

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205858Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA # 205858
Product Name: Zydelig (idelalisib, GS-1101)

PMR Description: Design and conduct a prospective trial and provide the full study report and data sets to evaluate dose reductions in patients that achieve a response or have stable disease in order to optimize the safety and efficacy of chronic administration of Zydelig in patients with follicular or small lymphocytic lymphoma. Include adequate PK sampling to provide dose-response data (for efficacy and safety).

PMR Schedule Milestones:	Draft Protocol Submission:	<u>09/2014</u>
	Final Protocol Submission:	<u>12/2014</u>
	Interim Report Submission (3-year):	<u>12/2017</u>
	Trial Completion:	<u>06/2019</u>
	Final Report Submission:	<u>12/2019</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The indolent lymphoma types included in these trials are life-threatening and incurable malignancies. Follicular lymphomas represent the greatest proportion and have a 3 year progression free survival of 51-91% (based on prognostic index) from initial diagnosis with a 3 year survival rate of 84-91%.

In the single arm clinical trial 101-09 reviewed in the NDA, the applicant reports an overall response rate of 57% with a median duration of response estimated to be 12.5 months. Nearly half of patients on trial were on study drug for more than 6 months and less than 10% of patients were on the study drug more than 12 months.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

FDA has previously accepted overall response rates supported by duration of response from a single arm trial as a basis for accelerated approval.

The goal of this PMR is to characterize the optimal dose that provides long term efficacy outcomes including progression free survival and long-term safety from a randomized controlled clinical trial.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Design and conduct a prospective trial and provide the full final report and data sets to evaluate dose reductions in patients who achieve a response or have stable disease in order to optimize the safety and efficacy of chronic administration of Zydelig in patients with follicular or small lymphocytic lymphoma. Include adequate PK sampling to provide dose-response data (for efficacy and safety).

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety

- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Confirmatory clinical trial under 21CFR314 Subpart H

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

RCK

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA # 205858
Product Name: Zydelig (idelalisib, GS-1101)

PMR Description: Submit the complete final study report and data showing clinical efficacy and safety from trial GS-US-313-0124, a Phase 3, 2-arm, randomized, double-blind, placebo-controlled, parallel-group study of idelalisib in combination with rituximab in subjects with previously treated indolent non-Hodgkin lymphomas.

PMR Schedule Milestones:	Final Protocol Submission:	<u>completed</u>
	Trial Completion:	<u>12/2017</u>
	Final Report Submission:	<u>06/2018</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The indolent lymphoma types included in these trials are life-threatening and incurable malignancies. Follicular lymphomas represent the greatest proportion and have a 3 year progression free survival of 51-91% (based on prognostic index) from initial diagnosis with a 3 year survival rate of 84-91%.

In the single arm clinical trial 101-09 reviewed in the NDA, the applicant reports an overall response rate of 57% with a median duration of response estimated to be 12.5 months. Nearly half of patients on trial were on study drug for more than 6 months and less than 10% of patients were on the study drug more than 12 months.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

FDA has previously accepted overall response rates supported by duration of response from a single arm trial as a basis for accelerated approval.

The goal of this PMR is to obtain long term efficacy outcomes including progression free survival and long-term safety from a randomized controlled clinical trial. Time to event endpoints cannot be adequately interpreted in single arm clinical trials due to confounding effects of the natural history of the disease.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Submit the complete study report and data showing clinical efficacy and safety from trial GS-US-313-0124, a Phase 3, 2-arm, randomized, double-blind, placebo-controlled, parallel-group study of idelalisib in combination with rituximab in subjects with previously treated indolent non-Hodgkin lymphoma.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Confirmatory clinical trial under 21CFR314 Subpart H

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

RCK

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA # 205858
Product Name: Zydelig (idelalisib, GS-1101)

PMR/PMC Description: Submit the complete final study report and data showing clinical efficacy and safety from trial GS-US-313-0125 Phase 3, 2-arm, randomized, double-blind, placebo controlled, parallel-group study of idelalisib in combination with bendamustine plus rituximab in subjects with previously treated indolent non-Hodgkin lymphomas.

PMR Schedule Milestones:	Final Protocol Submission:	<u>completed</u>
	Study/Trial Completion:	<u>02/2019</u>
	Final Report Submission:	<u>08/2019</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The indolent lymphoma types included in these trials are serious, life-threatening and incurable malignancies. Follicular lymphomas represent the greatest proportion of all lymphomas and have a 3 year progression free survival of 51-91% (based on prognostic index) from initial diagnosis with a 3 year survival rate of 84-91%.

In the single arm clinical trial 101-09 reviewed in the NDA, the applicant reports an overall response rate of 57% with a median duration of response estimated to be 12.5 months. About half of patients on trial were on study drug for more than 6 months, about half for less than 6 months, and less than 10% of patients were on the study drug more than 12 months.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

FDA has previously accepted overall response rates supported by duration of response from a single arm trial as a basis for accelerated approval.

The goal of this PMR is to obtain long term efficacy outcomes including progression free survival and long-term safety from a randomized controlled clinical trial. Time to event endpoints cannot be adequately interpreted in single arm clinical trials due to confounding effects of the natural history of the disease.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Submit the complete study report and data showing clinical efficacy and safety from trial GS-US-313-0125, a Phase 3, 2-arm, randomized, double-blind, placebo controlled, parallel-group study of idelalisib in combination with bendamustine plus rituximab in subjects with previously treated indolent non-Hodgkin lymphoma.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Confirmatory clinical trial under 21CFR314 Subpart H

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

RCK

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA # 205858
Product Name: Zydelig (idelalisib, GS-1101)

PMR Description: Conduct a study to characterize the incidence, diagnosis and effective treatment of Zydelig-related pneumonitis based on data and pooled analyses from randomized trials in iNHL and CLL (0115, 0119, 0124, and 0125).

PMR Schedule Milestones:	Analysis Plan Submission:	<u>10/2014</u>
	Interim Report Submission:	<u>06/2015</u>
	Interim Report Submission:	<u>06/2016</u>
	Interim Report Submission:	<u>06/2017</u>
	Study Completion:	<u>05/2020</u>
	Final Report Submission:	<u>11/2020</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The intended population has limited options available for disease control, and new therapies are needed.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

In the review of safety of idelalisib monotherapy, the incidence of pneumonia was 25%. Six were considered by the investigator to be related to idelalisib, five were treated with corticosteroids, and two cases were fatal. There were 8 (5%) subjects who did not have a Preferred Term in the System Organ Class Infections and Infestations concurrently, but in total 25 (17%) had a Preferred Term describing pneumonia or pneumonitis in general without a specific infectious etiology, so the actual incidence of drug-induced pneumonitis is not clear. Diagnostic criteria have not been established to rapidly distinguish drug-induced pneumonitis from an infection, so clear instructions have not been develop for when to discontinue use of idelalisib in patients with pneumonia. Better characterization of the disorder is needed.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
- Registry studies

- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
 - Are the objectives clear from the description of the PMR/PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

RCK

(signature line for BLAs)

APPEARS THIS WAY ON
ORIGINAL

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA # 205858
Product Name: Zydelig (idelalisib, GS-1101)

PMR Description: Conduct a trial to provide evidence sufficient to characterize the long-term safety of Zydelig. Submit the complete final report and data showing long-term safety with 5 years of follow-up from trial 101-99 Phase 1/2 extension study of safety and durability of idelalisib in hematologic malignancies.

PMR Schedule Milestones:	Final Protocol Submission:	Completed
	Interim Report Submission (3-year follow-up)	12/2017
	Trial Completion:	06/2019
	Final Report Submission (5-year follow-up):	12/2019

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Proposed labeling states that patients should remain on therapy until progression of disease. In the single arm clinical trial 101-09 reviewed in the NDA, only about half of patients on trial were on study drug for more than 6 months and less than 10% of patients were on the study drug more than 12 months, so there is no information on safety in a substantial number of patients for more than 6 months.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Safety of long-term use of idelalisib is unknown.

The goal of this PMR is to obtain long term safety data from a randomized controlled clinical trial.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Submit the results of the completed randomized, controlled trial of idelalisib: GS-US-313-0125 Phase 3, 2-arm, randomized, double-blind, placebo controlled, parallel-group study of idelalisib in combination with BR in subjects with previously treated iNHL

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial
(provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

RCK

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA# 205858
Product Name: Zydelig (idelalisib, GS-1101)

PMR Description: Conduct a trial to provide evidence sufficient to characterize the long-term safety of Zydelig. Submit the complete final report and data showing long-term safety with 5 years of follow-up from trial GS-US-313-0124, a Phase 3, 2-arm, randomized, double-blind, placebo-controlled, parallel-group study of idelalisib in combination with rituximab in subjects with previously treated indolent non-Hodgkin lymphomas.

PMR Schedule Milestones:	Final Protocol Submission:	<u>Completed</u>
	Trial Completion:	<u>12/2017</u>
	Interim Report Submission (3-year follow-up)	<u>12/2017</u>
	Final Report Submission (5-year follow-up):	<u>12/2019</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Proposed labeling states that patients should remain on therapy until progression of disease. In the single arm clinical trial 101-09 reviewed in the NDA, only about half of patients on trial were on study drug for more than 6 months and less than 10% of patients were on the study drug more than 12 months, so there is no information on safety in a substantial number of patients for more than 6 months, when combined with other therapy, as it will be used in practice.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Safety of long-term use of idelalisib is unknown.

The goal of this PMR is to obtain long term comparative safety data from a randomized controlled clinical trial.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Submit the results of the completed randomized, controlled trial of idelalisib: GS-US-313-0124 Phase 3, 2-arm, randomized, double-blind, placebo- controlled, parallel-group study of idelalisib in combination with rituximab in subjects with previously treated iNHL.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial
(provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

 RCK

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

NDA # 205858
Product Name: Zydelig (idelalisib, GS-1101)

PMR Description: Conduct a trial to provide evidence sufficient to characterize the long-term safety of Zydelig when used in combination with other agents such as bendamustine (B) and rituximab (R). Submit the complete final report and data showing long-term safety with 5 years of follow-up from trial GS-US-313-0125, a Phase 3, 2-arm, randomized, double-blind, placebo controlled, parallel-group study of idelalisib in combination with BR in subjects with previously treated indolent non-Hodgkin lymphomas.

PMR Schedule Milestones:	Final Protocol Submission:	<u>Completed</u>
	Interim Report Submission (3-year follow-up):	<u>12/2017</u>
	Trial Completion:	<u>02/2019</u>
	Final Report Submission (5-year follow-up):	<u>12/2019</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Proposed labeling states that patients should remain on therapy until progression of disease. In the single arm clinical trial 101-09 reviewed in the NDA, only about half of patients on trial were on study drug for more than 6 months and less than 10% of patients were on the study drug more than 12 months, so there is no information on safety in a substantial number of patients for more than 6 months.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Safety of long-term use of idelalisib is unknown.

The goal of this PMR is to obtain long term comparative safety data from a randomized controlled clinical trial of the add-on of Zydelig to other therapy.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Submit the results of the completed randomized, controlled trial of idelalisib: GS-US-313-0125 Phase 3, 2-arm, randomized, double-blind, placebo controlled, parallel-group study of idelalisib in combination with BR in subjects with previously treated iNHL

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

RCK

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA # 206545
Product Name: Zydelig (idelalisib, GS-1101)

PMR Description: Conduct a trial to provide evidence sufficient to characterize the long-term safety of Zydelig when used in combination with an anti-CD20 regimen. Submit the complete final study report and data from trial GS-US-312-0119, a Phase 3, randomized, study of idelalisib in combination with ofatumumab in patients with previously treated CLL.

PMR Schedule Milestones:	Final Protocol Submission:	Completed
	Trial Completion:	04/2015
	Interim Report Submission (3-year follow-up)	12/2017
	Final Report Submission (5-year follow-up):	12/2019

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Proposed labeling states that idelalisib should be used in combination with rituximab. There were significant safety concerns in study 312-0116, to better characterize the safety of idelalisib in combination with rituximab, additional safety information, including long-term safety data, should be submitted that explores the use of Idelalisib in combination with anti-CD20 agents.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

In Study 312-0116, the following grade 3-4 AEs were present in $\geq 2\%$ incidence and were more frequent in the Idelalisib arm: neutropenia, pneumonia, sepsis, pneumonitis, rash, colitis, and increased ALT. Additional safety issues that have been identified with the use of Idelalisib include: bowel perforation, AST/ALT elevations, serious and fatal hepatotoxicity, and severe cutaneous skin reactions.

The goal of this PMR is to further characterization of the safety profile of idelalisib used in combination with anti-CD20 monoclonal antibodies. Study GS-US-312-0119, a Phase 3, randomized, study of idelalisib in combination with ofatumumab in patients with previously treated CLL may be used to provide this information.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

APPEARS THIS WAY ON ORIGINAL



PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA # 206545
Product Name: Zydelig (idelalisib, GS-1101)

PMR Description: Conduct a trial to provide evidence sufficient to characterize the long-term safety of Zydelig when used in a combination therapy regimen. Submit the complete final study report and data showing long-term safety with 5 years of follow-up from trial GS-US-312-0117, a Phase 3, 2 arm, extension study of idelalisib in patients with previously treated CLL.

PMR Schedule Milestones:	Final Protocol Submission:	<u>Completed</u>
	Interim Report Submission (3-year follow-up):	<u>12/2017</u>
	Trial Completion:	<u>06/2019</u>
	Final Report Submission (5-year follow-up):	<u>12/2019</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Proposed labeling states that patients should remain on therapy until progression of disease. In the randomized clinical trial 312-0116 reviewed in the NDA, only half of patients on trial were on study drug for more than 5 months, so there is inadequate long-term safety data.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Safety of long-term use of idelalisib used in combination with rituximab is unknown.

The goal of this PMR is to obtain long term safety data from an extension trial of the initial pivotal trial reviewed in the NDA.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

There is a significant question about the public health risks of an approved drug

There is not enough existing information to assess these risks

Information cannot be gained through a different kind of investigation

The trial will be appropriately designed to answer question about a drug's efficacy and safety, and

The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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

/s/

MARA B MILLER
07/18/2014

ROBERT C KANE
07/18/2014

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: June 26, 2014

To: Ann Farrell, MD
Director
Division of Hematology Products (DHP)

Robert Kane, MD
Deputy Director for Safety
Division of Hematology Products (DHP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Nathan Caulk, MS, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Kathleen Davis, RN
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): Zydelig (idelalisib)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 205858 and NDA 206545

Applicant: Gilead Sciences, Inc.

1 INTRODUCTION

On September 11, 2013, Gilead Sciences, Inc. submitted for the Agency's review an original New Drug Application (NDA) 205858 for Zydelig (idelalisib) tablets for the proposed indication for the treatment of patients with refractory indolent non-Hodgkin lymphoma (iNHL). On December 6, 2013, Gilead Sciences, Inc. submitted for the Agency's review original New Drug Application (NDA) 206545 for Zydelig (idelalisib) tablets. The purpose of this submission is for the proposed indication for the treatment of patients with relapsed chronic lymphocytic leukemia and for the treatment of patients with refractory indolent B-cell non-Hodgkin lymphoma.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Hematology Products (DHP) on October 21, 2013 and January 30, 2014, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for Zydelig (idelalisib) tablets.

2 MATERIAL REVIEWED

- Draft Zydelig (idelalisib) tablets PPI received on September 11, 2013 and December 6, 2013, revised and resubmitted by the Applicant as draft Medication Guide (MG) on June 17, 2014, and received by DMPP and OPDP on June 18, 2014.
- Draft Zydelig (idelalisib) tablets Prescribing Information (PI) received on September 11, 2013 and December 6, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 18, 2014.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 10.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

NATHAN P CAULK
06/26/2014

KATHLEEN T DAVIS
06/26/2014

BARBARA A FULLER
06/26/2014

LASHAWN M GRIFFITHS
06/26/2014

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: June 25, 2014

To: Mara Miller, Regulatory Project Manager
Division of Hematology Products (DHP)

From: Kathleen Davis, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Karen Rulli, Team Leader, OPDP

Subject: Comments on draft labeling (Package Insert) for ZYDELIG®
(idelalisib) tablets, for oral use
NDA 205858 and NDA 206545

In response to your consult request dated October 21, 2013, we have reviewed the draft Package Insert (PI) for Zydelig and offer the following comments. OPDP has made these comments using the PI version provided via email link on June 18, 2014. OPDP's comments on the Medication Guide will be provided as a collaborative review with DMPP under separate cover.

Thank you for the opportunity to consult on this proposed labeling.

Section	Statement from draft	Comment
HIGHLIGHTS, Boxed Warning And Boxed Warning	(b) (4)	OPDP is concerned that the wording of the Boxed Warning header could be misconstrued to indicate that (b) (4) when this is not the case. OPDP recommends editing this language to ensure that there is no minimization of the other risk concepts in the boxed warning.
HIGHLIGHTS, Boxed Warning		Pursuant to discussions had on June 16, 2014 with the review division, OPDP suggests that this language be amended, if appropriate, to specify that fatalities have resulted from severe diarrhea/colitis in Zydelig-treated patients. Suggested language:

5 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

KATHLEEN T DAVIS
06/25/2014

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: April 10, 2014

TO: Mara Bauman Miller, M.A., Regulatory Project Manager
Donna Przepiorka, M.D., Ph.D., Medical Officer
Barry Miller, M.Sc., C.R.N.P., Clinical Analyst
Nicole Gormley, M.D.
R. Angelo de Claro, M.D., Cross Discipline Team Leader
Division of Hematology Products (DHP)

FROM: Anthony Orenca, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Good Clinical Practice Compliance
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THROUGH: Janice Pohlman, M.D., M.P.H.
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Kassa Ayalew, M.D., M.P.H.
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Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 205858

APPLICANT: Gilead Sciences, Inc.

DRUG: idelalisib

NME: Yes

THERAPEUTIC CLASSIFICATION/REVIEW: Priority review

INDICATION: Treatment of indolent Non-Hodgkins Lymphoma (iNHL) in patients refractory to rituximab and alkylating agents

CONSULTATION REQUEST DATE: November 6, 2013
INSPECTION SUMMARY GOAL DATE: February 27, 2014
(extended to April 10, 2014)
DIVISION ACTION GOAL DATE: May 11, 2014
PDUFA DATE: May 11, 2014

I. BACKGROUND:

Non-Hodgkin lymphoma represents a heterogeneous group of syndromes, manifesting as a progressive clonal expansion of T cells (such as cutaneous T cell lymphomas-Sezary syndrome, mycosis fungoides, and others), or natural killer cells or B cells (such as follicular lymphoma, small lymphocytic lymphoma, lymphoplasmacytoid lymphoma, and marginal zone lymphoma). Indolent non-Hodgkin lymphoma (iNHL) is a slowly progressive, disabling disease currently treated with alkylating agents and rituximab.

The proposed novel treatment, idelalisib, is a selective PI3K δ inhibitor. Idelalisib inhibits lymphoma growth in animal models of lymphoid malignancy, and potentially in patients with non-Hodgkin lymphoma subtypes such as iNHL.

Two domestic clinical sites participating in iNHL Study 101-09 were selected for inspection because the sites had enrollment of a large number of study subjects and treatment responders.

Protocol Number 101-09

Study 101-09 (PILLAR) was a Phase 2, open-label, single-arm, 2-stage, efficacy, safety, and pharmacodynamic study of CAL-101 in patients with previously treated iNHL that was refractory both to rituximab and to alkylating agent-containing chemotherapy. The primary objective was to assess the overall response rate. The primary efficacy endpoint was the “overall response rate” (ORR), defined as the proportion of patients who achieved a confirmed complete response (CR) or partial response (PR) during idelalisib treatment, based on the Cheson et al. 2007 criteria. The endpoints were adjudicated by an Independent Review Committee.

II. RESULTS:

Name of CI City, State	Protocol/Study Site/Number of Subjects Enrolled (n)	Inspection Date	Final Classification*
Ajay Gopal, M.D. Seattle, WA	101-09/Site 119 N=13	Dec. 12, 2013 to Jan. 9, 2014	Pending Preliminary: VAI
Peter Martin, M.D. NY, NY	101-09/Site 121 N=4	Dec. 16 to 18, 2013	NAI

Name of CI City, State	Protocol/Study Site/Number of Subjects Enrolled (n)	Inspection Date	Final Classification*
Gilead Sciences, Inc. Seattle, WA	Sponsor	Feb. 10 to March 6, 2014	Pending Preliminary: VAI

***Key to Classifications**

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested = Deviations(s) from regulations. Data acceptable.

OAI = Significant deviations from regulations. Data unreliable/critical findings may affect data integrity.

Preliminary= The Establishment Inspection Report (EIR) has not been received, findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), or final review of the EIR is pending. Once a final letter is issued by CDER to the inspected entity and the case file is closed, the preliminary designation is converted to a final regulatory classification.

CLINICAL STUDY SITE INVESTIGATORS

1. Ajay Gopal, M.D./Protocol 101-09/Site 119
Seattle, WA

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from December 12, 2013 to January 9, 2014. A total of 19 subjects were screened, and 13 subjects were enrolled. The study is ongoing. Three subjects (110-09-034, 110-09-005 and subject 110-09-009) are currently receiving the investigational product. An audit of all the enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. The efficacy endpoints were centrally adjudicated. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection by ORA staff.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was issued at the

end of the inspection for failure to follow the study protocol according to the investigational plan. Please see relevant examples below.

1. Subject 119-09-004 was dispensed the investigational drug product from his supply kit on (b) (6). The remaining 35 tablets returned from the (b) (6) to the (b) (4) on (b) (6) because the patient died. The returned supply kit was re-dispensed to another Subject 119-09-011 on (b) (6).
2. The investigational drug product returns were missing and not verifiable. The (b) (4) did not retain the investigational drug product for review by the study monitor prior to their destruction for following patients:
 - (a) Subject 119-09-093 who returned 58 tablets on 11/14/2012
 - (b) Subject 119-09-005 who returned 36 tablets on 9/14/2012
 - (c) Subject 119-09-034 who returned 22 tablets on 10/22/2012
 - (d) Subject 119-09-106 who returned 8 tablets on 10/22/2012
 - (e) Subject 119-09-093 who returned 7 tablets on 9/13/2012, and
 - (f) Subject 119-09-142 who returned 4 tablets on 10/31/2012
3. Subject 119-09-011's febrile neutropenia SAE occurred on 12/16/2011, but was reported to the sponsor on 12/19/2011.

Medical Officer's Comment: Although the clinical investigator failed to report the SAE on time, the finding was isolated.

The List of Inspectional Observations (Form FDA 483) was communicated to the DHP Medical Team. Dr. Gopal responded adequately to these observations in a letter dated January 29, 2014.

Medical Officer's Comment:

At the mid-cycle meeting, OSI discussed with DHP whether or not a systemic practice occurred for other clinical study sites destroying the investigational drug product before study monitors could confirm the pill counts. In response DHP sent the sponsor an Information Request. The sponsor responded that there were three additional sites with documentation of returned study drug destruction prior to monitor verification (1 instance at each site). These sites were Site # 406 (Dr. Gyan, Tours, France), Site # 405 (Dr. Tempescul, Brest, France), and Site #133 (Dr. Schuster, Philadelphia, PA).

c. Assessment of data integrity:

While the FDA inspection revealed regulatory deficiencies of clinical investigator obligations in the conduct of the study, overall data derived from Dr. Gopal's site

appear acceptable, as the findings were not considered pervasive and/or the nature of the findings is unlikely to impact data reliability.

2. Peter Martin, M.D./Protocol 101-09/Site 121
NY, NY

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from December 16 to 18, 2014. A total of four subjects were screened and enrolled in the study. Three subjects remained in a post-treatment follow-up period for five years. An audit of four subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for randomized subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. There were no limitations during conduct of the clinical site inspection by ORA staff. There was no under-reporting of serious adverse events at this clinical study site.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

c. Assessment of data integrity:

Data submitted by this clinical site appear acceptable for this specific indication.

SPONSOR

5. Gilead Sciences, Inc.
Seattle, WA

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.810, from February 10 to March 6, 2014.

The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, and training of study staff and site monitors.

b. General observations/commentary:

The sponsor generally maintained adequate oversight of the clinical trial. There was no evidence of under-reporting of adverse events. In general, there were no GCP noncompliant sites reported.

A Form FDA 483 was issued at the end of the sponsor inspection. Specifically, for Site 121, because the study monitor failed to resolve the issue of completion of the Site Delegation of Authority Log and the Training Log for the site personnel until 12/13/2013.

c. Assessment of data integrity:

While the FDA inspection revealed regulatory deficiencies of the sponsor obligations in the conduct of the study, data submitted by this sponsor appear acceptable in support of the respective indication

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Two domestic clinical sites were selected for inspection of Study 101-09 supporting this NDA: Ajay Gopal, M.D. and Peter Martin, M.D. The sponsor (Gilead Sciences) was also inspected.

The classification for Dr. Martin is NAI (No Action Indicated). The preliminary classification for Dr. Gopal and Gilead Sciences is VAI (Voluntary Action Indicated). The study data collected from these clinical sites that have been inspected and submitted by the sponsor appear generally reliable in support of the requested indication.

Note: The inspectional observations noted above are based on the preliminary communications with the field investigator and for Dr. Gopal on preliminary review of the EIR. CDER OSI classification of inspection is finalized when written correspondence is issued to the inspected entity (eg, principal investigator). A clinical inspection summary addendum will be generated if conclusions on the currently reported inspections change significantly upon receipt and/or final review of the Establishment Inspection Report (EIR).

{See appended electronic signature page}

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/s/

ANTHONY J ORENCIA
04/10/2014

JANICE K POHLMAN
04/10/2014

KASSA AYALEW
04/10/2014

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	205858
Generic Name	Idelalisib (IDELA)
Sponsor	Gilead Sciences, Inc.
Indication	Treatment of patients with refractory indolent non-Hodgkin lymphoma
Dosage Form	Tablets
Drug Class	PI3K delta inhibitor
Therapeutic Dosing Regimen	150 mg
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	400 mg
Submission Number and Date	SDN 001 /11 Sept 2013
Review Division	DHP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effects of idelalisib (150 mg and 400 mg) were detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between idelalisib (150 mg and 400 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the 2-sided 90% CI for the $\Delta\Delta\text{QTcN}$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 4, indicating that assay sensitivity was established.

In this randomized, partially-blinded, placebo- and positive-controlled, 4 period single-dose crossover study, 48 healthy subjects received idelalisib 150 mg, idelalisib 400 mg, placebo, and moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Idelalisib (150 mg and 400 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta\text{QTcN}$ (ms)	90% CI (ms)
Idelalisib 150 mg	4	1.7	(-1.6, 5.)
Idelalisib 400 mg	5	3.1	(0.2, 5.9)
Moxifloxacin 400 mg*	4	13.8	(10.5, 17.0)

- Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 9.3 ms

IDELA given at 400 mg provided higher exposures relative to 150 mg (~ 60% higher for C_{max} , and ~2.3-fold higher for AUC_{inf}) and were higher than those observed in subjects with impaired organ function (IDELA AUC ~60% higher in hepatically impaired subjects [313-0112] or ~30% higher in renally impaired subjects) or with strong CYP3A inhibitor coadministration (~26% higher C_{max} and 80% higher AUC upon coadministration with ketoconazole, which is also an inhibitor of aldehyde oxidase the major oxidative enzyme responsible for IDELA oxidation).

2 PROPOSED LABEL

2.1 SPONSOR'S PROPOSED LABEL

12.2 Pharmacodynamics

Electrocardiographic Effects

The effect of idelalisib (b) (4) (150 mg) and (b) (4) (400 mg) (b) (4) on the QTc interval was evaluated in a placebo- and positive-controlled (moxifloxacin 400 mg) crossover study in (b) (4) healthy subjects. (b) (4)

2.2 QT-IRT'S PROPOSED LABEL

QT-IRT's proposed labeling language is a suggestion only. We defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At a dose 2.7 times the maximum recommended dose, idelalisib did not prolong the QT interval (b) (4)

3 BACKGROUND

3.1 PRODUCT INFORMATION

Idelalisib is an oral, selective, small molecule inhibitor of the p110 δ isoform of phosphatidylinositol 3-kinase that has demonstrated a clinically meaningful benefit in a highly refractory population of patients with indolent non-Hodgkin lymphoma.

3.2 MARKET APPROVAL STATUS

Idelalisib is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

The IC₅₀ for the hERG potassium current was estimated to be greater than 50 μ M.

3.4 PREVIOUS CLINICAL EXPERIENCE

A total of 352 subjects received IDELA monotherapy and 290 subjects enrolled for treatment with IDELA combination therapy. No AEs as per ICH E14 guidance were reported.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of idelalisib's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under NDA 205858. The sponsor submitted the study report GS-US-313-0117 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Phase 1, Partially-Blinded, Randomized, Placebo- and Positive-Controlled Study to Evaluate the Effect of idelalisib (GS-1101) on the QT/QTc Interval in Healthy Subjects

4.2.2 Protocol Number

GS-US-313-0117

4.2.3 Study Dates

First subject enrolled: 06 Feb 2013

Last subject observation: 15 Apr 2013

4.2.4 Objectives

Primary objective:

To evaluate the effects of idelalisib (IDELA, formerly GS-1101, CAL-101) (at therapeutic and suprathreshold doses) and metabolite GS-563117 on time-

matched, baseline-adjusted, placebo-corrected QT interval corrected for heart rate calculated using Fridericia correction (QTcF)

Secondary objectives:

- To explore the effect of idelalisib (at therapeutic and suprathreshold doses) and metabolite GS-563117 on corrected QT using other approaches, such as QTc calculated using population correction (QTcN)
- To determine the pharmacokinetics (PK) of IDELA and metabolite GS-563117
- To explore the relationship between time-matched, baseline-adjusted, placebo corrected QTc ($\Delta\Delta\text{QTc}$) and idelalisib, and metabolite GS-563117, plasma concentrations
- To explore the effect of idelalisib (at therapeutic and suprathreshold doses) and metabolite GS-563117 on other electrocardiogram (ECG) parameters, including PR interval
- To evaluate the safety and tolerability of idelalisib in healthy subjects at the doses administered

4.2.5 Study Description

4.2.5.1 Design

This was a Phase 1, partially-blinded, randomized, placebo- and positive-controlled, 4-period single-dose crossover study was conducted to evaluate the effect of idelalisib on time-matched change from baseline of QTcF and QTcN, and to explore the effect of idelalisib on ECG parameters.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls

4.2.5.3 Blinding

Study drugs were provided to the study pharmacist in an unblinded fashion. To maintain the blinding, idelalisib and matching placebo tablets were visually identical, and the number of tablets administered for Treatments A, B, and C were the same. Moxifloxacin was administered as a positive control and were not blinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

Subjects were randomized in a 1:1 ratio to 1 of 2 Williams squares, and then 1 of 4 possible treatment sequences per Williams square: IDELA plus placebo (Treatment A), IDELA alone (Treatment B), placebo alone (Treatment C), and moxifloxacin alone (Treatment D).

Treatment A (Therapeutic Exposure):

- 150 mg IDELA (1 × 150-mg IDELA tablet), plus
- Placebo (1 × 100-mg placebo tablet plus 1 × 150-mg placebo tablet)

Treatment B (Suprathreshold Exposure):

- 400 mg IDELA (2 × 150-mg IDELA tablets plus 1 × 100-mg IDELA tablet)

Treatment C (Placebo Control):

- Placebo (1 × 100-mg placebo tablet plus 2 × 150-mg placebo tablet),

Treatment D (Positive Control):

- 400 mg moxifloxacin (1 × 400-mg moxifloxacin tablet)

4.2.6.2 Sponsor's Justification for Doses

A single dose of 150 mg IDELA was selected as the therapeutic dose for this study. Selection of this dose was based on safety and efficacy data from previous single-dose and multiple-dose clinical studies using IDELA in healthy subjects and subjects with hematologic malignancies. Safety results from clinical studies to date indicate that IDELA is well tolerated when administered to healthy subjects at single doses through 400 mg and upon multiple dosing to doses of 350 mg twice daily (BID) for subjects with hematologic malignancies (the highest dose levels tested).

A single dose of 400 mg IDELA was selected as the suprathereapeutic dose for this study, which provides overall exposures (AUC) approximately 60% to 100% higher and peak concentrations approximately 44% to 60% higher than the therapeutic dose of 150 mg (depending on fed or fasted dosing), in the unlikely event of additional and/or unexpected drug interactions or overdosage. IDELA is metabolized by aldehyde oxidase, cytochrome P450 (CYP) 3A, and UGT1A4. Co-administration of IDELA with the highly potent CYP3A inhibitor, ketoconazole, resulted in only modest to moderate increases in IDELA exposure (26% higher C_{max} , 80% higher AUC), consistent with the multiple metabolic pathways that contribute to IDELA disposition. Exposures of the primary circulating metabolite of IDELA, GS-563117, were also increased. As such, the 400-mg dose was expected to provide IDELA exposures that were suprathereapeutic and suitable for evaluation in a thorough QT/QTc study. The plasma AUC of metabolite GS-563117 with IDELA 400 mg was expected to represent/cover clinically observed exposures upon chronic dosing of IDELA 150 mg BID.

Reviewer's Comment: Sponsor's dose selection was reasonable based on exposure-dose relationship and PK result of drug-drug interaction with ketoconazole.

4.2.6.3 Instructions with Regard to Meals

Study treatment was administered in the morning following an overnight fast (no food or liquids, except water, for at least 8 hours) with 240 mL of water within 5 minutes of consuming a standard meal. Subjects were restricted from water consumption 1 hour before and 2 hours after dosing, except for the 240 mL of water given with the study drug; and food intake was restricted until after collection of the 4-hour postdose blood draw.

Reviewer's Comment: Agree with administration under fasted conditions. IDELA C_{max} was not different under fed or fasted conditions. IDELA AUC_{inf} was ~36% higher with a high-fat meal relative to fasted condition.

4.2.6.4 ECG and PK Assessments

Serial blood samples were collected for PK analysis relative to the dosing of IDELA and its metabolite, GS-563117, on Days 1, 11, 21, and 31 at the following time points:

predose (≤ 5 minutes before dose) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 8, 12, 20, 24, 36, and 48 hours postdose.

The time points for 24-hour ECG sampling were as follows:

- Predose (pre-meal) baseline triplicate ECGs collected at 1.5, 1, and 0.5 hours prior to the morning meal.
- Postdose triplicate ECGs at 1, 1.5, 2, 2.5, 3, 4, 5, 12, and 24 hours following administration of study drugs.

Reviewer's Comment: Agree with the timing of ECGs since it covers T_{max} and extends to 48 hours.

4.2.6.5 Baseline

The Sponsor used the average predose of the QTc values collected at 1.5, 1 and 0.5 hours as the QTc baseline values.

4.2.7 ECG Collection

Intensive 12-Lead Holter monitoring will be used to obtain digital ECGs. Standard 12-Lead ECGs will be obtained while subjects are recumbent.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 48 healthy subjects enrolled and 46 subjects (95.8%) completed the study. Subjects in the safety and pharmacodynamic analysis sets were predominantly black or African American (58.3%) or white (33.3%), evenly split between female (47.9%) and male (52.1%), and had a mean age of 33 years (range, 20 to 45 years), mean BMI of 27 kg/m². Two subjects (4.2%) withdrew consent and were withdrawn from study treatment.

4.2.8.1.1 Primary Analysis

The primary endpoint was time-matched baseline-adjusted mean differences between IDELA (150 mg and 400 mg) and placebo in QTcF. The sponsor used mixed model and the results are presented in Table 2. This model included sequence, period, time, treatment, and time-by-treatment interaction, and gender as fixed effects, subject within sequence as a random effect and baseline as covariate. The upper limits of the 2-sided 90% CI for idelalisib (150 mg and 400 mg) were below 10 ms.

Table 2: Sponsor Results Δ QTcF and $\Delta\Delta$ QTcF for IDELA 150 mg and IDELA 400 mg

Scheduled Time	Least-Squares Means			Treatment Difference		90% Confidence Intervals	
	IDELA 150 mg	IDELA 400 mg	Placebo	IDELA 150 mg -Placebo	IDELA 400 mg -Placebo	IDELA 150 mg -Placebo	IDELA 400 mg -Placebo
1 hour	-11.6	-10.3	-9.1	-2.5	-1.2	-4.9, 0.0	-3.7, 1.3
1.5 hours	-10.6	-11.4	-9.6	-1.0	-1.8	-3.4, 1.5	-4.2, 0.7
2 hours	-12.6	-10.4	-8.3	-4.3	-2.1	-6.7, -1.8	-4.6, 0.3
2.5 hours	-11.4	-12.5	-10.7	-0.7	-1.8	-3.1, 1.8	-4.2, 0.7
3 hours	-8.8	-8.2	-8.8	-0.0	0.6	-2.5, 2.4	-1.8, 3.1
4 hours	-9.7	-8.9	-10.7	1.0	1.8	-1.5, 3.4	-0.7, 4.3
5 hours	-11.1	-7.0	-10.0	-1.1	3.0	-3.6, 1.3	0.5, 5.5
12 hours	-8.6	-8.8	-10.3	1.7	1.5	-0.8, 4.1	-1.0, 3.9
24 hours	-0.8	-1.3	-0.9	0.0	-0.4	-2.5, 2.5	-2.9, 2.0

Source: *Clinical Study Report GS-US-313-0117, Section 10.2.2.1.1, Table 10-6, Pg 65/396*

Reviewer's Comments: We will provide our independent analysis results in Section 5.2.

4.2.8.1.2 Assay Sensitivity

The sponsor used the same mixed model to analyze the Δ QTcF effect for moxifloxacin. The analysis results were presented in Table 3. The largest unadjusted lower bound 1-sided 95% is 12.8 ms which was greater than 5 ms. Thus, assay sensitivity in this thorough QTcF study was established.

Table 3: Sponsor Results Δ QTcF and $\Delta\Delta$ QTcF for Moxifloxacin 400 mg

Scheduled Time	Least-Squares Means		Treatment Difference	90% Confidence Intervals
	Moxifloxacin	Placebo	Moxifloxacin - Placebo	Moxifloxacin - Placebo
1 hour	-4.0	-9.1	5.1	
1.5 hours	-0.8	-9.6	8.8	6.4, 11.3
2 hours	-1.6	-8.3	6.7	4.2, 9.1
2.5 hour	0.4	-10.7	11.2	8.7, 13.6
3 hours	2.0	-8.8	10.8	8.4, 13.3
4 hours	2.2	-10.7	12.8	10.4, 15.3
5 hours	-1.1	-10.0	8.9	-
12 hours	-4.8	-10.3	5.5	-
24 hours	4.1	-0.9	5.0	-

Note: Assay sensitivity analysis was performed only at postdose time points 1.5, 2, 2.5, 3, and 4 hours.
Source: *Clinical Study Report GS-US-313-0117*, Section 10.2.1, *Table 10-5*, Pg 63/396

4.2.8.1.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc \leq 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and $>$ 500 ms, and changes from baseline QTc \leq 30 ms, between 30 and 60 ms, and $>$ 60 ms. No subject's absolute QTc $>$ 480 ms and no subjects Δ QTc $>$ 60 ms.

Table 4: Sponsor Analyses of Categorical Analysis in QTcF

	IDELA 150 mg (N=47)	IDELA 400 mg (N=47)	Placebo (N=46)	Moxifloxacin 400 mg (N=47)
Observed Value				
> 500 msec	0	0	0	0
> 480 500 msec	0	0	0	0
> 450 480 msec	0	1 (2.1%)	2 (4.3%)	2 (4.3%)
- Missing -	0	0	0	0
Change from Predose/Baseline				
> 60 msec	0	0	0	0
> 30 60 msec	0	0	0	0
- Missing -	0	0	0	0

Note: Only subjects with treatment-emergent QTc interval prolongations (> 450, > 480, and > 500 msec) were counted as events for "Observed Value" and included in the numerator. Treatment-emergent means a subject had a QTc interval prolongation at any postdose assessment that was not present at the predose assessment.

4.2.8.2 Safety Analysis

No deaths or SAEs occurred during this study, and no subject discontinued the study due to an AE.

4.2.8.3 Clinical Pharmacology

4.2.8.3.1 Pharmacokinetic Analysis

The PK results are presented in Table 5 for IDELA and Table 6 for metabolite GS-563117. IDELA C_{max} and AUC values in the thorough QT study were 60% and 130% higher, respectively, following administration of 400 mg idelalisib compared with 150 mg, the intended clinical dose. GS-563117 C_{max} and AUC values for 400 mg were 70% and 140% higher, respectively, than 150 mg.

Table 5: GS-US-313-0117: IDELA Single-Dose Pharmacokinetic Parameters by Treatment (IDELA PK Analysis Set)

IDELA PK Parameter	IDELA 150 mg (N=47)	IDELA 400 mg (N=47)
C _{max} (ng/mL)	1927.74 (26.4)	3134.89 (16.4)
T _{max} (h)	2.00 (1.50, 2.50)	1.53 (1.50, 2.50)
t _{1/2} (h)	8.33 (5.19, 12.85)	10.42 (7.71, 15.70)
AUC _{last} (ng·h/mL)	8275.38 (28.9)	18560.31 (27.7)
AUC _{inf} (ng·h/mL)	8392.99 (28.6)	19072.39 (28.0)

Source: Page 59 of Sponsor's final clinical study report on the QTc study, GS-US-313-0117.

Table 6: GS-US-313-0117: IDELA Single-Dose Pharmacokinetic Parameters by Treatment (GS-563117 PK Analysis Set)

GS-563117 PK Parameter	IDELA 150 mg (N=47)	IDELA 400 mg (N=47)
C _{max} (ng/mL)	2038.6 (33.2)	3520.9 (27.7)
T _{max} (h)	3.00 (2.50, 3.52)	3.50 (3.50, 4.50)
t _{1/2} (h)	8.53 (8.05, 9.80)	9.99 (8.39, 12.72)
AUC _{last} (ng·h/mL)	21,479.7 (41.4)	49,942.6 (34.0)
AUC _{inf} (ng·h/mL)	21,987.1 (41.9)	52,778.8 (35.5)

Source: Page 61 of Sponsor's final clinical study report on the QTc study, GS-US-313-0117.

4.2.8.3.2 Exposure-Response Analysis

A linear mixed-effect model was used to quantify the relationship between plasma concentrations of IDELA and $\Delta\Delta\text{QTcF}$ with gender as a fixed effect and subject as a random effect. The statistical analyses of the relationship between IDELA plasma concentrations and $\Delta\Delta\text{QTcF}$ are summarized in Table 7 and the relationship between IDELA plasma concentrations and $\Delta\Delta\text{QTcF}$ is depicted graphically in Figure 1. The results suggest that there were no relevant relationships between IDELA plasma concentration and $\Delta\Delta\text{QTcF}$ interval.

Table 7: GS-US-313-0117: Statistical Analysis of the Relationship between IDELA Plasma Concentrations and Time-Matched, Baseline- Adjusted, and Placebo-Corrected QTcF (IDELA PK/PD Analysis Set)

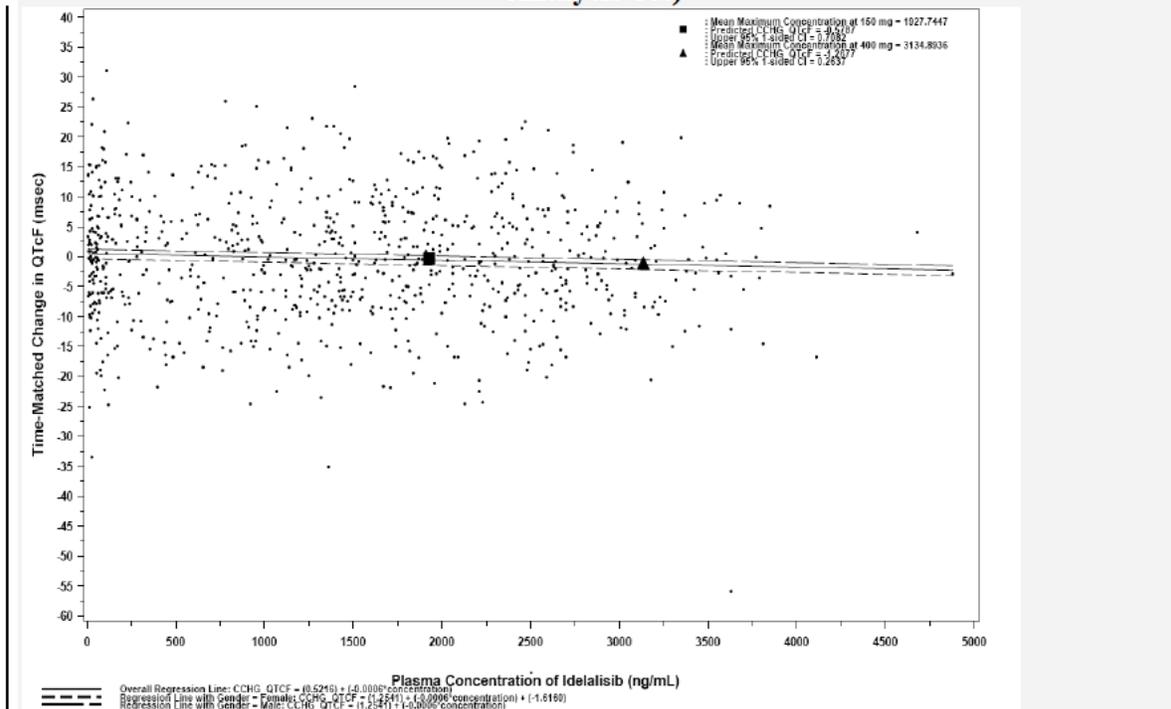
QTcF	Estimate	Standard Error	95% Confidence Interval		P-value
			Lower	Upper	
Time-Matched, Baseline-Adjusted, and Placebo-Corrected QTcF					
Overall Regression Equation: CCHG_QTcF = a + (b*Concentration)					
Intercept (a)	0.5216	0.8878	-1.2666	2.3098	0.5598
Concentration (b)	-0.0006	0.0003	-0.0012	0.0000	0.0666
Regression Equation with Gender as a Fixed Effect: CCHG QTcF = a + (b*Concentration) + (c*Gender)					
Intercept (a)	1.2541	1.1279	-1.0192	3.5273	0.2723
Concentration (b)	-0.0006	0.0003	-0.0012	0.0000	0.0687
Gender (c) ^a	-1.6160	1.5371	-4.7138	1.4819	0.2989

CCHG QTcF = time-matched, baseline-adjusted, and placebo-corrected QTcF

a 0=male,
1=female

Note: Overall PK/PD regression included concentration as a continuous covariate and subject within sequence as a random effect, and PK/PD regression with gender as a fixed effect included gender as a fixed effect, concentration as a continuous covariate, and subject within sequence as a random effect.

Figure 1: GS-US-313-0117: Scatter Plot of Time-Matched, Baseline- Adjusted, and Placebo-Corrected QTcF versus IDELA Plasma Concentration (IDELA PK/PD Analysis Set)



Note: Overall PK/PD regression included concentration as a continuous covariate and subject within sequence as a random effect, and PK/PD regression with gender included gender as a fixed effect, concentration as a covariate, and subject within sequence as a random effect.

A linear mixed-effect model was used to quantify the relationship between plasma concentrations of GS-563117 and $\Delta\Delta QTcF$ with gender as a fixed effect and subject as a random effect. The statistical analyses of the relationship between GS-563117 plasma concentrations and $\Delta\Delta QTcF$ are summarized in Table 8 and the relationship between GS-563117 plasma concentrations and $\Delta\Delta QTcF$ is depicted graphically in Figure 2. As noted with IDELA, the results suggest that there were no relevant relationships between GS-563117 plasma concentration and $\Delta\Delta QTcF$ interval.

Table 8: GS-US-313-0117: Statistical Analysis of the Relationship between IDELA Plasma Concentrations and Time-Matched, Baseline- Adjusted, and Placebo-Corrected QTcF (GS-563117 PK/PD Analysis Set)

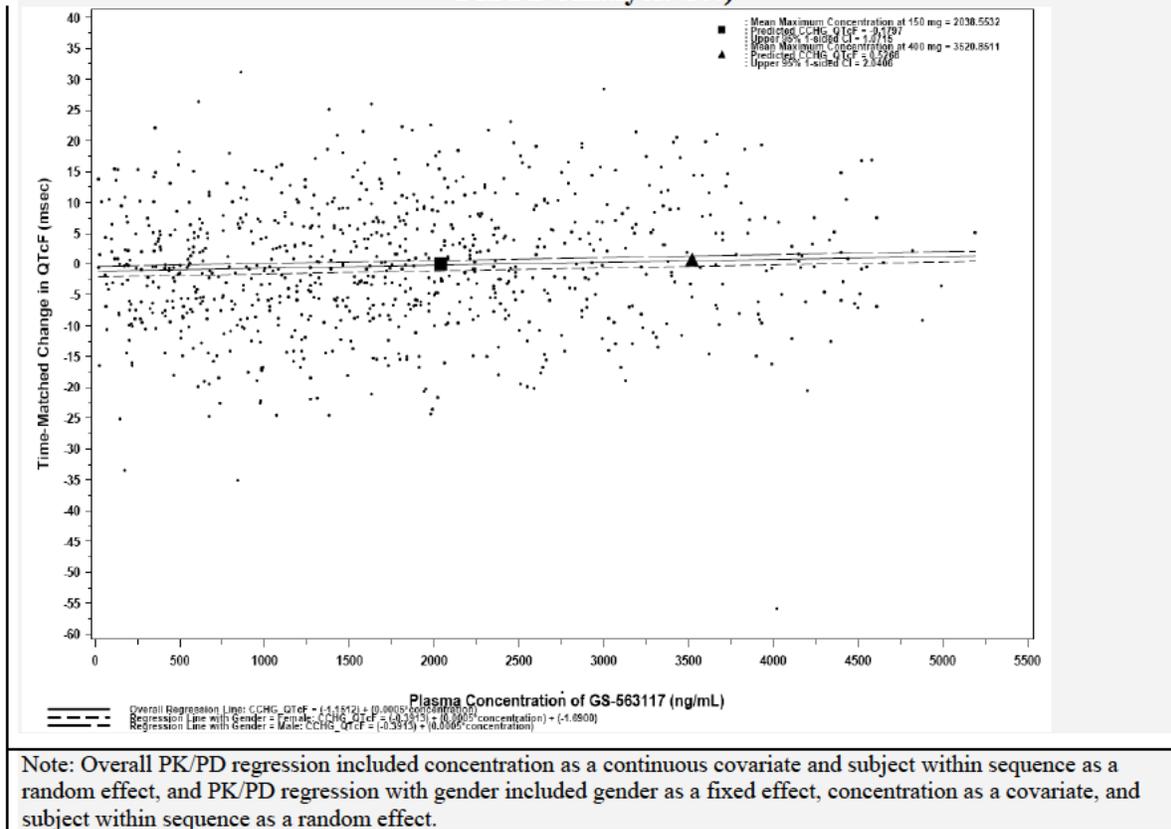
QTcF	Estimate	Standard Error	95% Confidence Interval		P-value
			Lower	Upper	
Time-Matched, Baseline-Adjusted, and Placebo-Corrected QTcF					
Overall Regression Equation: CCHG_QTcF = a + (b*Concentration)					
Intercept (a)	-1.1512	0.9224	-3.0090	0.7067	0.2185
Concentration (b)	0.0005	0.0003	-0.0001	0.0011	0.1114
Regression Equation with Gender as a Fixed Effect: CCHG QTcF = a + (b*Concentration) + (c*Gender)					
Intercept (a)	-0.3913	1.1452	-2.6993	1.9167	0.7342
Concentration (b)	0.0005	0.0003	-0.0001	0.0011	0.1061
Gender (c) ^a	-1.6900	1.5128	-4.7389	1.3588	0.2700

CCHG QTcF = time-matched, baseline-adjusted, and placebo-corrected QTcF

a 0=male,
1=female

Note: Overall PK/PD regression included concentration as a continuous covariate and subject within sequence as a random effect, and PK/PD regression included gender as a fixed effect, concentration as a continuous covariate, and subject within sequence as a random effect.

Figure 2: GS-US-313-0117: Scatter Plot of Time-Matched, Baseline- Adjusted, and Placebo-Corrected QTcF versus GS-563117 Plasma Concentration (GS-563117 PK/PD Analysis Set)



Analysis: A plot of $\Delta\Delta QTcN$ vs. drug concentrations is presented in Figure 7.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods. Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

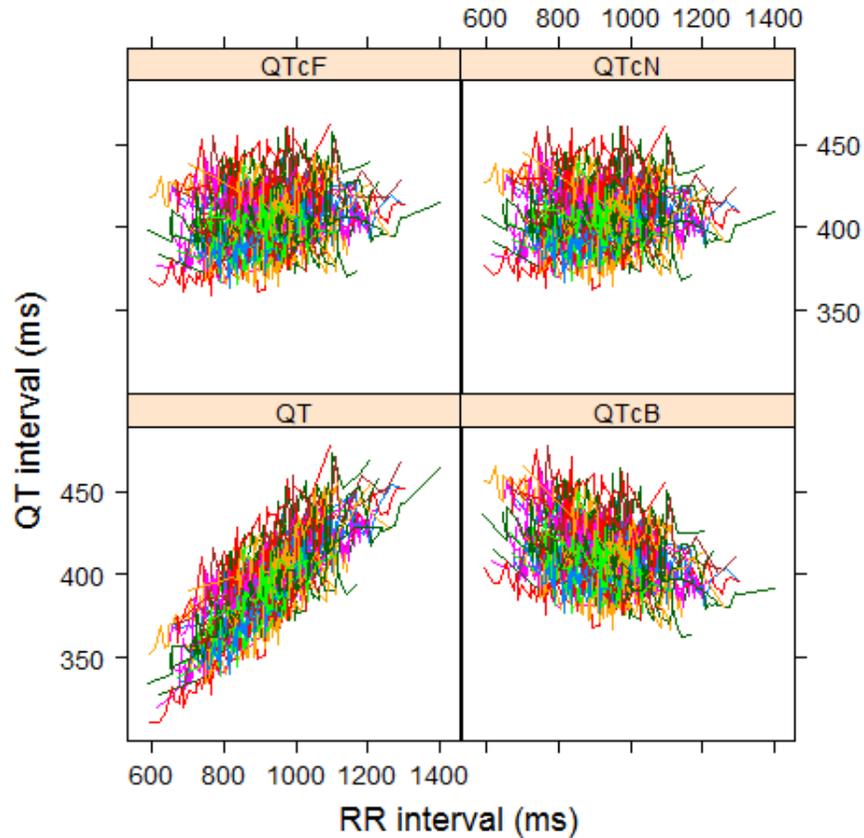
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 9, it appears that QTcN is the best correction method. Therefore, this statistical reviewer used QTcN for the primary statistical analysis.

Table 9: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	Correction Method							
	QTcB		QTcF		QTcI		QTcN	
	N	MSSS	N	MSSS	N	MSSS	N	MSSS
Idelalisib 150 mg	47	0.0045	47	0.0021	47	0.0018	47	0.0016
Idelalisib 400 mg	47	0.0050	47	0.0015	47	0.0020	47	0.0013
Moxifloxacin 400 mg	47	0.0066	47	0.0013	47	0.0013	47	0.0014
Placebo	46	0.0043	46	0.0020	46	0.0012	46	0.0015
All	48	0.0039	48	0.0009	48	0.0008	48	0.0005

The QT-RR interval relationship is presented in Figure 3 together with the Bazett's (QTcB), Fridericia (QTcF) and QTcN corrections.

Figure 3: QT, QTcB, and QTcF, QTcN vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for Idelalisib

The statistical reviewer used mixed model to analyze the Δ QTcN effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 10. The largest upper bounds of the 2-sided 90% CI for the mean differences between idelalisib 150 mg and placebo, and between idelalisib 400 mg and placebo are 5.0 ms and 5.9 ms, respectively. This reviewer also used same model to analyze the QTcF effect. The analysis results are similar with QTcN's results (see Table 11).

Table 10: Analysis Results of Δ QTcN and $\Delta\Delta$ QTcN for Idelalisib 150 mg, Idelalisib 400 mg and Moxifloxacin 400 mg

Time (h)	Placebo	Idelalisib 150 mg				Idelalisib 400 mg				Moxifloxacin				
	Δ QTcN	Δ QTcN		$\Delta\Delta$ QTcN		Δ QTcN		$\Delta\Delta$ QTcN		Δ QTcN		$\Delta\Delta$ QTcN		
	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	*Adj 90%CI
1	-6.9	47	-9.8	-2.9	(-5.3, -0.5)	46	-8.7	-1.8	(-4.2, 0.6)	47	-2.0	4.9	(2.5, 7.3)	(1.6, 8.2)
1.5	-8.2	47	-9.2	-1.0	(-3.3, 1.3)	46	-10.1	-1.9	(-4.2, 0.4)	47	1.0	9.2	(6.9, 11.5)	(6.1, 12.4)
2	-6.7	47	-11.3	-4.6	(-7.3, -2.0)	46	-9.2	-2.5	(-5.2, 0.1)	47	0.3	7.0	(4.3, 9.7)	(3.4, 10.6)
2.5	-10.1	47	-10.6	-0.5	(-3.5, 2.5)	46	-11.8	-1.7	(-4.7, 1.3)	47	1.7	11.8	(8.8, 14.7)	(7.7, 15.8)
3	-8.2	46	-8.2	-0.0	(-2.7, 2.6)	47	-7.4	0.8	(-1.9, 3.4)	47	3.2	11.4	(8.8, 14.0)	(7.8, 15.0)
4	-9.7	47	-8.0	1.7	(-1.6, 5.0)	47	-7.6	2.1	(-1.2, 5.4)	47	4.1	13.8	(10.5, 17.0)	(9.3, 18.3)
5	-7.4	46	-8.4	-1.0	(-3.9, 1.9)	46	-4.3	3.1	(0.2, 5.9)	46	1.7	9.0	(6.2, 11.9)	(5.1, 13.0)
12	-7.5	47	-6.3	1.3	(-1.4, 4.0)	47	-6.3	1.2	(-1.5, 3.9)	47	-1.8	5.7	(3.0, 8.4)	(2.0, 9.4)
24	0.1	45	0.1	-0.0	(-3.2, 3.2)	47	-0.3	-0.4	(-3.6, 2.7)	47	5.1	5.0	(1.8, 8.1)	(0.6, 9.3)

- Bonferroni method was applied for multiple endpoint adjustment for 4 time points.

Table 11 : Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for Idelalisib 150 mg, Idelalisib 400 mg and Moxifloxacin 400 mg

Time (h)	Placebo	Idelalisib 150 mg				Idelalisib 400 mg				Moxifloxacin 400 mg			
	Δ QTcF	Δ QTcF		$\Delta\Delta$ QTcF		Δ QTcF		$\Delta\Delta$ QTcF		Δ QTcF		$\Delta\Delta$ QTcF	
	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1	-9.0	47	-11.7	-2.7	(-5.0, -0.4)	46	-10.3	-1.3	(-3.7, 1.0)	47	-4.0	5.0	(2.6, 7.3)
1.5	-9.7	47	-10.7	-1.0	(-3.2, 1.2)	46	-11.3	-1.7	(-3.9, 0.6)	47	-0.7	9.0	(6.8, 11.2)
2	-8.3	47	-12.6	-4.3	(-6.9, -1.7)	46	-10.4	-2.1	(-4.7, 0.6)	47	-1.6	6.8	(4.2, 9.4)
2.5	-10.8	47	-11.5	-0.7	(-3.6, 2.2)	46	-12.5	-1.7	(-4.6, 1.2)	47	0.5	11.3	(8.4, 14.2)
3	-8.9	46	-9.1	-0.2	(-2.8, 2.4)	47	-8.2	0.7	(-1.9, 3.3)	47	2.1	11.0	(8.4, 13.6)
4	-10.8	47	-9.8	0.9	(-2.4, 4.2)	47	-8.9	1.9	(-1.4, 5.2)	47	2.2	13.0	(9.7, 16.3)
5	-10.0	46	-11.2	-1.2	(-4.0, 1.6)	46	-6.9	3.1	(0.3, 5.9)	46	-1.1	8.9	(6.1, 11.8)
12	-10.3	47	-8.7	1.6	(-1.1, 4.4)	47	-8.8	1.5	(-1.2, 4.2)	47	-4.8	5.5	(2.8, 8.2)
24	-1.0	45	-1.0	0.0	(-3.0, 3.0)	47	-1.3	-0.3	(-3.3, 2.7)	47	4.2	5.2	(2.2, 8.2)

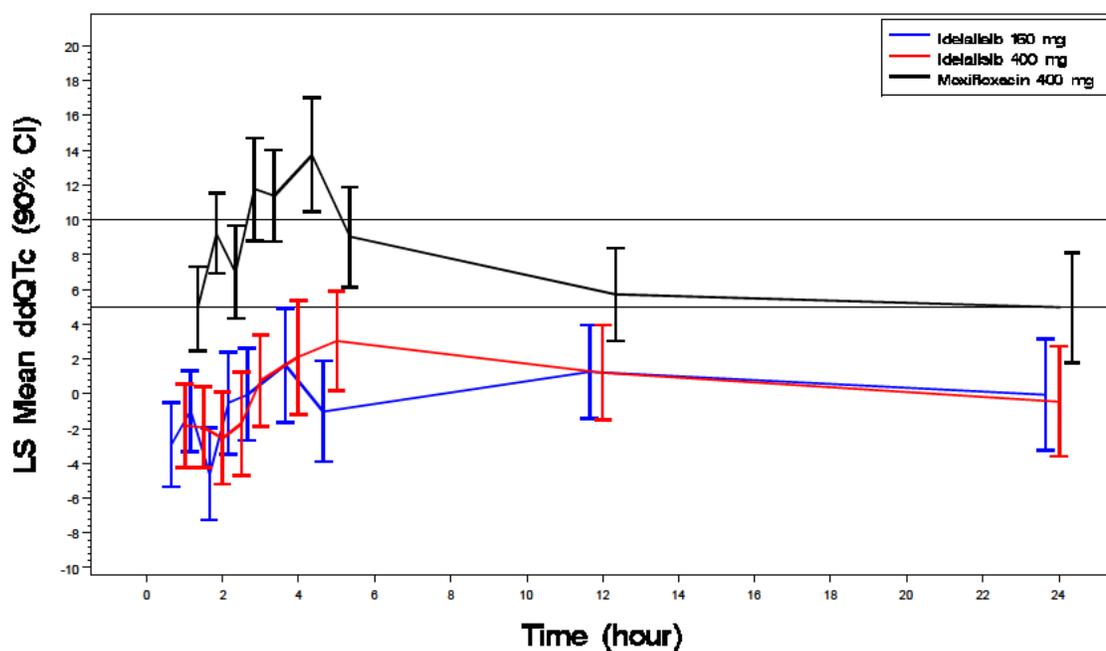
5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 10. The largest unadjusted of the 2-sided 90% lower confidence interval is 10.5 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 9.3 ms, which indicates that an at least 5 ms QTcN effect due to moxifloxacin can be detected from the study.

5.2.1.3 Graph of $\Delta\Delta$ QTcN Over Time

Figure 4 displays the time profile of $\Delta\Delta$ QTcN for different treatment groups and moxifloxacin 400 mg.

Figure 4: Mean and 90% CI $\Delta\Delta$ QTcN Time Course for Idelalisib 150 mg, Idelalisib 400 mg and Moxifloxacin 400 mg



5.2.1.4 Categorical Analysis

Table 12 lists the number of subjects as well as the number of observations whose QTcN values are ≤ 450 ms, and between 450 ms and 480 m, and changes from baseline QTc ≤ 30 ms, between 30 and 60 ms, and >60 ms. No subject's QTcN is above 480 ms. No subject's change from baseline is above 60 ms (see Table 13).

Table 12: Categorical Analysis for QTcN

Treatment Group	Total N	Value ≤ 450 ms	450 ms $<$ Value ≤ 480 ms
Idelalisib 150 mg	47	46 (97.9%)	1 (2.1%)
Idelalisib 400 mg	47	46 (97.9%)	1 (2.1%)
Moxifloxacin 400 mg	47	45 (95.7%)	2 (4.3%)
Placebo	46	44 (95.7%)	2 (4.3%)

Table 13: Categorical Analysis for Δ QTcN

Treatment Group	Total N	Value \leq 30 ms	30 ms<Value \leq 60 ms
Idelalisib 150 mg	47	47 (100%)	0 (0.0%)
Idelalisib 400 mg	47	47 (100%)	0 (0.0%)
Moxifloxacin 400 mg	47	46 (97.9%)	1 (2.1%)
Placebo	46	46 (100%)	0 (0.0%)

5.2.2 HR Analysis

The statistical reviewer used mixed model to analyze the Δ HR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 14. The largest upper bounds of the 2-sided 90% CI for the mean differences between idelalisib 150 mg and placebo, and between idelalisib 400 mg and placebo are 5.5 bpm and 3.9 bpm, respectively. Table 15 presents the categorical analysis of HR. One subject who experienced HR interval greater than 100 bpm is in idelalisib 150-mg groups.

Table 14: Analysis Results of Δ HR and $\Delta\Delta$ HR for Idelalisib 150 mg, Idelalisib 400 mg and Moxifloxacin 400 mg

Time (h)	Placebo	Idelalisib 150 mg				Idelalisib 400 mg				Moxifloxacin			
	Δ HR	Δ HR		$\Delta\Delta$ HR		Δ HR		$\Delta\Delta$ HR		Δ HR		$\Delta\Delta$ HR	
	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1	8.9	47	7.2	-1.7	(-4.0, 0.5)	46	7.0	-2.0	(-4.2, 0.3)	47	8.2	-0.7	(-3.0, 1.5)
1.5	6.0	47	6.0	0.0	(-2.1, 2.2)	46	5.2	-0.7	(-2.9, 1.4)	47	7.2	1.3	(-0.9, 3.4)
2	6.9	47	5.4	-1.5	(-3.5, 0.6)	46	5.2	-1.7	(-3.7, 0.3)	47	7.4	0.5	(-1.5, 2.6)
2.5	2.8	47	3.6	0.8	(-1.0, 2.6)	46	3.0	0.2	(-1.6, 2.0)	47	4.6	1.8	(-0.0, 3.6)
3	2.6	46	3.5	0.9	(-0.9, 2.6)	47	3.4	0.8	(-0.9, 2.5)	47	4.5	1.9	(0.2, 3.6)
4	4.0	47	7.2	3.2	(0.9, 5.5)	47	5.7	1.6	(-0.6, 3.9)	47	7.4	3.3	(1.1, 5.6)
5	11.2	46	11.9	0.7	(-1.8, 3.2)	46	11.4	0.2	(-2.4, 2.7)	46	11.2	0.0	(-2.5, 2.5)
12	11.7	47	10.2	-1.4	(-3.6, 0.7)	47	10.4	-1.3	(-3.5, 0.8)	47	12.3	0.7	(-1.5, 2.8)
24	4.3	45	4.0	-0.3	(-2.5, 1.9)	47	4.2	-0.1	(-2.2, 2.1)	47	3.5	-0.7	(-2.9, 1.4)

Table 15: Categorical Analysis for HR

Treatment Group	Total N	HR < 100 bpm	HR \geq 100 bpm
Idelalisib 150 mg	47	46 (97.9%)	1 (2.1%)
Idelalisib 400 mg	47	47 (100%)	0 (0.0%)
Moxifloxacin 400 mg	47	45 (95.7%)	2 (4.3%)
Placebo	46	46 (100%)	0 (0.0%)

5.2.3 PR Analysis

The statistical reviewer used mixed model to analyze the Δ PR effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 16. The largest upper bounds of the 2-sided 90% CI for the mean differences between idelalisib 150 mg and placebo, and between idelalisib 400 mg and placebo are 4.3 ms and 4.6 ms, respectively. Table 17 presents the categorical analysis of PR. Three subjects who experienced PR interval greater than 200 ms are in both idelalisib 150-mg and 400-mg groups.

Table 16: Analysis Results of Δ PR and $\Delta\Delta$ PR for Idelalisib 150 mg, Idelalisib 400 mg and Moxifloxacin 400 mg

Time (h)	Placebo	Idelalisib 150 mg				Idelalisib 400 mg				Moxifloxacin			
	Δ PR	Δ PR		$\Delta\Delta$ PR		Δ PR		$\Delta\Delta$ PR		Δ PR		$\Delta\Delta$ PR	
	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1	-3.1	47	-1.8	1.3	(-1.0, 3.7)	46	-1.3	1.8	(-0.6, 4.2)	47	-4.4	-1.2	(-3.6, 1.1)
1.5	-2.3	47	-3.4	-1.1	(-3.6, 1.4)	46	-1.8	0.5	(-2.0, 3.0)	47	-4.9	-2.6	(-5.1, -0.1)
2	-3.6	47	-3.7	-0.2	(-2.5, 2.1)	46	-2.0	1.6	(-0.7, 3.9)	47	-7.2	-3.6	(-5.9, -1.3)
2.5	-3.5	47	-4.4	-0.8	(-3.1, 1.4)	46	-3.4	0.1	(-2.1, 2.3)	47	-6.3	-2.7	(-5.0, -0.5)
3	-3.7	46	-3.7	-0.0	(-2.2, 2.1)	47	-4.3	-0.6	(-2.8, 1.5)	47	-5.3	-1.6	(-3.7, 0.6)
4	-5.9	47	-6.1	-0.3	(-2.5, 2.0)	47	-3.5	2.3	(0.1, 4.6)	47	-7.5	-1.6	(-3.9, 0.7)
5	-5.8	46	-5.2	0.6	(-1.9, 3.0)	46	-5.7	0.0	(-2.4, 2.5)	46	-8.1	-2.3	(-4.8, 0.2)
12	-5.5	47	-6.7	-1.2	(-3.7, 1.4)	47	-5.3	0.2	(-2.3, 2.7)	47	-8.0	-2.5	(-5.0, 0.0)
24	-3.7	45	-1.9	1.8	(-0.6, 4.3)	47	-2.6	1.2	(-1.3, 3.6)	47	-3.8	-0.0	(-2.4, 2.4)

Table 17: Categorical Analysis of PR

Treatment Group	Total N	PR < 200 ms	PR \geq 200 ms
Idelalisib 150 mg	47	45 (95.7%)	2 (4.3%)
Idelalisib 400 mg	47	44 (93.6%)	3 (6.4%)
Moxifloxacin 400 mg	47	47 (100%)	0 (0.0%)
Placebo	46	45 (97.8%)	1 (2.2%)

5.2.4 QRS Analysis

The statistical reviewer used mixed model to analyze the Δ QRS effect. The model includes treatment as fixed effect and baseline values as a covariate. The analysis results are listed in Table 18. The largest upper bounds of the 2-sided 90% CI for the mean differences between idelalisib 150 mg and placebo, and between idelalisib 400 mg and placebo are 3.1 ms and 3.0 ms, respectively. Table 19 presents the categorical analysis of QRS. Six subjects who experienced QRS interval greater than 110 ms are in both idelalisib 150-mg and 400-mg groups.

Table 18: Analysis Results of Δ QRS and $\Delta\Delta$ QRS for Idelalisib 150 mg, Idelalisib 400 mg and Moxifloxacin 400 mg

	Placebo	Idelalisib 150 mg				Idelalisib 400 mg				Moxifloxacin			
	Δ QRS	Δ QRS		$\Delta\Delta$ QRS		Δ QRS		$\Delta\Delta$ QRS		Δ QRS		$\Delta\Delta$ QRS	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
1	-0.3	47	0.4	0.8	(-0.5, 2.1)	46	-0.3	0.1	(-1.3, 1.4)	47	-0.3	0.1	(-1.3, 1.4)
1.5	-1.2	47	-0.4	0.8	(-0.4, 2.0)	46	-1.3	-0.1	(-1.3, 1.1)	47	0.0	1.2	(0.0, 2.4)
2	-1.8	47	-1.1	0.7	(-0.7, 2.0)	46	-1.1	0.7	(-0.7, 2.0)	47	-0.8	1.0	(-0.3, 2.4)
2.5	-1.8	47	-1.3	0.5	(-0.7, 1.7)	46	-0.7	1.1	(-0.1, 2.2)	47	-0.7	1.1	(-0.0, 2.3)
3	-1.9	46	-1.4	0.4	(-0.8, 1.6)	47	-1.9	-0.1	(-1.3, 1.1)	47	-1.5	0.4	(-0.8, 1.6)
4	-2.9	47	-3.1	-0.2	(-1.7, 1.3)	47	-2.1	0.9	(-0.6, 2.4)	47	-3.0	-0.1	(-1.6, 1.4)
5	-0.7	46	0.1	0.8	(-0.6, 2.2)	46	0.9	1.6	(0.2, 3.0)	46	-0.1	0.6	(-0.8, 2.0)
12	-2.6	47	-1.2	1.4	(-0.1, 3.0)	47	-1.3	1.4	(-0.2, 2.9)	47	-1.8	0.9	(-0.7, 2.4)
24	-2.2	45	-0.5	1.7	(0.2, 3.1)	47	-0.7	1.5	(-0.0, 2.9)	47	-0.8	1.4	(-0.1, 2.8)

Table 19: Categorical Analysis for QRS

Treatment Group	Total N	QRS < 110 ms	QRS \geq 110 ms
Idelalisib 150 mg	47	41 (87.2%)	6 (12.8%)
Idelalisib 400 mg	47	42 (89.4%)	5 (10.6%)
Moxifloxacin 400 mg	47	42 (89.4%)	5 (10.6%)
Placebo	46	42 (91.3%)	4 (8.7%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean IDELA concentration-time profile is illustrated in Figure 5. The mean GS-563117 concentration-time profile is illustrated in Figure 6.

Figure 5: Mean IDELA concentration-time profiles for 150 mg (blue line) and 400 mg IDELA (red line)

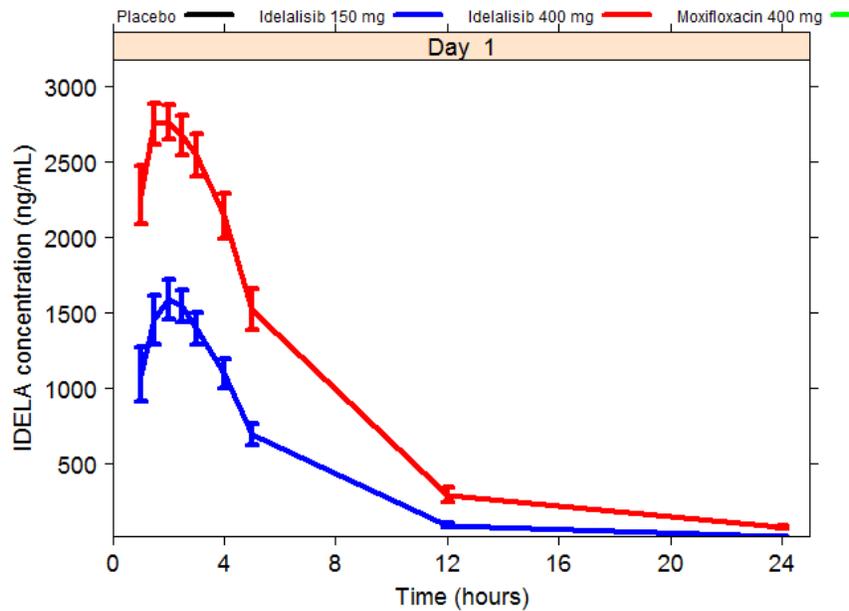
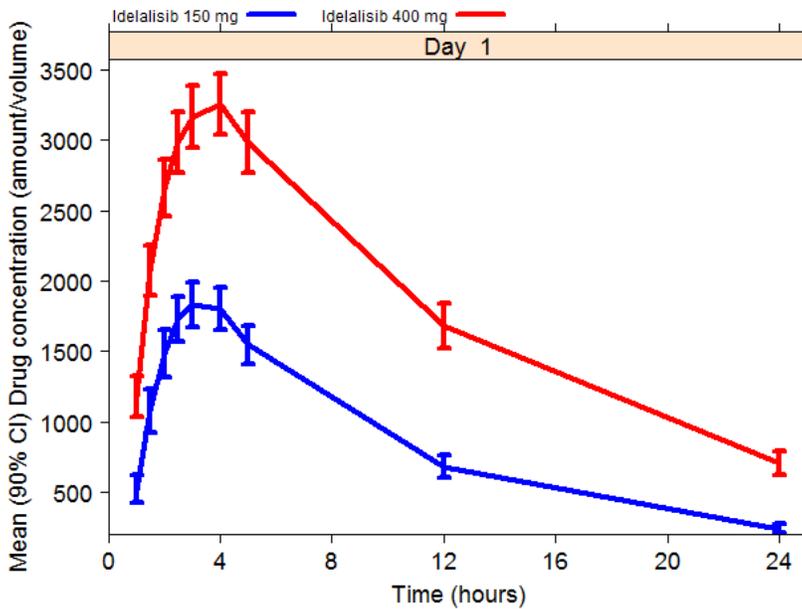


Figure 6: Mean GS-563117 concentration (ng/mL)-time profiles for 150 mg (blue line) and 400 mg IDELA (red line)



The relationship between $\Delta\Delta\text{QTcN}$ and idelalisib concentrations is visualized in Figure 7 with no evident exposure-response relationship. The relationship between $\Delta\Delta\text{QTcN}$ and GS-563117 concentrations is visualized in Figure 8 with no evident exposure-response relationship.

Figure 7: $\Delta\Delta$ QTcN vs. Plasma IDELA Concentration

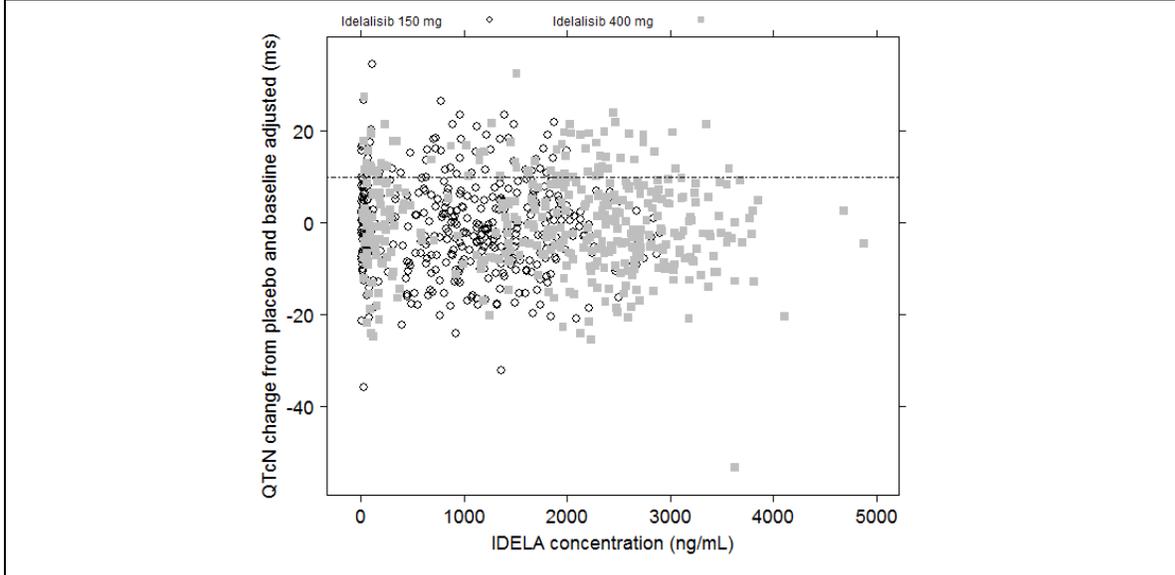
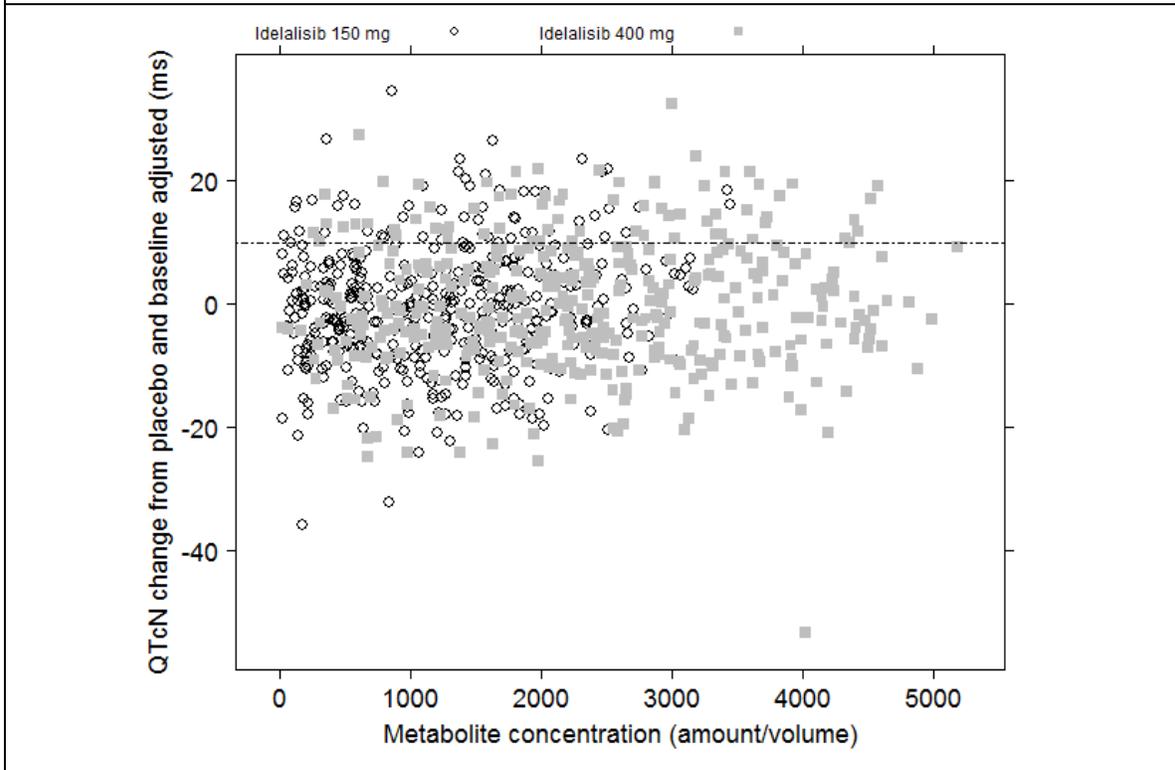


Figure 8: $\Delta\Delta$ QTcN vs. Plasma GS-563117 Concentration (ng/mL)



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. Measurements were performed on the 'global' presentation of superimposed representative (median) PQRST complexes from all leads. According to ECG warehouse statistics less than 0.2 % of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

Three subjects had a post-baseline PR > 200 ms (\leq 210 ms). Six subjects had QRS > 110 ms at baseline.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	150 mg twice daily (BID)	
Maximum tolerated dose	A maximum tolerated dose has not been established in humans.	
Principal adverse events	The most frequently reported (\geq 20% of subjects) AEs among 354 subjects with B-cell malignancies receiving IDELA monotherapy were diarrhea (35.9%), fatigue (31.6%), pyrexia (27.1%), nausea (25.7%), cough (22.6%), and neutropenia (20.3%). In the Phase 1 dose-ranging monotherapy Study 101-02, adverse events which occurred that met the protocol-specified definition of dose-limiting toxicity were: \geq Grade 3 alanine aminotransferase increased, aspartate aminotransferase increased, and liver function test abnormal. However, these events were shown to be transient, reversible, and not dose-limiting since they did not recur in the majority of subjects who were rechallenged with IDELA. Subsequent studies have further demonstrated that the \geq Grade 3 transaminase increases associated with IDELA are manageable with dose interruption until resolution to Grade 1 or less.	
Maximum dose tested	Single Dose	400 mg
	Multiple Dose	350 mg BID
Exposures Achieved at Maximum Tested Dose	Single Dose	400 mg Mean (%CV) C_{max} : ~3200 (18) ng/mL Mean (%CV) AUC_{inf} : ~19700 (28) ng•h/mL

	Multiple Dose	350 mg BID: Mean (%CV) C _{max} : ~2860 (26) ng/mL Mean (%CV) AUC _{tau} : ~16300 (23) ng•h/mL
Range of linear PK	IDELA exposures are less than dose-proportional over a range of 17 to 400 mg. Over this 24-fold dose range, AUC and C _{max} increases ~17-fold and ~10-fold, respectively. Upon multiple dose administrations of 50 to 350 mg BID, AUC _{tau} and C _{max} increased in a less than dose-proportional manner (~3.5-3.7-fold) over a 7-fold dose range.	
Accumulation at steady state	IDELA exhibits modest accumulation (1.2-1.8 fold) with BID administration over a dose range of 50 to 200 mg, consistent with its overall pharmacokinetics (PK).	
Metabolites	The biotransformation of IDELA was primarily via oxidation by aldehyde oxidase to its major and only circulating plasma metabolite, GS-563117. Other metabolic pathways involved to a lesser extent include oxidation by CYP3A and glucuronidation by UGT1A4. In plasma, the only two circulating species were IDELA (38%) and GS-563117 (62%). In urine, total radioactivity consisted primarily of IDELA (23%) and GS-563117 (49%). Trace metabolites were also observed (10% or less). In feces, radioactivity was accounted for mainly by IDELA (~12%), GS-563117 (~44%), and other oxidation products. Trace metabolites formed by oxidation and glucuronidation were also observed (6% or less) were also identified.	

Absorption	Absolute/Relative Bioavailability	The absolute bioavailability of IDELA has not been evaluated in humans. The oral bioavailability of IDELA is expected to be moderate to high based on overall PK, including the results from a human mass balance study.
	T _{max}	Median (range) for GS-1101: 2.00 (0.50, 4.02) hours Median (range) for GS-563117: 3.00 (1.00, 6.00) hours
Distribution	V _{ss} /F	Mean (%CV): ~96 L
	% bound	IDELA: 93-94% bound GS-563117: ~99% bound
Elimination	Route	Primary route: feces, ~78% of dose eliminated Other routes: urine, ~14.4% of dose eliminated
	Terminal t _{1/2}	IDELA: ~8.2 hours GS-563117: ~11.6 hours
	CL/F	IDELA: 14.9 L/h GS-563117: 4.4 L/h

Intrinsic Factors	Age	Population PK analyses of IDELA in subjects with hematologic malignancies indicated age did not have an effect on IDELA/GS-563117 PK and was not a clinically relevant covariate.
	Sex	Population PK analyses of IDELA in subjects with hematologic malignancies indicated sex did not have an effect on IDELA/GS-563117 PK and was not a clinically relevant covariate.
	Race	Population PK analyses of IDELA in subjects with hematologic malignancies indicated race did not have an effect on IDELA/GS-563117 PK and was not a clinically relevant covariate.
	Hepatic & Renal Impairment	<p>IDELA C_{max} and AUC increased ~5% and ~27%, respectively, in subjects with severe renal impairment relative to healthy matched controls. These changes were not considered to be clinically meaningful.</p> <p>IDELA C_{max} was generally comparable in subjects with moderate or severe hepatic impairment relative to healthy control subjects; IDELA AUC increased 58-60% in subjects with moderate or severe hepatic impairment relative to healthy matched controls. These changes were not considered to be clinically meaningful.</p>

Extrinsic Factors	Drug interactions	<p>When IDELA 400 mg was coadministered with ketoconazole 400 mg QD, IDELA C_{max} and AUC increased 26% and 79%, respectively.</p> <p>When IDELA 150 mg was coadministered with rifampin 600 mg QD, IDELA C_{max} and AUC decreased 58% and 75%, respectively.</p> <p>When oral midazolam 5 mg was coadministered with IDELA 150 mg BID, midazolam C_{max} and AUC increased 138% and 437%, respectively.</p> <p>When digoxin or rosuvastatin was coadministered with IDELA 150 mg BID, digoxin and rosuvastatin systemic exposures were not affected compared to those observed following their respective administration alone.</p>
	Food Effects	<p>IDELA C_{max} was not different under fed or fasted conditions. IDELA AUC_{inf} was ~36% higher with a high-fat meal relative to fasted condition.</p>
Expected High Clinical Exposure Scenario	<p>Coadministration of IDELA with multiple doses of a highly potent CYP3A4 inhibitor, ketoconazole, resulted in an increase in IDELA C_{max} and AUC_{inf} of 26% and 79%, respectively, indicating that IDELA is not a sensitive substrate of CYP3A4. This is consistent with the metabolic pathway: IDELA was primarily metabolized by aldehyde oxidase and to a lesser extent by CYP3A and by UGT1A4. Clinically relevant drug-drug interactions are not typically associated with aldehyde oxidase, a high capacity pathway. Based on the overall metabolic profile, the less than dose-proportional increases in IDELA exposures and the modestly higher exposures with food, the suprathreshold 400-mg single dose of IDELA provides IDELA/GS-563117 exposures that cover the unlikely event of additional and/or unexpected drug interactions or overdose.</p>	

a: Information represents data from completed clinical pharmacology studies and population PK analyses

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

/s/

MOH JEE NG
01/03/2014

QIANYU DANG
01/03/2014

HONGSHAN LI
01/03/2014

KEVIN M KRUDYS
01/03/2014

DEVI KOZELI on behalf of MONICA L FISZMAN
01/03/2014

NORMAN L STOCKBRIDGE
01/03/2014

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 205858 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: Zydelig Established/Proper Name: Idelalisib Dosage Form: Tablet Strengths: 100 mg and 150 mg		
Applicant: Gilead Sciences, Inc. Agent for Applicant (if applicable):		
Date of Application: 9/11/2013 Date of Receipt: 9/11/2013 Date clock started after UN:		
PDUFA Goal Date: 9/11/2014		Action Goal Date (if different):
Filing Date: 11/10/2013		Date of Filing Meeting: 10/18/2013
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Treatment of patients with refractory indolent non-Hodgkin lymphoma (iNHL) ;		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation- <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): 101254				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, explain in comment column.</i>				
<i>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</i>	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1619"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>																		

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: 5 <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index: Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Orphan Designation for all subtypes of iNHL post original submission

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<i>reviewed by PeRC prior to approval of the application/supplement.</i>				
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Full Waiver Request submitted for iNHL; received Orphan designation for iNHL subtypes after submission.
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Full Waiver Request submitted for iNHL; received Orphan designation for iNHL subtypes after submission.
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Full Waiver Request submitted for iNHL; received Orphan designation for iNHL subtypes after submission.
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to PLT? (<i>send WORD version if available</i>)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent: QT/IRT consult Pending</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	QT/IRT
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 7/1/2013 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		July 1, 2013
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 18, 2013; Supplemental meeting on November 7, 2013

BLA/NDA/Supp #: NDA 205858

PROPRIETARY NAME: Zydelig (conditional approval granted)

ESTABLISHED/PROPER NAME: Idelalisib

DOSAGE FORM/STRENGTH: 100 mg and 150 mg Tablets

APPLICANT: Gilead Sciences, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S):

- Treatment of refractory indolent non-Hodgkin lymphoma (iNHL)

BACKGROUND: IDELA is a potent competitive inhibitor of adenosine triphosphate (ATP) binding to the catalytic domain of the phosphatidylinositol 3-kinases (PI3K) p110δ. (b) (4) is being developed for the treatment of 4 mature B-cell neoplasms: follicular lymphoma (FL), small lymphocytic lymphoma (SLL), (b) (4)

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Mara Miller	Y
	CPMS/TL:	Ebla Ali Ibrahim and Amy Baird	Y/N
Cross-Discipline Team Leader (CDTL)	R. Angelo de Claro		Y
Clinical	Reviewer:	Barry Miller Donna Przepiorka	Y Y
	TL:	R. Angelo de Claro	Y
Clinical Pharmacology	Reviewer:	Stacy Shord	Y
	TL:	Julie Bullock	Y
Biostatistics	Reviewer:	Kyung Yul Lee	Y

Discipline/Organization	Names		Present at filing meeting? (Y or N)
	TL:	Lie Nei	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Natalie Simpson Ramadevi Gudi	Y
	TL:	Haleh Saber	Y
Product Quality (CMC)	Reviewer:	Li Shan Hsieh	Y
	TL:	Janice Brown	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Jessica Cole	Y
	TL:	Barry Riley	N
CMC Labeling Review	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:	Vipul Dholakia	N
	TL:		
OSE/DMEPA	Reviewer:	Tingting Gao	Y
	TL:	Yelena Maslov	Y
OSE/DRISK	Reviewer:	Namoi Redd	Y
	TL:	Cynthia LaCivita	Y
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:	N/A	

Bioresearch Monitoring (OSI)	Reviewer:	Anthony Orenca	N
	TL:	Janice Pohlman	N
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Pharmacometrics	DJ Maranthe Nitin Mehotra		Y
Biopharmaceutics	Sandra Suarez Angelica Dorantes		Y
OSE/DPV	Lynda McCulley Tracy Salaam		Y

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p> 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

If no, explain:	
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <ul style="list-style-type: none"> ○ Comments: <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: <i>the application did not raise significant safety or efficacy issues; the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i>
<ul style="list-style-type: none"> • Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

Comments:	<input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<u>Environmental Assessment</u> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Quality Microbiology (for sterile products)</u> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> • Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? • If so, were the late submission components all submitted within 30 days? 	<input type="checkbox"/> N/A <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • What late submission components, if any, arrived after 30 days? 	<p>Data for relapsed chronic lymphocytic leukemia (CLL) as agreed to by DHP/OHOP management.</p>
<ul style="list-style-type: none"> • Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Richard Pazdur, M.D</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): mid-cycle January 15, 2013</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter

<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

MARA B MILLER
11/08/2013

AMY C BAIRD
11/08/2013

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 205858

Application Type: New NDA

Name of Drug: Idelalisib

Applicant: Gilead Sciences, Inc

Submission Date: September 11, 2013; November 1, 2013

Receipt Date: September 11, 2013; November 4, 2013

1.0 Regulatory History and Applicant's Main Proposals

This application proposes approval of the new molecular entity, Idelalisib - a kinase inhibitor - for the treatment of refractory indolent non-Hodgkin lymphoma and for the treatment of relapsed chronic lymphocytic leukemia (CLL).

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI included in the submission dated 9/11/2013. For a list of these deficiencies see the Appendix.

In addition, the following labeling issues were identified in this PI:

1. **Highlights/Adverse Reactions:** Avoid the term (b) (4) Only "adverse reactions" as defined in 21 CFR 201.57(a)(11) are included in the highlights.
2. **Full Prescribing Information: Section 6 - Adverse Reactions:** Use the term "adverse reactions" rather than the terms (b) (4) and (b) (4). Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in the labeling.
3. **Full Prescribing Information: Section 7 - Drug Interactions:** Use numbered subsection headings to organize the information (7.1, 7.2).
4. **Full Prescribing Information: Section 17 - Patient Counseling Information:** Numbered subsections are not recommended because they may be redundant with subsection headings elsewhere in the label. Organize information by subsection headings or bulleted items.
5. **Full Prescribing Information: Section 17 - Patient Counseling Information:** Revise the first statement to read "Advise the patient to read the FDA-approved patient labeling (Patient Information).

RPM PLR Format Review of the Prescribing Information

All SRPI format deficiencies of the PI and other labeling issues identified above were conveyed to the applicant in an information request dated 10/13/2013. The applicant resubmitted the PI with the submission dated 11/1/2013. This PI dated 11/1/2013 will be used for further labeling review.

4.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- NO** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment: *Headings are not bolded*

- YES** 4. White space must be present before each major heading in HL.

Comment:

- YES** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

Selected Requirements of Prescribing Information (SRPI)

YES

6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state "None.")
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: "**HIGHLIGHTS OF PRESCRIBING INFORMATION**".

Comment:

Highlights Limitation Statement

YES

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**"

Comment:

Product Title

NO

10. Product title in HL must be **bolded**.

Comment:

Initial U.S. Approval

NO

11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment: *Initial US Approval is not immediately beneath the product title, nor is it bolded.*

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

- N/A** 12. All text must be **bolded**.
Comment:
- N/A** 13. Must have a centered heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).
Comment:
- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.
Comment:
- N/A** 15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)
Comment:
- N/A** 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).
Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
Comment:
- N/A** 18. Must be listed in the same order in HL as they appear in FPI.
Comment:
- N/A** 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.
Comment:
- N/A** 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).
Comment:

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”
Comment:

Dosage Forms and Strengths

Selected Requirements of Prescribing Information (SRPI)

- YES** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- YES** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- NO** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment: *Not bolded.*

Revision Date

- NO** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment: *Not bolded.*

Contents: Table of Contents (TOC)

GENERAL FORMAT

- YES** 28. A horizontal line must separate TOC from the FPI.

Comment:

- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”.

Comment:

Selected Requirements of Prescribing Information (SRPI)

- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
Comment:
- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
Comment:
- YES** 32. All section headings must be **bolded** and in UPPER CASE.
Comment:
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “**FULL PRESCRIBING INFORMATION: CONTENTS**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Comment:
-

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: “**FULL PRESCRIBING INFORMATION**”.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use

Selected Requirements of Prescribing Information (SRPI)

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

- N/A** 43. Must have a heading in UPPER-CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- YES** 45. If no Contraindications are known, this section must state “None”.

Selected Requirements of Prescribing Information (SRPI)

Comment:

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- YES** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:
- “See FDA-approved patient labeling (Medication Guide)”
 - “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information)”
 - “See FDA-approved patient labeling (Instructions for Use)”
 - “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment:

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/s/

MARA B MILLER
11/05/2013

AMY C BAIRD
11/05/2013

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: October 30, 2013

Reviewer: Tingting Gao, PharmD
Division of Medication Error Prevention and Analysis

Team Leader: Yelena Maslov, PharmD
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Zydelig (Idelalisib) Tablets, 100 mg and 150 mg

Application Type/Number: NDA 205858

Applicant/sponsor: Gilead Sciences, Inc.

OSE RCM #: 2013-2085

*** This document contains proprietary and confidential information that should not be released to the public.***

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1 INTRODUCTION

This review evaluates the proposed container label, carton and insert labeling for Zydelig (idelalisib), NDA 205858, for areas of vulnerability that could lead to medication errors.

1.1 PRODUCT INFORMATION

The following product information is provided in the September 10, 2013 submission.

- Active Ingredient: idelalisib
- Indication of Use: Treatment of patients with refractory indolent non-Hodgkin lymphoma (NHL)
- Route of Administration: Oral
- Dosage Form: Tablet
- Strength: 100 mg and 150 mg
- Dose and Frequency: Take 150 mg orally twice daily
- How Supplied: 60 count bottles
- Storage: Store below 30°C (86°F)

2 METHODS AND MATERIALS REVIEWED

2.1 LABELS AND LABELING

Using the principles of human factors and Failure Mode and Effects Analysis,¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Drug Container Labels submitted September 10, 2013 (Appendix A)
- Insert Labeling submitted September 10, 2013 (no image)

3 CONCLUSIONS

DMEPA concludes that the proposed container label can be improved to increase the readability and prominence of important information on the label to promote the safe use of the product to mitigate any confusion. Additionally, prescriber information labeling can be improved to clarify information. DMEPA provides the following recommendations in Section 4.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

4 RECOMMENDATIONS

4.1 COMMENTS TO THE DIVISION

DMEPA provides the following comments for consideration by the review Division prior to the approval of this NDA:

- A. Highlights of Prescribing Information and Dosage & Administration, Full Prescribing Information
 - 1. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations appear throughout the package insert. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise the those abbreviations, symbols, and dose designations as follows:
 - i. Revise the ">" and "≤" symbols to read "greater than" and "less than or equal to".
 - 2. We note the use of the abbreviations (e.g. ALT, AST, ULN) throughout the package insert. We recommend the Applicant to provide the intended meaning of those abbreviations prior to their use to prevent misinterpretation and confusion (e.g. Alanine Aminotransferase, Aspartate Aminotransferase, Upper Limit of Normal).

4.2 COMMENTS TO THE APPLICANT

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

- A. Drug container label for 100 mg and 150 mg bottles:
 - a. Both strengths use (b) (4) color for the boxes around the strength and the bar at the bottom of the container label. This can contribute to the selection of the wrong strength errors. Thus, please provide sufficient differentiation between the two strengths of the product by using different colors to highlight the strengths and to highlight the bar at the bottom of the label.
 - b. Bold the statement "Dispense only in original container".
 - c. Debold the statement "Rx Only".
 - d. Re-orientate the barcode to a vertical position to improve scannability of the barcode. Barcodes placed in a horizontal position may not scan due to bottle curvature if the bottle is round in shape.
 - e. Add the statement "Keep this and all medications out of the reach of children" on the side panel.

If you have further questions or need clarifications, please contact Sonny Saini, project manager, at 301-796-0532.

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

TINGTING N GAO
10/30/2013

YELENA L MASLOV
10/31/2013