

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209936Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	New Drug Application (NDA)
Application Number(s)	209936
Priority or Standard	Priority
Submit Date(s)	16 March 2017
Received Date(s)	16 March 2017
PDUFA Goal Date	16 November 2017
Division/Office	DHP/OHOP
Review Completion Date	13 September 2017
Established Name	Copanlisib
(Proposed) Trade Name	Aliqopa
Pharmacologic Class	Kinase inhibitor
Code name	Phosphatidylinositol 3-kinase (PI3K) inhibitor
Applicant	Bayer HealthCare Pharmaceuticals Inc.
Formulation(s)	60 mg intravenous infusion
Dosing Regimen	Days 1, 8, and 15 of a 28-day treatment cycle
Applicant Proposed Indication(s)/Population(s)	Indicated for the treatment of patients with relapsed (b) (4) follicular lymphoma who have received at least two prior therapies.
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	Indicated for the treatment of adult patients with relapsed follicular lymphoma who have received at least two prior systemic therapies.

Table of Contents

Reviewers of Multi-Disciplinary Review and Evaluation	9
Additional Reviewers of Application.....	9
Glossary.....	10
1 Executive Summary	12
1.1. Product Introduction.....	12
1.2. Conclusions on the Substantial Evidence of Effectiveness	12
1.3. Benefit-Risk Assessment	14
2 Therapeutic Context	17
2.1. Analysis of Condition.....	17
2.2. Analysis of Current Treatment Options	17
3 Regulatory Background	21
3.1. U.S. Regulatory Actions and Marketing History.....	21
3.2. Summary of Presubmission/Submission Regulatory Activity	21
4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety.....	22
4.1. Office of Scientific Investigations (OSI)	22
4.2. Product Quality	22
4.3. Devices and Companion Diagnostic Issues	23
5 Nonclinical Pharmacology/Toxicology.....	24
5.1. Executive Summary	24
5.2. Referenced NDAs, BLAs, DMFs.....	27
5.3. Pharmacology.....	27
5.4. ADME/PK	35
5.5. Toxicology.....	37
5.5.1. General Toxicology.....	37
5.5.2. Genetic Toxicology.....	44
5.5.3. Carcinogenicity.....	45
5.5.4. Reproductive and Developmental Toxicology	45
5.5.5. Other Toxicology Studies	49

6	Clinical Pharmacology.....	51
6.1.	Executive Summary	51
6.2.	Summary of Clinical Pharmacology Assessment.....	54
6.2.1.	Pharmacology and Clinical Pharmacokinetics	54
6.2.2.	General Dosing and Therapeutic Individualization.....	55
6.3.	Comprehensive Clinical Pharmacology Review	56
6.3.1.	General Pharmacology and Pharmacokinetic Characteristics.....	56
6.3.2.	Clinical Pharmacology Questions.....	58
7	Statistical and Clinical Evaluation	68
7.1.	Sources of Clinical Data and Review Strategy.....	68
7.1.1.	Table of Clinical Studies	68
7.1.2.	Review Strategy	69
7.2.	Review of Relevant Individual Trials Used to Support Efficacy.....	69
7.2.1.	Study 16349 Part B.....	69
7.2.2.	Study Results.....	75
7.3.	Integrated Review of Effectiveness.....	88
7.3.1.	Assessment of Efficacy Across Trials.....	88
7.3.2.	Integrated Assessment of Effectiveness.....	90
7.4.	Review of Safety	90
7.4.1.	Safety Review Approach	90
7.4.2.	Review of the Safety Database	91
7.4.3.	Adequacy of Applicant’s Clinical Safety Assessments	95
7.4.4.	Safety Results.....	95
7.4.5.	Analysis of Submission-Specific Safety Issues.....	113
7.4.6.	Safety Analyses by Demographic Subgroups.....	128
7.4.7.	Specific Safety Studies/Clinical Trials.....	130
7.4.8.	Additional Safety Explorations.....	130
7.4.9.	Safety in the Postmarket Setting	130
7.4.10.	Integrated Assessment of Safety.....	131
	SUMMARY AND CONCLUSIONS	134
7.5.	Statistical Issues	134
7.6.	Conclusions and Recommendations	134

8	Advisory Committee Meeting and Other External Consultations.....	136
9	Pediatrics	137
10	Labeling Recommendations	138
10.1.	Prescribing Information.....	138
10.2.	Patient Labeling	139
11	Risk Evaluation and Mitigation Strategies (REMS)	140
11.1.	Safety Issue(s) that Warrant Consideration of a REMS.....	140
11.2.	Conditions of Use to Address Safety Issue(s)	140
11.3.	Recommendations on REMS	140
12	Postmarketing Requirements and Commitment	141
13	Appendices	143
13.1.	References	143
13.2.	Financial Disclosure	145
13.3.	Nonclinical Pharmacology/Toxicology.....	145
13.4.	OCP Appendices (Technical documents supporting OCP recommendations)	146
13.4.1.	Summary of Bioanalytical Method Validation and Performance.....	146
13.4.2.	Clinical PK.....	148
13.4.3.	Pharmacometrics Review	153
14	Division Director (DHOT)	174
15	Division Director (OCP)	175
16	Division Director (OB)	176
17	Division Director (Clinical)	177
18	Office Director (or designated signatory authority).....	178

Table of Tables

Table 1 FDA-Approved Drugs for Follicular Lymphoma and Indolent Non-Hodgkin's Lymphoma	18
Table 2 Agents and Combinations for Treatment of Patients with Non-Hodgkin Lymphoma.....	19
Table 3 In Vitro Cytotoxicity Activity of Copanlisib, CAL-101 and Positive Control Cisplatin	28
Table 4 Summary of BAY 80-6946 In Vivo Anti-tumor Activity	32
Table 5: Effect of Concomitant Administration of Itraconazole on Copanlisib (60 mg) Exposure	65
Table 6: Effect of Concomitant Administration of Rifampin on Copanlisib (60 mg) Exposure	65
Table 7: Percentage Inhibition of MATE2-K and IC ₅₀ of Copanlisib (Metformin as the Substrate)	66
Table 8: Clinical Studies	68
Table 9 Patient Disposition by Disease Type and Study Phase.....	77
Table 10: Protocol Deviations	78
Table 11: Demographic Characteristics	79
Table 12 Other Baseline Disease Characteristics.....	80
Table 13 Concomitant Medications Used in ≥ 30% of Patients Treated with Copanlisib	80
Table 14: Objective Response Rate and Duration of Response	81
Table 15 Concordance of Response Assessment Between Investigator Assessment and Independent Review	82
Table 16 ORR by Demographics Characteristics and Other Baseline Disease Characteristics	85
Table 17: PRO Completion Rates	86
Table 18: PRO Scores over Time	87
Table 19 Efficacy Results in Study 12871 Based on Investigator Assessment.....	88
Table 20 Efficacy Results in Study 16349 Part A Based on Independent Assessment	89
Table 21: Duration of Treatment with Copanlisib	92
Table 22: Patient Demographics.....	93
Table 23: Summary of Deaths.....	96
Table 24: Serious Adverse Events in ≥ 2% of Patients	97
Table 25: Summary of Discontinuations, Dose Reductions, and Dose or Treatment Delays due to Treatment Emergent Adverse Events	99
Table 26: Treatment Emergent Adverse Events Leading to Discontinuation in ≥ 1% of Patients	99
Table 27: Treatment Emergent Adverse Events Leading to Dose Reduction in ≥ 1% of Patients	100
Table 28: Treatment Emergent Adverse Events Associated with Copanlisib Treatment Delay in ≥ 2% of Patients	101
Table 29: Summary of Adverse Events of Special Interest	102
Table 30: Treatment Emergent Adverse Events in ≥10% of Patients	103
Table 31: Adverse Drug Reactions in ≥5% of Patients with Indolent NHL.....	105
Table 32: Summary of Hematology Laboratory Abnormalities	107
Table 33: Clinical Biochemical Laboratory Abnormalities	110
Table 34 Liver Laboratory Abnormalities.....	111

Table 35: Summary of Pneumonitis Treatment Emergent Adverse Events and Associated Risk Factors.....	113
Table 36: Myelosuppression or Cytopenia Treatment Emergent Adverse Events by Preferred Term	115
Table 37: Summary of Infection Treatment Emergent Adverse Events	115
Table 38: Summary of Hypertension Treatment Emergent Adverse Events and Associated Risk Factors.....	117
Table 39: Summary of Systolic Blood Pressure on Cycle 1, Day 1	118
Table 40: Summary of Hyperglycemia Treatment Emergent Adverse Events and Associated Risk Factors.....	120
Table 41: Summary of Blood Glucose on Cycle 1, Day 1	122
Table 42: Mean HbA1c Change from Baseline to Last HbA1c Value on Treatment.....	125
Table 43: HbA1c Category Change from Baseline to Last HbA1c Value on Treatment.....	126
Table 44: Summary of Gastrointestinal Disorders Treatment Emergent Adverse Events	127
Table 45 Treatment Emergent Adverse Events by Age in Patients with Indolent NHL.....	128
Table 46 Treatment Emergent Adverse Events by Gender in Patients with Indolent NHL.....	129
Table 47: Summary of Bioanalytical Methods and Their Applications in Clinical Trials.....	146
Table 48 Summary of Copanlisib PK Parameters in Patients with Cancer after Single Dose	149
Table 49 Summary of Copanlisib PK Parameters in Patients with Cancer after Multiple Doses	149
Table 50 Comparison of PK Parameters Following the C1D1 and the C1D15 Administration at the 0.8 mg/kg.....	152
Table 51 Comparison of Copanlisib PK Parameters in Healthy Volunteers and Cancer Patients Following a Single IV Dose of 12 mg Copanlisib in Studies 16353 and 16270.....	152
Table 52 Summary of Data for the Population Pharmacokinetics Analysis	157
Table 53 Parameter estimates with standard errors and confidence intervals for covariate model built using all patient data file (Run_c044).....	160
Table 54 Analysis Data Sets.....	168
Table 55 General Dose Compliance Data For Each Subject of Study 16349 Part B.....	170

Table of Figures

Figure 1 Anti-proliferative Activities of PI3K and BTK inhibitors in DLBCL Cell Lines	30
Figure 2 Simultaneous inhibition of PI3K α/δ in DLBCL Cell Lines	31
Figure 3 Logistic Regression of ORR vs Average Exposure of Copanlisib in Patients with FL	59
Figure 4 Kaplan-Meier Curves for Progression-Free Survival in Patients with FL	59
Figure 5 Summary of Adverse Events by Dose Levels in Phase 1 Study 12871	60
Figure 6 Plot of Logistic Regression for Hyperglycemia - Grade ≥ 3 versus C _{max} or C _{ave}	61
Figure 7 Plot of Logistic Regression for Hypertension - Grade ≥ 3 versus AUC	61
Figure 8 The Time Course of Hyperglycemia and Hypertension Rates for Study 16349 Part B (N=143)	62
Figure 9 Plot of Copanlisib Concentration versus Observed and Predicted QTcI with 90% CI	63
Figure 10 Effect of Copanlisib on MATE2-K Activity (Metformin as the Substrate)	66
Figure 11: Patient Disposition	76
Figure 12 Maximum Percent Change from Baseline by Patient Response	84
Figure 13: Mean Change in Neutrophils from Baseline by Treatment Cycle	108
Figure 14: Mean Change in Hemoglobin from Baseline by Treatment Cycle	109
Figure 15: Mean Change in Platelets from Baseline by Treatment Cycle	109
Figure 16: Median Systolic Blood Pressure Before and After Copanlisib Infusion – Cycle 1, Day 1	119
Figure 17: Prevalence of Hyperglycemia by Treatment Cycle	122
Figure 18: Median Blood Glucose Before and After Copanlisib Infusion - Cycle 1, Day 1	124
Figure 19 Mean Hemoglobin A1c at Day 1 by Treatment Cycle	125
Figure 20 Semi-logarithmic Arithmetic Mean (SD) Plasma Concentration vs Time Profiles of Copanlisib after a Single 0.8 mg/kg (MTD) Dose	150
Figure 21 Dose Proportionality for Copanlisib PK Parameters at Cycle 1 Day 1 (C1D1) and at Cycle 1 Day 15 (C1D15) for AUC _{0-25h}	151
Figure 22 The Effect of Age, Body Weight, Sex, and Race on Copanlisib Clearance Based on Population Pharmacokinetics Analysis	154
Figure 23 The Relationship between Copanlisib Clearance and Organ Impairment with (Lower Panels) and without (Upper Panels) AEDC as Stratification Factor	155
Figure 24 The Exposure-Response Analysis Result for Adverse Event Rate and Objective Response Rate of the 124 Pharmacokinetics Evaluable Patients	156
Figure 25 The Exposure-Response Analysis Result for $\geq$ Grade 3 Hyperglycemia (Left Panel, n=124) and Maximal Blood Glucose Change from Baseline (Right Panel, n=140)	157
Figure 26 Graphical Representation of the Structural Population Pharmacokinetics Model	159
Figure 27 The General Goodness of Fit Plots for Run_c044.ctf	162
Figure 28 Plot of Logistic regression for ORR - C _{avg}	164
Figure 29 Kaplan-Meier curves of duration of response (full analysis set)	164
Figure 30 Kaplan-Meier curves of duration of Progression Free Survival (full analysis set)	165
Figure 31 Plot of Logistic regression for Hyperglycemia - Grade ≥ 3 versus C _{max} or C _{avg}	165
Figure 32 Comparison of individual predicted concentrations from Run048_cov and Run_c044 using the all patient data file	166

Figure 33 Comparison of individual parameter estimates from Run048_cov and Run_c044 using the all patient data file.....	166
Figure 34 The Time Course of Hyperglycemia and Hypertension Rates for Study 16349 Part B (N=143)	169
Figure 35 The Exposure-Response Analysis Result for $\geq$ Grade 2 Hypertension in Left Panel and for Blood Pressure Change from Baseline in Right Panel (n=124).....	169
Figure 36 Boxplots of Individual Patient's Copanlisib Doses of the 143 Subjects in Study 13469 Part B.....	173

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Rosa Lee-Alonzo, PharmD
Nonclinical Reviewer	Pedro DelValle, PhD
Nonclinical Team Leader	Christopher Sheth, PhD
Clinical Pharmacology Reviewer	Guoxiang Shen, PhD
Clinical Pharmacology Team Leader	Bahru Habtemariam, PharmD
Pharmacometrics Reviewer	Hongshan Li, PhD
Pharmacometrics Team Leader	Jiang Liu, PhD
Clinical Reviewer	Nicholas C. Richardson, DO, MPH
Clinical Team Leader	R. Angelo de Claro, MD
Statistical Reviewer	Xin Gao, PhD
Statistical Team Leader	Yuan-Li Shen, DrPh
Cross-Disciplinary Team Leader	R. Angelo de Claro, MD
Division Director (DHOT)	John Leighton, PhD
Division Director (OCP)	Nam Atiqur Rahman, PhD
Division Director (OB)	Rajeshwari Sridhara, PhD
Supervisory Associate Division Director	Albert Deisseroth, MD, PhD
Office Director	Richard Pazdur, MD

Additional Reviewers of Application

OPQ	Application Technical Lead: Sherita McLamore-Hines Drug Substance: Sharron Kelly; Benjamin Stevens Drug Product: Rajiv Agarwal; Anamitro Banerjee Process: Diane Goll; Rakhi Shah Microbiology: John Metcalfe; Christine Craig Facility: Rebecca Dombrowski; Derek Smith Environmental: Rajiv Agarwal; Anamitro Banerjee
OPDP	Nisha Patel; Kathleen Davis
OSI	Anthony Orenca; Janice Pohlman; Kassa Ayalew
OSE/DMEPA	Leeza Rahimi; Hina Mehta
OSE/DRISK	Joyce Weaver; Elizabeth Everhart; Cynthia LaCivita
QT/IRT	Mike Li; Lars Johannesen; Michael Bewernitz; Christine Garnett
DMPP	Shawna Hutchins; Barbara Fuller, LaShawn Griffiths

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
IRT=Interdisciplinary Review Team
DMPP=Division of Medical Policy Programs

Glossary

ADME	Absorption, distribution, metabolism, excretion
ADR	Adverse drug reaction
AE	Adverse event
AEDC	Adverse event related treatment discontinuation
AKT	Protein kinase B
ALL	Acute lymphoblastic leukemia
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloblastic leukemia
AST	Aspartate aminotransferase
AUC	Area under the curve
BCR	B-cell receptor
BCRP	Breast cancer resistance protein
BP	Blood pressure
BTK	Bruton's tyrosine kinase
BW	Bodyweight
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CI	Confidence interval
CL	Clearance
CLL	Chronic lymphocytic leukemia
CMC	Chemistry, manufacturing, and controls
CML	Chronic myeloid leukemia
CNS	Central nervous system
CR	Complete response
DDI	Drug-drug interaction
DHOT	Division of Hematology Oncology Toxicology
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
ECG	Electrocardiogram
ER	Exposure response
FACT-Lym	Functional Assessment of Cancer Therapy - Lymphoma
FAS	Full analysis set
FDA	Food and Drug Administration
FL	Follicular lymphoma
GD	Gestation day
GEPF	Guanosine triphosphate exchange factor
GLP	Good laboratory practice
HD	High dose
ICH	International Council for Harmonization

NDA/BLA Multi-disciplinary Review and Evaluation NDA 209936
Aliqopa (copanlisib)

IND	Investigation new drug
IV	Intravenous
LD	low dose
LPL	Lymphoplasmacytoid lymphoma
MAED	MedDRA-based adverse event diagnostics
MAPK	Mitogen-activated protein kinase
MATE2-K	Multidrug and toxin extrusion protein 2
MD	mid dose
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
MZL	Marginal zone lymphoma
NCA	Non-compartmental analysis
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	New drug application
NFκB	Nuclear factor-kappa beta
NME	New molecular entity
NHL	non-Hodgkin's lymphoma
ORR	Objective response rate
OS	Overall survival
OSS	Office of Scientific Investigations
P-gp	P-glycoprotein
PD	Pharmacodynamic
PDK1	3-phosphoinositide-dependent protein kinase-1
PFS	Progression-free survival
PIP3	Phosphoinositol-3-phosphate
PI3K	Phosphatidylinositol 3-kinase inhibitor
PK	Pharmacokinetic
PPK	Population pharmacokinetics
PMR	Postmarketing requirement
PR	Partial response
PRO	Patient-reported outcome
PTEN	Phosphatase and tensin homolog
SAE	Serious adverse event
SD	Standard deviation
SLL	Small lymphocytic lymphoma
SMQ	Standardized MedDRA query
SOC	System organ class
TEAE	Treatment emergent adverse event
TK	Toxicokinetic
ULN	Upper limit of normal
V _z	Volume of distribution
WM	Waldenström macroglobulinemia

1 Executive Summary

1.1. Product Introduction

Established Names: Copanlisib, BAY 80-6946

Trade Name: Aliqopa

Applicant: Bayer Healthcare Pharmaceuticals Inc.

Drug Class: Phosphatidylinositol 3-kinase (PI3K) inhibitor

Applicant's Proposed Indication: For the treatment of patients with relapsed follicular lymphoma who have received at least two prior therapies. (b) (4)

Applicant's Proposed Dosage and Administration: 60mg as a 1-hour intravenous (IV) infusion on Days 1, 8, and 15 of a 28-day treatment cycle.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends accelerated approval of copanlisib under Subpart H (21 CFR 314.510) for the treatment of adult patients with relapsed follicular lymphoma who have received at least two prior systemic therapies. The recommendation is based on the finding of durable complete or partial responses in Study 16349 Part B. The Agency has previously used durable complete or partial responses as a basis for accelerated approval on other new molecular entity (NME) applications. The Applicant will conduct a randomized controlled trial to verify and describe the clinical benefit of copanlisib (refer to Section 12).

Study 16349 Part B was an open-label, single-arm, multicenter, Phase 2 study in patients with relapsed or refractory follicular lymphoma, marginal zone lymphoma, small lymphocytic lymphoma, or lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia. The doses of 0.8 mg/kg or 60mg intravenous on Days 1, 8, and 15 of a 28-day treatment cycle were used in the pivotal trial. The weight-based dose and the fixed dose are equivalent based on the population pharmacokinetic evaluation because the pharmacokinetic parameters of copanlisib were not affected by body weight.

Study 16349 Part B used a primary endpoint of objective response rate (ORR) as determined by an independent review committee. An objective response was defined as patients who had a best response of either a partial response or complete response. The protocol specified that an exact binomial 95% confidence interval (CI) lower bound greater than 40% was considered clinically meaningful. The FDA analysis of 104 patients with follicular lymphoma demonstrated an ORR of 58.7% (95% CI: 48.6% – 68.2%), which met the Applicant's prespecified definition for clinical benefit. The median duration of response was 12.2 months.

In the pivotal study, patients with follicular lymphoma comprised 73.2% of the study population. The study also included patients with marginal zone lymphoma, small lymphocytic lymphoma, or lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia. However, there were too few patients with these diseases treated in the clinical study to support indications for these populations.

The effectiveness and safety of long term use of copanlisib remains to be determined. The median exposure to copanlisib in the pivotal study was 22 weeks or 5.5 cycles. Further, the median duration of follow-up among patients that achieved a partial response or a complete response was 5.7 months. Post-marketing studies will be needed to confirm the efficacy, safety, and tolerability of copanlisib. Nevertheless, the objective response rate and duration of response achieved in Study 16349 Part B constitutes substantial evidence of effectiveness and supports accelerated approval of copanlisib in patients with relapsed follicular lymphoma.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The benefit-risk assessment supports accelerated approval of copanlisib for the treatment of adult patients with relapsed follicular lymphoma who have received at least two prior systemic therapies.

The efficacy of copanlisib is primarily based on the results of a single-arm, open-label study evaluating copanlisib monotherapy in patients with relapsed follicular lymphoma, marginal zone lymphoma, small lymphocytic lymphoma, or lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia. The study used a primary endpoint of objective response rate (ORR), which was defined as patients who had a best response of either a partial response or complete response as determined by an independent review committee. The efficacy of copanlisib was established in 104 patients with follicular lymphoma on the basis of an ORR of 58.7% with a median duration of response of 12.2 months per independent review committee assessment. The complete response rate was 14.4% and partial response rate was 44.2%.

The safety profile of copanlisib is tolerable and manageable in patients with relapsed follicular lymphoma, marginal zone lymphoma, small lymphocytic lymphoma, or lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia. The safety of copanlisib was evaluated in 244 patients with hematologic malignancies exposed to copanlisib monotherapy. The primary safety issues identified include infection, hyperglycemia, hypertension, pneumonitis, neutropenia, gastrointestinal disorders, and severe cutaneous reactions. Common adverse reactions in greater than 20% of patients include hyperglycemia, diarrhea, fatigue, hypertension, leukopenia, neutropenia, nausea, lower respiratory tract infections, and thrombocytopenia. The identified risks with copanlisib can be mitigated with appropriate labeling. Further, the intravenous weekly administration schedule ensures that copanlisib will be given in the presence of healthcare professionals, which provides additional safety monitoring.

Taken together, the evidence of effectiveness, with a clinically significant ORR and duration of response, and a manageable safety profile form a strong basis for a conclusion of clinically meaningful benefit in patients with relapsed follicular lymphoma.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Approximately 14,000 patients will be newly diagnosis with follicular lymphoma in the United States in 2017. Around 35% to 45% of patients will relapse following initial therapy and patients with relapsed follicular lymphoma have an estimated 5-year progression free survival of 36%.	Relapsed follicular lymphoma is a serious and life-threatening disease.
Current Treatment Options	No curative treatment exists for patients with relapsed follicular lymphoma. The standard of care for patients who require systemic therapy is to administer immunochemotherapy repeatedly until fatal resistant disease occurs.	New treatments are needed for patients with relapsed follicular lymphoma.
Benefit	- Study 16349 Part B was a single-arm study of copanlisib for patients with indolent Non-Hodgkin lymphoma that failed at least 2 prior therapies. - Sixty-one patients (59%) with follicular lymphoma achieved an objective response, including 15 patients (14%) with a complete response and 46 patients (44%) with a partial response. - The median duration of response was 12.2 months.	Copanlisib is effective in treating patients with relapsed follicular lymphoma. The magnitude and duration of response are reasonably likely to predict for clinical benefit.
Risk	- The most common adverse reactions in greater than 20% of patients include hyperglycemia, diarrhea, fatigue, hypertension, leukopenia, neutropenia, nausea, lower respiratory tract infections, and thrombocytopenia. - The most common Grade 3-4 adverse reactions include hyperglycemia, leukopenia, hypertension, neutropenia, and lower respiratory tract infections. - Hyperglycemia and hypertension are associated on-target effects of copanlisib. Close monitoring and appropriate intervention are needed to prevent treatment-related morbidity. - Serious non-infectious pneumonitis occurred in 6% of patients. Early diagnosis and intervention are needed.	The short-term safety profile of copanlisib is tolerable and manageable for patients with relapsed follicular lymphoma. Long-term safety information is needed since copanlisib is intended for prolonged use and there may be potential for cumulative toxicity, especially with the on-target effects of hyperglycemia and hypertension.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Severe cutaneous reactions have occurred in patients treated with copanlisib	
Risk Management	- The protocol included monitoring for risks and instructions for intervention. Interventions included dose interruption, reduction or discontinuation, which were sufficient to mitigate the majority of treatment-related toxicities. - The proposed labeling includes warnings and dose modifications for infection, hyperglycemia, hypertension, pneumonitis, and neutropenia.	The risk associated with copanlisib can be adequately addressed with labeling. Labeling should include warnings and precautions, along with instruction for monitoring and dose modification, for infection, hypertension, hyperglycemia, pneumonitis, neutropenia, and severe cutaneous reactions.

Nicholas C. Richardson, DO, MPH
Primary Clinical Reviewer

R. Angelo M. de Claro, MD
Cross-Disciplinary Team Leader

2 Therapeutic Context

Analysis of Condition

Follicular lymphoma is the second most common subtype of non-Hodgkin's lymphoma (NHL), with an estimated 13,960 new cases diagnosed in 2016 in the United States (Teras et al. 2016). The median age of diagnosis is 60 years old and incidence is highest among whites (80.2%) and lowest among blacks (4.4%) (Luminari et al. 2012; Nabhan et al. 2014). Patients with follicular lymphoma typically present with waxing and waning, asymptomatic peripheral adenopathy. Bone marrow involvement occurs in 50% to 70% of patients (Freedman 2015; Luminari et al). Follicular lymphoma is characterized by an indolent clinical course, but the majority of patients have advanced stage disease at diagnosis (Freedman 2015). The indolent nature of follicular lymphoma affords responses to initial therapy, but is followed by frequent relapses and shorter durations of response to subsequent treatments (Rivas-Delgado et al. 2017). Moreover, patients with refractory follicular lymphoma or relapsed follicular lymphoma within 2 years of first-line therapy have a 5-year overall survival of 50% (range 40.3% to 58.8%) (Byrtek et al. 2013).

Treatment for patients with advanced stage follicular lymphoma ranges from observation to autologous stem cell transplantation. Patients with asymptomatic, advanced stage follicular lymphoma do not require immediate treatment and can be observed. Patients with symptomatic nodal disease, extranodal disease, B symptoms, cytopenias, and end organ dysfunction require immediate treatment. First-line therapy consists of rituximab monotherapy or combination chemotherapy plus rituximab (Colombat et al. 2001; Hiddemann et al. 2005; Martinelli et al. 2010; Rummel et al. 2013; Witzig et al. 2005). Treatment of patients with refractory or relapsed follicular lymphoma can consist of rituximab monotherapy, combination chemotherapy plus rituximab, radioimmunotherapy, and autologous stem cell transplantation (Freedman 2015). Given that treatment for follicular lymphoma is not curative, new drugs and approaches are still needed.

Follicular lymphoma arises from malignant germinal center B-cells, making B-cell kinases attractive targets for therapy in follicular lymphoma. The B-cell receptor (BCR) and phosphoinositide 3-kinase (PI3K) play a key role in the proliferation and survival of indolent B-cell lymphomas, including follicular lymphoma (Pongas and Cheson 2016; Wiestner 2015). Inhibition of BCR and PI3K have emerged as a treatment strategy for refractory or relapsed follicular lymphoma.

2.2. Analysis of Current Treatment Options

There are nine currently available agents approved for the treatment of patients with follicular lymphoma, low-grade Non-Hodgkin lymphoma, or indolent NHL. This includes idelalisib, a first-

in-class PI3K inhibitor. The indications relevant to this application are listed in Table 1.

Table 1 FDA-Approved Drugs for Follicular Lymphoma and Indolent Non-Hodgkin's Lymphoma

Drug	Year of Initial Approval	Excerpted Indication(s)
Chlorambucil	1957	In the treatment of chronic (lymphocytic) leukemia, malignant lymphomas including lymphosarcoma, giant follicular lymphoma, and Hodgkin's disease
Cyclophosphamide	1959	For treatment of malignant lymphomas: Hodgkin's disease, lymphocytic lymphoma, mixed-cell type lymphoma, Burkitt's lymphoma, multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, adenocarcinoma of ovary, retinoblastoma, breast carcinoma
Vincristine	1963	Useful in combination with other oncolytic agents in Hodgkin's disease, non-Hodgkin's malignant lymphomas, rhabdomyosarcoma, neuroblastoma, and Wilms' tumor
Doxorubicin	1974	For the treatment of: acute lymphoblastic leukemia, acute myeloblastic leukemia, Hodgkin lymphoma, Non-Hodgkin lymphoma, metastatic breast cancer, metastatic Wilms' tumor, metastatic neuroblastoma, metastatic soft tissue sarcoma, metastatic bone sarcomas, metastatic ovarian carcinoma, metastatic transitional cell bladder carcinoma, metastatic thyroid carcinoma, metastatic gastric carcinoma, metastatic bronchogenic carcinoma
Rituximab	1997	For the treatment of patients with: Non-Hodgkin's Lymphoma, Chronic Lymphocytic Leukemia
⁹⁰ Y-ibritumomab tiuxetan	2002	For the treatment of patients with: relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's lymphoma, and previously untreated follicular NHL who achieve a partial or complete response to first-line chemotherapy
Bendamustine	2008	For treatment of patients with: Chronic lymphocytic leukemia and indolent B-cell non-Hodgkin lymphoma that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen
Obinutuzumab	2013	In combination with chlorambucil, for the treatment of patients with previously untreated chronic lymphocytic leukemia and in combination with bendamustine followed by obinutuzumab monotherapy, for the treatment of patients with follicular lymphoma who

Drug	Year of Initial Approval	Excerpted Indication(s)
		relapsed after, or are refractory to, a rituximab-containing regimen
Idelalisib	2014	For the treatment of patients with: relapsed chronic lymphocytic leukemia, in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities; relapsed follicular B-cell non-Hodgkin lymphoma in patients who have received at least two prior systemic therapies; and relapsed small lymphocytic lymphoma in patients who have received at least two prior systemic therapies

Source: FDA table, created from review of drug labeling

In clinical practice, treatment regimens for relapsed follicular lymphoma, small lymphocytic lymphoma, marginal zone lymphoma, or lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia include single agent or combination of the following agents listed in Table 2. Involved-site radiation therapy, radioimmunotherapy, stem cell transplant, and observation are other appropriate treatments.

Table 2 Agents and Combinations for Treatment of Patients with Non-Hodgkin Lymphoma

Drug or Regimen	FL	SLL	MZL	LPL/ WM
Alemtuzumab ± rituximab		X		X
Bendamustine ± rituximab	X	X	X	X
Bendamustine + obinutuzumab	X		X	
Bortezomib + dexamethasone				X
Bortezomib + dexamethasone + rituximab				X
Bortezomib ± rituximab				X
Carfilzomib + rituximab + dexamethasone				X
Chlorambucil ± rituximab	X	X	X	X
Chlorambucil + obinutuzumab		X		
Cladribine ± rituximab				X
Cyclophosphamide ± rituximab	X		X	
Everolimus				X
Fludarabine + cyclophosphamide + mitoxantrone + rituximab	X		X	
Fludarabine + cyclophosphamide + rituximab		X		X
Fludarabine + cyclophosphamide + ofatumumab		X		
Fludarabine ± rituximab	X	X	X	X
Ibrutinib		X	X	X
Ibrutinib + bendamustine + rituximab		X		

Drug or Regimen	FL	SLL	MZL	LPL/ WM
Idelalisib ± rituximab		X	X	
Idelalisib + bendamustine + rituximab		X		
Lenalidomide ± rituximab	X	X	X	
Obinutuzumab	X	X		
Obinutuzumab + cyclophosphamide + doxorubicin + vincristine + prednisone	X			
Obinutuzumab + cyclophosphamide + vincristine + prednisone	X			
Ofatumumab ± chlorambucil		X		X
Oxaliplatin, fludarabine, cytarabine, rituximab		X		
Pentostatin + cyclophosphamide + rituximab		X		
Rituximab	X	X	X	X
Rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone	X		X	X
Rituximab + cyclophosphamide + vincristine + prednisone	X		X	
Rituximab + cyclophosphamide + prednisone				X
Rituximab + fludarabine + mitoxantrone + dexamethasone	X		X	
Thalidomide ± rituximab				X
Venetoclax ± rituximab		X		
Source: NCCN NHL, SLL, and LPL Guidelines Versions 3.2017, 2.2017, and 1.2017, respectively				

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Copanlisib is a new molecular entity and is not currently marketed in any country.

3.2. Summary of Presubmission/Submission Regulatory Activity

Date	Event Summary
23 October 2008	Pre-IND meeting was granted and advice provided on the first in human trial with copanlisib.
14 September 2012	IND 115916 was activated and opened in the United States.
14 May 2013	Type B, End-of-Phase 1 meeting to discuss overall development plan and the phase 2 trial design (single-arm versus randomized) to support NDA submission.
11 July 2014	Type B meeting, written response providing advice regarding a registration study in indolent NHL and use of symptom-related endpoint.
05 February 2015	Orphan drug designation granted for treatment of patients with follicular lymphoma.
03 February 2016	Fast Track designation granted for treatment of patients with follicular lymphoma and the development program includes trial involving an approved drug comparator.
18 October 2016	Type B, Pre-NDA meeting advising on the submission of a single-arm trial, the safety analysis, and additional technical aspects of the NDA submission.
16 March 2017	NDA submission complete

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

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations conducted inspections for Study 16349 – Part B at two clinical sites: Site 22005 (Humanitas Cancer Center, Italy) and Site 26003 (Hôpital Maisonneuve-Rosemont, Canada). These sites were selected based on highest patient accrual and slight differences in efficacy (response rates) and safety (adverse events, deaths, and protocol violations) compared to the overall study results. The preliminary regulatory classification for inspection for Site 22005 and Site 26003 is No Action Indicated. The Applicant Bayer Healthcare Pharmaceutical Inc. was also audited. The final regulatory classification of the Applicant is No Action Indicated. The study data derived from the inspected clinical sites and the Applicant are considered reliable in support of the requested indication.

4.2. Product Quality

Novel excipients: No

Any impurity of concern: None from a Pharmacology/Toxicology perspective. Refer to CMC review.

Refer to CMC Application Technical Lead review for details. The Office of Pharmaceutical Quality, CDER, recommends Approval of Aliqopa (Copanlisib Hydrochloride) for Injection, 60mg, manufactured by Bayer Pharma AG of Germany.

Drug substance, copanlisib dihydrochloride, is manufactured by Bayer Pharma AG of Germany (FEI 3003229486). This facility had an acceptable inspection history and years of experience of manufacturing non-sterile active pharmaceutical ingredients by chemical synthesis. This site has been the subject of several FDA inspections from 2005 to present with the most recent being in April of 2017. Accordingly, a pre-approval inspection was not requested and approval was based on capabilities and experience.

Drug product, Aliqopa (Copanlisib Hydrochloride) for Injection, 60mg, is manufactured by Bayer Pharma AG of Germany (FEI 3002808086). This site was considered high risk and had a history of findings of voluntary action indicated. A pre-approval inspection was requested and performed under this review due to lack of coverage and assessment of lyophilization operations. Based on this expedited pre-approval inspection review, the compliance status of this firm and the demonstrated controls and capabilities of the quality unit in controlling and releasing manufactured product, this site is recommended for approval under this application.

Two additional sites were included in this NDA: (b) (4) which is the (b) (4), and Bayer Healthcare, LLC (FEI 224325) which

is named as the distribution center for the finished product. [REDACTED] (b) (4)

[REDACTED] The Bayer site was
not further evaluated in this review.

4.3. **Devices and Companion Diagnostic Issues**

A device or companion diagnostic is not required to select patients for therapy with copanlisib and is not required to ensure safe use of copanlisib when marketed.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The nonclinical development program for copanlisib was conducted in cellular assay systems, and in the mouse, rat, and dog, to evaluate the pharmacology, general toxicology, reproductive effects, and genotoxic potential of copanlisib. BAY 80-6946 (copanlisib) is an inhibitor of phosphatidylinositol-3-kinase (PI3K). PI3K is a lipid kinase involved in activation of the PI3K/3-phosphoinositide-dependent protein kinase-1 (PDK1) and AKT pathways. PI3K also modulates guanosine triphosphate exchange factor (GEPFs) activity through generation of phosphoinositol-3-phosphate (PIP3). The PI3K- α and PI3K- δ isoforms are expressed in malignant B cells.

The pharmacology of copanlisib was established using a series of in vitro and in vivo studies. Copanlisib inhibits the kinase activity of PI3K α , β , γ and δ isoforms with IC_{50} values of 0.5, 3.7, 6.4 and 0.7 nM, respectively. In addition, the copanlisib metabolite M-1 inhibits PI3K α and β with IC_{50} s of 1.5 and 5.8 nM, respectively. Results from the pharmacological characterization indicate copanlisib reduces phosphorylation of certain serine and threonine residues of the protein kinase-1 substrate AKT. The results of in vitro studies using recombinant proteins suggest copanlisib can inhibit signaling through the oncogenic PI3K/AKT/mTOR pathway. Copanlisib showed antitumor activity in preclinical models with PI3K3CA mutations, PTEN deletions, and/or receptor tyrosine kinase overexpression. The established pharmacological class (EPC) of copanlisib is kinase inhibitor.

Comparative cytotoxicity studies with cell lines representing acute and chronic lymphocytic leukemias (ALL/CLL), acute and chronic myeloid leukemias (AML/CML), non-Hodgkins lymphoma (NHL), and myeloma were conducted using copanlisib and the PI3K δ inhibitor idelalisib as a comparator. Additional comparative studies with ibrutinib sensitive, insensitive, and resistant cell lines were conducted using copanlisib, ibrutinib, idelalisib and a PI3K α selective inhibitor. Copanlisib has been shown to induce tumor cell death by apoptosis and inhibition of proliferation of primary malignant B cell lines. Results of these studies suggest that dual inhibition of PI3K α and δ may result in greater anti-proliferative and anti-tumor activity, when compared to targeting either of the isoforms alone. In tumor xenograft studies in athymic mice and rats, copanlisib was well tolerated and produced significant inhibition of tumor growth at doses ≥ 36 mg/m², when administered intravenously twice daily for five days.

In a rat CNS safety pharmacology study, copanlisib-related behavioral abnormalities included stereotypic licking, swaying gait, vocalization upon touch, and reduced muscle tone beginning as early as 0.5 hours after a dose ≥ 18 mg/m². Additional clear signs of CNS effects were observed at 54 mg/m², and included piloerection, ptosis, salivation, played limbs, backward walking, stereotypic chewing, and hypoactivity. In a hotplate response study in rats, the same dose level (54 mg/m²) produced a significantly delayed response. The CNS effects appeared to

be generally reversible by 4 hours postdose. Other observations in rats undergoing safety pharmacology testing included increases in urine volumes and electrolyte excretion, inhibition of intestinal motility, and insulin resistance and hyperglycemia. While hERG potassium currents were unaffected, drug-related systolic and diastolic blood pressures (BP) were increased in anesthetized dogs.

The Applicant conducted repeat-dose toxicity studies to assess the chronic toxicity of copanlisib. Overall, the treatment schemes employed in the multi cycle systemic toxicity studies corresponded to the clinical treatment scheme of three weeks on / one week off. In the 16 week toxicity studies, Wistar rats were administered doses of 0, 1.8, 6, or 18 mg/m², and Beagle dogs were administered doses of 0, 2, 6, or 20/14 mg/m². The 20 mg/m² dose was administered through Day 36, at which time there was an off dose period, then dosing with a reduced dose of 14 mg/m² resumed from Day 43 onwards. The studies were conducted using the intravenous route of administration, which is consistent with the intended clinical route of administration.

In the repeat-dose toxicity study in rats, mortality was observed at the mid dose (MD) and high dose (HD). Findings in early decedents included clinical signs of poor general condition, effects on the CNS, discolored teeth, decreased body weight gain, decreased myelopoiesis, and immunosuppression. Copanlisib-related effects in surviving rats occurred mostly in the MD and HD, including effects on the CNS such as piloerection, high stepping gait, dragging hindlimbs, and/or lying on side. Other observations included decreased body weight gain; sunken flanks and/or labored breathing; and discolored teeth with microscopic findings of dentin alteration, odontoblast degeneration, and pulp necrosis/degeneration. Immunosuppression was observed in rats as well, in addition to toxic effects on myelopoiesis, altered liver morphology and function (increased liver weights, AST, ALT, and ALP), higher concentrations of cholesterol, triglycerides, creatinine, protein, and albumin, and altered glucose homeostasis (reduced plasma concentrations of glucose and hydroxybutyrate).

Additional noteworthy findings in rats were insulin resistance (increased HbA1c); altered renal parameters (presence of glucose, blood/ erythrocytes and decreased pH in urine as well as increased kidney weights); changes in thyroid function; and lower weights of male reproductive organs, heart, lungs, and lacrimal glands. Effects on the immune system/bone marrow and lung appeared to at least partially resolve by the end of the recovery period. An increased incidence of focal liver necrosis and eosinophilia in the HD, present at the end of the recovery period, indicated a delayed onset of hepatotoxicity.

In the repeat-dose toxicity study in dog, copanlisib administration resulted in severe injection site toxicity that impaired the mobility of the foreleg/hindleg. Doses ≥ 6.0 mg/m² were associated with mortality. The HD groups were terminated early due to tolerability issues that included immunosuppression and adverse effects on hematological parameters, such as decreases in red blood cells, packed cell volume, lymphocytes, and basophils, as well as increases in red cell distribution width and fibrinogen.

Copanlisib-related effects in surviving dogs occurred at doses $\geq 2.0 \text{ mg/m}^2$. Adverse findings included abscess, fasciitis/cellulitis, phlebitis/periphlebitis, and/or thrombosis. The opacity of the lens of the eye was impacted by copanlisib treatment. Minimal to moderate impaired mobility of the foreleg/hindleg was observed in addition to reduced food consumption and body weight loss. Markers of inflammation were noted in copanlisib treated dogs, as were sporadically altered red and white blood cell parameter values. Target organs of toxicity in the dog included the hematopoietic/lymphoid system (GALT, mandibular lymph node, mesenteric lymph node, spleen, thymus), reproductive organs (reduced testes and prostate weights, tubular atrophy in testes, oligospermia in the epididymides), and adrenal glands. Full or partial resolution of the observed findings occurred by the end of the recovery period.

Fertility studies with copanlisib were not conducted; however, adverse findings in male and female reproductive systems were observed in the repeat dose toxicity studies. Findings in male rats and/or dogs included effects on the testes (germinal epithelial degeneration, decreased weight, and/or tubular atrophy), epididymides (spermatic debris, decreased weight, and/or oligospermia), and prostate (reduced secretion and/or decreased weight). Findings in female rats included effects on ovaries (hemorrhage, hemorrhagic cysts, and decreased weight), uterus (atrophy, juvenile appearance, decreased weight), vagina (mononuclear infiltration), and a dose-related reduction in the numbers of female rats in estrus. These effects indicate that copanlisib may affect male and female fertility in humans.

In a pilot embryo-fetal developmental toxicity study, rats were administered copanlisib intravenously at doses of 0, 0.75, or 3.0 mg/kg (0, 4.5, or 18 mg/m²) from gestation day (GD) 6 to 17. The high dose resulted in maternal toxicity and no live fetuses. Copanlisib dosed at 4.5 mg/m² was maternally toxic and resulted in embryo-fetal death (increased resorptions, increased post-implantation loss, and decreased numbers of fetuses/dam). The dose of 4.5 mg/m² also resulted in increased incidence of fetal gross external (domed head, malformed eyeballs or eyeholes), soft tissue (hydrocephalus internus, ventricular septal defects, major vessel malformations), and skeletal (dysplastic forelimb bones, malformed ribs and vertebrae, and pelvis shift) abnormalities. The dose of 4.5 mg/m² in rats is approximately 12% of the recommended dose for patients. The dose comparison was used because the animal AUCs were not available for this pilot study and AUC values for the 4.5 mg/m² dose level were not found elsewhere in the animal toxicology database.

ALIQOPA can cause fetal harm when administered to a pregnant woman. Based on findings in animals and the elimination half-life of copanlisib, female patients of reproductive potential should use highly effective contraception during treatment with ALIQOPA and for at least one month after the last dose. Male patients with female partners of reproductive potential should also use highly effective contraception during treatment with ALIQOPA and for at least one month after the last dose.

Following administration of radiolabeled copanlisib to pregnant rats, approximately 1.5% of the radioactivity (copanlisib and metabolites) appeared to reach the fetal compartment. In a

quantitative whole-body autoradiography study of [¹⁴C]-labeled-copanlisib, the AUC ratio of fetal blood/maternal blood was 0.59. Relatively high radioactivity in mammary glands provides evidence for secretion of copanlisib and/or its metabolites into the milk. Secretion into milk was confirmed in another study in lactating rats. Approximately 2% of intravenously administered radioactivity was secreted into milk within 32 hours after administration; the milk to plasma ratio of radioactivity was approximately 25-fold. Because of the potential for serious adverse reactions from copanlisib in breastfed infants, lactating women should not breastfeed during treatment with ALIQOPA and for at least 1 month after the last dose.

Copanlisib does not appear to extensively bind to plasma protein as free fractions are approximately 10-48%. Data indicates that copanlisib is preferentially located in blood cells as compared to the plasma. For information on the biotransformation of copanlisib, refer to Section 6 (Clinical Pharmacology). Copanlisib is mainly excreted via the biliary/fecal route in rats however there is evidence of extra-biliary excretion as well. The pharmacokinetics of copanlisib are very similar in Wistar rats, Beagle dogs, and Cynomolgus monkeys, including moderate to high plasma clearance values and high volumes of distribution. This results in moderate to long elimination half-lives of the parent compound of between 4 and 17 hours in animals. The pharmacokinetic assessments of copanlisib in rats and dogs did not reveal any sex-dependent differences, and there were no indications of significant drug accumulation with repeated dosing.

Copanlisib was not genotoxic in the in vitro bacterial reverse mutation or mouse lymphoma assays, and also not genotoxic in the in vivo mouse bone marrow micronucleus test. No carcinogenicity studies were conducted or are required to support marketing of copanlisib for the current indication.

The nonclinical pharmacology and toxicology data submitted to this NDA are adequate to support the approval of copanlisib for the proposed indication.

Reviewer note: Unless explicitly noted otherwise, BAY 80-6946 free-base (copanlisib) was used for in vitro testing and BAY 84-1236 dihydrochloride (copanlisib dihydrochloride) was used for in vivo studies.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Primary pharmacology

A. In Vitro Studies

The inhibitory profile of copanlisib and its minor human plasma metabolite M-1

(BAY 84-5975) on class I PI3K isoforms was evaluated using a radioactive assay measuring the incorporation of ^{33}P into the p110 α , β , or γ substrate, phosphatidylinositol (PI). The inhibition of copanlisib on PI3K p110 δ was evaluated using homogenous time resolved fluorescence (HTRF®) technology to evaluate inhibition of lipid kinase activity. Copanlisib inhibits the activity of PI3K α , β , γ and δ isoforms with IC_{50} s of 0.5, 3.7, 6.4 and 0.7 nM, respectively. Copanlisib metabolite, BAY 84-5975, displayed similar inhibitory activity for PI3K α and β with IC_{50} s of 1.5 and 5.8 nM, respectively.

The class I PI3K is downstream of many cancer-associated tyrosine kinase growth factor receptors such as EGFR/HER, IGF-1R, PDGFR, VEGF, c-KIT or Met, cell adhesion molecules (such as integrins), G-protein-coupled receptors (GPCRs), and oncogenes (such as Ras). Once PI3K is activated, it activates PH-domain proteins including PI3K/3-phosphoinositide-dependent protein kinase-1 and AKT as well as guanosine triphosphate exchange factor by generation of phosphoinositol-3-phosphate. Copanlisib inhibited the phosphorylation of PDK1 substrate AKT and pathway activation in KPL-4 breast cancer cells with an $\text{IC}_{50} \leq 1$ nM. Additional evidence for inhibition of phosphorylation of the PI3K-AKT axis came from analysis of inhibition of p-PRAS40-T246, a cell line expressing GFP-PRAS40 (PerkinElmer), at two phosphorylation sites, pS183 and pThr246. The effects of copanlisib and its metabolite BAY 84-5975 on the phosphorylation state of the GFP-PRAS40 fusion protein were detected in cell lysates using the Tb-anti-pPRAS40 [pThr246] antibody. The parent compound has approximately 10-fold greater inhibitory activity than the metabolite M-1, with IC_{50} s for the phosphorylation sites pS183 and pThr246 of 227 and 595 nM for BAY 80-6946, and 1.69 and 7.57 μM for the metabolite BAY 84-5975.

The cytotoxicity of copanlisib was compared in vitro to that of the PI3K δ inhibitor CAL-101 (idelalisib). Cytotoxicity was assessed in a panel of 32 cell lines using the CellTiter-Glo® luminescent cell viability assay. The cell lines included those representing ALL, AML, CLL, CML, NHL, and myeloma. Two cell lines (Molt-4 and NCI-H929) were included in replicate assay runs in order to evaluate reproducibility of the results across experiments. Copanlisib had a lower IC_{50} than CAL-101 (idelalisib). IC_{50} values < 100 nM were observed for 14 cell lines from different tumor types tested, including ALL, AML, NHL, and myeloma, see Table 3 below. Copanlisib had also a very broad anti-proliferative effect in breast cancer cell lines.

Table 3 In Vitro Cytotoxicity Activity of Copanlisib, CAL-101 and Positive Control Cisplatin

Classification		Cell Line	IC ₅₀ (nM)			CAL-101 IC ₅₀ / Copanlisib IC ₅₀
			Copanlisib	CAL-101	Cisplatin	
Leukemia	ALL	Molt-4	18.32	23800	1772	1299.1
			18.94	25810	1664	1632.7
		RS4 (11)	3393	54850	699.9	16.2
		SUP-B15	460.5	47210	1850	102.5
	AML	HL-60	13.94	8950	4133	642.0
		Kasumi-1	1.115	1201	9451	1077.1
		ML-2	11.48	26400	1599	2299.7
		Molm-16	25.41	5330	2603	209.8
		MV4-11	4002	32290	1866	8.1
		NB4	25.34	20840	847.1	822.4

NDA/BLA Multi-disciplinary Review and Evaluation NDA 209936
Aliqopa (copanlisib)

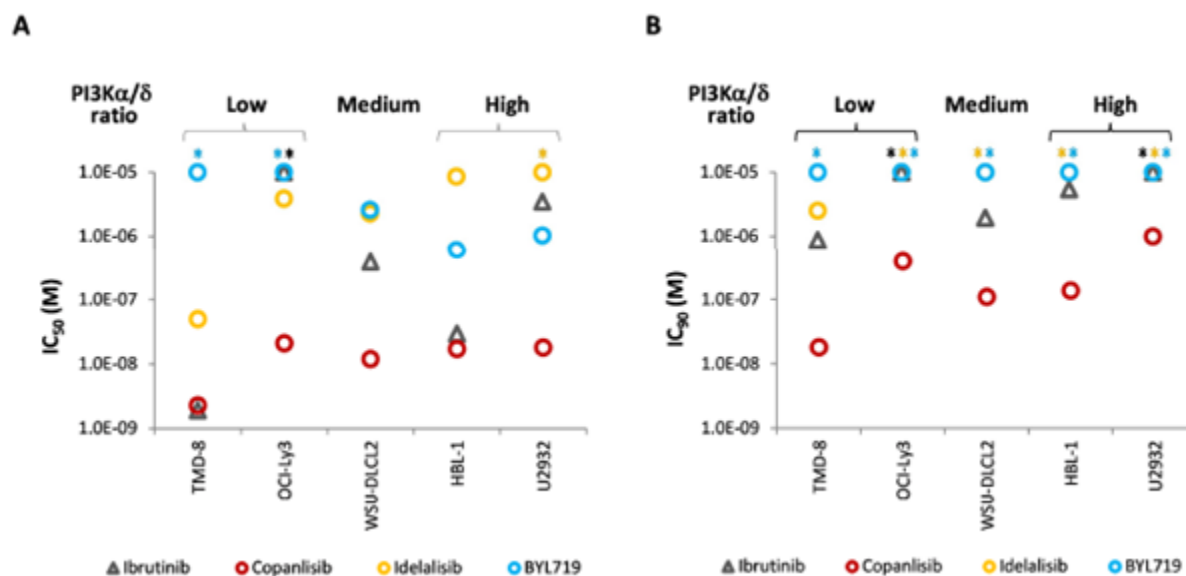
Classification		Cell Line	IC ₅₀ (nM)			CAL-101 IC ₅₀ / Copanlisib IC ₅₀
			Copanlisib	CAL-101	Cisplatin	
	CLL	TF-1	2991	50630	7392	16.9
		Jurkat	973	34210	1951	35.2
	CML	K562	7217	198700	24780	27.5
		K562/G(MDR)	522.2	41440	10580	79.4
		KU812	2306	30910	4859	13.4
		MEG-01	25520	178900	9812	7.0
Lymphoma	NHL	Daudi	24.89	34.87	61.65	1.4
		Namalwa	1.679	7153	395.4	4260.3
		Raji	692.8	1005000	1880	1450.6
		Ramos	208.6	158700	2001	760.8
		OCI-LY19	1994	111800	249	56.1
		Pfeiffer	0.849	47.47	5096	55.9
		Toledo	3498	2258000	1360	645.5
		WSU-DLCL2	123.4	18610	4870	150.8
		HuT 78	9151	362100	1169	39.6
		RL-2	874.8	51590	17040	59.0
		U937	92.84	32520	7087	350.3
Myeloma		ARH-77	928.1	126100	3114	135.9
		MM-1R	0.989	12730	1280	12870.3
		NCI-H929	2.728	16520	5526	6055.7
			2.155	14630	4790	6788.9
		OPM-2	157.6	40730	6042	256.4
		RPMI 8226	1064	42790	13290	40.2
		U266B1	2165	152700	15790	70.5

IC₅₀: half-maximal inhibitory concentration; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; CLL: chronic lymphocytic leukemia; CML: chronic myelogenous leukemia; NHL: non-Hodgkin's lymphoma

The importance of simultaneous inhibition of PI3K α and δ was evaluated in vitro using cell lines that were authenticated by fingerprint techniques. Ibrutinib sensitive HBL-1 and TMD-8 cell lines (CD79B^{mut}/MyD88^{mut}) and ibrutinib insensitive WSU-DLCL2 cell line (wt CD79 and NF- κ B) cell lines, in addition to ibrutinib resistant OCI-Ly3 (CARD11^{mut}) and U2932 (A20^{mut}) cell lines were tested. PI3K δ plays a critical role in regulating downstream events of the B-cell receptor (BCR) signaling in follicular lymphoma (FL) and diffuse large B-cell lymphoma (DLBCL). In one analysis of equal numbers of patients with activated B cell-like (ABC)-DLBCL and patients with FL, high PI3K α expression was more prevalent in ABC-DLBCL cases as compared to FL cases. PI3K δ was expressed in both tumor types. Cell lines HBL-1 and OCI-Ly3 carry activating nuclear factor-kappa Beta pathway (NF κ B) mutations. Cells were treated with either a PI3K α selective inhibitor (BYL-719), a PI3K δ selective inhibitor (idelalisib), a PI3K α / δ inhibitor (copanlisib), or a BTK inhibitor (ibrutinib). Cell viability was assessed using CellTiter-Glo luminescent cell viability assay to determine the number of metabolically active cells as presented below IC₅₀ (Figure 1 Panel A) and IC₉₀ (Figure 1 Panel B).

Figure 1 Anti-proliferative Activities of PI3K and BTK inhibitors in DLBCL Cell Lines

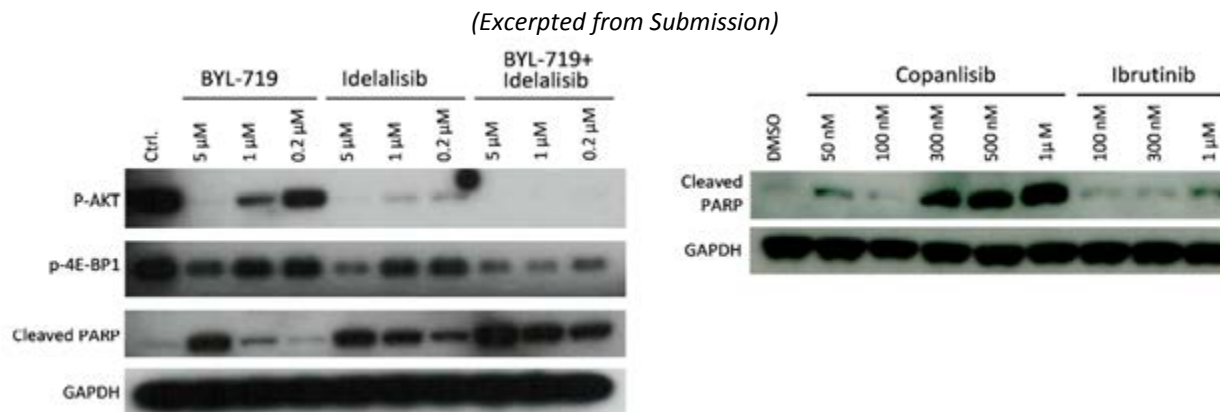
(Excerpted from Submission)



Copanlisib and ibrutinib displayed comparable IC₅₀ values in ibrutinib sensitive TMD-8 and HBL-1 cells, but copanlisib had lower IC₅₀s than idelalisib and BYL719 in all cell lines displaying low, medium or high PI3K α/δ ratio. Similarly, copanlisib reached IC₉₀ indicative of adequate tumor growth inhibition in both ibrutinib-sensitive and resistant cell lines carrying NF κ B mutations while ibrutinib displayed higher IC₉₀ in ibrutinib sensitive TMD-8 and HBL-1 cells and ibrutinib insensitive WSU-DLCL2 cell line. Idelalisib and BYL719 displayed only higher IC₉₀ in ibrutinib sensitive TMD-8 cell line. Results suggest that dual inhibition of PI3K α and δ might result in higher anti-proliferative and enhanced anti-tumor activity than inhibition of a single isoform alone.

Simultaneous inhibition of PI3K α and δ was further evaluated in these cell lines using either copanlisib or the combination of idelalisib and BYL719. Inhibition of PI3K, BTK or MAPK pathway and induction of apoptosis were assessed using antibodies against p-AKT(S473)/p-4E-BP1 (T65), p-ERK, p-BTK and cleaved PARP (cPARP) in TMD-8 cells 24 hours after treatment, respectively. Dual inhibition of PI3K α and δ by copanlisib or a combination of idelalisib and BYL-719 led to significantly enhanced anti-tumor activity in both ibrutinib-sensitive and resistant ABC-DLBCL cell lines compared to inhibition of a single isoform alone. The combination of idelalisib and BYL-719 reached greater inhibition of p-AKT and downstream p-4E-BP1, and induced substantial cleaved PARP at lower concentrations compared to each single agent alone (Figure 2, left panel). Copanlisib induced significant apoptosis at 300 nM (Figure 2, right panel).

Figure 2 Simultaneous inhibition of PI3K α/δ in DLBCL Cell Lines



A. In Vivo Studies

Several in vivo studies were conducted using athymic rats or nude mice bearing xenografts from various tumor histologies.

Female athymic nude rats were inoculated with cells from lung cancer (H460), colon cancer (HCT116), glioma (U87MG), and breast cancer (KPL-4). Copanlisib doses ranged from 0.5 to 10 mg/kg administered intravenously Q2D x4, Q2D x5, or x6. Copanlisib was well tolerated at all doses and schedules, with no mortality. The maximum tolerated dose (MTD) was defined at 10 mg/kg (Q2Dx5, i.v.) although similar tumor growth inhibition occurred at doses of 6 mg/kg or 10 mg/kg. Therefore, the 6 mg/kg (36 mg/m²) dose was selected as the maximum dose to be used in future animal activity studies (data not shown). Body weight loss occurred at 6 mg/kg generally during the first days of dosing returning to normal values before the end of the study. Significant body weight loss (22%) was observed at the end of a single trial with copanlisib at 10 mg/kg.

Table 4 Summary of BAY 80-6946 In Vivo Anti-tumor Activity

(Excerpted from Submission)

Tumor	Route	Dose ^a	TGI ^b (%)	Regressions. ^c	Maximum Weight Loss ^d (%)
H460 (NSCLC)	i.v.	1	32, 50, 52, 59, 56, 56	0	2, No Loss
		3	71, 72	0	3, 3, 2
		6	90, 89, 89	0	6, 10, 10
		10	94	0	22
		1 Q2Dx6	56, 54	0	No Loss
		3 Q2Dx6	70	0	No Loss
		6 Q2Dx6	92	0	10
HCT-116 (colon)	i.v.	6 Q3Dx4	82	0	8
HCT-116 (colon)	i.v.	3	75	0	No Loss
		6	86, 88	0	9, 15
U87 (glioma)	i.v.	1	38	0	No Loss
		3	59	0	5
		6	71	0	9
KPL-4 (breast)	i.v.	0.5	77, 80	1 PR	No Loss
		1	84, 86	1 PR, (1 PR + 1 CR)*	No Loss
		3	99, 100	10 CR, (5 PR + 5 CR)*	6
		6	100, 100	10 CR, (3 PR + 7 CR)*	15

^a Dose level expressed in mg/kg. The schedule of administration was Q2D x 5 unless noted otherwise.

^b TGI: percent tumor growth inhibition represented by $[(1-(T/C)) \times 100]$, where T and C are the average tumor weight (mg) of the Treated (T) and Control (C) groups at the optimal measurement after the end of dosing.

^c Regressions: Partial regressions (PR) = the number of tumors exhibiting >50% tumor shrinkage; Complete regressions = the number of tumors exhibiting 100% tumor shrinkage. Only durable regressions (lasting 7 – 10 days) are included. Complete cures last > 50 days, tumor free.

^d Weight Loss: the maximum mean net weight loss (body weight – tumor weight) expressed as a percent of the starting weight of the animal. Weight loss greater than 20% is considered toxic.

* The second experiment using the KPL-4 model was terminated early, at Day 32.

Secondary Pharmacology

The selectivity of copanlisib was tested in a panel of 220 kinases, and copanlisib displayed no significant off-target inhibitory activity with the exception of mTOR inhibition ($IC_{50} = 45$ nM). Further evaluation of the selectivity of copanlisib against PI3K vs. mTOR kinase suggests that copanlisib is 100- to 1000-fold more selective for PI3K than for mTOR, and indicates that copanlisib is not expected to be a dual PI3K/mTOR inhibitor in cells. Copanlisib also showed negligible activity against 32 potential pharmacological off-targets using enzyme and radioligand binding assays.

Safety Pharmacology

A. CNS

Male HsdCpb: WU rats (6 rats/group; about 6 weeks old) were administered a single IV dose of copanlisib dihydrochloride at 1.15, 3.45, or 10.35 mg/kg equivalent to 1, 3, or 9 mg/kg of copanlisib (6, 18, or 54 mg/m²) or vehicle control (aqueous mannitol solution (5 %, w/v)) in a

GLP-compliant study. CNS functional assessments (including sensory, motor, behavioral endpoints and body temperature) were evaluated predose and approximately 0.5, 1, 2, and 4 hours after dosing. Copanlisib plasma concentrations were determined in satellite groups; blood was collected from 3 rats/group at approximately 0, 0.5, 1, 2 and 4 hours after intravenous infusion of vehicle or copanlisib dihydrochloride.

Copanlisib-related adverse effects in 1-3/6 rats at the high dose of 9 mg/kg (54 mg/m²) included piloerection, ptosis, salivation, splayed limbs, backward walking, stereotypic chewing, hypoactivity, and reduced muscle tone. The highest frequency of adverse effects occurred at about 1 hour after treatment and severity gradually reduced with time thereafter. Similar behavioral abnormalities occurred in 1/6 rats at the mid-dose of 3 mg/kg (18 mg/m²). Copanlisib reduced the traveled distance, resting time and the number of rearings in the open field (horizontal and vertical locomotor activity) in a dose-dependent manner reaching statistical significance in the mid and high dose groups at 1h after treatment. Copanlisib affected body temperature regulation in a dose- and time-dependent manner with significance in the mid and high dose groups (the high dose of 9 mg/kg was associated with hypothermic effects significant at all time points). Copanlisib displayed dose-dependent increases in mean maximal drug plasma concentrations, reaching levels at the end of infusion of 138, 229, and 457 µg/L of copanlisib at doses of 1.15, 3.45, and 10.35 mg/kg, respectively.

Nocifensive responsiveness was assessed in rats given a single intravenous infusion of copanlisib dihydrochloride at doses of 0, 1.15, 3.45, or 10.35 mg/kg equivalent to 0, 1, 3, or 9 mg/kg of copanlisib (0, 18, or 54 mg/m²) in a GLP-compliant study. Approximately 60 minutes after the end of infusion, rats were placed singly on an electrically heated hotplate with a temperature of about 52°C and the latency to a distinct pain-induced reaction (i.e., licking the hindpaws) was measured for a maximal time of 90 seconds. A significant delay in response (mean of 8.3 seconds) occurred at the high dose of 9 mg/kg.

Motor coordination was assessed in rats that were trained for three consecutive days on the rotating rod (set at a constant speed of 4 rpm) so that they had to walk for a maximum of 60 seconds. Animals which did not stay on the rod in 2 of the 3 trials of the third training day were excluded from the study. On the fourth day, rats were administered a single intravenous infusion of copanlisib dihydrochloride at doses equivalent to 0, 1, 3, or 9 mg/kg of copanlisib in a GLP-compliant study. At the end of the 20 minute infusion, individual animals were placed on the rotating rod which accelerated continuously from 4 to 33 rpm over 240 seconds. The measurement was repeated 11 minutes after the end of the first acceleration sequence. Rotarod performance was reduced by 20, 30 and 11% after administration of copanlisib at 1, 3, and 9 mg/kg, respectively, indicating that copanlisib causes an impairment of motor coordination in rats.

B. Cardiovascular and Respiratory System

In vitro Repolarization (hERG K⁺ current)

Copanlisib dihydrochloride was tested at a range of concentrations from 0-10 μ M in a GLP-compliant study. The effects of the drug on repolarization were compared to predrug control values, and to the results of the positive control E-4031 (a class III antiarrhythmic drug that blocks potassium channels of the hERG-type). Copanlisib dihydrochloride was not associated with toxicologically significant effects on the hERG-mediated tail current.

In vivo Cardiovascular and Respiratory System

The potential for copanlisib dihydrochloride to have effects on cardiovascular function, ECG and respiration were examined in anesthetized (droperidol/fentanyl/nitrous oxide) artificially ventilated Beagle dogs in a GLP-compliant study. Copanlisib dihydrochloride was infused at doses of 0.0111, 0.0369, or 0.111 mg/kg/h (n = 4 dogs, low dose infusion, equivalent to copanlisib at 0.01, 0.032, or 0.1 mg/kg/h) and 0.345, 1.15, or 3.45 mg/kg/h (n = 4 dogs, high dose infusion, equivalent to copanlisib at 0.3, 1.0, or 3.0 mg/kg/h). Control animals were infused with the vehicle (5% mannitol solution) at the same infusion rates (0.15, 0.5, or 1.5 mL/kg/h; n = 4 dogs). Each dog received 3 consecutive infusions over 60 minutes with escalating infusion rates of BAY 84-1236 or the vehicle. At the end of the highest infusion rate the data was collected for an additional 2 h. Blood samples were taken for pharmacokinetics before the first infusion rate, at 30 and 60 minutes of each infusion rate and at 30, 60, and 120 minutes after the end of infusion.

At the end of the infusion step, mean copanlisib plasma concentrations of 1.4, 4.9, 18.4, 69.5, 224, and 504 μ g/L were obtained at doses of 0.01, 0.032, 0.1, 0.3, 1.0, and 3.0 mg/kg of copanlisib, respectively. At 2 hours after the end of infusion, copanlisib concentrations were in the range of 23 to 27% of C_{max} . Systemic exposure of copanlisib in dogs as measured by C_{max} and $AUC_{(0-5h)}$ increased dose proportionally in the cumulative dose range from 0.01 to 3.0 mg/kg. Copanlisib dihydrochloride salt caused hemodynamic effects that were not completely resolved at 2 hours after the end of infusion. Hemodynamic effects included a dose-dependent peripheral vasoconstriction leading to elevated arterial blood pressure (up to 30% increase in diastolic blood pressure) with slightly reduced stroke volume. A transient reduction of heart rate occurred. Threshold cardiovascular effects of up to 10% increases in diastolic blood pressure occurred at plasma levels of 6 μ g/L, whereas maximum effects were seen at plasma levels of 70 μ g/L. ECG parameters (e.g. PQ, QRS, QT, QTcF interval) were not affected.

Respiratory Function in Rats

Whole-body plethysmography was conducted in unrestrained rats after single IV infusions of copanlisib dihydrochloride (infusion duration $\approx$ 25 minutes) at doses equivalent to 0 (vehicle), 1, 3, or 9 mg/kg of copanlisib in a GLP-compliant study. There were no physiologically significant effects on respiration rate, tidal volume, or minute volume.

5.4. ADME/PK

Type of Study	Major Findings																																			
Distribution																																				
<i>BAY 80-6946: Quantitative Whole-body Autoradiography. Distribution of Radioactivity and Elimination from Blood, Organs and Tissues after Single Intravenous Infusion of [¹⁴C]BAY 80-6946 to Rats / Study Report A51160 (non-GLP).</i>	Maximal concentrations of [¹⁴C]copanlisib-derived radioactivity occurred in most organs and tissues between 1 and 1.5 hours after the start of the infusion. The highest concentrations (up to 190 times higher than the AUC in blood) were measured in the gastrointestinal contents, thyroid, kidneys and spleen. High concentrations (up to 53 times higher than the AUC in blood) were detected in liver, bone marrow, lacrimal and salivary glands, adrenals, thymus, brown adipose tissue, and pancreas. Low concentrations (up to 10 times higher than the AUC in blood) were contained in cardiac muscle, lungs, testes, prostate, skeletal muscles, and white adipose tissue. The lowest concentration was detected in brain (24% of the corresponding blood AUC). Radioactivity only appeared to be retained in melanin-bearing tissues such as eye wall and skin in pigmented rats.																																			
Metabolism																																				
<i>Study Reports: PH-35871V2, PH-35824V2, PH-35755, PH-35583V2, PH-37205, A48127, and PH-38371V3.</i>	The biotransformation of copanlisib was studied in vivo in male CD-1 mice, male Wistar rats, female Beagle dogs, and humans. <table><tr><th>Species</th><th>Mouse</th><th>Rat</th><th>Dog</th><th>Human</th></tr><tr><th>Dose</th><th>3 mg/kg</th><th>1 mg/kg</th><th>1 mg/kg</th><th>12 mg</th></tr><tr><th>Analyzed interval</th><th>0-24 h</th><th>0-24 h</th><th>0-240 h</th><th>0-tn^c</th></tr><tr><td>Component</td><td colspan="4">% of AUC (total radioactivity)</td></tr><tr><td>Copanlisib</td><td>97.3</td><td>84.1</td><td>95.5</td><td>84.4</td></tr><tr><td>M-1</td><td>trace^b</td><td>10.3</td><td>-</td><td>4.9</td></tr><tr><td>M-3</td><td>trace^b</td><td>-</td><td>-</td><td>-</td></tr></table> a = based on HPLC-LSC analytics b = only occasionally appearing c = based on LSC and LC-MS/MS analytics	Species	Mouse	Rat	Dog	Human	Dose	3 mg/kg	1 mg/kg	1 mg/kg	12 mg	Analyzed interval	0-24 h	0-24 h	0-240 h	0-tn ^c	Component	% of AUC (total radioactivity)				Copanlisib	97.3	84.1	95.5	84.4	M-1	trace ^b	10.3	-	4.9	M-3	trace ^b	-	-	-
Species	Mouse	Rat	Dog	Human																																
Dose	3 mg/kg	1 mg/kg	1 mg/kg	12 mg																																
Analyzed interval	0-24 h	0-24 h	0-240 h	0-tn ^c																																
Component	% of AUC (total radioactivity)																																			
Copanlisib	97.3	84.1	95.5	84.4																																
M-1	trace ^b	10.3	-	4.9																																
M-3	trace ^b	-	-	-																																
Excretion																																				
<i>Excretion of the Radioactivity in Male Wistar Rats after Single Intravenous Administration of [¹⁴C]BAY 80-6946 / Study Report PH-35583.</i>	In intact rats [¹⁴C]copanlisib was mainly excreted via the biliary/fecal route (84.6 %), with less than 10 % excretion via the renal route, seven days after IV administration. In bile duct-cannulated rats [¹⁴C]copanlisib was excreted in the feces (7.9 %), the bile (41.6 %), and in																																			

Type of Study	Major Findings																																																														
	urine (8.6 %), with an additional 26.9 % found in the gastrointestinal tract indicating an extra-biliary excretion.																																																														
TK data from general toxicology studies																																																															
Multi Cycle Systemic Toxicity Study in Wistar Rats (Administration via Intravenous Infusion, Three/ Four Treatment Cycles (Females/ Males) Followed by a 8-Weeks Recovery Period) / Study Report PH-37826	Copanlisib dihydrochloride administration (1 hour IV infusion). Blood samples were collected before the end of infusion and at 2, 4, 7, and 24 hours after the start of infusion on Day 1 (the first treatment of the first cycle), Day 72 (the third treatment of the third cycle for females), and Day 102 (the third treatment of the fourth cycle for males). There were no sex-related differences. Accumulation occurred after multiple doses. Hemolysis of most Day 72 samples for females and some Day 102 samples for males impacted the interpretation of toxicokinetics. TK Parameters in Rats after Multi-Cycle Dosing <table><tr><th rowspan="2"></th><th colspan="3">Day 72 - Females</th><th colspan="3">Day 102 - Males</th></tr><tr><th colspan="3">Dose level (mg/kg)</th><th colspan="3">Dose level (mg/kg)</th></tr><tr><td>Copanlisib dihydrochloride</td><td>0.35</td><td>1.15</td><td>3.46</td><td>0.35</td><td>1.15</td><td>3.46</td></tr><tr><td>Copanlisib</td><td>0.3</td><td>1.0</td><td>3.0</td><td>0.3</td><td>1.0</td><td>3.0</td></tr><tr><td>AUC₍₀₋₂₄₎ [µg*h/L]</td><td>NC</td><td>4410</td><td>15099</td><td>314</td><td>2351</td><td>14925</td></tr><tr><td>C_{max} [µg/L]</td><td>NC</td><td>929</td><td>2751</td><td>78</td><td>426</td><td>3074</td></tr><tr><td>t_{max} [h]</td><td>NC</td><td>2.0</td><td>0.92</td><td>0.92</td><td>0.92</td><td>0.92</td></tr><tr><td>AUC day 72 or 102/ AUC day 1 [%]</td><td>NC</td><td>12.4</td><td>12.0</td><td>3.8</td><td>14.4</td><td>19.3</td></tr><tr><td>C_{max} day 72 or 102/ C_{max} day 1 [%]</td><td>NC</td><td>9.7</td><td>8.6</td><td>2.5</td><td>7.5</td><td>8.0</td></tr></table> NC = not calculated		Day 72 - Females			Day 102 - Males			Dose level (mg/kg)			Dose level (mg/kg)			Copanlisib dihydrochloride	0.35	1.15	3.46	0.35	1.15	3.46	Copanlisib	0.3	1.0	3.0	0.3	1.0	3.0	AUC ₍₀₋₂₄₎ [µg*h/L]	NC	4410	15099	314	2351	14925	C _{max} [µg/L]	NC	929	2751	78	426	3074	t _{max} [h]	NC	2.0	0.92	0.92	0.92	0.92	AUC day 72 or 102/ AUC day 1 [%]	NC	12.4	12.0	3.8	14.4	19.3	C _{max} day 72 or 102/ C _{max} day 1 [%]	NC	9.7	8.6	2.5	7.5	8.0
	Day 72 - Females			Day 102 - Males																																																											
	Dose level (mg/kg)			Dose level (mg/kg)																																																											
Copanlisib dihydrochloride	0.35	1.15	3.46	0.35	1.15	3.46																																																									
Copanlisib	0.3	1.0	3.0	0.3	1.0	3.0																																																									
AUC ₍₀₋₂₄₎ [µg*h/L]	NC	4410	15099	314	2351	14925																																																									
C _{max} [µg/L]	NC	929	2751	78	426	3074																																																									
t _{max} [h]	NC	2.0	0.92	0.92	0.92	0.92																																																									
AUC day 72 or 102/ AUC day 1 [%]	NC	12.4	12.0	3.8	14.4	19.3																																																									
C _{max} day 72 or 102/ C _{max} day 1 [%]	NC	9.7	8.6	2.5	7.5	8.0																																																									
16 Week Intravenous (Infusion) Administration Toxicity Study in the Dog Followed by a 4 Week Treatment-free Period / Study Report R-9617	Copanlisib dihydrochloride administration (1 hour IV infusion). Blood samples were collected on Day 1 (groups 1 to 5), Day 43 (group 4) and on Day 99 (groups 1 to 3) at predose, 0.5, 1, 2, 7, 24, 72, and 167 hours after the start of the infusion. No evidence of sex-related differences. Accumulation occurred after multiple doses. TK Parameters in Dogs after Multi-Cycle Dosing <table><tr><th>Copanlisib (mg/kg)</th><th>0.1</th><th>0.3</th><th>1.0/0.7</th></tr><tr><th>Day</th><th>99</th><th>99</th><th>43</th></tr><tr><td>AUC_(0-t-last) [µg*h/L]</td><td>33.1</td><td>142</td><td>325</td></tr><tr><td>C_{max} [µg/L]</td><td>12.7</td><td>37.9</td><td>87.8</td></tr><tr><td>t_{max} [h]</td><td>0.89</td><td>0.78</td><td>0.57</td></tr><tr><td>t_{last} [h]</td><td>7.0</td><td>24.0</td><td>24.0</td></tr><tr><td>AUC day 99 or 43/ AUC day 1 [%]</td><td>115.6</td><td>150.8</td><td>NC</td></tr><tr><td>C_{max} day 99 or 43/ C_{max} day 1 [%]</td><td>115.6</td><td>92.1</td><td>NC</td></tr></table> NC = not calculated	Copanlisib (mg/kg)	0.1	0.3	1.0/0.7	Day	99	99	43	AUC _(0-t-last) [µg*h/L]	33.1	142	325	C _{max} [µg/L]	12.7	37.9	87.8	t _{max} [h]	0.89	0.78	0.57	t _{last} [h]	7.0	24.0	24.0	AUC day 99 or 43/ AUC day 1 [%]	115.6	150.8	NC	C _{max} day 99 or 43/ C _{max} day 1 [%]	115.6	92.1	NC																														
Copanlisib (mg/kg)	0.1	0.3	1.0/0.7																																																												
Day	99	99	43																																																												
AUC _(0-t-last) [µg*h/L]	33.1	142	325																																																												
C _{max} [µg/L]	12.7	37.9	87.8																																																												
t _{max} [h]	0.89	0.78	0.57																																																												
t _{last} [h]	7.0	24.0	24.0																																																												
AUC day 99 or 43/ AUC day 1 [%]	115.6	150.8	NC																																																												
C _{max} day 99 or 43/ C _{max} day 1 [%]	115.6	92.1	NC																																																												
Toxicity Study in Wistar Rats:	Copanlisib lyophilisate drug product administration.																																																														

Type of Study	Major Findings																																										
<i>Exposure for 1 hour Once a Week via Intravenous Infusion over 3 Weeks+ 4 Weeks Recovery (Single Cycle) / Study Report PH-35706</i>	Blood samples were collected on Day 1 and during the third treatment of the cycle before the end of infusion and at 2, 4, 7, and 24 hours after the start of infusion. There were no sex-related differences. Accumulation occurred after multiple doses. TK Parameters in Rats after Single-Cycle Dosing <table><tr><th></th><th colspan="3">Males</th><th colspan="3">Females</th></tr><tr><th>Copanlisib (mg/kg)</th><th>0.6</th><th>2.0</th><th>6.0</th><th>0.6</th><th>2.0</th><th>6.0</th></tr><tr><td>AUC₍₀₋₂₄₎ [µg*h/L]</td><td>252</td><td>627</td><td>1994</td><td>NC</td><td>592</td><td>1755</td></tr><tr><td>C_{max} [µg/L]</td><td>102</td><td>239</td><td>652</td><td>NC</td><td>246</td><td>566</td></tr><tr><td>t_{max} [h]</td><td>0.91</td><td>0.91</td><td>0.91</td><td>NC</td><td>0.91</td><td>0.91</td></tr><tr><td>C_{max} day 15 / C_{max} day 1 [%]</td><td>146</td><td>118</td><td>136</td><td>NC</td><td>136</td><td>209</td></tr></table> NC = not calculated		Males			Females			Copanlisib (mg/kg)	0.6	2.0	6.0	0.6	2.0	6.0	AUC ₍₀₋₂₄₎ [µg*h/L]	252	627	1994	NC	592	1755	C _{max} [µg/L]	102	239	652	NC	246	566	t _{max} [h]	0.91	0.91	0.91	NC	0.91	0.91	C _{max} day 15 / C _{max} day 1 [%]	146	118	136	NC	136	209
	Males			Females																																							
Copanlisib (mg/kg)	0.6	2.0	6.0	0.6	2.0	6.0																																					
AUC ₍₀₋₂₄₎ [µg*h/L]	252	627	1994	NC	592	1755																																					
C _{max} [µg/L]	102	239	652	NC	246	566																																					
t _{max} [h]	0.91	0.91	0.91	NC	0.91	0.91																																					
C _{max} day 15 / C _{max} day 1 [%]	146	118	136	NC	136	209																																					
<i>BAY 84-1236: Subacute Toxicity Study in Beagle Dogs (Once per Week i.v.-Infusion over 2 Weeks with 2 Week Recovery Period) / Study Report PH-33540</i>	Copanlisib lyophilisate drug product administration. Blood samples were collected on Day 1 and during the third treatment of the cycle before the end of infusion and at 30 min, 55 minutes, and 2, 4, 7, and 24 hours after the start of infusion. No evidence of sex-related differences. No accumulation after multiple dose administration. TK Parameters in Dogs after Single-Cycle Dosing <table><tr><th>Copanlisib (mg/kg)</th><th>0.2</th><th>0.6</th><th>2.0</th></tr><tr><td>AUC_(0-t-n) [µg*h/L]</td><td>47.7</td><td>232</td><td>920</td></tr><tr><td>C_{max} [µg/L]</td><td>17.8</td><td>55.6</td><td>152</td></tr><tr><td>t_{max} [h]</td><td>0.92</td><td>0.92</td><td>0.83</td></tr><tr><td>AUC day 15 / AUC day 1 [%]</td><td>103</td><td>112</td><td>119</td></tr><tr><td>C_{max} day 15 / C_{max} day 1 [%]</td><td>96.8</td><td>107</td><td>108</td></tr></table>	Copanlisib (mg/kg)	0.2	0.6	2.0	AUC _(0-t-n) [µg*h/L]	47.7	232	920	C _{max} [µg/L]	17.8	55.6	152	t _{max} [h]	0.92	0.92	0.83	AUC day 15 / AUC day 1 [%]	103	112	119	C _{max} day 15 / C _{max} day 1 [%]	96.8	107	108																		
Copanlisib (mg/kg)	0.2	0.6	2.0																																								
AUC _(0-t-n) [µg*h/L]	47.7	232	920																																								
C _{max} [µg/L]	17.8	55.6	152																																								
t _{max} [h]	0.92	0.92	0.83																																								
AUC day 15 / AUC day 1 [%]	103	112	119																																								
C _{max} day 15 / C _{max} day 1 [%]	96.8	107	108																																								

5.5. Toxicology

5.5.1. General Toxicology

Multi Cycle Systemic Toxicity Study in Wistar Rats (Administration via Intravenous Infusion, Three/ Four Treatment Cycles (Females/ Males) Followed by a 8-Weeks Recovery Period) / Study Report PH-37826

Key Study Findings

- Mortality at the MD and HD.
- Toxicities include behavioral changes, discolored teeth, reduced fur, decreased body weight gain, immunosuppression, decreased hematological parameters, and increased serum chemistry parameters, glycosylated hemoglobin, and thyroid function.
- Target organs of toxicity included the liver, reproductive organs, hematopoietic/lymphoid system, heart, endocrine system (thyroid), skin, and

teeth.

Conducting laboratory and location: Bayer Pharma AG Toxicology, Wuppertal Germany
GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 0.35, 1.15, or 3.46 mg/kg (copanlisib dihydrochloride)
0, 0.3, 1.0, or 3.0 mg/kg (copanlisib)
28-day cycle with 3-weekly doses/1-week off (males 4 cycles; females 3 cycles)

Route of administration: 1 hour intravenous infusion

Formulation/Vehicle: Saline solution (0.9% NaCl pH 3.9 ± 0.2)

Species/Strain: Wistar rats / Crl:(WI) BR

Number/Sex/Group: Toxicology: 10/sex/group ; additional 10/sex/group in the control and HD for recovery combined with 6/sex from the TK-HD group
TK: 6/sex/group, no control group

Age: Approximately 8-9 weeks old

Satellite groups/ unique design: TK, Immunotoxicity, and drug metabolizing enzymes assessments

Deviation from study protocol affecting interpretation of results: No

Observations and Results: Changes from control

Parameters	Major findings
Mortality	Main study rats Control: 1 male LD : 1 female MD : 1 male, 2 females HD : 7 males, 4 females TK rats LD : 1 male, 1 female MD : 2 females HD : 1 male, 1 female
Clinical Signs	↑incidence at MD, ↑↑incidence at HD Stepping gait and/or hindlimbs dragging and/or lying on side and/or sunken flanks, piloerection, and/or labored breathing (CNS), hairless area(s)/reduced fur/diminished growth of hair, swellings (increased girth), wounds at different locations and discolored teeth. Tonic spasms after administration (3rd cycle) in high dose females. Few rats with less severe hairless area(s)/reduced fur/diminished growth of hair at the end of recovery.
Body Weight gain	Dosing Period: Body weight gain percent change compared to control

NDA/BLA Multi-disciplinary Review and Evaluation NDA 209936
Aliqopa (copanlisib)

	<table><tr><th>Sex</th><th colspan="4">Males</th><th colspan="4">Females</th></tr><tr><th>Dose mg/kg</th><th>0</th><th>0.35</th><th>1.15</th><th>3.46</th><th>0</th><th>0.35</th><th>1.15</th><th>3.46</th></tr><tr><td>Day 106/77#</td><td>549</td><td>-9%</td><td>-5%</td><td>-8%</td><td>323</td><td>-9%**</td><td>-5%</td><td>-8%*</td></tr><tr><td>Day 1-106/1-77#</td><td>252</td><td>-14%</td><td>-6%</td><td>-20%*</td><td>86</td><td>-17%</td><td>-17%</td><td>-33%**</td></tr></table> #= males 4 cycles, females 3 cycles; A 28-day cycle=3x1h infusion/week/rat– 2-week off Necropsy= 1 week after last dose End of recovery: HD similar body weight gain compared to control Food and water consumption: unremarkable.	Sex	Males				Females				Dose mg/kg	0	0.35	1.15	3.46	0	0.35	1.15	3.46	Day 106/77#	549	-9%	-5%	-8%	323	-9%**	-5%	-8%*	Day 1-106/1-77#	252	-14%	-6%	-20%*	86	-17%	-17%	-33%**																																																																																								
Sex	Males				Females																																																																																																																								
Dose mg/kg	0	0.35	1.15	3.46	0	0.35	1.15	3.46																																																																																																																					
Day 106/77#	549	-9%	-5%	-8%	323	-9%**	-5%	-8%*																																																																																																																					
Day 1-106/1-77#	252	-14%	-6%	-20%*	86	-17%	-17%	-33%**																																																																																																																					
Ophthalmoscopy	Unremarkable																																																																																																																												
Hematology	% Mean differences vs. controls (end of dosing) <table><tr><th rowspan="3"></th><th colspan="3">Males</th><th colspan="3">Females</th></tr><tr><th colspan="3">Dose level (mg/kg)</th><th colspan="3">Dose level (mg/kg)</th></tr><tr><th>0.35</th><th>1.15</th><th>3.46</th><th>0.35</th><th>1.15</th><th>3.46</th></tr><tr><td>RET1</td><td>↓14.3</td><td>↓39.4**</td><td>↓56.6**</td><td>↓29.2*</td><td>↓49.1**</td><td>↓42.9**</td></tr><tr><td>THRO</td><td>↑7.9</td><td>↑9.8</td><td>↑24.3*</td><td>–</td><td>↑1.4</td><td>↑6.2</td></tr><tr><td>LEUC</td><td>↓15.6</td><td>↓22.8*</td><td>↓42.9**</td><td>↓28.2*</td><td>↓35.3*</td><td>↑2.4</td></tr><tr><td>LYMP</td><td>↓25.5*</td><td>↓31.3*</td><td>↓55.4**</td><td>↓23.3</td><td>↓39.1*</td><td>↓27.3</td></tr></table> *= p≤0.05 **= p≤0.01 –= no difference End of recovery: HD similar values compared to control.		Males			Females			Dose level (mg/kg)			Dose level (mg/kg)			0.35	1.15	3.46	0.35	1.15	3.46	RET1	↓14.3	↓39.4**	↓56.6**	↓29.2*	↓49.1**	↓42.9**	THRO	↑7.9	↑9.8	↑24.3*	–	↑1.4	↑6.2	LEUC	↓15.6	↓22.8*	↓42.9**	↓28.2*	↓35.3*	↑2.4	LYMP	↓25.5*	↓31.3*	↓55.4**	↓23.3	↓39.1*	↓27.3																																																																													
	Males			Females																																																																																																																									
	Dose level (mg/kg)			Dose level (mg/kg)																																																																																																																									
	0.35	1.15	3.46	0.35	1.15	3.46																																																																																																																							
RET1	↓14.3	↓39.4**	↓56.6**	↓29.2*	↓49.1**	↓42.9**																																																																																																																							
THRO	↑7.9	↑9.8	↑24.3*	–	↑1.4	↑6.2																																																																																																																							
LEUC	↓15.6	↓22.8*	↓42.9**	↓28.2*	↓35.3*	↑2.4																																																																																																																							
LYMP	↓25.5*	↓31.3*	↓55.4**	↓23.3	↓39.1*	↓27.3																																																																																																																							
Clinical Chemistry	% Mean differences vs. controls (end of dosing) <table><tr><th rowspan="3"></th><th colspan="3">Males</th><th colspan="3">Females</th></tr><tr><th colspan="3">Dose level (mg/kg)</th><th colspan="3">Dose level (mg/kg)</th></tr><tr><th>0.35</th><th>1.15</th><th>3.46</th><th>0.35</th><th>1.15</th><th>3.46</th></tr><tr><td>AST</td><td>↓9.7</td><td>↑4.1</td><td>↑33.4*</td><td>↑20.2</td><td>↑27.5</td><td>↑30.9**</td></tr><tr><td>ALT</td><td>–</td><td>↑7.6</td><td>↑41.3**</td><td>–</td><td>↑25.1</td><td>↑26.9**</td></tr><tr><td>CHOL</td><td>↑10.4</td><td>↑26.9*</td><td>↑46.2**</td><td>–</td><td>↑8.0</td><td>↑14.6</td></tr><tr><td>TRIG</td><td>–</td><td>–</td><td>–</td><td>↑10.0</td><td>↑37.5**</td><td>↑25*</td></tr><tr><td>CREA</td><td>–</td><td>↑10.5*</td><td>↑16.0**</td><td>↑5.1</td><td>↑2.0</td><td>–</td></tr><tr><td>PROT</td><td>↑2.3</td><td>↑4.3*</td><td>↑13.1**</td><td>–</td><td>↑4.0</td><td>↑5.2*</td></tr><tr><td>ALBU</td><td>–</td><td>↑2.3</td><td>↑7.1**</td><td>↑5.1</td><td>↑7.0</td><td>–</td></tr><tr><td>GLUC</td><td>–</td><td>–</td><td>↓13.7**</td><td>–</td><td>–</td><td>↓26.1**</td></tr><tr><td>b-HBUT</td><td>–</td><td>↓12.8</td><td>↓32.9*</td><td>↑40.3*</td><td>↑10.1</td><td>↑10.9</td></tr><tr><td>HbA1c</td><td>–</td><td>↑7.7</td><td>↑40.4**</td><td>–</td><td>↑16.4*</td><td>↑37.7**</td></tr><tr><td>T3</td><td>–</td><td>↑17.1*</td><td>–</td><td>↑2.9</td><td>↑9.4</td><td>↑9.4</td></tr><tr><td>T4</td><td>↓5.7</td><td>↓2.6</td><td>↓17.5</td><td>↑19.7</td><td>↑12.3</td><td>↓9.8</td></tr><tr><td>TSH</td><td>–</td><td>↓9.1</td><td>↑296**</td><td>↑19.3</td><td>↑43.9</td><td>↑143**</td></tr><tr><td>K</td><td>↓6.4</td><td>↓10.6**</td><td>↓14.9**</td><td>↓2.6</td><td>↓7.7*</td><td>↓10.3**</td></tr><tr><td>Ca</td><td>–</td><td>↑3.6**</td><td>↑4.8**</td><td>–</td><td>–</td><td>–</td></tr></table> *= p≤0.05 **= p≤0.01 –= no difference End of recovery: HD similar values compared to control except males with AP (↑48.2%**) and HbA1c (↑7.8%*).		Males			Females			Dose level (mg/kg)			Dose level (mg/kg)			0.35	1.15	3.46	0.35	1.15	3.46	AST	↓9.7	↑4.1	↑33.4*	↑20.2	↑27.5	↑30.9**	ALT	–	↑7.6	↑41.3**	–	↑25.1	↑26.9**	CHOL	↑10.4	↑26.9*	↑46.2**	–	↑8.0	↑14.6	TRIG	–	–	–	↑10.0	↑37.5**	↑25*	CREA	–	↑10.5*	↑16.0**	↑5.1	↑2.0	–	PROT	↑2.3	↑4.3*	↑13.1**	–	↑4.0	↑5.2*	ALBU	–	↑2.3	↑7.1**	↑5.1	↑7.0	–	GLUC	–	–	↓13.7**	–	–	↓26.1**	b-HBUT	–	↓12.8	↓32.9*	↑40.3*	↑10.1	↑10.9	HbA1c	–	↑7.7	↑40.4**	–	↑16.4*	↑37.7**	T3	–	↑17.1*	–	↑2.9	↑9.4	↑9.4	T4	↓5.7	↓2.6	↓17.5	↑19.7	↑12.3	↓9.8	TSH	–	↓9.1	↑296**	↑19.3	↑43.9	↑143**	K	↓6.4	↓10.6**	↓14.9**	↓2.6	↓7.7*	↓10.3**	Ca	–	↑3.6**	↑4.8**	–	–	–
	Males			Females																																																																																																																									
	Dose level (mg/kg)			Dose level (mg/kg)																																																																																																																									
	0.35	1.15	3.46	0.35	1.15	3.46																																																																																																																							
AST	↓9.7	↑4.1	↑33.4*	↑20.2	↑27.5	↑30.9**																																																																																																																							
ALT	–	↑7.6	↑41.3**	–	↑25.1	↑26.9**																																																																																																																							
CHOL	↑10.4	↑26.9*	↑46.2**	–	↑8.0	↑14.6																																																																																																																							
TRIG	–	–	–	↑10.0	↑37.5**	↑25*																																																																																																																							
CREA	–	↑10.5*	↑16.0**	↑5.1	↑2.0	–																																																																																																																							
PROT	↑2.3	↑4.3*	↑13.1**	–	↑4.0	↑5.2*																																																																																																																							
ALBU	–	↑2.3	↑7.1**	↑5.1	↑7.0	–																																																																																																																							
GLUC	–	–	↓13.7**	–	–	↓26.1**																																																																																																																							
b-HBUT	–	↓12.8	↓32.9*	↑40.3*	↑10.1	↑10.9																																																																																																																							
HbA1c	–	↑7.7	↑40.4**	–	↑16.4*	↑37.7**																																																																																																																							
T3	–	↑17.1*	–	↑2.9	↑9.4	↑9.4																																																																																																																							
T4	↓5.7	↓2.6	↓17.5	↑19.7	↑12.3	↓9.8																																																																																																																							
TSH	–	↓9.1	↑296**	↑19.3	↑43.9	↑143**																																																																																																																							
K	↓6.4	↓10.6**	↓14.9**	↓2.6	↓7.7*	↓10.3**																																																																																																																							
Ca	–	↑3.6**	↑4.8**	–	–	–																																																																																																																							
Urinalysis	HD: presence of glucose (3 males, 1 female) and blood/erythrocytes (1 female)																																																																																																																												
Gross Pathology	LD: testes (enlarged) MD: testes (enlarged), uterus (dilation), adrenal glands (discoloration/enlarged), spleen (enlarged) HD: adrenal glands (discoloration/enlarged), spleen (enlarged), thymus females (small), mandibular lymph nodes (enlarged), skin/subcutis (sparse hair coat, hairless, incrustations, sores) End of recovery HD: single rats with adrenal glands (discoloration/enlarged)																																																																																																																												

NDA/BLA Multi-disciplinary Review and Evaluation NDA 209936
Aliqopa (copanlisib)

	and skin (incrustations /thickening/nodule)
Organ Weights	HD males: ↓spleen (21.6%**), thymus (32.3%**), testes (12.9%), epididymides (5.8%), prostate (15.9%), seminal vesicles (7.7%) and popliteal lymph node (21.3%). ↑liver (14.3%*) and heart (10.2%). MD females: ↓spleen (15.1%*). HD females: ↓thymus (34.2%**). HD females: ↑liver (18.9%**), kidneys (9.4%**), uterus (12.1%), and heart (14.3%). LD and HD females: ↑brain (10.8%** and 8.6%**).
Histopathology Adequate battery: Yes	MD and higher: incisor teeth (dentin alteration, odontoblast degeneration, pulp necrosis/degeneration), pancreas (more prominent islets cells), bone marrow (hypocellularity, increased myelopoiesis), spleen (cellular depletion marginal zone and follicles, lymphoid necrosis, decrease mature hematopoietic cells, increase immature blood forming cells), thymus (cellular depletion cortex, altered cellularity medulla, lymphocytic necrosis), mesenteric and popliteal lymph node (cellular depletion, sinus histiocytosis, plasmacytosis, blood resorption), mammary gland/males (atrophy), heart (focal myocardial degeneration), lung (perivascular lymphocytes, perivascular granulocytes, media hypertrophy, mineralization, perivascular edema, alveolar macrophages, pigment, thrombosis), liver (diffuse Kupffer cell activation, periportal inflammation, hematopoiesis, glycogen reduced/increased, reduced fat content), skin/other (inflammation, reactive epidermal - hyperplasia, incrustation, ulcer, thrombophlebitis), and local tolerance to the catheter. HD: testes (degeneration germinal epithelium), epididymides (spermatic debris), vagina (mononuclear cell infiltration), cecum (thickening of mucosa), lacrimal glands (mononuclear cell infiltration), and skin/mammary region (folliculitis). Findings that resolved by the end of recovery (HD): teeth (dental alteration), heart (focal myocardial degeneration), male sexual organs (testicular degeneration, spermatic debris), female sexual organs (mononuclear cell infiltration of the vagina), pancreas (prominent islets), and lacrimal glands (mononuclear cell infiltration). Findings that partially resolved by the end of recovery (HD): immune system/bone marrow (cellular depletion, hypocellularity), lung (perivascular lymphocytes, vascular mineralization, pigments), cecum (mucosal thickening), skin (folliculitis, incrustation, inflammation, reactive epidermal hyperplasia), and reduced local tolerability along the catheter. Findings that developed during the recovery (HD): increased incidence of focal liver necrosis and eosinophilia indicative of a delayed onset of hepatotoxicity.
Liver Metabolizing Enzymes	HD ↓for activity of p-Nitroanisole-O-Demethylase (females from mid dose), N-Demethylase, glutathione-s-transferase (females) and P450 concentration (females).
Immunotox	HD males significantly decreased splenic cell counts and B cells MD and HD statistically significantly reduced IgG antibody titers

LD: low dose; MD: mid dose; HD: high dose. ↓: reduction or ↑ increase in parameters compared to control

**BAY 84-1236 (Project PI3K Inhibitor, BAY 80-6946): 16 Week Intravenous (Infusion)
Administration Toxicity Study in the Dog Followed by a 4 Week Treatment-free Period
/ Study Report R-9617**

Key Study Findings

- Mortality at MD and HD. HD terminated early.
- Toxicities include injection site toxicities (e.g., abscess), immunosuppression, decreased hematological parameters, body weight loss, behavioral changes, impaired mobility, and opaque lens.
- Target organs include hematopoietic/lymphoid system (GALT, mandibular lymph node, mesenteric lymph node, spleen, thymus), and reproductive organs (reduced testes and prostate weights, tubular atrophy in testes, oligospermia in the epididymides) and adrenal glands.

Conducting laboratory and location:

(b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:

Group number	Group description	Dose level (mg/kg/hr/week) dose of BAY 84-1236	Number of Animals:			
			Toxicity		Treatment-free	
			Male	Female	Male	Female
1	Control	0	3	3	3	3
2	Low	0.115	3	3	-	-
3	Intermediate	0.35	3	3	3	3
4	High 1	1.15a / 0.86b	3	3	3	3
5	High 2	1.15c / 0.86d	3	3	3	3

a – on Days 1, 8, 15, 22 and 29; not dosed on Day 36

b – on Days 43, 50, 57, 64

c – dosed in one cycle of once weekly dosing for three consecutive weeks (Days 1, 8, 15) followed by one week off-dose (Day 22), then once weekly for two weeks (Days 29, 36); not dosed on Days 43 and 50

d – on Day 57 only

Doses equivalent to 0, 0.1, 0.3, or 1.0/0.7 mg/kg copanlisib

Groups 1-4: weekly doses for 16-weeks except as noted in table above for HD1 (weekly dosing)

Group 5-HD2 (cycle dosing): 28-day cycle with 3-weekly doses/one week off except as noted in table above for HD2

Terminal necropsy Day 70. Recovery period 11 weeks total

Route of administration: 1 h intravenous infusion

Formulation/Vehicle: sterile isotonic sodium chloride solution

Species/Strain: Beagle dog

Number/Sex/Group: 3/sex/group ; additional 3/sex/group in the control, MD, HD1 and HD2 for recovery

Age: Males 43 to 48 weeks old
Females 47 to 52 weeks old

Satellite groups/ unique design: None

NDA/BLA Multi-disciplinary Review and Evaluation NDA 209936
Aliqopa (copanlisib)

Deviation from study protocol affecting interpretation of results: No

Observations and Results: changes from control

Parameters	Major findings
Mortality	MD: 1 male HD1: 3 males HD2: 1 male, 1 female
Clinical Signs	LD and higher: after 5 to 9 weeks of dosing minimal to moderate impaired mobility of the foreleg/hindleg. These signs persisted for at least 12 hours after dosing. MD, HD1 and HD2: subdued/sluggish behavior, salivation, vomiting and abnormal (e.g. soft, liquid, mucoid) feces and panting respiration.
Body Weight Gain	Weeks 1-16: LD males ↓33.8%, females ↓21.0%. MD females ↓25.9%. Corresponded with decreased food consumption. Unremarkable during recovery.
Ophthalmoscopy	MD and HD: opacity of the lens in one or both eyes. Onset of this finding generally occurred in Week 15 of the study, and persisted throughout the recovery period in the majority HD dogs.
ECG and Blood Pressure	Unremarkable
Hematology	Intermittent changes occurred usually after dosing compared to pre-dosing values LD: ↑PCT, MPV, PDW MD: ↑PCT, MPV, PDW HD1: ↓RBC, PCV, ↑↑↑RDW, ↑PCT, PDW, PLT, APTS, ↑↑fibrinogen, WBC, NEUT, MONO, ↓LYMP, ↓↓BASO HD2: ↓RBC, PCV, ↑↑↑RDW, ↑PCT, PDW, PLT, APTS, ↑↑fibrinogen, WBC, NEUT, MONO, ↓LYMP, ↓↓BASO Findings resolved by the end of recovery period.
Clinical Chemistry	Intermittent changes occurred usually after dosing compared to pre-dosing values HD1 and HD2: ↑GLDH, ↑↑↑AP, ↓ALBU, ↑↑↑GLOB, ALBU/GLOB, ↓Urea Findings resolved by the end of recovery period.
Urinalysis	Unremarkable
Gross Pathology	HD1: small thymus 1 male
Organ Weights	Adjusted organ to body weight ratios compared to controls LD: testes (↓25%) MD: testes (↓29%), prostate (↓22%), adrenals female (↑32%) HD1: testes (↓31%), prostate (↓35%), spleen males (↓44%) w/ microscopic correlates, adrenals male (↑65%) HD2: testes (↓30%) Findings resolved by the end of recovery period.
Histopathology Adequate battery: Yes	LD and higher: At the injection site, fasciitis/cellulitis and/or phlebitis/periphlebitis and/or thrombosis in all dosed groups with increased incidence and/or severity in HD1 and HD2 . Slight to moderate decreased germinal center development in the lymphoid system (GALT, mandibular and mesenteric lymph nodes). Minimal to slight tubular atrophy of testes with decreased size and cellularity of the tubules,

	primarily of the spermatid and spermatocyte stages, with the presence of occasional sloughed and degenerate cell in the lumen. LD and MD: minimal spleen lymphoid atrophy HD: minimal to moderate thymus atrophy with increased cellularity, moderate oligospermia in the epididymides characterized by decreased numbers of spermatozoa in the epididymal ducts, and minimal to slight cellular debris. Most findings were resolved at the end of recovery except for partial resolution of the mandibular lymph node reduction in germinal center development in females and partial resolution of effects in the testes and epididymides at MD and HD.
Other evaluations	No effects on glycosylated hemoglobin, hydroxybutyrate, acetoacetate, or thyroid hormones

LD: low dose; MD: mid dose; HD: high dose. ↓: reduction or ↑ increase in parameters compared to control; ↑= higher, ↑↑ significantly higher $p \leq 0.05$, ↑↑↑ significantly higher $p \leq 0.01$

General toxicology; additional studies

Toxicity Study in Wistar Rats: Exposure for 1 hour once a Week via intravenous Infusion over 3 Weeks+ 4 Weeks Recovery (Single Cycle) / Study Report PH-35706

GLP-compliant toxicity study conducted in Wistar rats with the copanlisib lyophilisate formulation (drug product batch nos. N5064A01 and N5250A01) at doses of 0, 0.6, 2.0 and 6.0 mg/kg administered as intravenous infusion for 1 hour once weekly for 3 administrations followed by a 4-week recovery period for control and HD rats. Additional groups were dosed for TK evaluations. Mortality at the HD (6 mg/kg) associated with clinical signs of poor general condition, decreased body weight gain and food consumption, myelopoiesis, bone marrow suppression after last infusion, and immunosuppressive effects including lower spleen and thymus weight. Higher glycosylated hemoglobin, lower hydroxybutyrate and acetoacetate observed in MD and HD rats. Target organs of toxicity include liver, reproductive organs (non-reversible), hematopoietic/ lymphoid system, heart, endocrine system (thyroid), glucose metabolism, skin and teeth. Effects on male rats reproductive organs included the testes (tubular atrophy), epididymides (spermatic debris and decreased weight), and prostate (reduced secretion and decreased weight). Effects on female rats reproductive organs included effects on ovaries (hemorrhagic cysts, and decreased weight), uterus (juvenile appearance and decreased weight), and a dose-related reduction in the numbers of female rats in estrus.

The frequency and severity of the signs decreased and/or disappeared as recovery progressed, with the exception of white teeth, repetitive chewing, wounds, palpable masses, alopecia, high-stepping gait, and ↓grip strength (CNS findings) which persisted until necropsy.

BAY 84-1236: Subacute Toxicity Study in Beagle Dogs (Once per Week i.v.-Infusion over 2 Weeks with 2 Week Recovery Period) / Study Report PH-33540

GLP- compliant toxicity study conducted in Beagle dogs with the copanlisib lyophilisate formulation (drug product batch N5250A01) at doses of 0, 0.2, 0.6 and 2.0 mg/kg (0, 4, 12, and 40 mg/m²) administered as intravenous infusion for 1 hour once weekly for 3 administrations

followed by a 2-week recovery period for control and MD dogs. Administration of copanlisib lyophilisate was tolerated with moderate signs of toxicity including impaired immune system and signs of local intolerance at the injections site. Transient decrease in blood pressure occurred at all doses before the third weekly dose, increased leucocytes/neutrophils at LD and higher, increased monocytes, atypical leucocytes, and erythrocyte sedimentation rates and the incidence of anisochromasia in HD, and increased values for β -hydroxybutyrate, AST, ALT, and CHOL with findings resolved at the end of the recovery period for MD. Target organs of toxicity included $\uparrow$ hematopoietic/ $\downarrow$ lymphoid system, immunosuppressive effects including lower spleen and thymus weight, stomach, reproductive organs (not reversible), and endocrine system (thyroid).

Additional Studies

- The binding of copanlisib to plasma proteins was low in all species investigated. The mean unbound fractions were 19.0% in male human, 42% in male dog and 42.5% in male rat plasma. For all species the plasma protein binding was independent of the concentration tested and there was no saturation of protein binding in the concentration range up to 10,000 $\mu\text{g/L}$. The ratio $C_{\text{Blood}}/C_{\text{Plasma}}$ of copanlisib was 2.06, 3.01 and 1.74 in rat, dog, and human blood, respectively, indicating copanlisib was mainly located in blood cells.
- The hemolytic potential of the test formulation of copanlisib (1 mg/mL) in 5 % Mannitol is low.
- Due to light absorption in the UV range, the phototoxic potential of copanlisib dihydrochloride was assessed in the in vitro 3T3 NRU (Neutral Red Uptake) phototoxicity test. Copanlisib was a non-phototoxic compound in this assay.

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Evaluation of BAY 84-1236 in a bacterial reverse mutation study using *Salmonella typhimurium* (Ames-Test) and *Escherichia coli* / Study Report A41390

Key Study Findings:

- Copanlisib did not increase the number of revertant colony counts of any tester strain with or without metabolic activation.

GLP compliance: Yes

Test system: *Salmonella typhimurium* (TA1535 and TA100 for detection of base-pair substitutions; TA1537, TA1538 and TA98 for detection of frame-shift mutations) and in the tryptophan-dependent strain *Escherichia coli* WP2uvrA (detects base-pair substitutions); up to 5000 $\mu\text{g/plate}$; +/- S9]

Study is valid: Yes

In Vitro Assays in Mammalian Cells

Forward cell mutation assay with BAY 84-1236 at the thymidine kinase locus (TK+/-) in mouse lymphoma L5178Y cells / Study Report A41591

Key Study Findings:

- Copanlisib did not increase the number of mutant colonies that exceeded the threshold of twice the mutant colony counts of the corresponding solvent controls, when tested up to the recommended level of cytotoxicity or to precipitating concentrations in the absence or presence of metabolic activation.

GLP compliance: Yes

Test system: mouse lymphoma cell line L5178Y; up to 15 µg/mL; +/-S9]

Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study on the mutagenic potential of BAY 84-1236 in the bone marrow micronucleus test after a single i.v. administration to male and female mice / Study Report A41145

Key Study Findings:

- Copanlisib showed neither a biologically relevant nor statistically significant increase ($p < 0.05$) in micronucleated PCE or NCE as compared to the vehicle control at either of the two sampling times (i.e., 24 or 48 hours after a single intravenous injection).

GLP compliance: Yes

Test system: Crl: NMRI, BR mice; single IV dose (0, 2.5, 5 or 10 mg/kg).

Study is valid: Yes

5.5.3. Carcinogenicity

Not conducted per ICH S6, ICH S1, and ICH S9.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Copanlisib-effects on reproductive organs occurred in rats and dogs. In male rats, effects were observed on the testes (germinal epithelial degeneration, decreased weight), epididymides (spermatic debris, decreased weight), prostate (reduced secretion, decreased weight) and decreased seminal vesicle weights. In female rats, effects were observed on the ovaries (hemorrhage, hemorrhagic cysts, and decreased weight) and uterus (atrophy, decreased weight). In dogs, findings were observed on the testes (tubular atrophy, decreased weight), epididymides (oligospermia/ cellular debris) and prostate (decreased weight). Based on findings in the rat and dog, copanlisib may affect male and female fertility in humans.

No other studies were conducted.

Embryo-Fetal Development

Pilot Prenatal Developmental Toxicity Study in Rats after Intravenous Administration / Study Report PH-36692

Key Study Findings

- Maternal toxicity mainly at HD (3 mg/kg), BW loss, decreased food consumption, small spleen, dark and hardened liver that resulted in no live fetuses.
- Increased post implantation loss, decreased number of live fetuses, decreased fetal weights, increased incidence of fetal malformations (mainly hydrocephalus internus, malformations of eyes, heart, major vessels, and skeletal system), and effects on skeletal deviations (retardations, variations) at the LD (0.75 mg/kg).
- Copanlisib produced maternal toxicity, developmental toxicity, and teratogenicity at approximately 12% of the recommended human dose.

Conducting laboratory and location: Bayer Pharma AG Toxicology Germany
GLP compliance: No

Methods

Dose and frequency of dosing: 0, 0.86, or 3.45 mg/kg (copanlisib dihydrochloride)
0, 0.75, or 3.0 mg/kg (0, 4.5, or 18 mg/m²) (copanlisib)
Daily from GD 6 to 17

Route of administration: 1 hour intravenous infusion

Formulation/Vehicle: Saline solution (0.9% NaCl pH 3.9 ± 0.2)

Species/Strain: Wistar rats / Hsd Cpb:WU

Number/Sex/Group: 7 inseminated females/group

Satellite groups: None

Study design: Pregnant rats were administered copanlisib dihydrochloride daily on GDs 6-17, with necropsy/cesarean on GD 21

Deviation from study protocol affecting interpretation of results: No

Observations and Results

Parameters	Major findings
Mortality	None
Clinical Signs	LD: few incidences of pale ears, and reddish vaginal discharge. HD: ↑ incidences of sunken flanks, pale ears, piloerection, hypoactivity, high-stepping gait (CNS), water consumption, urination and reddish vaginal discharge.

Body Weight gain	Percent of BW gain compared to control LD: BW gain GDs 6-17 ↓68.6% BW gain GDs 6-21 ↓59.6% Corrected BW gain GDs 6-21 ↓29.4% HD: BW loss in all females, none with viable fetuses, BW gain not calculated ↓ BW gain corresponded with ↓mean food consumption																																																												
Necropsy findings Cesarean Section Data	HD: spleen (↓size), liver (hardened, dark reddish area in the tissue), and hind limb (edema). <table><tr><th colspan="4">Summary of Laparohysterectomy Evaluations and Intrauterine Development in Rats</th></tr><tr><th>Copanlisib (mg/kg/day)</th><th>0</th><th>0.75</th><th>3.0</th></tr><tr><td>Number of females tested</td><td>7</td><td>7</td><td>7</td></tr><tr><td>Number of females pregnant</td><td>7</td><td>7</td><td>5</td></tr><tr><td>Number of females with implantations</td><td>5</td><td>5</td><td>2</td></tr><tr><td>Females with viable fetuses</td><td>5</td><td>4</td><td>0</td></tr><tr><td>Dams with any resorptions</td><td>0</td><td>1</td><td>2</td></tr><tr><td>Mean number Corpora lutea</td><td>13.6</td><td>14.0</td><td>12.0</td></tr><tr><td>Mean number of Implantations</td><td>13.4</td><td>13.8</td><td>12.0</td></tr><tr><td>Mean Pre-implantation loss</td><td>0.2</td><td>0.2</td><td>0.0</td></tr><tr><td>Mean placental weight (g)</td><td>0.56</td><td>0.41**</td><td>NC</td></tr><tr><td>Number of fetuses/dam</td><td>12.8</td><td>3.5**</td><td>NC</td></tr><tr><td>Post-implantation loss</td><td>0.6</td><td>11.5*</td><td>NC</td></tr><tr><td>Percent males</td><td>55.8</td><td>53.6</td><td>NC</td></tr><tr><td>Mean fetal weight (g)</td><td>4.8</td><td>2.8</td><td>NC</td></tr></table> *= p≤0.05 **= p≤0.01 NC= not calculated	Summary of Laparohysterectomy Evaluations and Intrauterine Development in Rats				Copanlisib (mg/kg/day)	0	0.75	3.0	Number of females tested	7	7	7	Number of females pregnant	7	7	5	Number of females with implantations	5	5	2	Females with viable fetuses	5	4	0	Dams with any resorptions	0	1	2	Mean number Corpora lutea	13.6	14.0	12.0	Mean number of Implantations	13.4	13.8	12.0	Mean Pre-implantation loss	0.2	0.2	0.0	Mean placental weight (g)	0.56	0.41**	NC	Number of fetuses/dam	12.8	3.5**	NC	Post-implantation loss	0.6	11.5*	NC	Percent males	55.8	53.6	NC	Mean fetal weight (g)	4.8	2.8	NC
Summary of Laparohysterectomy Evaluations and Intrauterine Development in Rats																																																													
Copanlisib (mg/kg/day)	0	0.75	3.0																																																										
Number of females tested	7	7	7																																																										
Number of females pregnant	7	7	5																																																										
Number of females with implantations	5	5	2																																																										
Females with viable fetuses	5	4	0																																																										
Dams with any resorptions	0	1	2																																																										
Mean number Corpora lutea	13.6	14.0	12.0																																																										
Mean number of Implantations	13.4	13.8	12.0																																																										
Mean Pre-implantation loss	0.2	0.2	0.0																																																										
Mean placental weight (g)	0.56	0.41**	NC																																																										
Number of fetuses/dam	12.8	3.5**	NC																																																										
Post-implantation loss	0.6	11.5*	NC																																																										
Percent males	55.8	53.6	NC																																																										
Mean fetal weight (g)	4.8	2.8	NC																																																										
Necropsy findings Offspring	<table><tr><th colspan="4">Summary of Fetal Malformations</th></tr><tr><th>Copanlisib (mg/kg/day)</th><th>0</th><th>0.75</th><th>3.0</th></tr><tr><td>tail shortened and kinked</td><td>--</td><td>4**(2)</td><td>NC</td></tr><tr><td>tail shortened</td><td>--</td><td>2(2)</td><td>NC</td></tr><tr><td>multiple malformations including hydrocephalus internus, eye ball(s) reduced in size unilateral or bilateral, ventricular septal defect of the heart with/without esophagus lying on the right side and/or malformation of major vessels</td><td>--</td><td>5(2)</td><td>NC</td></tr><tr><td>dysplastic forelimb bones unilateral or bilateral with/without malformation of</td><td>--</td><td>4(3)</td><td>NC</td></tr></table>	Summary of Fetal Malformations				Copanlisib (mg/kg/day)	0	0.75	3.0	tail shortened and kinked	--	4**(2)	NC	tail shortened	--	2(2)	NC	multiple malformations including hydrocephalus internus, eye ball(s) reduced in size unilateral or bilateral, ventricular septal defect of the heart with/without esophagus lying on the right side and/or malformation of major vessels	--	5(2)	NC	dysplastic forelimb bones unilateral or bilateral with/without malformation of	--	4(3)	NC																																				
Summary of Fetal Malformations																																																													
Copanlisib (mg/kg/day)	0	0.75	3.0																																																										
tail shortened and kinked	--	4**(2)	NC																																																										
tail shortened	--	2(2)	NC																																																										
multiple malformations including hydrocephalus internus, eye ball(s) reduced in size unilateral or bilateral, ventricular septal defect of the heart with/without esophagus lying on the right side and/or malformation of major vessels	--	5(2)	NC																																																										
dysplastic forelimb bones unilateral or bilateral with/without malformation of	--	4(3)	NC																																																										

ribs, vertebrae, pelvis shift, and eye hole(s) reduced in size unilateral or bilateral			
malformation of vertebrae and pelvis shift with/without eye hole(s) reduced in size unilateral or bilateral	1	2(1)	NC
head of 1st rib missing unilateral, eyeholes reduced in size bilateral with/without one supernumerary vertebra pelvis shift	--	2(2)	NC
pelvis shift	--	1	
number of fetuses per group	64	14	0
number of fetuses with malformations	1	14**	NC
malformed fetuses per group (%)	1.6	100.0	NC
number of litters per group	5	4	0
number of litters with malformations	1	4	NC
malformed litters per group (%)	20.0	100.0	NC

**= p≤0.01 (X) number of litters affected NC= not calculated

Summary of Fetal External and Visceral Deviations			
Copanlisib (mg/kg/day)	0	0.75	3.0
umbilical cord shortened	--	4**(1)	NC
domed head	--	11**(4)*	NC
eye rudiment flat	--	12**(4)*	NC
innominate artery reduced in length	--	1	NC

*= p≤0.05 **= p≤0.01 NC= not calculated

LD fetal skeletal retardations and variations included retarded ossification at the 1st distal phalanges of digits bilateral, 2nd-4th proximal phalanges of digits bilateral, 5th metacarpals bilateral, 1st and 5th distal phalanges of toes unilateral, 1st metatarsals bilateral, 1st-6th sternebra, 6th cervical vertebral arches right, 2nd-7th cervical vertebral bodies, 1st thoracic vertebral bodies, 4th sacral vertebral arches bilateral, 3rd caudal vertebral arches bilateral, 5th-7th caudal vertebral bodies, nasal bones bilateral, frontal bones bilateral, and supraoccipital bones. Retarded ossification occurred in several of these localizations, when calculation was done on a litter basis.

Copanlisib-related effect on skeletal deviations (retardations, variations) is based on findings of retarded

	ossification of various bones and increased incidences of fused sternebra, wavy ribs, 14 th ribs, and enlarged fontanelle at the LD.
--	---

LD: low dose; MD: mid dose; HD: high dose

5.5.5. Other Toxicology Studies

Quantitative Whole-body Autoradiography. Distribution of Radioactivity and Elimination from Blood, Organs, Tissues, and Fetuses after Single Intravenous Administration of [¹⁴C]BAY 80-6946 to Pregnant Rats / Study Report PH-38386

In a non-GLP-compliant toxicology study, [¹⁴C]copanlisib was administered as a single intravenous bolus of 1 mg/kg to pregnant albino Wistar rats on GD 18. The radioactivity of [¹⁴C]copanlisib was rapidly and thoroughly distributed to maternal and fetal organs and tissues, with maximum concentrations mostly reached at the end of infusion (1 hour). Maternal organs showed higher maximum levels than blood (173 µg-eq/L), with the exception of brain and amniotic fluid which were significantly lower. Fetal maximum blood and organ concentrations were between 73 and 494 µg-eq/L with highest levels for liver and kidneys and the lowest level for fetal blood. Fetal maximum organ concentrations were lower than the concentrations in the analogous maternal organs, with the exception of brain. Based on AUC, all maternal organs and tissues exceeded the maternal blood exposure with the exception of brain suggesting a high tissue affinity of copanlisib-associated radioactivity. The highest exposure was observed for maternal spleen which was 406-fold higher than blood (970 µg-eq·h/L), for kidney cortex and outer medulla (more than 100-fold higher), adrenals and submandibular glands (50 to 60-fold higher), and liver (31-fold higher). Exceptions were amniotic fluid and brain which reached approximately 20% of blood exposure. This suggests a moderate blood-brain penetration of radioactivity in the dam. The AUCs for amnion were 30-fold the maternal blood AUCs, for mammary glands 23-fold, for uterus 12-fold, for ovaries 13-fold and for the placenta 4-fold. The relatively high exposure in mammary glands gives evidence for secretion of the drug and/or metabolites with the milk. The highest exposure of radioactivity in the fetuses was found for the fetal liver, kidneys and the meconium, likely due to its excretory functions. The AUC ratios fetal blood/maternal blood and fetal tissue/maternal blood were 0.59 and 2.1, respectively. This indicated an overall moderate placental transfer of [¹⁴C]copanlisib and/or its labeled metabolites. In contrast to the dam, a high fetal blood-brain penetration had occurred, likely due to the incompletely developed function of the fetal blood-brain barrier. The estimated terminal elimination half-lives were mostly between 6 hours for blood and 19 hours for spleen and fetuses as determined from elimination data between 4 and 48 hours after the start of infusion.

BAY 80-6946: Secretion of Radioactivity into Milk of Lactating Rats after Single Intravenous Administration of [¹⁴C]BAY 80-6946 / Study Report PH-38299

In a non-GLP-compliant toxicology study, [¹⁴C]copanlisib was administered as single intravenous bolus of 1 mg/kg to lactating Wistar rats. Blood and milk samples were collected after 1, 2, 4, 8, 24 and 32 hours after dosing. [¹⁴C]copanlisib-derived radioactivity was secreted into the milk of

NDA/BLA Multi-disciplinary Review and Evaluation NDA 209936
Aliqopa (copanlisib)

lactating rats to a low extent. The estimated amount of radioactivity excreted with milk was 1.7% of the dose within 32 hours after administration. The milk/plasma ratio for AUC was 25.3.

Pedro Del Valle, Ph.D.
Primary Reviewer

Christopher Sheth, Ph.D.
Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

Copanlisib (ALIQOPA) is a PI3K inhibitor, which predominantly targets PI3K- α and PI3K- δ isoforms. The proposed indication is for the treatment of patients with relapsed (b) (4) follicular lymphoma who have received at least two prior therapies. The recommended dosing regimen is 60 mg administered as a 1-hour intravenous infusion on Days 1, 8, and 15 of a 28-day treatment cycle on an intermittent schedule (three weeks on and one week off).

The recommended dosing regimen was selected based on results of a phase 1 dose escalation study, which determined 0.8 mg/kg as the maximum tolerated dose. The 0.8 mg/kg regimen was further evaluated in Part A of the pivotal phase 2 study (16349) and shown to have acceptable safety and efficacy profiles. The fixed dose of 60 mg (equivalent of the MTD dose) regimen was then evaluated in Part B of Study 16349 in patients with FL. The primary efficacy endpoint of objective response rate was achieved by 58.7% of patients that include complete response achieved by 14.4% of patients (see Table 14). The most common treatment-emergent adverse events (TEAE) in the pivotal trial were hyperglycemia (49.2%), diarrhea (37.3%), hypertension (34.1%), fatigue (27.8%), nausea (26.2%), neutropenia (23.0%) and pyrexia (26.2%).

The proposed dosing regimen is efficacious and has manageable safety profile. A positive but not statistically significant exposure-response (ER) relationship is observed for ORR, all grade and Grade 3 or higher TEAEs, including hyperglycemia. The incidence of hyperglycemia and hypertension is transient and drops significantly after the first cycle of treatment. Although 72% of patients experienced dose interruption or delay and 25% of patients experienced a dose reduction, 77% of patients were on the recommended dosing regimen at the time of primary analysis of the pivotal trial. Instructions to adequately manage (b) (4) and dose reductions due to adverse reactions are included in the labeling of ALIQOPA. There is no concern of QT prolongation at the recommended dosing regimen.

Recommendations

The Office of Clinical Pharmacology has reviewed the information submitted in NDA 209936. This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal and Supportive evidence of effectiveness	The primary evidence of effectiveness comes from Part B of phase 2 Study 16349.

Review Issue	Recommendations and Comments
General dosing instructions	The proposed copanlisib dosing regimen of 60 mg with intermittent schedule is effective and has a manageable safety profile. • There is a positive but not statistically significant relationship between exposure and efficacy or safety (all grade as well as grade 3/4 hyperglycemia, hypertension, diarrhea and infection). These findings support the selection of proposed dosing regimen along with the dose modification and toxicity management strategy outlined in the label. • There were 77% of patients on the recommended dosing regimen at the time of primary analysis in the pivotal trial, suggesting that the dosing regimen is tolerated. Although 72% patients had a dose interruption or delay and 25% patients had a dose reduction in the pivotal trial, among the total of 2295 planned dosing records, dose interruption or delay and dose reduction accounted for only 8.1% and 1.4% of the total dose records, respectively. • The incidence of most common TEAE hyperglycemia and hypertension is transient and drops significantly after the first cycle of treatment.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• No dose adjustment is needed for patients with mild hepatic impairment. The PK of copanlisib in patients with moderate and severe hepatic impairment is unknown. See Post-Marketing Requirements and Commitments for PMR regarding hepatic impairment. • No dose adjustment is needed for patients with mild and moderate renal impairment. The PK of copanlisib in patients with severe renal impairment is unknown. See Post-Marketing Requirements and Commitments for PMR regarding severe renal impairment. • A dose reduction to 45 mg is recommended for patients concomitantly taking strong CYP3A inhibitors. • Avoid concomitant use with strong CYP3A inducers. • Dose adjustment recommendation for concomitant medications that are sensitive substrate of transporter multidrug and toxin extrusion protein 2 (MATE2-K) cannot be provided as the drug-drug interaction (DDI) potential cannot be ruled out based on available data. See Post-Marketing Requirements and Commitments for PMR regarding DDI assessment.
Labeling	Generally acceptable. The review team has specific content and formatting change recommendations.
Bridge between the to-be-marketed and clinical trial formulations	Not applicable. The to-be-marketed formulation was used in the clinical trials.

Post-Marketing Requirements and Commitments

PMR or PMC	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
PMR	Copanlisib dose in patients with moderate and severe hepatic impairment	Hepatic metabolism and biliary excretion plays a major role in the elimination of copanlisib and its metabolites. There is no PK data to determine copanlisib dose for patients with moderate to severe hepatic impairment. The clinical study can provide understanding for copanlisib dose adjustment for these patient subpopulations.	Amend and complete on-going PK Study 18041 to determine an appropriate dose of copanlisib in patients with moderate to severe hepatic impairment.
PMR	Copanlisib dose in patients with severe renal impairment	Severe renal impairment can affect the renal clearance of copanlisib; it may also affect the expression of hepatic metabolism enzymes and transporters. Therefore, the biliary excretion of copanlisib and its metabolites may also be affected. A subpopulation of patients with FL is expected to have severe renal impairment (eGFR < 30 mL/min/1.73m ²). There is no PK data to determine copanlisib dose for patients with severe renal impairment. The clinical study can provide understanding for copanlisib dose adjustment for this patient subpopulation.	Complete ongoing PK Study 18041 to determine an appropriate dose of copanlisib in patients with severe renal impairment.

PMR or PMC	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
PMR	Effect on PK of MATE2-K substrates	There is a DDI potential between copanlisib and substrates of renal transporter MATE2-K at recommended dosing regimen. Several concomitant medications are substrates of MATE2-K, such as metformin and cisplatin. The clinical study can provide dose adjustment recommendation for such concomitant medications.	Conduct a clinical study to assess the effect of copanlisib dosing on PK of MATE2-K substrate metformin.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Copanlisib is a PI3K- α and PI3K- δ inhibitor. The drug exhibits dose-proportional increases in exposure (C_{max} and AUC) across the dose range of 0.1 mg/kg to 1.2 mg/kg following both single dose and repeated doses. Steady-state is achieved at second week (Cycle 1 Day 15) and accumulation of copanlisib is minimal with the weekly intermittent dosing schedule (geometric mean accumulation ratio is 1.1). See section 13.4.2 for details of clinical PK.

Distribution

Based on non-compartmental analysis (NCA) of plasma concentration after IV infusion, the geometric mean volume of distribution (V_z) is 871 L (range: 423 to 2150 L, CV: 47.4%). Plasma protein binding is 84.2% in human plasma. The blood-to-plasma ratio is 1.7.

Elimination

The geometric mean clearance (CL) based on NCA is 17.9 L/hour (range: 7.3 to 51.4 L/hour; SD: 8.5 L/hour). The geometric mean terminal elimination half-life is 39.1 hours (range: 14.6 to 82.4 hours; SD: 15.0 hours).

Metabolism: Metabolism of copanlisib is mediated by CYP3A4/5 (> 90%) and to a minor extent by CYP1A1 (< 10%) in vitro. Following IV administration of a single 12 mg dose of radio-labeled copanlisib in the human mass balance Study 16353, copanlisib was the major circulating drug-derived entity (84% of the AUC) in plasma. Although copanlisib forms an active metabolite M1, this metabolite is not considered to have clinically relevant contribution to both efficacy and safety as systemic exposure to M1 was only about 5% of the total radioactivity AUC. Therefore, data related to M1 are not further presented in this review.

Excretion: Following a single IV dose of 12 mg in Study 16353 with mean recovery of 86%, 64% and 22% of the total administered radioactivity excreted into feces and urine, respectively. The unchanged parent drug accounted for 30% and 15% in feces and urine, respectively. Metabolite M1 was found to be 6% and 4% of the dose in feces and urine, respectively.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant proposes a dosing regimen of 60 mg administered as a 1-hour IV infusion on Days 1, 8, and 15 of a 28-day treatment cycle on an intermittent schedule (three weeks on/ one week off). Phase 1 Study 12871 identified a MTD dose of 0.8 mg/kg with the same intermittent schedule in patients with advanced solid tumor. Part B of Phase 2 Study 16349 evaluated the efficacy and safety of copanlisib at the dose of 0.8 mg/kg (initially in 12 patients with this starting dose) and later at the fixed dosing regimen of 60 mg in patients with relapsed FL (N=104). The proposed dosing regimen is effective and achieves an ORR of 59% with a median duration of response (DOR) of 12.2 months (370 days). Subgroup analysis shows that ORR in 12 patients who started with 0.8 mg/kg is similar (58.3%).

The results of the ER analysis for efficacy suggest that efficacy reaches a plateau at the recommended dosing regimen. Logistic regression analysis showed a positive but not statistically significant correlation between copanlisib exposure (average plasma concentration, C_{ave} , or AUC) and ORR (see Figure 3 in section 6.3.2 and Figure 28 in section 13.4.3). Both DOR and progression-free survival (PFS) has no correlation with C_{ave} based on Kaplan-Meier graphs stratified by quartiles of C_{ave} until progression (see Figure 4 in section 6.3.2).

The recommended dosing regimen has a manageable safety profile. There is a positive but not significant ER relationship between exposure and Grade 3 or higher AEs, including hyperglycemia and hypertension (see Figure 6 and Figure 7 in section 6.3.2). The most frequent TEAEs including hyperglycemia and hypertension appear to be transient (see Figure 8 in section 6.3.2). In the pivotal trial, at the time of primary efficacy analysis to support the application, 77% of patients were on the recommended dosing regimen. A total of 23% patients were at a dose smaller than scheduled, with 18% at 45-51 mg and 5% at 30 mg (see Table 55 and Figure 36 in section 13.4.3).

Therapeutic Individualization

Specific Populations

Patients with hepatic impairment: No dose adjustment is necessary in patients with mild hepatic impairment based on population PK analysis. Due to the lack of data, no dose recommendation can be provided for patients with moderate or severe hepatic impairment.

Patients with renal impairment: No dose adjustment is needed in patients with mild or moderate renal impairment based on population PK analysis. The number of patients with severe renal impairment (n = 2) is too small to draw a conclusion for this category and dose recommendation for this group of patients cannot be provided.

Drug-Drug Interactions

CYP3A inhibitor: A dose reduction to 45 mg is recommended for patients taking strong CYP3A inhibitors with ALIQOPA. Concomitant administration of strong CYP3A inhibitor itraconazole increased copanlisib AUC by 53% (or 1.53-fold) although there was no substantial change in C_{max} after a single IV dose of 60 mg.

CYP3A inducer: The concomitant use of strong CYP3A inducers with ALIQOPA should be avoided. Coadministration of strong CYP3A inducer rifampin decreased the AUC of copanlisib by 63%.

MATE2-K Substrate: Dose adjustment recommendation for concomitant medications that are sensitive substrate of transporter MATE2-K cannot be provided as the DDI potential cannot be ruled out based on available data.

Outstanding Issues

The Applicant has an ongoing clinical Study 18041 to assess the effect of moderate hepatic impairment and severe renal impairment on PK of copanlisib. To address the remaining uncertainty in dose recommendation, we have issued three PMRs to study (1) effect of severe renal impairment, (2) moderate and severe hepatic impairment on PK of copanlisib; and (3) to assess the DDI risk with substrate of MATE2-K. Refer to Post-Marketing Requirements and Commitments for detail.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The general overview of copanlisib ADME and clinical PK information are presented in the table below.

Pharmacology	
Mechanism of Action	Copanlisib is an inhibitor of PI3K with predominant PI3K- α (IC ₅₀ = 0.5 nM) and PI3K- δ (IC ₅₀ = 0.7 nM) inhibitory activity.
Active Moieties	Copanlisib and its active metabolite M1 which has no clinically relevant contribution to efficacy and safety given its 5% exposure (AUC) relative to the parent in plasma.
QT Prolongation	No clinical concern as the predicted upper boundary of the 90% confidence interval of Δ QTcI was 0.99 ms at supra-therapeutic exposure.

NDA/BLA Multi-disciplinary Review and Evaluation NDA 209936
Aliqopa (copanlisib)

General Information	
Bioanalysis	Copanlisib and its active metabolite M1 were measured using validated LC/MS/MS methods. A summary of the method validation reports is included as an appendix (section 13.4.1).
Healthy Volunteers vs. Patients	Copanlisib exposure is considered comparable between healthy volunteers and patients with solid tumor based on the observed means and the ranges of AUC and C _{max} . Following a single IV 12 mg dose, the geometric mean (range) of C _{max} and AUC in healthy subjects in the mass balance study were 44 (26 to 63) µg/L and 442 (269 to 769) h·µg/L, respectively. At the same dose, the geometric mean C _{max} and AUC in patients with solid tumor were 86 (47 to 290) µg/L and 537 (286 to 747) h·µg/L, respectively.
Drug exposure at steady state following the therapeutic dosing regimen	At 0.8 mg/kg (equivalent to 60 mg fixed dose), the geometric means (CV%) of C _{max} and AUC ₀₋₂₅ were 463 (64.4%) µg/L and 1570 (38.4%) h·µg/L, respectively, on Cycle 1 day 15 based on intensive PK data from 36 patients of Study 12871.
Minimal effective dose or exposure	Not available. Copanlisib 60 mg was the only dose regimen tested in patients with FL.
Maximal tolerated dose or exposure	Copanlisib 0.8 mg/kg administered on Days 1, 8, and 15 of a 28-day cycles (3 weeks on /1 week off) as a monotherapy was determined to be the MTD in patients with advanced solid tumors in Study 12871.
Dose Proportionality	Copanlisib showed dose-proportional increase in both C _{max} and AUC across the dose range of 0.1 to 1.2 mg/kg. See section 13.4.2 for detail.
Accumulation	Copanlisib has minimal accumulation with the weekly dosing schedule. The mean accumulation ratio was 1.1 (90% CI: 0.98 to 1.26).
Variability	At 0.8 mg/kg or 60 mg dose, the inter-subject variability of copanlisib exposure was moderate to high with a CV of 65.4% for C _{max} and 40.8% for AUC ₍₀₋₂₅₎ (n = 64).
Absorption	
Substrate transporter systems [in vitro]	A substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).
Distribution	
Volume of Distribution	The geometric mean of volume of distribution was 871 L (range: 423 to 2150 L; SD: 479 L) based on non-compartmental analysis.
Plasma Protein Binding	The in vitro human plasma protein binding of copanlisib is 84.2%. Albumin is the main binding protein.
Blood to Plasma Ratio	The mean blood-to-plasma ratio is 1.7 for copanlisib.
Elimination	
Half-life	The geometric mean terminal elimination half-life of copanlisib was 39.1 hours (range: 14.6 to 82.4 hours; SD: 15.0 hours).
Clearance	The geometric mean clearance of copanlisib was 17.9 L/hour (range: 7.3 to 51.4 L/hour; SD: 8.5 L/hour)
Metabolism	
Primary metabolic pathway(s)	In vitro, primarily by CYP 3A4/5 (~90%) and to a lesser extent CYP1A1 (~10%). In vivo, copanlisib is a victim of CYP3A modulators.
Inhibitor/Inducer	In vitro, copanlisib and its metabolite do not inhibit major human CYP450 enzymes. In vitro, copanlisib inhibited P-gp (IC ₅₀ =7 µM), breast cancer resistance protein (IC ₅₀ = 11.5 µM), and multidrug and toxin extrusion protein 1 (MATE1, IC ₅₀ =10.8 µM), and MATE2-K (IC ₅₀ =0.09 µM).
Excretion	

Primary excretion pathways (% dose) ±SD	In a human mass balance Study 16353 with mean total radioactivity recovery of 86%, radioactivity recoveries in feces and urine were 64.2% (30% unchanged copanlisib) and 21.7% (15% unchanged copanlisib), respectively.
--	--

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. In the expansion cohort of phase 1 Study 12871, 9 patients with NHL (6 FL and 3 DLBCL) were treated with copanlisib at MTD of 0.8 mg/kg. Objective responses were observed in 7 out of 9 NHL patients including all 6 FL patients, 2 of which had CR based on independent blinded review. In Part A of phase 2 Study 16349, objective responses were observed in 14 out of 32 (44%) patients with indolent forms of NHL or chronic lymphocytic leukemia at dose of 0.8 mg/kg.

Based on the preliminary efficacy results and dose-safety analysis (see Figure 5 in next section) from these two early studies, the Applicant selected the dosing regimen of 0.8 mg/kg for Part B of the pivotal Study 16349. The dosing regimen was then switched to a fixed dose of 60 mg after the Applicant's population PK analysis showed that body weight was not a significant covariate of copanlisib PK.

The ORR per independent assessment is 59% (95% confidence interval [CI]: 49%, 68%) in Part B of Study 16349 with copanlisib treatment at 60 mg or 0.8 mg/kg (N=104). Subgroup analysis shows that ORR in these 12 patients started with 0.8 mg/kg dose is similar (58%). Evaluations of ER using logistic regression analysis show that there is a positive but not statistically significant relationship between steady state copanlisib exposure (Cave) and ORR (see Figure 3). In addition, there is no systematic difference in the probability for the duration of PFS observable among the quartile groups of copanlisib exposure (Cave, see Figure 4). The lack of significant ER relationship in efficacy (ORR and PFS) suggests that maximum effectiveness is achieved in majority of subjects. Therefore, the ER analysis results support the efficacy of the proposed dosing regimen for copanlisib in patients with FL.

Figure 3 Logistic Regression of ORR vs Average Exposure of Copanlisib in Patients with FL

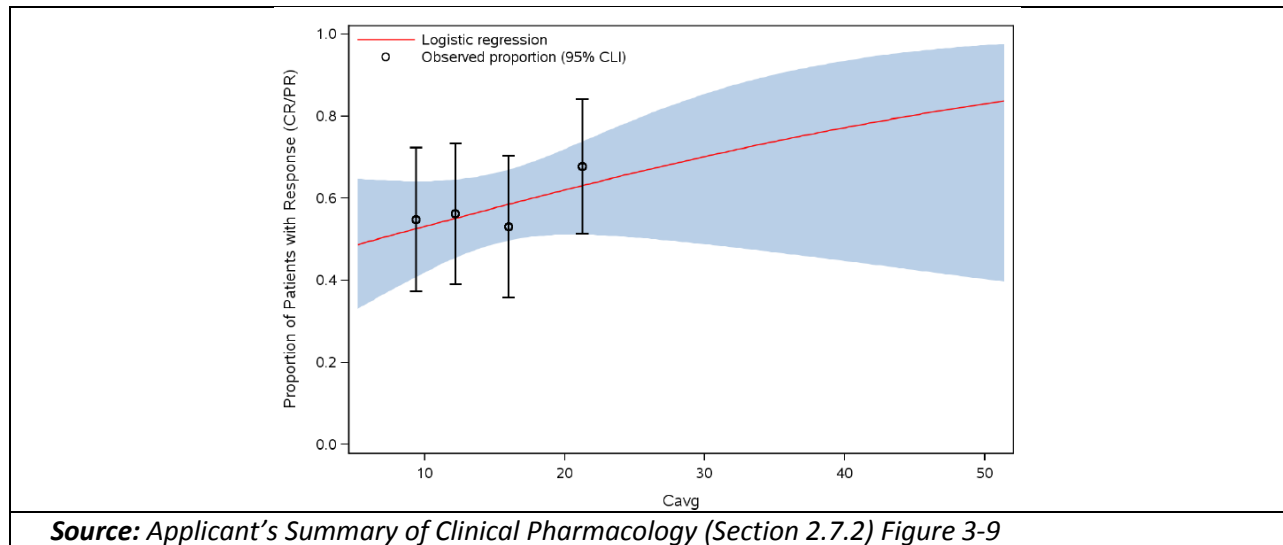
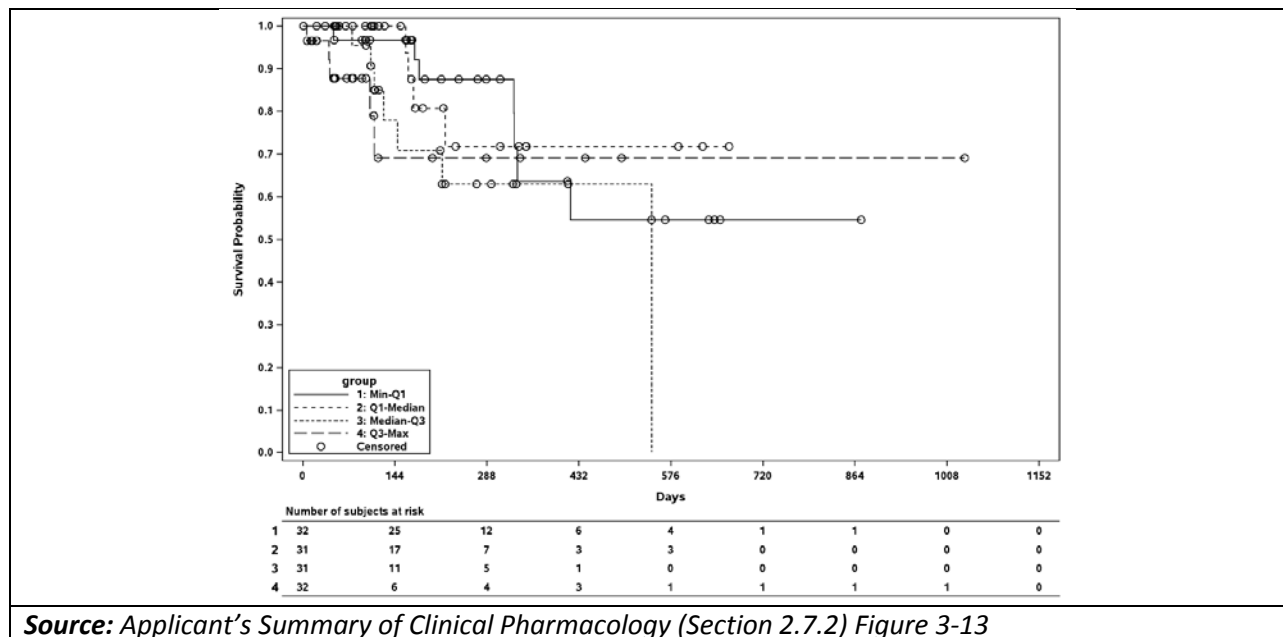


Figure 4 Kaplan-Meier Curves for Progression-Free Survival in Patients with FL

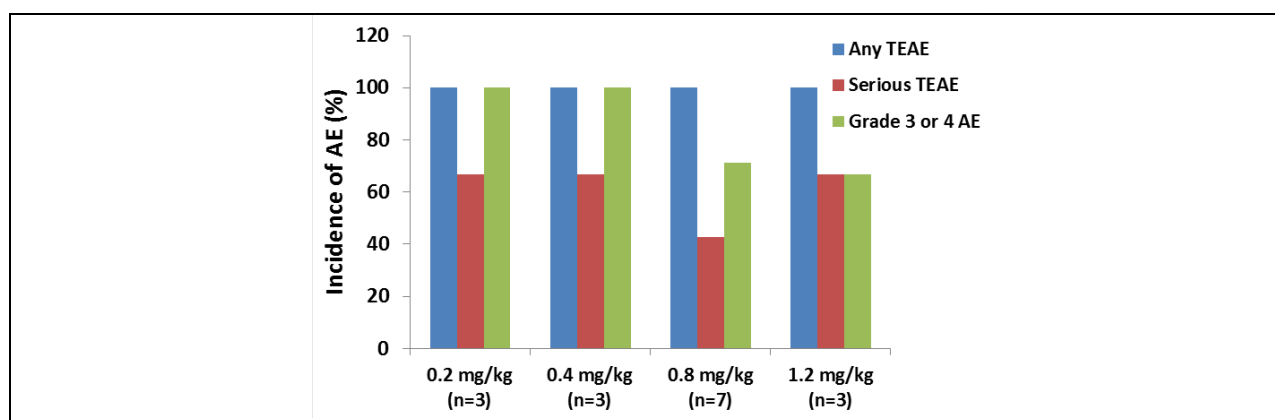


Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The safety profile of the proposed dosing regimen is acceptable.

In the dose-escalation cohort of phase 1 Study 12871, the dose of 0.8 mg/kg with intermittent schedule was determined as the MTD with similar safety profile compared to the lower dose levels (see Figure 5). Therefore, this dosing regimen was further evaluated for efficacy and safety in phase 2 Study 16349.

Figure 5 Summary of Adverse Events by Dose Levels in Phase 1 Study 12871



Source: FDA reviewer's analysis based on Applicant's study report PH-37433 Table 10-3

Part B of Study 16349 results show that copanlisib treatment has acceptable tolerability in patients with FL. There is no statistically significant ER relationship within the tested concentration range between steady state exposure (C_{ave}, C_{max} or AUC) and AE of interest (any grade or grade 3 above), including hyperglycemia (see Figure 6), hypertension (see Figure 7).

Figure 6 Plot of Logistic Regression for Hyperglycemia - Grade ≥ 3 versus Cmax or Cave

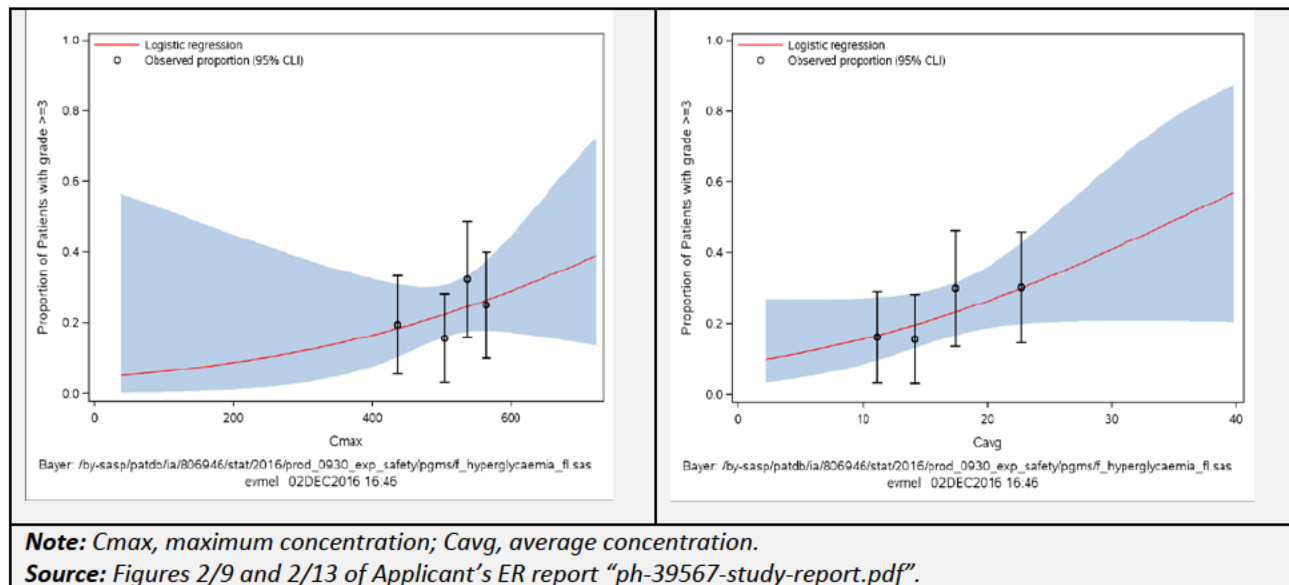
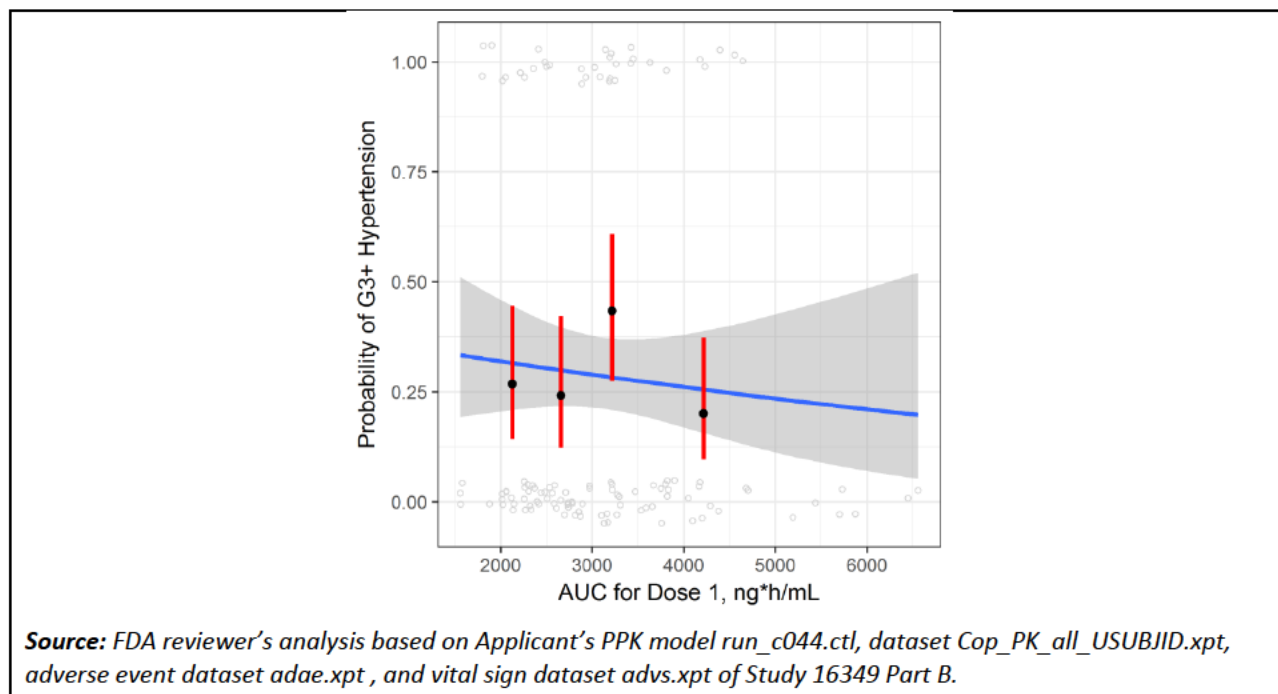
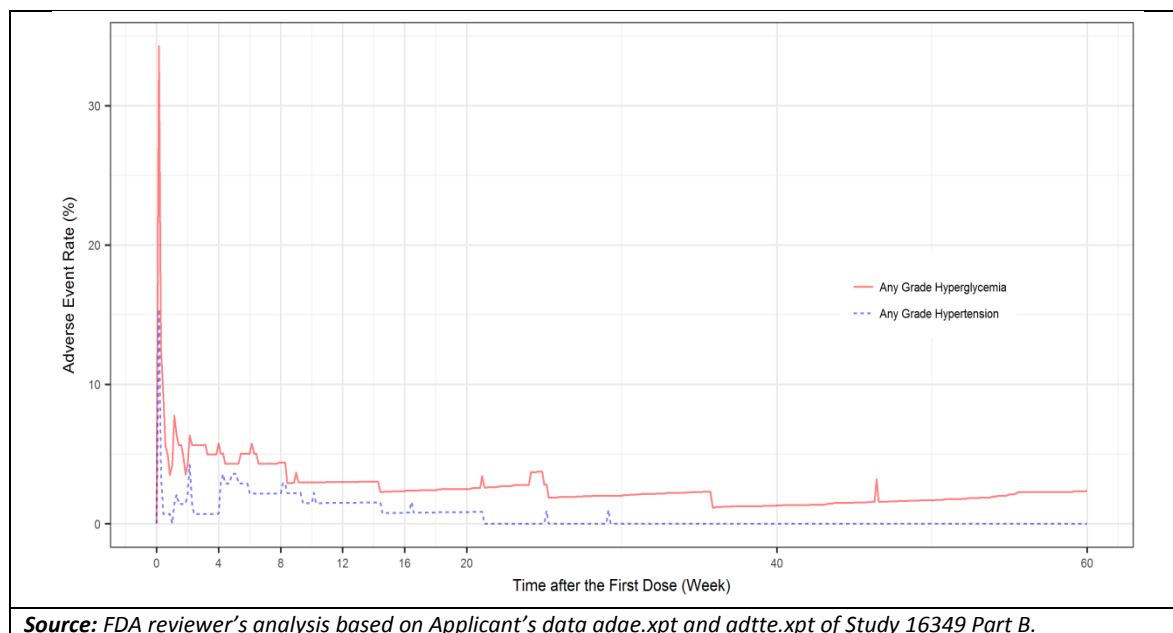


Figure 7 Plot of Logistic Regression for Hypertension - Grade ≥ 3 versus AUC



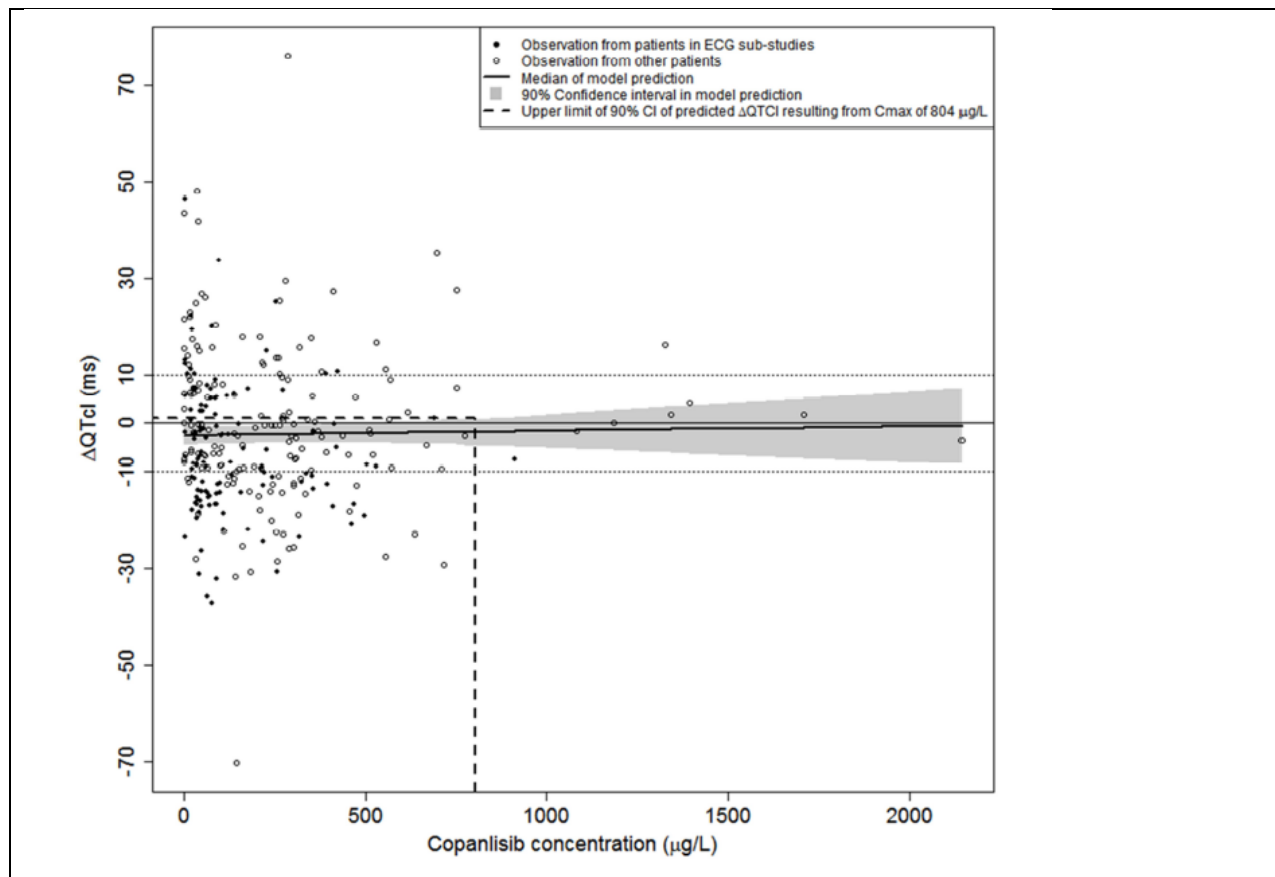
The prevalence of hyperglycemia and hypertension is transient. For example, after the first copanlisib dose, the rate of Grade 3 or higher hyperglycemia was about 25% on Study Day 1, and decreased to about 2.6% on Study Day 7. After the second dose, the rate rebounded to about 7%, then decreased to about 2.6% again, and remained 1-5% for the following doses (see Figure 8).

Figure 8 The Time Course of Hyperglycemia and Hypertension Rates for Study 16349 Part B (N=143)



In addition, there is no QT prolongation risk concern as the predicted upper boundary of the 90% confidence interval of ΔQT_{cl} is 0.99 ms at supra-therapeutic exposure (see Figure 9).

Figure 9 Plot of Copanlisib Concentration versus Observed and Predicted QTcI with 90% CI



Source: Applicant's Summary of Clinical Pharmacology (Section 2.7.2) Figure 3-17

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

Yes. Copanlisib is primarily metabolized by liver enzymes. Copanlisib and its metabolites are mainly eliminated through biliary excretion. In a human mass balance Study 16353 with mean total radioactivity recovery of 86%, radioactivity recoveries in feces and urine were 64.2% (30% unchanged copanlisib) and 21.7% (15% unchanged copanlisib), respectively.

Hepatic Impairment: In a population pharmacokinetic analysis that included 251 patients with normal hepatic function and 47 patients with mild hepatic impairment, mild hepatic impairment has no effect on the exposure (CL) of copanlisib (see Figure 23 in Section 13.4.3) and dose adjustment is not necessary. However, effect of moderate and severe hepatic impairment on PK of copanlisib has not been studied. Dose recommendation for these subpopulations cannot be provided. A dedicated hepatic impairment PMR study is required to provide dose recommendation in patients with moderate and severe hepatic impairment.

Renal Impairment: Based on a population PK analysis that included 125 patients with normal renal function, 113 patients with mild renal impairment ($60 \text{ mL/min/1.73m}^2 \leq \text{eGFR} < 90 \text{ mL/min/1.73m}^2$) and 58 patients with moderate renal impairment ($30 \text{ mL/min/1.73m}^2 \leq \text{eGFR} < 60 \text{ mL/min/1.73m}^2$), mild and moderate renal impairment has no effect on the exposure (CL) of copanlisib (see Figure 23 in Section 13.4.3) and dose adjustment is not necessary. The pharmacokinetics of copanlisib in patients with severe renal impairment ($\text{eGFR} < 30 \text{ mL/min/1.73m}^2$) is unknown (See Post-Marketing Requirements and Commitments for a PMR study for patients with severe renal impairment).

Other intrinsic factors: There are no clinically relevant effects of age (20 to 90 years), body weight (41 to 130 kg), gender, or race (White, Asian, Hispanic and Black) on the systemic exposure of copanlisib (see Figure 22 in Section 13.4.3) that would require a dose adjustment based on population PK analysis.

The Applicant conducted a retrospective exploratory gene expression analysis using archival baseline tumor samples from 24 patients in study 16349 Part A. Response rate and PFS were utilized as clinical outcome variables. Histologies included follicular lymphoma (n=10), marginal zone lymphoma (n=2), mantle cell lymphoma (n=2), diffuse large B-cell lymphoma (n=5), transformed indolent lymphoma (n=2) and chronic lymphocytic leukemia (n=3). Results obtained with the whole subset (N=24; included 3 CR, 5 PR, 11 SD, and 5 PD) suggested that copanlisib was active in tumors with up-regulated PI3K/B-cell receptor signaling components, and low expression of genes from stromal and inflammation signatures. As the data are based on a small and heterogeneous subset of patients, the results should be interpreted with caution but are generally consistent with copanlisib mechanism of action. Analysis of PTEN loss, which would also be expected to influence pathway activation, was ongoing at the time of NDA submission.

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

Yes. Copanlisib is primarily metabolized by CYP3A. Strong CYP3A modulators have significant effect on copanlisib exposures. Avoid concomitant use of strong CYP3A inducers and consider alternative concomitant medications with less potential for CYP3A induction. Dose reduction to 45 mg is recommended when coadministration of ALIQOPA with a strong CYP3A inhibitor.

There is a DDI potential between copanlisib and substrates of renal transporter MATE2-K. At recommended dosing regimen, copanlisib achieves C_{max} around $1 \mu\text{M}$ that is about 10-fold of its IC_{50} ($0.09 \mu\text{M}$) for MATE2-K. Metformin is a sensitive MATE2-K substrate used as a concomitant medicine in the pivotal trial to control hyperglycemia. It is also expected that metformin could be used in the management of copanlisib induced hyperglycemia in the clinical setting. Therefore, in order to assess the influence of copanlisib on the PK of MATE2-K substrates such as metformin, a post-marketing requirement will be issued.

Effect of CYP3A Inhibitors and Inducers

CYP3A inhibitors: Itraconazole, a strong CYP3A inhibitor which is also with inhibitory activity against human transporter P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP), administered at a dose of 200 mg once daily for 10 days increased the mean AUC of a single IV dose of 60 mg ALIQOPA 53% with no effect on C_{max} in patients with cancer (see Table 5). Because copanlisib is given by IV infusion, the contribution of P-gp/BCRP inhibition to the increase of copanlisib exposure is expected to be small. Because the recommended dose of 60 mg is the MTD, dose reduction of ALIQOPA to 45 mg is recommended for patients concomitantly taking strong CYP3A inhibitors.

Table 5: Effect of Concomitant Administration of Itraconazole on Copanlisib (60 mg) Exposure

Parameter	Copanlisib alone (Reference)	Copanlisib + Itraconazole (Test)	Geometric Mean Ratio (90%CI) (Test/Reference)
C _{max} (µg/mL)	387	402	1.038 (0.778, 1.384)
AUC ₀₋₁₆₈ (µg*h/mL)	2462	3598	1.418 (1.248, 1.612)
AUC _∞ (µg*h/mL)	2581	4070	1.530 (1.340, 1.745)

Source: Applicant's Summary of Clinical Pharmacology (Section 2.7.2) Table 2-10

CYP3A inducers: Rifampin, a strong CYP3A inducer (also a P-gp inducer), administered at a dose of 600 mg once daily for 12 days with a single IV dose of 60 mg ALIQOPA in patients with cancer resulted in a 63% decrease in the mean AUC and a 15% decrease in C_{max} of copanlisib (see **Table 6**). The concomitant use of strong CYP3A inducers with ALIQOPA should be avoided.

Table 6: Effect of Concomitant Administration of Rifampin on Copanlisib (60 mg) Exposure

Parameter	Copanlisib alone (Reference)	Copanlisib + Rifampin (Test)	Geometric Mean Ratio (90%CI) (Test/Reference)
C _{max} (µg/mL)	464	384	0.848 (0.704, 1.021)
AUC ₀₋₁₆₈ (µg*h/mL)	2734	1069	0.391 (0.352, 0.435)
AUC _∞ (µg*h/mL)	2885	1068	0.370 (0.338, 0.405)

Source: Applicant's PK Report PH-39626 Table 9-1 and Table 9-2

Transporters related DDI

In vitro, copanlisib inhibited P-gp (IC₅₀=7 µM). Copanlisib also showed a concentration-dependent inhibition of renal transporter MATE2-K using metformin as a probe substrate (Table 7 and Figure 10). The calculated IC₅₀ is 0.089 µM. This may translate into clinically relevant

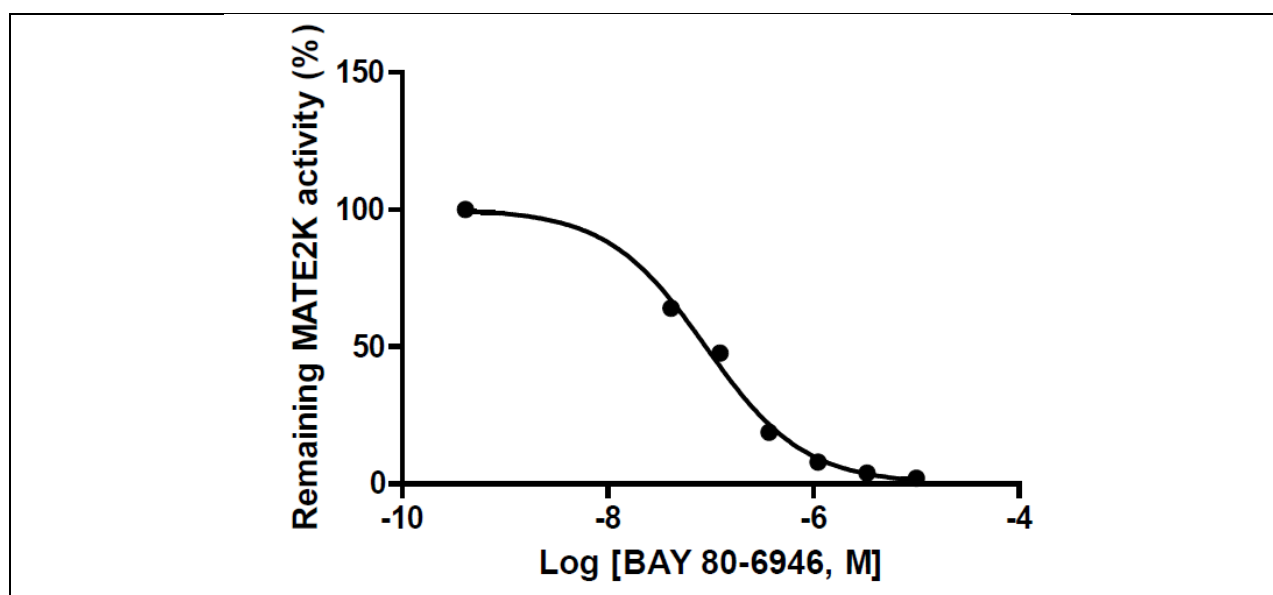
inhibition at therapeutic doses (e.g. for MATE2-K, $[I]_1/IC_{50} = 11.1$ with C_{max} of 1 μ M at recommended dose) according to the FDA guidance for drug interaction studies (2012).

Table 7: Percentage Inhibition of MATE2-K and IC_{50} of Copanlisib (Metformin as the Substrate)

Nominal BAY 80-6946 concentration (μ M)	Percentage inhibition towards MATE2K	Remaining MATE2K Activity (%)
10	97.9	2.08
3.33	96.0	3.98
1.11	92.1	7.93
0.370	81.2	18.8
0.123	52.3	47.7
0.0412	35.9	64.1
0	0	100
IC_{50} (μ M)		0.0892 ± 1.14

Source: Applicant's DMPK report R-9434

Figure 10 Effect of Copanlisib on MATE2-K Activity (Metformin as the Substrate)



Source: Applicant's DMPK report R-9434 Figure 1

Copanlisib is a substrate of both P-gp and BCRP. Clinically significant DDI with P-gp and BCRP inhibitors is not expected in the gut given the route of IV administration. The DDI study results with itraconazole (also an inhibitor of P-gp and BCRP) suggest that the main contribution of increase of exposure come from CYP3A inhibition (fm by CYP3A is around 0.5), not from systemic inhibition of P-gp and BCRP.

Copanlisib is not an inhibitor of drugs that are substrates of the major CYP isoforms (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4) or uridine diphosphate-glucuronosyltransferase isoforms (UGT) or dihydropyrimidine dehydrogenase (DPD). Copanlisib is not an inhibitor of

NDA/BLA Multi-disciplinary Review and Evaluation NDA 209936
Aliqopa (copanlisib)

BCRP, multi-drug resistance-associated protein (MRP2), bile salt export pump (BSEP), OATP1B1, OATP1B3, OAT 1, OAT3, OCT1, OCT2, and MATE1 at therapeutic 60 mg dose plasma concentrations.

Hongshan Li, Ph.D.
Primary Pharmacometrics Reviewer

Jiang Liu, Ph.D.
Pharmacometrics Team Leader

Guoxiang Shen, Ph.D.
Primary Clinical Pharmacology Reviewer

Bahru Habtemariam, Pharm.D.
Clinical Pharmacology Team Lead

7 Statistical and Clinical Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

The Applicant submitted data from 16 clinical studies of copanlisib alone or in combination with other agents. Of these 16 studies, 3 studies evaluating copanlisib monotherapy for treatment of patients with relapsed or refractory follicular lymphoma, marginal zone lymphoma, small lymphocytic lymphoma, or lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia were included to support efficacy and safety. Additionally, 2 studies of copanlisib monotherapy in patients with advanced non-Hodgkin lymphoma or solid tumors were included to further support the analysis of safety. To provide a comprehensive analysis of safety, the Applicant included data from completed studies of copanlisib in combination with other therapies, other NHL indications, healthy volunteers, and pharmacovigilance data for all ongoing studies. Table 8 lists the efficacy and safety studies emphasized in this review.

Table 8: Clinical Studies

Study identity	Design	Treatment regimen	Study population	Study endpoint	No. of patients enrolled
Studies to support efficacy and safety					
12871	Phase 1, dose-escalation, single-arm study	0.1-1.2 mg/kg IV on Day 1, 8, and 15 of 28-day cycle	Relapsed or refractory NHL, advanced solid tumors	MTD	57 (9 patients with NHL)
16349	Phase 2, open-label, single-arm, parallel group study	0.8 mg/kg IV on Day 1, 8, and 15 of 28-day cycle	Relapsed or refractory indolent NHL, CLL, aggressive NHL	ORR	84 (33 patients with iNHL)
16349 Part B	Phase 2, open-label, single-arm study	0.8 mg/kg IV or 60 mg IV on Day 1, 8, and 15 of 28-day cycle	Relapsed or refractory indolent NHL	ORR	142 (104 patients with FL)
Studies to support safety					
15205	Phase 1, open-label, single center study	0.4 mg/kg or 0.8 IV on Day 1, 8, and 15 of 28-day cycle	Japanese patients with advanced or refractory solid tumors	Safety	10

Study identity	Design	Treatment regimen	Study population	Study endpoint	No. of patients enrolled
16790	Phase 1, open-label, pharmacodynamic study	0.4 mg/kg or 0.8 IV on Day 1, 8, and 15 of 28-day cycle	Relapsed or refractory NHL or select solid tumors	PD	84
CLL: Chronic lymphocytic leukemia, NHL: non-Hodgkin lymphoma, iNHL: Indolent NHL, MTD: Maximum tolerated dose, ORR: Objective response rate, PD: Pharmacodynamics Source: Summary of Clinical Safety, Section 1.1.1.1					

7.1.2. Review Strategy

The key materials used for the review of efficacy and safety included:

- NDA datasets (raw and derived), clinical study reports, and responses to the review team's information requests.
- Relevant published literature
- Relevant information in the public domain

The clinical review of efficacy was primarily based on an analysis of Study 16349 Part B. Further, the review of efficacy was primarily based on patients with follicular lymphoma. Analyses were also performed for patients with other forms of non-Hodgkin lymphoma if applicable.

The results from the 5 studies listed in Table 8 and safety data from 11 studies of copanlisib in combination with other therapies, monotherapy, other NHL indications, and healthy volunteers were used in the analysis of safety. The review of safety is primarily based on the pooled data from the 5 studies in Table 8. The review emphasis was placed on the 0.8 mg/kg IV dose or the 60mg IV fixed dose administered on Days 1, 8, and 15 of a 28-day cycle.

Studies 16349 Part A, 16349 Part B, 17119, 16790, 17322, 17067, 17833, 17792, and 16270 were ongoing at the time of submission of the NDA, and it is acknowledged that the safety dataset used was therefore incomplete.

All major efficacy and safety analyses were reproduced or audited. Statistical analyses by the reviewers were performed using SAS/JMP 12.0 (SAS Institute, Inc., Cary, NC) and MedDRA-Based Adverse Event Diagnostics (MAED) 1.6 (Enterprise Performance and Lifecycle System Design).

7.2. Review of Relevant Individual Trials Used to Support Efficacy

Study 16349 Part B

16349 Part B – Open-label, uncontrolled Phase II trial of intravenous PI3K inhibitor BAY 80-6946 in patients with relapsed, indolent Non-Hodgkin's lymphomas

Study Design

Study 16349 Part B was an open-label, single arm, multicenter, Phase II study of copanlisib in patients with relapsed or refractory follicular lymphoma, marginal zone lymphoma, small lymphocytic lymphoma, or lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia.

Study Population

Inclusion Criteria

Patients eligible for inclusion into the study Part B had to meet all of the following inclusion criteria at the time of screening:

- Histologically confirmed diagnosis of indolent B-cell NHL, with histological subtype limited to the following:
 - Follicular lymphoma (FL) grade 1, 2, and 3a.
 - Marginal zone lymphoma (MZL) (splenic, nodal, or extra-nodal).
 - Small lymphocytic lymphoma (SLL) with absolute lymphocyte count $< 5 \times 10^9/L$ at the time of diagnosis and at study entry.
 - Lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia (LPL/WM).
- Relapsed or refractory after ≥ 2 prior lines of therapy (refractory defined as not responding to a standard regimen or progressing within 6 months of the last course of a standard regimen). Patients must have received rituximab and alkylating agents.
- Ability to understand and willingness to sign written informed consent. Signed informed consent must be obtained before any study specific procedure.
- Male or female patients > 18 years of age.
- Patients must have at least one bi-dimensionally measurable lesion (that has not been previously irradiated) according to the recommendations of the Revised Response Criteria for Malignant Lymphoma.
- In addition to the measurable criterion above, patients affected by lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia must have also measurable disease, defined as presence of immunoglobulin M paraprotein with a minimum IgM level of equal to or greater than 2 times the upper limit of normal (ULN) or over 10% of lymphoplasmacytic cells in bone marrow.
- Availability of archival tumor tissue or fresh tumor tissue for central pathology review and biomarker analysis.
- ECOG performance status ≤ 2 .
- Life expectancy of at least 3 months.
- Women of childbearing potential and men must agree to use adequate contraception since signing of the informed consent form until at least 3 months after the last test drug administration. The investigator or a designated associate is requested to advise the patient how to achieve adequate birth control. Adequate contraception is defined in the study as any medically recommended method (or

- combination of methods) as per standard of care. An adequate contraception includes a hormonal contraception with implants or combined oral, transdermal or injectable contraceptive, certain intrauterine devices, bilateral tubal ligation, hysterectomy, or vasectomy of the partner. In addition, the use of condoms for patients or their partners is required unless the woman has had a hysterectomy.
- Adequate bone marrow, liver, and renal function as assessed by the following laboratory requirements conducted within 7 days before starting study treatment:
 - Total bilirubin $\leq 1.5 \times$ the upper limit of normal ($< 3 \times$ ULN for patients with Gilbert-Meulengracht syndrome or for patients with cholestasis due to compressive adenopathies of the hepatic hilum).
 - Alanine transaminase (ALT) and aspartate aminotransferase (AST) $\leq 2.5 \times$ ULN ($\leq 5 \times$ ULN for patients with lymphomatous liver involvement of their cancer).
 - Amylase and lipase $\leq 1.5 \times$ the ULN.
 - Serum creatinine $\leq 1.5 \times$ the ULN.
 - Glomerular filtration rate (GFR) ≥ 30 ml/min/1.73 m² according to the modified diet in renal disease abbreviated formula.
 - International normalized ratio (INR) and partial thromboplastin time (PTT) $\leq 1.5 \times$ ULN.
 - Platelet count $\geq 75,000/\text{mm}^3$, hemoglobin (Hb) ≥ 9 g/dL, absolute neutrophil count (ANC) $\geq 1,500/\text{mm}^3$.
 - Left ventricular ejection fraction (LVEF) $\geq$ lower limit of normal (LLN) for the institution.

Exclusion Criteria

Patients eligible for inclusion into the study Part B must not have met any of the following exclusion criteria at the time of screening:

- Histologically confirmed diagnosis of follicular lymphoma grade 3B or transformed disease or chronic lymphocytic leukemia (CLL).

Excluded medical conditions

- Previous or concurrent cancer that is distinct in primary site or histology from indolent B-cell NHL within 5 years prior to treatment start EXCEPT for curatively treated cervical cancer *in situ*, non-melanoma skin cancer and superficial bladder tumors (Ta [non-invasive tumor], Tis [carcinoma in situ], and T1 [tumor invades lamina propria]).
- Known lymphomatous involvement of the central nervous system.
- Congestive heart failure > New York Heart Association (NYHA) class 2.
- Unstable angina (angina symptoms at rest), new-onset angina (begun within the last 3 months). Myocardial infarction less than 6 months before start of test drug.
- Uncontrolled hypertension. (Blood pressure $\geq 150/90$ mmHg despite optimal medical management).
- Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism within the 6 months before start of study medication.
- Non-healing wound, ulcer, or bone fracture.

- Active clinically serious infection (>CTCAE grade 2).
- Known history of human immunodeficiency virus (HIV) infection.
- Hepatitis B or C. All subjects must be screened for hepatitis B and C up to 28 days prior to study drug start using the hepatitis viral panel laboratorial routine. Subjects positive for HBsAg or HBcAb will be eligible if they are negative for HBV-DNA; subjects positive for HCV IgG will be eligible if they are negative for HCV-RNA.
- Patients with seizure disorder requiring medication.
- Patients with evidence of history of bleeding diathesis. Any hemorrhage or bleeding event $\geq$ CTCAE grade 3 within 4 weeks of start of study medication.
- Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results.
- Known hypersensitivity to any of the test drugs, test drug classes, or excipients in the formulation.
- History or concurrent condition of interstitial lung disease or severely impaired pulmonary function (as judged by the investigator).
- Unresolved toxicity higher than CTCAE grade 1 (NCI-CTCAE version 4.03) attributed to any prior therapy/procedure excluding alopecia.
- Type I or II diabetes mellitus with HbA1c > 8.5% or fasting plasma glucose > 160 mg/dL at screening.
- Concurrent diagnosis of pheochromocytoma.
- Pregnant or breast-feeding patients. Women of childbearing potential must have pregnancy test performed a maximum of 7 days before start of treatment, and a negative result must be documented before start of treatment.
- Close affiliation with the investigational site; e.g., a close relative of the investigator, dependent person (e.g., employee or student of the investigational site).
- Any illness or medical conditions that are unstable or could jeopardize the safety of the patient and his/her compliance in the study.
- Previous assignment to treatment during this study. Patients permanently withdrawn from study participation will not be allowed to re-enter the study.
- Proteinuria of CTCAE grade 3 or higher (urine protein:creatinine ratio > 3.5 on a random urine sample).

Excluded previous therapies and medications

- Prior treatment with PI3K inhibitors.
- Treatment with investigational drug other than PI3K inhibitors within 28 days prior to treatment start.
- Ongoing immunosuppressive therapy.
- Radiotherapy or immuno/chemotherapy within 4 weeks prior to treatment start.
- Radioimmunotherapy or autologous transplant within 3 months prior to treatment start.
- Myeloid growth factors within 14 days prior to treatment start.
- Blood or platelet transfusion within 14 days prior to treatment start.

- Systemic corticosteroid therapy (ongoing). Previous corticosteroid therapy must be stopped at least 7 days prior to first study drug administration. Patients may be using topical or inhaled corticosteroids.
- History of having received an allogeneic bone marrow or organ transplant.
- Major surgical procedure, or significant traumatic injury within 28 days before start of study medication; open biopsy within 7 days before the start of study medication.
- Cardiac arrhythmias requiring anti-arrhythmic therapy (beta blockers or digoxin are permitted).
- Use of strong inhibitors of CYP3A4 is prohibited from Day -14 and for the duration of the study.
- Use of inducers of CYP3A4 is prohibited from Day -14 of Cycle 1 and for the duration of the study.

Statistical Analysis Plan

Study Endpoints

The primary efficacy endpoint is objective response rate, which is assessed in all patients up to 16 weeks after the last patient eligible for full analysis data set has started treatment. Objective response rate is defined as best response rate of complete response or partial response according to the criteria defined in the Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007).

The secondary endpoints specified by the protocol include:

- Progression free survival, defined as the time from treatment assignment to disease progression or death.
- Duration of response, defined as the time from first observed tumor response (CR or PR) until progressive disease or until death due to any cause.
- Overall survival (OS), defined as the time from treatment assignment until death from any cause or the last date the patient is known to be alive.
- Quality of Life questionnaire at week 16.
 - FACT-Lym: Functional Assessment of Cancer Therapy – Lymphoma

Quality of life questionnaire FACT-Lym is performed at baseline (within 7 days prior to the first test drug administration), and also on the days of tumor assessments (start of each cycle) with the schedule of every 2 cycles in the first year, every 3 cycles in the second year and every 6 cycles in the third year. FACT-Lym is also assessed at the end of treatment visit (within 7 days after the decision is made to discontinue study treatment).

The radiological evaluation for efficacy is done by central blinded review, and all primary analysis of efficacy endpoint regarding response assessments is analyzed based on the central assessment of an independent review.

Analysis Population

The primary analysis set for the efficacy variables is full analysis set (FAS), which is defined as all patients assigned to study treatment.

The per protocol set is defined as all patients with study drug administration that are evaluable for ORR and that have no major protocol deviation affecting the primary efficacy variable. At least one evaluable post baseline tumor assessment should be available for independent assessment in order to consider the patient evaluable.

Analysis Method

The Applicant analyzed the primary endpoint, ORR, by one-sample exact binomial test for hypothesis testing, with Null hypothesis $H_0: p \leq p_0$, where $p_0 = 0.4$ and Alternative hypothesis $H_1: p > p_0$. The null hypothesis was tested by exact one sided binomial test with type one error rate of $\alpha = 0.025$. Point estimate along with its exact 95% Clopper Pearson confidence interval were calculated.

Duration of response was evaluated for patients with at least one tumor response of complete response or partial response. The median and its 95% CI of duration of response were calculated based on Kaplan-Meier methodology and Kaplan-Meier plots were produced. The Applicant planned to compare the lower bound of the 2-sided 95% CI of the Kaplan-Meier estimator for the median DOR with 8.5 months, and null hypothesis of having a median ≤ 8.5 months would be rejected.

For patient-reported outcomes, change from baseline until week 16 in FACT-Lym symptoms subscale and FACT-Lym total score was planned to be analyzed using a two-sided signed-rank test. Additionally, for all FACT-Lym total and subscores, 95% confidence intervals based on the Hodges-Lehmann estimator would be provided, together with other descriptive analyses.

Reviewer Comment

Due to the single arm study design, in FDA reviewer analysis, all the efficacy endpoints were analyzed with descriptive statistics without formal hypothesis testing.

Time-to-event endpoints are not interpretable in single arm studies.

There is no specific statistical test that was described to test the hypothesis of median DOR > 8.5 months.

For patients with missing FACT-Lym questionnaire data at week 16, the Applicant's analysis used the last observation carried forward approach. The Applicant considered this analysis as the main designated strategy for FACT-Lym related evaluations.

Reviewer Comment

Patients who cannot complete the questionnaire, such as patients who were off study or died were not considered missing data. Patients who would be able to complete the questionnaire but did not do so were considered missing data.

FDA summarized the completion rate of PRO by visit. FDA analyses of PRO Scores were based on observed PRO.

Interim Analysis

No interim analyses were planned in this study

7.2.2. Study Results

Compliance with Good Clinical Practices

The protocol, protocol amendments, and patient informed consent forms for Study 16349 Part B were reviewed and approved by the Institutional Review Boards or Independent Ethics Committees of the participating study centers.

Study 16349 Part B was conducted in accordance with the International Council for Harmonization guideline for Good Clinical Practice, the principles of the Declaration of Helsinki, and the US Code of Regulations, Title 21, Parts 50, 56, and 312 providing the protection of the rights and welfare of human patients participating in biomedical research. All patients or their legal representatives voluntarily consented prior to trial enrollment.

Financial Disclosure

The Applicant submitted financial disclosure information from 828 investigators from two studies indicating that none of the investigators had disclosable financial interests or arrangements. For details, refer to the Clinical Investigator Financial Disclosure Review Template in Section 13.2. None of the disclosures submitted revealed a potential conflict of interest.

Patient Disposition

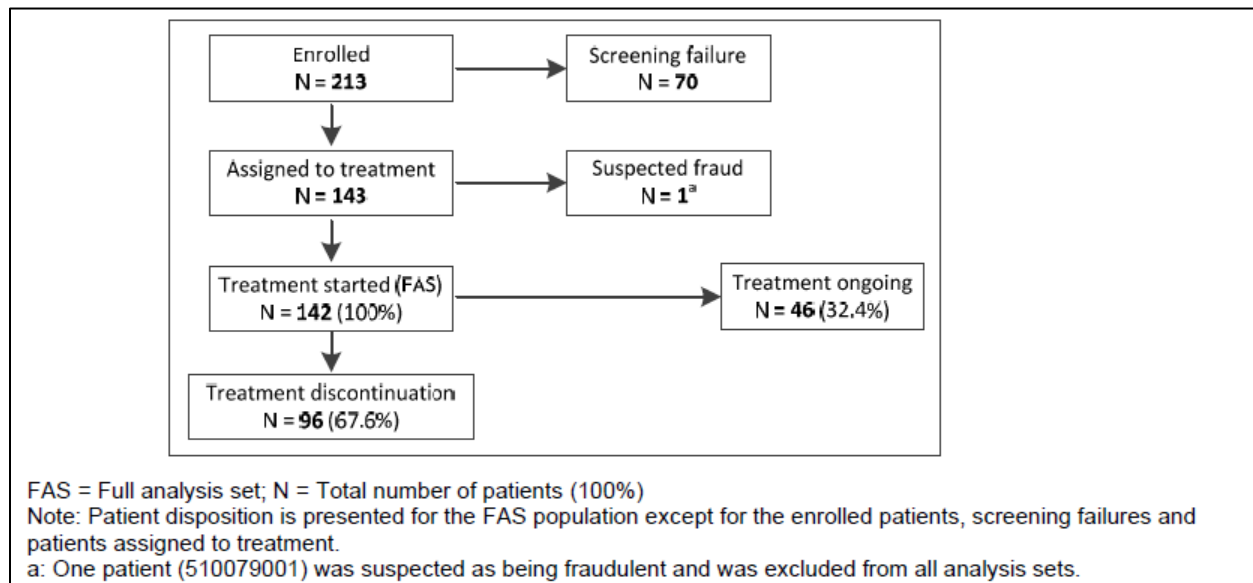
An overview of patient disposition is shown in Figure 11 and Table 9 below. Of the 142 patients in the FAS who started treatment, 46 patients (32.4%) were ongoing with study treatment at the time of data cut-off while 96 patients (67.6%) had discontinued treatment. The most common reason for treatment discontinuation was progressive disease in 31 patients (21.8%). For the 104 patients with follicular lymphoma, 33 patients (31.7%) were ongoing with study treatment at the time of data cut-off while 71 patients (68.3%) had discontinued treatment. The most common reason for treatment discontinuation was progressive disease in 29 patients (27.9%).

In the FAS, a total 87 patients (61.3%) had entered the safety follow-up. Of these patients, 64 patients (45.1%) had completed safety follow-up and 23 patients (16.2%) had prematurely discontinued the safety follow-up. The safety follow up period was most frequently discontinued due to patient withdrawal (10 patients, 7.0%). For patients with follicular lymphoma, a total of 65 patients (62.5%) had entered the safety follow-up. Of these patients, 46 patients (47.1%) had completed safety follow-up and 16 patients (15.4%) had prematurely discontinued the safety follow-up. The safety follow-up period was most frequently discontinued due to patient withdrawal (7 patients, 6.7%).

Only patients who terminated study treatment for reasons other than progressive disease entered the active follow-up period. At the time cut-off, in the FAS, 20 patients (14.1%) had entered active follow-up and 13 patients (9.2%) had discontinued. The most common reason for discontinuation was progressive disease (radiological progression) in 6 patients (4.2%). For patients with follicular lymphoma, at the time of cut-off, 14 patients (13.5%) had entered active follow-up and 9 patients (8.7%) had discontinued. The most common reason was progressive disease (radiological progression) in 4 patients (3.8%).

In the FAS, a total of 74 patients (52.1%) had entered the survival follow-up, of which 16 patients (11.3%) had discontinued, and the most frequent reason was death in 15 patients. For patients with follicular lymphoma, a total of 56 patients (53.8%) had entered the survival follow-up, of which 14 patients (13.5%) had discontinued because of death.

Figure 11: Patient Disposition



Source: Figure 8-1 in the Clinical Study Report for Study 16349 – Part B.

Table 9 Patient Disposition by Disease Type and Study Phase

Study Phase	FL N = 104 n (%)	MZL N = 23 n (%)	SLL N = 8 n (%)	LPL/WM N = 6 n (%)	iNHL ^a N = 141 n (%)	Total ^b N = 142 n (%)
Treatment	104 (100.0)	23 (100.0)	8 (100.0)	6 (100.0)	141 (100.0)	142 (100)
Ongoing	33 (31.7)	10 (43.5)	1 (12.5)	2 (33.3)	46 (32.6)	46 (32.4)
Discontinued	71 (68.3)	13 (56.5)	7 (87.5)	4 (66.7)	95 (67.4)	96 (67.6)
Safety follow-up^c	65 (62.5)	12 (52.2)	5 (62.5)	4 (66.7)	86 (61.0)	87 (61.3)
Ongoing	0	0	0	0	0	0
Completed	49 (47.1)	8 (34.8)	5 (62.5)	2 (33.3)	64 (45.4)	64 (45.1)
Prematurely discontinued	16 (15.4)	4 (17.4)	0	2 (33.3)	22 (15.6)	23 (16.2)
Active follow-up^d	14 (13.5)	4 (17.4)	2 (25.0)	0	20 (14.2)	20 (14.1)
Ongoing	5 (4.8)	1 (4.3)	1 (12.5)	0	7 (5.0)	7 (4.9)
Discontinued	9 (8.7)	3 (13.0)	1 (12.5)	0	13 (9.2)	13 (9.2)
Survival follow-up^{e, f}	56 (53.8)	9 (39.1)	6 (75.0)	3 (50.0)	74 (52.5)	74 (52.1)
Ongoing	42 (40.4)	9 (39.1)	4 (50.0)	3 (50.0)	58 (41.1)	58 (40.8)
Discontinued	14 (13.5)	0	2 (25.0)	0	16 (11.3)	16 (11.3)

FAS = Full analysis set; FL = Follicular lymphoma; MZL = Marginal zone lymphoma; SLL = Small lymphocytic lymphoma; LPL = Lymphoplasmacytoid lymphoma; WM = Waldenström macroglobulinemia; iNHL = Indolent Non-Hodgkin's lymphoma; N = Total number of patients (100%); n = Number of patients with event; DLBCL = Diffuse large B-cell lymphoma

a: iNHL: FL grade 1-2-3a, MZL, SLL and LPL/WM.

b: Total includes patients with iNHL and 1 patient who had DLBCL (further details in Section 8.5). Data for the DLBCL patient can be found in Table 14.1.1/4, Table 14.1.1/5, Table 14.1.1/6 and Table 14.1.1/7.

c: Within 35 days after the last dose of study treatment.

d: Only patients who discontinued study drug for reasons other than disease progression entered the active follow-up period.

e: One patient (470019003) was included in the survival follow-up even though there were no data from safety or active follow-up.

f: Not all patients who discontinued the safety follow-up entered the survival follow-up (see Table 8-3).

Source: Table 8-2 in the Clinical Study Report for Study 16349 – Part B.

Protocol Violations/Deviations

Of the 143 patients who were assigned to treatment (including a patient suspected as being fraudulent and excluded from the FAS), 129 patients (90.2%) had protocol deviations during Study 16349 Part B. Table 10 displays a summary of the protocol deviations in Study 16349 Part B. The most common protocol deviations included procedure deviations in 114 patients (79.7%). A total of 30 patients (21.0%) had major protocol deviations.

Table 10: Protocol Deviations

Deviation type	Total N = 143 n (%)
Total – any type	129 (90.2)
Procedure deviations	114 (79.7)
Time schedule deviations	66 (46.2)
Treatment deviations	60 (42.0)
Excluded concomitant medication treatment	20 (14.0)
Other protocol deviations	18 (12.6)
Inclusion/exclusion criteria not met but subject entered treatment	11 (7.7)
Withdrawal criteria during treatment but not withdrawn	3 (2.1)
Conditional validity deviations	1 (0.7)
Of these, major – any type	30 (21.0)
Procedure deviations	15 (10.5)
Inclusion/exclusion criteria not met but subject entered treatment	9 (6.3)
Excluded concomitant medication treatment	9 (6.3)
Time schedule deviations	4 (2.8)

N = Total number of patients (100%); n = Number of patients with event

Source: Table 8-4 in the Clinical Study Report for Study 16349 – Part B.

The major protocol deviations included procedure deviations, unmet eligibility criteria, use of prohibited concomitant medications, and time schedule deviations. Nine patients (6.3%) did not meet eligibility criteria, but were enrolled and entered treatment with copanlisib. The reasons for unmet eligibility include DLBCL within 5 years, incorrect diagnosis, missing baseline diagnostics, and prior chemotherapy washout < 4 weeks. Nine patients (6.3%) reported excluded concomitant medications which included systemic corticosteroids and 4 others. The procedure and time schedule deviations were due to missed examinations and missed laboratory or radiologic assessments.

Reviewer Comment: None of the major protocol deviations would likely bias the study in favor of copanlisib and all patients were included in the FDA's analysis of efficacy endpoints. An additional analysis of the per protocol population that excludes the 30 patients with major protocol deviations revealed similar efficacy findings to the FAS population. The inclusion of the 30 patients in the FAS population does not bias the study in favor of copanlisib, however, the single-arm study design interferes with a true analysis of bias in the absence of a control arm.

Demographic Characteristics

Demographic characteristics and some other disease baseline characteristics are summarized in Table 11 and Table 12 below. Overall, 50% of the patients in the FAS were male. The majority of the patients were White (84.5%). Overall, 9.2% of patients were from the United States (U.S.). There were 28.2% of patients who received more than 3 prior therapies, 60.6% of patients who were refractory to the last treatment regimen, and 41.6% of patients who received prior bendamustine treatment.

For patients with follicular lymphoma, 51.9% were male. A majority of the patients were White (82.7%) and not Hispanic or Latino (85.6%). There were 10.5% of patients from the U.S. There were 30.8% of patients who received more than 3 prior therapies, 62.5% of patients who were refractory to the last treatment regimen, and 45.2% of patients who received prior bendamustine treatment.

Table 11: Demographic Characteristics

	FL (N= 104) n (%)	iNHL (N = 141) n (%)	Total (N = 142) n (%)
Sex			
Male	54 (51.9)	70 (49.6)	71 (50.0)
Female	50 (48.1)	71 (50.4)	71 (50.0)
Age			
Mean years (SD)	60.3 (11.9)	61.5 (12.0)	61.4 (12.1)
Median (years)	62.0	63.0	63.0
Min, max (years)	25, 81	25, 82	25, 82
Age Group			
< 65 years	63 (60.6)	77 (54.6)	78 (54.9)
≥ 65 years	41 (39.4)	64 (45.4)	64 (45.1)
Race			
White	86 (82.7)	119 (84.4)	120 (84.5)
Asian	13 (12.5)	15 (10.6)	15 (10.6)
Not reported	5 (4.8)	7 (5.0)	7 (4.9)
Ethnicity			
Hispanic or Latino	6 (5.8)	6 (4.3)	6 (4.2)
Not Hispanic or Latino	89 (85.6)	123 (87.2)	124 (87.3)
Not reported	9 (8.7)	12 (8.5)	12 (8.5)
Region			
United States (U.S.)	11 (10.6)	13 (9.2)	13 (9.2)
Non-U.S.	93 (89.4)	128 (90.8)	129 (90.8)

FL: Follicular lymphoma, iNHL: indolent Non-Hodgkin lymphoma, SD: Standard deviation

Source: FDA reviewer analysis

Table 12 Other Baseline Disease Characteristics

	FL (N= 104) n (%)	iNHL (N = 141) n (%)	Total (N = 142) n (%)
Number of prior therapy			
≤ 3	72 (69.2)	101 (71.6)	102 (71.8)
> 3	32 (30.8)	40 (28.4)	40 (28.2)
Refractory to last regimen			
Yes	65 (62.5)	85 (60.3)	86 (60.6)
No	39 (37.5)	56 (39.7)	56 (39.4)
Received prior bendamustine treatment			
Yes	47 (45.2)	59 (41.8)	59 (41.6)
No	57 (54.8)	82 (58.2)	83 (58.4)

Source: FDA reviewer analysis

Treatment Compliance and Concomitant Medications

Treatment Compliance

In the 141 patients with indolent NHL, the median dose-intensity of copanlisib was 95.2% (range 51.2% to 102.8%). Dose interruptions occurred in 105 patients (73.9%) and dose reductions occurred in 38 patients (27.0%), which accounted for all of the reduced dose-intensities reported. The majority of dose interruptions were due to adverse events and all dose reductions were due to an adverse event. The events of reduced dose intensity were not due to medication errors.

Concomitant Medications

Nearly all patients (140/142, 98.6%) received at least one concomitant medication during the study. Table 13 displays the categories of concomitant medications administered during treatment with copanlisib.

Table 13 Concomitant Medications Used in ≥ 30% of Patients Treated with Copanlisib

ATC Subclass	FAS Population N=142 n (%)
Any concomitant medication	140 (98.6)
Antibacterials for systemic use	104 (73.2)
Analgesics	80 (56.3)
Drugs for acid-related disorders	72 (50.7)
Anti-diarrheal, intestinal anti-inflammatory or anti-infective agents	71 (50.0)
Drugs used in diabetes	57 (40.1)

ATC Subclass	FAS Population N=142 n (%)
Antivirals for systemic use	57 (40.1)
Anti-emetics and anti-nausea	55 (38.7)
Drugs for constipation	50 (35.2)
Stomatological preparations	48 (33.8)
ATC: Anatomical therapeutic chemical, FAS: Full analysis set Source: FDA analysis of ADCM dataset for full analysis set	

The most common concomitant medication used was systemic antibiotics for infection prophylaxis or treatment of an infection. The other commonly used concomitant medications included analgesics, gastrointestinal prophylaxis, and anti-diarrheal medications.

Efficacy Results – Primary Endpoint

The review of the efficacy endpoints focuses on the follicular lymphoma study population (n = 104) and the total study population (n = 142), because the indication the Applicant seeks is for patients with follicular lymphoma (relapsed and refractory FL who have received at least two prior therapies). The database cutoff date was June 22, 2016.

Table 14 below summarizes the analysis results of primary efficacy endpoint objective response rate. Of the 142 patients in the FAS, 84 patients achieved an objective response. The percentage of ORR is 59% (95% CI [51%, 67%]). Of all these patients who achieved an objective response, 17 patients (12%) achieved a complete response and 67 patients (47%) achieved a partial response.

Of the follicular lymphoma patient population (n = 104), 61 patients achieved an objective response. The percentage of ORR is 59% (95% CI [49%, 68%]). Of all these patients who achieved an objective response, 15 patients (14%) achieved a complete response and 46 patients (44%) achieved a partial response (Table 14).

Table 14: Objective Response Rate and Duration of Response

	FL (N = 104) n (%)	Total (N = 142) n (%)
ORR	61 (59%) 95% CI (49%, 68%)	84 (59%) 95% CI (51%, 67%)
CR	15 (14%)	17 (12%)
PR	46 (44%)	67 (47%)
Median DOR, month (range)	12.2 (0, 22.6)	22.6 (0, 22.6)
ORR: Objective response rate, CR: Complete response, PR: Partial response, DOR: Duration of response		

Source: FDA reviewer analysis

The investigator assessment of objective response rate in the total study population (N = 142) demonstrated an ORR of 51.4% (95% CI: 42.9, 59.9) with 73 patients achieving a complete response or partial response. Six patients (4.2%) achieved a CR and 67 patients (47.2%) achieved a PR. The overall concordance between the independent review committee and the investigator was 63.4%. The independent review identified more complete responses (17 patients vs. 6 patients) and fewer patients with progressive disease (3 patients vs. 11 patients). The investigator assessment identified 9 patients assessed as achieving a partial response who were determined to have achieved a complete response by independent review. Additionally, 2 patients assessed as achieving stable disease by investigator assessment were determined to have a complete response by independent review. Table 15 displays a summary of the concordance between independent review assessment and investigator assessment.

Table 15 Concordance of Response Assessment Between Investigator Assessment and Independent Review

Investigator assessment	Independent Review						Total n (%)
	CR	PR	SD	PD	NE	NA	
CR	6	0	0	0	0	0	6 (4.2)
PR	9	46	12	0	0	0	67 (47.2)
SD	2	18	26	0	1	0	47 (33.1)
PD	0	2	4	3	0	2	11 (7.8)
NE	0	1	0	0	0	0	1 (0.7)
NA	0	0	1	0	0	9	10 (7.0)
Total (%)	17 (12.0)	67 (47.2)	43 (30.3)	3 (2.1)	1 (0.7)	11 (7.8)	142 (100.0)
CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease, NE: Not evaluable – post-baseline tumor assessment not able to be assessed by independent review, NA: Not available – no available post-baseline tumor assessment Source: FDA analysis of ADCM dataset for full analysis set							

Reviewer Comment: The discordance between investigator and independent review appears to be associated with the timing of assessment. For instance, a patient with an assessment of PR by the investigator is based on the tumor assessment available at that time, whereas the independent review committee was able to assess the best overall response based on tumor assessments that occurred at a later time and demonstrated no evidence of disease, which upgraded the patient to a CR. The discordance does not interfere with the evaluation of efficacy and a determination of the risk-benefit profile of copanlisib.

Efficacy Results – Secondary and other relevant endpoints

Duration of Response

The analysis results of duration of response are summarized in Table 14 shown above. Of the 84 patients who achieved an objective response in the FAS, the median follow up time for duration of response was 5.5 months. The estimated median duration of response was 22.6 months (95% CI [7.4, 22.6], range [0, 22.6]).

Of the 61 patients with follicular lymphoma who achieved an objective response, the median follow up time for duration of response was 5.7 months. The estimated median duration of response was 12.2 months (95% CI [6.9, 22.6], range [0, 22.6]).

Reviewer Comment: Since the median follow-up for responders is 5.7 months in patients with follicular lymphoma, the ability to interpret duration of response beyond 5.7 months is uncertain. However, a duration of response of 6 months and possibly greater remains clinically meaningful in this population. The clinical benefit will need to be closely monitored and further established in a confirmatory trial because of the short exposure duration of copanlisib (median 5.5 cycles) and the short follow-up in responders.

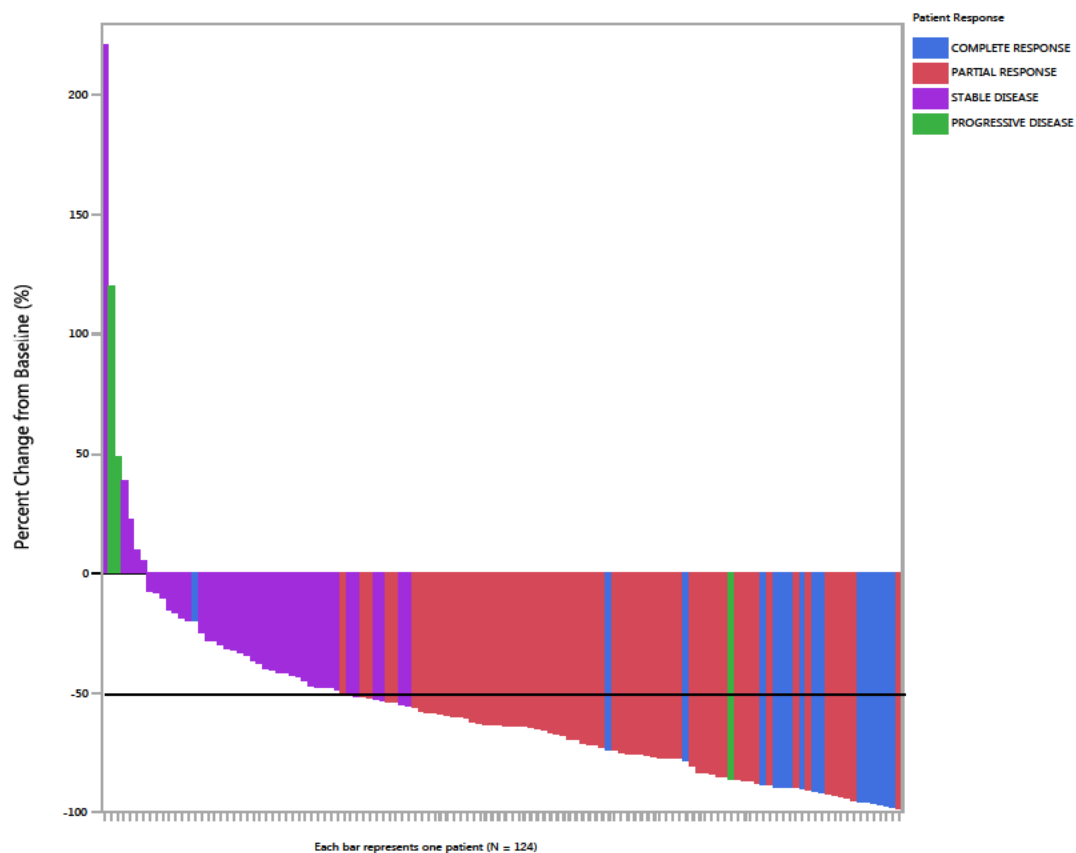
Time to Response

Based on responders per the independent review, the median time to response was 1.7 months (range 1.3 to 9.7 months). The time to response was defined as the time from the start of treatment to the first observed response (CR or PR). The time to response per investigator was similar with a median of 1.8 months.

Response - Change from Baseline

The maximum percent change from baseline is displayed in Figure 12. A total of 124 patients of 142 had available data to review response from baseline. Eighty-seven patients (61.3%) experienced at least a 50% maximum reduction from baseline.

Figure 12 Maximum Percent Change from Baseline by Patient Response



Reviewer Comment: The analysis of maximum percent change from baseline demonstrated disease response in the majority of patients, which provides further evidence of copanlisib activity in patients with relapsed follicular lymphoma.

Additional Analyses Conducted on the Individual Trial

The analysis results of primary efficacy endpoint objective response rate in the subgroups based on demographics, age, gender, race and geographic region are summarized in Table 16 shown below within the follicular lymphoma study population and FAS. In general, the results from these subgroup analyses appear to be consistent with the primary ORR results except in the subgroup with a small sample size (e.g., in U.S.).

Table 16 ORR by Demographics Characteristics and Other Baseline Disease Characteristics

	FL n/N (%)	Total n/N (%)
Age		
< 65 years	39/63 (61.9)	46/78 (59.0)
≥ 65 years	22/41 (53.7)	38/64 (59.4)
Gender		
Male	30/54 (55.6)	41/71 (57.8)
Female	31/50 (62.0)	43/71 (60.6)
Race		
White	51/86 (59.3)	71/120 (59.2)
Asian	7/13 (53.9)	8/15 (53.3)
Unknown	3/5 (60.0)	5/7 (71.4)
Geographic Region		
U.S.	4/11 (36.4)	5/13 (38.5)
Non-U.S.	57/93 (61.3)	79/129 (61.2)
Number of prior therapy		
≤ 3	43/72 (59.7)	61/102 (59.8)
> 3	18/32 (56.3)	23/40 (57.5)
Refractory to last regimen		
Yes	39/65 (60.0)	52/86 (60.5)
No	31/50 (56.4)	32/56 (57.1)
Received prior bendamustine		
Yes	27/47 (57.5)	37/59 (62.7)
No	34/57 (59.7)	47/83 (58.5)

Source: FDA reviewer analysis

Patient-Reported Outcome (PRO)

The patient reported outcome (completion rates and scores) were analyzed with descriptive statistics.

1. PRO Completion Rates

The PRO completion rates are summarized in Table 17 below. The completion rate at baseline was 94.2% for patients with follicular lymphoma and 93.0% for FAS, and around 50%-60% in the first year for both patient populations. After the first year, the completion rate is very low (around 30%) for both patient populations.

Table 17: PRO Completion Rates

	# of Expected Patients*	FACT-Lym Total Score
Follicular Lymphoma Study Population N = 104		
Baseline	104	98 (94.2%)
Week 8	93	59 (63.4%)
Week 16	75	44 (58.7%)
Week 24	47	28 (59.6%)
Week 32	32	18 (56.3%)
Week 40	25	15 (60.0%)
Week 48	19	10 (52.6%)
Week 56	11	3 (27.3%)
Follicular Lymphoma and Other NHL Types in Study N = 142		
Baseline	142	132 (93.0%)
Week 8	123	82 (66.7%)
Week 16	100	65 (65.0%)
Week 24	64	39 (60.9%)
Week 32	44	24 (54.5%)
Week 40	32	17 (53.1%)
Week 48	22	11 (50.0%)
Week 56	13	4 (30.8%)

Source: FDA reviewer analysis

2. PRO Scores over Time

The PRO scores in the first year are summarized in Table 18 below. For patients with follicular lymphoma and overall FAS, the FACT-Lym total score and FACT-Lym symptom subscale score increased with time, indicating that the symptoms was getting better with time.

For patients with follicular lymphoma, the mean of FACT-Lym total score was 131.8 at baseline and increased to 147.0 by the end of week 56. The mean of FACT-Lym symptom subscale score was 47.4 at baseline and increased to 57.0 by the end of week 56.

For overall FAS patient population, the mean of FACT-Lym total score was 126.6 at baseline and increased to 144.7 by the end of week 56. The mean of FACT-Lym symptom subscale score was 45.3 at baseline and increased to 54.5 by the end of week 56.

Table 18: PRO Scores over Time

	FACT-Lym Total Score Mean (SD)	FACT-Lym Subscale Score Mean (SD)
Follicular Lymphoma Study Population, N = 104		
Baseline	131.8 (20.8)	47.4 (8.5)
Week 8	131.3 (21.9)	47.4 (9.2)
Week 16	135.1 (21.1)	49.8 (7.0)
Week 24	136.2 (21.3)	49.1 (7.1)
Week 32	133.7 (19.4)	49.1 (7.3)
Week 40	150.5 (12.6)	53.9 (5.4)
Week 48	142.0 (13.8)	54.2 (4.3)
Week 56	147.0 (14.1)	57.0 (1.7)
Follicular Lymphoma and All Other Types in the Study, N = 142		
Baseline	126.6 (23.0)	45.3 (9.5)
Week 8	128.9 (22.1)	46.6 (8.7)
Week 16	130.7 (21.3)	48.2 (7.3)
Week 24	130.0 (22.4)	47.3 (7.7)
Week 32	128.4 (19.8)	48.2 (6.6)
Week 40	145.3 (19.3)	52.1 (7.5)
Week 48	140.7 (13.8)	53.8 (4.2)
Week 56	144.7 (12.4)	54.5 (5.2)

Source: FDA reviewer analysis

Reviewer Comment: Quality of life is important in patients with lymphoma. The FACT-Lym is used to assess health-related quality of life in patients with lymphoma. The questionnaire covers physical wellbeing, social wellbeing, emotional wellbeing, functional wellbeing, and an additional subscale evaluating concerns experienced by lymphoma patients. The pre-specified analysis plan in Study 16349 Part B was to evaluate the baseline FACT-Lym score and the week 16 score. The FACT-Lym score increased with time, indicating that the symptoms were getting better with time. The FACT-Lym subscale assesses lymphoma specific concerns such as pain, itching, night sweats, fatigue, etc. The improvement in the FACT-Lym symptom subscale provides supportive evidence of copanlisib activity in patients with follicular lymphoma. Further, the scores for the FACT-Lym total score and the FACT-Lym subscale score continue to increase over time with continued copanlisib treatment. However, the number of patients with completed PRO assessments decreases over time, which can cause a selection bias. Thus the trend needs to be interpreted with caution. There appears to be a trend in improved health-related quality of life in patients treated with copanlisib, however, this hypothesis needs to be tested in a randomized study. Further study of health-related quality of life is imperative in patients with relapsed follicular lymphoma because they experience significantly worse quality of life compared to patients with newly diagnosed follicular lymphoma or those with partial or complete remission (Pettengell et al. 2008).

7.3. Integrated Review of Effectiveness

7.3.1. Assessment of Efficacy Across Trials

Study 12871 and 16349 Part A generated efficacy data used to further support the establishment of efficacy based on the pivotal study 16349 Part B.

Study 12871

Study 12871 was an open-label, Phase 1 dose-escalation study in patients with advanced cancer. The primary objective of the study was to determine the maximum tolerated dose. Fifty-seven patients received treatment with copanlisib, 48 patients with solid tumors and 9 patients with Non-Hodgkin lymphoma. Of the patients with NHL, 6 patients had follicular lymphoma and 3 patients had diffuse large B-cell lymphoma.

Of the patients with NHL, all patients had received prior rituximab and 4 patients had received prior bendamustine. Patients with NHL received copanlisib 0.8 mg/kg on Days 1, 8, and 15 of a 28-day cycle. In patients with follicular lymphoma, the median duration of exposure was 50.1 weeks (12.5 cycles) with a median dose-intensity of 87.7% of the planned dose. Four of the 6 patients with follicular lymphoma required dose interruptions and 1 patients required a dose reduction.

The key efficacy results are displayed in Table 19. Response was assessed according to the Cheson 2007 criteria (Cheson et al. 2007).

Table 19 Efficacy Results in Study 12871 Based on Investigator Assessment

Response	FL Group N = 6 n (%)	NHL Group N = 9 n (%)
ORR (CR or PR)	6 (100.0)	7 (77.8)
Best Response		
CR	1 (16.7)	1 (11.1)
PR	5 (83.3)	6 (66.7)
SD	0	0
PD	0	2 (22.2)
ORR: Objective response rate, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease Source: FDA analysis of ADTR dataset for study 12871 NHL patients		

A retrospective independent review was conducted for the patients with follicular lymphoma and 2 patients were assessed as achieving a complete response by the independent review that were previously classified as achieving a partial response by the investigator. The patients with a complete response had durable remissions and were on treatment ranging from 16 cycles to greater than 40 cycles of copanlisib.

Study 16349 Part A

Study 16349 Part A was an open-label, parallel group Phase 2 study to evaluate efficacy and safety in patients with indolent or aggressive NHL. The primary endpoint was objective response rate, defined as the proportion of patients who had a best response of complete response or partial response according to the Cheson 1999 criteria (Cheson et al. 1999). A total of 84 patients were treated on study with copanlisib 0.8 mg/kg on Days 1, 8, and 15 of a 28-day treatment cycle. The distribution of lymphoma subtypes included 51 patients with aggressive NHL, 16 patients with follicular lymphoma, 13 patients with chronic lymphocytic leukemia, 3 patients with marginal zone lymphoma, and 1 patient with small lymphocytic lymphoma.

Of the 33 patients with FL, CLL, MZL, and SLL, 90.9% received prior treatment with rituximab and the median number of prior systemic therapies was 4.0 (range 2 to 10). The median exposure was 22.7 weeks (5.7 cycles) with a median dose-intensity of 86.8% of the planned dose. Twenty-six (78.8%) of 33 patients required a dose interruption and 6 patients (18.2%) required dose reductions.

The efficacy results are displayed in Table 20. Of the 33 patients with FL, CLL, MZL, and SLL, 32 patients had data available to assess response. An objective response rate (CR or PR) was achieved in 14 patients (43.8%) with a median duration of response of 12.8 months. In patients with follicular lymphoma, 6 patients achieved an objective response for an ORR of 40.0%. Three patients with follicular lymphoma achieved a complete response.

Table 20 Efficacy Results in Study 16349 Part A Based on Independent Assessment

Response	FL Group N = 15 n (%)	NHL Group N = 32 n (%)
ORR (CR or PR)	6 (40.0)	14 (43.8)
Best Response		
CR	3 (20.0)	3 (9.4)
PR	3 (20.0)	11 (34.4)
SD	8 (53.3)	15 (46.9)
PD	0	1 (3.1)
NA	1 (6.7)	2 (6.3)
Duration of Response (months)		
Median	NA	12.8
Min, Max	NA	2.0, 18.9
ORR: Objective response rate, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease, NA: Not available Source: FDA analysis of ADTR dataset for study 16349 patients		

Study 12871 and 16349 Part A demonstrate similar efficacy results to the pivotal Study 16349 Part B, albeit the sample size is small in Study 12871 and 16349 Part A. Further, the patients baseline demographic characteristics are similar and the patients disease characteristics are similar amongst the trials in regard to time since diagnosis and prior therapy. However, there is significant heterogeneity across the trials and a pooled analysis of efficacy is not warranted.

Additional Efficacy Considerations

Due to the single-arm study design, various efficacy endpoints, such as change in the size of lymph nodes, progression-free survival, and overall survival were not analyzed because the clinical significance cannot be adequately interpreted due to the confounding effects of an uncontrolled study and the natural history of the disease.

7.3.2. Integrated Assessment of Effectiveness

The efficacy of copanlisib was assessed in the pivotal study 16349 Part B, which was a an open-label, single arm, multicenter, Phase II study of copanlisib in patients with relapsed or refractory follicular lymphoma, marginal zone lymphoma, small lymphocytic lymphoma, or lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia.

The primary efficacy endpoint was objective response rate, which was analyzed with descriptive statistics. Of the 142 patients in the FAS, 84 patients achieved an objective response. The percentage of ORR is 59% (95% CI [51%, 67%]). Of all the patients who achieved an objective response, 17 patients (12%) achieved a complete response and 67 patients (47%) achieved a partial response. The estimated median duration of response was 22.6 months (95% CI [7.4, 22.6], range [0, 22.6]).

In patients with follicular lymphoma (n = 104), 61 patients achieved an objective response. The percentage of ORR is 59% (95% CI [49%, 68%]). Of all these patients who achieved an objective response, 15 patients (14%) achieved a complete response and 46 patients (44%) achieved a partial response. The estimated median duration of response was 12.2 months (95% CI [6.9, 22.6], range [0, 22.6]).

The effectiveness of copanlisib treatment for patients with relapsed follicular lymphoma is established by the objective response rate in Study 16349 Part B and the durability of the response. There is insufficient information to support an expectation of long-term benefit with long-term use of copanlisib as the exposure duration is limited. Nevertheless, the effectiveness of copanlisib treatment in patients with relapsed follicular lymphoma is clinically meaningful.

7.4. Review of Safety

Safety Review Approach

The safety population is defined as all patients assigned to study treatment with at least one

study drug administration.

The clinical review of safety for this NDA is based on the following:

- Clinical study report for study 16349, 16349 Part B, 12871, 15205, and 16790
- Protocol and statistical analysis plan for study 16349 Part B
- Integrated datasets from the five studies listed in Table 8 in Section 7.1.1.
- Case report forms and safety narratives
- Summary of Clinical Safety
- Integrated Summary of Safety and integrated datasets
- Proposed labeling for Aliqopa

7.4.2. Review of the Safety Database

The safety review was conducted using the integrated datasets provided by the Applicant from clinical studies 16349, 16349 Part B, 12871, 15205, and 16790 (Table 8). A data pool including patients with relapsed or refractory follicular lymphoma, marginal zone lymphoma, small lymphocytic lymphoma, or lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia was used to develop the safety profile in patients with indolent forms of NHL treated with copanlisib 0.8 mg/kg or 60mg IV on Day 1, 8, and 15 of 28-day cycle (referred to as “indolent NHL or iNHL group” in text). Additionally, a data pool with patients with follicular lymphoma was analyzed separately because the proposed indication is specific to patients with follicular lymphoma (referred to as “FL or FL group” in text). Furthermore, data from patients with aggressive NHL and CLL were used to provide supporting safety information in hematologic malignancies (referred to as “NHL/CLL or NHL/CLL group” in text). The safety review will focus on patients with indolent forms of NHL in order to characterize the safety profile in the population of interest.

Overall Exposure

The doses 0.8 mg/kg and 60mg intravenous were evaluated in patients with indolent NHL and patients with aggressive NHL and CLL. The copanlisib doses of 0.8 mg/kg and 60mg fixed dose are considered the same based on the population pharmacokinetic evaluation as the pharmacokinetic parameters of copanlisib were not affected by body weight. Copanlisib 60mg IV administered on Days 1, 8, and 15 of 28-day cycle is the proposed dosing regimen.

The median exposure duration for patients with indolent NHL was 22.0 weeks (range 1.0 to 206.0 weeks). The median exposure duration for patients with follicular lymphoma was similar to the indolent NHL group. Patients with NHL/CLL had a slightly decreased median exposure of 18.9 weeks (range 1.0 to 206.0 weeks) due to an increased number of patients only receiving treatment for 0 to 3 cycles. Table 21 shows a summary of duration of copanlisib treatment by patient group.

Table 21: Duration of Treatment with Copanlisib

	FL Group N = 126	iNHL Group N = 168	NHL/CLL Group N = 244
Exposure duration (weeks)			
Median	22.4	22.0	18.9
Min, Max	1.0, 206.0	1.0, 206.0	1.0, 206.0
Number of cycles			
Median	5.6	5.5	4.7
Min, Max	0.3, 51.5	0.3, 51.5	0.3, (51.5)
Number of cycles (n, %)			
0 to 3 cycles	36 (28.6)	47 (28.0)	92 (37.7)
>3 to 6 cycles	31 (24.6)	47 (28.0)	62 (25.4)
>6 to 9 cycles	21 (16.7)	27 (16.1)	33 (13.5)
>9 to 12 cycles	14 (11.1)	20 (11.9)	22 (9.0)
>12 cycles	24 (19.0)	27 (16.1)	35 (14.3)
Source: FDA analysis of ADEX dataset for safety analysis population			

Patients with follicular lymphoma received a median of 5.6 cycles and 16.0 copanlisib infusions. Patients with indolent NHL and patients with NHL/CLL received 5.5 and 4.7 cycles, and 16.0 and 14.0 infusions, respectively. The median dose per administration was 60mg for each patient group and the median dose intensity for the FL group, iNHL group, and NHL/CLL group was 95.2%, 95.0%, and 93.4%, respectively.

Relevant characteristics of the safety population:

Safety data were available for 168 patients with follicular lymphoma, marginal zone lymphoma, small lymphocytic lymphoma, or lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia, a subset of 126 patients with follicular lymphoma, and a total of 244 patients with indolent and aggressive forms of NHL and CLL treated with single agent copanlisib. The 244 patients were treated with copanlisib 0.8 mg/kg or 60mg fixed dose on Days 1, 8, and 15 of 28-day cycle. The copanlisib doses of 0.8 mg/kg and 60mg fixed dose are considered the same based on the population PK evaluation as the PK parameters of copanlisib were not affected by body weight. Copanlisib 60mg IV administered on Days 1, 8, and 15 of 28-day cycle is the proposed dosing regimen. The demographics of the 168 patients with iNHL, the 126 patients with follicular lymphoma, and the 244 total patients with NHL and CLL are shown in Table 22.

Table 22: Patient Demographics

Characteristic	FL Group N = 126	iNHL Group N = 168	NHL/CLL Group N = 244
Sex (n, %)			
Male	60 (47.6)	78 (46.4)	124 (50.8)
Female	66 (52.4)	90 (53.6)	120 (49.2)
Race (n, %)			
White	104 (82.5)	140 (83.3)	192 (78.7)
Black	0	0	0
Asian	13 (10.3)	15 (8.9)	15 (6.1)
Not reported	9 (7.1)	13 (7.7)	37 (15.2)
Age (years)			
Median	62	64	64
Min, Max	25, 81	25, 82	22, 90
Age group (n, %)			
<65 years	73 (57.9)	88 (52.4)	125 (51.2)
≥65 years	53 (42.1)	80 (47.6)	119 (48.8)
Diagnosis			
FL	126 (100.0)	126 (75.0)	127 (52.0)
MZL	0	26 (15.5)	26 (10.7)
SLL	0	9 (5.3)	9 (3.7)
LPL/WM	0	7 (4.2)	7 (2.9)
CLL	0	0	13 (5.3)
DLBCL	0	0	23 (9.4)
MCL	0	0	11 (4.5)
PMBCL	0	0	1 (0.4)
T-cell NHL	0	0	20 (8.2)
Transformed iNHL	0	0	7 (2.9)
Weight (kg)			
Median	73.0	72.4	71.5
Min, Max	45.8, 128.0	45.8, 128.0	45.8, 129.7
BMI (kg/m ²)			
Median	25.8	25.8	25.6
Min, Max	19.2, 43.5	17.4, 43.5	16.1, 43.5
ECOG status (n, %)			
0	75 (59.5)	94 (55.9)	125 (51.2)
1	46 (36.5)	68 (40.5)	98 (40.2)
2	5 (4.0)	6 (3.6)	21 (8.6)
Number of prior systemic therapies			
Median	3	3	3
Min, Max	1, 8	1, 10	1, 10

Characteristic	FL Group N = 126	iNHL Group N = 168	NHL/CLL Group N = 244
eGFR (n, %)			
Normal	41 (32.5)	53 (31.5)	69 (28.3)
Mildly impaired	68 (54.0)	94 (56.0)	137 (56.1)
Moderately impaired	17 (13.5)	21 (12.5)	35 (14.3)
Missing	0	0	3 (1.2)
Hepatic impairment (n, %)			
Normal	112 (88.9)	152 (90.5)	215 (88.1)
Mild impairment	13 (10.3)	15 (8.9)	26 (10.7)
Missing	1 (0.8)	1 (0.6)	3 (1.2)
Hemoglobin A1c (n, %)			
<5.7%	78 (61.9)	105 (62.5)	153 (62.7)
5.7% to <6.5%	33 (26.2)	44 (26.2)	66 (27.0)
≥6.5%	12 (9.5)	16 (9.5)	18 (7.4)
Missing	3 (2.4)	3 (1.8)	7 (2.9)
History of diabetes (n, %)			
Yes	16 (12.7)	20 (11.9)	20 (8.2)
No	110 (87.3)	148 (88.1)	224 (91.8)
History of hypertension (n, %)			
Yes	42 (33.3)	53 (31.5)	70 (28.7)
No	84 (66.7)	115 (68.5)	174 (71.3)
History of respiratory distress (n, %)			
Yes	34 (27.0)	48 (28.6)	75 (30.7)
No	92 (73.0)	120 (71.4)	169 (69.3)
BMI: Body mass index; CLL: Chronic lymphocytic leukemia; DLBCL: Diffuse large B-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; eGFR: Estimated glomerular filtration rate; FL: Follicular lymphoma; LPL/WM: Lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia; MCL: Mantle cell lymphoma; MZL: Marginal zone lymphoma; NHL: Non-Hodgkin's lymphoma; iNHL: indolent NHL; PMBCL: Primary mediastinal large B-cell lymphoma; SLL: Small lymphocytic lymphoma; Source: FDA analysis of ADSL dataset for safety analysis population			

Reviewer Comment: The number of patients with indolent forms of NHL is 168 patients, 126 of 168 are patients with follicular lymphoma. The number of patients with follicular lymphoma is relatively small considering the prevalence of the disease. Although, the demographic characteristics appear consistent with the general population of patients with indolent forms of NHL and follicular lymphoma.

Adequacy of the safety database:

The size of the safety database for patients with follicular lymphoma is small with 126 patients. The pooled safety database that includes 168 patients with indolent forms of NHL and 244

patients with NHL and CLL may be sufficient to provide a reasonable estimate of adverse reactions observed with copanlisib. The duration of treatment - a median of 5 cycles - is moderate. The assessment of adverse reactions over time will need to be expanded once more mature data is available. The pooled patient populations in the safety analysis are representative of patients with relapsed or refractory NHL and CLL. However, Blacks and Hispanics are under-represented compared with the overall NHL population in the United States.

7.4.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The data submitted to this NDA was of adequate quality to perform the safety review. Overall, there were no concerns regarding the integrity of the NDA submission.

Categorization of Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.0. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03. Treatment-emergent adverse events were defined as any event arising or worsening after the start of study drug administration until 35 days after the last study drug administration. Where indicated in the tables or text, some adverse events are presented as group terms.

Routine Clinical Tests

Clinical laboratory assessments were performed as specified in each individual protocol with routine blood tests performed at least every 4 weeks. In study 16349 Part B, laboratory abnormalities were to be reported as adverse events if meeting any of the following criteria:

- Causing apparent clinical manifestations
- Requiring treatment
- Results in change of study treatment (e.g., treatment interruption, treatment discontinuation, dose administered)
- Causes the patient to withdraw from the study
- Clinically significant in the investigator's judgement

The safety assessments and frequency of assessments described in the protocols are adequate for the patient population, disease, and indication being investigated.

7.4.4. Safety Results

Deaths

Deaths were assessed by the Applicant for all deaths during treatment and up to 35 days post permanent treatment discontinuation. Overall, 6 patients in the FL group and iNHL group (4.8% and 3.6%, respectively) died and 17 patients (7.0%) died in the NHL/CLL group during treatment

or up to 35 days post permanent treatment discontinuation.

Table 23: Summary of Deaths

	FL Group N = 126 n(%)	iNHL Group N = 168 n(%)	NHL/CLL Group N = 244 n(%)
All Deaths	25 (19.8)	29 (17.3)	75 (30.7)
During treatment or up to 35 days after last dose	6 (4.8)	6 (3.6)	17 (7.0)
Pneumonia	3 (2.4)	3 (1.8)	4 (1.6)
Progressive disease	1 (0.8)	1 (0.6)	6 (2.5)
Acute kidney injury	1 (0.8)	1 (0.6)	1 (0.4)
Embolism	1 (0.8)	1 (0.6)	1 (0.4)
Heart Failure	0	0	1 (0.4)
Myocardial infarction	0	0	1 (0.4)
Meningitis	0	0	1 (0.4)
Sepsis	0	0	1 (0.4)
Renal Failure	0	0	1 (0.4)

Source: FDA analysis of ADAE and ADSL dataset for safety analysis population

iNHL Patients

Case 1: Subject 280119001 is a 75 year-old female with follicular lymphoma who received 3 cycles of copanlisib and achieved an overall response of stable disease. Following completion of cycle 3, the patient developed *Acinobacter* central line infection (blood culture) and *Pneumocystis jirovecii* pneumonia (bronchoalveolar lavage). Concomitantly, the patient developed atrial fibrillation and thrombotic thrombocytopenia purpura, leading to a fatal acute ischemic stroke. The patient died 21 days after last study dose. The investigator determined the *Pneumocystis jirovecii* pneumonia, thrombotic thrombocytopenia purpura, and thrombo-embolic event (acute ischemic stroke) to be “related” to study drug.

Case 2: Subject 140519001 is a 77 year-old male with follicular lymphoma who received 1 cycle (2 of 3 infusions) of copanlisib and developed acute kidney injury secondary to dehydration and contrast nephropathy. The patient experienced worsening renal dysfunction and died 14 days after last study dose. The investigator determined the Grade 5 event to be “not related” to study drug.

Case 3: Subject 260019002 is a 77 year-old male with follicular lymphoma who received 11 cycles of copanlisib and achieved stable disease. The patient developed fatal pneumonia during cycle 11 (7 days after last study dose). The patient also had Grade 4 neutropenia at the time of the pneumonia. The investigator determined the Grade 5 event to be “not related” to study drug.

Case 4: Subject 220019002 is a 68 year-old female with follicular lymphoma who received 3 cycles of copanlisib and achieved a response of stable disease after 2 cycles. The patient developed pneumonitis and pneumonia following cycle 1 of therapy. Treatment was administered for infectious pneumonitis and pneumonia due to *Pseudomonas* (sputum culture) that resolved. Following the 3rd cycle of copanlisib, the patient presented with a subsequent clinical pneumonia and died 21 days after last study dose due to respiratory failure secondary to progressive pneumonia. The investigator determined the Grade 5 event to be “related” to study drug.

Case 5: Subject 280099001 is a 77 year-old male with follicular lymphoma who received 2 cycles of copanlisib and achieved a partial response. The patient developed pneumonia during the 3rd cycle and the patient discontinued treatment. The pneumonia progressed to respiratory failure and the patient died 33 days after last study dose. The investigator determined the Grade 5 event to be “related” to study drug.

Case 6: Subject 280050003 is a 76 year-old female with follicular lymphoma who received 4 cycles of copanlisib and experienced progressive disease. During cycle 4, the patients developed a pleural effusion followed by general health deterioration, likely due to progressive disease. The patient underwent euthanasia 22 days after last study dose.

Reviewer Comment: Cases 1, 3, 4, and 5 are consistent with fatal pneumonia, with case 3 also associated with Grade 4 neutropenia. The other cases exhibit sufficient alternative explanations to be considered not-related to copanlisib. Labeling should reflect the potential for fatal drug-related infections, specifically pneumonia.

Serious Adverse Events

A serious adverse event (SAE) during treatment or within 35 days after end of treatment occurred in 62 patients (49.2%) with follicular lymphoma, 81 patients (48.2%) with indolent NHL, and 125 patients (51.2%) with NHL or CLL. The distribution of SAEs by system organ class (SOC) is shown in Table 24.

Table 24: Serious Adverse Events in ≥ 2% of Patients

System Organ Class Preferred Term	FL Group N = 126 n (%)	iNHL Group N = 168 n (%)	NHL/CLL Group N = 244 n (%)
Any SAE	62 (49.2)	81 (48.2)	124 (50.8)
Blood and lymphatic system disorders	7 (5.6)	8 (4.8)	13 (5.3)
Neutropenia	3 (2.4)	4 (2.4)	4 (1.6)
Febrile neutropenia	3 (2.4)	3 (1.8)	6 (2.5)
Gastrointestinal disorders	7 (5.6)	9 (5.4)	18 (7.4)

System Organ Class Preferred Term	FL Group N = 126 n (%)	iNHL Group N = 168 n (%)	NHL/CLL Group N = 244 n (%)
Diarrhea	3 (2.4)	4 (2.4)	7 (2.9)
General disorders and administration site conditions	9 (7.1)	14 (8.3)	22 (9.0)
Pyrexia	5 (4.0)	9 (5.4)	10 (4.1)
General health deterioration	3 (2.4)	3 (1.8)	8 (3.3)
Infections and infestations	33 (26.2)	39 (23.2)	55 (22.5)
Pneumonia	25 (19.8)	30 (17.9)	35 (14.3)
Sepsis	3 (2.4)	3 (1.8)	5 (2.0)
Metabolism and nutrition disorders	7 (5.6)	11 (6.5)	13 (5.3)
Hyperglycemia	5 (4.0)	8 (4.8)	8 (3.3)
Respiratory, thoracic and mediastinal disorders	13 (10.3)	16 (9.5)	23 (9.4)
Pneumonitis	9 (7.1)	10 (6.0)	10 (4.1)
Cardiac disorders	1 (0.8)	2 (1.2)	4 (1.6)
Hepatobiliary disorders	0	2 (1.2)	3 (1.2)
Musculoskeletal and connective tissue disorders	2 (1.6)	2 (1.2)	4 (1.6)
Nervous system disorders	0	1 (0.6)	2 (0.8)
Renal and urinary disorders	4 (3.2)	4 (2.4)	7 (2.9)
Skin and subcutaneous tissue disorders	1 (0.8)	2 (1.2)	3 (1.2)
Vascular disorders	1 (0.8)	3 (1.8)	7 (2.9)
Source: FDA analysis of ADAE dataset for safety analysis population			

Serious adverse events that were considered at least possibly related to copanlisib occurred in 35 patients (27.8%) in the FL group, 44 patients (26.2%) in the iNHL group, and 69 patients (28.3%) in the NHL/CLL group. The most common treatment related SAEs were pneumonia, pneumonitis, hyperglycemia, febrile neutropenia, and diarrhea.

Reviewer Comment: The pattern of serious adverse events is consistent with the identified safety signals associated with copanlisib that include pneumonia, pneumonitis, hyperglycemia, neutropenia, and diarrhea. Labeling should contain appropriate warning and precautions for the identified safety signals associated with copanlisib.

Dropouts and/or Discontinuations Due to Adverse Effects

Table 25 provides a summary of discontinuations, dose reduction, and dose delays due to treatment emergent adverse events in the safety analysis population.

Table 25: Summary of Discontinuations, Dose Reductions, and Dose or Treatment Delays due to Treatment Emergent Adverse Events

	FL Group N = 126 n(%)	iNHL Group N = 168 n(%)	NHL/CLL Group N = 244 n(%)
Discontinuation due to AE	31 (24.6)	41 (24.4)	58 (23.8)
Dose reduction due to AE	30 (23.8)	41 (24.4)	50 (20.5)
Dose or treatment delay due to AE	79 (62.7)	107 (63.7)	146 (59.8)
AE: Adverse event Source: FDA analysis of ADAE dataset for safety analysis population			

The most common treatment emergent adverse events leading to permanent treatment discontinuation of copanlisib in patients with indolent NHL were pneumonitis and pneumonia (3.6% each), fatigue (2.4%), hyperglycemia, neutropenia, and thrombocytopenia (1.8% each). The frequency and reasons for discontinuation were similar for patients in the FL group and the NHL/CLL group (Table 26).

Table 26: Treatment Emergent Adverse Events Leading to Discontinuation in ≥ 1% of Patients

System Organ Class Preferred Term	FL Group N = 126 n (%)	iNHL Group N = 168 n (%)	NHL/CLL Group N = 244 n (%)
Any TEAE leading to discontinuation	31 (24.6)	41 (24.4)	57 (23.4)
Blood and lymphatic system disorders	2 (1.6)	5 (3.0)	6 (2.5)
Thrombocytopenia	2 (1.6)	3 (1.8)	3 (1.2)
Neutropenia	1 (0.8)	3 (1.8)	3 (1.2)
Anemia	0	2 (1.2)	2 (0.8)
Gastrointestinal disorders	3 (2.4)	4 (2.4)	5 (2.0)
Nausea	1 (0.8)	2 (1.2)	2 (0.8)
General disorders and administration site conditions	4 (3.2)	6 (3.6)	7 (2.9)
Fatigue	2 (1.6)	4 (2.4)	5 (2.0)
Infections and infestations	6 (4.8)	8 (4.8)	10 (4.1)
Pneumonia	4 (3.2)	6 (3.6)	7 (2.9)
Metabolism and nutrition disorders	5 (4.0)	5 (3.0)	5 (2.0)
Hyperglycemia	3 (2.4)	3 (1.8)	3 (1.2)
Hypercalcemia	2 (1.6)	2 (1.2)	2 (0.8)
Renal and urinary disorders	2 (1.6)	2 (1.6)	3 (1.2)
Acute kidney injury	2 (1.6)	2 (1.6)	2 (0.8)
Respiratory, thoracic and mediastinal disorders	5 (4.0)	8 (4.8)	12 (4.9)
Pneumonitis	5 (4.0)	6 (3.6)	7 (2.9)

System Organ Class Preferred Term	FL Group N = 126 n (%)	iNHL Group N = 168 n (%)	NHL/CLL Group N = 244 n (%)
TEAE: Treatment emergent adverse event Source: FDA analysis of ADAE dataset for safety analysis population			

The most common treatment emergent adverse events leading to copanlisib dose reduction in patients with indolent NHL included pneumonia (17.9%), pneumonitis (6.0%), pyrexia (5.4%), and hyperglycemia (4.8%). Patients in the FL group and NHL/CLL group had similar results (Table 27).

Table 27: Treatment Emergent Adverse Events Leading to Dose Reduction in $\geq 1\%$ of Patients

System Organ Class Preferred Term	FL Group N = 126 n (%)	iNHL Group N = 168 n (%)	NHL/CLL Group N = 244 n (%)
Any TEAE leading to dose reduction	62 (49.2)	81 (48.2)	124 (50.8)
Blood and lymphatic system disorders	7 (5.6)	8 (4.8)	13 (5.3)
Neutropenia	3 (2.4)	4 (2.4)	4 (1.6)
Febrile neutropenia	3 (2.4)	3 (1.8)	6 (2.5)
Gastrointestinal disorders	7 (5.6)	9 (5.4)	18 (7.4)
Diarrhea	3 (2.4)	4 (2.4)	7 (2.9)
General disorders and administration site conditions	9 (7.1)	14 (8.3)	22 (9.0)
Pyrexia	5 (4.0)	9 (5.4)	10 (4.1)
General health deterioration	3 (2.4)	3 (1.8)	8 (3.3)
Infections and infestations	33 (26.2)	39 (23.2)	55 (22.5)
Pneumonia	25 (19.8)	30 (17.9)	35 (14.3)
Sepsis	3 (2.4)	3 (1.8)	5 (2.0)
Metabolism and nutrition disorders	7 (5.6)	11 (6.5)	13 (5.3)
Hyperglycemia	5 (4.0)	8 (4.8)	8 (3.3)
Respiratory, thoracic and mediastinal disorders	13 (10.3)	16 (9.5)	23 (9.4)
Pneumonitis	9 (7.1)	10 (6.0)	10 (4.1)
Cardiac disorders	1 (0.8)	2 (1.2)	4 (1.6)
Hepatobiliary disorders	0	2 (1.2)	3 (1.2)
Musculoskeletal and connective tissue disorders	2 (1.6)	2 (1.2)	4 (1.6)
Nervous system disorders	0	1 (0.6)	2 (0.8)
Renal and urinary disorders	4 (3.2)	4 (2.4)	7 (2.9)
Skin and subcutaneous tissue disorders	1 (0.8)	2 (1.2)	3 (1.2)

System Organ Class Preferred Term	FL Group N = 126 n (%)	iNHL Group N = 168 n (%)	NHL/CLL Group N = 244 n (%)
Vascular disorders	1 (0.8)	3 (1.8)	7 (2.9)
TEAE: Treatment emergent adverse event Source: FDA analysis of ADAE dataset for safety analysis population			

Treatment emergent adverse events leading to a treatment delay occurred in 63.7% of patients with indolent NHL. The most common treatment emergent adverse events associated with copanlisib treatment delays were neutropenia (16.1%), pneumonia (10.7%), hypertension (6.0%), and bronchitis (5.4%). Patients in the FL group and NHL/CLL group had similar results (Table 28).

Table 28: Treatment Emergent Adverse Events Associated with Copanlisib Treatment Delay in $\geq 2\%$ of Patients

System Organ Class Preferred Term	FL Group N = 126 n (%)	iNHL Group N = 168 n (%)	NHL/CLL Group N = 244 n (%)
Any TEAE leading to treatment delay	79 (62.7)	107 (63.7)	146 (59.8)
Blood and lymphatic system disorders	26 (20.6)	37 (22.0)	51 (20.9)
Neutropenia	17 (13.5)	27 (16.1)	36 (14.8)
Thrombocytopenia	5 (4.0)	7 (4.2)	9 (3.7)
Leukopenia	3 (2.4)	3 (1.8)	3 (1.2)
Gastrointestinal disorders	8 (6.3)	13 (7.7)	20 (8.2)
Diarrhea	3 (2.4)	4 (2.4)	7 (2.9)
General disorders and administration site conditions	14 (11.1)	21 (12.5)	32 (13.1)
Pyrexia	5 (4.0)	8 (4.8)	12 (4.9)
Fatigue	3 (2.4)	6 (3.6)	9 (3.7)
General health deterioration	3 (2.4)	3 (1.8)	4 (1.6)
Infections and infestations	39 (31.0)	48 (28.6)	58 (23.8)
Pneumonia	15 (11.9)	18 (10.7)	21 (8.6)
Bronchitis	8 (6.3)	9 (5.4)	10 (4.1)
Respiratory tract infection	4 (3.2)	4 (2.4)	4 (1.6)
Nasopharyngitis	3 (2.4)	3 (1.8)	3 (1.2)
Metabolism and nutrition disorders	2 (1.6)	4 (2.4)	4 (1.6)
Hyperglycemia	2 (1.6)	3 (1.8)	3 (1.2)
Respiratory, thoracic and mediastinal disorders	11 (8.7)	15 (8.9)	17 (7.0)
Pneumonitis	5 (4.0)	6 (3.6)	7 (2.9)
Vascular disorders	7 (5.6)	13 (7.7)	16 (6.6)

System Organ Class Preferred Term	FL Group N = 126 n (%)	iNHL Group N = 168 n (%)	NHL/CLL Group N = 244 n (%)
Hypertension	7 (5.6)	10 (6.0)	13 (5.3)
TEAE: Treatment emergent adverse event Source: FDA analysis of ADAE dataset for safety analysis population			

Reviewer Comment: The reasons for discontinuation (pneumonia, pneumonitis, fatigue, hyperglycemia, neutropenia, and thrombocytopenia) are consistent with the serious adverse events associated with copanlisib. It appears that dose reductions and dose delays are reasonable strategies to allow most patients to resume treatment with copanlisib following an adverse event.

Significant Adverse Events

The Applicant identified adverse events of special interest including non-infectious pneumonitis, infections, neutropenia, thrombocytopenia, hypertension, hyperglycemia, gastro-intestinal disorders, and hepatotoxicity. Table 29 describes the adverse events of special interest for patients with follicular lymphoma, indolent NHL, and NHL/CLL.

Table 29: Summary of Adverse Events of Special Interest

Adverse Events of Special Interest	FL Group N = 126 n(%)		iNHL Group N = 168 n(%)		NHL/CLL Group N = 244 n(%)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Non-infectious pneumonitis	12 (9.5)	5 (4.0)	15 (8.9)	5 (3.0)	17 (7.0)	6 (2.5)
Infections	91 (72.2)	33 (26.2)	112 (66.7)	39 (23.2)	155 (63.5)	56 (23.0)
Respiratory tract infection	63 (50.0)	24 (19.0)	80 (47.6)	29 (17.3)	105 (43.0)	38 (15.6)
Opportunistic infection	8 (6.3)	4 (3.2)	9 (5.4)	5 (3.0)	12 (4.9)	7 (2.9)
Neutropenia	37 (29.4)	28 (22.2)	50 (29.8)	39 (23.2)	74 (30.3)	61 (25.0)
Thrombocytopenia	33 (26.2)	11 (8.7)	37 (22.0)	14 (8.3)	46 (18.9)	20 (8.2)
Hypertension	43 (34.1)	32 (25.4)	58 (34.5)	45 (26.8)	92 (37.7)	71 (29.1)
Hyperglycemia	66 (52.4)	47 (37.3)	90 (53.6)	66 (39.3)	131 (53.7)	82 (33.6)
Gastro-intestinal disorders	86 (68.3)	15 (11.9)	109 (64.9)	18 (10.7)	163 (66.8)	29 (11.9)
Hepatotoxicity	9 (7.1)	2 (1.6)	12 (7.1)	2 (1.2)	15 (6.1)	4 (1.6)
Source: FDA analysis of ADAE dataset for safety analysis population						

In patients with indolent NHL treated with copanlisib, 66.7% experienced an adverse event of infection. Twenty-three percent of patients experienced a Grade 3 or greater event of infection. There were 3 fatal infections of pneumonia in patients with indolent NHL and 7 fatal infections within the NHL/CLL group and 4 of 7 were pneumonia. Neutropenia (29.8%) and thrombocytopenia (22.0%) were common amongst patients treated with copanlisib. There was a considerable number of patients that experienced hypertension (34.5%) and hyperglycemia

(53.6%), with the majority of patients having Grade 3 or greater hypertension (26.8%) or hyperglycemia (39.3%). The most common gastro-intestinal disorder was diarrhea in 35.7% of patients with indolent NHL.

Treatment Emergent Adverse Events and Adverse Reactions

Treatment emergent adverse events were assessed from the start of study drug until 35 days after the last study drug administration. Treatment emergent adverse events were reported in 124 (98.4%) patients with follicular lymphoma and 166 (98.8%) patients with indolent NHL. Grade ≥ 3 TEAEs were reported in 106 (84.1%) patients with follicular lymphoma and 142 (84.5%) patients with indolent NHL. The number of patients with common treatment emergent adverse events ($\geq 10\%$ of patients) is displayed in Table 30 in decreasing order of incidence by system organ class and preferred term.

Table 30: Treatment Emergent Adverse Events in $\geq 10\%$ of Patients

System Organ Class Preferred Term	FL Group N = 126 n (%)		iNHL Group N = 168 n (%)		NHL/CLL Group N = 244 n (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4
Any TEAE	124 (98.4)	106 (84.1)	166 (98.8)	142 (84.5)	240 (98.4)	208 (85.2)
Blood and lymphatic system disorders	59 (46.8)	39 (31.0)	81 (48.2)	53 (31.5)	115 (47.1)	80 (32.8)
Neutropenia	29 (23.0)	23 (18.3)	42 (25.0)	34 (20.2)	62 (25.4)	52 (21.3)
Thrombocytopenia	20 (15.9)	6 (4.8)	24 (14.3)	9 (5.4)	28 (11.5)	12 (4.9)
Anemia	19 (15.1)	7 (5.6)	27 (16.1)	8 (4.8)	45 (18.4)	19 (7.8)
Gastrointestinal disorders	86 (68.3)	15 (11.9)	109 (64.9)	18 (10.7)	163 (66.8)	29 (11.9)
Diarrhea	47 (37.3)	7 (5.6)	60 (35.7)	8 (4.8)	88 (36.1)	12 (4.9)
Nausea	33 (26.2)	1 (0.8)	43 (25.6)	1 (0.6)	70 (28.7)	2 (0.8)
Constipation	19 (15.1)	0	22 (13.1)	0	34 (13.9)	0
Vomiting	18 (14.3)	0	21 (12.5)	0	31 (12.7)	0
Abdominal pain ¹	16 (12.7)	2 (1.6)	21 (12.5)	3 (1.8)	30 (12.3)	5 (2.0)
General disorders and administration site conditions	80 (63.5)	11 (8.7)	104 (61.9)	15 (8.9)	157 (64.3)	31 (12.7)
Fatigue ²	46 (36.5)	2 (1.6)	61 (36.3)	6 (3.6)	94 (38.5)	13 (5.3)
Pyrexia	33 (26.2)	5 (4.0)	41 (24.4)	6 (3.6)	57 (23.4)	9 (3.7)
Infections and infestations	91 (72.2)	33 (26.2)	112 (66.7)	39 (23.2)	155 (63.5)	56 (23.0)
URI	18 (14.3)	2 (1.6)	23 (13.7)	3 (1.8)	25 (10.2)	3 (1.2)
Pneumonia ³	16 (12.7)	14 (11.1)	20 (11.9)	17 (10.1)	22 (9.0)	19 (7.8)
Bronchitis	14 (11.1)	1 (0.8)	15 (8.9)	1 (0.6)	23 (9.4)	2 (0.8)
Metabolism and nutrition disorders	81 (64.3)	54 (42.9)	107 (63.7)	74 (44.0)	155 (63.5)	99 (40.6)
Hyperglycemia	62 (49.2)	45 (35.7)	85 (50.6)	63 (37.5)	125 (51.2)	79 (32.4)
Decreased appetite	14 (11.1)	0	18 (10.7)	0	30 (12.3)	1 (0.4)
Musculoskeletal and						

System Organ Class Preferred Term	FL Group N = 126 n (%)		iNHL Group N = 168 n (%)		NHL/CLL Group N = 244 n (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4
connective tissue disorders	37 (29.4)	1 (0.8)	48 (28.6)	2 (1.2)	72 (29.5)	5 (2.0)
Muscle spasms	13 (10.3)	0	17 (10.1)	1 (0.6)	23 (9.4)	1 (0.4)
Nervous system disorders	32 (25.4)	1 (0.8)	41 (24.4)	2 (1.2)	67 (27.5)	3 (1.2)
Headache	15 (11.9)	1 (0.8)	16 (9.5)	1 (0.6)	30 (12.3)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	61 (48.4)	11 (8.7)	80 (47.6)	14 (8.3)	114 (46.7)	20 (8.2)
Cough ⁴	28 (22.2)	0	36 (21.4)	0	51 (20.9)	0
Dyspnea ⁵	16 (12.7)	5 (4.0)	20 (11.9)	5 (3.0)	29 (11.9)	7 (2.9)
Skin and subcutaneous tissue disorders	46 (36.5)	3 (2.4)	65 (38.7)	4 (2.4)	89 (36.5)	7 (2.9)
Rash ⁶	18 (14.3)	1 (0.8)	24 (14.3)	2 (1.2)	36 (14.8)	4 (1.6)
Vascular disorders	48 (38.1)	33 (26.2)	67 (39.9)	47 (28.0)	105 (43.0)	76 (31.1)
Hypertension	43 (34.1)	32 (25.4)	58 (34.5)	45 (26.8)	91 (37.3)	71 (29.1)
URI: Upper respiratory tract infection ¹ Abdominal Pain: includes preferred terms (PT) abdominal discomfort, abdominal pain, abdominal pain upper and lower; ² Fatigue: includes preferred terms fatigue and asthenia; ³ Pneumonia: includes PTs pneumonia, pneumonia bacterial, and pneumonia pneumococcal; ⁴ Cough: includes PTs cough, productive cough, and upper-airway cough syndrome; ⁵ Dyspnea: includes PTs dyspnea, dyspnea at rest, dyspnea exertional; ⁶ Rash: includes PTs rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, and exfoliative rash Source: FDA analysis of ADAE dataset for safety analysis population						

The most frequently reported TEAEs in patients with indolent NHL were hyperglycemia (50.6%), fatigue (36.3%), diarrhea (35.7%), hypertension (34.5%), nausea (25.6%), neutropenia (25.0%), pyrexia (24.4%), and cough (21.4%). The most frequent TEAEs in the FL group and NHL/CLL group were similar to the indolent NHL group.

The number of patients with Grade 3 or 4 treatment emergent adverse events are shown in Table 30 by system organ class and preferred term. The Grade 3-4 TEAEs reported for at least 5% of patients in the indolent NHL group were hyperglycemia (37.5%), hypertension (26.8%), neutropenia (20.2%), pneumonia (10.1%), thrombocytopenia (5.4%), and diarrhea (4.8%)

Adverse Drug Reactions

Adverse drug reactions (ADR) were identified by the Applicant in patients with indolent NHL (excluding patients with aggressive NHL and CLL). A treatment emergent adverse event was determined to be an ADR if >50% of these events were assessed as drug-related by the investigators. The number of patients with adverse drug reactions (≥5% of patients) is displayed in Table 31 in decreasing incidence by system organ class and preferred term.

Table 31: Adverse Drug Reactions in ≥5% of Patients with Indolent NHL

System Organ Class Preferred Term	iNHL Group N = 168 n (%)		
	All Grades	Grade 3-4	Grade 5
Blood and lymphatic system disorders			
Leukopenia ¹	61 (36.3)	46 (27.4)	0
Neutropenia ²	53 (31.5)	42 (20.2)	0
Thrombocytopenia ³	37 (22.0)	14 (8.3)	0
Anemia ⁴	30 (17.9)	8 (4.8)	0
Gastrointestinal disorders			
Diarrhea	60 (35.7)	8 (4.8)	0
Nausea	43 (25.6)	1 (0.6)	0
Constipation	22 (13.1)	0	0
Vomiting	21 (12.5)	0	0
Abdominal pain ⁵	21 (12.5)	3 (1.8)	0
Stomatitis	13 (7.7)	2 (1.2)	0
Oropharyngeal ulcer	10 (6.0)	1 (0.6)	0
General disorders and administration site conditions			
Fatigue ⁶	61 (36.3)	6 (3.6)	0
Pyrexia	41 (24.4)	6 (3.6)	0
Edema	14 (8.3)	0	0
Infections and infestations			
Lower respiratory tract infection ⁷	35 (20.8)	23 (13.7)	2 (1.2)
Rhinitis	14 (8.3)	0	0
Sinusitis	9 (5.4)	0	0
Metabolism and nutrition disorders			
Hyperglycemia ⁸	90 (53.6)	66 (39.3)	0
Decreased appetite	19 (11.3)	0	0
Musculoskeletal and connective tissue disorders			
Muscle spasms	17 (10.1)	1 (0.6)	0
Arthralgia	13 (7.7)	0	0
Nervous system disorders			
Headache	17 (10.1)	1 (0.6)	0
Paresthesia and dysesthesia ⁹	11 (6.5)	0	0
Peripheral neuropathy	9 (5.4)	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnea ¹¹	20 (11.9)	5 (3.0)	0
Pneumonitis ¹⁰	15 (8.9)	5 (3.0)	0
Skin and subcutaneous tissue disorders			
Rash ¹²	26 (15.5)	3 (1.8)	0

System Organ Class Preferred Term	iNHL Group N = 168 n (%)		
	All Grades	Grade 3-4	Grade 5
Pruritus	16 (9.5)	0	0
Vascular disorders Hypertension	58 (34.5)	45 (26.8)	0
¹ Leukopenia preferred terms (PT): leukopenia, lymphopenia, neutropenia, neutrophil count decreased, and white blood cell count decreased ² Neutropenia PTs: neutropenia, neutrophil count decreased, and febrile neutropenia ³ Thrombocytopenia PTs: thrombocytopenia and platelet count decreased ⁴ Anemia PTs: anemia and hemoglobin decreased ⁵ Abdominal pain PTs: abdominal discomfort, abdominal pain, abdominal pain upper and lower ⁶ Fatigue PTs: fatigue and asthenia ⁷ Lower respiratory tract infection PTs: pneumonia, pneumonia bacterial, pneumonia pneumococcal, pneumonia fungal, pneumonia viral, pneumocystis jirovecii pneumonia, bronchopulmonary aspergillosis, and lung infection ⁸ Hyperglycemia PTs: hyperglycemia, blood glucose increase, glucose tolerance impaired, and glycosylated hemoglobin increased ⁹ Paresthesia and dysesthesia PTs: paresthesia, paresthesia oral, and oral dysesthesia ¹⁰ Pneumonitis PTs: pneumonitis and interstitial lung disease ¹¹ Dyspnea PTs: dyspnea, dyspnea at rest, and dyspnea exertional ¹² Rash PTs: rash, rash erythematous, rash macular, rash maculo-papular, exfoliative rash, and dermatitis exfoliative Source: FDA analysis of ADAE dataset for safety analysis population			

The adverse drug reactions reported for at least 20% of patients with indolent NHL were hyperglycemia (53.6%), leukopenia and fatigue (36.3% each), diarrhea (35.7%), hypertension (34.5%), neutropenia (31.5%), nausea (25.6%), pyrexia (24.4%), thrombocytopenia (22.0%), and lower respiratory tract infection (20.8%). The adverse drug reactions of hyperglycemia, leukopenia, hypertension, neutropenia, and lower respiratory tract infection were mostly Grade 3-4 events. Two patients experienced a Grade 5 adverse drug reaction of a lower respiratory tract infection.

Reviewer Comment: The Applicant utilized acceptable grouped MedDRA preferred terms to more accurately describe the adverse reaction profile to copanlisib. FDA review of adverse reactions utilized the same group terms as the Applicant (Table 31). The most common adverse reactions are similar to the most common treatment emergent adverse events (Table 30). The Applicant proposed to use a threshold of an adverse reaction incidence of $\geq 10\%$ in patients with indolent NHL for the USPI to describe the adverse event profile. The use of adverse reactions and a threshold of $\geq 10\%$ incidence in patients is acceptable as it will accurately describe the adverse event profile associated with copanlisib treatment.

Hypersensitivity

FDA conducted an evaluation for hypersensitivity adverse events using the preferred terms:

anaphylactic reactions, anaphylactic shock, drug hypersensitivity, hypersensitivity, urticaria.

A review of all patients treated with copanlisib revealed two patients with hematologic malignancies and 9 patients with solid tumors had a hypersensitivity adverse event of Grade 2 or greater (6 hypersensitivity and 5 urticaria) reported. There were no reports of anaphylaxis in patients treated with copanlisib. Four patients had hypersensitivity reactions considered to be related to copanlisib. The cases consisted of skin manifestations only in the form of a rash.

Reviewer Comment: There were no reported events of copanlisib-related anaphylaxis or severe hypersensitivity or severe infusion-related reactions. Review of the four cases of possibly-related hypersensitivity demonstrated that all cases exhibit skin manifestations only described as a rash or urticarial rash. It is unclear if the reactions were truly hypersensitivity reactions or adverse events of rash. Additional information is needed to further characterize the risk of hypersensitivity versus the risk of skin-related adverse events with copanlisib treatment.

Laboratory Findings

The Applicant included an analysis of laboratory parameters that included patients with changes from baseline with respect to the reference ranges of laboratory values. The FDA was able to independently reproduce the analysis and the results were consistent with those of the Applicant.

Clinical Hematology Laboratory

Table 32 displays the hematology laboratory abnormalities in patients treated with copanlisib.

Table 32: Summary of Hematology Laboratory Abnormalities

Hematology laboratory abnormality	FL Group N = 126 n (%)		iNHL Group N = 168 n (%)		NHL/CLL Group N = 244 n (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4
Lymphocytes decreased	99 (81.1)	33 (26.2)	126 (75.0)	47 (28.0)	176 (72.1)	82 (33.6)
Hemoglobin decreased	96 (76.2)	6 (4.8)	130 (77.4)	7 (4.2)	199 (81.6)	16 (6.6)
Platelets decreased	88 (69.8)	11 (8.7)	109 (64.9)	14 (8.3)	158 (64.8)	24 (9.8)
Neutrophils decreased	77 (61.1)	34 (27.0)	104 (61.9)	45 (26.8)	146 (59.8)	71 (29.1)
PTT increased	25 (21.4)	0	38 (22.6)	2 (1.2)	47 (19.3)	3 (1.2)
PT increased	8 (7.3)	1 (0.8)	20 (11.9)	4 (2.4)	30 (12.3)	6 (2.5)
PTT: Partial thromboplastin time, PT: prothrombin time Source: FDA analysis of ADXT dataset for safety analysis population						

Cytopenias were common during treatment with copanlisib in the majority of patients. In patients with indolent NHL, 47 patients (28.0%) experienced a Grade 3-4 decrease in lymphocytes and 45 patients (26.8%) experienced a Grade 3-4 decrease in neutrophils.

The Applicant observed consistent trends among hematology laboratory parameters during treatment with copanlisib. Patients experienced an average decrease in neutrophils around $1 \times 10^9/\text{L}$ throughout treatment (Figure 13). Change in hemoglobin was minimal during treatment (Figure 14). Patients experienced oscillating platelet counts during treatment, with platelets recovering to baseline around Day 8 of the subsequent cycle (Figure 15)

Figure 13: Mean Change in Neutrophils from Baseline by Treatment Cycle

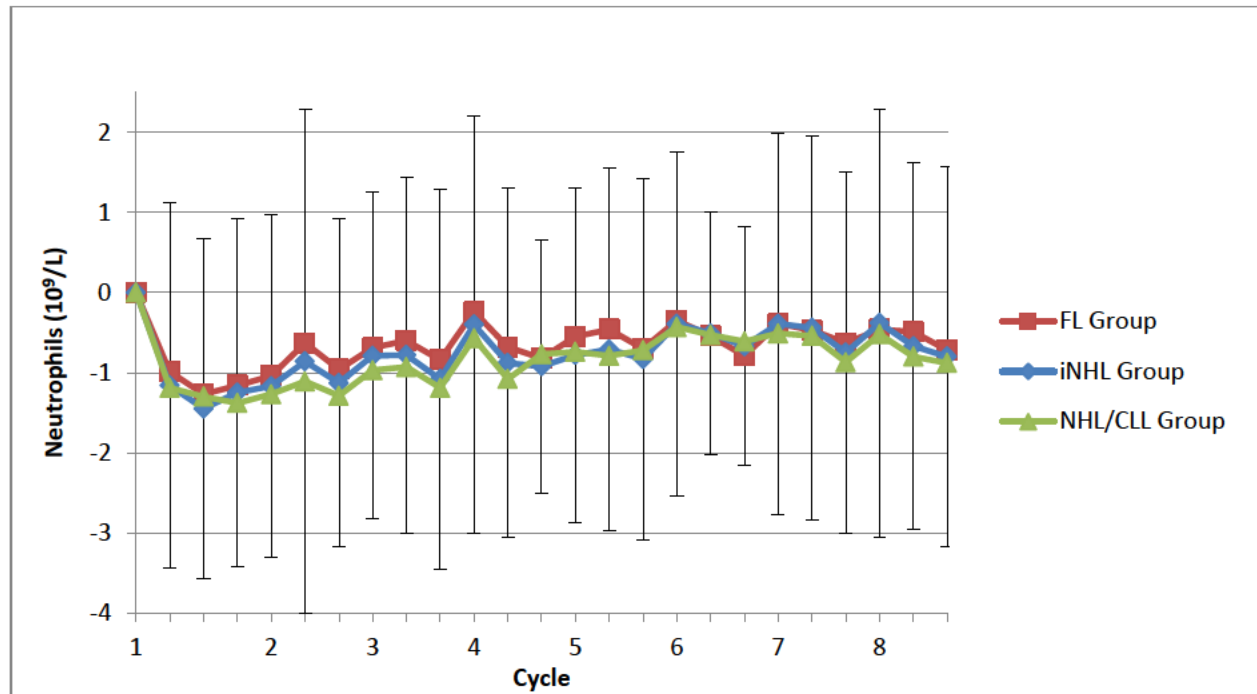


Figure 14: Mean Change in Hemoglobin from Baseline by Treatment Cycle

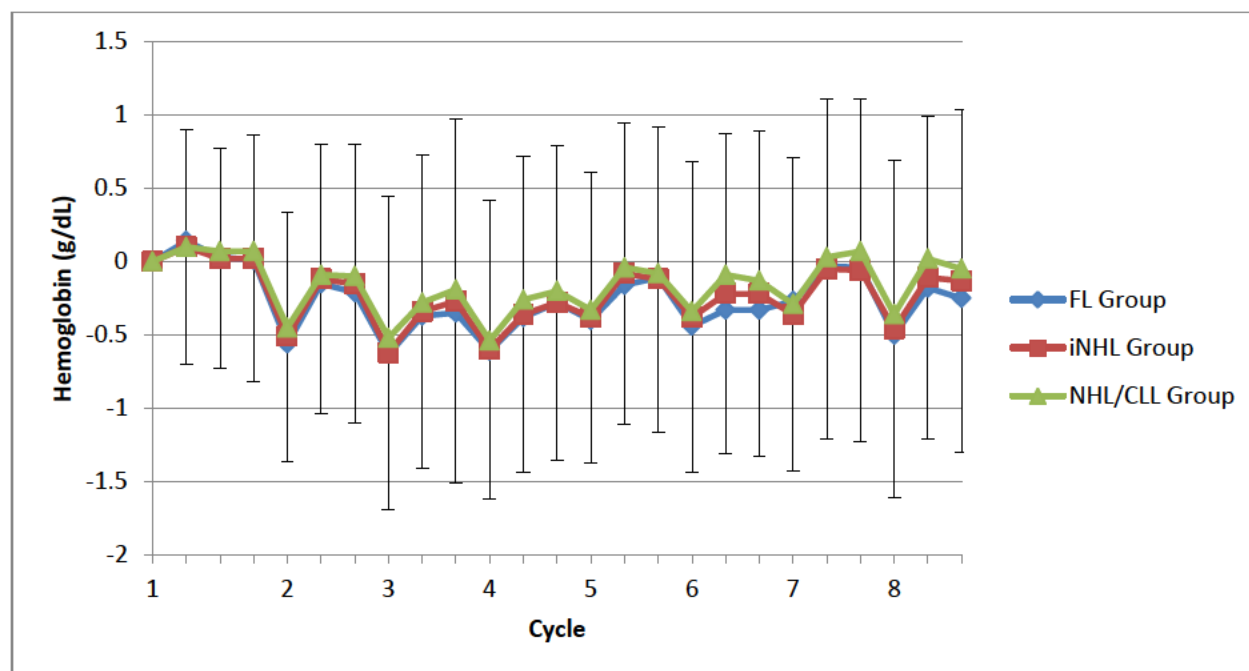
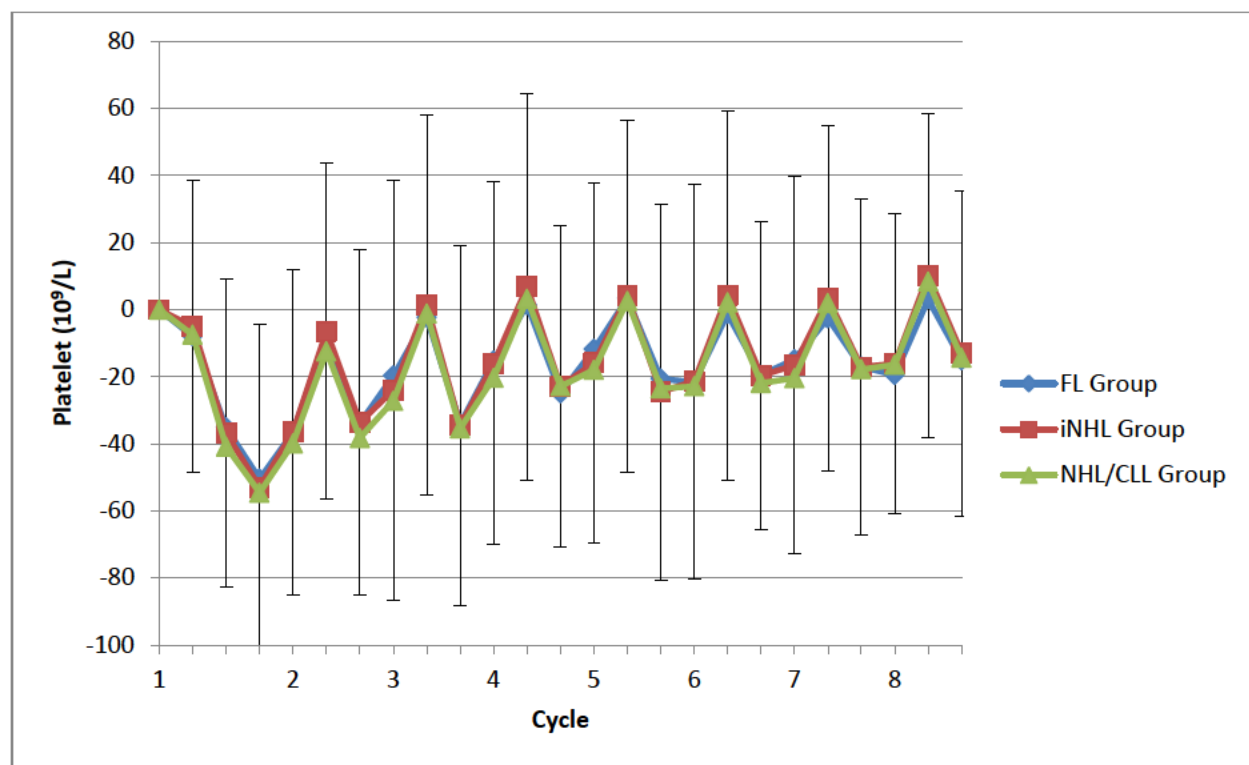


Figure 15: Mean Change in Platelets from Baseline by Treatment Cycle



Reviewer Comment: The decrease in neutrophils of $1 \times 10^9/L$ appears to occur early in treatment and is sustained throughout treatment. Given the incidence of serious infections, dose modifications (delay or reduction) may need to be considered in patients with prolonged, severe neutropenia. Additionally, patients that have a pronounced decrease in platelets or prolonged recovery of platelets may be at risk for bleeding complications. Dose modification strategies need to be considered for thrombocytopenia.

Clinical Chemistry

The majority of chemistry laboratory parameters were Grade ≤ 2 in severity except for hyperglycemia and hyperuricemia. Table 33 displays the chemistry laboratory abnormalities in the safety analysis population.

Table 33: Clinical Biochemical Laboratory Abnormalities

Biochemical laboratory abnormality	FL Group N = 126 n (%)		iNHL Group N = 168 n (%)		NHL/CLL Group N = 244 n (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4
Hyperglycemia	119 (94.4)	59 (46.8)	160 (95.2)	81 (48.2)	230 (94.3)	100 (41.0)
Creatinine increased	117 (92.9)	2 (1.6)	153 (91.1)	2 (1.2)	210 (86.1)	4 (1.6)
Hypertriglyceridemia	59 (46.8)	3 (2.4)	74 (44.0)	6 (3.6)	75 (30.7)	6 (2.5)
Hypercholesterolemia	57 (45.2)	0	76 (45.2)	0	76 (31.1)	0 ()
Hypophosphatemia	55 (43.7)	17 (13.5)	72 (42.9)	24 (14.3)	110 (45.1)	36 (14.8)
ALP increased	46 (36.5)	0	64 (38.1)	1 (0.6)	91 (37.3)	2 (0.8)
Hypoalbuminemia	42 (33.3)	0	59 (35.1)	0	101 (41.4)	3 (1.2)
Hypomagnesemia	40 (31.7)	2 (1.6)	54 (32.1)	3 (1.8)	75 (30.7)	5 (2.0)
AST increased	36 (28.6)	0	46 (27.4)	2 (1.2)	71 (29.1)	5 (2.0)
Proteinuria	36 (28.6)	1 (0.8)	43 (25.6)	1 (0.6)	55 (22.5)	1 (0.4)
Hypoglycemia	35 (27.8)	2 (1.6)	53 (31.5)	2 (1.2)	67 (27.5)	2 (0.8)
Hyperuricemia	33 (26.2)	33 (26.2)	42 (25.0)	42 (25.0)	57 (23.4)	57 (23.4)
Hypocalcemia	31 (24.6)	2 (1.6)	38 (22.6)	3 (1.8)	57 (23.4)	3 (1.2)
Hypokalemia	31 (24.6)	4 (3.2)	37 (22.0)	5 (3.0)	59 (24.2)	9 (3.7)
ALT increased	29 (23.0)	1 (0.8)	38 (22.6)	2 (1.2)	61 (25.0)	5 (2.0)
Amylase increased	26 (20.6)	3 (2.4)	35 (20.8)	4 (2.4)	50 (20.5)	6 (2.5)
Lipase increased	24 (19.0)	8 (6.3)	34 (20.2)	13 (7.7)	49 (20.1)	19 (7.8)
Hyponatremia	24 (19.0)	3 (2.4)	29 (17.3)	4 (2.4)	58 (23.8)	8 (3.3)
Hyperbilirubinemia	22 (17.5)	1 (0.8)	29 (17.3)	2 (1.2)	46 (18.9)	4 (1.6)
Hypercalcemia	19 (15.1)	1 (0.8)	25 (14.9)	2 (1.2)	30 (12.3)	4 (1.6)
Hyperkalemia	17 (13.5)	1 (0.8)	24 (14.3)	2 (1.2)	38 (15.6)	8 (3.3)
Hypernatremia	13 (10.3)	1 (0.8)	17 (10.1)	1 (0.6)	22 (9.0)	1 (0.4)
Hypermagnesemia	9 (7.1)	1 (0.8)	11 (6.5)	1 (0.6)	14 (5.7)	2 (0.8)

ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, AST: Aspartate aminotransferase
Source: FDA analysis of ADXT dataset for safety analysis population

Over 94% of patients experienced hyperglycemia during treatment with 81 patients (48.2%) experiencing Grade ≥ 3 hyperglycemia. Hyperglycemia is further discussed in Section 7.4.5. Additionally, all episodes of hyperuricemia were Grade ≥ 3 by laboratory parameters, but no patients had clinical tumor lysis syndrome. Liver-related abnormalities were mostly Grade 1-2 in severity.

Reviewer Comment: Overall, the biochemical profile is composed of mild elevations (Grade 1 or 2) of transaminases and electrolytes. It is important to note Grade 1-2 hypertriglyceridemia and hypercholesterolemia were common in patients treated with copanlisib. With the adverse event of hypertension, consideration of cardiac risk-factors is needed to ensure an appropriate assessment of risk for patients.

Hy's Law

The Applicant performed an analysis for Hy's law cases and used a definition of AST or ALT values >3 times the upper limit of normal and total bilirubin value > 2 times the upper limit of normal. Table 34 displays the liver-related laboratory parameters greater than the specified upper limit of normal.

Table 34 Liver Laboratory Abnormalities

Liver Laboratory Parameter	FL Group N = 126		iNHL Group N = 168		NHL/CLL Group N = 244	
	Event #/ Subject #	% of Subjects	Event #/ Subject #	% of Subjects	Event #/ Subject #	% of Subjects
AST or ALT						
AST or ALT $> 3\times$ ULN	3/124	2.4	4/165	2.4	6/235	2.6
AST or ALT $> 5\times$ ULN	1/124	0.8	2/165	1.2	4/235	1.7
AST or ALT $> 10\times$ ULN	1/124	0.8	2/165	1.2	3/235	1.3
AST or ALT $> 20\times$ ULN	0/124	0	0/165	0	0/235	0
Total Bilirubin						
TB $> 1.5\times$ ULN	4/120	3.3	4/160	2.5	8/228	3.5
TB $> 2\times$ ULN	3/120	2.5	3/160	1.9	5/228	2.2
Combination						
AST or ALT $> 3\times$ ULN, TB $> 2\times$ ULN	0/118	0	0/158	0	1/224	0.4
ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, TB: Total bilirubin, ULN: Upper limit of normal Source: FDA analysis of ADXT dataset for safety analysis population						

FDA Analysis of Hy's Law

The FDA clinical reviewer performed an analysis of potential Hy's law cases and identified two possible cases based on AST or ALT greater than 3 times the upper limit of normal and total bilirubin greater than 2 times the upper limit of normal. The analysis used all laboratory data and evaluated the combination of lab results at any point in the study.

The two patients identified had concomitant elevation of alkaline phosphatase and review of the medical records revealed both patients experienced hepatobiliary obstruction and inflammation due to alternative causes (cholangitis and gallbladder obstruction).

Reviewer Comment: The medical histories were reviewed by the clinical reviewer which confirmed that the 2 patients had alternative explanations and did not meet criteria for Hy's law. Overall, the evidence suggests copanlisib is associated with mild elevation of transaminases and bilirubin. A safety signal for severe or serious hepatotoxicity is not present at this time.

Vital Signs

The Applicant provided a record of the vital signs and a description of the changes in vital signs during treatment with copanlisib. Hypertension is an important identified risk associated with copanlisib and is discussed in Section 7.4.5. A review of weight, heart rate, and temperature did not reveal any identified safety signals.

Electrocardiograms

Electrocardiograms were performed at baseline and on day 1 of every 3rd cycle and at the end of treatment. Additional ECG evaluation occurred at the end of copanlisib infusion (1 hour) in study 12871 and 15205. Treatment emergent adverse events related to ECG changes were reviewed along with all cardiac events.

In patients with indolent NHL treated with copanlisib, there were no ECG-related TEAEs in the system organ class investigations. There was 1 patient in the NHL/CLL group with a TEAE of prolonged QT. For patients with indolent NHL, ECG-related treatment emergent adverse events in the SOC Cardiac disorders included atrial fibrillation (1.8%), tachycardia, bradycardia, and arrhythmia (0.06%). There was 1 patient with an event of syncope, but was not associated with QT interval prolongation. The incidence of ECG-related treatment emergent adverse events was similar in NHL/CLL group.

The evaluation of electrocardiogram QTc interval prolongation was based on Bazett's correction (QTcB) and Fridericia's correction (QTcF). Bazett's correction is known to overestimate the number of patients with QTc prolongation. In patients with indolent NHL, no patients had a QTcB or QTcF >500 ms. At subsequent visits during treatment, 4/137 patients (2.9%) and 2/118 patients (1.7%) had a QTcB and QTcF >500 ms, respectively. Further, 9/137 patients (6.6%) and 2/118 (1.7%) had a QTcB and QTcF >480 - 500 ms, respectively. Three patients (2.2%) experience a QTcB increase ≥60 ms and 5 patients (4.2%) with QTcF ≥60 ms. The NHL/CLL Group had similar findings.

QT

The FDA Interdisciplinary Review Team (IRT) for QT studies reviewed the QT study report. The following summary statements were taken from the QT-IRT review.

The QT-IRT reviewed the study report provided by the Applicant, which describes a meta-analysis of five studies. The data included in this meta-analysis are inadequate to characterize the potential for QTc prolongation for copanlisib because there were issues with the quality of the data for which information requests were sent to the Applicant for clarification. The data quality issues were not resolved during the time of the review period. Furthermore, the Applicant was informed previously that the ECG and PK data from study 16270 – an ongoing study designed to evaluate the potential for QTc prolongation – would be the pivotal data for QTc evaluation. Thus, the QT-IRT assessment of the potential for QTc prolongation for copanlisib will be deferred until the data collected in study 16270 is submitted and the data quality issues resolved.

Reviewer Comment: There were no clinical safety signals for the effects of copanlisib on ECGs in the safety population. However, due to the inadequacy of the submitted data for the evaluation of the potential for QTc prolongation with copanlisib, a postmarketing requirement was developed in order to obtain the necessary information.

Immunogenicity

There were no studies of anti-drug antibodies performed.

7.4.5. Analysis of Submission-Specific Safety Issues

Pneumonitis

The Applicant identified suspected non-infectious pneumonitis events using a standardized MedDRA query (SMQ) for interstitial lung disease that included the preferred terms 1) pneumonitis, 2) interstitial lung disease, and 3) pulmonary fibrosis. In patients with iNHL, 15 patients (8.9%) experienced a pneumonitis event and 5 patients developed Grade 3 pneumonitis. There were no Grade 4 or 5 events of pneumonitis. Ten patients (6.0%) with iNHL had pneumonitis reported as an SAE due to the need for hospitalization (5 patients) or designation as a medically important event (5 patients). Table 35 displays a summary of non-infectious pneumonitis events in patients treated with copanlisib.

Table 35: Summary of Pneumonitis Treatment Emergent Adverse Events and Associated Risk Factors

Pneumonitis	FL Group N = 126 n (%)	iNHL Group N = 168 n (%)	NHL/CLL Group N = 244 n (%)
All grade adverse events	12 (9.5)	15 (8.9)	17 (7.0)
Grade 3-4	5 (4.0)	5 (3.0)	6 (2.5)
Serious adverse events	9 (7.1)	10 (6.0)	11 (4.5)
Adverse event recovered or resolved	8 (6.3)	9 (5.4)	10 (4.1)

Pneumonitis	FL Group N = 126 n (%)	iNHL Group N = 168 n (%)	NHL/CLL Group N = 244 n (%)
History of respiratory disorder			
Yes	34	48	75
Pneumonitis incidence	5 (14.7)	6 (12.5)	6 (8.0)
No	92	120	169
Pneumonitis incidence	7 (7.6)	9 (7.5)	11 (6.5)
Prior radiotherapy			
Yes	39	45	66
Pneumonitis incidence	2 (5.1)	2 (4.4)	2 (3.0)
No	87	123	178
Pneumonitis incidence	10 (11.5)	13 (10.6)	15 (8.4)
Prior upper body radiotherapy¹			
Yes	9	9	16
Pneumonitis incidence	0	0	0
No	117	159	228
Pneumonitis incidence	12 (10.3)	15 (9.4)	17 (7.5)
¹ Excludes prior radiotherapy to head and neck Source: FDA analysis of ADAE dataset for safety analysis population			

Time to onset ranged from 7 weeks to 19.4 months on copanlisib. The patients treated with corticosteroids had resolution of their pneumonitis. There is a trend of increased incidence of pneumonitis in patients with a history of a respiratory disorder at baseline. Prior treatment with radiotherapy in general or radiotherapy to the chest did not increase the incidence of pneumonitis in patients treated with copanlisib.

Reviewer Comment: The evidence suggests that copanlisib may be a direct cause of lung toxicity. The overall incidence of pneumonitis is unclear since it is a diagnosis of exclusion. Eight patients were treated with corticosteroids, but the optimal treatment strategy is not established. Labeling will need to include a warning for pneumonitis and appropriate dose modifications or discontinuation to ensure safe use.

Cytopenias, Infections, and Hemorrhage

A review of treatment emergent adverse events revealed that 53.6% of patients with indolent NHL experienced an adverse event of myelosuppression or cytopenia. Table 36 displays the preferred terms and all grades and grades 3-4 for adverse events of myelosuppression or cytopenia in patients treated with copanlisib.

Table 36: Myelosuppression or Cytopenia Treatment Emergent Adverse Events by Preferred Term

Preferred Term	FL Group N = 126 n (%)		iNHL Group N = 168 n (%)		NHL/CLL Group N = 244 n (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4
Any TEAE	67 (53.2)	43 (34.1)	90 (53.6)	57 (33.9)	126 (51.6)	87 (35.7)
Neutropenia	29 (23.0)	23 (18.3)	42 (25.0)	34 (20.2)	62 (25.4)	52 (21.3)
Anemia	19 (15.1)	7 (5.6)	27 (16.1)	8 (4.8)	44 (18.0)	19 (7.8)
Thrombocytopenia	20 (15.9)	6 (4.8)	24 (14.3)	9 (5.3)	28 (11.5)	12 (4.9)
Platelet count decreased	13 (10.3)	5 (4.0)	13 (7.7)	5 (3.0)	19 (7.8)	8 (3.3)
Neutrophil count decreased	8 (6.3)	5 (4.0)	10 (6.0)	7 (4.2)	15 (6.1)	12 (4.9)
Lymphopenia	8 (6.3)	3 (2.4)	9 (5.4)	2 (1.2)	10 (4.1)	5 (2.0)
White blood cell count decreased	8 (6.3)	6 (4.8)	9 (5.4)	7 (4.2)	9 (3.7)	7 (2.9)
Febrile neutropenia	5 (4.0)	5 (4.0)	5 (3.0)	5 (3.0)	9 (3.7)	9 (3.7)
Leukopenia	5 (4.0)	2 (1.6)	5 (3.0)	2 (1.2)	6 (2.5)	3 (1.2)
Lymphocytosis	1 (0.8)	0	4 (2.4)	3 (1.8)	4 (1.6)	3 (1.2)
Hemoglobin decreased	3 (2.4)	0	3 (1.8)	0	4 (1.6)	1 (0.4)
Leukocytosis	2 (1.6)	1 (0.8)	3 (1.8)	2 (1.2)	3 (1.2)	2 (0.8)

TEAE: Treatment emergent adverse event
Source: FDA analysis of ADAE dataset for safety analysis population

Complications of myelosuppression include infection and hemorrhagic events. For infections, 66.7% of patients with indolent NHL experienced an adverse event of infection (Table 37).

Table 37: Summary of Infection Treatment Emergent Adverse Events

Infections and infestations	FL Group N = 126 n (%)	iNHL Group N = 168 n (%)	NHL/CLL Group N = 244 n (%)
All grade AEs	91 (72.2)	112 (66.7)	155 (63.5)
Grade 3-4	33 (26.2)	39 (23.2)	56 (23.0)
SAE	33 (26.2)	39 (23.2)	55 (22.5)
Most common TEAEs			
Upper respiratory tract infection	18 (14.3)	23 (13.7)	25 (10.2)
Pneumonia	16 (12.7)	20 (11.9)	22 (9.0)
Bronchitis	14 (11.1)	15 (8.9)	23 (9.4)
Urinary tract infection	11 (8.7)	12 (7.1)	22 (9.0)
Oral herpes	9 (7.1)	10 (6.0)	12 (4.9)
Rhinitis	7 (5.6)	9 (5.4)	11 (4.5)
Sinusitis	7 (5.6)	8 (4.8)	11 (4.5)
Most common Grade 3-4 TEAEs			

Infections and infestations	FL Group N = 126 n (%)	iNHL Group N = 168 n (%)	NHL/CLL Group N = 244 n (%)
Pneumonia	14 (11.1)	17 (10.1)	19 (7.8)
Sepsis	3 (2.4)	3 (1.8)	5 (2.0)
Pneumocystis jirovecii pneumonia	2 (1.6)	2 (1.2)	3 (1.2)
AE: Adverse event, SAE: Serious adverse event, TEAE: Treatment emergent adverse event Source: FDA analysis of ADAE dataset for safety analysis population			

Upper respiratory tract infections, pneumonia, and bronchitis were the common infections reported. The most common Grade 3-4 infection was pneumonia in 10.1% of patients with indolent NHL. There were 3 patient deaths due to pneumonia in the indolent NHL group.

Reviewer Comment: Treatment with copanlisib appears to be associated with an increased risk of upper and lower respiratory tract infections, including life-threatening and fatal cases of lower respiratory tract infections. The incidence of pneumonitis and neutropenia with copanlisib treatment may increase the risk of acquiring a respiratory infection. Labeling should reflect the risk of infection, neutropenia, and pneumonitis.

Complications associated with hemorrhage occurred in 17 patients (10.1%) with indolent NHL. The most common preferred terms in the hemorrhage SMQ included contusion (3/164, 1.8%), hematoma (2/164, 1.2%), and epistaxis (2/164, 1.2%).

Seven patients (4.2%) with indolent NHL experienced a gastrointestinal bleed during treatment with copanlisib. The review used a group term for gastrointestinal bleed that included: rectal hemorrhage, gastrointestinal hemorrhage, hematochezia, gastritis hemorrhagic, hematemesis, intra-abdominal hemorrhage, mesenteric hemorrhage, upper gastrointestinal hemorrhage, lower gastrointestinal hemorrhage, hemorrhoidal hemorrhage, and melena. Two patients experienced Grade 3 events of hemorrhoidal hemorrhage and melana, respectively, and one patient experienced Grade 4 gastrointestinal hemorrhage.

Reviewer Comment: Copanlisib is associated with gastrointestinal toxicity and the gastrointestinal tract is exposed to copanlisib, despite intravenous administration, as it is primarily excreted through the biliary tract. The direct exposure and oscillating thrombocytopenia may cause a risk for gastrointestinal bleeding. Patients should be aware that severe gastrointestinal bleeding can occur with copanlisib treatment.

Hypertension

Hypertension is an important identified risk for patients who receive treatment with copanlisib. Table 38 summarizes the treatment emergent adverse event of hypertension.

Table 38: Summary of Hypertension Treatment Emergent Adverse Events and Associated Risk Factors

Hypertension (HTN)	FL Group N = 126 n (%)	iNHL Group N = 168 n (%)	NHL/CLL Group N = 244 n (%)
All grade adverse events	43 (34.1)	58 (34.5)	91 (37.3)
Grade 3	32 (25.4)	45 (26.8)	71 (29.1)
Serious adverse events	0	0	2 (0.8)
HTN recovered or resolved	36 (28.6)	49 (29.2)	76 (31.1)
HTN leading to:			
Dose delay	7 (5.6)	10 (6.0)	13 (5.3)
Dose reduction	4 (3.2)	8 (4.8)	9 (3.7)
Discontinuation	1 (0.8)	1 (0.6)	1 (0.4)
History of hypertension			
Yes	42	53	70
HTN incidence	18 (42.9)	25 (47.2)	37 (52.9)
Grade 3	16 (38.1)	23 (43.4)	34 (48.6)
No	84	115	174
HTN incidence	25 (29.8)	33 (28.7)	55 (31.6)
Grade 3	16 (19.0)	22 (19.1)	37 (21.3)

Source: FDA analysis of ADAE dataset for safety analysis population

Hypertension occurred in 34.5% of patients with indolent NHL and the majority of events were Grade 3 events (45/58, 77.6%). There was no Grade 4 or 5 events of hypertension. Hypertension was a reason for treatment delay in 6.0% of patients with indolent NHL. Despite the number of Grade 3 events, there were no serious adverse events of hypertension in the indolent NHL group. Patients with a history of hypertension were more likely to experience an adverse event of hypertension and be a Grade 3 event.

Hypertension was further evaluated in the pre-dose and post-dose setting. Overall, 37 patients (37/58, 63.8%) with indolent NHL received an anti-hypertensive medication. There were 25 patients (25/58, 43.1%) that had a pre-dose blood pressure of systolic ≥ 150 mmHg or diastolic ≥ 90 mmHg. Sixteen (64.0%) of the 25 patients required an anti-hypertensive medication prior to receiving the scheduled dose of copanlisib. Treatments included diuretics, calcium channel blockers, beta blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs). All patients that received an anti-hypertensive medication for a pre-dose blood pressure $\geq 150/90$ mmHg were able to receive their scheduled copanlisib dose.

In the post-dose setting, 52 patients (52/58, 89.7%) with indolent NHL had a post-dose blood pressure of systolic ≥ 150 mmHg or diastolic ≥ 90 mmHg. Twenty-nine patients (29/52, 55.8%)

received an anti-hypertension medication following administration of copanlisib. The treatments were the same as the agents used for pre-dose hypertension and included diuretics, calcium channel blockers, beta blockers, ACE inhibitors, and ARBs. Furthermore, 8 patients required new or an additional chronic anti-hypertensive medication during treatment with copanlisib.

Reviewer Comment: Copanlisib caused hypertension, including events that required medical intervention. Multiple classes of anti-hypertensive agents were used including diuretics, calcium channel blockers, beta-blockers, ACE inhibitors, and ARBs. The agents utilized allowed for administration of copanlisib if used in the pre-dose setting. Short-acting anti-hypertensive agents used in the post-dose setting appear to be sufficient to control copanlisib-related hypertension. However, given the variety of anti-hypertensive agents used there is no established standard treatment for copanlisib-associated hypertension. Moreover, patients with ongoing hypertension or a history of hypertension should be made aware of the risk of hypertension and the potential for hypertension-related events.

The pattern of hypertension in patients treated with copanlisib was further explored. Table 39 and Figure 16 displays the median systolic blood pressure on Cycle 1, Day 1 pre-dose and at intermittent measurements post-dose by treatment group.

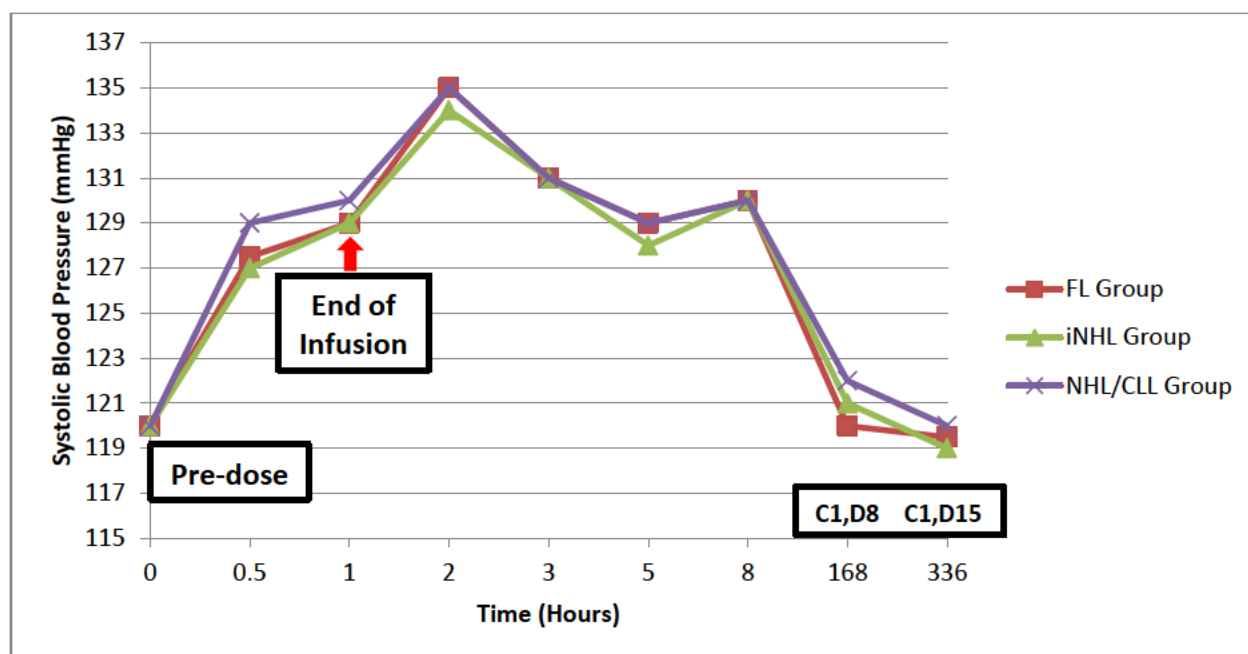
Table 39: Summary of Systolic Blood Pressure on Cycle 1, Day 1

Time point	FL Group n = 126	iNHL Group n = 168	NHL/CLL Group n = 244
Pre-dose			
Median	120.0	120.0	120.0
Min, Max	85.5, 149.5	85.5, 150.0	85.5, 150.0
30 minutes post dose			
Median	127.5	127.0	129.0
Min, Max	90.0, 172.0	90.0, 172.0	90.0, 200.0
1 hour post dose (end of infusion)			
Median	129.0	129.0	130.0
Min, Max	89.0, 175.0	89.0, 176.0	89.0, 190.0
2 hours post-dose			
Median	135.0	134.0	135.0
Min, Max	97.0, 188.0	97.0, 188.0	95.0, 188.0
3 hours post-dose			
Median	131.0	131.0	131.0
Min, Max	99.0, 195.0	99.0, 195.0	92.0, 195.0
4-5 hours post-dose			
Median	129.0	128.0	129.0
Min, Max	95.0, 195.0	95.0, 195.0	81.0, 195.0
6-8 hours post-dose			

Time point	FL Group n = 126	iNHL Group n = 168	NHL/CLL Group n = 244
Median	130.0	130.0	130.0
Min, Max	95.0, 169.0	91.0, 185.0	86.0, 185.0
Cycle 1, Day 8 pre-dose			
Median	120.0	121.0	122.0
Min, Max	89.0, 164.0	89.0, 164.0	88.0, 164.0
Cycle 1, Day 15 pre-dose			
Median	119.5	119.0	120.0
Min, Max	89.0, 151.0	89.0, 156.0	89.0, 156.0

Source: FDA analysis of ADVS dataset for safety analysis population

Figure 16: Median Systolic Blood Pressure Before and After Copanlisib Infusion – Cycle 1, Day 1



Systolic and diastolic blood pressure increase during copanlisib infusion and peak around 2 hours post the start of the infusion. The mean change in systolic and diastolic blood pressure from baseline at 2 hours post the start of the infusion is 14.4 mmHg (SD: 13.6 mmHg) and 6.8 mmHg (SD: 8.5 mmHg), respectively. Systolic and diastolic blood pressure returns to near baseline at the time of the next infusion of copanlisib. Throughout treatment, the mean Day 1, pre-dose, systolic and diastolic blood pressure remained relatively constant at 117 mmHg to 122 mmHg and 70 mmHg to 72 mmHg, respectively.

Transient hypertension may pose a risk for hypertension related events such as transient ischemic attack, cerebrovascular accidents, cardiac disorders, and kidney dysfunction. A review

of the safety dataset that includes NHL/CLL and solid tumor patients revealed 5 patients with vascular events associated with the central nervous system. A review of the medical narratives revealed that 1 patient (15205-20001-0007) with a cerebrovascular accident had concomitant hypertension. Twelve patients experienced cardiac manifestations that can be associated with hypertension, which included congestive heart failure, myocardial infarction, left ventricular dysfunction, and cardiac failure. Following copanlisib infusion, one patient (16270-26001-2002) was reported to have developed Grade 3 hypertension followed by a fatal myocardial infarction and another patient (12871-14001-1008) developed severe left ventricular dysfunction immediately following copanlisib infusion. Twenty-nine patients experienced hypertension and a kidney-associated adverse event (increased creatinine, proteinuria, acute kidney injury, and renal failure). A review of the safety dataset and patient narratives revealed no kidney-related adverse events attributed to hypertension.

Reviewer Comment: The pattern of hypertension with copanlisib is consistent with an on-target effect. The underlying mechanism of copanlisib induced hypertension is not established, but likely involves dysregulation of the differing PI3K isoforms, which play an integral role in cardiovascular physiology.

A mean increase of systolic blood pressure by 14 mmHg (SD: 13.6 mmHg) two hours after the start of the infusion is clinically relevant as it poses a risk of hypertensive urgency or emergency. Patients may be at increased risk of TIA, stroke, cardiac dysfunction, and renal dysfunction. A review of all patients (NHL, CLL, and Solid tumors) treated with copanlisib did reveal cases of hypertension-associated events of stroke, myocardial infarction, and decreased left ventricular function. Patients with cardiac and stroke risk factors (coronary heart disease, high cholesterol, obesity, hypertension, diabetes, and smoking) may be at a further increased risk of hypertension-associated events especially because several exclusion criteria in the protocols were for patients with cardiovascular risk factors. Labeling will need to include a warning for hypertension and appropriate dose modifications and toxicity management guidelines to ensure safe use.

Hyperglycemia

The incidence of hyperglycemia was common amongst patients treated with copanlisib. Table 40 summarizes the hyperglycemia treatment emergent adverse events experienced by patients with indolent NHL.

Table 40: Summary of Hyperglycemia Treatment Emergent Adverse Events and Associated Risk Factors

Hyperglycemia	FL Group N = 126 n (%)	iNHL Group N = 168 n (%)	NHL/CLL Group N = 244 n (%)
All grade adverse events	66 (52.4)	90 (53.6)	131 (53.7.2)
Grade 3-4	47 (37.3)	66 (39.3)	82 (33.6)

Hyperglycemia	FL Group N = 126 n (%)	iNHL Group N = 168 n (%)	NHL/CLL Group N = 244 n (%)
Serious adverse events	5 (4.0)	8 (4.8)	8 (3.3)
Hyperglycemia leading to:			
Dose delay	2 (1.6)	3 (1.8)	3 (1.2)
Dose reduction	9 (7.1)	12 (7.1)	12 (4.9)
Discontinuation	3 (2.4)	3 (1.8)	3 (1.2)
History of diabetes			
Yes	16	20	20
Hyperglycemia incidence	13 (81.3)	17 (85.0)	17 (85.0)
Grade 3-4	13 (81.3)	15 (75.0)	15 (75.0)
No	110	148	224
Hyperglycemia incidence	53 (48.2)	73 (49.3)	114 (50.9)
Grade 3-4	34 (30.9)	51 (34.5)	67 (29.9)

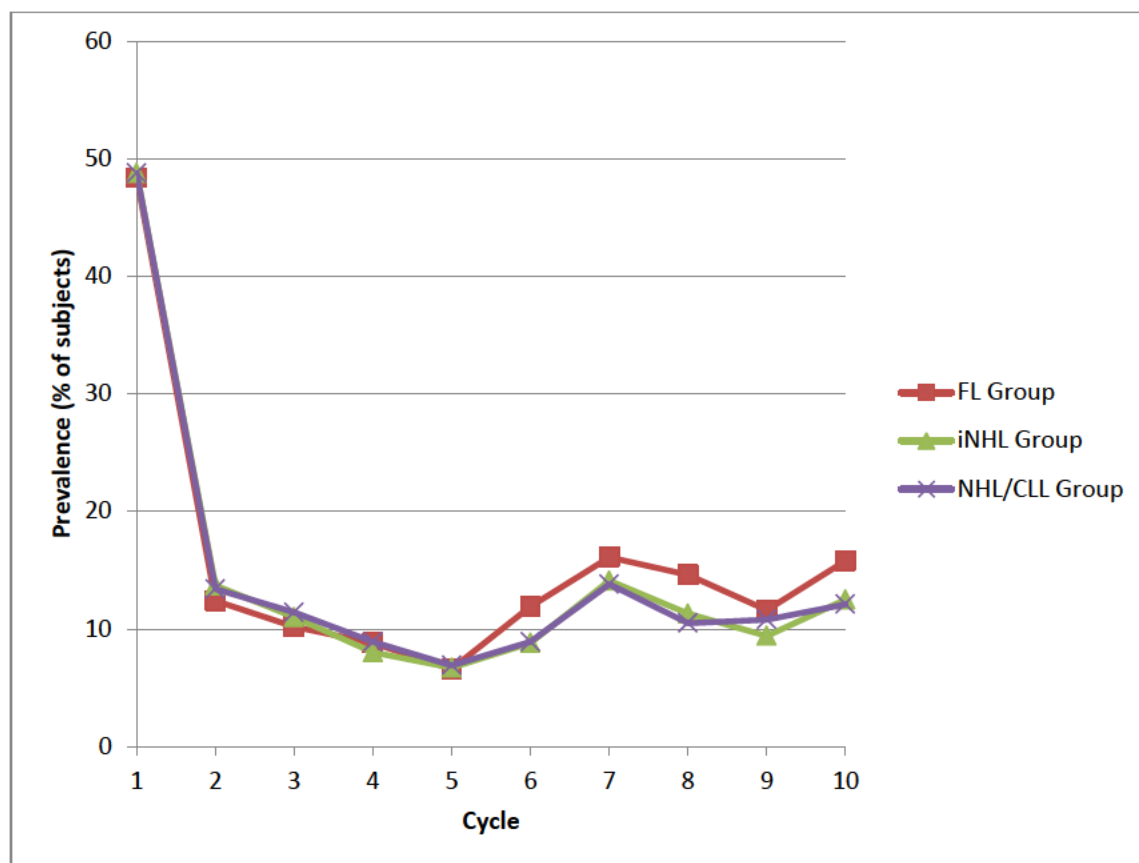
Source: FDA analysis of ADAE dataset for safety analysis population

Hyperglycemia occurred in 53.6% of patients with indolent NHL treated with copanlisib. Sixty-six patients (39.3%) experienced a Grade 3-4 adverse event of hyperglycemia. Hyperglycemia led to dose reductions in 7.1% of patients with indolent NHL. Patients with a history of diabetes were more likely to experience hyperglycemia and a Grade 3 or 4 event (Table 40). Of the 20 patients (11.9%) with diabetes with indolent NHL, 7 patients (7/20, 35%) developed Grade 4 hyperglycemia. Six patients (6/20, 30%) underwent dose reductions and 2 patients (2/20, 10%) discontinued copanlisib due to hyperglycemia.

Hyperglycemia was further evaluated in the pre-dose and post-dose setting. Overall, 23 patients (23/90, 25.6%) with indolent NHL required a diabetic medication for hyperglycemia. In the pre-dose setting, 3 patients (3/90, 3.3%) had a pre-dose blood glucose ≥ 160 mg/dL. Two of the three patients required short-acting insulin prior to receive their scheduled dose of copanlisib. In the post-dose setting, 48 patients (48/90, 53.3%) received at least one concomitant treatment for hyperglycemia. The majority of patients received short-acting human insulin and a minority of patients were given sulfonylureas. During treatment with copanlisib, 4 patients (4/90, 4.4%) received diabetic medications for > 7 days but ≤ 28 days and 3 patients (3/90, 3.3%) received new or additional diabetic medications for > 28 days.

The prevalence of hyperglycemia decreased after the 1st cycle and remained relatively constant during the subsequent cycles (Figure 17). Almost half (48.8%) of the patients treated with copanlisib experienced hyperglycemia in the 1st cycle and then the prevalence ranged from 6.9% to 16.1% for subsequent cycles.

Figure 17: Prevalence of Hyperglycemia by Treatment Cycle



Reviewer Comment: The underlying reason for the decrease in prevalence of hyperglycemia is unknown. It is possible that a tolerance is developed (down-regulation of alpha receptors) that decreased the prevalence of hyperglycemia in subsequent cycles.

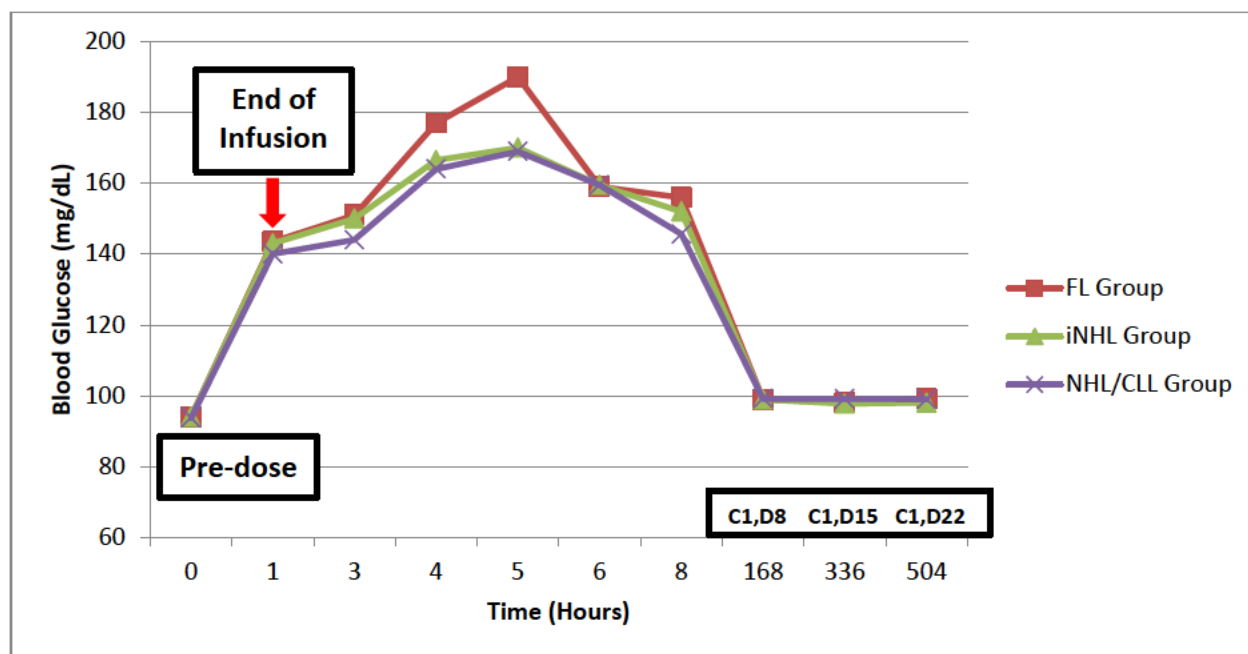
The pattern of hyperglycemia in patients treated with copanlisib was further explored. Table 41 and Figure 18 display blood glucose levels before and after copanlisib infusion on Cycle 1, Day 1.

Table 41: Summary of Blood Glucose on Cycle 1, Day 1

Time point	FL Group n = 126	iNHL Group n = 168	NHL/CLL Group n = 244
Pre-dose			
Median	94.0	94.0	93.7
Min, Max	71, 152	71, 152	64, 152
1 hour (end of infusion)			
Median	143.5	143.0	140.0
Min, Max	134, 172	85, 172	85, 180
3 hours post-dose			

Time point	FL Group n = 126	iNHL Group n = 168	NHL/CLL Group n = 244
Median	151.0	150.0	144.0
Min, Max	94, 320	94, 320	78, 320
4 hours post-dose			
Median	177.0	166.5	164.0
Min, Max	106, 331	104, 366	72, 366
5 hours post-dose			
Median	190.0	170.0	169.0
Min, Max	103, 477	103, 477	103, 477
6 hours post-dose			
Median	159.0	159.5	159.5
Min, Max	105, 321	99, 433	97, 433
8 hours post dose			
Median	155.9	152.0	145.6
Min, Max	73, 365	73, 365	73, 365
Cycle 1, Day 8 pre-dose			
Median	99.0	98.9	99.1
Min, Max	68.5, 175.0	68.0, 185.6	68.0, 197.0
Cycle 1, Day 15 pre-dose			
Median	98.0	97.7	99.1
Min, Max	65.0, 256.0	65.0, 256.0	65.0, 256.0
Cycle 1, Day 22 pre-dose			
Median	99.1	98.0	99.0
Min, Max	70.3, 246.0	70.3, 246.0	61.3, 246.0
Source: FDA analysis of ADLB dataset for safety analysis population			

Figure 18: Median Blood Glucose Before and After Copanlisib Infusion - Cycle 1, Day 1



Blood glucose increases during copanlisib infusion, peaks around 5 hours after the start of the infusion, and returns to near baseline by the time the next infusion is due to be administered. The mean baseline blood glucose was 98.3 mg/dL (SD: 16.4) and the mean change in blood glucose at 5 hours from the start of infusion was 106.3 mg/dL (SD: 81.8 mg/dL) in patients with indolent NHL. The mean blood glucose on Day 1 on subsequent treatment cycles remained in the normal range and ranged from 96.7 mg/dL to 105.4.

Hemoglobin A1c values increased over the course of treatment. The mean baseline HbA1c was 5.54% (SD: 0.69%) in patients with indolent NHL. Patients experience a mean change from baseline of 0.81% in HbA1c (Table 42, Figure 19). Evaluation of change from baseline HbA1c to the last recorded HbA1c while on treatment demonstrated that patients may transition to a new HbA1c category. Hemoglobin A1c was categorized into 3 categories: 1) < 5.7%, 2) 5.7% to < 6.5%, and 3) ≥ 6.5%. Table 43 displays the patients' baseline HbA1c category and the resulting HbA1c category based on the last HbA1c value while on treatment. In patients with indolent NHL, 42/94 patients (44.7%) with a baseline HbA1c < 5.7% transitioned to a higher HbA1c category following treatment with copanlisib. Additionally, 16 patients (16/37, 43.2%) with a baseline HbA1c 5.7% to < 6.5% transitioned to a HbA1c ≥ 6.5%.

Table 42: Mean HbA1c Change from Baseline to Last HbA1c Value on Treatment

Hemoglobin A1c (reference range: 0.0 – 6.0%)	FL Group n = 126	iNHL Group n = 168	NHL/CLL Group n = 244
Baseline			
Mean	5.53	5.54	5.50
SD	±0.70	±0.69	±0.67
Last HbA1c value on treatment			
Mean	6.32	6.33	6.22
SD	±3.54	±3.10	±2.78
Change from baseline to last HbA1c value on treatment			
Mean	0.82	0.81	0.72
SD	±3.49	±3.04	±2.72

SD: Standard deviation
Source: FDA analysis of ADLB dataset for safety analysis population

Figure 19 Mean Hemoglobin A1c at Day 1 by Treatment Cycle

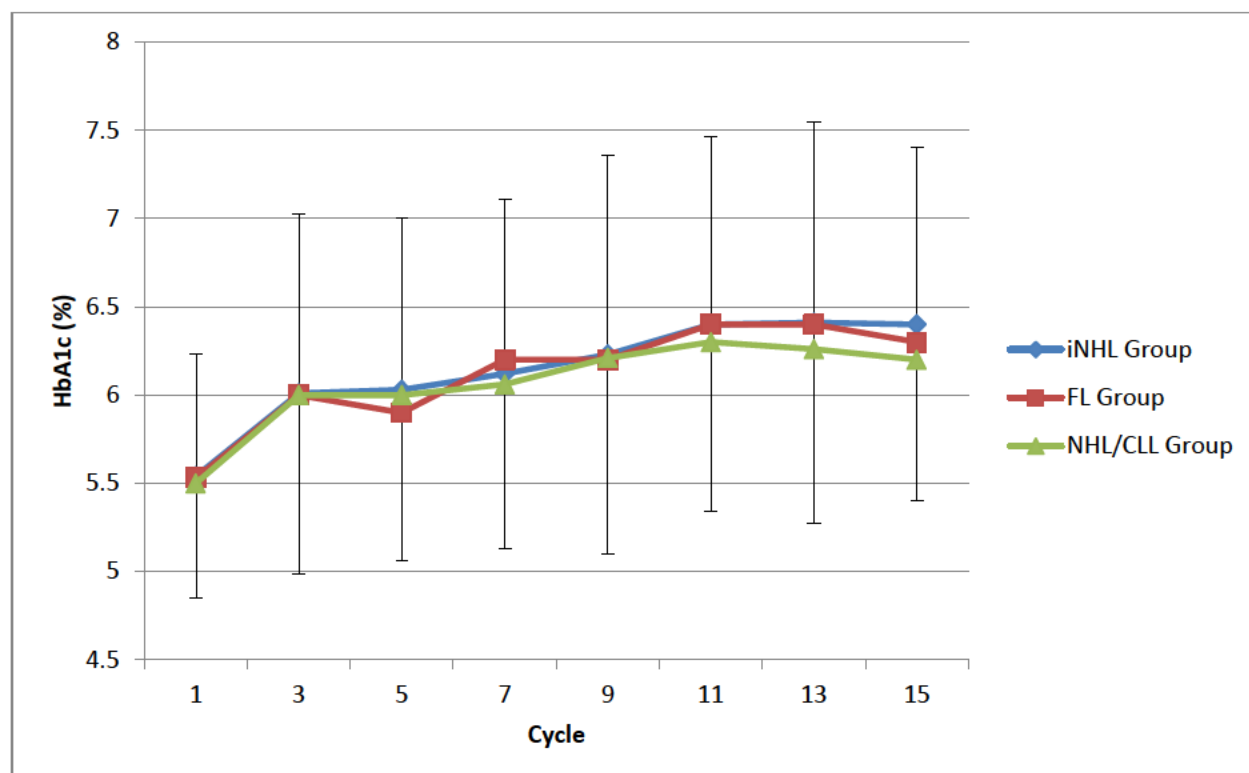


Table 43: HbA1c Category Change from Baseline to Last HbA1c Value on Treatment

	Baseline HbA1c Category	Last HbA1c Value on Treatment n (%)			Total n (%)
		< 5.7%	5.7% - <6.5%	≥ 6.5%	
FL Group n = 126	< 5.7%	42 (39.3)	20 (18.7)	7 (6.5)	69 (64.5)
	5.7% - <6.5%	2 (1.9)	14 (13.1)	12 (11.2)	28 (26.2)
	≥ 6.5%	0	2 (1.9)	8 (7.5)	10 (9.3)
	Total	44 (41.1)	36 (33.6)	27 (25.2)	107 (100.0)
iNHL Group n = 168	< 5.7%	52 (35.9)	28 (19.3)	14 (9.7)	94 (64.8)
	5.7% - <6.5%	2 (1.4)	19 (13.1)	16 (11.0)	37 (25.5)
	≥ 6.5%	0	2 (1.4)	12 (8.3)	14 (9.7)
	Total	54 (37.2)	49 (33.8)	42 (29.0)	145 (100.0)
NHL/CLL Group n = 244	< 5.7%	70 (37.4)	38 (20.3)	14 (7.5)	122 (65.2)
	5.7% - <6.5%	5 (2.7)	25 (13.4)	20 (10.7)	50 (26.7)
	≥ 6.5%	0	2 (1.1)	13 (7.0)	15 (8.0)
	Total	75 (40.1)	65 (34.8)	47 (25.1)	187 (100.0)

Source: FDA analysis of ADLB dataset for safety analysis population

Reviewer Comment: The pattern of hyperglycemia is consistent with an on-target effect (PI3K alpha inhibition). It is postulated that PI3K alpha inhibition causes glucose intolerance and insulin resistance. The hyperglycemia appears to be a transient effect since blood glucose levels are at or near baseline by the time the next copanlisib infusion is administered. However, the gradual increase in hemoglobin A1c over time suggests a cumulative effect. Twenty percent of patients transitioned from a normal HbA1c to a category considered to be "at risk" for diabetes (5.7% to <6.5%). Further, an additional 20% of patients transitioned to a HbA1c ≥ 6.5%, which meets criteria for a diagnosis of diabetes. The appropriate management of patients who are "at risk" or meet criteria for diabetes is not established. Further, patients with pre-existing diabetes were more likely to experience an adverse event of hyperglycemia and 35% of the patients with diabetes developed Grade 4 hyperglycemia. Labeling will need to include a warning for hyperglycemia and appropriate dose modifications and toxicity management to ensure safe use. Additionally, diabetic patients will need to be closely monitored and in communication with endocrinology to promote adequate glucose control.

Gastrointestinal disorders

In patients with indolent NHL, gastrointestinal disorders occurred in 64.9% of patients and included diarrhea, nausea, constipation, vomiting, and abdominal pain. Table 44 provides a summary of common and severe gastrointestinal disorders evaluated.

Table 44: Summary of Gastrointestinal Disorders Treatment Emergent Adverse Events

Gastrointestinal disorders	FL Group N = 126 n (%)		iNHL Group N = 168 n (%)		NHL/CLL Group N = 244 n (%)	
	All Grades	Grade 3-4	All Grades	Grade 3-4	All Grades	Grade 3-4
Any TEAE	86 (68.3)	15 (11.9)	109 (64.9)	18 (10.7)	163 (66.8)	29 (11.9)
Diarrhea	47 (37.3)	7 (5.6)	60 (35.7)	8 (4.8)	88 (36.1)	12 (4.9)
Nausea	33 (26.2)	1 (0.8)	43 (25.6)	1 (0.6)	70 (28.7)	2 (0.8)
Constipation	19 (15.1)	0	22 (13.1)	0	34 (13.9)	0
Vomiting	18 (14.3)	0	21 (12.5)	0	31 (12.7)	0
Abdominal pain	16 (12.7)	2 (1.6)	21 (12.5)	3 (1.8)	30 (12.3)	5 (2.0)
Colitis	1 (0.8)	1 (0.8)	1 (0.6)	1 (0.6)	1 (0.4)	1 (0.4)
Fistula	1 (0.8)	0	1 (0.6)	0	2 (0.8)	0
Perforation	0	0	0	0	0	0

TEAE: Treatment emergent adverse event
Source: FDA analysis of ADAE dataset for safety analysis population

Diarrhea was the most common gastrointestinal disorder experienced by patients treated with copanlisib. In patients with indolent NHL, 35.7% of patients had a treatment emergent adverse event of diarrhea. Grade 3 diarrhea occurred in 8 patients (4.8%). There were no Grade 4 events of diarrhea. Four patients had serious adverse events of diarrhea due to the need for hospitalization. The median time to onset of all diarrhea was 3.2 months (range, 0 – 31.1 months) with a median duration of 1 day (range, 1 – 99 days). The median time to onset for those with Grade 3 diarrhea was 2.4 months (range, 0.1 – 20.7 months) with a median duration of 8 days (range, 2 – 10 days) for those with a provided end date. Diarrhea led to dose reduction in 4 patients (2.4%) and treatment delays in 4 patients (2.4%).

One patient developed Grade 4 colitis that was a serious adverse event due to hospitalization. The patients had overlapping intermittent diarrhea as well. The Grade 4 colitis resulted in a prolonged treatment delay, but once the colitis resolved, treatment was restarted at a reduced dose with no recurrence of the colitis or diarrhea.

Two patients were reported to have a gastrointestinal fistula during the treatment emergent period for copanlisib. The events were Grade 1 and 2 and no narrative was included for these events. No events of intestinal perforation were reported.

Reviewer Comment: Copanlisib was associated with mild to moderate diarrhea. Information on the ability to control the diarrhea is unknown. Labeling should include information characterizing the diarrhea experienced by patients treated with copanlisib. Additionally, the possibility of colitis and fistula formation with the use of copanlisib is uncertain. A review of all patients treated with copanlisib revealed two patients with hematologic malignancies and 1 patient with a solid tumor that experienced severe colitis. Information on long-term use of

copanlisib is needed to further explore this relationship.

Skin Disorders

Rash occurred in 24 patients (14.3%) with indolent NHL treated with copanlisib. The typical rash recorded was a maculopapular rash on the extremities, neck, or trunk. Two patients (1.2%) experienced Grade 3 events of rash. The median time to onset was 3.7 months (range, 0.2 to 22.8 months) with a median duration of 32 days (range, 8 – 113 days).

A review of all patients treated with copanlisib revealed severe cutaneous manifestations in 6 patients that include Stevens-Johnson syndrome (SJS), dermatitis exfoliative, and exfoliative rash. One patient with SJS, 3 patients with dermatitis exfoliative, and 2 patients with Grade 3 exfoliative rash.

Reviewer Comment: Copanlisib is associated with rash, which can be severe. Labeling needs to include a warning regarding severe skin manifestations.

7.4.6. Safety Analyses by Demographic Subgroups

There were no relevant differences in treatment emergent adverse events when assessed by age in patients with indolent NHL. Seventy-nine patients (79/80, 98.8%) $\geq$ 65 years of age compared to 87 patients (87/88, 98.9%) $<$ 65 years of age experienced treatment emergent adverse events. For Grade $\geq$ 3 adverse events, 71 patients (71/80, 88.8%) $\geq$ 65 years of age versus 71 patients (71/88, 80.7%) $<$ 65 years of age were reported. There were slightly more patients $\geq$ 65 years of age (44/80, 55.0%) that experienced a serious adverse event compared to patients $<$ 65 years of age (37/88, 42.0%). Table 45 lists the adverse events by age group in decreasing order of the difference in incidence between patients $<$ 65 years of age versus patients $\geq$ 65 years of age. Patients over the age of 65 years reported substantially more fatigue and hypertension events.

Table 45 Treatment Emergent Adverse Events by Age in Patients with Indolent NHL

Preferred Term ¹	$\geq$ 65 Years of Age N = 80		$<$ 65 Years of Age N = 88		Risk Difference
	n	%	n	%	
Fatigue	40	50.0	24	27.3	23
Hypertension	37	46.3	21	23.9	22
Decreased appetite	14	17.5	4	4.5	13
Hyperglycemia	45	56.3	40	45.5	11
Hypokalemia	10	12.5	3	3.4	9
Hypomagnesemia	9	11.3	2	2.3	9
Pain in extremity	9	11.3	2	2.3	9
Constipation	14	17.5	8	9.1	8
Neutropenia	23	28.6	19	21.6	7

¹ Using grouped terms as defined in Table 30
Source: FDA analysis of ADAE dataset for safety analysis population

The analysis of treatment emergent adverse events by gender did not reveal any clinically relevant differences. Eighty-nine female patients (89/90, 98.9%) and 77 male patients (77/78, 98.7%) experienced a treatment emergent adverse event. There were 77 female patients (77/90, 85.6%) compared to 65 male patients (65/78, 83.3%) that experienced a Grade ≥ 3 adverse event. Serious adverse events were reported for 43 female patients (43/90, 47.8%) versus 38 male patients (38/78, 48.7%). Table 46 lists the adverse events by gender in decreasing order of the difference in incidence between female patients and male patients. Female patients had a higher incidence of nausea, hyperglycemia, fatigue, and urinary tract infections when compared to male patients.

Table 46 Treatment Emergent Adverse Events by Gender in Patients with Indolent NHL

Preferred Term ¹	Female N = 90		Male N = 78		Risk Difference
	n	%	n	%	
Nausea	31	34.4	12	15.4	19
Hyperglycemia	53	58.9	32	41.0	18
Fatigue	40	44.4	24	30.8	14
Urinary tract infection	11	12.2	1	1.3	11
Neutropenia	27	30.0	15	19.2	11
Cough	25	27.8	14	17.9	10
Hypertension	35	38.9	23	29.5	9
Chills	9	10.0	3	3.8	6
Oral herpes	3	3.3	7	9.0	-6

¹ Using grouped terms as defined in Table 30
Source: FDA analysis of ADAE dataset for safety analysis population

A further analysis of treatment emergent adverse events by race, ethnicity, and body mass index (BMI) did not reveal any clinically meaningful differences. When separated by race or ethnicity, the number of patients were unequal with the majority of patients being Caucasian and not Hispanic or Latino (140/160, 83.3% each). Similar incidences of treatment emergent adverse events were reported among three BMI categories 1) BMI < 25, 2) BMI ≥ 25 to < 30, and 3) BMI ≥ 30 .

Reviewer Comment: There were no clinically meaningful differences in safety when assessed by the demographics of age, gender, race, and BMI.

7.4.7. Specific Safety Studies/Clinical Trials

Study 16353 was single center, open-label study in healthy volunteers to evaluate the metabolism, excretion, pharmacokinetics, and safety of a single intravenous dose of copanlisib. Six healthy male volunteers participated in the study and received an intravenous dose of 12mg of copanlisib. The median age of the participants was 55 years (range: 47 to 61 years) and five participants were White and 1 participant was Asian. Safety was assessed one day before copanlisib administration to 14 days after administration. Three (50.0%) of the six participants experienced a treatment-emergent adverse event. The treatment emergent adverse events included abdominal pain, nausea, flatulence, diarrhea, myalgia, and oropharyngeal pain. The adverse events assessed as being related were nausea, diarrhea, and abdominal pain. There were no serious or fatal adverse events.

Reviewer Comment: The small sample size of 6 healthy volunteers prevents any substantial conclusions. However, the gastrointestinal issues experienced by the healthy volunteers are consistent with those reported in the NHL and CLL population, supporting the conclusion they are drug-related and not due to the underlying malignancy. More information in healthy volunteers and in patients in placebo-controlled trials will assist in further characterizing the safety profile associated with copanlisib.

7.4.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

There were no analyses for second cancers submitted by the Applicant. FDA reviewed the adverse event dataset for patients that developed neoplasms (identified using the Neoplasms, Benign, Malignant, and Unspecified SOC). Four patients were identified who developed neoplasms. Two patients developed basal cell carcinoma and one patient each developed squamous cell carcinoma and secondary acute myeloid leukemia.

Pediatrics and Assessment of Effects on Growth

There were no children enrolled in any of the studies submitted with this application. The safety of copanlisib in pediatric patients has not been established.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There was no experience of overdose reported in the clinical studies of copanlisib. Copanlisib is administered intravenously under the supervision of a healthcare professional and prescribed by specialists in hematology and oncology. There is no evidence that copanlisib produces physical or psychological dependence in patients with hematologic malignancies.

7.4.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Copanlisib is not marketed in any country. There is no postmarketing safety data available.

Expectations on Safety in the Postmarket Setting

Safety in the postmarket setting is expected to be similar to that observed on the clinical trials reviewed in this application. Although, safety with long-term use of copanlisib will need to be closely monitored since the median duration of treatment was 5.5 cycles.

7.4.10. Integrated Assessment of Safety

Safety Summary

The safety of copanlisib was evaluated in 244 patients with relapsed or refractory NHL and CLL, with 168 of 244 patients being those with relapsed or refractory follicular lymphoma, marginal zone lymphoma, small lymphocytic lymphoma, or lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia. Patients received copanlisib 0.8 mg/kg or 60mg intravenous on Days 1, 8, and 15 of a 28-day treatment cycle. The median duration of exposure was 19 weeks (4.7 cycles) in patients with NHL/CLL and 22 weeks (5.5 cycles) in patients with indolent NHL.

Analysis of the NHL/CLL safety population revealed:

- Seventeen deaths (7%) were reported during treatment and up to 35 days after the last dose of copanlisib. The root causes of death were progressive disease for 6 patients (35%), pneumonia for 4 patients (24%), and other adverse events for 7 patients (41%).
- Serious adverse events were reported for 51% of patients. Sixty-nine patients (28%) had serious adverse events considered to be treatment related. The most common treatment related serious adverse events were pneumonia, pneumonitis, hyperglycemia, febrile neutropenia, and diarrhea.
- The most common treatment emergent adverse events include hyperglycemia (51%), fatigue (39%), hypertension (37%), diarrhea (36%), nausea (29%), neutropenia (25%), pyrexia (23%), and cough (21%).
- The most frequently reported Grade 3-4 treatment emergent adverse events were hyperglycemia (32%), hypertension (29%), neutropenia (21%), pneumonia and anemia (8% each), thrombocytopenia, fatigue, and diarrhea (5% each).
- Treatment emergent adverse events resulting in treatment discontinuation were reported for 57 of 244 patients (23%). The most common adverse events leading to discontinuation were pneumonia and pneumonitis (3% each). One hundred twenty four of 244 patients (51%) required a dose reduction due to an adverse event; most common reasons were pneumonia (14%), pneumonitis and pyrexia (4% each), and hyperglycemia (3%).

The safety analysis of patients with indolent forms of NHL demonstrated consistent results with the overall population of patients with hematologic malignancies (NHL/CLL group). The safety review focuses on patients with indolent forms of NHL as that is the intended population for use.

The safety review revealed 3 adverse reactions that warrant close consideration:

- **Hyperglycemia:** Patients treated with copanlisib develop hyperglycemia because of copanlisib induced PI3K α inhibition, which causes glucose intolerance and insulin resistance. Hyperglycemia occurred in 54% of patients with indolent NHL, with 66 of 90 patients (73%) developing Grade 3 or 4 hyperglycemia. Patients with ongoing or a history of diabetes were more likely to developed hyperglycemia and be more severe. The hyperglycemia is characterized by a peak in blood glucose around 5 hours after the start of copanlisib infusion with a mean increase of blood glucose of 106 mg/dL (SD: 82 mg/dL). The mean pre-dose blood glucose remained in the normal range throughout subsequent treatment cycles, consistent with a transient effect. However, patients treated with copanlisib experienced an increase in hemoglobin A1c over the course of treatment. In patients with indolent NHL, 14 of 94 patients (15%) transitioned from a normal baseline hemoglobin A1c to a hemoglobin A1c $\geq$ 6.5%, which meets criteria for a diagnosis of diabetes. Further, an additional 30% of patients with a normal hemoglobin A1c at baseline transitioned to a hemoglobin A1c considered “at risk” for diabetes. The management recommended during the clinical trials included short-acting insulin for patients with a post-infusion blood glucose greater than 250 mg/dL per institutional sliding scale and communication with endocrinology as warranted. Nevertheless, copanlisib induced hyperglycemia management and dose modification strategies have not been fully determined.
- **Hypertension:** The underlying mechanism of copanlisib induced hypertension is not established. However, it likely involves dysregulation of the differing PI3K isoforms, which play an integral role in cardiovascular physiology.

Hypertension occurred in 35% of patients with indolent NHL and the majority of hypertension events (45/58, 78%) were Grade 3 (blood pressure $\geq$ 160/100 mmHg) events. Patients with ongoing or a history of hypertension were more likely to experience hypertension and be Grade 3 in severity. The pattern of hypertension demonstrated an increase during copanlisib infusion that peaks around 2 hours after the start of the infusion. The mean change in systolic blood pressure from baseline at 2 hours was 14.4 mmHg (SD: 13.6 mmHg). Blood pressure returns to baseline prior to the next copanlisib infusion. A review of hypertension-related events such as stroke, transient ischemic attack, cardiac disorders, and kidney disorders didn't reveal any safety signals. Although, several exclusion criteria in the protocols were for patients with cardiovascular risk factors. Thus, patients with cardiac and stroke risk factors may be at increased risk of hypertension-related events. Moreover, post-dose hypertension was managed on an individual basis and the trial protocol recommended consideration of dihydropyridine calcium channel blockers (i.e., amlodipine, felodipine). Finally, the defining characteristics, associated risks, and best management practices for copanlisib induced hypertension are not established.

- **Pneumonitis:** Treatment with copanlisib was associated with the development of pneumonitis. Fifteen patients (9%) developed pneumonitis and 5 of the 15 patients

developed Grade 3 pneumonitis. The overall incidence of pneumonitis is unclear since it is a diagnosis of exclusion. Pneumonitis occurred from 7 weeks to 19.4 months on copanlisib. Prior treatment with radiation therapy and more specifically chest radiation did not increase the incidence of pneumonitis. Recommended management for pneumonitis included copanlisib interruption, dose reduction, and discontinuation of copanlisib depending on severity. Guidelines for pneumonitis treatment were not included in the clinical protocols, although patients treated with systemic corticosteroids had resolution of their pneumonitis. Yet, the optimal approach to managing pneumonitis has not been fully defined.

A comprehensive review of the safety data demonstrates that the safety profile of copanlisib is tolerable and manageable in patients with indolent forms of NHL.

SUMMARY AND CONCLUSIONS

7.5. Statistical Issues

The primary study supporting efficacy was a single arm study with objective response rate as the primary endpoint. Given that it is a single-arm study, no statistical inference can be drawn and only estimates of response rates can be obtained based on the observed data. Time to event endpoints, such as progression-free survival and overall survival, are not interpretable in single-arm studies. Additionally, the follow-up time is limited in the primary study supporting efficacy.

7.6. Conclusions and Recommendations

The benefit-risk assessment supports accelerated approval of copanlisib for the treatment of adult patients with relapsed follicular lymphoma who have received at least two prior systemic therapies.

The efficacy of copanlisib is primarily based on the results of a single-arm, open-label study evaluating copanlisib monotherapy in patients with relapsed follicular lymphoma, marginal zone lymphoma, small lymphocytic lymphoma, or lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia. The study used a primary endpoint of objective response rate per independent review assessment. The efficacy of copanlisib was established in patients with follicular lymphoma (N = 104) on the basis of an ORR of 58.7% with a median duration of response of 12.2 months. The complete response rate was 14.4% and the partial response rate was 44.2%.

The safety profile of copanlisib is tolerable and manageable in patients with relapsed follicular lymphoma, marginal zone lymphoma, small lymphocytic lymphoma, or lymphoplasmacytic

lymphoma/Waldenström's macroglobulinemia. The safety of copanlisib was evaluated in 244 patients with hematologic malignancies exposed to copanlisib monotherapy. The primary safety issues identified include infection, hyperglycemia, hypertension, pneumonitis, neutropenia, gastrointestinal disorders, and severe cutaneous reactions. The identified risks with copanlisib can be mitigated with appropriate labeling. Further, the intravenous weekly administration schedule ensures that copanlisib will be given in the presence of healthcare professionals, which provides additional safety monitoring.

Taken together, the evidence of effectiveness, with a clinically significant ORR and duration of response, and a manageable safety profile form a strong basis for a conclusion of a favorable benefit-risk profile in patients with relapsed follicular lymphoma.

Cindy Gao, PhD
Primary Statistical Reviewer

Yuan-Li Shen, DrPh
Statistical Team Leader

Nicholas C. Richardson, DO, MPH
Primary Clinical Reviewer

R. Angelo M. de Claro, MD
Clinical Team Leader

8 Advisory Committee Meeting and Other External Consultations

This application was not presented to the Oncologic Drug Advisory Committee or any other external consultants because the application did not raise significant efficacy or safety issues for the proposed indication.

9 Pediatrics

Patients less than 18 years of age were excluded from Applicant sponsored clinical studies of copanlisib. The efficacy and safety of copanlisib in pediatric patients has not been studied.

10 Labeling Recommendations

10.1 Prescribing Information

The following are recommended major changes to the proposed copanlisib prescribing information based on this review:

- **1. INDICATIONS AND USAGE:** Add “two prior systemic therapies” to reflect the patient population in the pivotal trial. Remove (b) (4)
Add “adult” to indication statement to provide clear communication about the indicated population.
- **2. DOSAGE AND ADMINISTRATION:** (b) (4)
(b) (4) Create clear formatting for reconstitution instructions and dilution instructions. Add dose modifications for thrombocytopenia, severe cutaneous reactions, and other non-life-threatening and life-threatening toxicities. Modify dose modifications for neutropenia, pre- and post-dose hypertension, pre- and post-dose hyperglycemia to provide more specific and detailed guidance for healthcare providers. Add dose reduction to 45 mg when used concomitantly with strong CYP3A inhibitors because AUC is significantly increased.
- **4. CONTRAINDICATIONS:** (b) (4)
(b) (4)
- **5. WARNINGS AND PRECAUTIONS:** Reorder section to reflect severity and clinical relevance. Use pneumonia as a grouped term to describe the most common serious infection. Update pneumonitis section with symptoms concerning for pneumonitis and that patients were treated with interruption and corticosteroids. Include a description of the pattern of hypertension and hyperglycemia. Add a section for severe cutaneous reactions.
- **6. ADVERSE REACTIONS:** Revise list of adverse reactions to occur in descending order by system organ class. Include laboratory abnormalities reported in ≥20% of patients and ≥4% of Grade ≥3 treated with Aliqopa.
- **7. DRUG INTERACTIONS:** Recommend using list of clinical examples of strong CYP3A inducers and inhibitors from FDA drug interaction website.
- **8. USE IN SPECIFIC POPULATIONS:** Update information per the Pregnancy and Lactation Labeling Rule Guidance within section cross-reference format (b) (4)

- [REDACTED] (b) (4)
- **12. CLINICAL PHARMACOLOGY:** [REDACTED] (b) (4)
[REDACTED] Redistribute information pertaining to the metabolite M-1, which is an active metabolite but not a major metabolite. Incorporate information on hepatic impairment and renal impairment into one paragraph.
- **13. NONCLINICAL TOXICOLOGY:** Delete information deemed not relevant or informative for healthcare providers.
- **17. PATIENT COUNSELING INFORMATION:** Revise section to be consistent with the updated Warnings and Precautions section.

10.2. Patient Labeling

This subsection is not applicable because copanlisib is administered as an intravenous infusion to patients in a supervised healthcare setting.

11 Risk Evaluation and Mitigation Strategies (REMS)

There are no additional risk management strategies needed beyond recommended labeling.

11.1. Safety Issue(s) that Warrant Consideration of a REMS

The review teams considered all items included in Section 5, Warnings and Precautions, of labeling. The items included infections, pneumonitis, neutropenia, hypertension, hyperglycemia, and severe cutaneous reactions.

11.2. Conditions of Use to Address Safety Issue(s)

The review teams agreed that labeling is sufficient to address safety concerns for treatment with copanlisib.

11.3. Recommendations on REMS

Review of the application and of the findings from the review teams, the Division of Risk Management in the Office of Surveillance and Epidemiology agree that a REMS is not needed to ensure the benefits of copanlisib exceed its risk.

12 Postmarketing Requirements and Commitment

The following Postmarketing Requirements (PMRs) are recommended:

1. In order to verify the clinical benefit of Aliqopa (copanlisib), submit the complete final clinical report and datasets from a randomized, double-blind, placebo-controlled trial of Aliqopa in combination with immunochemotherapy versus immunochemotherapy alone in patients with relapsed follicular lymphoma, marginal zone lymphoma, small lymphocytic lymphoma, or lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia. The primary endpoint is progression-free survival. Enroll approximately 520 patients.
2. In order to characterize the safety of copanlisib from a randomized controlled trial, submit the complete final clinical report and datasets from a randomized, double-blind, placebo-controlled trial of Aliqopa (copanlisib) in combination with rituximab in patients with relapsed follicular lymphoma, marginal zone lymphoma, small lymphocytic lymphoma, or lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia. Enroll at least 400 patients.
3. Characterize the long-term safety of Aliqopa (copanlisib) as monotherapy and in combination with immunochemotherapy, along with safety-related concomitant medication use, in patients with hematological malignancies. Submit annual interim and final reports and integrated analysis datasets, from a prospective cohort of at least 400 patients for at least 5 consecutive years. Evaluations will include analysis of new safety concerns and increased frequency or severity of known safety concerns in subjects exposed to copanlisib. Reports to be submitted from all sponsored studies, including ongoing studies and pharmacovigilance data, will include:
 - Integrated analyses of all completed studies that includes exposure
 - Summary of safety data from individual enrolling studies that are open label
 - Serious adverse event data from safety databases for all studies
 - Outcome of data monitoring committee decisions for blinded trials
4. Amend and complete your ongoing clinical pharmacokinetic trial to determine an appropriate safe dose of Aliqopa (copanlisib) in patients with moderate and severe hepatic impairment and in patients with severe renal impairment. This trial should be designed and conducted in accordance with the FDA Guidance for Industry entitled, "*Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*" and the FDA Guidance for Industry entitled, "*Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*." Interim report will include subjects with moderate hepatic impairment and severe renal impairment. Final study report will include the subjects with severe hepatic impairment.

5. Conduct a clinical pharmacokinetic (PK) trial to evaluate the effect of Aliqopa (copanlisib) on the pharmacokinetics of metformin (a sensitive MATE2-K substrate) to address the potential for PK and pharmacodynamic (such as serum lactate) interaction. This trial should be designed and conducted in accordance with the FDA Guidance for Industry entitled, *“Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.”*
6. Complete and submit results of a study to determine the effect of Aliqopa on QT/QTc interval in subjects with advanced solid tumors and non-Hodgkin’s lymphoma. The trial should be designed and conducted in accordance with the FDA Guidance for Industry entitled, *“E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.”*

13 Appendices

13.1. References

- Byrtek, Michelle, Keith L. Dawson, Xiaolei Zhou, Charles Farber, Christopher R. Flowers, John D. Hainsworth, Brian K. Link, Andrew D. Zelenetz, and Jonathan W. Friedberg. 2013. 'Early Relapse Of Follicular Lymphoma After R-CHOP Uniquely Defines Patients At High Risk For Death: An Analysis From The National Lymphocare Study', *Blood*, 122: 510.
- Cheson, B. D., S. J. Horning, B. Coiffier, M. A. Shipp, R. I. Fisher, J. M. Connors, T. A. Lister, J. Vose, A. Grillo-Lopez, A. Hagenbeek, F. Cabanillas, D. Klippensten, W. Hiddemann, R. Castellino, N. L. Harris, J. O. Armitage, W. Carter, R. Hoppe, and G. P. Canellos. 1999. 'Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group', *J Clin Oncol*, 17: 1244.
- Cheson, B. D., B. Pfistner, M. E. Juweid, R. D. Gascoyne, L. Specht, S. J. Horning, B. Coiffier, R. I. Fisher, A. Hagenbeek, E. Zucca, S. T. Rosen, S. Stroobants, T. A. Lister, R. T. Hoppe, M. Dreyling, K. Tobinai, J. M. Vose, J. M. Connors, M. Federico, and V. Diehl. 2007. 'Revised response criteria for malignant lymphoma', *J Clin Oncol*, 25: 579-86.
- Colombat, P., G. Salles, N. Brousse, P. Eftekhari, P. Soubeyran, V. Delwail, E. Deconinck, C. Haioun, C. Foussard, C. Sebban, A. Stamatoullas, N. Milpied, F. Boue, B. Taillan, P. Lederlin, A. Najman, C. Thieblemont, F. Montestruc, A. Mathieu-Boue, A. Benzohra, and P. Solal-Celigny. 2001. 'Rituximab (anti-CD20 monoclonal antibody) as single first-line therapy for patients with follicular lymphoma with a low tumor burden: clinical and molecular evaluation', *Blood*, 97: 101-6.
- Freedman, Arnold. 2015. 'Follicular lymphoma: 2015 update on diagnosis and management', *American Journal of Hematology*, 90: 1171-78.
- Hiddemann, W., M. Kneba, M. Dreyling, N. Schmitz, E. Lengfelder, R. Schmits, M. Reiser, B. Metzner, H. Harder, S. Hegewisch-Becker, T. Fischer, M. Kropff, H. E. Reis, M. Freund, B. Wormann, R. Fuchs, M. Planker, J. Schimke, H. Eimermacher, L. Trumper, A. Aldaoud, R. Parwaresch, and M. Unterhalt. 2005. 'Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group', *Blood*, 106: 3725-32.
- Luminari, Stefano, Monica Bellei, Irene Biasoli, and Massimo Federico. 2012. 'Follicular lymphoma - treatment and prognostic factors', *Revista Brasileira de Hematologia e Hemoterapia*, 34: 54-59.
- Martinelli, G., S. F. Schmitz, U. Utiger, T. Cerny, U. Hess, S. Bassi, E. Okkinga, R. Stupp, R. Stahel, M. Heizmann, D. Vorobiof, A. Lohri, P. Y. Dietrich, E. Zucca, and M. Ghilmini. 2010. 'Long-term follow-up of patients with follicular lymphoma receiving single-agent rituximab at two different schedules in trial SAKK 35/98', *J Clin Oncol*, 28: 4480-4.

- Nabhan, C., B. Aschebrook-Kilfoy, B. C. Chiu, K. Kruczek, S. M. Smith, and A. M. Evens. 2014. 'The impact of race, age, and sex in follicular lymphoma: A comprehensive SEER analysis across consecutive treatment eras', *Am J Hematol*, 89: 633-8.
- Pettengell, R., C. Donatti, P. Hoskin, C. Poynton, P. J. Kettle, B. Hancock, S. Johnson, M. J. Dyer, S. Rule, M. Walker, and D. Wild. 2008. 'The impact of follicular lymphoma on health-related quality of life', *Ann Oncol*, 19: 570-6.
- Pongas, G., and B. D. Cheson. 2016. 'PI3K signaling pathway in normal B cells and indolent B-cell malignancies', *Semin Oncol*, 43: 647-54.
- Rivas-Delgado, A., L. Magnano, M. Moreno-Velazquez, O. Garcia, P. Mozas, I. Dlouhy, T. Baumann, J. Rovira, B. Gonzalez, A. Martinez, O. Balague, J. Delgado, N. Villamor, E. Campo, E. Gine, J. M. Sancho, and A. Lopez-Guillermo. 2017. 'Progression-free survival shortens after each relapse in patients with follicular lymphoma treated in the rituximab era', *Hematological Oncology*, 35: 360-61.
- Rummel, M. J., N. Niederle, G. Maschmeyer, G. A. Banat, U. von Grunhagen, C. Losem, D. Kofahl-Krause, G. Heil, M. Welslau, C. Balser, U. Kaiser, E. Weidmann, H. Durk, H. Ballo, M. Stauch, F. Roller, J. Barth, D. Hoelzer, A. Hinke, and W. Brugger. 2013. 'Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: an open-label, multicentre, randomised, phase 3 non-inferiority trial', *Lancet*, 381: 1203-10.
- Teras, L. R., C. E. DeSantis, J. R. Cerhan, L. M. Morton, A. Jemal, and C. R. Flowers. 2016. '2016 US lymphoid malignancy statistics by World Health Organization subtypes', *CA Cancer J Clin*.
- Wiestner, A. 2015. 'The role of B-cell receptor inhibitors in the treatment of patients with chronic lymphocytic leukemia', *Haematologica*, 100: 1495-507.
- Witzig, T. E., A. M. Vukov, T. M. Habermann, S. Geyer, P. J. Kurtin, W. R. Friedenberg, W. L. White, H. I. Chalhah, P. J. Flynn, T. R. Fitch, and D. A. Welker. 2005. 'Rituximab therapy for patients with newly diagnosed, advanced-stage, follicular grade I non-Hodgkin's lymphoma: a phase II trial in the North Central Cancer Treatment Group', *J Clin Oncol*, 23: 1103-8.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): 16349 Part A and B; 12871

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>828</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Nonclinical Pharmacology/Toxicology

No additional nonclinical data reviewed.

13.4. OCP Appendices (Technical documents supporting OCP recommendations)

13.4.1. Summary of Bioanalytical Method Validation and Performance

Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Yes, plasma and urine concentrations of active copanlisib lactam metabolite M1 (BAY 84-5719) were measured in the clinical pharmacology trials. Based on results of human mass-balance Study 16353, copanlisib is the predominant circulating moiety in plasma covering 84% of the total radioactivity in term of AUC. Although M1 has comparable pharmacology activity as copanlisib, its systemic exposure in plasma was only 5% of the total radioactivity $AUC_{0-tlast}$. Therefore, M1 is not considered a major metabolite and has limited contribution to clinically efficacy and safety.

For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

The total plasma concentrations of copanlisib and its metabolite M1 (where applicable) were measured in the clinical trials. This is appropriate due to the concentration-independent plasma protein binding of both copanlisib and M1. The average binding of copanlisib and M1 is low with free fractions of 15.8% and 20.0%, respectively.

What bioanalytical methods are used to assess concentrations?

Copanlisib and M1 concentrations in human plasma and urine were measured using validated high performance liquid chromatography with tandem mass spectrometric detection (LC-MS/MS) methods.

The assay accuracy and precision of the above bioanalytical methods are summarized in Table 47 below.

Table 47: Summary of Bioanalytical Methods and Their Applications in Clinical Trials

Bioanalytical Report No.	Analyte	Method	Individual Study Report	LLOQ (ng/mL)	Linear Range (µg/L)	Accuracy, %	Precision, % CV	Incurred Sample Analysis
BAY 80-6946/12871 with validation report MET095 v1	Copanlisib (Plasma)	LC-MS/MS	12871	0.5 & 2.0	0.5 - 265 & 2 - 1057	87.1 to 110.5	≤ 11.1	Yes, with - 3.9% deviation

NDA/BLA Multi-disciplinary Review and Evaluation NDA 209936
Aliqopa (copanlisib)

Bioanalytical Report No.	Analyte	Method	Individual Study Report	LLOQ (ng/mL)	Linear Range (µg/L)	Accuracy, %	Precision, % CV	Incurred Sample Analysis
BAY 80-6946/16349 with validation report MET095M v1	Copanlisib (Plasma)	LC-MS/MS	16349 Part A & B	2.0	2 - 1057	98.9 to 101.5	≤ 6.3	No
BAY 80-6946/16349 with validation report MET095M v1	M1 (BAY 84-5795) (Plasma)	LC-MS/MS	16349 Part A	1.0	1 - 511	98.8 to 101.1	≤ 7.0	No
BAY 80-6946/16270 with validation report MET095M v2	Copanlisib (Plasma)	LC-MS/MS	16270 Part A	0.5	0.5 - 106	99.3 to 101.4	≤ 6.9	No
BAY 80-6946/16270 with validation report MET095M v2	M1 (BAY 84-5795) (Plasma)	LC-MS/MS	16270 Part A	0.5	0.5 - 108	98.2 to 101.3	≤ 7.0	No
BAY 80-6946/16270 with validation report MET095M v1	Copanlisib (Urine)	LC-MS/MS	16270 Part A	0.5	0.5 to 106	97.0 to 102.8	≤ 6.5	Yes
BAY 80-6946/16270 with validation report MET095M v1	M1 (Urine)	LC-MS/MS	16270 Part A	0.5	0.5 to 108	96.8 to 102.4	≤ 6.7	Yes
145040ALJC & 140247AKQO with validation report ANI 10755.02	Itraconazole (Plasma)	LC-MS/MS	16270 Part A	1.0	1.0 - 1000	96.5 to 101	≤ 5.4	Yes, with - 0.99% deviation
BAY 80-6946/16970 with validation report MET095M v2	Copanlisib (Plasma)	LC-MS/MS	16970	0.5	0.5 - 106	95.8 to 102.4	≤ 10.2	No
BAY 80-6946/16970 with validation report MET095M v2	M1 (BAY 84-5795) (Plasma)	LC-MS/MS	16970	0.5	0.5 - 108	97.0 to 101.1	≤ 7.7	No

Bioanalytical Report No.	Analyte	Method	Individual Study Report	LLOQ (ng/mL)	Linear Range (µg/L)	Accuracy, %	Precision, % CV	Incurred Sample Analysis
BAY 80-6946/15205 with validation report MET095 v1	Copanlisib (Plasma)	LC-MS/MS	15205	0.5	2.5 - 1048	96.5 to 104.0	≤ 8.3	Yes, with mean deviation of 6.8%
BAY 80-6946/12874 with validation report MET095M v2	Copanlisib (Plasma)	LC-MS/MS	12874	2	2.0 - 1100	96.7 to 103.6	≤ 7.2	Yes, mean deviation - 0.2%
BAY 80-6946/16270 with validation report MET095M v2	M1 (BAY 84-5795) (Plasma)	LC-MS/MS	12874	1.0	1.0 - 530	94.5 to 105.5	≤ 9.6	Yes, mean deviation 1.5%
BAY 80-6946/12874 with validation report MET095M v1	Copanlisib (Urine)	LC-MS/MS	12874	2	2 - 1000	98.7 to 101.4	≤ 3.5	No
BAY 80-6946/12874 with validation report MET095M v1	M1 (BAY 84-5795) (Urine)	LC-MS/MS	12874	1	1 - 514	99.0 to 101.5	≤ 8.5	No

13.4.2. Clinical PK

Copanlisib PK characteristics in patients with solid tumors and NHL were first evaluated after single dose and multiple doses in Study 12871 with extensive PK sampling. The PK parameters after single dose across the dose range of 0.2 to 1.2 mg/kg are summarized in Table 48. PK parameters after multiple doses at the MTD of 0.8 mg/kg are summarized in Table 49. The PK profiles after a single 0.8 mg/kg dose in the dose escalation and expansion cohorts are shown in Figure 20. Based on non-compartmental analysis, the geometric mean copanlisib terminal half-life (n = 28) at the MTD 0.8 mg/kg was 38.2 hours (CV: 42.5%).

Table 48 Summary of Copanlisib PK Parameters in Patients with Cancer after Single Dose

Parameter	Unit	Dose-escalation cohorts				
		Cohort 1 (0.1 mg/kg) n = 1	Cohort 2 (0.2 mg/kg) n = 3	Cohort 3 (0.4 mg/kg) n = 2	Cohort 4 (0.8 mg/kg) n = 7	Cohort 5 (1.2 mg/kg) n = 2
C1D1						
C _{max}	µg/L	32.9	79.8 (53.5-110)	(143-144)	293 (252-385)	(616-739)
AUC(0-25)	µg·h/L	170	384 (275-455)	(348-556)	1590 (1000-2180)	(2510-3820)
AUC(0-t _{last})	µg·h/L	254	472 (389-598)	(722-1450)	2940 (1850-5970)	(4090-5230)

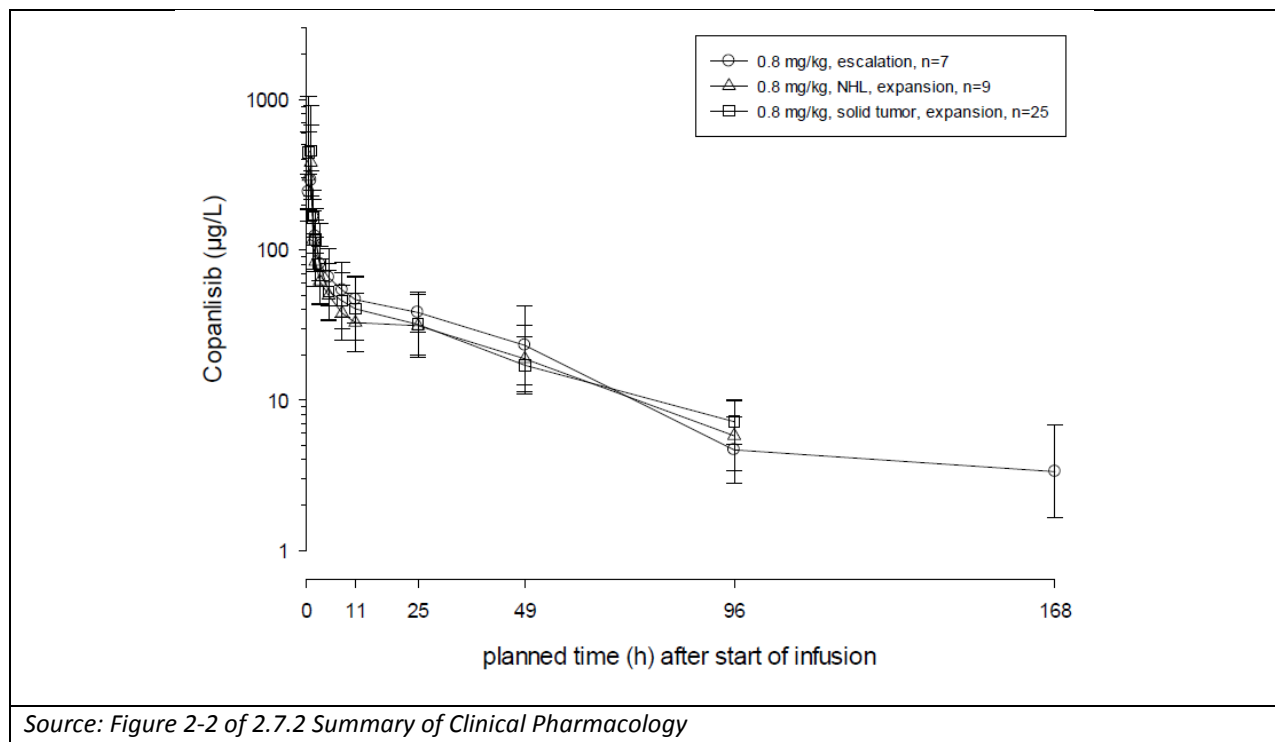
Source: Table 2-1 of 2.7.2 Summary of Clinical Pharmacology

Table 49 Summary of Copanlisib PK Parameters in Patients with Cancer after Multiple Doses

Geometric mean / %CV (range)									
Parameter	Unit	Dose-escalation cohort		Expansion cohorts				Cohorts 4, 6, and 8 combined	
		Cohort 4 MTD		Cohort 6 NHL		Cohort 8 solid tumors			
C1D15		n		n		n		n	
C _{max}	µg/L	6	370 / 29.8 (236-505)	8	507 / 52.2 (294-1020)	22	477 / 76.4 (105-1670)	36	463 / 64.4 (105-1670)
AUC(0-25)	µg·h/L	6	1480 / 22.3 (1240-2260)	8	1760 / 46.3 (885-3410)	21	1530 / 39.7 (536-2460)	35	1570 / 38.4 (536-3410)
AUC(0-t _{last})	µg·h/L	6	1640 / 27.7 (1240-2340)	8	1760 / 46.2 (885-3320)	22	1530 / 40.0 (510-2480)	36	1600 / 39.0 (510-3320)
t _{max} ^a	h	6	1.01 (0.500-1.08)	8	0.750 (0.500-1.03)	22	1.00 (0.500-1.27)	36	1.00 (0.500-1.27)
t _{last} ^a	h	6	25.1 (25.0-48.8)	8	25.0 (24.3-26.8)	22	25.0 (11.1-25.7)	36	25.0 (11.1-48.8)

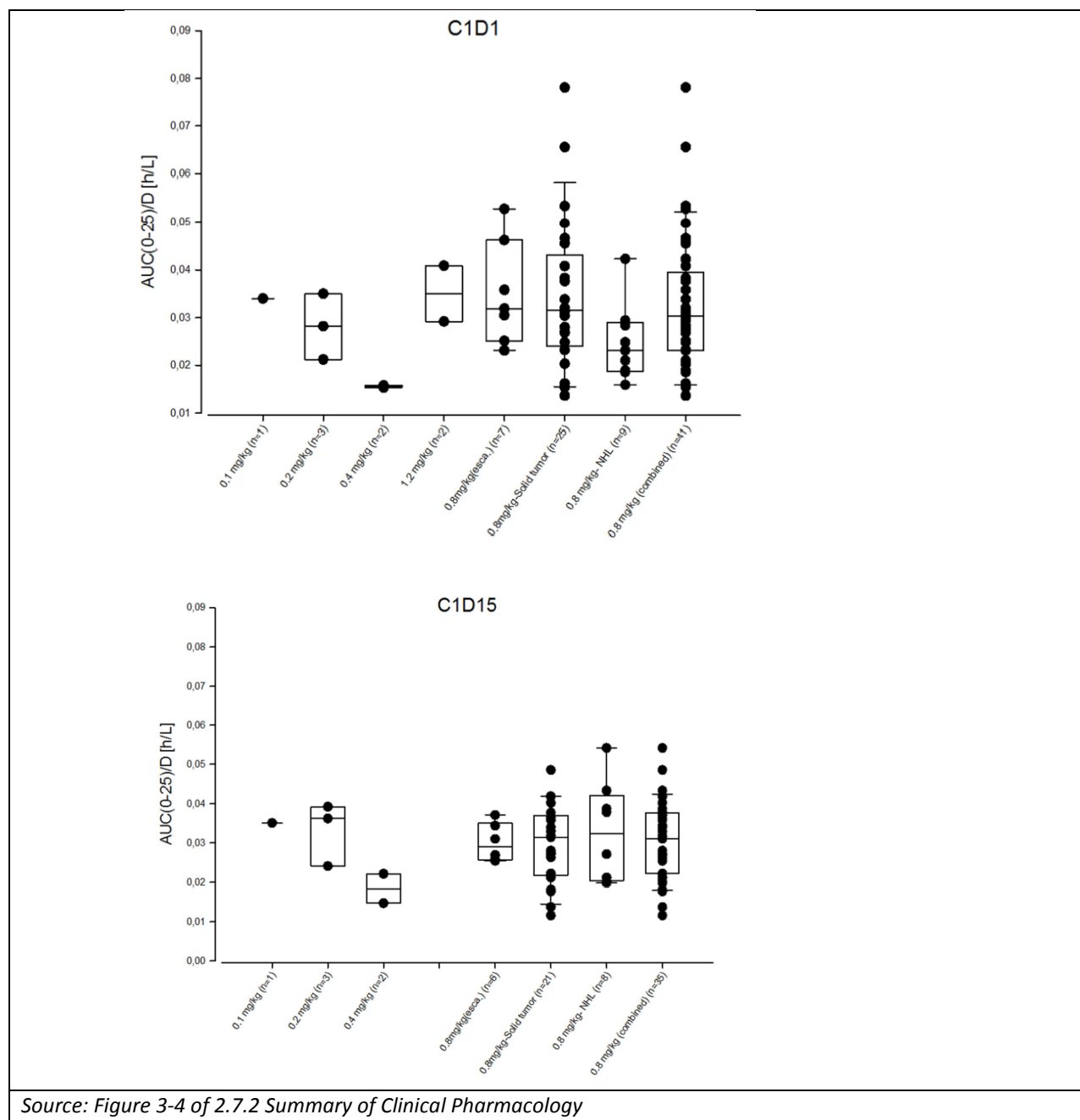
Source: Table 2-3 of 2.7.2 Summary of Clinical Pharmacology

Figure 20 Semi-logarithmic Arithmetic Mean (SD) Plasma Concentration vs Time Profiles of Copanlisib after a Single 0.8 mg/kg (MTD) Dose



Comparison of dose-normalized exposure across the dose range of 0.1 to 1.2 mg/kg after single and multiple doses suggests that copanlisib exposure (AUC) increases dose-proportionally (see Figure 21).

Figure 21 Dose Proportionality for Copanlisib PK Parameters at Cycle 1 Day 1 (C1D1) and at Cycle 1 Day 15 (C1D15) for AUC(0-25h)



PK of copanlisib is not time-dependent based on comparable C_{max} and AUC(0-25) on C1D1 and C1D15 (see Table 50). The accumulation with the weekly intermittent dosing schedule is also low based on the data shown in Table 50.

Table 50 Comparison of PK Parameters Following the C1D1 and the C1D15 Administration at the 0.8 mg/kg

Geometric mean / %CV (range)									
Parameter	Unit	Dose-escalation cohort Cohort 4 MTD		Expansion cohorts				Cohorts 4, 6, and 8 combined	
		n		n		n		n	
C1D1									
C _{max}	µg/L	7	293 / 16.5 (252-385)	9	402 / 58.5 (270-1330)	25	537 / 82.7 (193-3370)	41	454 / 73.3 (193-3370)
AUC(0-25)	µg·h/L	7	1590 / 25.6 (1000-2180)	9	1350 / 36.8 (701-2500)	25	1690 / 46.7 (749-4610)	41	1590 / 41.9 (701-4610)
C1D15									
C _{max}	µg/L	6	370 / 29.8 (236-505)	8	507 / 52.2 (294-1020)	22	477 / 76.4 (105-1670)	36	463 / 64.4 (105-1670)
AUC(0-25)	µg·h/L	6	1480 / 22.3 (1240-2260)	8	1760 / 46.3 (885-3410)	21	1530 / 39.7 (536-2460)	35	1570 / 38.4 (536-3410)

Source: Table 3-5 of 2.7.2 Summary of Clinical Pharmacology

Most PK data of copanlisib are obtained in patients with cancer except that in the human mass balance Study 16353. A comparison between these two groups suggests that PK parameters are comparable between healthy volunteers and patients with cancer (see Table 51).

Table 51 Comparison of Copanlisib PK Parameters in Healthy Volunteers and Cancer Patients Following a Single IV Dose of 12 mg Copanlisib in Studies 16353 and 16270

Parameter	Unit	Geometric mean/%CV (Range)			
		Study 16353		Study 16270	
		Healthy volunteers n = 6		Cancer patients n = 6	
AUC	µg·h/L	442/41.2	(269-769)	537/45.1	(286-747) ^b
AUC(0-t _{last})	µg·h/L	392/46.4	(223-710)	524/40.0	(267-708) ^c
AUC(0-24)	µg·h/L	176/30.7	(121-273)	291/39.9	(170-482) ^c
C _{max}	µg/L	44.1/33.6	(25.6-63.4)	86.1/71.3	(47.2-290)
t _{max} ^a	h	0.97	(0.50-0.97)	0.94	(0.17-1.00)
t _{last} ^a	h	168	(96.0-240)	144	(24.1-168)
t _{1/2}	h	52.1/20.9	(40.4-67.5)	34.8/55.4	(18.2-54.8) ^b

Source: Table 3-7 of 2.7.2 Summary of Clinical Pharmacology

13.4.3. Pharmacometrics Review

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

NDA Number	209936
Drug Name	ALIQOPA™ (copanlisib)
Dose Regimen	60 mg administered as a 1-hour intravenous (IV) infusion on Days 1, 8, and 15 of a 28-day treatment cycle
Indication	Treatment of patients with relapsed (b) (4) follicular lymphoma (FL) who have received at least two prior therapies
Pharmacometrics Reviewer	Hongshan Li, Ph.D.
Pharmacometrics Team Lead	Jiang Liu, Ph.D.
Applicant	Bayer AG

Summary of Findings

Pivotal trial 16349 Part B studied copanlisib maximum tolerable dose, 60 mg in 131 patients and 0.8 mg/kg in 12 patients, administered as a 1-hour intravenous infusion on Days 1, 8, and 15 of a 28-day treatment cycle. The primary objective was to determine the objective response rate in patients with relapsed or refractory follicular lymphoma who have received at least two prior therapies. The secondary objectives were to evaluate progression free survival, treatment duration, safety, population pharmacokinetics (PPK), exposure-response relationship, etc.

The major findings of the FDA reviewer's exploratory PPK and ER analysis of the data from 16349 Part B are:

- There was no evidence that bodyweight, age, or sex had effect on copanlisib clearance. CL was similar between White and other races combined.
- There was no evidence that mild hepatic impairment, mild or moderate renal impairment had effect on copanlisib CL. Regardless of renal/hepatic function category, copanlisib CL was similar between patients with adverse event related treatment discontinuation (AEDC) and patients without AEDC.
- A slightly positive ER relationship was observed for ORR and overall Grade 3 or higher adverse events. When non-zero dose is considered, 77% (110/143) patients exited the study at a dose not smaller than 60 mg or 0.8 mg/kg. The proposed dosing regimen, coupled with dose modification strategy, appears to be acceptable for treating the proposed indication.

- There was a slightly positive ER relationship for hyperglycemia. There was a positive ER relationship for blood glucose elevation. These support the dose modification strategy for the management of hyperglycemia.

In summary, the PPK based labeling in Section 12.3 of the package insert is acceptable. The proposed copanlisib dose regimen of 60 mg, IV infused on Days 1, 8, and 15 of a 28-day treatment cycle, coupled with dose modification strategy for adverse events is supported by the efficacy and safety data from the pivotal trial.

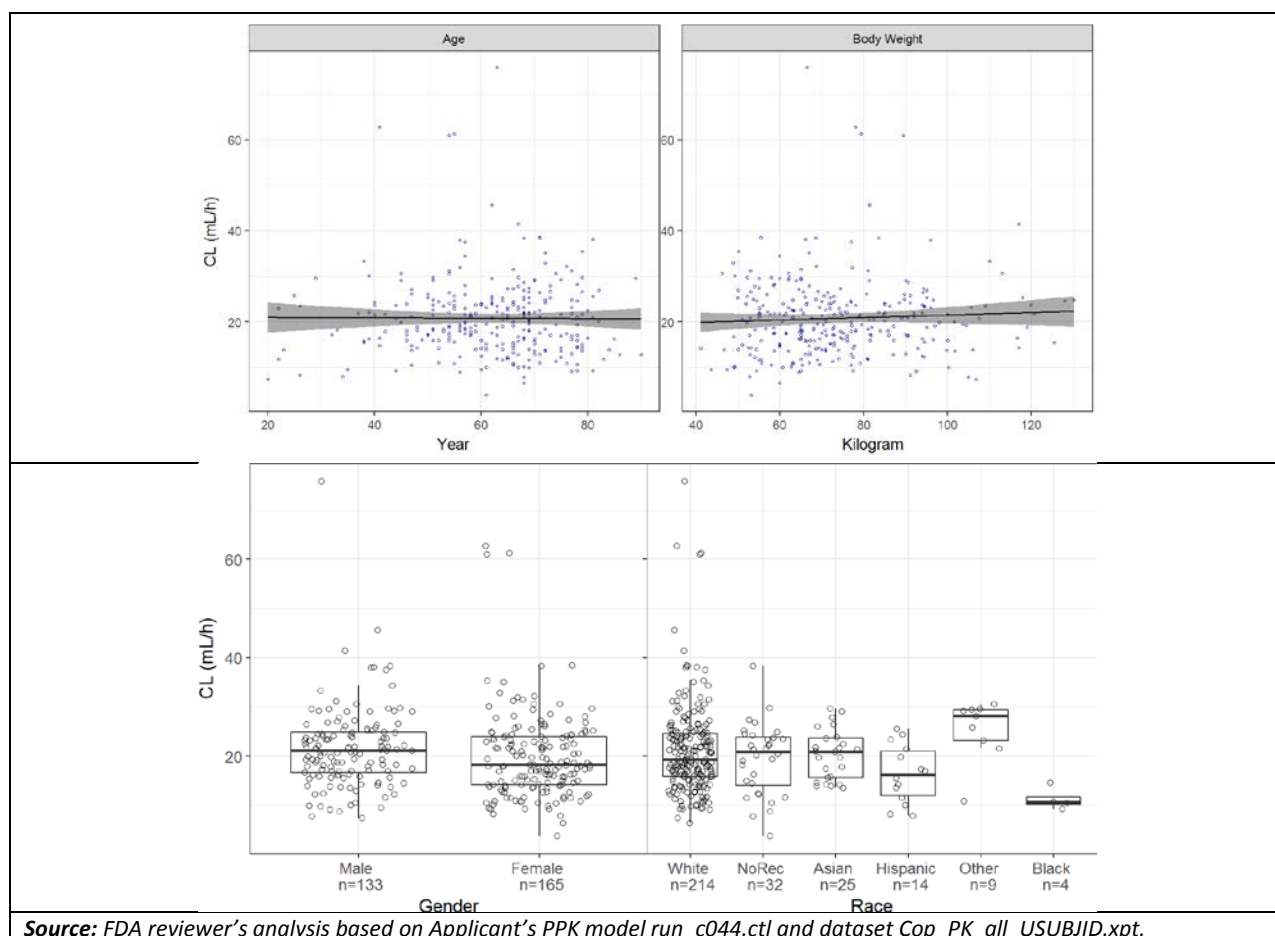
Key Review Questions

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

Is the proposed labeling language of no effect of body weight, age, race, sex, mild hepatic impairment, mild or moderate renal impairment on copanlisib pharmacokinetics appropriate?

Based on PPK analysis, the proposed labeling language of no effect of BW, age, race, sex, mild hepatic impairment, mild or moderate renal impairment on copanlisib PK is appropriate.

Figure 22 The Effect of Age, Body Weight, Sex, and Race on Copanlisib Clearance Based on Population Pharmacokinetics Analysis

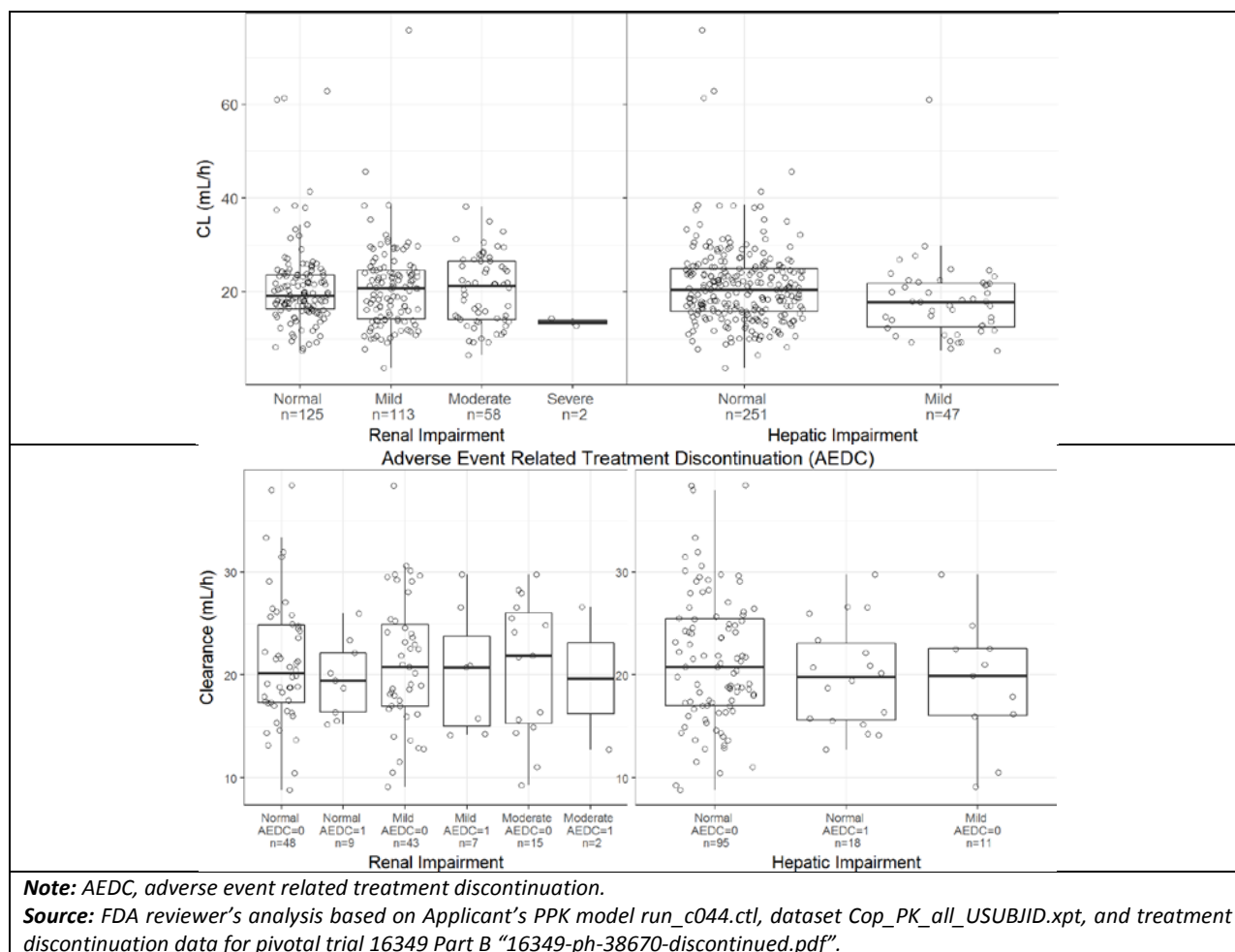


The Applicant's PPK model (run_c044.cti) associated with dataset "Cop_PK_all_USUBJID.xpt" was executed at the FDA system, and post-hoc CL of 124 patients of Study 16349 Part B was utilized to explore the covariate effect on copanlisib CL, and the results are:

- As shown in Figure 22, there appeared to be no effect of age, BW, or gender on copanlisib CL, which was similar between White (n=79) and other races (n=45).
- There appeared to be no effect of mild hepatic impairment, mild or moderate renal impairment on copanlisib CL as shown in the upper panels of Figure 23.
- Regardless of the renal/hepatic function category tested, there appeared to be no relationship between CL and adverse event related treatment discontinuation as shown in the lower panels of Figure 23.

In summary, the PPK related language in Section 12.3 of the label is acceptable.

Figure 23 The Relationship between Copanlisib Clearance and Organ Impairment with (Lower Panels) and without (Upper Panels) AEDC as Stratification Factor



Is the proposed copanlisib dose of 60 mg supported by the dose compliance outcome and the exposure-response relationship?

The proposed copanlisib dose of 60 mg is generally supported by dose compliance outcome and ER relationship of Study 16349 Part B.

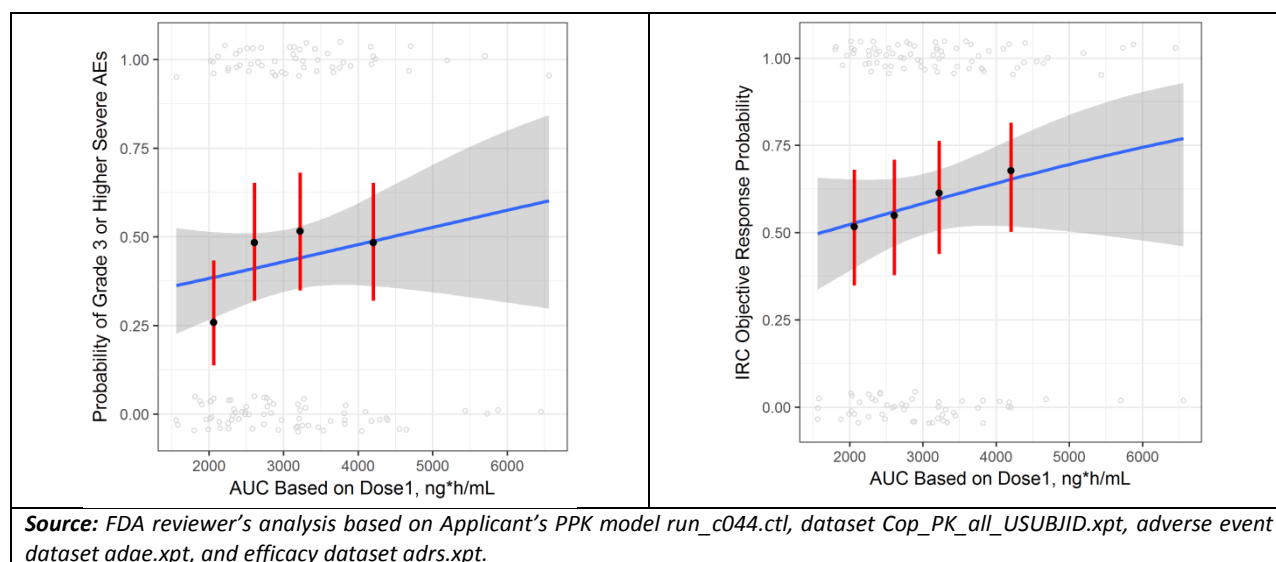
At first, the proposed dose seems to be supported by the dose compliance outcome of the 143 patients from Study 16349 Part B, as shown in Figure 36 and listed in Table 55.

- There were 77% (110/143) patients exited the study at a dose ≥ 60 mg or 0.8 mg/kg. Of these patients, 31% (44/143) never reduced or skipped a dose, and 46% (66/143) patients reduced or skipped at least one dose.
- Total 23% (33/143) patients ended the study at a dose smaller than scheduled, with 18% (26/143) at 45-51 mg, and 5% (7/143) at 30 mg.

At second, the findings based on ER analysis also appeared to support the proposed dose regimen of 60 mg administered as a 1-hour IV infusion on Days 1, 8, and 15 of a 28-day treatment.

- Based on adverse event dataset adae.xpt and exposure data from the PPK analysis, the probability of overall Grade 3 or higher adverse events is shown in the left panel of Figure 24. The adverse event rate is higher when the exposure is higher.
- The ORR from independent assessor versus exposure is shown in the right panel of Figure 24. The ORR is higher when the exposure is higher.

Figure 24 The Exposure-Response Analysis Result for Adverse Event Rate and Objective Response Rate of the 124 Pharmacokinetics Evaluable Patients



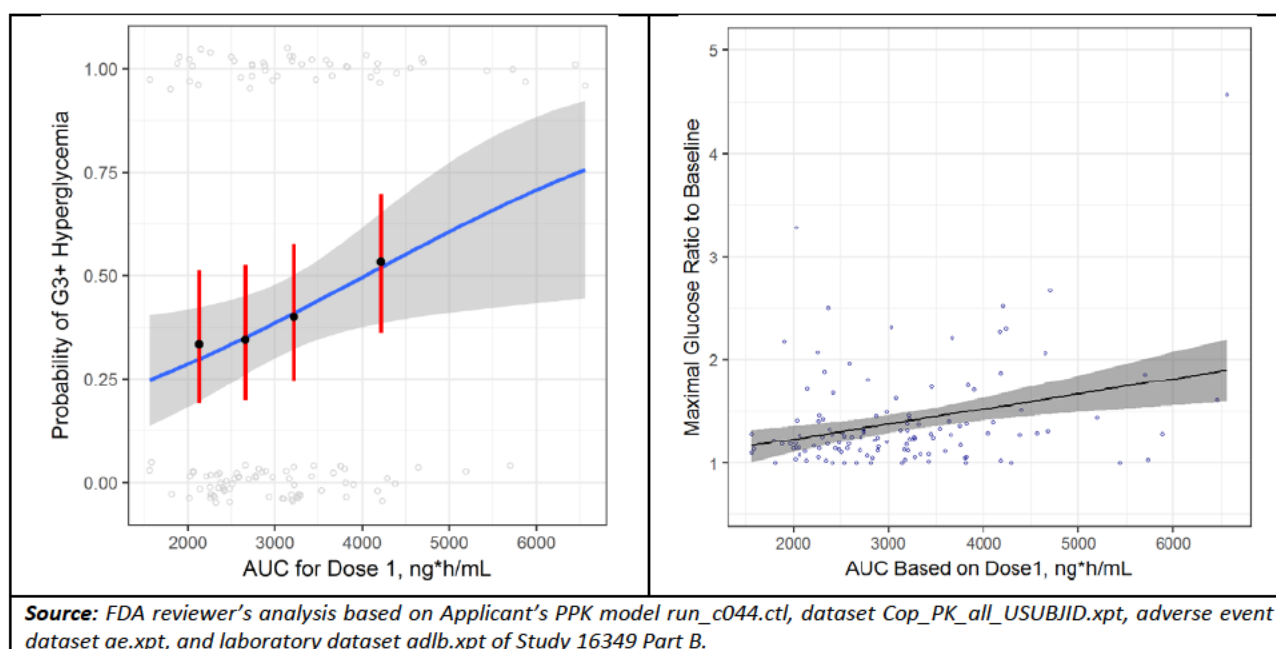
In summary, the dose of 60 mg administered as a 1-hour IV infusion on Days 1, 8, and 15 of a 28-day treatment cycle was the maximum tolerated dose identified in the Phase I dose

escalation study, where the dose limiting toxicity was observed at 1.2 mg/kg (3 weeks on/ 1 week off). The observed insignificant positive ER relationships for efficacy and safety support this dose, which is subject to modification based on individual patient's clinical tolerability.

Is the proposed dose modification strategy for hyperglycemia management appropriate?

For Study 16349 Part B, there was a slightly positive ER relationship for Grade 3 or higher hyperglycemia (left panel of Figure 25). Also, there appeared to be a correlation between exposure and blood glucose maximum change from baseline in the 140 patients (right panel of Figure 25). The Applicant's dose modification strategy for hyperglycemia management appears to be acceptable.

Figure 25 The Exposure-Response Analysis Result for $\geq$ Grade 3 Hyperglycemia (Left Panel, n=124) and Maximal Blood Glucose Change from Baseline (Right Panel, n=140)



Applicant's Population Pharmacokinetics and E-R Analysis

PPK Analysis

Data: Data from the clinical studies 12871, 15205, 16270, 16790, and 16349 were used in the population PK analysis (Table 52).

Table 52 Summary of Data for the Population Pharmacokinetics Analysis

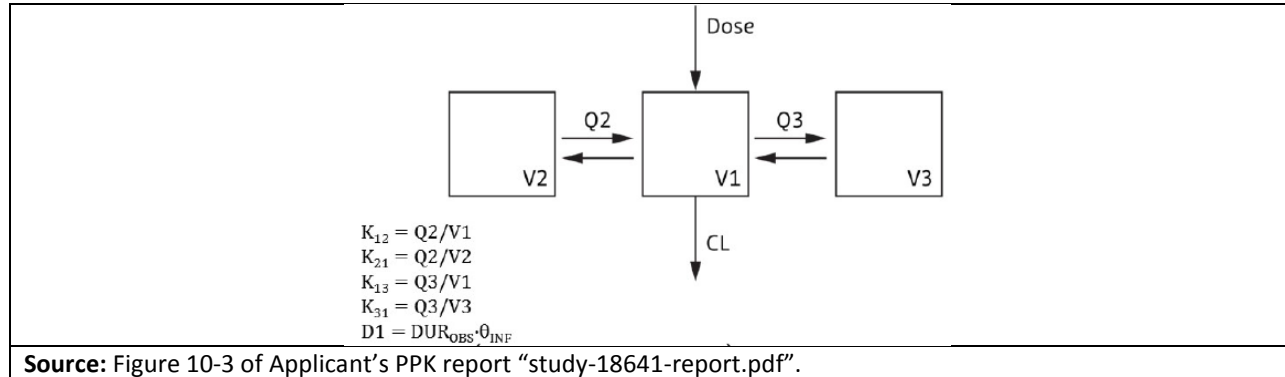
Study No.	Description	Treatment	N of Subjects ^a
12871	Phase 1, dose escalation of copanlisib in cancer patients with solid tumors and NHL	0.1 mg/kg to 1.2 mg/kg as one hour infusion given 3 weeks on / 1 week off.	65
15205	Phase 1, dose escalation of copanlisib in	0.4 mg/kg or 0.8 mg/kg as one hour	12

Study No.	Description	Treatment	N of Subjects ^a
	Japanese cancer patients with solid tumors	infusion given 3 weeks on / 1 week off.	
16270	Phase 1, drug-drug interaction study of copanlisib in subjects with advanced solid tumors	Arm A: 12 mg copanlisib in Part 1 and 60 mg copanlisib in Part 2. In cycle 1 copanlisib is given on Day 1 and on Day 15. Itraconazole 200 mg is given twice a day on Day 12 and thereafter once a day.	Arm A Part 1: 10 Arm A Part 1: 16
16790	Phase 1, pharmacodynamics study of copanlisib in patient with iNHL or solid tumors	0.4 mg/kg or 0.8 mg/kg as one hour infusion given 3 weeks on / 1 week off.	24
16349	Phase 2, Open-label uncontrolled study of copanlisib in aNHL and iNHL patients	Part A: aNHL + iNHL patients; 0.8 mg/kg copanlisib (3 weeks on / 1 week off) Part B: iNHL patients; 0.8 mg/kg until Amendment 4 (n=12), then 60 mg copanlisib 3 weeks on / 1 week off)	Part A: 84 Part B: 143
^a number of enrolled patients. For example, only 124 patients contributed to PPK and ER analysis although 143 enrolled in Study 16349 Part B. Refer to Applicant's PPK report "study-18641-report.pdf" for more information.			

Methods: The PK model development was conducted using nonlinear mixed-effects modelling with NONMEM (ICON Development Solutions, version 7.3). All other preparation, analysis and visualization of data was done using R version 3.1.1 (<https://www.r-project.org/>).

Results: The PK data of copanlisib administered as a weekly 1-hour IV infusion on Days 1, 8 and 15 of each 28-day treatment cycle on an intermittent schedule (3 weeks on/1 week off) in patients from studies 12871, 15205 and the 16349 Part A were used to develop a population PK model. The model contains three-compartments, with linear elimination from the central compartment (Figure 26). The inter-individual variability on clearance, the volume of the first peripheral compartment (V2), and the volume of the second peripheral compartment (V3) was 51%, 88%, and 42% expressed as coefficient of variation (CV), respectively. The inter-occasion variability on CL was 23% CV. The residual variability was 68% CV and 24% CV for during and after the infusion, respectively. To adequately describe the observed concentrations it was necessary to estimate a correction factor of 0.84 for the recorded infusion durations. All model parameters were estimated with acceptable standard errors (RSE<40%) and shrinkage. External qualification of the model was accomplished using data from studies 16790, 16270 Arm A, and 16349 Part B. No relevant individual or population bias was detected, and it was concluded that the final model was generally applicable across studies. Only in study 16790 a slight under-prediction of post-infusion concentrations was observed.

Figure 26 Graphical Representation of the Structural Population Pharmacokinetics Model



A covariate analysis of the influence of intrinsic (gender, body weight, age, race, creatinine clearance, albumin concentration, hepatic impairment, renal impairment) and extrinsic (geographic region, smoking) factors on all three PK parameters with inter-individual variability (CL, V2, V3) was first performed using only the data for model-building (123 patients) and later repeated with all data (297 patients). The former analysis found three significant covariate

APPEARS THIS WAY ON
ORIGINAL

Table 53 Parameter estimates with standard errors and confidence intervals for covariate model built using all patient data file (Run_c044)

Parameter	Unit	Estimate	RSE [%] ^a	LLCI ^b	ULCI ^c	Description
Fixed effects (THETA)						
CL _{TV}	L/h	19.5	3.5	18.2	21.0	Clearance for patient with median albumin concentration (3.8 g/dL)
V ₁	L	45.7	5.2	41.0	50.4	Volume of distribution of central compartment
Q ₂	L/h	58.2	5.0	52.5	63.9	Inter-compartmental clearance between central / first peripheral compartment
V _{2TV}	L	95.5	9.7	77.3	114	Volume of distribution of first peripheral compartment for patient with median body weight (70 kg)
Q ₃	L/h	54.7	2.7	51.8	57.6	Inter-compartmental clearance between central / second peripheral compartment
V _{3TV}	L	743	4.3	680	806	Volume of distribution of second peripheral compartment for patient with median age (66 years)
θ _{INF}	-	0.797	3.4	0.744	0.850	Parameter that modifies observed infusion duration
θ _{ALBU_CL}	(g/dL) ⁻¹	0.197	22.0	0.112	0.282	Parameter describing the linear influence of albumin concentration on CL
θ _{WGHT_V2}	-	1.27	25.4	0.639	1.90	Parameter describing the allometric influence of patient body weight on V2
θ _{AGE_V3}	Year ⁻¹	0.0104	18.5	0.066	0.014	Parameter describing the linear influence of patient age on V3
Random effects ^d : Inter-individual variability (OMEGA)						
CL (ω ²)	-	0.189	10.4	0.150	0.228	Inter-individual variability on CL
CL (CV)	%	45.6		40.3	50.6	
CL (Shrinkage)	%	22.8				
V2 (ω ²)	-	0.728	14.4	0.522	0.934	Inter-individual variability on V2
V2 (CV)	%	103		82.8	124	
V2 (Shrinkage)	%	22.5				
V3 (ω ²)	-	0.148	17.4	0.097	0.199	Inter-individual variability on V3
V3 (CV)	%	39.9		32.0	46.9	
V3 (Shrinkage)	%	30.7				
Random effects ^d : Inter-occasion variability (OMEGA)						
CL (ω ²)	-	0.0465	18.6	0.030	0.064	Inter-occasion variability on CL
CL (CV)	%	21.8		17.3	25.6	
Residual error (SIGMA)						
Resid1 (σ ²)	-	0.636	3.33	0.594	0.678	Additive residual error of model predictions (on natural log scale) during infusion
Resid1 (CV)	%	79.7		77.1	82.3	
Resid2 (σ ²)	-	0.0640	2.56	0.0608	0.067	Additive residual error of model predictions (on natural log scale) post infusion
Resid2 (CV)	%	25.3		24.7	25.9	
^a RSE = relative standard error (100·SE/estimate)						
^b LLCI = lower limit of 95% confidence interval (estimate - 1.96·SE)						
^c ULCI = upper limit of 95% confidence interval (estimate + 1.96·SE)						
^d the coefficient of variation (CV) is calculated as 100·SQRT(EXP(OMEGA ²)-1) and 100·SQRT(SIGMA ²). The confidence intervals of CV are derived through transformation of confidence intervals of OMEGA ² and SIGMA ² . Eta shrinkage is calculated as 100·(1-standard deviation of individual eta estimates/ω).						

Source: Table 10-10 of Applicant's PPK report "study-18641-report.pdf".

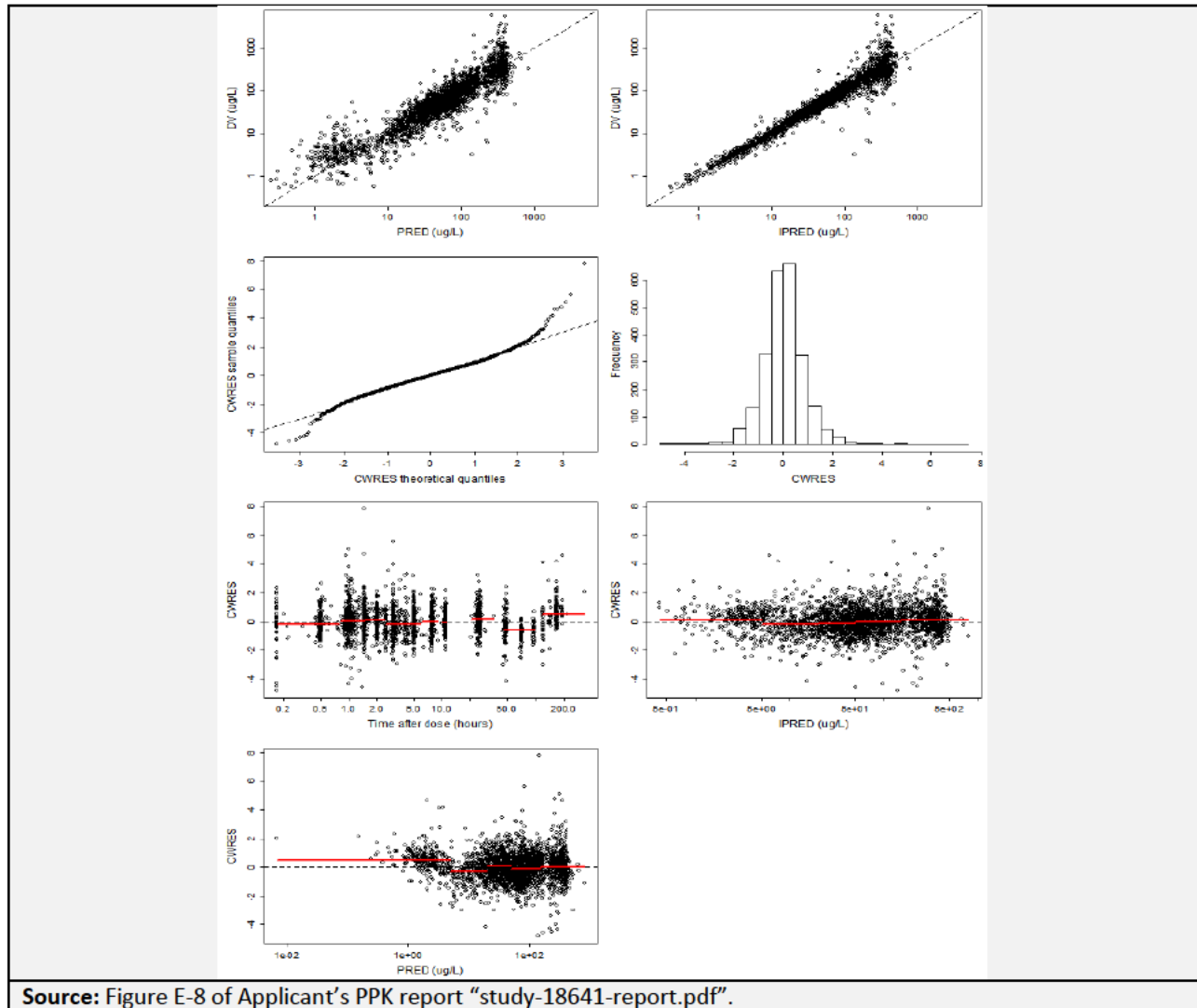
Source: Table 10-10 of Applicant's PPK report "study-18641-report.pdf".

relationships: age on V₂ (V₂ increasing with increasing age explained 27.5% of variability), age on V₃ (V₃ increasing with increasing age explained 21.3% of variability) and serum albumin concentration on CL (CL increasing with increasing albumin concentration explained 6.0% of

variability). With age on V3, serum albumin on CL and body weight on V2 remained as covariate relationships, Run_c044 passes all model selection criteria with the exception that η -shrinkage on V3 (30.7%) is slightly higher than the limit for acceptance (30%). The final model (Run048_cov) using the smaller model-building data file (where 16349 Part B PK data were not included), the η -shrinkage on V3 was 27.0%, slightly lower than 30%.

When the maximal copanlisib concentration ($C_{max_{nd}}$) and the area under the curve ($AUC_{(0-168)nd}$) were simulated after nominal dosing of 60 mg, the influence of age at the 5th and 95th percentage of the distribution across all 297 patients was negligible (<1%) for $AUC_{(0-18)nd}$. $C_{max_{nd}}$ also only changed by +5.5% and - 1.4%, respectively. The impact of serum albumin at the 5th and 95th percentile was only +3.2% and -2.8% on $C_{max_{nd}}$, but +30% and -19% on $AUC_{(0-168)nd}$, respectively. Yet, none of the extremes of the covariates warranted a dosage adjustment. A repeat covariate search using the data of all 297 patients found very similar relationships between covariates and structural model parameters: age on V3, serum albumin on CL, and body weight on V2. The individual predictions of copanlisib plasma concentration and individual model parameters were almost identical between the former and the latter model.

Figure 27 The General Goodness of Fit Plots for Run_c044.ctl



Simulations of $C_{max_{nd}}$ and $AUC_{(0-168)_{nd}}$ at the 5th and 95th percentiles of the covariates, based on the model for all patient data, demonstrated minor influences (<3%) compared to the covariate median for age and body weight. The influence of serum albumin at the 5th and 95th percentile was negligible on $C_{max_{nd}}$ (+2.5% and -2.3%, respectively) but more pronounced on $AUC_{(0-168)_{nd}}$ (+24.5% and -16.4%, respectively). Again, it was concluded that also this covariate model did not justify any dosage adjustment, based on extreme values of covariates. The fact that higher serum albumin levels were associated with higher clearance was interpreted as albumin being a marker of liver function rather than of plasma binding. Individual values of C_{max} and C_{av} were estimated based on the final population PK model. These values have been provided to the model-based evaluation of exposure-response relationships, which will be reported separately.

Overall conclusions

- A population pharmacokinetic model for copanlisib was successfully developed for 123 patients with solid tumors or with lymphomas. The model consists of one central compartment with linear elimination and two peripheral compartments. Inter-individual variability is included on CL (51% CV), V2 (88% CV) and V3 (42% CV), and inter-occasion variability (23% CV) is estimated for CL. The model was validated with external data of 174 patients.
- Intrinsic and extrinsic factors were tested with a model-based approach of forward inclusion and backward elimination. This procedure was executed based in the data of 123 patients and again with additional 174 patients. Both approaches led to very similar results. Individual predictions of PK parameters and plasma concentrations by the two models were almost identical.
 - 1) Significant covariates were age on V2 and on V3 and albumin on CL in the first approach and body weight on V2, age on V3, and albumin on CL in the second approach. These covariates could only partially explain the inter-individual variability.
 - 2) Categories for mild or moderate renal impairment and for mild hepatic impairment could not explain PK variability. Severe renal impairment was only represented in two patients. Also gender, race, geographic region, and smoking did not explain variability.
 - 3) Extreme values of the significant covariates age and body weight influenced $C_{max,nd}$ and $AUC_{(0-168)nd}$ by less than 10%. The strongest influence on copanlisib exposure was shown in the first approach by serum albumin with a 30% increase and a 19% decrease in $AUC_{(0-168)nd}$ for the 5th and 95th percentile compared to the median, respectively. Overall, extreme values in significant covariates did not warrant a dosage adjustment of copanlisib.
- Individual values of C_{max} and C_{avg} will be used in the exposure-response analysis.

E-R Analysis

Introduction: This statistical report is to describe across-study analyses on the effects between safety and efficacy endpoints and the study drug exposure in patients with follicular lymphoma or marginal zone lymphoma. Source Figures references are referring to 126 FL patients (see Table 3 of ER report “ph-39567-study-report.pdf” on Page 22) for this section.

Exposure-Efficacy Relationship: The results of the ER for efficacy showed a not significant positive trend association between copanlisib exposure (average plasma concentration, C_{avg} , until either first response, for responders, or end of last PPK measurement interval, for non-responders) and the primary efficacy endpoint objective response rate in Figure 28. This had been analyzed using a logistic regression. With regard to duration of response and progression-free survival, a relationship to C_{avg} was not identified (Figure 29 and Figure 30). This result had

been determined visually based on Kaplan-Meier graphs including four groups of patients, as defined by quartiles of Cavg until progression. Additionally, Cox Proportional Hazards models with per weekly/bi-weekly PPK interval Cavg as a time-varying covariate could not identify a dependency.

Figure 28 Plot of Logistic regression for ORR - Cavg

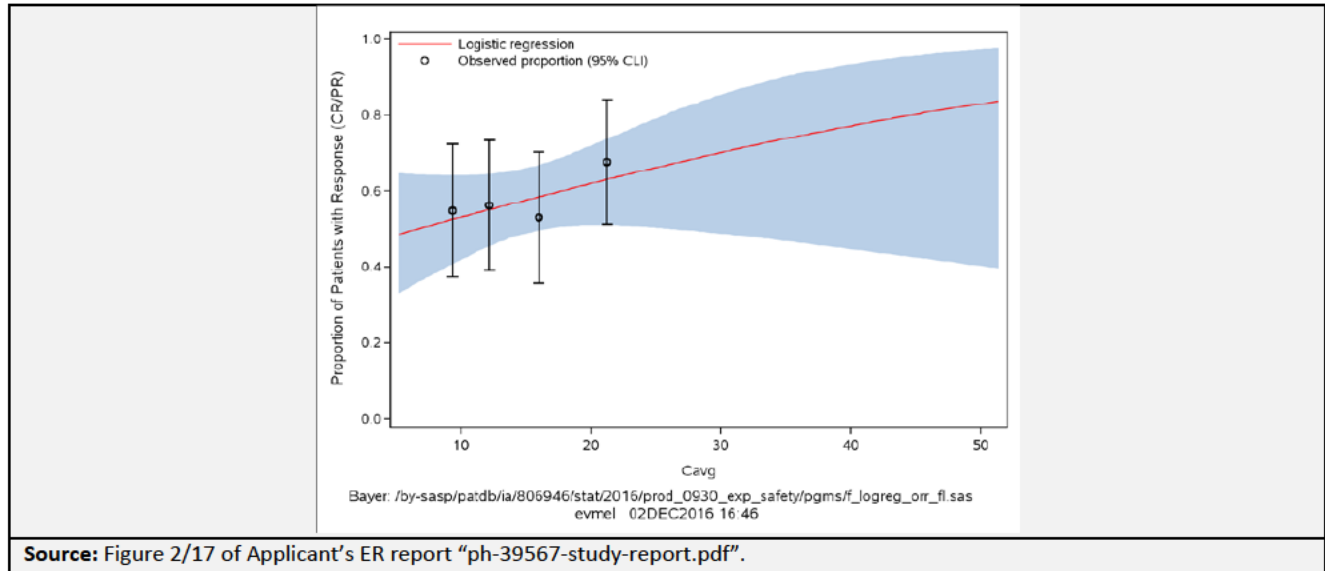


Figure 29 Kaplan-Meier curves of duration of response (full analysis set)

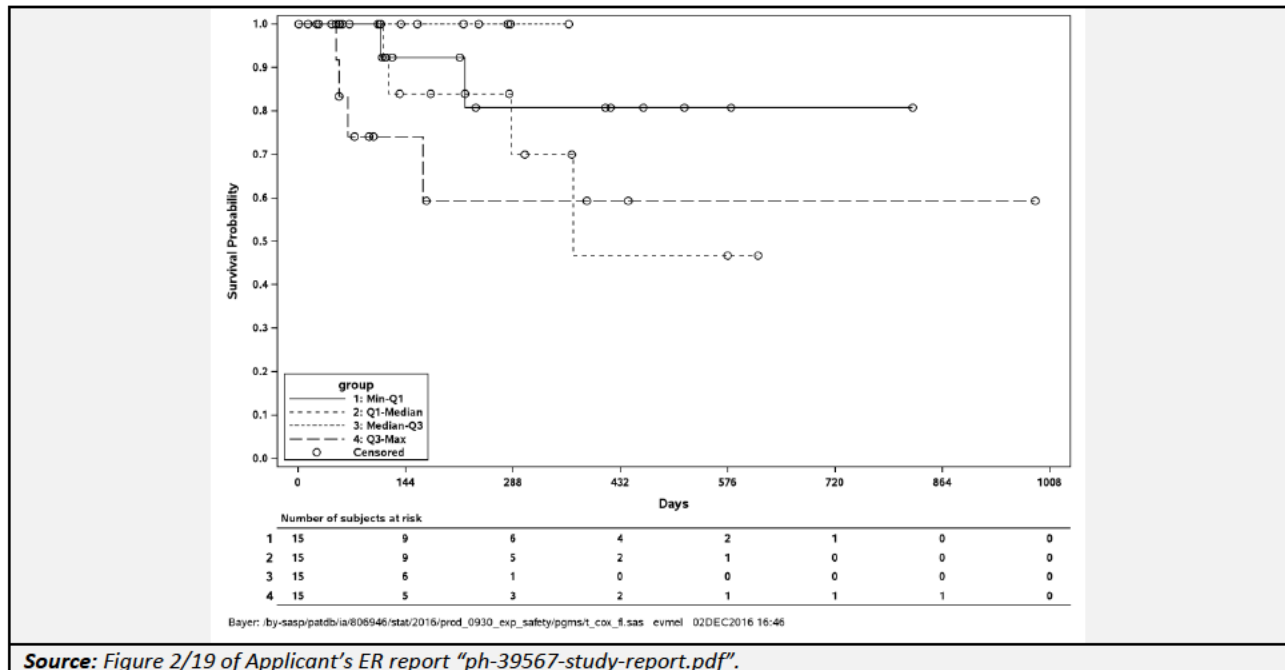
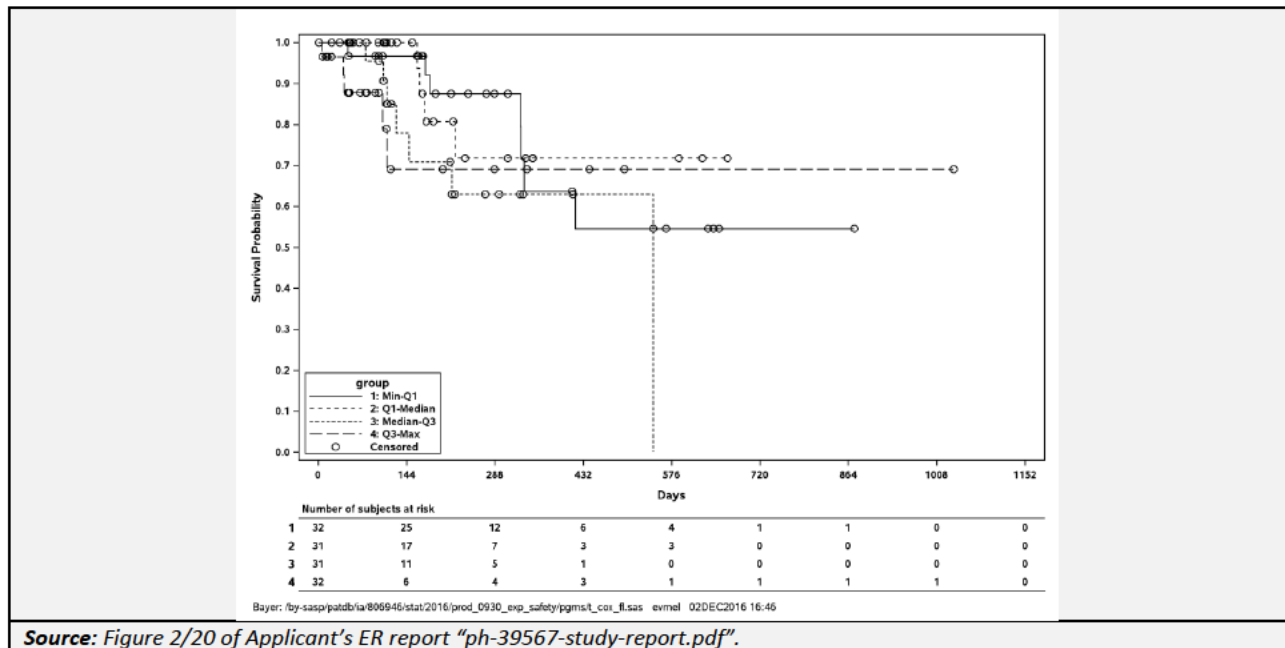


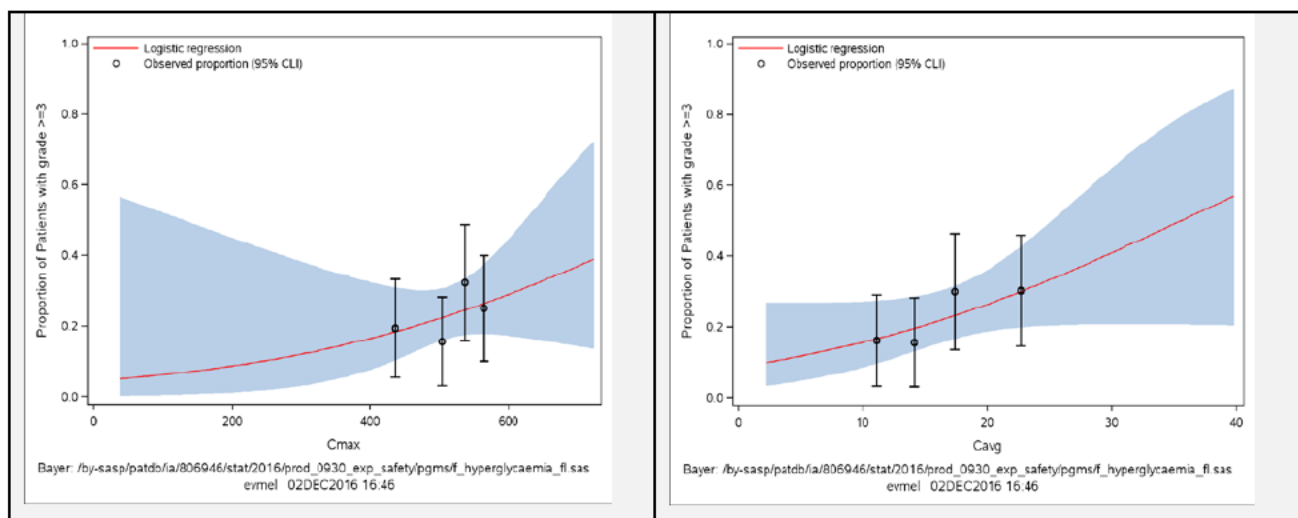
Figure 30 Kaplan-Meier curves of duration of Progression Free Survival (full analysis set)



Source: Figure 2/20 of Applicant's ER report "ph-39567-study-report.pdf".

Exposure-Safety Relationship: Incidence of hypertension and hyperglycemia adverse event occurring in first injection interval with according Cavg and maximum concentration, Cmax, from PPK was evaluated using logistic regression models. No relationship was found between exposure (Cavg, Cmax) and hypertension (any grade, grade ≥ 2 or ≥ 3). Higher copanlisib exposure appeared to be associated with grade 3 hyperglycemia (too few events at grade 4) in Figure 31, but the influence was not significant.

Figure 31 Plot of Logistic regression for Hyperglycemia - Grade ≥ 3 versus Cmax or Cavg



Source: Figures 2/9 and 2/13 of Applicant's ER report "ph-39567-study-report.pdf".

Figure 32 Comparison of individual predicted concentrations from Run048_cov and Run_c044 using the all patient data file

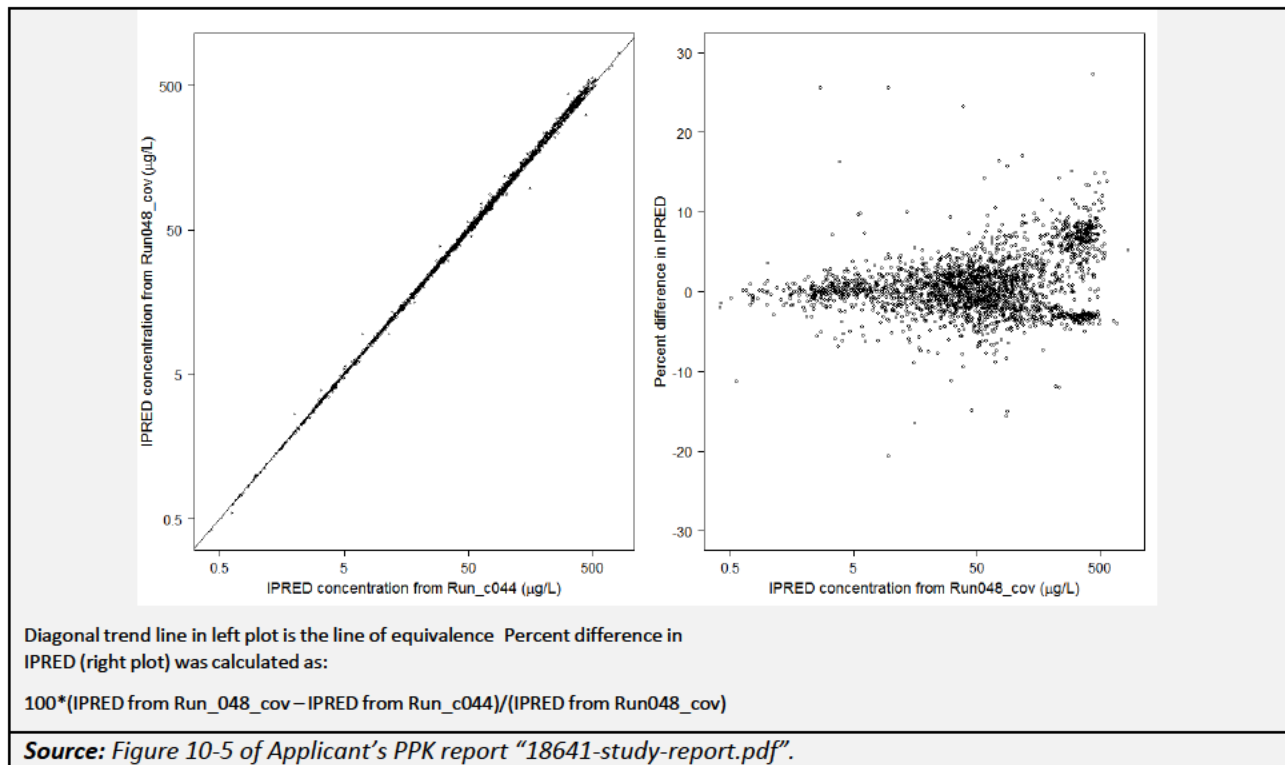
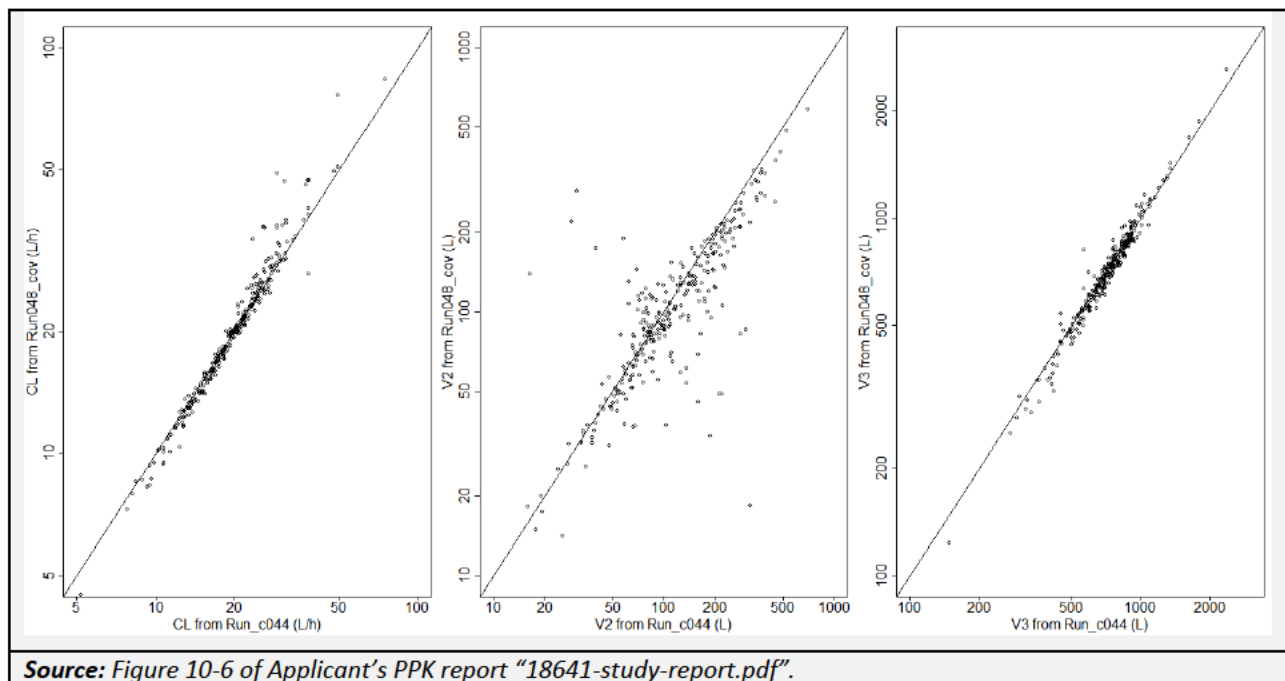


Figure 33 Comparison of individual parameter estimates from Run048_cov and Run_c044 using the all patient data file



Reviewer's Comments: Run048_cov was Applicant's final PPK model based on data from studies 12871, 15205 and the 16349 Part A. Run_c044.ctf (ADVAN11 TRANS4) was associated with a PPK dataset including copanlisib concentrations from Study 16349 Part B, therefore was used to generate CL for FDA reviewer's ER analysis. The two models showed good concordances (Figure 32 and Figure 33). For ER analysis of FL population, there are some differences between the analyses of the Applicant and the FDA reviewer:

- The Applicant did the ER analysis for 126 patients (6 from Phase I open-label dose-escalation Study 12871, 16 from Study 16349 Part A and 104 from Study 16349 Part B).
- The FDA reviewer did the ER analysis for the 124 PK evaluable patients from Study 16349 Part B.

Reviewer's Analysis

Introduction

The Applicant submitted 3 PPK analysis reports and 5 ER analysis reports, with two of them (Report #R-11088 for PPK, and Report #39567 for ER) related to pivotal trial, Part B of Study 16349. The final PPK model for 16349 Part B was Run_c044.ctf, for which unique subject identification number (USUBJID) was not included in the PPK dataset, and the information was submitted upon request. The information is necessary for FDA reviewer's ER analysis for primary efficacy (i.e., ORR), adverse events (hyperglycemia, hypertension, diarrhea, and overall adverse event rate).

Treatment discontinuation data for 16349 Part B was also submitted upon request. The information is necessary for FDA reviewer's analysis for verifying the labeling statement about the effect of renal/hepatic impairment on PK.

Objectives

The objectives of FDA reviewer's ER analysis were:

1. To explore the ER relationship for ORR of Study 16349 Part B.
2. To explore the ER relationships for adverse events, particularly hyperglycemia, of Study 16349 Part B.
3. To confirm the PPK related labeling language in Section 12.3 of the package insert.

Methods

Data Sets

The exposure, area under the curve of concentration-time plot for a dose interval at steady-state (AUCs), was imputed from post-hoc parameters of Run_c044.ctf. Data sets used for the analysis are summarized in Table 54.

Table 54 Analysis Data Sets

Name	Link to EDR
ae.xpt	\\cdsesub1\evsprod\nda209936\0001\m5\datasets\16349-ph-38670\tabulations\sdtm\ae.xpt
adex.xpt	\\cdsesub1\evsprod\nda209936\0001\m5\datasets\16349-ph-38670\analysis\adam\datasets\adex.xpt
adrs.xpt	\\cdsesub1\evsprod\nda209936\0001\m5\datasets\16349-ph-38670\analysis\adam\datasets\adrs.xpt
adsl.xpt	\\cdsesub1\evsprod\nda209936\0001\m5\datasets\16349-ph-38670\analysis\adam\datasets\adsl.xpt
Discontinuation Data	\\cdsesub1\evsprod\nda209936\0006\m5\53-clin-stud-rep\535-rep-effic-safety-stud\inhl\5352-stud-rep-uncontr\16349-ph-38670\16349-ph-38670-response.pdf
cop_pk_all_usubjid.xpt	\\cdsesub1\evsprod\nda209936\0009\m5\datasets\18641\analysis\legacy\datasets\cop_pk_all_usubjid.xpt
run_c044.ctf	\\cdsesub1\evsprod\nda209936\0001\m5\datasets\18641\analysis\legacy\programs\run_c044-control-file.txt

Software

NONMEM (v7.3) and R (v3.2.2) were used for the FDA reviewer's analysis.

Results

PPK Analysis Results

The Applicant's PPK analysis (run_c044.ctf) was confirmed, and the effect of BW, age, gender, race, and renal/hepatic impairment on copanlisib CL is presented in Figure 22 and Figure 23.

Exposure-Response Analysis Results

The ER analysis results for primary efficacy end point and safety are presented in Figure 24 and Figure 25. There appeared to be an insignificantly positive ER trend for ORR, ≥Grade3 severe adverse events, and Grade 3 or higher hyperglycemia. There appeared to be a slight ER relationship for blood glucose elevation for the 122 PK evaluable patients.

The hyperglycemia and hypertension appear to be transient. After the first copanlisib dose, the rate of Grade 3 or higher hyperglycemia was about 25% on Study Day 1, and decreased to about 2.6% on Study Day 7. After the second dose, the rate rebounded to about 7%, and decreased to about 2.6% again, and remained 1-5% for the following doses. Grade 2 or higher hypertension showed similar pattern but in far lower rates (Figure 34) for the first 2 doses. When hyperglycemia showed positive ER trend (Figure 25). There was no ER trend for hypertension or blood pressure change from baseline (Figure 35) although the drug showed hypertension effect.

Figure 34 The Time Course of Hyperglycemia and Hypertension Rates for Study 16349 Part B (N=143)

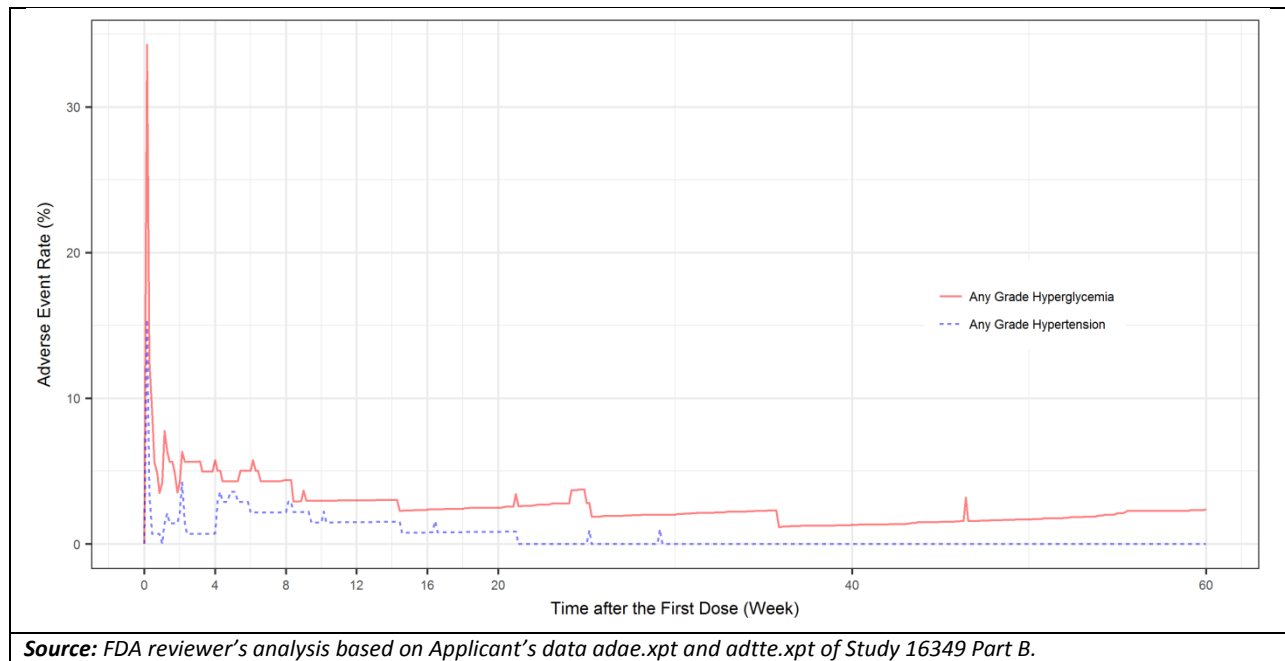
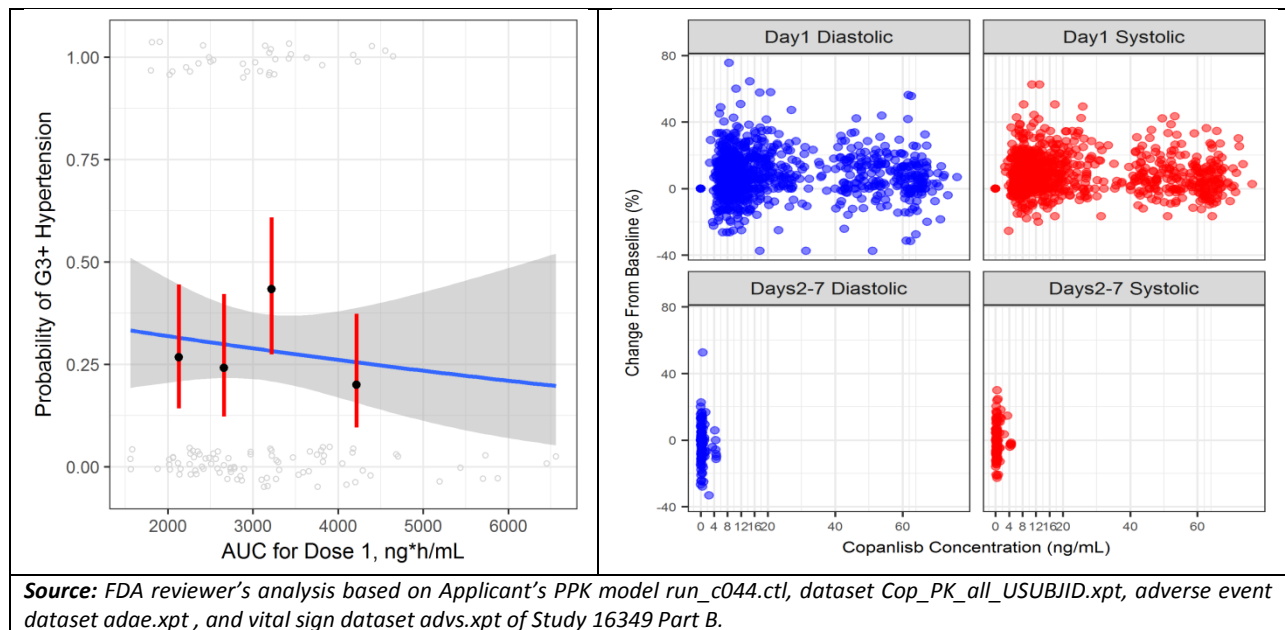


Figure 35 The Exposure-Response Analysis Result for $\geq$ Grade 2 Hypertension in Left Panel and for Blood Pressure Change from Baseline in Right Panel (n=124)



NDA/BLA Multi-disciplinary Review and Evaluation NDA 209936
Aliqopa (copanlisib)

Table 55 General Dose Compliance Data For Each Subject of Study 16349 Part B

USUBJID	ID	Dose1	Mean1	Mean2	Mean3	Last	Last2	Dose Compliance Category
16349100019001	1	65	43.3	65	65	0	65	Skipped at Least One Dose
16349100019002	2	60	53.1	60	51	60	60	Skipped at Least One Dose
16349100039001	3	60	60	60	57	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349100069001	4	60	45	60	60	0	60	Skipped at Least One Dose
16349100089001	5	60	54	60	54	60	60	Skipped at Least One Dose
16349100109002	6	60	57.1	60	57.1	60	60	Skipped at Least One Dose
16349100109004	7	60	40	60	48	0	60	Skipped at Least One Dose
16349100109005	8	60	51.1	55.6	51.1	45	45	Skipped at Least One Dose
16349100109006	9	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349100109008	10	60	46.8	56.8	46.8	60	60	Skipped at Least One Dose
16349120079001	11	51	44.3	51	43.4	51	51	Skipped at Least One Dose
16349120079002	12	65	45.5	65	41.4	65	65	Skipped at Least One Dose
16349120079003	13	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349120079004	14	60	52.5	55.6	55.6	0	45	Skipped at Least One Dose
16349120079005	15	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349120079006	16	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349120099002	17	60	38	57	38	45	45	Skipped at Least One Dose
16349140129002	18	61.6	52	60.3	52	60	60	Skipped at Least One Dose
16349140229001	19	60	58.2	59.1	59.1	0	45	Skipped at Least One Dose
16349140239001	20	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349140269003	21	65	61.7	61.7	61.7	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349140339002	22	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349140359001	23	59	59.7	59.7	58	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349140359002	24	60	57.6	60	57.6	60	60	Skipped at Least One Dose
16349140379001	25	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349140399001	26	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349140459001	27	60	60	60	52.9	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349140459002	28	60	43.9	46.2	43.9	30	30	Skipped at Least One Dose
16349140489001	29	60	55	60	60	0	60	Skipped at Least One Dose
16349140519001	30	60	40	60	60	0	60	Skipped at Least One Dose
16349160019001	31	52	43.3	50.5	46.6	0	50.4	Skipped at Least One Dose
16349160019004	32	48	46.3	51.4	46.3	60	60	Skipped at Least One Dose
16349160039001	33	54	59.4	59.4	59.4	60	60	Lowest Dose Was 45 mg Without Skipping One Dose
16349160049001	34	60	42	45.6	42	45	45	Skipped at Least One Dose
16349160049002	35	60	55	60	60	0	60	Skipped at Least One Dose
16349160049003	36	60	38.5	48.1	38.5	45	45	Skipped at Least One Dose
16349160109001	37	60	51.3	57.4	51.3	45	45	Skipped at Least One Dose
16349160159002	38	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349180059001	39	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349180069003	40	60	57.3	60	60	0	60	Skipped at Least One Dose
16349220019001	41	42	52.1	59.2	54.3	0	60	Skipped at Least One Dose
16349220019002	42	44	46.4	58	46.4	60	60	Skipped at Least One Dose
16349220019003	43	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349220039001	44	58	54.4	57	54.4	0	30	Skipped at Least One Dose
16349220039002	45	60	40.2	52.1	38.5	30	30	Skipped at Least One Dose
16349220059002	46	60	51.7	60	53.9	0	60	Skipped at Least One Dose
16349220059003	47	60	58.4	60	57.7	60	60	Skipped at Least One Dose
16349220059004	48	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349220059005	49	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349220059006	50	60	50.6	57.9	51.9	0	45	Skipped at Least One Dose
16349220059007	51	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349220059008	52	60	54.5	60	51.4	60	60	Skipped at Least One Dose

NDA/BLA Multi-disciplinary Review and Evaluation NDA 209936

Aliqopa (copanlisib)

USUBJID	ID	Dose1	Mean1	Mean2	Mean3	Last	Last2	Dose Compliance Category
16349220059009	53	60	35	60	52.5	0	60	Skipped at Least One Dose
16349220059010	54	60	46.7	60	49.4	0	60	Skipped at Least One Dose
16349220069001	55	60	30	60	60	0	60	Skipped at Least One Dose
16349220069002	56	60	45	60	54	0	60	Skipped at Least One Dose
16349240019001	57	65	48.3	49.7	46.9	45	45	Skipped at Least One Dose
16349240019002	58	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349240019003	59	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349240069001	60	60	52.5	60	51.4	60	60	Skipped at Least One Dose
16349240069002	61	60	53.3	60	56.5	0	60	Skipped at Least One Dose
16349260019001	62	60	53.1	60	54.7	0	60	Skipped at Least One Dose
16349260019002	63	60	50.3	53.4	48.9	45	45	Skipped at Least One Dose
16349260039002	64	0	48.8	52	47.3	45	45	Skipped at Least One Dose
16349260039003	65	60	56.8	60	60	0	60	Skipped at Least One Dose
16349260039004	66	60	40	60	60	0	60	Skipped at Least One Dose
16349260039005	67	60	32.7	45	36	0	30	Skipped at Least One Dose
16349260039007	68	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349260039008	69	60	45	60	60	0	60	Skipped at Least One Dose
16349260039010	70	60	40	60	40	60	60	Skipped at Least One Dose
16349280049003	71	60	54	60	60	0	60	Skipped at Least One Dose
16349280099001	72	60.8	60.3	60.3	60.3	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349280119001	73	60	54	60	60	0	60	Skipped at Least One Dose
16349390019001	74	60	43.4	45.2	42.9	45	45	Skipped at Least One Dose
16349390019003	75	60	33.9	40.3	30.7	30	30	Skipped at Least One Dose
16349390019004	76	60	53.6	53.6	41.7	45	45	Lowest Dose Was 45 mg Without Skipping One Dose
16349390019006	77	60	45	51.6	46.2	0	45	Skipped at Least One Dose
16349390019007	78	60	42.9	60	50	0	60	Skipped at Least One Dose
16349390029001	79	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349400019001	80	60	53.3	60	60	0	60	Skipped at Least One Dose
16349400019002	81	60	57.3	60	60	0	60	Skipped at Least One Dose
16349400019003	82	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349410029001	83	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349420019001	84	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349440039001	85	60	56	60	56	60	60	Skipped at Least One Dose
16349460019001	86	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349460019002	87	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349460019003	88	60	36	60	60	0	60	Skipped at Least One Dose
16349460019004	89	60	56.8	60	56.8	60	60	Skipped at Least One Dose
16349460019005	90	60	49.4	60	56	0	60	Skipped at Least One Dose
16349460029001	91	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349460029002	92	60	45.9	52.5	43.2	45	45	Skipped at Least One Dose
16349460039001	93	60	56.5	60	56.5	60	60	Skipped at Least One Dose
16349460039002	94	60	56.4	60	56.4	60	60	Skipped at Least One Dose
16349460039003	95	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349470019001	96	65	60.4	62.1	60.4	60	60	Skipped at Least One Dose
16349470019002	97	60	57	57	53.4	60	60	Lowest Dose Was 30 mg Without Skipping One Dose
16349470019003	98	60	55.2	59.7	54.2	60	60	Skipped at Least One Dose
16349470019005	99	60	59.1	59.1	52.5	60	60	Lowest Dose Was 45 mg Without Skipping One Dose
16349470039001	100	61.6	47.2	60.3	47.2	0	60	Skipped at Least One Dose
16349470039003	101	60	46.1	46.1	42.9	45	45	Lowest Dose Was 45 mg Without Skipping One Dose
16349470049001	102	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349470059001	103	60	51.4	60	60	0	60	Skipped at Least One Dose
16349490019001	104	60	53.7	60	53.7	60	60	Skipped at Least One Dose
16349490019002	105	60	30	60	60	0	60	Skipped at Least One Dose
16349490019003	106	60	22.5	60	60	0	60	Skipped at Least One Dose

NDA/BLA Multi-disciplinary Review and Evaluation NDA 209936

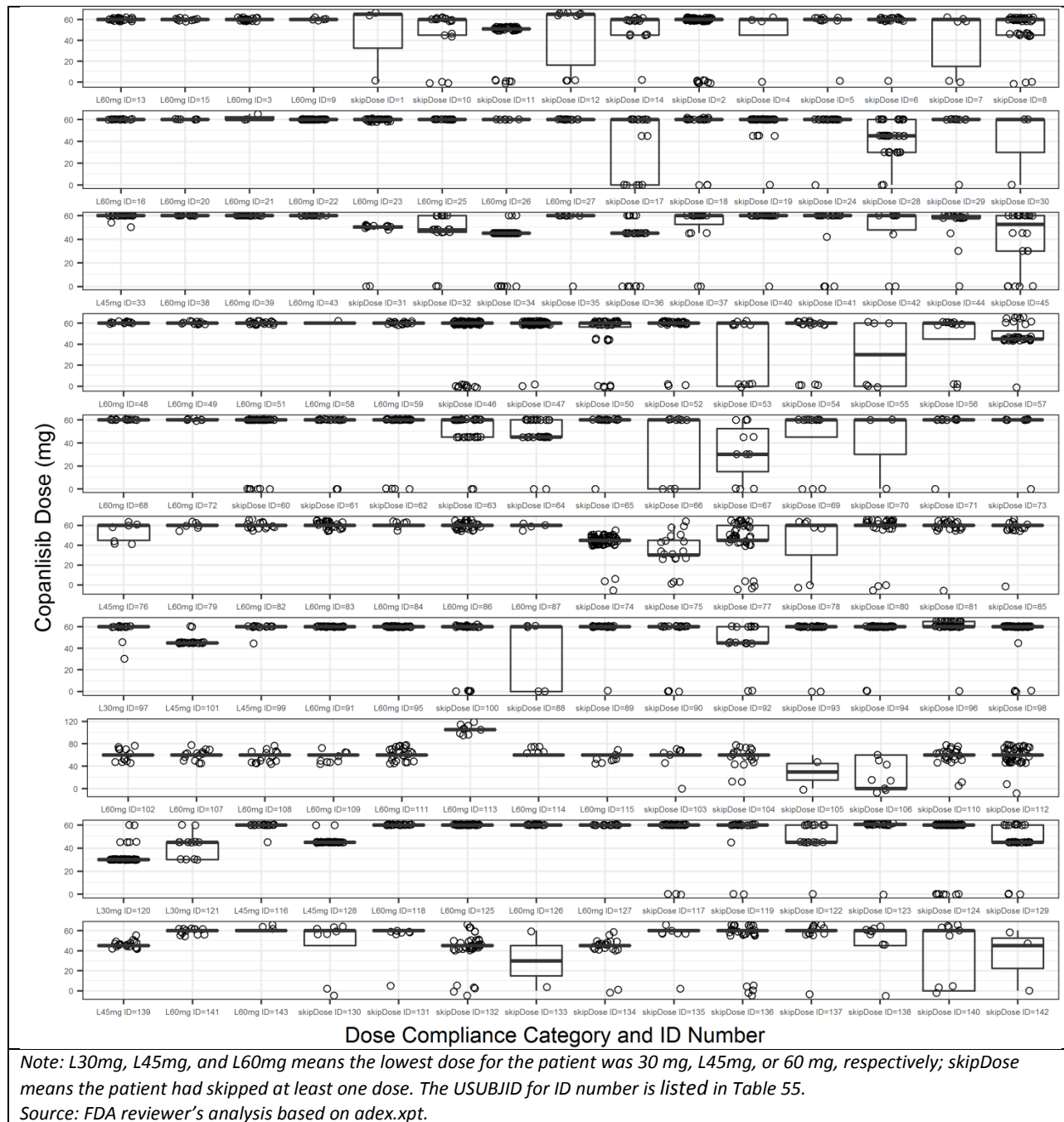
Aliqopa (copanlisib)

USUBJID	ID	Dose1	Mean1	Mean2	Mean3	Last	Last2	Dose Compliance Category
16349490019004	107	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349490019005	108	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349510019002	109	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349510039001	110	60	55	60	55	60	60	Skipped at Least One Dose
16349510039002	111	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349510059002	112	60	57.1	60	57.1	60	60	Skipped at Least One Dose
16349510079001	113	105	105	105	105	105	105	Lowest Dose Was 60 mg Without Skipping One Dose
16349510099001	114	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349510099002	115	60	60	60	53.3	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349510109001	116	60	59.1	59.1	59.1	60	60	Lowest Dose Was 45 mg Without Skipping One Dose
16349510109002	117	60	54	60	55.9	0	60	Skipped at Least One Dose
16349510109003	118	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349510109004	119	60	51.6	58.9	51.6	60	60	Skipped at Least One Dose
16349560019001	120	60	31.5	31.5	31.5	30	30	Lowest Dose Was 30 mg Without Skipping One Dose
16349560019002	121	60	42.5	42.5	42.5	30	30	Lowest Dose Was 30 mg Without Skipping One Dose
16349560019003	122	60	49	52.5	49	45	45	Skipped at Least One Dose
16349560029002	123	61	57.2	60.5	57.2	60	60	Skipped at Least One Dose
16349560029003	124	60	53.3	60	51.7	60	60	Skipped at Least One Dose
16349560029004	125	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349560029006	126	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349560029007	127	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349560039001	128	60	46.1	46.1	46.1	45	45	Lowest Dose Was 45 mg Without Skipping One Dose
16349590019003	129	60	45	49.5	45	45	45	Skipped at Least One Dose
16349590019006	130	60	45	60	60	0	60	Skipped at Least One Dose
16349590019007	131	60	51.4	60	60	0	60	Skipped at Least One Dose
16349590019008	132	60	40.7	47.5	40.7	45	45	Skipped at Least One Dose
16349590019009	133	60	30	60	60	0	60	Skipped at Least One Dose
16349590019010	134	60	42.3	46.5	44.3	0	45	Skipped at Least One Dose
16349590029001	135	60	51.4	60	60	0	60	Skipped at Least One Dose
16349590049001	136	60	48.9	60	48.9	60	60	Skipped at Least One Dose
16349590059001	137	60	55	60	60	0	60	Skipped at Least One Dose
16349650029001	138	60	50	56.3	56.3	0	60	Skipped at Least One Dose
16349680019001	139	60	45.8	45.8	45.8	45	45	Lowest Dose Was 45 mg Without Skipping One Dose
16349680019002	140	60	40	60	60	0	60	Skipped at Least One Dose
16349680019003	141	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose
16349680029001	142	60	35	52.5	52.5	0	45	Skipped at Least One Dose
16349700019001	143	60	60	60	60	60	60	Lowest Dose Was 60 mg Without Skipping One Dose

Note: Dose1, first dose; For ID=64 and USUBJID=16349260039002, the first dose was skipped, other doses are 60,45, and 0; Last, last dose; Last2, last non-zero dose; Mean1, mean dose counting each skipped dose as 0 mg dose; Mean2, mean dose ignoring the skipped dose(s); Mean3, mean dose ignoring the skipped doses after the last non-zero dose.

Source: FDA reviewer's analysis based on dataset adex.xpt for Study 16349 Part B.

**Figure 36 Boxplots of Individual Patient's Copanlisib Doses of the 143 Subjects in Study 13469
Part B**



14 Division Director (DHOT)

John Leighton, PhD
Division Director

15 Division Director (OCP)

NAM A RAHMAN, Ph.D.
Division Director

16 Division Director (OB)

Rajeshwari Sridhara, Ph.D.
Division Director

17 Division Director (Clinical)

On March 16, 2017, Bayer HealthCare Pharmaceuticals Inc. submitted NDA 2009936 which requested approval of copanlisib (Aliqopa), an inhibitor of the alpha and delta catalytic subunits of phosphoinositide-3-kinase, for the treatment of patients with (b) (4) follicular lymphoma who have received at least two prior systemic therapies. This request was supported by the treatment of 104 patients with follicular lymphoma who had previously received two prior therapies, with copanlisib by intravenous infusion on Days 1, 8, and 15 every 28 days on Study 16349, a single arm, open label phase 2 trial. The primary endpoint was overall response rate defined as either a partial or complete response as determined by blinded independent review committee. Clinical benefit was defined as when the lower bound of the 95% confidence intervals around the point estimate of the ORR excludes 40%. The ORR observed was 58.7% (95% CI: 48.6%, 68.2%), which met the pre-specified definition of benefit. The PR rate was 44.2% while the complete response rate was 14.4%. The median duration of the responses was 12.2 months.

The short term toxicity was manageable. The most common adverse reactions which occurred in greater than 20% of patients included hyperglycemia, diarrhea, fatigue, hypertension, leukopenia, neutropenia, nausea, lower respiratory tract infections and thrombocytopenia. The most common Grade 3-4 adverse reactions included hyperglycemia, leukopenia, hypertension, neutropenia and lower respiratory tract infections.

There are six post-marketing requirements (see Section 12 for details): PMR1 to verify clinical benefit, PMR2 and PMR3 to further characterize the safety of copanlisib, PMR4 to study copanlisib in patients with hepatic and renal impairment, PMR5 to study drug-drug interactions, and PMR6 to complete the QT assessment.

Final Regulatory Recommendation: I agree with the review team's recommendation for accelerated approval of copanlisib for the treatment of patients with (b) (4) follicular lymphoma who have received at least two prior systemic therapies.

Albert Deisseroth, MD, PhD
Supervisory Associate Division Director
Division of Hematology Products

18 Office Director (or designated signatory authority)

This application was reviewed under the auspices of the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. The risk-benefit profile was also assessed by Drs. Deisseroth, de Claro, and Richardson who recommend approval. I also recommend approval of this application. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

Richard Pazdur, MD

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

/s/

ROSA J LEE-ALONZO

09/13/2017

NICHOLAS C RICHARDSON

09/13/2017

PEDRO L DEL VALLE

09/13/2017

CHRISTOPHER M SHETH

09/13/2017

JOHN K LEIGHTON

09/13/2017

GUOXIANG SHEN

09/13/2017

HONGSHAN LI

09/13/2017

JINGYU YU on behalf of JIANG LIU

09/13/2017

BAHRU A HABTEMARIAM

09/13/2017

NAM ATIQUR RAHMAN

09/13/2017

I concur.

XIN GAO

09/13/2017

YUAN L SHEN

09/13/2017

RAJESHWARI SRIDHARA
09/13/2017

ROMEO A DE CLARO
09/13/2017

ALBERT B DEISSEROTH
09/13/2017

RICHARD PAZDUR
09/14/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF HEMATOLOGY PRODUCTS

MEMORANDUM

DATE: 08 September 2017

FROM: Nicholas Richardson, DO, MPH, Medical Officer

SUBJECT: Consult from OPDP: Copanlisib press release

TO: Nisha Patel, Lead Safety Officer, OPDP

THROUGH:

Angelo de Claro, MD, Clinical Team Leader

The Division of Hematology Products (DHP) received a consult from the Office of Prescription Drug Promotion (OPDP) in regards to a press release on the approval of copanlisib for the treatment of adult patients with relapsed follicular lymphoma who have received at least two prior systemic therapies. The request was for opinion on whether the claims used by the Sponsor in the press release are accurate or misleading.

Questions from OPDP are in bold:

- 1. We note that Section 14.1 of the PI states in a total of 142 subjects, which included 104 subjects with follicular B-cell non-Hodgkin lymphoma...” Do you have any concerns with the Applicant specifically mentioning NHL? Do you have any concerns with this statement broadening the indication for Aliqopa?**

Yes, accelerated approval was primarily based on the efficacy, objective response rate and durability of the response, in patients with relapsed follicular lymphoma. There was an insufficient number of patients with other forms of non-Hodgkin lymphoma (NHL) such as marginal zone lymphoma, small lymphocytic lymphoma, or lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia in the CHRONOS-1 study to support indications for these populations. Although, the safety of copanlisib was based on all patients with NHL included in the CHRONOS-1 study. Because the sentence states “Accelerated approval based on

(b) (4)

” we recommend referencing the 104 patients with relapsed follicular lymphoma because that is the primary data that accelerated approval is based upon.

2. Is this accurate? “First approval of a (b) (4) intravenous phosphatidylinositol-3-kinase (PI3K) inhibitor”

No.

(b) (4)
The use of (b) (4) is not recommended and was taken out of the prescribing information and agreed upon by the Applicant.

3. We note that the Agency requested deletion of “indolent NHL” or “iNHL” (b) (4) as the term 1) may be interpreted that Aliqopa has a broad indication and 2) is not a recognized category in the WHO Classification of Tumours of Hematopoietic and Lymphoid Tissues. Do you agree with deletion here and throughout where underlined?

Yes. As mentioned the term “indolent NHL” is no longer recognized by the WHO. The Applicant may use “NHL” to describe the patient population in the CHRONOS-1 study or focus the press release on patients with relapsed follicular lymphoma.

4. Is this accurate? “The response rates and duration of response fall with each line of therapy (b) (4) ...”

Yes, however the Applicant should focus on patients with relapsed follicular lymphoma because that is the indication being approved and the statement is supported by the literature.

Rivas-Delgado, A., et al. (2017). “Progression-free survival shortens after each relapse in patients with follicular lymphoma treated in the rituximab era.” *Hematological Oncology* 35: 360-361.

5. Is this accurate? “ The PI3K pathway is activated in many tumor types.”

Yes. The PI3K-AKT-mTOR pathway is important in regulating the cell cycle and is activated in several hematologic and solid malignancies.

Do you have any concerns with this statement broadening the indication for Aliqopa?

No. The context of the sentence regarding the PI3K pathway is appropriate and should not be misleading concerning the indication for Aliqopa.

6. We note that Aliqopa is pending accelerated approval and that “continued approval for this indication may be contingent upon verification and descriptions of clinical benefit in a confirmatory trial” and that CHRONOS 1

is a single-arm trial. Is Aliqopa considered an advance in third-line follicular lymphoma?

Yes. Aliqopa has demonstrated a more favorable safety profile compared to Zydelig (idelalisib), which is approved for the third-line. Additionally, the intermittent schedule may be an added benefit for some patients.

- 7. Is this accurate? “It is the only one to be administered intravenously on an intermittent schedule.”**

Yes. The only other approved PI3K inhibitor, Zydelig (idelalisib), is administered orally twice daily.

- 8. Is this accurate? “The FDA had previously granted Aliqopa Fast Track Designation in follicular lymphoma as well as Orphan Drug Designation for the treatment of patients with follicular lymphoma and for the treatment of splenic, nodal, and extranodal subtypes of marginal zone lymphoma.”**

Yes.

Follicular lymphoma – 02/05/2015

Splenic, nodal, extranodal marginal zone lymphoma – 02/07/2017

- 9. Do you have any concerns with the applicant presenting median duration of response without the footnote from Table 5 (Kaplan-Meier estimate)?**

No. The information on median duration of response will not be misleading as written.

- 10. Is this accurate? “There were also patients with small lymphocytic leukemia, lymphoplasmacytic lymphoma/Waldenström’s macroglobulinemia and marginal zone lymphoma enrolled in the study.”**

Yes, however there were small numbers of patients with these types of cancer.

Do you have any concerns with this statement broadening the indication for Aliqopa?

Yes. There were insufficient numbers of patients with marginal zone lymphoma, small lymphocytic lymphoma, or lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia in the CHRONOS-1 study to support indications for these populations

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

/s/

NICHOLAS C RICHARDSON
09/12/2017

ROMEO A DE CLARO
09/13/2017

OFFICE OF CLINICAL PHARMACOLOGY MEMO

NDA	209936
Link to EDR	\\CDSESUB1\evsprod\NDA209936\0001
Applicant	Bayer
Submission Date	March 16, 2017
Submission Type	NME (priority expedited review)
Brand Name	ALIQOPA
Generic Name:	Copanlisib
Dosage Form and Strength	60 mg per vial, sterile lyophilized solid
Route of Administration	Intravenous injection
Proposed Indication	(For Accelerated Approval) For the treatment of patients with relapsed (b) (4) follicular lymphoma who have received at least two prior therapies
Proposed Dosing Regimen	60 mg administered as a 1-hour intravenous (IV) infusion on Days 1, 8, and 15 of a 28-day treatment cycle on an intermittent schedule (three weeks on/ one week off)
Associated IND	115916
OCP Review Team	Guoxiang Shen, Ph.D., Hongshan, Li. Ph.D., Jiang Liu, Ph.D., Bahru Habtemariam, Pharm.D.
OCP Final Signatory	NAM Atiqur Rahman, Ph.D. (Division Director)

The Office of Clinical Pharmacology review is complete and has been added to the Multi-Disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. This NDA is approvable from a clinical pharmacology perspective.

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

/s/

GUOXIANG SHEN
08/01/2017

HONGSHAN LI
08/01/2017

JIANG LIU
08/01/2017

BAHRU A HABTEMARIAM
08/01/2017

NAM ATIQRUR RAHMAN
08/01/2017
I concur.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 1, 2017

APPLICATION/DRUG: NDA 209936 copanlisib (ALIQOPA)

FROM: Pedro L. Del Valle, PhD
Pharmacology-Toxicology Reviewer
Division of Hematology Oncology Toxicology
Office of Hematology and Oncology Products

THROUGH: Christopher Sheth, PhD
Pharmacology-Toxicology Supervisor
Division of Hematology Oncology Toxicology
Office of Hematology and Oncology Products

SUBJECT: Pharmacology and Toxicology Review

Please see my nonclinical review in the Multi-Disciplinary Review document. My regulatory recommendation is “Approvable”.

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

/s/

PEDRO L DEL VALLE
08/01/2017

CHRISTOPHER M SHETH
08/01/2017

MEMORANDUM

NDA #: 209936
Supplement #: 0
Drug Name: Copanlisib
Indication(s): treatment of patients with relapsed (b) (4) follicular lymphoma who have received at least two prior therapies
Applicant: Bayer HealthCare Pharmaceuticals
Date(s): Letter Date: March 16, 2017
Stamp Date: March 16, 2017
Biometrics Division: Division of Biometrics V
Statistical Reviewer: Cindy Gao, Ph.D.

Please see the statistical review in the Multi-disciplinary Review document for details, which will be uploaded to DARRTs when it is finalized. There are no major statistical issues that would prevent approval of this application.

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

/s/

XIN GAO
08/01/2017

LEI NIE on behalf of YUAN L SHEN
08/01/2017