to inhibit CYP2C8, CYP2C9, CYP2C19 and UGT1A1 in humans based on in vitro data. An additional study to assess the effect of idelalisib on the PK of CYP2C8, CYP2C9 or UGT1A1 substrates is not being recommended, because few sensitive or narrow therapeutic drugs are predominantly metabolized by these enzymes. A drug interaction in humans with sensitive CYP2C19 substrates is possible based on available data. More diarrhea and rash were observed in patients taking idelalisib with a PPI. The interaction could be caused by overlapping toxicities or increased exposure to the PPI as described below.

Idelalisib could induce CYP2B6 based on in vitro data. As few commercially available drugs are predominantly metabolized by CYP2B6, an additional study to assess the effect of idelalisib on

the PK of CYP2B6 substrates is not being recommended.

Nonclinical Data

CYP Inhibition

Table 18 lists the concentrations at which the catalytic activity of several cytochrome P450 enzymes was reduced by 50% following the application of idelalisib or GS-563117.

Table 18. The potential for idelalisib (top) and GS-563117 (bottom) to inhibit the catalytic activity of cytochrome P450 enzymes

Type of Study:	In Vitro Inhibition of Human Hepatic Microsomal Cytochrome P450 Enzymes		
Method:	Human Hepatic Microsomal Fractions; Monitoring Metabolite Formation by LC/MS/MS		
		Calculated IC_{50} (μM)[a]	
CYP Isozyme	**Probe Activity**	**Control Inhibitor[b]**	**IDELA**
CYP1A	Ethoxyresorufin O-deethylase	37	> 100[c]
CYP2B6	Bupropion 4-hydroxylase	4.3	> 25[b]
CYP2C8	Paclitaxel 6α-hydroxylase	2.0	13
CYP2C9	Diclofenac 4'-hydroxylase	0.83	> 100[c]
CYP2C19	Omeprazole 5-hydroxylase	8.1	76
CYP2D6	Dextromethorphan O-demethylase	0.12	> 100[c]
CYP3A	Midazolam 1'-hydroxylase	0.89	44
CYP3A	Testosterone 6ß-hydroxylase	2.0	> 100[c]

a Mean, n = 8 (except for CYP2B6, n = 7)

b Control Inhibitors: CYP1A, Furafylline; CYP2B6, Ticlopidine (0–10 μM); CYP2C8 Nicardipine; CYP2C9, Sulfaphenazole; CYP2C19, Oxybutynin; CYP2D6, Quinidine; CYP3A, Ketoconazole

c The concentration-response curve showed < 25% inhibition at 100 μM.

d At 25 μM, IDELA showed no inhibition of CYP2B6.

Type of Study:	In Vitro Inhibition of Human Hepatic Microsomal Cytochrome P450 Enzymes		
Method:	Human Hepatic Microsomal Fractions; Monitoring Metabolite Formation by LC/MS/MS		
		Calculated IC50 (μM)[a]	
CYP Isozyme	**Probe Activity**	**Control Inhibitor[b]**	**GS-563117**
CYP1A2	Phenacetin O-deethylase	0.11 ± 0.02	> 100
CYP2B6	Bupropion 4-hydroxylase	0.89 ± 0.13	> 100
CYP2C8	Paclitaxel 6α-hydroxylase	0.91 ± 0.22	39.8 ± 4.06
CYP2C9	Tolbutamide 4-hydroxylase	0.45 ± 0.07	90.7 ± 9.80
CYP2C19	S-Mephenytoin 4'-hydroxylase	10.1 ± 2.55	60.4 ± 7.69
CYP2D6	Dextromethorphan O-demethylase	0.05 ± 0.005	> 100
CYP3A	Midazolam 1'-hydroxylase	0.06 ± 0.007	5.1 ± 1.00
CYP3A	Testosterone 6ß-hydroxylase	0.23 ± 0.05	16.6 ± 2.14

a Mean ± SEM, n = 7

b Control Inhibitors: CYP1A2, ⟨α-Napthoflavone (0–3 μM); CYP2B6, Ticlopidine (0–10 μM); CYP2C8 Montelukast (0–3 μM); CYP2C9, Sulfaphenazole (0–10 μM); CYP2C19, Tranylcypromine (0–50 μM); CYP2D6, Quinidine (0–3 μM); CYP3A, Ketoconazole (0–3 μM)

Source: Section 2.6.5. Pharmacokinetics Tabulated Summary, Study AD-313-2019

Idelalisib likely competitively inhibits CYP2C8 (R_1=1.4), CYP3A (R_1=1.1), and CYP2C19 (R_1=1.1) based on the R values. The R values were calculated using an [I] of 4.6 μM (or 1,915 ng/mL) (population analysis) and a K*i* value that is the IC_{50} value divided by 2. Assuming an $[I]_{gut}$ of 1.4 mM (or 0.6 mg/mL) and a K*i* value of the IC_{50} value divided by 2, idelalisib is also likely to inhibit CYP3A in the gastrointestinal tract. Gilead conducted an independent study to access the effects of idelalisib on the PK of a sensitive substrate of CYP3A (313-0130) as described below.

GS-563117 likely competitively inhibits CYP2C9 (R_1=1.1) in addition to inhibiting these

enzymes [CYP3A (R_1=1.6, 2.8), CYP2C8 (R_1=1.2), and CYP2C19 (R_1=1.2)]. The R values were calculated using an [I] value of 9.4 µM (or 4,039 ng/mL). GS-563117 is also a mechanism-based inhibitor of human CYP3A (IC_{50}: 5.1 µM, KI: 0.18 µM, kinact: 0.033 min^{-1}) (AD-313-2016). Assuming an [I] of 9.4 µM and a K_{deg} of 0.000825 min^{-1}(Watkins et al., 1986), the R_2 value exceeds 1.1.

Relatively few patients were coadministered CYP2C8, CYP2C9 or UGT1A1 substrates, but about 30% of patients enrolled in NHL and CLL trials were coadministered sensitive CYP2C19 substrates, including lansoprazole and omeprazole. The incidence of diarrhea and rash were higher in patients taking PPI (*Section 2.1.1*). These adverse events are associated with both PPI (1% to 4%) [PMC2014999] and idelalisib. The exposure to idelalisib is similar in patients taking ARA as compared to patients not taking these agents. Overlapping adverse events or an increased exposure to PPI (CYP2C19 substrates) could explain the increased incidence of adverse events. Higher exposures (5-12 times) for PPI have been observed in poor CYP2C19 metabolizers [PMID: 15245569] and dose-response has been observed with diarrhea and infections [PMC2886361]. No dose adjustment is recommended for patients taking CYP2C19 substrates.

CYP Induction

Idelalisib at concentrations of 10 µM did not induce CYP1A2, but did induce CYP2B6 and CYP3A4 messenger mRNA levels in human hepatocytes (AD-312-2008). GS-563117 did not induce these enzymes in human hepatocytes (AD-312-2008). **Table 19** lists the percent of positive control or fold increase compared to vehicle.

Table 19. The potential for idelalisib and GS-563117 to induce mRNA levels of cytochrome P450 enzymes

	Maximum increase in mRNA at 10 µM across all three donors (Percent of positive control or fold increase over vehicle)	
Endpoint	**GS-1101**	**GS-563117**
CYP1A2	2%	2%
CYP2B6	46%	10%
CYP3A4	54%	5%
CYP2C8	3.9-fold	1.4-fold
CYP2C9	3.1-fold	1.5-fold
CYP2C19	1.3-fold	1.0-fold
Pgp	1.6-fold	1.2-fold
UGT1A1	2.4-fold	1.3-fold
UGT1A4	2.1-fold	1.2-fold
Aldehyde oxidase	1.5-fold	1.0-fold

Source: Study report, AD-313-2008

UGT Inhibition

Idelalisib and GS-563117 inhibited UGT1A1-catalyzed glucuronidation of β-estradiol with an IC_{50} of 42 and 22 µM, respectively (AD-313-2017). Assuming a C_{max} of 4.6 µM for idelalisib and of 9.4 µM for GS-563117 following idelalisib 150 mg BID, idelalisib and GS-563117 could inhibit UGT1A1 in humans. The ratio of the C_{max} to IC_{50} value was > 0.1.

Clinical Data

CYP Inhibition or Induction

An open label, fixed sequence study was conducted in healthy volunteers to evaluate the effect of idelalisib on PK of midazolam (313-0130). A single oral dose of midazolam 5 mg (as an oral solution of 2 mg/mL) was administered with a standard meal in the morning on days 3 and 12. Idelalisib 150 mg BID was administered with a standard meal on days 5 to 12. PK samples were collected up to 24 h after each dose of midazolam. The elimination half-life of midazolam is relatively short at less than 7 h.

Coadministration of idelalisib increased midazolam C_{max} by 2.4-fold and AUC by 5.4-fold (**Table 20**). Coadministration of idelalisib with sensitive substrates or substrates with a narrow therapeutic index should be avoided, since idelalisib or its metabolite is a strong CYP3A inhibitor.

Table 20. Effect of idelalisib on the pharmacokinetics of midazolam

Midazolam PK Parameter	Mean (%CV)		% GLSM Ratio (90% CI)
	Midazolam Alone (Reference) (N = 12)	Midazolam + IDELA 150 mg BID (Test) (N = 11)	
C_{max} (ng/mL)	16.47 (28.0)	38.07 (13.5)	238 (200, 283)
T_{max} (h)[a]	1.75 (0.50, 2.00)	3.00 (2.00, 4.00)	—
$t_{1/2}$ (h)[a]	5.77 (4.97, 6.48)	9.47 (8.57, 10.64)	—
AUC_{0-last} (ng•h/mL)	84.8 (33.9)	366.3 (15.7)	455 (379, 546)
AUC_{inf} (ng•h/mL)	88.2 (34.8)	454.4 (23.6)	537 (456, 632)

a Median (Q1, Q3)

Source: Final Study Report, GS-US-313-0130

2.4.2.4 *Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?*

Idelalisib is a substrate of P-gp and BCRP, but not of OATP1B1, OATP1B3, OCT2, OAT1, OAT3 in vitro. It is plausible that idelalisib is transported by P-gp in humans, since idelalisib exposure was affected by rifampin (CYP3A and P-gp inducer) and ketoconazole (CYP3A and P-gp inhibitor); however, it is not possible to separate the effects of rifampin or ketoconazole on the transport or metabolism of idelalisib. GS-563117 is a substrate of P-gp and BCRP, but not of OATP1B1 or OATP1B3 in vitro.

Idelalisib is not an inhibitor of P-gp, OATP1B1 or OAT1B3 in humans, since the administration of idelalisib did not affect the PK of substrates of these transporters. Idelalisib is not likely to inhibit BCRP, OAT1, OAT3 or OCT2 and GS-563117 is not likely to inhibit P-gp, BCRP, OAT1 and OAT3 in humans based on in vitro data.

Substrate

Idelalisib and GS-563117 are substrates of P-gp and BCRP (*Section 2.2.5.3*). Idelalisib is not a substrate of OATP1B1, OATP1B3, OAT1, OAT3, and OCT2. GS-563117 is not a substrate of OATP1B1 and OATP1B3 and it is not known if GS-563117 is a substrate of OAT1, OAT3 and OCT1 (*Section 2.2.5.4*).

Inhibitor

Table 21 lists the IC_{50} values for various efflux and uptake transporters estimated in vitro using cell lines transfected with the individual transporters and fluorescent model substrates.

Idelalisib does not inhibit BCRP and GS-5631117 does not inhibit P-gp or BCRP. Idelalisib could inhibit P-gp in humans as the ratio of the C_{max} to IC_{50} is ≥ 0.1, assuming a C_{max} of 4.6 μM. Gilead conducted a study to determine the effects of idelalisib on the PK of a P-gp substrate (313-0130).

Idelalisib and GS-563117 could inhibit OATP1B1 and OATP1B3 in humans as the ratio of the C_{max} to IC_{50} is ≥ 0.1. Gilead conducted a study to determine the effect of idelalisib on the PK of a sensitive substrate of these transporters (313-0130).

Idelalisib does not inhibit OCT2, OAT1 and OAT3 and GS-563117 does not inhibit OAT1 and OAT3 in vitro. GS-563117 is not likely to inhibit OCT2 in humans as the ratio of the unbound C_{max} to IC_{50} is < 0.1.

Table 21. Potential for idelalisib and GS-563117 to inhibit various transporters

Transporter	Idelalisib	GS-563117
P-gp	8 μM	> 100 μM
BCRP	> 100 μM	> 100 μM
OATP1B1	10 μM	26 μM
OATP1B3	7 μM	36 μM
OAT1	> 10 μM	> 100 μM
OAT3	> 10 μM	> 100 μM
OCT2	> 10 μM	50 μM

Source: Data from Studies 400571, AD-313-2011, AD-313-2005, AD-313-2012 and OPT-2010-087

Clinical Data

Transporters ABCG2, SLCO1B1 and SLCO1B3

An open label, fixed sequence study was conducted in healthy volunteers to evaluate the effect of idelalisib on the PK of rosuvastatin (313-0130). Rosuvastatin was administered at a dose of 10 mg on day 1 with a standard meal. Idelalisib at a dose of 150 mg was administered on day 3 once daily and on days 4 to 8 twice daily with a standard meal. Idelalisib at a dose of 150 mg and rosuvastatin at a dose of 10 mg were coadministered on day 9 with a standard meal. PK samples were collected up to 36 h after the rosuvastatin dose; this sampling time was relatively short compared to the elimination half-life of 19 h.

The exposure of rosuvastatin, a substrate for BCRP, OATP1B1, and OATP1B3 transport, was not affected by the coadministration of idelalisib, suggesting that idelalisib or its metabolite is unlikely to inhibit these transporters in humans (**Table 22**).

Table 22. Effect of idelalisib on pharmacokinetics of rosuvastatin

Rosuvastatin PK Parameter	Mean (%CV)		% GLSM Ratio (90% CI)
	Rosuvastatin Alone (Reference) (N = 12)	Rosuvastatin + IDELA 150 mg BID (Test) (N = 12)	
C_{max} (ng/mL)	1.56 (52.1)	1.88 (66.8)	115 (97, 137)
T_{max} (h)[a]	3.75 (3.50, 4.00)	3.50 (3.25, 4.00)	—
$t_{1/2}$ (h)[a]	20.25 (14.73, 24.79)	21.32 (14.43, 23.39)	—
AUC_{0-last} (ng•h/mL)	17.9 (40.0)	19.7 (59.9)	103 (87, 121)
AUC_{inf} (ng•h/mL)	23.1 (31.9)	25.7 (59.4)	102 (83, 124)

a Median (Q1, Q3)

Source: Final Study Report, GS-US-313-0130

Transporter ABCB1

Twelve healthy volunteers were administered a single oral dose of digoxin 0.5 mg administered in the morning on day 1 with a standard meal (313-0130). Idelalisib was administered at a dose of 150 mg BID on days 5 to 13 with a standard meal. Idelalisib at a dose of 150 mg and digoxin at a dose of 0.5 mg were coadministered on day 14 with a standard meal. PK samples were collected up to 48 h after the digoxin dose. This sampling time is relatively short compared to the elimination half-life of 36 to 48 h. The exposure of digoxin was not affected when coadministered with idelalisib administered at a dose of 150 mg BID, suggesting that idelalisib is unlikely to inhibit P-gp in humans (**Table 23**).

Table 23. Effect of idelalisib on pharmacokinetics of digoxin

Digoxin PK Parameter	Mean (%CV)		% GLSM Ratio (90% CI)
	Digoxin Alone (Reference) (N = 12)	Digoxin + IDELA 150 mg BID (Test) (N = 11)	
C_{max} (ng/mL)	1.55 (18.5)	1.94 (19.4)	124 (115, 133)
T_{max} (h)[a]	1.50 (1.50, 2.25)	2.00 (1.50, 2.50)	—
$t_{1/2}$ (h)[a]	39.26 (32.47, 47.41)	35.15 (34.05, 40.91)	—
AUC_{0-last} (ng•h/mL)	20.7 (26.7)	21.9 (25.3)	104 (98, 111)
AUC_{inf} (ng•h/mL)	37.0 (35.4)	37.0 (28.2)	100 (87, 115)

a Median (Q1, Q3)

Source: Final Study Report, GS-US-313-0130

2.4.2.5 *Are there other metabolic/transporter pathways that may be important?*

Yes. Idelalisib is metabolized by the cytosolic enzyme aldehyde oxidase (~43% of its overall metabolism). It is also metabolized by UGT1A4 with glucuronidated metabolites in the urine and feces accounting for < 10% of radioactivity in these matrices. Glucuronidation likely accounts for ~3% of the overall metabolism of idelalisib. **Figure 9** provides a schematic for the proposed metabolism of idelalisib.

2.4.2.6 *Does the label specify co-administration of another drug and if so, has the interaction potential between the drugs been evaluated?*

Zydelig is to be administered as monotherapy for patients with FL or SLL.

Zydelig is to be administered in combination with rituximab for patients with CLL. The potential for a PK interaction between rituximab and idelalisib was not examined as recommended in the draft FDA Guidance for Industry entitled, *Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.* A study post marketing will not be recommended as the safety and effectiveness of this combination has been demonstrated in a randomized controlled trial (312-0116).

2.4.2.7 *What other co-medications are likely to be administered to the target population?*

Patients taking idelalisib will likely be taking other medications to prevent or treat adverse events or concurrent illnesses.

2.4.2.8 *Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?*

No.

2.4.2.9 *Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?*

No.

2.4.2.10 *Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?*

No.

2.4.3 What issues related to dose, dosing regimens, or administrations are unresolved and represent significant omissions?

None.

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Gilead stated that idelalisib is a low-solubility, high-permeability (BCS Class 2) compound. The review completed by Chemistry, Manufacturing and Controls (CMC) contains a description of the data supporting this classification.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The drug product administered in the clinical trials that support the proposed indications is the to-be-marketed drug product. No relative bioavailability study was needed to compare the trial drug product to the to-be-marketed drug product. A relative bioavailability study was conducted to compare PK of drug products used in earlier clinical trials to a tablet drug product that contains (b) (4) than the to-be-marketed drug product. The PK of idelalisib is

similar for the different drug products, indicating that the PK data for different drug products can be evaluated collectively to characterize the PK of idelalisib. The change in (b) (4) is considered a minor change and it not expected to affect the bioavailability. For additional details, refer to the ONDQA review.

Drug Products

Five oral solid dosage formulations were developed and used during clinical evaluation: (b) (4) and tablet (b) (4) as listed in **Table 24.**

Table 24. Formulations used during clinical development

Tablet	(b) (4)
(b) (4)	
101-06	
101-07	
101-10	
101-11	
(b) (4)	
312-0115	
312-0116	
312-0117	
312-0119	
313-0112	
313-0117	
313-0118	
313-0124	
313-0125	
313-0130	
339-0101	
101-02	
101-07	
101-08	
101-09	
101-10	
101-11	
101-99	

Source: Data from NDA 205/858 Seq 17, Response to Information Request

Relative Bioavailability

A single crossover study was conducted in 15 healthy men to evaluate the PK of a single 100 mg dose of idelalisib administered as a (b) (4) in the fasted state (101-06). Subjects were randomized to 1 of 6 treatment sequences and idelalisib was administered in a fasted state (midnight to 3 h after a dose) on days 1, 5, and 9. PK samples were collected up to 48 h after the dose.

The exposure following administration of the tablet or of the (b) (4) is similar (**Table 25**). The (b) (4) was only used in this study, but another (b) (4) was used in other studies as listed in **Table 24**. The (b) (4) product demonstrated higher C_{max} and similar

AUC compared to the (b) (4) product, as expected due to the (b) (4) process which (b) (4) These data suggest that the exposure with the (b) (4) is likely similar to the (b) (4) and tablets, since the exposure as measured by the AUC was similar for (b) (4) and tablets in this study.

Table 25. Relative bioavailability of three idelalisib drug products

PK Parameter	Comparison	GLSM		Ratio Test/Reference		P-Value Treatment
		Test	Reference	Estimated	90% CI	
C_{max} (ng/mL)	(b) (4)	1720	1350	1.28	1.06 – 1.53	0.0306
	Tablet vs (b) (4)	1230	1350	0.91	0.76 – 1.09	0.3896
$AUC_{0\text{-last}}$ (ng·hr/mL)	(b) (4)	6570	5810	1.13	1.05 – 1.21	0.0065
	Tablet vs (b) (4)	6260	5810	1.08	1.00 – 1.16	0.0846
$AUC_{0\text{-inf}}$ (ng·hr/mL)	(b) (4)	6610	5870	1.13	1.05 – 1.21	0.0082
	Tablet vs (b) (4)	6310	5870	1.08	1.00 – 1.16	0.0915

Source: Table 5, Study report, 101-06

2.5.2.1 *What data support or do not support a waiver of in vivo BE data?*

Not applicable.

2.5.2.2 *What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?*

None. The exposure for the different drug products is similar.

2.5.2.3 *If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and efficacy data support the approval of the to-be-marketed product?*

Not applicable.

2.5.3 What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

FDA agrees with the proposed labeling without regard to food. A high-fat breakfast increased the AUC by 1.4-fold compared to fasted state. No E-R relationship has been demonstrated for the primary efficacy endpoints or selected safety endpoints (except diarrhea in the NHL population) and no MTD has been identified. The NHL and CLL trials were conducted without regard to food.

Food Effect Study

An open-label, crossover study was conducted in healthy men to assess the effects of food on the PK of idelalisib (101-05). In two separate treatment periods (1 and 2), six volunteers were administered idelalisib 400 mg in the fed state and in the fasted state. For the fasted state,

subjects were required to fast from midnight until 4 h post dose the next day. For the fed state, subjects were fed a standard high-fat breakfast and dosing occurred within 30 minutes of the start of the meal. PK samples were collected up to 48 h. The geometric mean exposure is 1.4-fold higher in the fed state compared to the fasted (**Table 26**).

The current FDA Guidance for Industry, entitled *Food-Effect Bioavailability and Fed Bioequivalence Studies* generally recommends that the highest strength of a drug product intended to be marketed should be tested in food-effect studies. Gilead conducted the study using a (b) (4) formulation that was not the to-be-marketed drug product and at a dose higher than the highest proposed strength of the drug product. As the relative bioavailability is likely similar between the (b) (4) and the to-be-marketed, a post marketing study to conduct a food effect study in which the to-be-marketed tablet is administered will not be recommended.

Table 26. Comparative pharmacokinetics of idelalisib in fed and fasted state

IDELA PK Parameter	GLSM		GLSM Ratio (Test/Reference)		
	Fed (Test)	Fasted (Reference)	Estimate	90% CI	
				Lower	Upper
C_{max} (ng/mL)	3410	3500	0.97	0.81	1.17
AUC_{0-last} (ng•h/mL)	21,200	15,000	1.41	1.24	1.61
AUC_{inf} (ng•h/mL)	21,300	15,700	1.36	1.19	1.56

Source: Study 101-05, pp.xpt

Other Studies

Table 27 lists which studies were conducted in the fed or fasted state. Gilead conducted the studies supporting the indications for NHL and CLL without regard to food and proposed labeling states that idelalisib should be taken with or without food. Several studies were conducted with a standard meal. No study was conducted to compare the effects of a standard meal on the PK of idelalisib to the PK of idelalisib in the fasted state or with a high-fat meal. As a high-fat meal has limited effect on the PK of idelalisib, it is likely that a standard meal as described in *Section 2.2.4.3* will not have a clinically meaningful effect on the PK of idelalisib.

Table 27. Studies listed by fed or fasted state

Fed	Fasted	Without Regard
Standard Meal 313-0111 313-0112 313-0117 313-0118 313-0126 313-0130 339-0101 High-Fat Breakfast 101-05	101-01 101-02 101-04 101-05 101-06 101-08	101-09 101-10 101-11 101-99 (extension) 312-0116

Source: Final study reports, all studies

2.5.4 When would a fed BE study be appropriate and was one conducted?

Not applicable.

2.5.5 How do the dissolution conditions and specifications ensure in vivo performance and quality of the product?

Please read the ONDQA review for more information.

2.5.6 If different strengths are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed formulation tested?

Not applicable as no bioequivalence studies are necessary. Please read the CMC review for more information.

2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

Not applicable.

2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

Not applicable.

2.5.9 What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

None.

2.6 ANALYTICAL SECTION

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

High performance liquid chromatography coupled to tandem mass spectrometry (LC/MS/MS)

methods were developed and validated for the identification and quantification of idelalisib and GS-563117 in the human biological matrices (plasma and urine).

Gilead provided additional reports for the assays used to measure rifampin (313-0130, Report 8251203), digoxin (Study 313-0130, Report 8274044), rosuvastatin (313-0130, Report 8281135) and midazolam (313-0130, Report 8280288) in human plasma using validated LC/MS/MS methods. The accuracy and precision of the methods were consistent with the current draft FDA Guidance for Industry, entitled, *Bionalytical Method Validation* and the calibration range was appropriate to support the concentrations measured in the associated study.

2.6.2 Which metabolites have been selected for analysis and why?

Plasma concentrations of GS-563117 were measured in at least six clinical trials, as this metabolite is a major metabolite.

2.6.3 For all moieties measured, is free, bound or total measured?

Total concentrations were measured for GS-563117 and idelalisib.

2.6.4 What bioanalytical methods are used to assess concentrations?

Table 28 lists the biological methods used to measure idelalisib and GS-563117 for each study that included PK sampling. The bioanalytical method was first developed by (b) (4) and subsequently validated at (b) (4) and (b) (4) The parameters described for the various methods indicate that the methods were adequate to estimate the concentration data.

Table 28. Bioanalytical methods for idelalisib and GS-563117

Study No.	Matrix	Analyte	Most Current Validation Report[a]	Analytical Method	Limits of Quantification	Sample Analysis Report
101-01	Human Plasma	IDELA	(b) (4) RD-962, RD-962 Amendment 1	LC/MS/MS (b) (4) RD-962, RD-962 Amendment 1	0.5–1500 ng/mL	(b) (4) 539EC-076391
	Human Urine		(b) (4) RD-963	LC/MS/MS (b) (4) RD-963	1–1000 ng/mL	(b) (4) 539EC-076391
101-02	Human Plasma	IDELA	(b) (4) 5378.083008, 5753.042009, 6395.101510 6222.011510	LC/MS/MS (b) (4) 5378.083008, 5753.042009, 6395.101510 6222.011510	0.5–1500 ng/mL	(b) (4) 5377.122009
		GS-563117	(b) (4) 5222.011510	LC/MS/MS (b) (4) 6222.011510	0.5–1500 ng/mL	(b) (4) 5377.122009
101-04	Human Plasma	IDELA	(b) (4) 5378.083008, 5753.042009, 6395.101510	LC/MS/MS (b) (4) 5378.083008, 5753.042009, 6395.101510	0.5–1500 ng/mL	(b) (4) 516.033109
101-05	Human Plasma	IDELA	(b) (4) RD-962, RD-962 Amendment 1	LC/MS/MS (b) (4) RD-962, RD-962 Amendment 1	0.5–1500 ng/mL	(b) (4) 200EC-092073-A
		GS-563117	(b) (4) 5222.011510	LC/MS/MS (b) (4) 6222.011510	0.5–1500 ng/mL	(b) (4) 5444.092010

Study No.	Matrix	Analyte	Most Current Validation Report[a]	Analytical Method	Limits of Quantification	Sample Analysis Report
101-06	Human Plasma	IDELA	(b) (4) (b) (4) RD-962, RD-962 Amendment 1	LC/MS/MS (b) (4) (b) (4) RD-962, (b) (4) RD-962 Amendment 1	0.5–1500 ng/mL	(b) (4) (b) (4) 004EC-100041
101-07	Human Plasma	IDELA	(b) (4) (b) (4) 5378.083008, 5753.042009, 6395.101510	LC/MS/MS (b) (4) (b) (4) 378.083008, 753.042009, 395.101510	0.5–1500 ng/mL	(b) (4) 6394.100810
		Bendamustine	(b) (4) 1000-05886-2 (Report not Available)	LC/MS/MS (b) (4) 1000-05886-2	0.1–100 ng/mL	(b) (4) 1121-10280-1
	Whole Blood	Everolimus	(b) (4) 1003-091478-001	LC/MS/MS (b) (4) 1003-091478-001	0.25–250 ng/mL	(b) (4) 1121-12330-1
101-08	Human Plasma	IDELA	(b) (4) 8234402 Amendment 1	LC/MS/MS (b) (4) 8234402 Amendment 1	5–5000 ng/mL	(b) (4) 8263555
		GS-563117				
101-09	Human Plasma	IDELA	(b) (4) 8234402 Amendment 1	LC/MS/MS (b) (4) 8234402 Amendment 1	5–5000 ng/mL	(b) (4) 8234400
		GS-563117				
101-11	Human Plasma	IDELA	(b) (4) 8234402 Amendment 1	LC/MS/MS (b) (4) 8234402 Amendment 1	5–5000 ng/mL	(b) (4) 82949529
		GS-563117				
GS-US-312-0116	Human Plasma	IDELA	(b) (4) 8234402 Amendment 1	LC/MS/MS (b) (4) 8234402 Amendment 1	5–5000 ng/mL	(b) (4) 8257271
		GS-563117				
GS-US-313-0111	Human Plasma	IDELA	(b) (4) 8234402 Amendment 1	LC/MS/MS (b) (4) 8234402 Amendment 1	5–5000 ng/mL	(b) (4) 8275764
		GS-563117				

Study No.	Matrix	Analyte	Most Current Validation Report[a]	Analytical Method	Limits of Quantification	Sample Analysis Report
	Human Urine	IDELA	(b) (4) 8275763 Amendment 1	LC/MS/MS (b) (4) 8275763 Amendment 1	50–50,000 ng/mL	
		GS-563117				
GS-US-313-0112	Human Plasma	IDELA	(b) (4) 8234402 Amendment 1	LC/MS/MS (b) (4) 8234402 Amendment 1	5.0–5000 ng/mL	(b) (4) 8275396
		GS-563117				
GS-US-313-0117	Human Plasma	IDELA	(b) (4) 8234402 Amendment 1	LC/MS/MS (b) (4) 8234402 Amendment 1	5.0–5000 ng/mL	(b) (4) 8276175
		GS-563117				
GS-US-313-0118	Human Plasma	IDELA	(b) (4) 8234402 Amendment 1	LC/MS/MS (b) (4) 8234402 Amendment 1	5.0–5000 ng/mL	(b) (4) 8275789
		GS-563117				
	Human Urine	IDELA	(b) (4) 8275763 Amendment 1	LC/MS/MS (b) (4) 8275763 Amendment 1	5–50,000 ng/mL	
		GS-563117				

2.6.4.1 *What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?*

Table 28 provides the range of the standard curve for each study. The standard curve was generated using weighted ($1/x^2$) quadratic (b) (4) or linear (b) (4) regression. This standard curve range was adequate for the purposes of determining plasma concentrations of idelalisib and GS-563117 in the clinical studies.

2.6.4.2 *What are the lower and upper limits of quantification?*

Table 29 provides the lower limit of quantification, the precision and accuracy and the stability for each assay.

Table 29. Bioanalytical method validation

PLASMA

[redacted] Studies 101-01, 101-05, and 101-06

	IDELA
Linear Range (ng/mL)	0.5 to 1500
Lower Limit of Quantitation (ng/mL)	0.5
Interassay Precision Range (%CV)	0.0 to 10.2
Interassay Accuracy Range (%RE)	−2.5 to 9.7
Stability (days)	249 at −20°C 1059 at −70°C

Source: m5.3.1.4, [redacted] validation report [redacted]-RD-962 and [redacted]-RD-962 Amendment 1 and [redacted] report [redacted]5483.070711

[redacted]: Studies 101-02, 101-04, and 101-07

	IDELA	
Linear Range (ng/mL)	0.5 to 1500	10 to 6000
Lower Limit of Quantitation (ng/mL)	0.5	10
Interassay Precision Range (%CV)	≤ 5.36	≤ 5.98[a]
Interassay Accuracy Range (%RE)	−10.0 to −1.2	0.60 to 2.0[a]
Stability (days)	249 at −20°C and 1059 at −70°C	—

a Intraday ranges are reported.

Source: m5.3.1.4, [redacted] validation reports [redacted]5378.083008, [redacted]5753.042009, [redacted]6395.101510, [redacted] report [redacted]5483.070711, and [redacted] validation report [redacted]RD-962 Amendment 1

[redacted] Studies 101-02 and 101-05

	IDELA	GS-563117
Linear Range (ng/mL)	0.5 to 1500	0.5 to 1500
Lower Limit of Quantitation (ng/mL)	0.5	0.5
Interassay Precision Range (%CV)	≤ 6.5	≤ 10.6
Interassay Accuracy Range (%RE)	−4.2 to 2.0	−3.0 to 0.67
Stability (days)	249 at −20°C 1059 at −70°C	25 at −70°C

Source: m5.3.1.4, [redacted] validation report [redacted]222.011510, [redacted] report [redacted]5483.070711, and [redacted] validation report [redacted]RD-962 Amendment 1

[redacted] Studies 101-08, 101-09, 101-11, 312-0116, 313-0111, 313-0112, 313-0117, 313-0118, 313-0130, and 339-0101

	IDELA	GS-563117
Linear Range (ng/mL)	5 to 5000	5 to 5000
Lower Limit of Quantitation (ng/mL)	5	5
Interassay Precision Range (%CV)	3.8 to 13.4	2.5 to 11.9
Interassay Accuracy Range (%RE)	−4.7 to 1.6	−5.6 to 0.0
Stability (days)	868 at −10°C to −30°C and −60°C to −80°C	868 at −10°C to −30°C and −60°C to −80°C

Source: m5.3.1.4, [redacted] validation report 8234402 Amendment 1

URINE

(b) (4) Study 101-01

	IDELA
Linear Range (ng/mL)	1 to 1000
Lower Limit of Quantitation (ng/mL)	1
Interassay Precision Range (%CV)	0.0 to 13.6
Interassay Accuracy Range (%RE)	−6.1 to 6.1
Stability (days)	204 at −20°C and −70°C

Source: 5.3.1.4, (b) (4) validation report (b) (4) -RD-963

(b) (4) Studies 313-0111 and 313-0118

	IDELA	GS-563117
Linear Range (ng/mL)	50 to 50,000	50 to 50,000
Lower Limit of Quantitation (ng/mL)	50	50
Interassay Precision Range (%CV)	2.8 to 6.9	3.0 to 13.6
Interassay Accuracy Range (%RE)	2.8 to 12.0	0.7 to 4.0
Stability (days)	160 at −10°C to −30°C and −60°C to −80°C	160 at −10°C to −30°C and −60°C to −80°C

Source: m5.3.1.4, (b) (4) validation report 8275763 Amendment 1

2.6.4.3 *What are the accuracy, precision and selectivity at these limits?*

Table 29 provides the precision and accuracy for each assay.

2.6.4.4 *What is the sample stability under the conditions used in the study? (long-term, freeze-thaw, sample-handling, sample transport, autosampler)*

Table 29 provides the stability for each assay.

2.6.4.5 *What is the QC sample plan?*

Low, middle and high quality controls were included in each analytical run. About two-thirds of the quality controls included in each run appropriately needed to have a calculated concentration within ± 15.0% of nominal concentration for the analytical run to be accepted.

3 APPENDICES

3.1 PHARMACOMETRICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

Application Number	NDA 205-858 and NDA 206-545
Compound	Idelalisib (Zydelig); 100 mg and 150 mg tablets
Indication	Refractory indolent non-Hodgkin lymphoma Relapsed chronic lymphocytic leukemia
Submission Date	September 11, 2013 and December 2, 2013
Sponsor	Gilead Sciences
Pharmacometrics Reviewer	Dhananjay D. Marathe, PhD
Pharmacometrics Team Leader	Nitin Mehrotra, PhD
Related IND	101254

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions:

1.1.1 What are the characteristics of the exposure-response relationships for efficacy and safety for Idelalisib?

Efficacy: No exposure-response (E-R) relationship was observed for the primary endpoint of overall response rate (ORR) in the efficacy trial supporting the indication of iNHL (indolent non-hodgkin's lymphoma, 101-09; no placebo arm) where a single dosing regimen of 150 mg BID was used (**Figure 1**). Moreover, no E-R relationship was evident for progression free survival (PFS) in this efficacy study (**Figure 2**). Similarly, there was no exposure-response (E-R) relationship observed for the primary endpoint of PFS in the efficacy trial supporting the indication of CLL (312-0116; with placebo arm) where a single dosing regimen of 150 mg BID was used (**Figure 3**).

As shown in **Figure 2** and **Figure 3** below, there was no significant difference in PFS between the four exposure quartiles of idelalisib for both iNHL and CLL trials. All the exposure quartiles of idelalisib were uniformly beneficial relative to placebo (background rituximab regimen) in CLL pivotal trial (**Figure 3**). Steady state trough concentrations (C_{tau}) were used as exposure metric in these efficacy evaluations, since C_{tau} was found to be more closely related with reduction in tumor size in the relevant patient population in the earlier dose ranging study (101-02). Besides the primary endpoints, the pharmacodynamic response of best reduction in tumor size (sum of products of greatest perpendicular diameters of index lesions; SPD) showed no specific relationship with the four exposure quartiles in the pivotal efficacy trials for iNHL as well as CLL population (**Figure 4**).

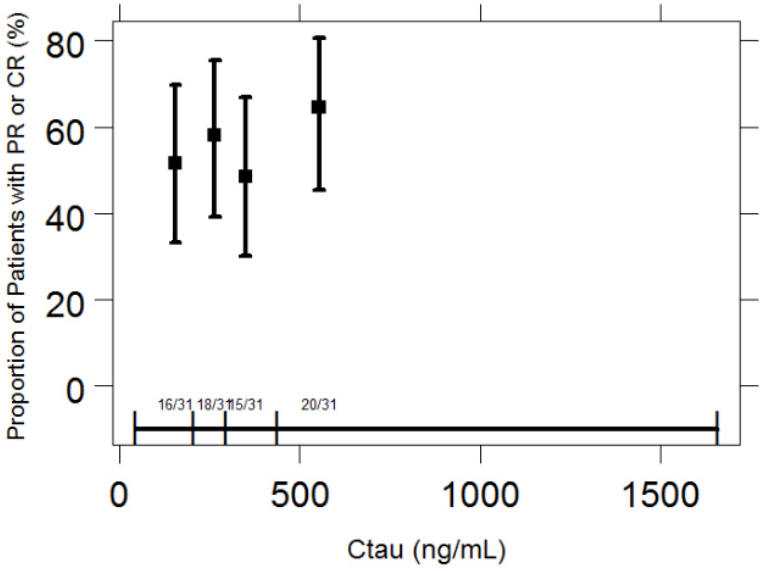


Figure 1: Exposure-response analysis for primary endpoint of ORR (CR+PR) in iNHL single arm pivotal trial 101-09 with 150 mg BID dose. Idelalisib C_{tau} was used for exposure quartiles (C_{tau} range: 43–1658 ng/mL)**.** *Source: Reviewer's analysis*

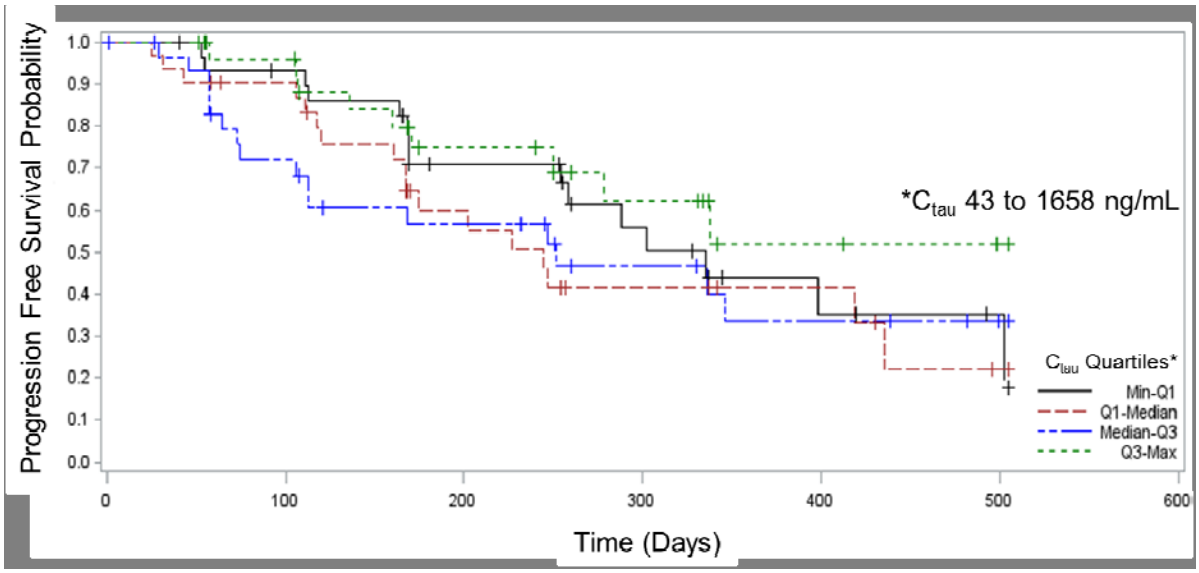


Figure 2: Kaplan-Meier plot of exposure-response analysis for progression free survival (PFS) in iNHL single arm pivotal trial 101-09 with 150 mg BID dose. Idelalisib C_{tau} was used for exposure quartiles. *Source: Reviewer's analysis*

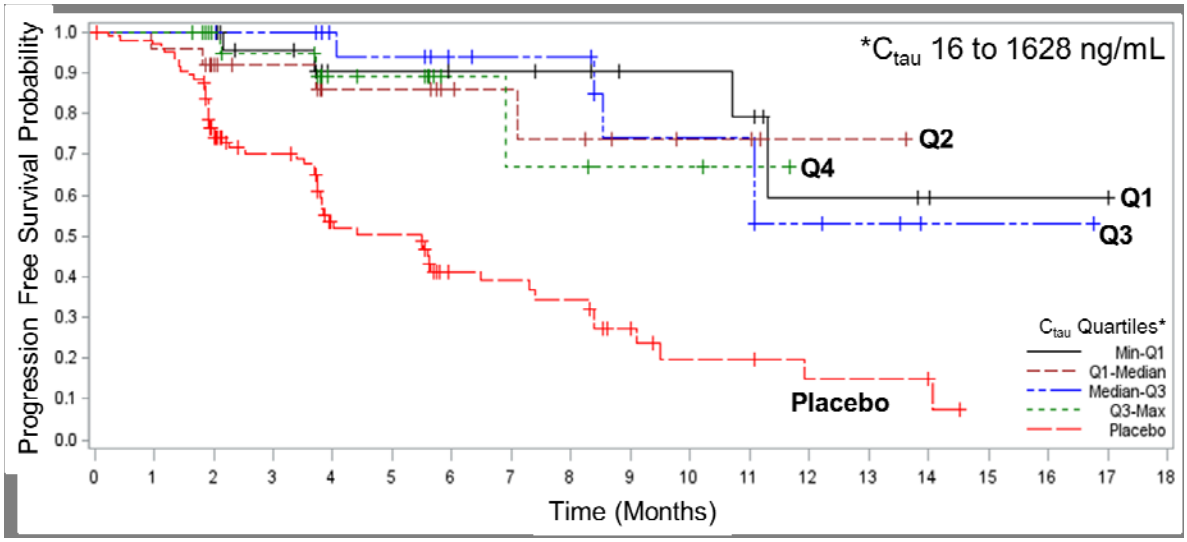


Figure 3: Kaplan-Meier plot of exposure-response analysis for progression free survival (PFS) in CLL pivotal trial 312-0116 with 150 mg BID dose. Idelalisib C_{tau} was used for exposure quartiles in the idelalisib treatment arm. Red line indicates the PFS response in the placebo arm. Both the arms had background rituximab treatment regimen. *Source: Reviewer's analysis*

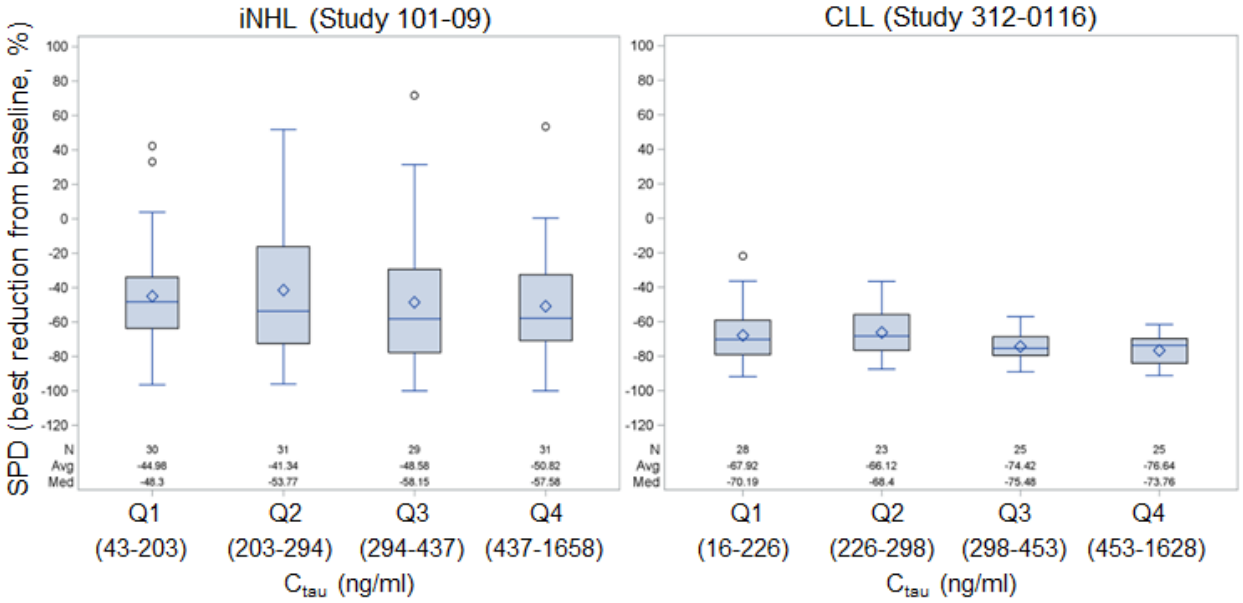


Figure 4: Boxplots of exposure-response analysis for pharmacodynamic response of best reduction in tumor size (sum of products of greatest perpendicular diameters of index lesions; SPD) in iNHL and CLL pivotal trials. Idelalisib C_{tau} was used for exposure quartiles. *Source: Reviewer's analysis*

Overall, the idelalisib C_{tau} quartile groups were uniformly beneficial relative to placebo in CLL population, and there was no specific threshold of plasma concentrations in patients receiving idelalisib that was associated with achieving a significantly better response within a single dosing regimen of 150 mg BID.

In a dose ranging study (101-02) in patients with hematological malignancies (both iNHL and CLL populations were represented in the study), tumor responses as assessed by changes in tumor size were evaluated and the relationship of the predicted exposures based on population PK modeling to activity was assessed. The study evaluated following idelalisib dosing regimens: 50, 100, 150, 200 and 350 mg BID and 150, 300 mg QD. The univariate E-R analysis suggested that the response of best reduction in tumor size was low in the lowest exposure quartile as compared to any of the higher exposure quartiles, and this efficacy response seemed to plateau from second quartile of exposure (Q2) onwards (**Figure 5**).

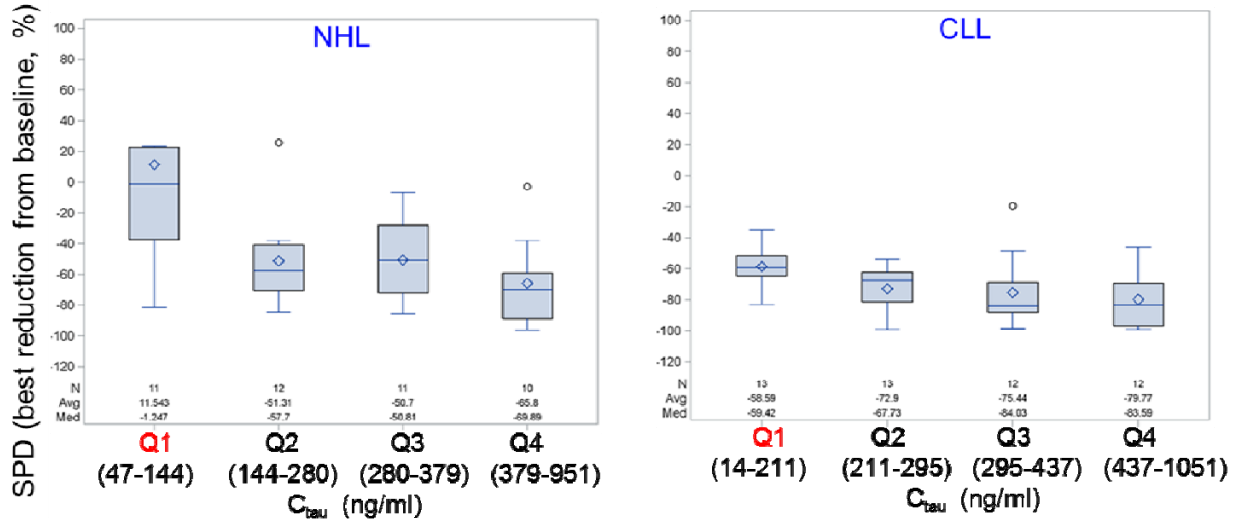


Figure 5: Boxplots of exposure-response analysis for response of best reduction in tumor size in iNHL and CLL populations in the dose ranging study (101-02). Idelalisib C_{tau} was used for exposure quartiles. *Source: Reviewer's analysis*

Safety: There was no significant and clinically meaningful exposure-response relationship for selected safety endpoints of interest (≥grade 3 ALT/AST elevation, diarrhea, rash, infection/ pneumonia) except for diarrhea in iNHL population, within the exposure range of a single dosing regimen (150 mg BID) explored in pivotal efficacy studies for iNHL (101-09) and CLL (312-0116) (**Figure 6** and **Figure 7**, respectively).

The E-R relationship for selected safety endpoints with idelalisib and GS-563117 exposures was evaluated in iNHL patients who received idelalisib as monotherapy in Study 101-09 using logistic regression analysis with steady state exposures (AUC) derived from population PK modeling. Safety parameters that were evaluated included grade ≥ 3AST or ALT laboratory abnormalities and grade ≥3 neutropenia, diarrhea, skin rash, and infection. No E-R relationships were identified for these selected safety endpoints for idelalisib or GS-365117 exposures in this study, except that there was a positive slope with statistically significant relationship of grade ≥3 diarrhea with idelalisib exposures (AUC) in the iNHL population (**Figure 6**; results for GS-563117 not shown). Thus, patients experiencing Grade 3 or higher diarrhea could benefit from lowering the dose which would lead to lower exposures and likely lower probability of experiencing recurrence of diarrhea. The proposed labeling includes dose modifications for grade ≥ 3 diarrhea. Overall, there was no specific threshold of plasma concentrations in patients receiving idelalisib that was identified to be associated with a greater risk of experiencing any of these adverse events. The analysis for identification of covariates that could help determine a priori the patients at risk of the diarrhea events on idelalisib treatment did not result in meaningful identification of any covariates.

Similar E-R analysis was conducted for selected safety endpoints with idelalisib and GS-563117 exposures in CLL patients who received idelalisib in combination with Rituximab in Study 312-0116. No E-R relationships were identified for these selected safety endpoints for idelalisib or GS-365117 exposures in this study (**Figure 7**; results for GS-563117 not shown).

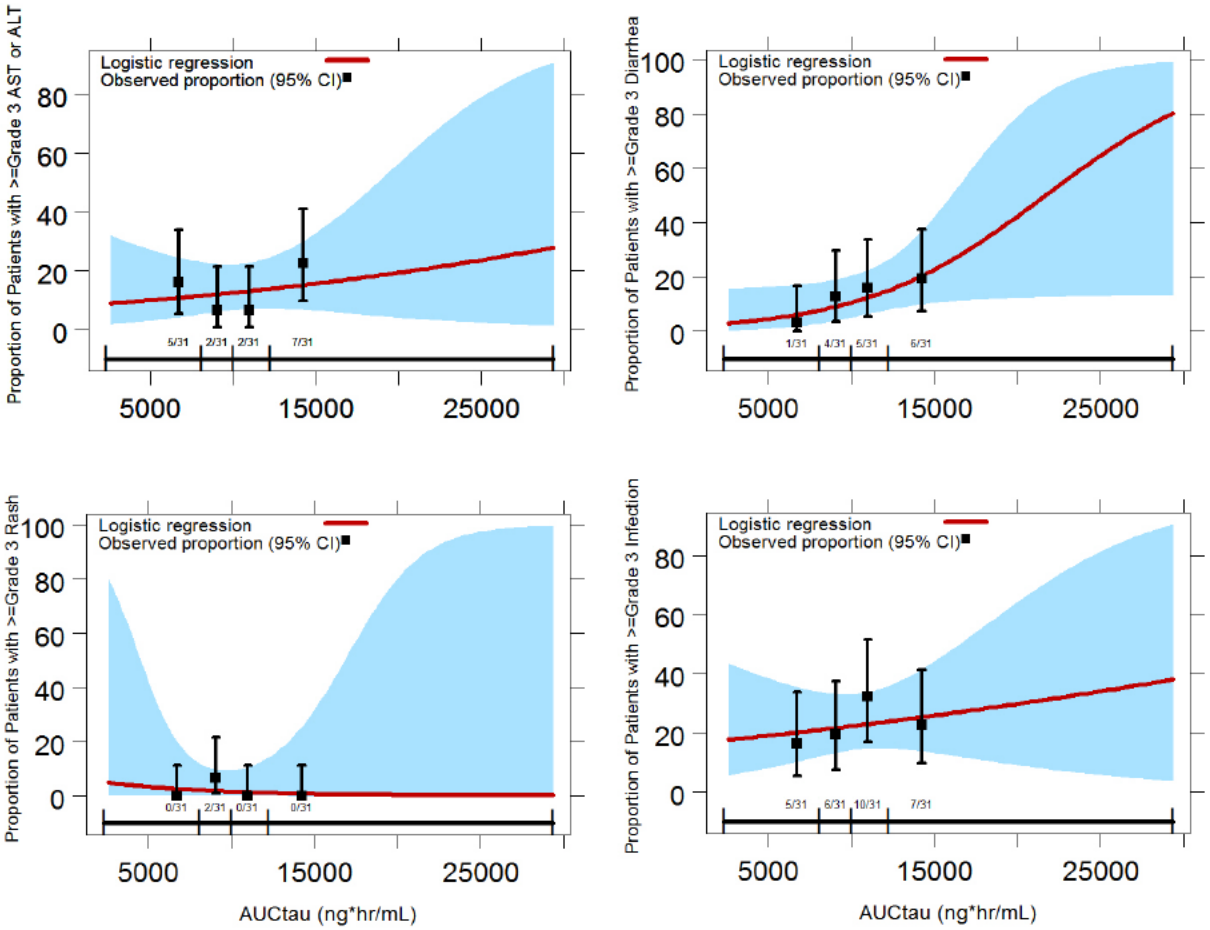


Figure 6: Proportion of patients (with 95% CI) with AEs of clinical interest (safety events of ≥Grade 3 for ALT/AST elevation, Diarrhea, Rash, Infection) for idelalisib exposure quartiles in pivotal efficacy study 101-09 for iNHL population. Idelalisib AUC is used for exposure quartiles. *Source: Reviewer's analysis*

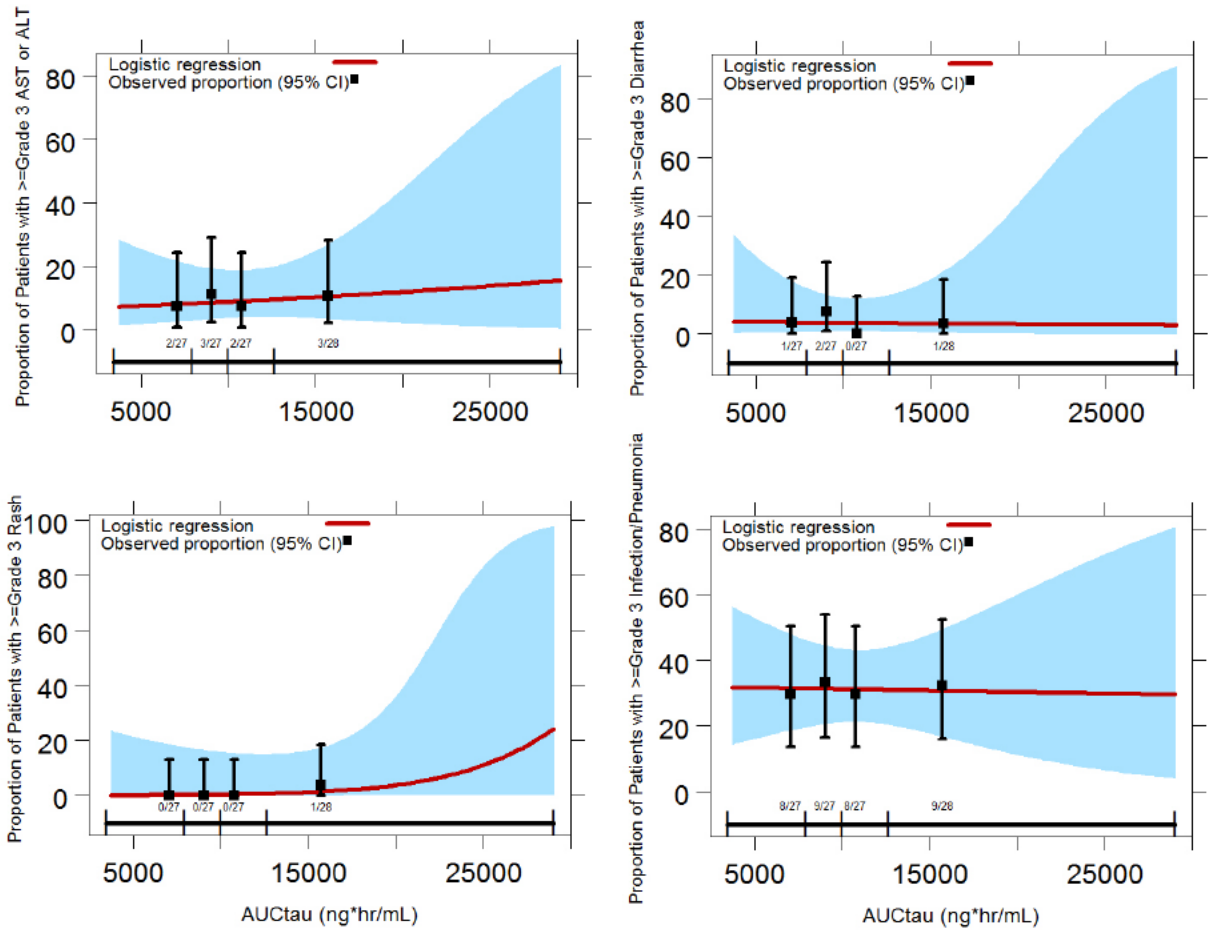


Figure 7: Proportion of patients (with 95% CI) with AEs of clinical interest (safety events of ≥Grade 3 for ALT/AST elevation, Diarrhea, Rash, Infection/Pneumonia) for idelalisib exposure quartiles in pivotal phase 3 efficacy study 312-0116 for CLL population. Idelalisib AUC is used for exposure quartiles. *Source: Reviewer's analysis*

1.1.2 Is the dose and dosing regimen proposed for iNHL and CLL appropriate?

The 150 mg BID dose proposed for the iNHL and CLL indications seems reasonable.

Following points were considered for evaluating the suitability of BID over QD dosing regimen and possible alternatives of lower or higher dose compared to 150 mg BID dose in the overall population.

Regarding the suitability of BID over QD:

In phase 1 dose escalation study, there was a trough concentration dependent reduction in tumor size (SPD) at lower exposures (C_{tau}) and this relationship seemed to plateau at higher trough concentrations (**Figure 5**). Thus, BID dosing would be preferable to QD dosing, since QD dosing results in lower C_{tau} values in subjects (**Figure 8**).

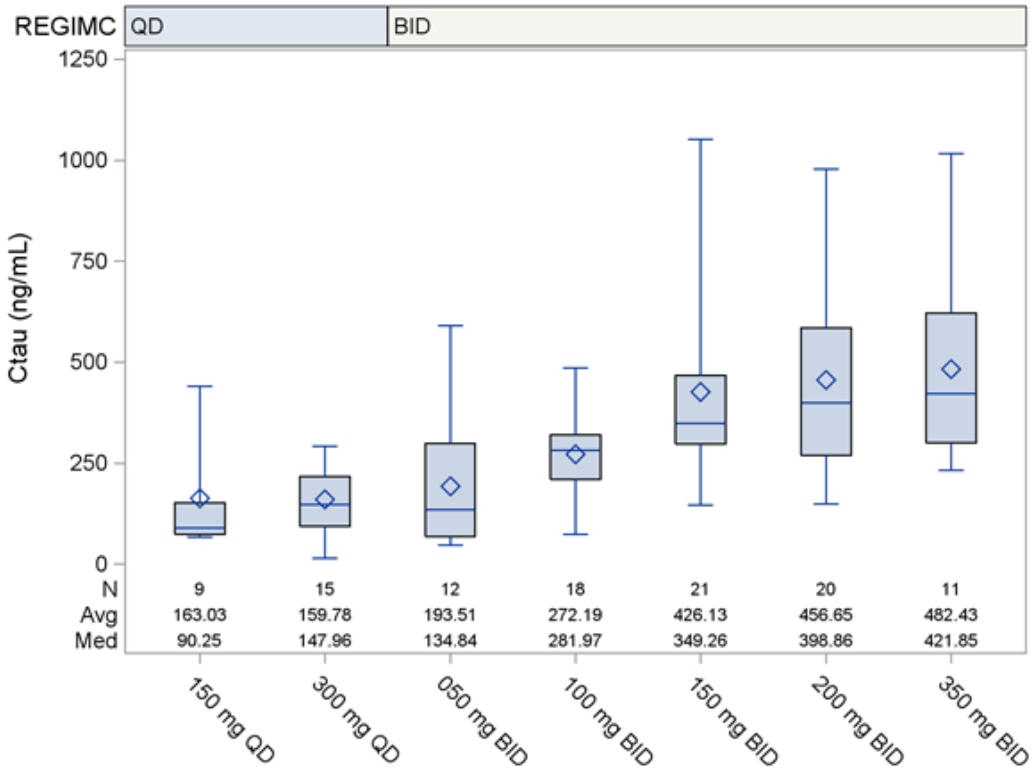


Figure 8: Boxplots of pre-dose trough concentrations (pop-pk predicted) with various dosing regimens in the dose ranging study 101-02 for iNHL and CLL patients. *Source: Reviewer's analysis*

Based on the cumulative evidence from following points, we concluded that a lower dose compared to 150 mg BID dose could be less suitable:

- Lowest exposure quartile in dose ranging study 101-02 showed lower efficacy of reduction in tumor size (**Figure 5**)
- Reviewer's simulation based analysis showed that 150 mg BID dose would ensure less probability of patients with exposures below EC_{90} (in vitro EC_{90} of PI3Kδ inhibition ~125 ng/mL) of target inhibition compared to any lower doses (50 or 100 mg BID) as shown in **Figure 9**.
- In the pivotal efficacy trials in both iNHL and CLL populations, there was no meaningful E-R for safety (except diarrhea in iNHL) to justify recommending a lower dose for the entire population. There was positive relationship between ≥Grade 3 diarrhea and exposures in iNHL population. Thus, reduction in dose for patients experiencing these diarrhea safety events would likely reduce the probability of recurrence of these events. The sponsor has proposed in the label a dose interruption and dose reduction strategy to mitigate diarrhea events and also employed similar strategy in the pivotal efficacy studies reasonably.
- In the dose-ranging study 101-02 where doses up to 350 mg BID were studied, although there were more dose reductions at highest dose level during the trial conduct (**Table 1**), there was no dose limiting toxicity encountered and thus MTD was not reached in the dose escalation phase (3+3 design). The sponsor already chose to pursue a dose (150 mg BID)

which was likely at the saturation of exposure-efficacy curve while likely minimizing the safety events that could have resulted from pursuing a higher dose in the pivotal trials.

Cumulatively, further lowering the dose below 150 mg BID in the overall population would not likely impact the safety aspect significantly, while at the same time the efficacy could be likely impacted.

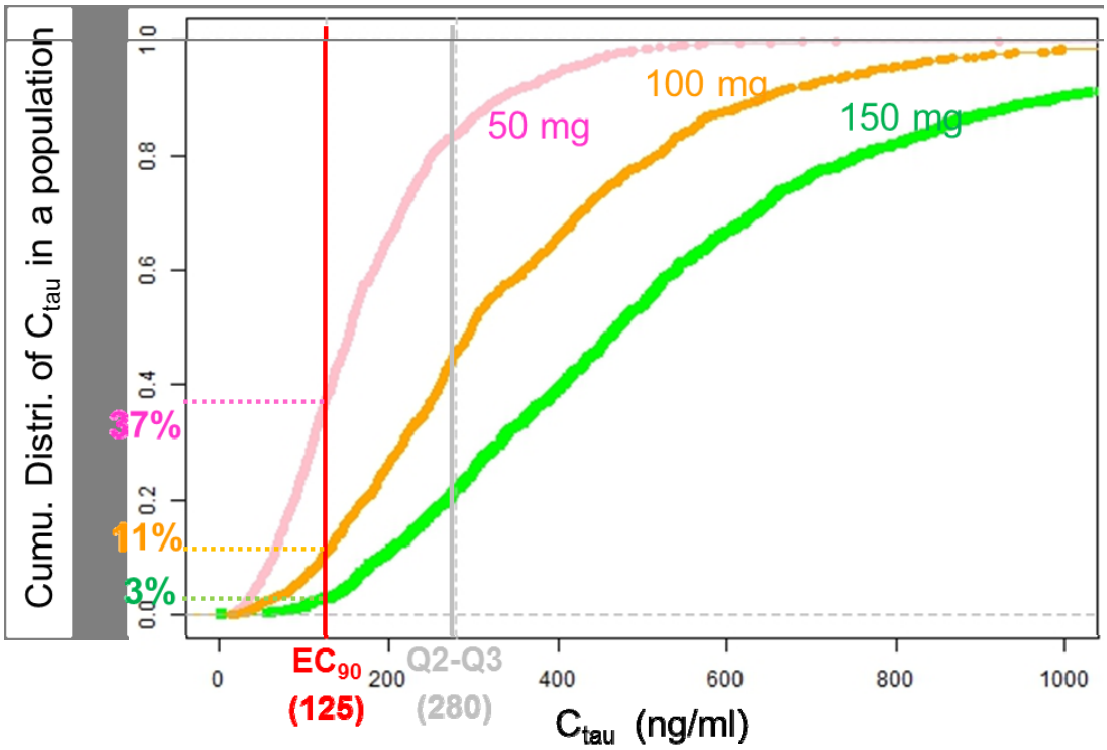


Figure 9: Analysis of simulated population for percentage of patients with C_{tau} < EC_{90} (125 ng/mL) with various BID dosing (50, 100 and 150 mg BID). A thousand patients with 75 kg weight were simulated for each dose level using final population-PK parameters and with between subject variability and residual variability in the population PK model. Cumulative distribution of C_{tau} in the simulated population is plotted against C_{tau} and the proportion of patients with steady state trough levels of idelalisib below EC90 were quantified for each dose level. *Source: Reviewer's analysis*

Table 1: Dose Modifications by Dose Cohort in the Dose Ranging Study 101-02

	50 mg BID	150 mg nce daily	100 mg BID	150 mg BID x 21 Days	300 mg once daily	150 mg BID	200 mg BID	350 mg BID	Total
	N = 17	N = 16	N = 25	N = 17	N = 19	N = 45	N = 35	N = 17	N = 191
Number of Subjects with ≥ 1 Dose Modification	5 (29.4)	2 (12.5)	5 (20.0)	3 (17.6)	4 (21.1)	6 (13.3)	8 (22.9)	8 (47.1)	41 (21.5)
Type of Dose Modification									
Increase from Starting Dose	5 (29.4)	1 (6.3)	1 (4.0)	0	0	0	3 (8.6)	0	10 (5.2)
Decrease from Starting Dose	0	1 (6.3)	4 (16.0)	3 (17.6)	4 (21.1)	6 (13.3)	5 (14.3)	8 (47.1)	31 (16.2)

Percentages are based on the number of subjects in the safety analysis set.

Source: Sponsor's Study 101-02 Final Clinical Study Report, Table 11-3, Page 189

Based on the cumulative evidence from following points, we concluded that a higher dose compared to 150 mg BID dose may not be more suitable:

- There was higher hepatotoxicity signal associated with the drug treatment compared to placebo, also there was an incidence of Hy's law on idelalisib treatment (noted for a patient in the pivotal efficacy study for CLL. The patient with Hy's law case belonged in the fourth (highest) quartile of idelalisib exposure (C_{tau} 812 ng/mL and AUC_{tau} 18633 ng*h/mL). Also there was positive relationship of grade 3 or higher diarrhea adverse events with idelalisib exposure.
- In both pivotal studies (for iNHL and CLL population), there was no meaningful relationship of efficacy (PFS/ORR/reduction in tumor size) with exposures with 150 mg BID dose. Also the efficacy (reduction in tumor size) seemed to plateau at higher exposures in the dose ranging study. Thus, higher doses may not result in higher efficacy for these populations.

Cumulatively, further increasing the dose above 150 mg BID in the overall population may not result in higher efficacy for these populations while the safety or compliance (number of drug interruptions/discontinuations on therapy) could be likely impacted.

Another issue of concern during our review was likely dose reductions or discontinuations on treatment which could eventually impact the efficacy. Recently during the approval of two oncology drugs, cabozantinib and ponatinib, post-marketing requirements (PMR) were issued to explore the possibility of a better safety/efficacy profile with lower doses (with study of lower dose in a new trial in case of cabozantinib and conduct of exposure-response analyses on data in the ongoing trial in case of ponatinib), since there were a high number of dose reductions (75-80%) seen in pivotal trials for these drugs. Even though there were 34% dose reductions and 24% dose discontinuations due to AEs with idelalisib treatment in the single arm pivotal trial for iNHL, the placebo controlled trial (rituximab as background therapy) had lesser dose reductions/discontinuations (14.5% and 10% respectively) with idelasib treatment (**Table 2**) and these numbers were comparable to the placebo arm, which alleviated this concern with 150 mg BID treatment.

Table 2: Dose reductions/discontinuations in pivotal efficacy trials for idelalisib

	NHL (101-09), N = 125	CLL (312-116), N = 110
% Dose reduction (n)	34% (42)	14.5% (16)
Median time to reduced dose (min, max)	82 (17, 504) days	114 (21, 343) days
% Discontinued for AEs (n)	24% (30)	10% (11)
Median duration of exposure (min, max)	6.6 (0.6, 24) months	5.0 (0.3, 16) months

Thus, with these cumulative evidences, the dosing regimen of 150 mg BID proposed for the patient population seems reasonable.

1.1.3 Is a dose adjustment required based on any intrinsic factors?

There is no dose adjustment warranted based on any of the intrinsic factors including age, body weight, gender, race and renal impairment.

Effect of following baseline demographic covariates was assessed graphically on each of the idelalisib PK parameters in pop-PK analysis in a univariate analysis: age, body weight, gender, race, cancer and treatment history related covariates (disease status, cancer type, background treatment), hepatic function related covariates (ALT, AST), and renal function related covariates (CrCL). Out of these baseline age, body weight, gender, CrCL, and disease status had significant effect ($p<0.01$) on clearance (CL); baseline body weight, gender, and rituximab usage had significant effect on V_c; baseline age, body weight, disease status, and rituximab usage had significant effect on Q; baseline age and disease status had significant effect on V_p, and disease status had significant effect on k_a. In the covariate selection process (step wise forward addition), only body weight and disease status (healthy/cancer) came out be the significant covariates on clearance and these were finally included in the model. The analysis of idelalisib exposures using Bayesian post-hoc parameters showed that there was no meaningful effect of race, gender, age, renal function on exposures. Although baseline body weight was identified as statistically significant in the pop-PK analysis, the impact across the body weight range on idelalisib clearance was low (<20%; **Table 3**). Thus no dose adjustment is warranted based on body weight. A dedicated hepatic impairment trial showed an increase in idelalisib exposure (AUC) by 1.6-1.7 fold in subjects with moderate and severe Child-Pugh criteria as compared to healthy volunteers (refer to section 2.3.2.6 in Clinical Pharmacology QBR). But no starting dose adjustment is recommended for patients with baseline hepatic function, since no E-R relationship was identified for selected safety endpoints. Instead, dose modifications are outlined in the labeling to mitigate impact of adverse events and the labeling will state that patients with baseline hepatic impairment will need to be closely monitored for serious adverse events. The impact of renal impairment on idelalisib exposures was assessed with a dedicated renal impairment study that compared subjects with severe renal impairment and corresponding age, gender, and BMI matched healthy volunteers. The exposure in subjects with severe renal impairment was higher as compared to healthy volunteers by 1.3-fold (geometric mean ratio). Based on the E-R relationships for efficacy and safety, this increase was not clinically significant and thus no dose adjustment in the starting dose is recommended for renally impaired patients with CLcr ≥ 15 mL/min (refer to section 2.3.2.5 in Clinical Pharmacology QBR).

Table 3: Covariate Effects on Idelalisib PK parameters

PK Parameters and Baseline Covariates		Baseline Covariate Value	Estimate	Change from Typical (%)	Inter-individual Variability (%)
Typical CL with body weight of 75 kg (L/hr)			**14.88**	—	**38.21**
Body weight (kg)	*5th Percentile*	*53*	*13.67*	*-8.155*	—
	95th Percentile	*112*	*16.42*	*10.32*	—
Disease status	*Patient*		*14.88*	—	—
	Healthy volunteer		*19.69*	*32.31*	—
Typical Q (L/hr)			**11.82**	—	**38.86**
Disease status	*Patient*		*11.82*	—	—
	Healthy volunteer		*7.846*	*-33.63*	—

Source: Sponsor's Population PK Study Report, Table 16, Page 48

1.2 Recommendations

Division of Pharmacometrics has reviewed NDA 205-858 and NDA 206-545 and has the following recommendations:

- The proposed dose of 150 mg BID is reasonable for both iNHL and CLL indications
- No dose modifications are required based on age, weight, race, gender and renal impairment.

1.3 Label Statements

Please refer to the labeling recommendations in Clinical Pharmacology Review.

2 PERTINENT REGULATORY BACKGROUND

Idelalisib, a selective inhibitor of PI3Kδ, is currently being developed by Gilead Sciences for the treatment of indolent non-Hodgkin's lymphoma (iNHL) and refractory chronic lymphocytic leukemia (CLL). The previously FDA approved therapies for NHL population are Rituximab, Bendamustine, and radioimmunotherapies like [^{131}I]-tositumomab, [^{90}Y]-ibritumomab. The approved therapies for CLL include Rituximab, Ibrutinib, and Ofatumumab.

The pivotal trial of idelalisib for iNHL population was a single arm trial (study 101-09), and the ORR achieved was 56% with median duration of ORR of 12.5 months. **Table 4** shows the comparative performance of previously approved therapies for iNHL.

Table 4: Efficacy in Pivotal Studies of Approved Therapies for Treatment of Relapsed and/or Refractory iNHL and Idelalisib (IDELA) Pivotal Study 101-09

Therapy	N	ORR	CR	DOR (months)
Rituximab (Study 1)	166	48%	6%	11.2
Rituximab (Study 2)	37	57%	14%	13.4
Rituximab (Study 3)	60	38%	10%	15
^{90}Y-ibritumomab tiuxetan (rituximab refractory iNHL)	54	74%	15%	6.4
^{131}I-tositumomabb (rituximab-refractory iNHL)	35	63%	29%	25
Bendamustine (rituximab-refractory iNHL)	100	74%	13%	9.2
IDELA (rituximab- and alkylator-refractory iNHL)	125	57%	6%	12.5

Source: US Prescribing Information for Rituxan (rituximab) {24530}; MabThera EPAR, Zevalin® (^{90}Y-ibritumomab tiuxetan) {24221}; Zevalin EU Summary of Product Characteristics (SmPC), Bexxar® (^{131}I-tositumomab) {24220}, and Treanda® (bendamustine) {25544}; Levact EU SmPC

Source: Sponsor's Clinical Overview Report, Table 1, Page 20

The pivotal trial for refractory CLL population was a two arm trial (study 312-0116) with idelalisib (+ background rituximab treatment) as the treatment arm and placebo (+ background rituximab treatment) as the comparator arm. The adjusted hazard ratio for idelalisib treatment was 0.18 (95% CI: 0.10, 0.32) with a p value of < 0.0001. The median PFS was not reached for

idelalisib in CLL trial. **Table 5** shows the comparative performance of previously approved therapies for CLL.

Table 5: Efficacy from Pivotal Studies Designed to Support Regulatory Approval for Drugs for Previously-treated CLL

Drug	Approval Date	Indications/studies	N (treated with drug)	PFS	ORR	DOR
Alemtuzumab[1] (single agent)	2008 EU	Frontline CLL • Alemtuzumab vs Ch	149	15 vs 12 months (HR 0.58)	83% vs 55% (24% vs 2% CRs)	16.2 vs 12.7 months
Bendamustine[2] (single agent)	2010 EU	Frontline CLL • Bendamustine vs Ch	153	21.5 vs 8.3 months	59% vs 26% (8% vs <1% CRs)	19 vs 6 months
Rituximab[3] (R) (as FCR)	2009 EU	Frontline CLL • FCR vs FC	408	55 vs 33 months	86% vs 73%	57.3 vs 36.2 months
Obinutuzumab[4] (G) (as GCh)	Not yet approved (filed April 2013)	Frontline CLL • GCh vs Ch vs RCh	238 (Stage 1)	23 vs 11 vs 16 months (HR 0.14/0.32)	76% vs 30% vs 66% (22% vs 0% vs 8% CRs)	NR

NR = not reported, HR = hazards ratio

Sources: (1) US 2001 and 2007 Alemtuzumab Package Inserts; MabCampath EPAR 2008 (2) (5) EU SmPC Levact (bendamustine) and US 2008 Bendamustine Package Insert; (3) EU SmPC MabThera (Rituximab); (4) Goede V et al.2013 {26530}

Source: Sponsor's Clinical Overview Report, Table 5, Page 25

Adverse events (AEs) of clinical interest for idelalisib included AST/ALT elevations, infections/colitis/pneumonia/pneumonitis, diarrhea, and rash. The AEs resulted in 34% and 14.5% dose reductions in iNHL and CLL pivotal trials respectively.

Following 3 clinical studies for the idelalisib program are main contributors to this review:

1. a phase 1 dose escalation study in NHL and CLL population (study 101-02)
2. a single arm pivotal efficacy study in iNHL population (study 101-09)
3. a phase 3 randomized, placebo-controlled pivotal efficacy study in CLL population (study 312-0116).

The dose escalation study involved idelalisib doses of 50, 100, 150, 200, and 350 mg BID and 150, 300 mg QD. Both pivotal efficacy studies used idelalisib dosing of 150 mg BID.

The sponsor provided pharmacometric reports for population PK models developed for both populations and exposure-response analyses results for efficacy and safety parameters.

3 RESULTS OF SPONSOR'S ANALYSIS AND REVIEWER'S COMMENTS

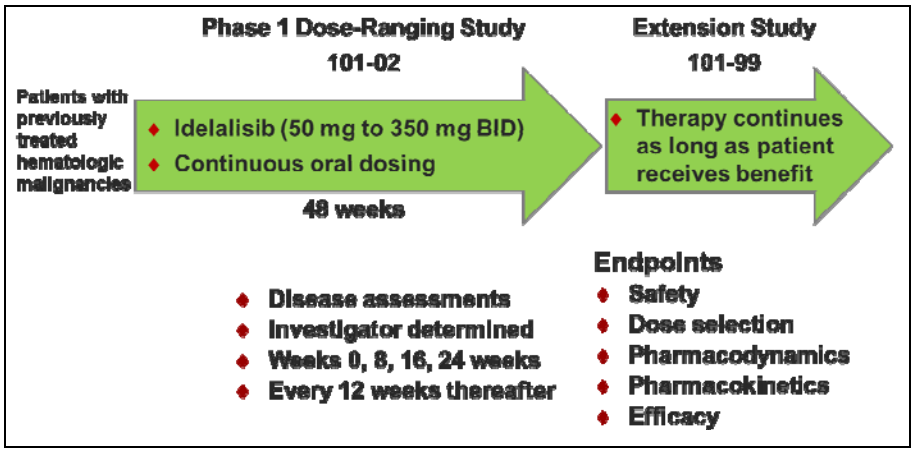
3.1 Dose Selection

Dose selection was based on Phase 1 dose ranging study in patients with hematologic malignancies (**Figure 10**). Sections 1.1.1 and 1.1.2 along with the results in **Figure 5** detail the dose selection aspect.

3.2 Phase 1 Dose Ranging Study and Pivotal Efficacy Trials in iNHL and CLL populations

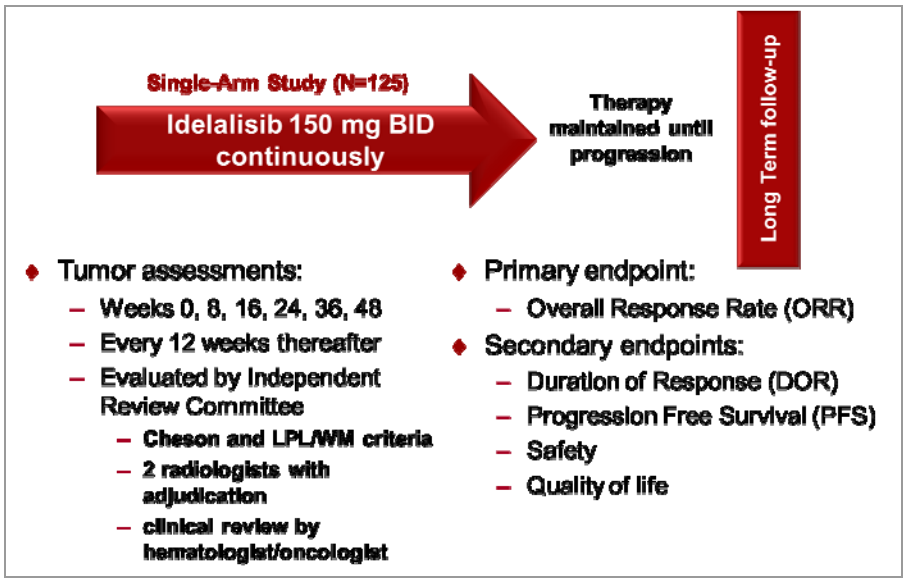
A brief schematic description of phase 1 dose ranging study (**Figure 10A**) in patients with hematologic malignancies (including iNHL and CLL populations) and pivotal efficacy studies in iNHL (**Figure 10B**) and CLL (**Figure 10C**) population is shown below.

A.



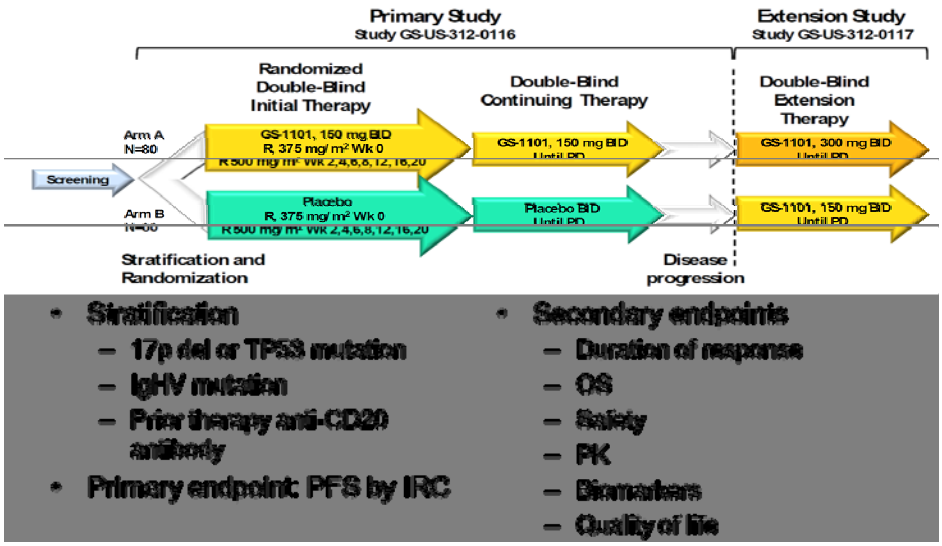
Source: Modified from Sponsor's Application Orientation Slides

B.



Source: Modified from Sponsor's Application Orientation Slides

C.



Source: Clinical and Statistical Review Team Midcycle Presentation

Figure 10: Overview for Phase 1 Dose Ranging Study 101-02 (A), and Pivotal Efficacy Studies 101-09 in iNHL (B) and 312-0116 in CLL (C) populations.

3.3 Population Pharmacokinetic Analysis

A brief synopsis of sponsor's population pharmacokinetic (PPK) analysis for idelalisib is given below (*source: excerpted from Sponsor's Population Pharmacokinetics Report*):

STUDIES INCLUDED	Phase I trials: 101-01 (n=48), 101-02 (n=189), 101-04 (n=39), 101-05 (n=12), 101-06 (n=15), 101-07 (n=197), and 339-0101 (n=23) Phase II trials: 101-08 (n=64), 101-09 (n=124), and 101-11 (n=25)

OBJECTIVES

The goals of the population pharmacokinetic (PopPK) analysis were to:

- Perform PopPK analysis of GS-1101 using the data collected from 10 clinical studies (101-01, 101-02, 101-04, 101-05, 101-06, 101-07, 101-08, 101-09, 101-11, and 339-0101) and estimate typical values and inter-patient variability (IIV) of pharmacokinetic (PK) parameters in healthy subjects and oncology patient population.
- Determine the effects of patient demographics, cancer and treatment history related factors, renal function, and hepatic function on the PK of GS-1101 in order to better understand clinical factors that might affect exposure in individual patients.

METHODS

Plasma concentrations of GS-1101 were measured, using validated liquid chromatography-mass spectrometry/mass spectrometry (LC/MS/MS) methods. The minimum quantifiable concentration in plasma was 0.5 or 5 ng/mL.

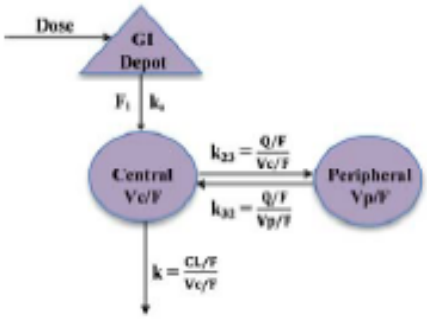
The PK of GS-1101 in plasma was evaluated in 736 subjects with 7842 samples from ten studies. A nonlinear mixed effects modeling approach with the first-order conditional estimation (FOCE) method in NONMEM 7, version 7.1.2 (ICON, Maryland) was used for the PopPK analysis.

The impact of baseline covariates, as detailed above, including age, body weight, gender, race, ALT, AST, CrCL, cancer type, disease status, background treatment, and study on the PK of GS-1101 were investigated. Covariates were selected using a forward addition and backward elimination method (based on the significance levels of $p<0.01$ and $p<0.001$, respectively).

RESULTS

Plasma PK of GS-1101 in the clinical dose range can be described by a two-compartment model with first order absorption, first order elimination from the central compartment and a lag time, as illustrated in Figure A. The PK model was parameterized in clearance (CL), central volume (V_c), distributional clearance (Q), peripheral volume (V_p), absorption rate constant (k_a), and bioavailability (F_1).

Figure A – Two-compartment model describing plasma GS-1101 concentration time course data following an oral dose in healthy volunteers and cancer patients



F_1 = relative bioavailability
k_a = absorption rate constant
k = elimination rate constant
k_{23} = rate constant from central to peripheral
k_{32} = rate constant from peripheral to central
CL/F = apparent oral clearance
Q/F = apparent inter-compartmental clearance
Vc/F = apparent central volume
Vp/F = apparent peripheral volume

The following statistically significant parameter-covariate relationships were identified:

- *Effect of disease status and body weight on clearance*

(b) (4)

The population median (or typical) estimated clearance was 14.9 L/hr for a patient with a body weight of 75 kg and 19.7 L/hr for a HV with a body weight of 75 kg. There was a weak relationship between baseline body weight and clearance. The estimated population elimination half-life for a typical patient was 8.2 hours. The inter-individual variability in clearance was estimated to be 38.2%.

- *Effect of disease status on distributional clearance*

(b) (4)

The population median (or typical) estimated distributional clearance was 11.8 L/hr for a patient and 7.8 L/hr for a HV. The inter-individual variability in distributional clearance was estimated to be 38.9%.

- *Effect of dose on bioavailability*

(b) (4)

Bioavailability is dose-dependent. The typical bioavailability was set to be 1 for GS-1101 150 mg. The estimated bioavailability was 1.11 for GS-1101 100 mg, and 0.83 for GS-1101 300 mg.

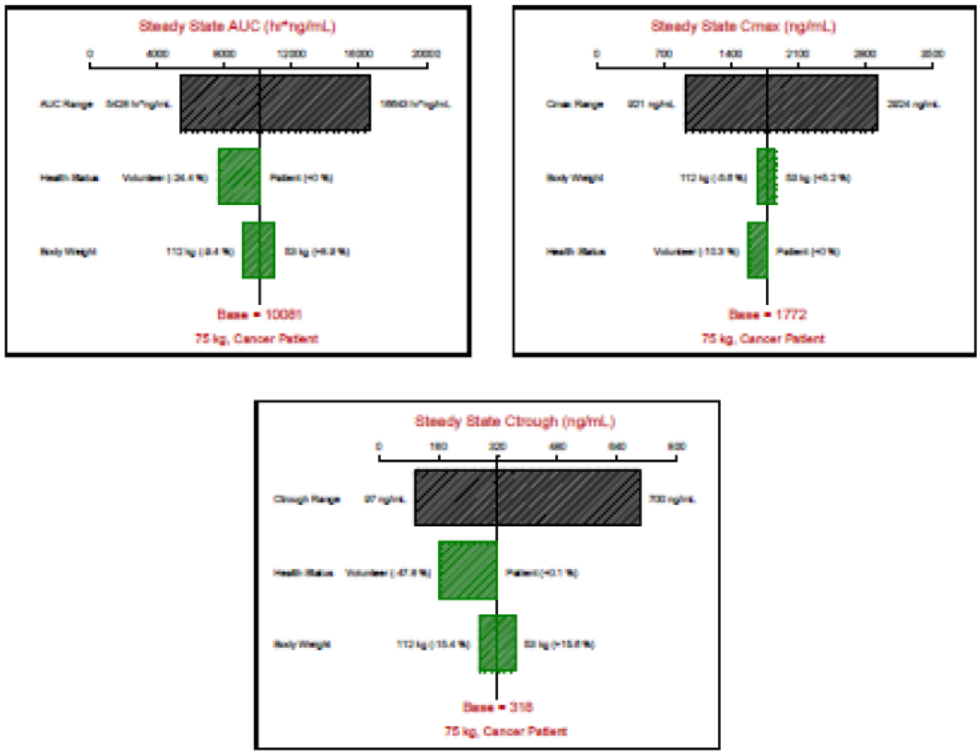
A summary of key PopPK parameters and covariate effects is presented in Table A.

Table A. Key PopPK parameters and covariate effects for representative subjects

PK Parameters and Baseline Covariates		Baseline Covariate Value	Estimate	Change from Typical (%)	Inter-individual Variability (%)
Typical CL with body weight of 75 kg (L/hr)			**14.88**	—	**38.21**
Body weight (kg)	*5th Percentile*	*53*	*13.67*	*-8.155*	—
	95th Percentile	*112*	*16.41*	*10.32*	—
Disease status	*Patient*		*14.88*	—	—
	Healthy volunteer		*19.69*	*32.31*	—
Typical Q (L/hr)			**11.82**	—	**38.86**
Disease status	*Patient*		*11.82*	—	—
	Healthy volunteer		*7.846*	*-33.63*	—
Typical V_c (L)			**22.65**	—	**85.15**
Typical V_p (L)			**72.97**	—	**73.35**
Typical k_a (hr^{-1})			**0.482**	—	**38.34**
Residual variability as coefficient of variation (%)			**53.48**	—	—

A sensitivity analysis was performed to examine the influence of the statistically significant covariates on the steady state exposure of GS-1101. Figure B shows the isolated influence of each covariate on the steady state exposure of GS-1101 after repeated doses of 150 mg twice daily (BID).

Figure B – Sensitivity plot comparing the effect of covariates on GS-1101 steady state exposure (AUC, C_{max} and C_{trough})



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Base, as represented by the black vertical line and red values, refers to the predicted steady state exposure (AUC or C_{max} or C_{trough}) of GS-1101 in a typical cancer patient with body weight of 75 kg. The black shaded bar with a value at each end shows the 5th to 95th percentile exposure range across the entire population. Each green shaded bar represents the influence of a single covariate on the steady state exposure after repeated GS-1101 dose of 150 mg BID. The label at the left end of the bar represents the covariate being evaluated. The upper and lower values for each covariate capture 90% of the plausible range in the population. The length of each bar describes the potential impact of that particular covariate on GS-1101 exposure at steady state, with the percentage value in the parentheses at each end representing the percent change of exposure from the base value. The most influential covariate is at the top of the plot for each exposure parameter.

The sensitivity analysis suggested that the magnitude of effect of disease status and body weight on GS-1101 steady-state C_{trough}, AUC and C_{max} was minor/modest (C_{trough}: 31%; AUC and C_{max}: <20%) for a patients with extreme covariate values (5^{th} and 95^{th} percentile) relative to the typical patient. These covariates are not considered to have clinical meaningful impact on GS-1101 PK in cancer patients.

Other tested baseline covariates, such as age, gender, race, AST, ALT, CrCL, and rituximab usage did not show statistically significant impact on the PK of GS-1101.

Further comparison of expected GS-1101 exposure simulated from post-hoc PK parameters showed similar GS-1101 exposure in elderly vs. young patients, Caucasian vs. non-Caucasian, and patients with impaired renal functions vs. normal functions.

CONCLUSIONS

- GS-1101 PK in the clinical dose range can be adequately described by a two-compartment model with first-order absorption, first-order elimination from the central compartment, and a lag time.
  - — Typical CL was 14.9 L/hr for a cancer patient with a body weight of 75 kg, typical V_c was 22.65 L, and typical elimination half-life was 8.2 hours.
- The covariates tested did not have a clinically meaningful impact on GS-1101 exposure. Accordingly, dose adjustments based on covariates are not considered necessary.

Final parameter estimates for the population PK model are summarized in **Table 6**.

Table 6: Pharmacokinetic and covariate parameter estimates of the final model

Parameter	Parameter Description		Population Estimate	Bootstrap Final Model Median (2.5th, 97.5th Percentiles)
$exp(\theta_1)$	Apparent oral clearance, CL/F (L/hr)	Patient	14.88	14.90 (14.38, 15.55)
$exp(\theta_8)$		HV	19.69	19.68 (18.43, 21.25)
θ_{10}	Influence of body weight on CL/F		0.245	0.244 (0.141, 0.293)
$exp(\theta_2)$	Apparent central volume, V_c/F (L)		22.65	22.65 (20.52, 24.80)
$exp(\theta_3)$	Apparent inter-compartmental clearance, Q/F (L/hr)	Patient	11.82	11.81 (10.47, 12.99)
$exp(\theta_9)$		HV	7.846	7.855 (7.024, 9.002)
$exp(\theta_4)$	Apparent peripheral volume, V_p/F (L)		72.97	72.90 (66.16, 77.83)
$exp(\theta_5)$	Absorption rate constant, k_a (1/hr)		0.482	0.482 (0.463, 0.518)
$exp(\theta_6)$	Lag time (hr)		0.247	0.247 (0.245, 0.248)
θ_7	Influence of dose on bioavailability (F1)		-0.262	-0.262 (-0.317, -0.226)
Inter-Individual Variability (%)	CL/F		38.21	38.22 (35.54, 41.06)
	V_c/F		85.15	85.40 (83.05, 101.3)
	Q/F		38.86	39.06 (38.84, 56.59)
	V_p/F		73.35	70.36 (56.18, 77.13)
	k_a		38.34	37.77 (15.60, 38.34)
	Lag time		45.50	45.51 (40.33, 52.37)
$\omega^2_{CL,Vc}$	Covariance between CL/F and V_c/F		0.112	0.112 (0.058, 0.166)
$\omega^2_{Q,Vp}$	Covariance between Q/F and V_p/F		0.231	0.228 (0.183, 0.348)
σ	Residual error (%)		53.48	53.46 (50.77, 55.58)

Source: Sponsor's Population PK Study Report, Table 15, Page 47

The point estimates in the above table represent typical values for a patient with 75 kg weight. The goodness of fit (Observed vs individual predicted concentrations etc.) plots are provided in *Figure 11: Goodness-of-Fit Diagnostic Plots for* **the** *Final* **Pop-PK Model** *Source: Sponsor's Population PK Study Report, Figure 15 and 16, Page 49*

.

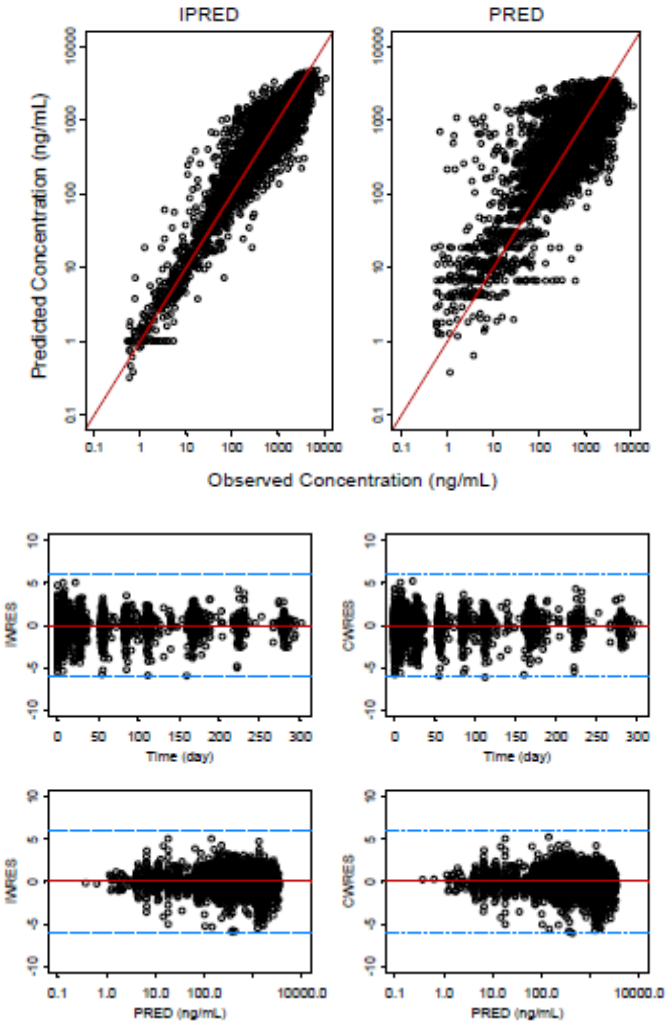


Figure 11: Goodness-of-Fit Diagnostic Plots for the Final Pop-PK Model *Source: Sponsor's Population PK Study Report, Figure 15 and 16, Page 49*

With the already developed Pop-PK model, the sponsor performed external validation with PK data from 109 CLL patients (this data was not used in model development) in phase 3 study 312-0116. In this model validation, predicted idelalisib plasma concentrations for validation patients were derived by fixing the parameters in the structural and variance model to the parameter estimates in the final model using post-hoc Bayesian forecasting with NONMEM 7. The $ESTIMATION command was set as (b) (4) The predicted idelalisib concentrations (PRED) were compared with the corresponding observed concentrations (DV). The goodness of fit (Observed vs individual predicted concentrations etc.) plots for these validation patients are provided in **Figure 12**.

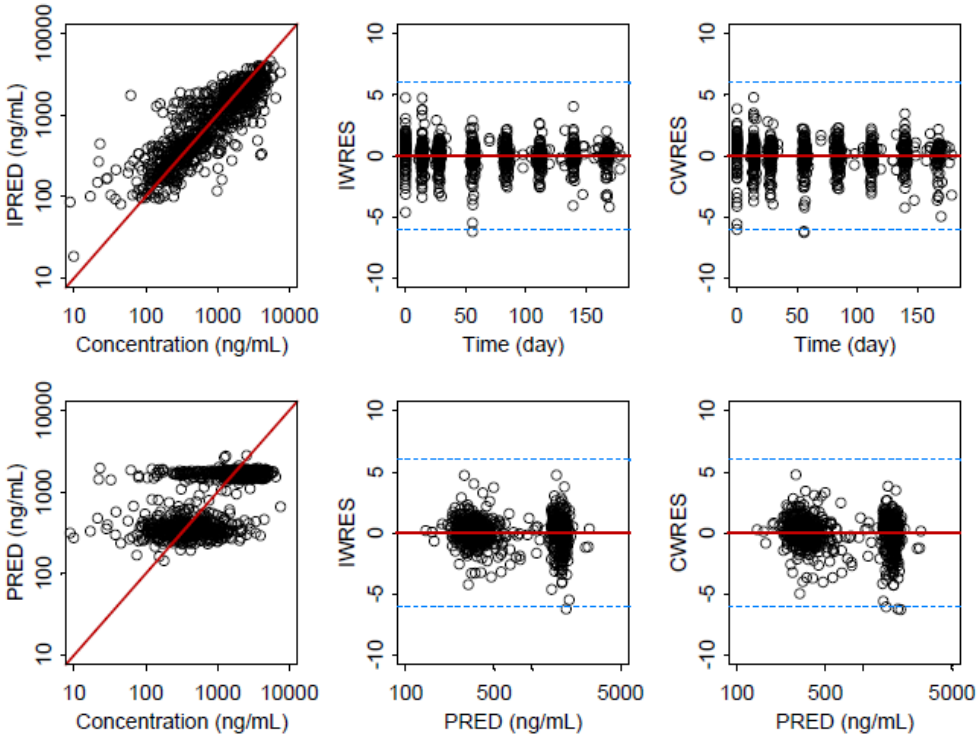


Figure 12: Goodness-of-Fit Diagnostic Plots for idelalisib external validation patients from pivotal phase 3 study 312-0116 in CLL population. *Source: Sponsor's CLL Population PK Study Report, Figure 1, Page 9*

Reviewer's comments:

1. *The sponsor's Pop-PK model provides reasonable description of idelalisib concentrations for individual predictions (observed vs. individual predicted concentrations). Visual inspection shows that the model reasonably predicts individual data over a range of concentrations with slight over-prediction at lower observed concentrations for a limited number of observations in CLL study 312-0116.*
2. *A separate model for major metabolite GS-563117, which is an inactive moiety for PI3Kδ inhibition, was developed by the sponsor and external validation was done to predict concentrations in phase 3 CLL patients similar to the strategy with idelalisib concentrations as described above. There was no exposure-response relationship for efficacy or safety seen with this inactive metabolite in sponsor's analyses, thus the description of this metabolite pop-pk is not included in this review.*
3. *From the covariate analysis, effect of body weight was the most significant covariate on clearance in patients. However, the small magnitude of this covariate effect on exposure (-8% to 10% change in typical value going from 5 to 95 percentile of body weight range) is not clinically relevant and there is no need for dose adjustment based on this covariate.*

3.4 Exposure-Response Analysis

3.4.1 Objective

The sponsor conducted the exposure-response analysis to evaluate the relationship of patient plasma exposure to idelalisib and its major inactive metabolite GS-563117 with following outcomes for iNHL and CLL populations:

- efficacy endpoints (pivotal efficacy studies)- best overall response (BOR) status, lymph node response (LNR) status, best reduction in tumor growth (SPD), duration of response (DOR), progression free survival (PFS)
- adverse events (pooled analysis with dose ranging study and pivotal study)- treatment-emergent adverse events of lab abnormality of AST or ALT elevation (by all grades or by ≥ grade 3), neutropenia, diarrhea, rash and infection (≥ grade 3).

3.4.2 Exposure Parameters

Pop-PK predicted exposure metrics of AUC, Cmax and Ctau were used for these analyses.

3.4.3 Methods

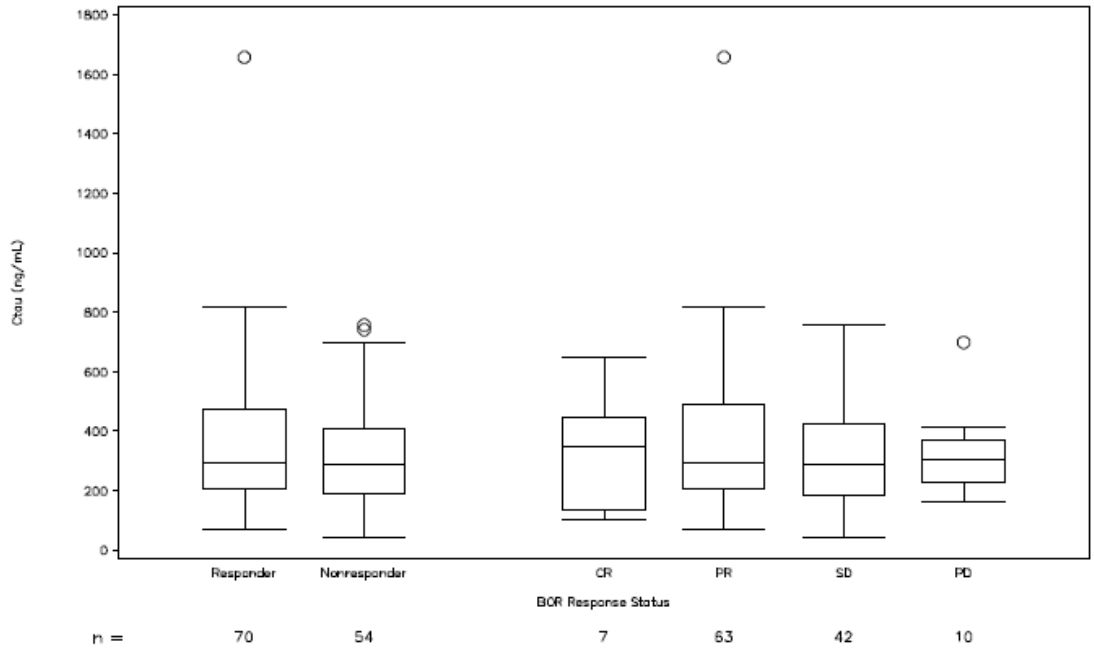
Both continuous and quartile grouped exposure parameters were used in the exposure-response analysis. Kaplan-Meier estimates were used to estimate the distribution of duration and median duration of PFS. Further Cox regression analysis was performed with continuous exposure parameters to determine the slope estimate for E-R relationship. Exposure effects on safety were evaluated by graphical observation of incidences grouped by quartiles of exposure and time to first event for ALT/AST elevation by quartiles of exposure.

3.4.4 Results

Exposure-Response for Efficacy

The analyses showed that there was no E-R relationship for efficacy within the exposures achieved with single dosing regimen of 150 mg BID used in the pivotal studies. Representative boxplots for BOR status and BOR responder vs. C_{tau} for iNHL population are shown in **Figure 13**. Also representative K-M plot for PFS and DOR with idelalisib exposure in CLL population are shown in **Figure 14**. (For more results, refer to sponsor's PK-PD Tables, Figures and Listings document provided for PK-PD analysis in section M5.3.4.2 of EDR).

A.



B.

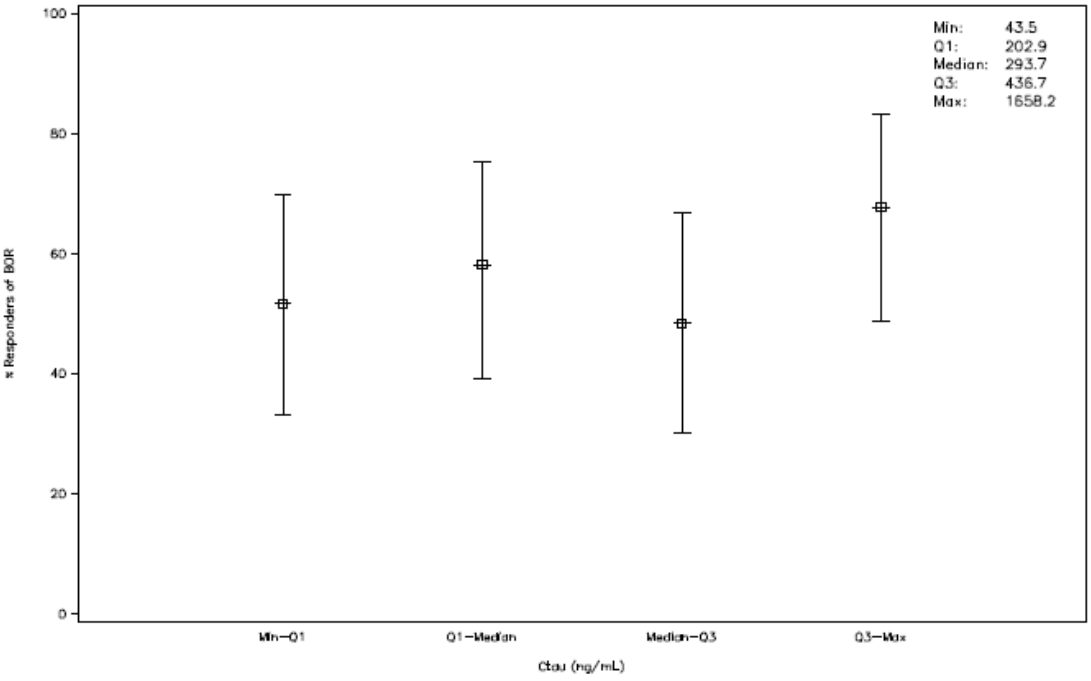
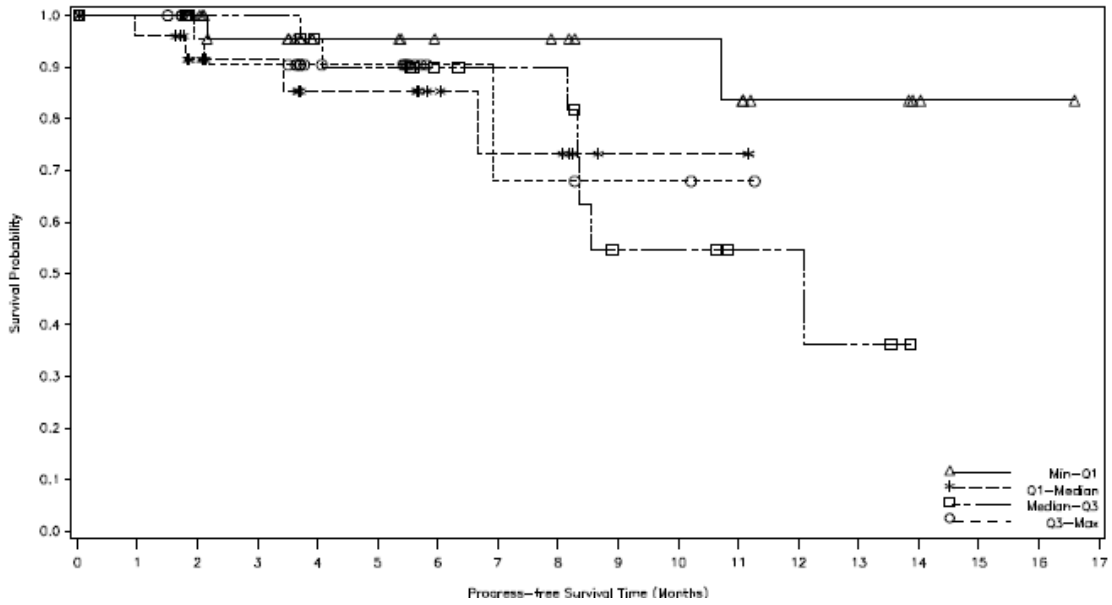


Figure 13: Boxplot of C_{tau} by BOR status (A) and Responders of BOR by quartile of C_{tau} for idelalisib in iNHL pivotal efficacy study 101-09. *Source: Sponsor's PK-PD Tables, Figures and Listings Document for iNHL population, Figure 1.2, page 107 and Figure 3.2, Page 111*

A.



B.

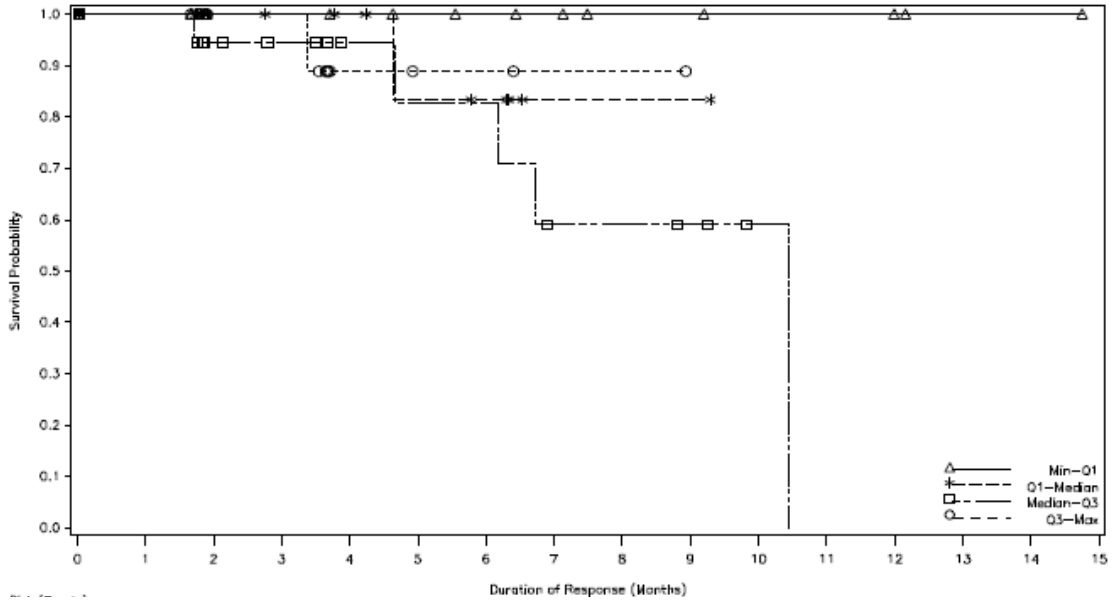


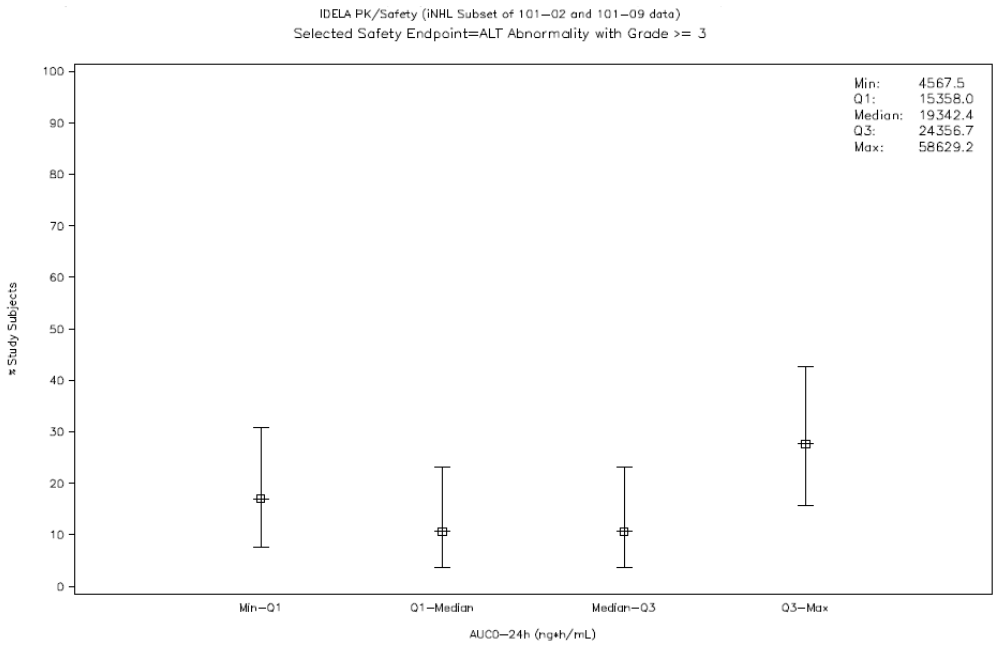
Figure 14: K-M curve for PFS (A) and DOR (B) stratified by quartiles of C_{tau} for idelalisib in CLL pivotal efficacy study 312-0116. *Source: Sponsor's PK-PD Tables, Figures and Listings Document for CLL population, Figure 7.2.2, page 141 and Figure 6.2.2, Page 137*

Exposure-Response for Safety

The analyses showed that no statistically significant E-R for safety was seen for any of the adverse events of interest within the exposures achieved with single dosing regimen of 150 mg BID used in the pivotal studies. Representative incidences of ALT abnormality of Grade ≥3 and diarrhea with Grade ≥3 severity for iNHL population in a pooled analysis of study 101-02 and 101-09 with idelalisib AUC is shown in **Figure 15**. Similar analyses were done for other AEs of interest and also in CLL Population and no clinically significant relationship that could be of

potential concern was observed for dosing of ≤150 mg BID. (For more results, refer to sponsor's PK-PD Tables, Figures and Listings document provided for PK-PD analysis in section M5.3.4.2 of EDR).

A.



B.

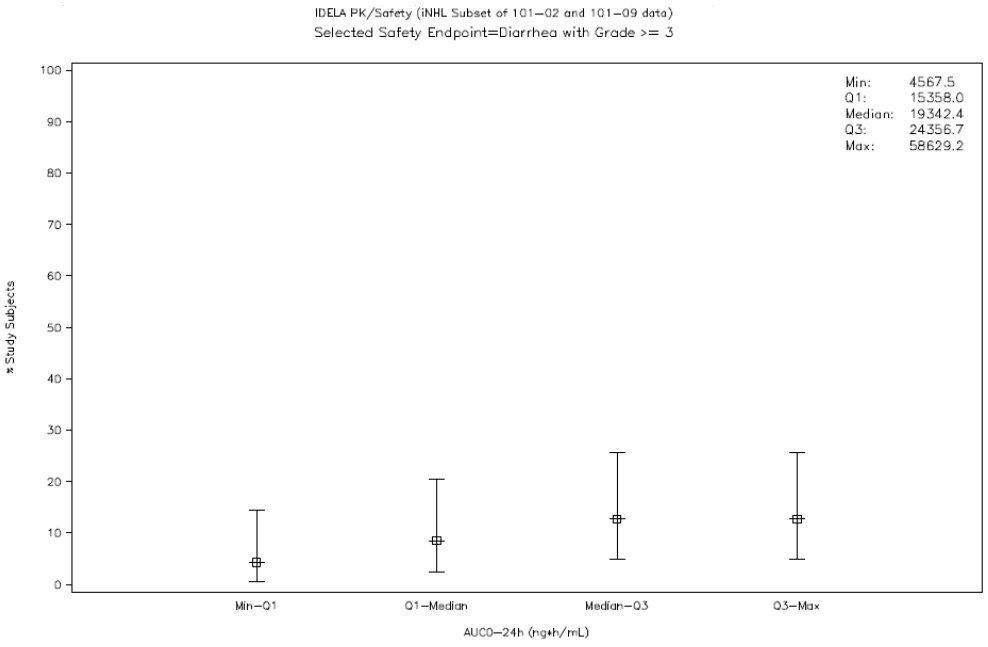


Figure 15: Incidences of adverse events of Grade ≥3 ALT abnormality (A) and Grade ≥3 diarrhea (B) by quartiles of exposure (AUC) for idelalisib in iNHL population (pooled analysis with pivotal efficacy study 101-09 and dose ranging study 101-02). *Source: Sponsor's PK-PD Tables, Figures and Listings Document for iNHL population, Figure 1.2, page 107 and Figure 9.1.2, Page 155*

Reviewer's comments:

1. *The results of reviewer' analysis of E-R relationship for efficacy and safety is described in section 1.1.1 of this review.*

4 LISTING OF ANALYSES DATASETS, CODES AND OUTPUT FILES

Table 7: Analysis Data Sets

Study Number	Name	Link to EDR
101-02 and 101-09	Adidela xpt (iNHL PKPD analysis dataset)	\\cdsesub1\evsprod\nda205858\0000\m5\datasets\pk-pd\analysis\adam\datasets\
	Adsl xpt Adae xpt	\\cdsesub1\evsprod\nda205858**0000**\m5\datasets**101-09**\analysis\adam\datasets\
Dosing/ covariate data from various studies for pop-pk	pk1101 xpt (pop-pk input file)	\\cdsesub1\evsprod\nda205858**0000**\m5\datasets\pop-pk-gs-**1101**\analysis\legacy\datasets\
312-0116	Adidela xpt (CLL PKPD analysis dataset)	\\cdsesub1\evsprod\nda205858\0009\m5\datasets\pk-pd\analysis\adam\datasets\
	Adsl xpt	\\cdsesub1\evsprod\nda205858\0006\m5\datasets\gs-us-312-0116\analysis\adam\datasets\
	adttei.xpt	\\cdsesub1\evsprod\nda205858\0009\m5\datasets\gs-us-312-0116\analysis\adam\datasets\

Table 8: Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\ Reviews\Ongoing PM Reviews\
	Simulations of various BID dosing regimen:	
Sim.mod and Sim.csv	Control stream and input csv file for simulations with final POP-PK model	Idelalisib_NDA205858_DDM\PPK_Analyses\final_sim2
Simulated_Cmin_analysis_phase2 r	Code for analysis of simulation output	Idelalisib_NDA205858_DDM\PPK_Analyses\codes
CMIN_DOSELEVEL_density7.jpg	Output figure for cumulative distribution of C_{tau} at steady state with simulations of 50, 100 and 150 mg BID dosing	Idelalisib_NDA205858_DDM\PPK_Analyses\results
phase1_analysis_iNHL_CLL_PK_AllDoses.sas poppk_Ctau_estimates_pivotal_iNHL_CLL_trials.sas	PK analyses for predicted Ctau with different (QD/BID) dosing regimen in phase 1 dose ranging study	Idelalisib_NDA205858_DDM\PPK_Analyses\codes
phase1_analysis_iNHL_CLL_ER_SPD.sas	PK/PD analysis (SPD) of Phase 1 dose ranging study data	Idelalisib_NDA205858_DDM\PPK_Analyses\codes

quart_plot_ORR_iNHL.ssc	E-R analysis (ORR vs Ctau) for iNHL	
PFS_analysis_CLL_iNHL.sas	E-R analysis (PFS vs Ctau) for iNHL and CLL	
quart_plot_LFT_iNHL.ssc	E-R analysis for safety for iNHL	
quart_plot_LFT_CLL.ssc	E-R analysis for safety for CLL	
macro_Universal.sas	SAS macro library for import/plotting purposes	

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STACY S SHORD
05/09/2014

DHANANJAY D MARATHE
05/09/2014

NITIN MEHROTRA
05/09/2014

ROSANE CHARLAB ORBACH
05/12/2014
Agree with Genomics portion.

JULIE M BULLOCK
05/15/2014

BIOPHARMACEUTICS REVIEW

Office of New Drug Quality Assessment

Application No.:	NDA 205-858 (000)	**Reviewer:** Sandra Suarez Sharp, Ph.D.	
Division:	DOHP		
Applicant:	Gilead Sciences, Inc.	**Team Leader:** Angelica Dorantes, Ph.D.	
Trade Name:	(b) (4)	**Acting Biopharmaceutics Supervisor:** Richard Lostritto, Ph.D.	
Generic Name:	Idelalisib Immediate Release Tablets	**Date Assigned:**	December 05, 2013
Indication:	Treatment for indolent non-Hodgkin lymphoma	**Date of Review:**	May 05, 2014
Formulation/strength	IR Tablets, 100 mg, and 150 mg		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Submission Dates	Date of informal/Formal Consult	Primary Review due in DARRTS
Sep 11, 2013 Dec 16, 2013 March 21, 2014 April 15, 2014	Dec 05, 2013	May 09. 2014

Type of Submission:	Original NDA (Priority Review)
Key review points	1. Dissolution method and acceptance criteria 2. Bridging Across Phases of Drug Development 3. Role of dissolution in supporting several specifications for the drug product

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criteria based on data from clinical and registration batches? If not, is the setting based on BE or IVIVC data?

C) DRUG PRODUCT FORMULATION DEVELOPMENT AND BRIDGING ACROSS PHASES **15**

12. What are the highlights of the drug product formulation development?

13. Are all the strengths evaluated in the pivotal clinical trials? What data are available to support the approval of lower strengths?

14. Are there any manufacturing changes implemented (e.g. formulation changes, process changes, site change, etc.) to the clinical trial formulation? What information is available to support these changes?

D) DISSOLUTION APPLICATIONS **17**

D.1 BIOWAIVERS

15. Is there a waiver request of in vivo BE data (Biowaiver)? If yes, what is/are the purpose/s of the biowaiver request/s? What data support the biowaiver request/s?

16. Is there any IVIVC information submitted? What is the regulatory application of the IVIVC in the submission? What data are provided to support the acceptability of the IVIVC model?

D.2 SURROGATES IN LIEU OF DISSOLUTION **18**

17. Are there any manufacturing parameters (e.g. disintegration, drug substance particle size, etc.) being proposed as surrogates in lieu of dissolution testing? What data are available to support the approval of the proposed surrogate test?

D.3 DISSOLUTION AND QBD **18**

18. Does the application contain QbD elements? If yes, is dissolution identified as a CQA for defining design space?

19. Was dissolution included in the DoE? What raw materials and process variables are identified as having an impact on dissolution? What is the risk assessment been performed to evaluate the criticality of dissolution?

20. What biopharmaceutics information is available to support the clinical relevance of the proposed design space?

21. Is there any dissolution model information submitted as part of QbD implementation? What is the regulatory application of the dissolution model in the submission? What data are provided to support the acceptability of the dissolution model?

BIOPHARMACEUTICS ASSESSMENT

I) SUMMARY OF BIOPHARMACEUTICS FINDINGS

Gilead Sciences is seeking approval of IDELA (Idelalisib) immediate release tablets for the twice-daily (BID) treatment for indolent non-Hodgkin lymphoma. The IDELA 100-mg BID dose was selected for dose reduction in subjects who are not able to tolerate a 150-mg BID dose.

According to the Applicant, IDELA is a low-solubility, high-permeability (BCS Class 2) compound. Idelalisib drug substance solubility strongly depends on pH, with an intrinsic solubility of 0.05 mg/mL at pH = 7. At pH 1.2 the solubility is 16 mg/mL and at pH 2.0 the solubility is 1.1 mg/mL. Both pH 1.2 and 2.0 provide sink conditions for the 100 mg and 150 mg tablets at volumes between 500 mL and 1,000 mL, but pH 2.0 was chosen as the medium because it provides (b) (4). Two (b) (4) forms of idelalisib, Form I and Form II, have been observed and characterized in laboratory studies. According to the Applicant, the drug substance is (b) (4) and the manufacturing process is designed to produce the (b) (4) polymorph. (b) (4) (b) (4). There is not a specification for solid state and it is not being monitored upon release and stability, because according to the Applicant, Form I and Form II of idelalisib are indistinguishable by melting point, solubility, and stability. The final clinical tablet formulation is also the proposed commercial formulation.

The 150 mg and 100 mg strengths are (b) (4) There are PK/PD data for both strengths conducted with the tablet formulation (Study 101-02: Phase 1, sequential dose-escalation: study of the safety, PK, PD, and activity of (b) (4) in subjects with relapsed or refractory hematologic malignancies. This study is being reviewed by OCP.

This review focuses on the evaluation of: **1)** The acceptability of the dissolution method and acceptance criterion; **2)** The data supporting appropriate bridging across the phases of drug development; and **3)** The role of dissolution in supporting several drug product specification limits.

1) Dissolution Method and Acceptance Criterion:

The following dissolution method and dissolution acceptance criterion have been agreed upon with the Applicant (refer to submission dated April 15, 2014):

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Acceptance Criterion
II	75 rpm	750 mL	37°C	0.01 N HCl pH 2.0	Q= (b) (4) in 20 min

The Applicant submitted adequate information to support the discriminating ability of the dissolution method. The selection of the dissolution acceptance criterion was based on the mean dissolution profiles of pivotal clinical (BE batches) and stability batches.

2) Appropriate Bridging Across Phases of Drug Development

There were some major process and formulation changes implemented to the Phase 1 clinical trial formulation. These changes are supported by the result of a BA study linking the early

formulations to the to-be-marketed formulation as described in formulation development section. This study is being reviewed by OCP. The to-be-marketed (TBM) formulation was used in the phase 3 clinical trials and there is PK information on this final formulation. However, the food effect study was conducted with the (b) (4) which is not the TBM formulation. This observation was communicated to the OCP reviewer team during the filing meeting. In addition, since studies 101-01, 04 and 05 (phase 1 studies) were also conducted with an earlier formulation; the OCP team was advised to evaluate the need for bridging these formulations depending on the impact of these PK studies has on the drug product labeling. Note that because there were major changes in formulations (b) (4) vs. (b) (4) vs. (b) (4) dissolution CANNOT be used to establish a bridge.

The change in (b) (4) is considered a minor change and is expected not to have an impact on BA. Dissolution has been provided for all these batches; also there is PK for both formulations and the final formulation (b) (4) was tested in phase 3 trials.

The commercial product will be manufactured at (b) (4) The biobatch was manufactured at (b) (4) Dissolution profile comparison data were submitted in response to the FDA's request to support the bridge between the two manufacturing sites. The mean f2 values are above 50, indicating that all strengths of the batches manufactured at either site have similar in vitro and in vivo performance.

3) The Role of Dissolution in Supporting Several Drug Product Specifications

During the course of formulation development several DoE studies were conducted to determine the effect product and process changes had on drug release. The following product characteristics and process changes which have an impact on drug release were identified:

***a.* Drug substance particle size**

The proposed specification for the drug substance particle size is: ***The d90 of the particle size distribution is NMT*** (b) (4) ***μm***

This specification is not supported by data because of the following;

- There are not dissolution data in the range of particle size (d90) between (b) (4) μm and (b) (4) μm.
- The clinical bathes were manufactured with a maximum d90 of (b) (4) μm and batches with a d90 above (b) (4) μm failed the acceptance criterion of Q= (b) (4)% at 20 minutes.

Therefore, it is recommended that the d90= (b) (4) ***μm specification range for drug substance particle size be established and also d10, d50 specification ranges be implemented. The implementation of these controls will help in reducing the high variability in the dissolution profile data observed for this product. It is noted that although batches with d90 particle size in the range of*** (b) (4) ***μm were tested in the clinical trials, the impact that fast releasing product with d90 very close to the lower limit will have on the safety of this product, is rather difficult to determine because there are no available PK data linking particle size to systemic exposure. It is likely that fast dissolving batches will result in shorter Tmax and higher Cmax values, leading to higher frequency of side effects.***

This recommendation was conveyed to the CMC team and to the Applicant in a teleconference dated April 10, 2014. On a teleconference dated May 07, 2014, the Applicant agreed on setting

upper specification limits for d90 and d50 and to report d10 values. For the specific details on this issue refer to the CMC review.

b. Tablet Hardness

The proposed specification ranges for the tablets hardness are:

Tablet Hardness, kp 100 mg strength: (b) (4)
Tablet Hardness, kp 150 mg strength:

The proposed specifications for the 100 mg and 15 mg tablets hardness are supported by dissolution data. Clinical batches with hardness values in these ranges meet the recommended dissolution acceptance criterion.

c. Effect of Percent Weight Gain

The level of coating weight gain on idelalisib tablets between (b) (4) and (b) (4) (proposed range (b) (4)) does not have a significant effect on the dissolution of idelalisib tablets.

d. Effect of (b) (4) and (b) (4)

The proposed specifications for (b) (4) are:

(b) (4)

The (b) (4) (duration) values tested in the DOE studies range from (b) (4) rpm and (b) (4) min, respectively. There is no dissolution data for batches manufactured at the proposed specification range of (b) (4) Since it seems that increasing the (b) (4) time decreases the dissolution profile, it is likely that the proposed ranges will result in dissolution profiles that meet the acceptance criterion; however it is unknown whether this will result in much faster dissolution profiles which may fail the similarity f2 criterion. Also it is noted that the Applicant indicated that (b) (4) (b) (4) rpm correspond to (b) (4) respectively. The (b) (4) (b) (4) does not correspond to a range of (b) (4) rpm. The CMC reviewing team was notified of this observation in an email dated April 8, 2014.

II) RECOMMENDATION

From the Biopharmaceutics perspective, NDA 205-858 for Idelalisib IR Tablets, 100 mg, and 150 mg, is recommended for APPROVAL.

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc; RLostritto

III) QUESTION BASED REVIEW APPROACH

A) GENERAL ATTRIBUTES

1. ***What are the highlights of the chemistry and physico-chemical properties of the drug substance (e.g. solubility) and formulation of the drug product?***

Drug Substance

Idelalisib is a Biopharmaceutical Classification System (BCS) Class 2 drug, with high permeability (5.9 x 10^{-6} cm/s in Caco-2 cells at a concentration of 10 µM) and low solubility in water (both Form I and Form II exhibited similar solubilities of 0.05 mg/mL). Idelalisib has three ionizable moieties within the pH range of 1 – 12. The aqueous solubility of idelalisib can be greatly influenced by the pH of the medium. At pH values below the ionization constant of the pyrimidinyl group, pK_a = 3.4, the solubility increases as shown in Figure 1.

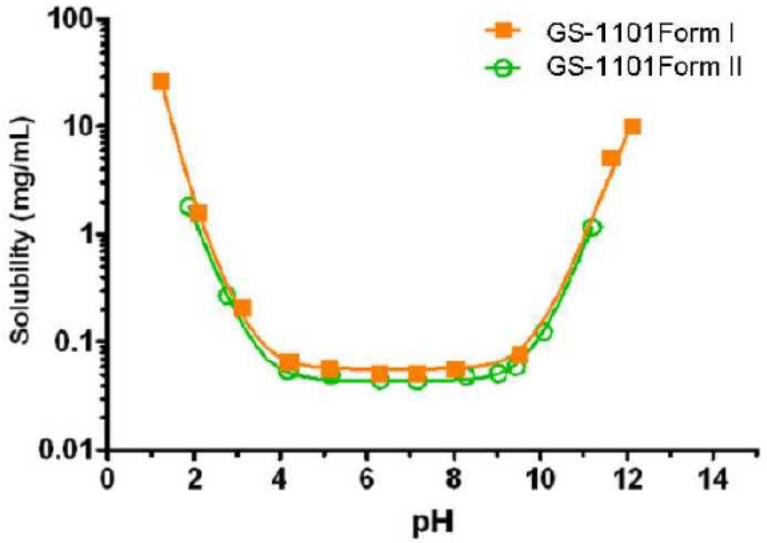

Figure 1. Aqueous pH-Solubility Profile of Idelalisib (b) (4) as Form I and Form II at Room Temperature.

There are two known (b) (4) polymorphs of idelalisib, Form I and Form II. According to the Applicant, all idelalisib drug substance lots have been manufactured as (b) (4) Form II has been shown to be biopharmaceutically, chemically, and physically equivalent to Form I. (b) (4) Idelalisib Form I and Form II have equivalent properties, including, aqueous solubility, hygroscopicity, intrinsic dissolution, and chemical stability (see CMC review and Section 3.2.P.2.1/pharmaceutical development-components.pdf for more details \\cdsesub1\evsprod\NDA205858\0000\m3\32-body-data\32p-drug-prod\idelalisib-tablet\32p2-pharm-dev). The Applicant concludes that

Form I and Form II are considered equivalent, and the [redacted] tablets will have no impact on tablet manufacturing or performance.

Drug Product

The proposed commercial formulation of [redacted] 150 mg is a pink, film-coated, oval-shaped tablet debossed with "GSI" on one side and "150" on the other side. The proposed commercial formulation of [redacted] 100 mg is an orange, film-coated, oval-shaped tablet debossed with "GSI" on one side and "100" on the other side. The qualitative and quantitative formulation is summarized in Table 1.

Table 1. Qualitative and Quantitative Composition of [redacted] Tablets

Component	% w/w	Unit Formula (mg/tablet)		Function
		150 mg	100 mg	
[redacted]	[redacted]	150.0	100.0	Active Ingredient
Microcrystalline Cellulose	[redacted]	[redacted]	[redacted]	[redacted]
Hydroxypropyl-cellulose	[redacted]	[redacted]	[redacted]	[redacted]
Sodium Starch Glycolate	[redacted]	[redacted]	[redacted]	[redacted]
Croscarmellose Sodium	[redacted]	[redacted]	[redacted]	[redacted]
Magnesium Stearate	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total (tablet core)	[redacted]	[redacted]	[redacted]	[redacted]
Film Coating				
[redacted] Pink [redacted]	[redacted]	[redacted]	[redacted]	Film coat
[redacted] Orange [redacted]	[redacted]	[redacted]	[redacted]	Film coat
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	—

Reviewer's Comments

The two strengths are [redacted]

2. ***Is there any information on BCS classification? What claim did the applicant make based on BCS classification? What data are available to support this claim?***

The proposed commercial IDELA tablet (150 and 100 mg) is an immediate-release, solid oral dosage form. According to the BCS, Idelalisib is reported as a low-solubility, high-permeability (BCS Class 2) compound.

B) DISSOLUTION INFORMATION

3. ***What is the proposed dissolution method?***

The dissolution method proposed as a quality control test for all the strengths of Idelalisib IR Tablets is summarized below:

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium
II	75 rpm	750 mL	37°C	0.01 N HCl pH 2.0

4. ***What data are provided to support the adequacy of the proposed dissolution method (e.g medium, apparatus selection, etc.)?***

Dissolution Method Development

Briefly, the dissolution method was evaluated to determine the effect varying dissolution parameters would have on the *in vitro* drug release (for more details refer to pdm-1442 at \\cdsesub1\evsprod\NDA205858\0000\m3\32-body-data\32p-drug-prod\idelalisib-tablet\32p5-contr-drug-prod\32p56-justif-spec). The following method parameters were evaluated.

(b) (4)

From these series of studies, the method described in the table above was selected. The effect of pH on the robustness of the dissolution profile for idelalisib tablets is shown in Figure 2.

Reviewer's Comments

This Reviewer agrees with the following conclusions reached by the Applicant:

- *The selected dissolution medium of 0.01 N HCl (pH 2.0) at 37 °C provided sufficient solubility to give reproducible dissolution of idelalisib tablets and reflects typical pH conditions seen in the stomach.*
- *The agitation rate was set at 75 RPM as the minimum speed required preventing coning and giving reproducible results.*
- *A degassed medium volume of 750 mL was selected for both 100 mg and 150 mg strengths to maximize discriminating power, reproducibility and method robustness.*
- *No sinker is used to ensure consistently complete release of idelalisib.*

5. *What information is available to support the robustness (e.g. linearity, accuracy, etc.) of the dissolution methodology?*

Dissolution Method Validation

The Applicant provided enough information to support the validity of the analytical method for dissolution testing for idelalisib tablets (refer to CMC review for more details; also see bionalytical-procedures.pdf at \\cdsesub1\evsprod\NDA205858\0000\m3\32-body-data\32p-drug-prod\idelalisib-tablet\32p5-contr-drug-prod\32p52-analyt-proc).

6. What data are available to support the discriminating power of the method?

The discriminating ability of the method was demonstrated by altering the following attributes:

(b) (4)

The dissolution method was also capable of discriminating tablets stressed under high heat and humidity. For more details refer to the following link: \\cdsesub1\evsprod\NDA205858\0000\m3\32-body-data\32p-drug-prod\idelalisib-tablet\32p5-contr-drug-prod\32p56-justif-spec).

(b) (4)

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7. Is the proposed dissolution method biorelavant? What data are available to support this claim?

There were no data in the submission to help in the assessment of the bio-relevancy of the method (e.g. the ability of the method to reject batches that are not bioequivalent). A single dose, three-way, cross over BA study (Study 101-06) was performed to compare the relative PK of a single 100 mg dose of idelalisib administered as a [redacted] and film-coated tablet. Data from this study showed that the two products were not BE interns of Cmax. However, the method used to assess for dissolution was an early method [redacted] that showed no difference is dissolution between the two bathes. It is uncertain whether the current method would be able to reject for these batches since the dissolution profile for the developmental batch ([redacted] formulation) was not tested using the currently proposed dissolution method which appears to be more discriminating. Note, that the method is able to reject for batches with drug substance particle size outside the ranges tested in clinical trials (Figure 4)

8. Is the proposed method acceptable? if not, what are the deficiencies?

The Applicant provided adequate information to support the acceptability and discriminating power of the proposed dissolution method.

B.2. ACCEPTANCE CRITERIA

9. What is the proposed dissolution acceptance criterion for this drug product?

The following dissolution acceptance criterion was originally proposed by the Applicant as a QC for the release of all strengths of idelalisib IR Tablet:

Proposed Dissolution Acceptance criterion
Q= [redacted] in [redacted] min

10. What data are available to support it?

According to the Applicant, the proposed criteria are based on release data from tested in clinical trials formulations and commercial batches manufactured at both manufacturing sites (Figure 5). Note that the data for the 150 mg strength is not shown in here (for more details refer to \\cdsesub1\evsprod\NDA205858\0000\m3\32-body-data\32p-drug-prod\idelalisib-tablet\32p5-contr-drug-prod\32p56-justif-spec).

Figure 5. Dissolution Profile of (b) (4) Tablets, 100 mg, Used in Clinical Studies which were also part of the stability testing.

11. Is the acceptance criterion acceptable? If not, what is the recommended criterion? Is the setting of the dissolution acceptance criterion based on data from clinical and registration batches?

The originally proposed dissolution acceptance criterion of Q = (b) (4) at (b) (4) minutes was NOT acceptable, because it was not supported by the provided data. Based on the data (Figure 4), the dissolution acceptance criterion below was recommended in an IR letter dated Feb 8, 2014, and discussed in a teleconference with the Applicant on April 10, 2014.

The comment sent in the IR dated Feb 08, 2014, is as follows:

1. *The provided dissolution data do not support the selection of your proposed acceptance. Implement the following dissolution acceptance criterion for your proposed product and provide the updated specifications table for your product with the revised recommended acceptance criterion.*

Acceptance criterion
Q= (b) (4) in 20 min

In submissions dated March 21, 2014 and April 15, 2014, the Applicant submitted the updated specification tables for the drug product, reflecting the above recommended revision to the dissolution acceptance criterion for the 100 mg and 150 mg strengths, respectively.

C) DRUG PRODUCT FORMULATION DEVELOPMENT AND BRIDGING ACROSS PHASES

12. What are the highlights of the drug product formulation development?

Three oral solid dosage formulations and dosage forms were developed sequentially and used during clinical evaluation of idelalisib as follows:

(b) (4)

According to the Applicant, in all cases, the drug product was manufactured using (b) (4) The only difference between the earlier and the to-be-marketed (TBM) tablet formulations is the level of (b) (4) used. The first tablet lot manufactured (Lot B090557), dosed in Study 101-06, contained (b) (4) (wt %) (b) (4) To improve manufacturability, the amount of (b) (4) was (b) (4) This final TBM tablet formulation was used in all subsequent clinical and primary stability lots.

Figure 6 gives a Schematic Overview on the Idelalisib Formulation Development and the data provided to support the bridging between the formulations used in the different phases. Study 101-06, a single dose, three-way, crossover BA study was performed to compare the relative BA of a single 100 mg dose of idelalisib administered as a (b) (4) and as a film-coated tablet. This study is being reviewed by OCP.

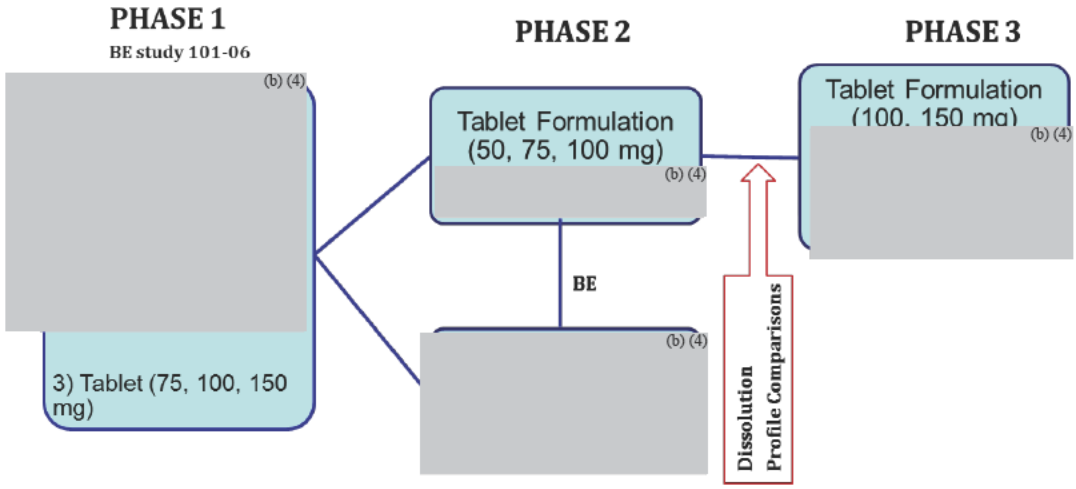

Figure 6. Schematic Overview on the Idelalisib Formulation Development

Reviewer's Comments

The TBM formulation was used in the phase 3 clinical trials and there is PK on this final formulation. However, the food effect study was conducted with the (b) (4) *which is*

not the TBM formulation. Since food-effect is formulation dependent, this observation was communicated to the OCP reviewing team during the filing meeting. In addition, since studies 101-01, 04 and 05 (phase 1 studies) were also conducted with an earlier formulation; the OCP team was advised to evaluate the need for bridging formulations, depending on the impact of these studies on the drug product labeling. Note that because there were major changes in the composition of the formulations ([(b) (4)] vs. [(b) (4)] vs. tablet), dissolution CANNOT be used to establish a bridge.

The change in [(b) (4)] is considered a minor change and is expected not to have an impact on BA. Dissolution has been provided for all these batches which meet the recommended dissolution acceptance criterion; also there is PK for both formulations and the final formulation [(b) (4)] was tested in phase 3 trials.

13. Are there any manufacturing changes implemented (e.g. formulation changes, process changes, site change, etc.) to the clinical trial formulation? What information is available to support these changes?

As mentioned above, the only difference between the earlier and the TBM tablet formulations is the level of [(b) (4)] used. In addition, an additional manufacturing site was added. The commercial product will be manufactured at [(b) (4)] [(b) (4)] The biobatch was manufactured at [(b) (4)] [(b) (4)] Table 2 summarizes the batches manufactured at each site. In order to bridge these two sites, the Applicant was requested to provide dissolution profiles comparisons during the review cycle. The mean f2 values are above 50 indicating that for both strengths the batches manufactured at either site have similar in vitro and in vivo performance (\\cdsesub1\evsprod\NDA205858\0013\m1\us\111-info-amendment).

Table 2. Summary of the Clinical Lots of idelalisib tablets Analyzed

Lot No.	Tablet Strength	Manufacturer	Note
		[(b) (4)]	
B090557	100 mg		Bioavailability batch
B100326	100 mg		-
B100734	100 mg		-
B100735	150 mg		-
B110369 (CV1104C)	100 mg		First Primary stability batch
B110370 (CV1104D)	150 mg		First Primary stability batch
FZPX (CV1107B)	100 mg		Second Primary stability batch
FZPY (CV1107D)	150 mg		Second Primary stability batch
GCBM (CV1110C)	100 mg		Third Primary stability batch
GCBN (CV1110D)	150 mg		Third Primary stability batch

HCBX (CV1201B)	100 mg	(b) (4)	-
HCBZ (CV1202B)	150 mg		-
HZWH (CV1204B)	150 mg		-
KTYX (CV1205C)	100 mg		Commercial Image
KFPC (CV1205D)	150 mg		Commercial Image
KFPG (CV1206B)	150 mg		-
KXNV (CV1301C)	100 mg		Commercial Image
KXNW (CV1301D)	150 mg		Commercial Image

Source: Table 7, \\Cdsesub1\evsprod\NDA205858\0000\m3\32-body-data\32p-drug-prod\idelalisib-tablet\32p5-contr-drug-prod\32p56-justif-spec; PDM-1442

14. Are all the strengths evaluated in the pivotal clinical trials? What data are available to support the approval of lower strengths?

The 150 mg and 100 mg strengths are (b) (4) (Table 1, section 3.2.p.1). There is PK/PD data for both strengths conducted with the tablet formulation (Study 101-02: Phase 1, sequential dose-escalation: study of the safety, PK, PD, and activity of (b) (4) in subjects with relapsed or refractory hematologic malignancies. This study is being reviewed by OCP.

In addition, based on graphical dissolution data between the 100 mg (e.g. data from Figure 5) and 150 mg tablets (not shown in here), this reviewer concludes that it is likely that the two formulations are dose-proportional.

D) DISSOLUTION APPLICATIONS

D.1 BIOWAIVERS

15. Is there a request for waiver of in vivo BE data (Biowaiver)? What is/are the purpose/s of the biowaiver request/s? What data support the biowaiver request/s?

There was no biowaiver request.

16. Is there any IVIVC information submitted? What is the regulatory application of the IVIVC in the submission? What data is provided to support the acceptability of the IVIVC?

There were no IVIVC models included.

D.2 SURROGATES IN LIEU OF DISSOLUTION

17. Are there any manufacturing parameters (e.g. disintegration, drug substance particle size, etc.) being proposed as surrogates in lieu of dissolution testing? What data are available to support this claim?

No. Dissolution testing is being implemented.

D.3 DISSOLUTION AND QBD

18. If the application contains QbD elements, is dissolution identified as a CQA for defining design space?

Elements of Quality by Design and Quality Risk Management were applied to the development of this product. Although DOEs were run for a number of unit operations, Gilead is not filing a quality by design (QbD) application and intents to operate within the proposed normal operating ranges (NOR) and movement outside of the proposed normal operating ranges will be considered a change to the manufacturing process.

A risk assessment and optimization study were performed on the idelalisib film-coated tablet manufacturing process to establish and characterize influential process parameters (IPPs) and critical quality attributes (CQAs) of the final (b) (4) and final drug product. This study defined proven acceptable ranges (PARs) and normal operating ranges (NORs) for IPPs based on CQA responses and support the control strategy for the proposed commercial process. The risk assessment identified the manufacturing steps of (b) (4) as having the greatest influence over proposed CQAs (Table 3). Dissolution was identified as a CQA.

Table 3. Initial Risk Assessment of the Manufacturing Process for Idelalisib Tablets, 100 mg and 150 mg

Intermediate and Drug Product CQA	Unit Operation (b) (4)	Film-Coating
Final (b) (4) Properties[a]	NA	NA
Appearance		
Dosage Strength and Uniformity		
Dissolution		
Tablet Physical Properties[b]		
Stability		
(b) (4)		
Overall Risk		

Low risk Medium risk High risk

a Final (b) (4) properties include d_{50}, (b) (4) content, bulk density, and (b) (4)

b Tablet physical properties include weight, hardness, weight variability, and hardness variability.

19. Was dissolution included in the DoE? What material attributes and process variables are identified as having an impact on dissolution? What is the risk assessment been performed to evaluate the criticality of dissolution?

As mentioned above, during the course of formulation development several DoE studies were conducted to determine the effect product and process changes had on drug release. The following product characteristics and process changes which have an impact on drug release were identified:

(b) (4)

Effect of Drug Substance Particle Size

As noted above, developmental batches were manufactured with a wider range of d_{90} (b) (4) to (b) (4) µm) than those tested in clinical trials (maximum d_{90} of (b) (4) µm) to define where tablet manufacturing or dissolution performance would be adversely impacted by drug substance particle size; however no data were submitted on the relationship between dissolution and d10 and d50.

During the review cycle (IR dated Feb 10, 2014) the Applicant was requested to provide this information which was received on March 21, 2014 (Figure 7). According to the Applicant, the correlation between d_{90} and dissolution has a lower slope making it a more discriminating attribute for evaluating the effect of drug substance particle size on dissolution.

(b) (4)

Figure 7. Effect of Drug Substance Particle Size (d10, d50 and d90) on the Dissolution of Clinical and Experimental Idelalisib Tablets, 150 mg

Reviewer's Comments

The proposed specification for the drug substance particle size is:

The d90 of the particle size distribution is NMT (b) (4) µm

This specification is not supported by data because of the following;

- There are not dissolution data in the range of particle size (d90) between (b) (4) µm and (b) (4) µm.
- The clinical bathes were manufactured with a maximum d90 of (b) (4) µm and batches with a d90 above (b) (4) µm failed the acceptance criterion of Q= (b) (4) at 20 minutes (Figure 7).

Therefore, it is recommended that a d90= (b) (4) µm specification range for drug substance particle size be established and also d10, d50 specification ranges be implemented. The implementation of these controls will help in reducing the high variability in the dissolution profile data observed for this product.

It should be noted that although batches with d90 particle size in the range of (b) (4) µm were tested in the clinical trials, the impact that fast releasing batches with d90 very close to the lower limit will have on the safety of this product, is rather difficult to determine because there are no available PK data linking particle size to systemic exposure. It is likely that fast dissolving batches will result in shorter Tmax and higher Cmax values, leading to higher frequency of side effects.

This recommendation was conveyed to the CMC team and to the Applicant in a teleconference dated April 10, 2014. On a teleconference dated May 07, 2014, the Applicant agreed on setting upper specification limits for d90 and d50 and to report d10 values. For the specific details on this issue refer to the CMC review.

Effect of Hardness on Dissolution

During the review cycle the Applicant was quested to provide data on the relationship between dissolution and hardness. The Applicant responded (March 21, 2014) that the assessment of the effect of hardness on dissolution was studied on six (b) (4) prepared for the 150 mg strength tablets; whereas, the effect of hardness on the 100 mg strength tablets was studied only on a single (b) (4) For the 150 mg strength tablets the target tablet hardness was (b) (4) kp, and for the 100 mg strength tablets the target tablet hardness was (b) (4) kp.

The dissolution profiles were comparable at the low and mid-range tablet hardness for both the 100 mg and 150 mg strength tablets. However, the high range tablet hardness exhibited a (b) (4) resulting in dissolution profiles that are not similar (Figure 8) for the 100 mg tablet (for more details refer to \\cdsesub1\evsprod\NDA205858\0032\m1\us\111-info-amendment) .

Figure 8. Effect of Hardness on the Dissolution of Idelalisib Tablets, 100 mg.

Reviewer's Comments
The proposed specifications for the drug hardness are:

Tablet Hardness, kp 100 mg strength:
Tablet Hardness, kp 150 mg strength:

The proposed specification for the 100 mg tablet is supported by data. Figure 9 shows that the batches meet the acceptance criterion when hardness value is up to kp, but it seems that this batch does not meet the similarity criterion; therefore, an upper level of kp seems more appropriate.

For the 150 mg tablet, a batch with a hardness value of kp meets the dissolution acceptance criterion of Q= at 20 min; a batch with a value of kp, although does not meet the dissolution acceptance criterion, the shape of the profile is not significantly affected; therefore, a hardness value of kp seems appropriate from biopharmacutics perspective.

Effect of Percent Weight Gain
The level of coating weight gain on idelalisib tablets between (proposed range does not have a significant effect on the dissolution of idelalisib tablets (for more details refer to \\cdsesub1\evsprod\NDA205858\0032\m1\us\111-info-amendment) .

Effect of
DOE experiments showed that cumulative release at minutes decreased significantly with

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correspond to a range of (b) (4) rpm). The CMC review team was notified on this observation on an email dated April 8, 2014.

20. What biopharmaceutics information is available to support the clinical relevance of the proposed design space?

There is no design space being proposed.

21. Is there any dissolution model information submitted as part of QbD implementation? What is the regulatory application of the dissolution model in the submission? What data are provided to support the acceptability of the dissolution model?

A dissolution model was not proposed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANDRA SUAREZ
05/09/2014

ANGELICA DORANTES
05/09/2014

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	205-858	**Brand Name**	Under review
OCP Division	DCP V	**Generic Name**	Idelalisib
OND Division	DHP	**Drug Class**	Kinase inhibitor
OCP Reviewer	Stacy S Shord, Pharm.D.	**Indication(s)**	Indolent non-Hodgkin lymphoma
OCP Team Leader	Julie Bullock, Pharm.D.	**Dosage Form**	Tablet
Pharmacometrics Reviewer	Nitin Mehrotra, Ph.D. DJ Marathe, Ph.D.	**Dosing Regimen**	150 mg twice daily
Date of Submission	September 11, 2013	**Route of Administration**	Oral
Priority Classification	Standard / Priority	**Sponsor**	Gilead Sciences, Inc.
PDUFA Due Date	September 11, 2014 / May 09, 2014		

Idelalisib inhibits ATP binding to the catalytic domain of PI3Kδ. The proposed dose is 150 mg twice daily without regard to food. Gilead supports the proposed indication and dose with a single arm trial (Study 101-09) in patients with indolent non-Hodgkin lymphoma (58% follicular lymphoma, 22% small lymphocytic leukemia) who received the proposed dose continuously. The objective response rate (ORR) as assessed by investigators was 57% (95% confidence interval: 48%, 66%). Common adverse events (any grade ≥ 20%) were diarrhea, fatigue, nausea, cough, pyrexia and transaminitis. Multiple nonclinical and clinical studies were conducted to characterize the clinical pharmacology of idelalisib as listed below.

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x	1		

Reference Bioanalytical and Analytical Methods	x	16		[redacted] 1003-091478-001 (everolimus), [redacted] 8234402 (idelalisib and GS-561137, plasma), [redacted] 8249436 (GS-9973), [redacted] 8251203 (rifampin), [redacted] 8274044 (digoxin), [redacted] 8275763 (idelalisib and GS563117, urine), [redacted] 8280288 (midazolam), [redacted] 8281135 (rosuvastatin), [redacted]-RD-962 (idelalisib, plasma), [redacted]-RD-963 (idelalisib, urine), [redacted]5378.083008 (idelalisib plasma), [redacted]5753.042009 (idelalisib , plasma), [redacted]6222.011510 (idelalisib and GS-561137, plasma), [redacted]6395.101510 (idelalisib); [redacted]1003-091478-002 (stability, everolimus), [redacted]5483.070711 (stability, idelalisib)
I. Clinical Pharmacology				
Mass balance:	x	2		313-0111 (healthy) 101-05 (microdose, healthy)
Isozyme characterization:	x	5		794306 (CYP phenotyping) [redacted]312-2023 (hepatic metabolism) [redacted]070003 (metabolite characterization, hepatocytes) [redacted]312-2002 and [redacted]2010-001 (UGT phenotyping)
Blood/plasma ratio:	x	1		[redacted]312-2014 (idelalisib, GS-563117)
Plasma protein binding:	x	1		[redacted]312-2009 (idelalisib, GS-563117)
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	x	2		101-01 (men) 313-0126 (Asian, White)
multiple dose:	x	1		101-01 (men) 339-0101 (combination)
Patients-				
single dose:	x	4		101-02 (cancer) 101-04 (rhinitis) 101-07 (combination) 101-09 (activity)
multiple dose:	x	2		101-02 (cancer) 101-08 (activity, combination) 101-09 (activity) 101-11 (activity)
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	2		101-05 (ketoconazole) 313-0130 (rifampin)
In-vivo effects of primary drug:	x			313-0130 (substrates CYP3A4, PGP, OATP)

In-vitro:	x	18		Parent 13558 (inhibition, CYP) 13567 (inhibition, CYP3A) 400571 (substrate, inhibition, PGP) (b) (4)-312-2008 (induction CYP) -312-2011 (inhibition, OATP, BCRP) (b) (4)-312-2017 (inhibition, UGT) (b) (4)-312-2018 (inhibition, CYP2B6) (b) (4)-312-2024 (inhibition, CYP3A) OPT-2010-087 (inhibition, OAT, OCT) OPT-2010-124 (substrate, BCRP, OAT, OCT, OATP) Metabolite (b) (4)-312-2005 (inhibition, PGP, OATP, BCRP) (b) (4)-312-2006 (substrate, PGP, BCRP) (b) (4)-312-2008 (induction, CYP) (b) (4)-312-2010 (substrate, OATP) (b) (4)-312-2012 (inhibition, OAT, OCT) (b) (4)-312-2016 (inhibition, CYP3A) (b) (4)-312-2017 (inhibition, T) (b) (4)-312-2019 (inhibition, CYP)
Subpopulation studies -				
ethnicity:	x			313-0126 (healthy, Asian, White) PPK
gender:	x			PPK
pediatrics:				Full waiver requested
geriatrics:				PPK
renal impairment:	x	1		313-0118 (healthy, impaired) PPK
hepatic impairment:	x	1		313-0112 (healthy, impaired) PPK
PD -	x			101-01, 330-0101, 101-02
Phase 2:				
Phase 3:				
PK/PD -	x	1		pk-pd
Phase 1 and/or 2, proof of concept:	x	1		313-0117 (QT) 101-02, 101-09 (biomarkers)
Phase 3 clinical trial:				
Population Analyses -	x	2		POP-PK-GS-1101 POP-PK-GS-563117
Data rich:	x			101-01, 101-02, 101-04, 101-05, 101-06, 101-07, 101-08, 101-09, 101-11, 331-1101
Data sparse:	x			
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	x	1		101-06 ((b) (4) tablet)
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	x			101-05 (food effect)

Bio-waiver request based on BCS				
BCS class	**2**			
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	x			Request full waiver under PREA
Literature References				
Total Number of Studies		**62**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			RBA study - two (b) (4) products, one tablet product
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose	x			

	adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?				
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	Request full waiver under PREA
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant: not applicable.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter: No review issues need to be conveyed.

Stacy S. Shord — 10/30/2013
Reviewing Clinical Pharmacologist — Date

Julie Bullock — 10/30/2013
Team Leader/Supervisor — Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STACY S SHORD
10/28/2013

JULIE M BULLOCK
10/30/2013

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	205-858
Product name, generic name of the active, and dosage form and strength	Idelalisib Immediate Release Tablet, 100 mg and 150 mg
Submission date	Sep 11, 2013
Indication	Treatment for indolent non-Hodgkin lymphoma
Applicant	Gilead Sciences, Inc.
Medical Division	DOHP
Type of Submission	NME
Biopharmaceutics Reviewer	Sandra Suarez Sharp, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.

Background

Gilead Sciences is seeking approval of IDELA (Idelalisib) immediate release tablets for the twice-daily (BID) treatment for indolent non-Hodgkin lymphoma. The (b) (4) 100-mg BID dose was selected for dose reduction in subjects who are not able to tolerate a 150-mg BID dose.

According to the Applicant, (b) (4) is a low-solubility, high-permeability (BCS Class 2) compound. Idelalisib drug substance solubility strongly depends on pH, with an intrinsic solubility of 0.05 mg/mL at pH = 7. At pH 1.2 the solubility is 16 mg/mL and at pH 2.0 the solubility is 1.1 mg/mL. Both pH 1.2 and 2.0 provide sink conditions for the 100 mg and 150 mg tablets at volumes between 500 mL and 1,000 mL, but pH 2.0 was chosen as the medium because it provides (b) (4) Two (b) (4) forms of idelalisib, Form I and Form II, have been observed and characterized in laboratory studies. According to the Applicant, the drug substance is (b) (4) and the manufacturing process is designed to produce the (b) (4) polymorph. (b) (4) There is not a specification for solid state and it is not being monitored upon release and stability, because according to the Applicant, Form I and Form II of idelalisib are indistinguishable by melting point, solubility, and stability. The final clinical tablet formulation is also the proposed commercial formulation.

The following parameters from the ONDQA Quality (Biopharmaceutics) filing checklist are necessary in order to initiate a full Biopharmaceutics review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A.	BIOPHARMACEUTICS			
	Parameter	**Yes**	**No**	**Comment**
1.	Does the application contain dissolution data?	X		The following dissolution method is proposed for routine testing: Medium: 750 mL of 0.01 N HCl Apparatus: USP II (paddle) Speed: 75 rpm Temperature: 37°C (b) (4)

2.	Is the dissolution test part of the DP specifications?	X		The proposed acceptance criteria is as follows: (b) (4) at (b) (4) minutes is proposed for both (b) (4) 100 mg and 150 mg tablets. Note: The acceptability of the proposed acceptance criteria is a review issue.
3.	Does the application contain the dissolution method development report including data supporting the discriminating ability?	X		Yes, there is sufficient information (see sections 3.2.P.2.2; 3.2.P.5.6, and 3.2.P.2.3; document PDM-1442 under section 3.2.p.5.6). The acceptability of this method is a review issue.
4.	Is there a validation package for the analytical method and dissolution methodology?	X		The amount of idelalisib dissolved is assayed by UV spectrophotometry at (b) (4) nm and quantified using an external standard.
5.	Does the application include a biowaiver request?		X	
6.	Is there information/data supporting the biowaiver request?		X	
7.	Is dissolution testing being proposed as a tool to monitor for crystalline/amorphous content? If so, are data provided to support the discriminating ability of the dissolution method towards different crystalline/amorphous content?		X	Form I and Form II of idelalisib are indistinguishable by melting point, solubility (0.05 mg/mL) and stability (sections 3.2.p.2.1 and 3.2.S.4.5). The intrinsic dissolution rates of idelalisib Form I (Batch 60182-09-004) and Form II (Batch 4903-58) were determined in pH 2.0 water (0.01 N HCl) at 37 ºC. Form I and Form II exhibit nearly identical aqueous dissolution rates of (b) (4) and (b) (4) respectively.
8.	Is there enough information to assess the extended release designation claim?		X	NA
9.	Is there any information to support the approval of the lower strength (s)?			The 150 mg and 100 mg strengths are (b) (4) (Table 1, section 3.2.p.1). There is PK/PD data for both strengths conducted with the tablet formulation (Study 101-02: Phase 1, sequential dose-escalation: study of the safety, PK, PD, and activity of (b) (4) in subjects with relapsed or refractory hematologic malignancies. This study will be reviewed by OCP.
10.	Does the application include an IVIVC model?		X	
11.	Does the application include information/data on in vitro alcohol dose-dumping potential?		X	NA

12.	Is there any in *vivo* BA or BE information in the submission?	X		There are two BA/BE studies included in the submission: ▪ Food effect study: Note that this study was conducted with an early formulation of the product (b) (4) which was shown not to be BE to the clinical formulation (e.g. Cmax upper bound was (b) (4). ▪ BA/BE study comparing an early formulation (b) (4) to the tablet formulation. Note: These studies will be reviewed by OCP.
13.	Is there any design space proposed using in vitro release as a response variable?		X	This submission does not have QbD elements. However, dissolution is being used to support for CMAs and CMPs.
14.	Are there any data supporting a manufacturing change?			The commercial product will be manufactured at (b) (4) The biobatch was manufactured at (b) (4) The Applicant will be requested to provide dissolution profile comparisons to bridge these two sites.
15.	Is the control strategy related to in vitro drug release?		X	Not applicable

B.	**filing conclusion**			
	Parameter	**Yes**	**No**	**Comment**
16.	**IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	X		• The NDA is fileable from Biopharmaceutics Perspective • The acceptability of the proposed dissolution method and acceptance criterion will be a review issue.
17.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable.
18.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable.
19.	Are there any potential review issues identified?		X	

20.	Are there any comments to be sent to the Applicant as part of the 74-Day letter?	X		*The following comments need to be included in the 74-Day letter.* ▪ *Provide individual dissolution data for all the batches used to support the proposed acceptance criterion.* ▪ *Provide dissolution profile comparisons in the proposed QC medium between the products manufactured at the* (b) (4) *(biobatch) and* (b) (4) *(commercial product). These data are needed to support the bridging between these two manufacturing sites.*
21.	Are there any internal comment to other disciplines:			**Comments to the Clinical Pharmacology team:** ▪ *The food effect study was conducted with an early formulation that was not BE to the clinical trial formulation. The Applicant may need to conduct an additional BE study or address this deficiency through labeling.*

{See appended electronic signature page}

Sandra Suarez Sharp, Ph.D. Date
Senior Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

{See appended electronic signature page}

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader Date
Office of New Drug Quality Assessment

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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10/16/2013

ANGELICA DORANTES
10/16/2013