CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210259Orig1s000

OTHER REVIEW(S)

PMR/PMC DEVELOPMENT TEMPLATE

For 506B Reportable[1] PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the *instructions* (see Appendix A) and by referring to ***MAPP 6010.9***, "Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements."

Note: Do ***not*** use this template for CMC PMCs. Instead, use the CMC PMC Development Template.[1]

SECTION A: Administrative Information

NDA/BLA/Supplement #	**NDA 210259**
PMR/PMC Set (####-#)	**PMR** 3291-1
Product Name:	**Calquence™ (acalabrutinib) capsules, 100 mg**
Applicant Name:	**Acerta Pharma B.V**
ODE/Division:	**OHOP/DHP**

SECTION B: PMR/PMC Information

1. PMR/PMC Description

Submit the complete final report and datasets demonstrating clinical efficacy and safety from a randomized, double-blind, placebo-controlled, clinical trial of Calquence in combination with standard immunochemotherapy versus immunochemotherapy alone in patients with mantle cell lymphoma.

2. PMR/PMC Schedule Milestones[2, 3]

Final Protocol Submitted:	09/2016
Enrollment Completed Submission:	12/2020
Trial Completion:	10/2023
Final Report Submission:	04/2024

[1] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

[2] *Final protocol*, *study/trial completion*, and *final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

[3] Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

1. Describe the particular review issue and the goal of the study[4] or clinical trial[5] in the text box below.

The clinical trial ACE-L-Y-004 is a single arm study of Calquence® (acalabrutinib) monotherapy in patients with mantle cell lumphoma. Overall response rate (ORR) defined as CR or PR per nvestigator assessed Lugano response criteria was the primary endpoint of the trial and the basis for accelerated approval. In this trial the ORR was 80.6% in patients with mantle cell lymphoma who had received between 1 and 5 prior therapies The median duration of response was not reached with at least 12 months of follow-up for all responders. Overall response rate is a surrogate endpoint likely to predict clinical benefit and, with documentation of duration of resposne, has been accepted by the Agency as an endpoint for accelerated approval for mantle cell lymphoma and other non-Hodgin lymphomas. This PMR seeks to verify efficacy of Calquence® as measured by progression-free survival (PFS) and overall survival (OS) in a randomiazed controlled clinical trial, ie (Study ACE-LY-308).

2. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☒ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ PREA PMR: Meets PREA postmarketing pediatric study *requirements* ***[Skip to Q.5]***
- ☐ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial ***[Go to Q.3]***
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. ***[Go to Q.3]***

3. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: *[Select all that apply]*

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☐ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

---

[4] A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

[5] A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

[If you selected "other reason," expand on the reason(s) why it is appropriate to conduct the study/trial postapproval and why the issue does not need to be addressed *prior to* approval.]

4. **For FDAAA PMRs only** ***[for PMCs skip to Q.5]*****.** ***Complete this entire section***

a. The purpose of the study/clinical trial is to: ***[Select one, then go to Q.4.b]***

- ☐ Assess a known serious risk related to the use of the drug
- ☐ Assess a signal 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

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS[6] and Sentinel's postmarket ARIA[7] system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

[6] FDA Adverse Event Reporting System (FAERS)

[7] Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: ***[Select all that apply then go to Q.4.e]***

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

[If you selected "other," expand on the reason(s) why ARIA is not sufficient.]

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?** ***[Select either "Yes" or "No" and provide the appropriate responses.]***

☐ **Yes**, a study is sufficient ***[Explain your answer in the textbox and then go to Q.5]***

[Explain why a study is sufficient]

☐ **No**, a study is not sufficient ***[Select all explanations that apply then go to Q.4.f]***

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

[If you selected "other," expand on the reason(s) why a study is not sufficient.]

f. ☐ **Because a study is not sufficient, a clinical trial is required.** ***[Go to Q.5]***

5. **<u>For all PMRs and PMCs</u>: What type of study or clinical trial is needed to achieve the goal described in Q1 *<u>or</u>* Q4.a above?**
[Select ONE OPTION only under <u>either</u> "Type of Study" <u>or</u> "Type of clinical Trial"]

TYPE OF STUDY
☐ Drug interaction or bioavailability studies (nonclinical only)
☐ Epidemiologic (observational) study related to safe drug use
☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Immunogenicity study (nonclinical)
☐ Meta-analysis or pooled analysis of previous observational studies
☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
☐ Pharmacogenetic or pharmacogenomic study
☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
☐ Quality CMC study (e.g., manufacturing, studies on impurities)
☐ Quality stability study
☐ Registry-based observational study
☐ Other (describe) _____

TYPE OF CLINICAL TRIAL
☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
☐ Dose-response clinical trial
☐ Dosing trial (e.g., alternative dosing schedule)
☐ Drug interaction or bioavailability clinical trial (clinical only)
☐ Immunogenicity trial (clinical)
☐ Meta-analysis or pooled analysis of previous clinical trials
☐ Pharmacogenetic or pharmacogenomic clinical trial
☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
☒ Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
☐ Safety outcomes trial (SOT)**
☐ Thorough Q-T clinical trial
☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies." However, for the purposes of this template, PREA investigations are categorized according to the established definitions of "studies" and "trials" (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

1. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

☐ Yes

☒ No

2. This study or clinical trial focuses on the following special population(s) or circumstance(s):
[Select all that apply]

☐ *For non-PREA pediatric studies/trials only*: Pediatric population

☐ Geriatric population

☐ Lactating/nursing mothers

☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)

☐ Orphan or rare disease population

☐ Pregnant women

☐ Racial/ethnic population

☒ Not applicable

3. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 "core" milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements[8]

1. **The PMR/PMC is clear, feasible, and appropriate[9] because:** ***[Select all that apply]***

   ☒ The study/clinical trial meets criteria for a PMR or a PMC.

   ☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.

   ☒ The applicant has adequately justified the choice of milestone dates.

   ☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

2. ☒ (***If the PMR/PMC is a randomized controlled clinical trial***) **The following ethical considerations were made with regard to:**

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

3. ☒ **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**.

Insert electronic signature (usually the Deputy Director for Safety)

[8] This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

[9] See POLICY section of CDER MAPP 6010.9.

PMR/PMC DEVELOPMENT TEMPLATE

For 506B Reportable[10] PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the *instructions* (see Appendix A) and by referring to ***MAPP 6010.9***, "Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements."

Note: Do ***not*** use this template for CMC PMCs. Instead, use the CMC PMC Development Template.[1]

SECTION A: Administrative Information

NDA/BLA/Supplement #	**NDA 210259**
PMR/PMC Set (####-#)	**PMR** 2
Product Name:	Calquence™ (acalabrutinib) capsule, 100 mg
Applicant Name:	Acerta Pharma B.V.
ODE/Division:	**OHOP/DHP**

SECTION B: PMR/PMC Information

3. PMR/PMC Description

Conduct a study to characterize the long-term safety of Calquence monotherapy. Submit interim and complete final reports showing long-term safety with a minimum of 24 months of follow-up from study ACE-LY-004 in patient with mantle cell lymphoma.

4. PMR/PMC Schedule Milestones[11, 12]

Trial Completion:	02/2018
Final Report Submission:	12/2018

[10] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

[11] *Final protocol*, *study/trial completion*, and *final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

[12] Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

6. Describe the particular review issue and the goal of the study[13] or clinical trial[14] in the text box below.

In patients treated with Calquence from clinical trial ACE-LY-004, the Applicant reported a median duration of exposure of 13.8 months of Calquence monotherapy. Since it is anticipated that patients may take Calquence for an indefinite period of time, the exposure to Calquence in the pivotal trial is not sufficient to clearly define the type and incidence of adverse events with prolonged therapy. Suspected and known risks include hemorrhage, infection, cytopenias, second primary malignancies, atrial fibrillation, and tumor lysis syndrome. There is a need to characterize the safety of Calquence with long-term use. The goal of this PMR is to characterize the long-term safety of Calquence monotherapy in patients with marginal zone lymphoma.

7. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ PREA PMR: Meets PREA postmarketing pediatric study *requirements* ***[Skip to Q.5]***
- ☒ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial ***[Go to Q.3]***
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. ***[Go to Q.3]***

8. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: ***[Select all that apply]***

- ☒ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☒ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☒ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☐ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☒ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

[13] A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

[14] A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

9. **For FDAAA PMRs only** ***[for PMCs skip to Q.5]. Complete this entire section***

a. The purpose of the study/clinical trial is to: ***[Select one, then go to Q.4.b]***

- ☐ Assess a known serious risk related to the use of the drug
- ☒ Assess a signal 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

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS[15] and Sentinel's postmarket ARIA[16] system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

[15] FDA Adverse Event Reporting System (FAERS)

[16] Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☒ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☒ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: *[Select all that apply then go to Q.4.e]*

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☒ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☒ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?** *[Select either "Yes" or "No" and provide the appropriate responses.]*

☐ **Yes**, a study is sufficient *[Explain your answer in the textbox and then go to Q.5]*

☒ **No**, a study is not sufficient *[Select all explanations that apply then go to Q.4.f]*

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☒ Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☒ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

[If you selected "other," expand on the reason(s) why a study is not sufficient.]

f. ☒ **Because a study is not sufficient, a clinical trial is required.** *[Go to Q.5]*

10. **<u>For all PMRs and PMCs</u>: What type of study or clinical trial is needed to achieve the goal described in Q1 *<u>or</u>* Q4.a above?**
*[Select ONE OPTION only under *<u>either</u>* "Type of Study" *<u>or</u>* "Type of clinical Trial"]*

TYPE OF STUDY
☐ Drug interaction or bioavailability studies (nonclinical only)
☐ Epidemiologic (observational) study related to safe drug use
☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Immunogenicity study (nonclinical)
☐ Meta-analysis or pooled analysis of previous observational studies
☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
☐ Pharmacogenetic or pharmacogenomic study
☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
☐ Quality CMC study (e.g., manufacturing, studies on impurities)
☐ Quality stability study
☐ Registry-based observational study
☐ Other (describe) _____

TYPE OF CLINICAL TRIAL
☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
☐ Dose-response clinical trial
☐ Dosing trial (e.g., alternative dosing schedule)
☐ Drug interaction or bioavailability clinical trial (clinical only)
☐ Immunogenicity trial (clinical)
☐ Meta-analysis or pooled analysis of previous clinical trials
☐ Pharmacogenetic or pharmacogenomic clinical trial
☐ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
☐ Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
☒ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
☐ Safety outcomes trial (SOT)**
☐ Thorough Q-T clinical trial
☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies." However, for the purposes of this template, PREA investigations are categorized according to the established definitions of "studies" and "trials" (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

4. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

☐ Yes
☒ No

5. This study or clinical trial focuses on the following special population(s) or circumstance(s):
[Select all that apply]

☐ *For non-PREA pediatric studies/trials only*: Pediatric population
☐ Geriatric population
☐ Lactating/nursing mothers
☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)
☐ Orphan or rare disease population
☐ Pregnant women
☐ Racial/ethnic population
☒ Not applicable

6. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 "core" milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements[17]

4. **The PMR/PMC is clear, feasible, and appropriate[18] because:** ***[Select all that apply]***

☒ The study/clinical trial meets criteria for a PMR or a PMC.

☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.

☒ The applicant has adequately justified the choice of milestone dates.

☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

5. ☐ (***If the PMR/PMC is a randomized controlled clinical trial***) **The following ethical considerations were made with regard to:**

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

6. ☒ **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**.

Insert electronic signature (usually the Deputy Director for Safety)

[17] This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

[18] See POLICY section of CDER MAPP 6010.9.

PMR/PMC DEVELOPMENT TEMPLATE

For 506B Reportable[19] PMRs and PMCs only

This form describes and provides the rationale for postmarketing requirements/commitments (PMRs/PMCs) subject to reporting requirements under section 506B of the FDCA.

Complete this form using the *instructions* (see Appendix A) and by referring to ***MAPP 6010.9***, "Procedures and Responsibilities for Developing Postmarketing Commitments and Requirements."

Note: Do ***not*** use this template for CMC PMCs. Instead, use the CMC PMC Development Template.[1]

SECTION A: Administrative Information

NDA/BLA/Supplement #	**NDA 210259**
PMR/PMC Set (####-#)	**PMR** 3
Product Name:	Calquence™ (acalabrutinib) capsule, 100 mg
Applicant Name:	Acerta Pharma B.V.
ODE/Division:	**OHOP/DHP**

SECTION B: PMR/PMC Information

5. PMR/PMC Description

Conduct a clinical pharmacokinetic trial to determine an appropriate safe dose of acalabrutinib in patients with severe hepatic impairment. This trial should be designed and conducted in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling".

6. PMR/PMC Schedule Milestones[20, 21]

Final Protocol Submission:	06/2018
Trial Completion:	1/2020
Final Report Submission:	07/2020

[19] 506B "reportable" includes all studies/trials an applicant has agreed upon or is required to conduct related to clinical safety, clinical efficacy, clinical pharmacology, or nonclinical toxicology (21 CFR 314.81(b)(2)(vii) and 21 CFR 601.70(a)). All PMRs are considered 506 "reportable." A separate development template is used for 506 B non-reportable (e.g., chemistry, manufacturing, and controls (CMC)) PMCs, which is located in the CST.

[20] *Final protocol*, *study/trial completion*, and *final report* submissions are required milestones. *Draft protocol submissions* and *interim* milestones are optional. EXCEPTION: PMRs/PMCs for medical countermeasures may have only draft/final protocol submission dates and no other milestones, since the study/trial will only be initiated in the event of an emergency. Interim milestones may include interim report milestones for studies/trials that may be of long duration. May include interim subject accrual milestone (e.g., for accelerated approval PMRs). Other milestones should be justified in Section D, question 3.

[21] Dates should be numerical (e.g., 05/2016). PREA PMR date format may be MM/DD/YYYY if a day is specified.

SECTION C: PMR/PMC Rationale

11. Describe the particular review issue and the goal of the study[22] or clinical trial[23] in the text box below.

identify an unexpected serious risk of excessive drug toxicity from impaired hepatic function on the pharmacokinetics of acalabrutinib.

12. Explain why this issue can be evaluated post-approval and does not need to be addressed prior to approval. (Select one explanation below.)

- ☐ Subpart I or H (animal efficacy rule) PMR: Approved under Subpart I or H (animal efficacy rule) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ Subpart H or E (accelerated approval) PMR: Approved under Subpart H or E (accelerated approval) authorities; postmarketing study/trial required to verify and describe clinical benefit ***[Skip to Q.5]***
- ☐ PREA PMR: Meets PREA postmarketing pediatric study *requirements* ***[Skip to Q.5]***
- ☒ FDAAA PMR (safety): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's safety profile. Because the investigation will evaluate a serious risk, it meets FDAAA requirements for a postmarketing safety study or trial ***[Go to Q.3]***
- ☐ PMC (506B reportable): Benefit/risk profile of the drug appears favorable; however, there are uncertainties about aspects of the drug's efficacy profile or other issues. The purpose of the investigation does not meet requirements under Subpart I/H , H/E, PREA, or FDAAA to be a PMR, and therefore the investigation is a PMC. ***[Go to Q.3]***

13. For FDAAA PMRs and 506B PMCs only

The study or trial can be conducted post-approval because: ***[Select all that apply]***

- ☐ Longer-term data needed to further characterize the safety/efficacy of the drug
- ☐ Based on the purpose and/or design, it is only feasible to conduct the study/trial post-approval
- ☐ Prior clinical experience (e.g., with other drugs in the class) indicates adequate safety or efficacy data to support approval, but some uncertainties about safety or efficacy remain and should be further characterized
- ☒ Only a small subpopulation is affected (e.g., patients with severe renal impairment) and effects of the drug in the subpopulation can be further evaluated after approval
- ☒ Study/trial is to further explore a theoretical concern that does not impact the approval determination
- ☐ Other reason (describe in text box below)

[If you selected "other reason," expand on the reason(s) why it is appropriate to conduct the study/trial postapproval and why the issue does not need to be addressed *prior to* approval.]

[22] A "study" is an investigation that is not a clinical trial, such as an observational (epidemiologic) study, animal study, or laboratory experiment.

[23] A "clinical trial" is any prospective investigation in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects. Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies."

14. **<u>For FDAAA PMRs only</u>** ***[for PMCs skip to Q.5]. Complete this entire section***

a. The purpose of the study/clinical trial is to: ***[Select one, then go to Q.4.b]***

- ☐ Assess a <u>known serious risk</u> related to the use of the drug
- ☐ Assess a <u>signal of serious risk</u> related to the use of the drug
- ☒ Identify an <u>unexpected serious risk</u> when available data indicate the potential for a serious risk

Complete Q4.b if the necessary data can only be obtained through a particular type of nonclinical study or clinical pharmacology trial. Otherwise complete Q4.c and Q4.d.

b. FAERS[24] and Sentinel's postmarket ARIA[25] system are not sufficient for the purposes described in Q1. and Q4.a because the safety issue involves:

[Select all that apply then to skip to Q.5. If none apply, answer both Q4.c and Q4.d]

- ☐ A serious risk of genotoxicity, carcinogenicity, or reproductive toxicity, and these signals are initially best assessed through in vitro or animal studies.
- ☐ A potential drug interaction resulting in lower/higher drug exposure and resultant serious drug risks, and accurate assessment of an interaction is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☒ The potential for lower/higher drug exposure and resultant serious drug risks in patients with hepatic or renal impairment, or other metabolic abnormalities, and accurate assessment is feasible only through in vitro mechanistic studies or clinical pharmacokinetic and pharmacodynamics trials.
- ☐ An immunologic concern for which accurate assessment requires in vitro development or validation of specific assays.

[24] FDA Adverse Event Reporting System (FAERS)

[25] Active Risk Identification and Analysis (ARIA)

Complete Q4.c when FAERS cannot provide the necessary data and Q4.b does not apply

c. FAERS data cannot be used to fully characterize the serious risk of interest because:

[Select all that apply then go to Q.4.d]

- ☐ Assessment of the serious risk necessitates calculation of the rate of occurrence (e.g., incidence or odds ratio) of the adverse event(s), and FAERS data cannot be used for such a calculation.
- ☐ The serious risk of concern has a delayed time to onset, or delayed time to detection after exposure (e.g., cancer), and FAERS data are more useful for detecting events that are closely linked in time to initiation of drug therapy.
- ☐ The serious risk of concern occurs commonly in the population (e.g., myocardial infarction) and FAERS data are more useful in detecting rare serious adverse events for which the background rates are low.
- ☐ Other

[If you selected "other," expand on the reason(s) why FAERS is not sufficient.]

Complete Q4.d when the ARIA system cannot provide the necessary data and Q4.b does not apply.

d. The currently available data within the ARIA system cannot be used to fully characterize the serious risk of interest because: ***[Select all that apply then go to Q.4.e]***

- ☐ Cannot identify exposure to the drug(s) of interest in the database.
- ☐ Serious risk (adverse event) of concern cannot be identified in the database.
- ☐ The population(s) of interest cannot be identified in the database.
- ☐ Long-term follow-up information required to assess the serious risk are not available in the database.
- ☐ Important confounders or covariates are not available or well represented in the database.
- ☐ The database does not contain an adequate number of exposed patients to provide sufficient statistical power to analyze the association between the drug and the serious risk of concern.
- ☐ The purpose of the evaluation is to rule out a modest relative risk, and observational studies, such as an ARIA analysis, are not well suited for such use.
- ☐ Other

e. **If FAERS and the ARIA system are not sufficient for the purpose in Q1. and Q4.a, is a study sufficient?** ***[Select either "Yes" or "No" and provide the appropriate responses.]***

☐ **Yes**, a study is sufficient ***[Explain your answer in the textbox and then go to Q.5]***

[Explain why a study is sufficient]

☐ **No**, a study is not sufficient ***[Select all explanations that apply then go to Q.4.f]***

- ☐ Need to minimize bias and/or confounding via randomization
- ☐ Need for placebo control
- ☐ Need to capture detailed information about covariates or confounders that are either not routinely collected during the ususal course of medical practice, or are not collected at the frequency needed for assessment of the safety issue (e.g. hourly blood glucose measures, etc.).
- ☐ Need pre-specified and prospective active data collection of the outcome/endpoint of interest
- ☐ Other

[If you selected "other," expand on the reason(s) why a study is not sufficient.]

f. ☐ **Because a study is not sufficient, a clinical trial is required.** ***[Go to Q.5]***

15. **<u>For all PMRs and PMCs</u>: What type of study or clinical trial is needed to achieve the goal described in Q1 *<u>or</u>* Q4.a above?**
[Select ONE OPTION only under <u>either</u> "Type of Study" <u>or</u> "Type of clinical Trial"]

TYPE OF STUDY
☐ Drug interaction or bioavailability studies (nonclinical only)
☐ Epidemiologic (observational) study related to safe drug use
☐ Epidemiologic (observational) study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☐ Immunogenicity study (nonclinical)
☐ Meta-analysis or pooled analysis of previous observational studies
☐ Nonclinical (animal) study (e.g., genotoxicity, carcinogenicity, reproductive toxicology)
☐ Nonclinical (in vitro) study (laboratory/microbiology resistance, receptor affinity)
☐ Pharmacogenetic or pharmacogenomic study
☐ Pharmacokinetic (PK) and/or pharmacodynamics (PD) study (nonclinical only)
☐ Quality CMC study (e.g., manufacturing, studies on impurities)
☐ Quality stability study
☐ Registry-based observational study
☐ Other (describe) _____

TYPE OF CLINICAL TRIAL
☐ Combined PK/PD, safety and/or efficacy trial (*PREA* PMRs only*)
☐ Dose-response clinical trial
☐ Dosing trial (e.g., alternative dosing schedule)
☐ Drug interaction or bioavailability clinical trial (clinical only)
☐ Immunogenicity trial (clinical)
☐ Meta-analysis or pooled analysis of previous clinical trials
☐ Pharmacogenetic or pharmacogenomic clinical trial
☒ Pharmacokinetic (PK) and/or pharmacodynamic (PD) clinical trial
☐ Primary efficacy clinical trial (i.e, with a primary efficacy endpoint; to further define efficacy; may include secondary safety endpoints)
☐ Primary safety clinical trial (e.g., to evaluate the long-term safety of a drug; to evaluate drug toxicity in a subpopulation; may include secondary efficacy endpoints) – *excludes SOT*
☐ Safety outcomes trial (SOT)**
☐ Thorough Q-T clinical trial
☐ Other (describe) _____

* Note that under PREA, clinical trials involving pediatric patients are specifically referred to as "studies." However, for the purposes of this template, PREA investigations are categorized according to the established definitions of "studies" and "trials" (see Footnotes 3 and 4).

** A safety outcomes trial (SOT) is defined as a large, prospective, randomized, controlled trial that is specifically designed and adequately powered to test a safety hypothesis using a clinical outcome, generally irreversible morbidity or mortality, as the primary trial endpoint. A cardiovascular outcomes trial (CVOT) is an example of an SOT.

SECTION D: PMR/PMC Additional Information

7. This PMR/PMC applies to other drugs or applications (e.g. drugs in a therapeutic class; different formulations of the same drug).

☐ Yes

☒ No

8. This study or clinical trial focuses on the following special population(s) or circumstance(s):
[Select all that apply]

☐ *For non-PREA pediatric studies/trials only*: Pediatric population

☐ Geriatric population

☐ Lactating/nursing mothers

☐ Medical Countermeasures (e.g. anthrax exposure, bioterrorism)

☐ Orphan or rare disease population

☐ Pregnant women

☐ Racial/ethnic population

☒ Not applicable

9. **(Complete if applicable) Additional comments about the PMR/PMC** (e.g., points or concerns not previously described; explanation for inclusion of milestones other than the 3 "core" milestones or draft protocol submission)

SECTION E: PMR/PMC Development Coordinator Statements[26]

7. **The PMR/PMC is clear, feasible, and appropriate[27] because:** ***[Select all that apply]***

☒ The study/clinical trial meets criteria for a PMR or a PMC.

☒ The objectives of the study/clinical trial are clear from the description of the PMR/PMC.

☒ The applicant has adequately justified the choice of milestone dates.

☒ The applicant has had sufficient time to review the PMR/PMC, ask questions, determine feasibility, and contribute to the development process.

8. ☒ (***If the PMR/PMC is a randomized controlled clinical trial***) **The following ethical considerations were made with regard to:**

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

9. ☒ **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**.

Insert electronic signature (usually the Deputy Director for Safety)

[26] This section is completed by the PMR/PMC Development Coordinator, who is usually the OND division's Deputy Director for Safety (DDS). See DEFINITIONS section of CDER MAPP 6010.9, *Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments*.

[27] See POLICY section of CDER MAPP 6010.9.

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/s/

BARRY W MILLER
10/30/2017

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:	October 20, 2017
To:	Ann Farrell, MD Director **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:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nisha Patel, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	CALQUENCE (aclabrutinib)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 210259
Applicant:	Acerta Pharma B.V.

1 INTRODUCTION

On June 13, 2017, Acerta Pharma B.V. submitted for the Agency's review an original New Drug Application (NDA) 210259 for CALQUENCE (acalabrutinib) capsules. The proposed indication for CALQUENCE (acalabrutinib) capsules is for the treatment of patients with mantel cell lymphoma (MCL) who have received at least one prior therapy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on June 19, 2017, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for CALQUENCE (acalabrutinib) capsules.

2 MATERIAL REVIEWED

- Draft CALQUENCE (acalabrutinib) capsules PPI received on June 13, 2017, and received by DMPP on October 6, 2017.
- Draft CALQUENCE (acalabrutinib) capsules PPI received on June 13, 2017, and received by OPDP on October 6, 2017.
- Draft CALQUENCE (acalabrutinib) capsules Prescribing Information (PI) received on June 13, 2017, revised by the Review Division throughout the review cycle, and received by DMPP on October 6, 2017.
- Draft CALQUENCE (acalabrutinib) capsules PI received on June 13, 2017, revised by the Review Division throughout the review cycle, and received by OPDP on October 6, 2017.

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 PPI, 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 reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

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

- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI 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 PPI 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 PPI.

Please let us know if you have any questions.

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

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/s/

SHARON R MILLS
10/20/2017

LISA M HUBBARD
10/20/2017
For Nisha Patel

LASHAWN M GRIFFITHS
10/20/2017

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

NDA	210259
Generic Name	Acalabrutinib (ACP-196)
Sponsor	Acerta Pharma, BV
Indication	Treatment of patients with mantel cell lymphoma (MCL) who have received at least one prior therapy
Dosage Form	Capsule
Drug Class	Bruton's tyrosine kinase (BTK) inhibitor
Therapeutic Dosing Regimen	100 mg BID
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	MTD has not been reached. 400 mg QD is the highest dose explored to date and no DLTs or drug-related SAEs occurred at this dose level or below in subjects with CLL.
Submission Number and Date	001; 6/13/2017
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 effect of acalabrutinib (ACP-196) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean differences between acalabrutinib (dosed at 100 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 two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 3, indicating that assay sensitivity was established.

In this randomized, double-blind, double dummy, placebo- and positive-controlled, 4-way crossover study, 48 healthy adult subjects received acalabrutinib 100 mg, acalabrutinib 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 Acalabrutinib (100 mg and 400 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	N	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
Acalabrutinib 100 mg	44	0.75	1.7	(-0.3, 3.7)
Acalabrutinib 400 mg	43	0.75	1.7	(-0.3, 3.7)
Moxifloxacin 400 mg*	45	4	13.4	(11.4, 15.4)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 timepoints is 10.7 ms.

The supratherapeutic single dose (400 mg) produces geometric mean C_{max} values of 3.6-fold higher than the C_{max} for the maximum therapeutic single dose (100 mg). No accumulation is expected with multiple dosing with the proposed therapeutic dosing regimen of 100 mg BID. The worst case scenario is DDI with itraconazole (strong CYP3A and P-gp inhibitor) which results in 3.7-fold increase in C_{max} of acalabrutinib. The concentrations with supratherapeutic dose could cover this predicted worst case scenario and at these concentrations there are no detectable prolongations of the QTc interval. The exposure-response relationship between ΔΔQTcF and acalabrutinib concentrations did not show a statistically significant slope.

2 PROPOSED LABEL

The sponsor included following QT-related language in their current proposed label:

(b) (4)

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

12.2 Pharmacodynamics

Cardiac Electrophysiology

The effect of acalabrutinib on the QTc interval was evaluated in a randomized, double-blind, double dummy, placebo- and positive-controlled, 4-way crossover thorough QTc study in 48 healthy adult subjects. Administration of a single dose of acalabrutinib that is 4-fold the maximum recommended single dose did not prolong the QTc interval to any clinically relevant extent.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Acalabrutinib (ACP-196) is a second generation, irreversible small molecule inhibitor of Bruton's tyrosine kinase (BTK) currently under investigation for lymphoid cancers (b) (4)

3.2 MARKET APPROVAL STATUS

Acalabrutinib is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

See Appendix 6.1 for preclinical information.

3.4 PREVIOUS CLINICAL EXPERIENCE

See Appendix 6.1 for clinical cardiac safety experience.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of clinical pharmacology of acalabrutinib (ACP-196).

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 118,717. The sponsor submitted the study report ACE-HV-005 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

Randomized, Double-Blind, Double-Dummy, Placebo- and Positive Controlled, 4-Way Crossover Study to Assess the Effect of Single-Dose ACP-196 on the QTc Interval in Healthy Adult Subjects

4.2.1 Protocol Number

ACE-HV-005

4.2.2 Study Dates

First subject dosed: 01 April 2016

Last subject completed: 09 May 2016

4.2.3 Objectives

Primary: To evaluate effects of single therapeutic and supratherapeutic oral doses of ACP-196 on QT corrected for heart rate using Fridericia's correction (QTcF).

Secondary:

1. To demonstrate sensitivity of this QTc assay using moxifloxacin as a positive control.
2. To evaluate the safety and tolerability of single therapeutic and supratherapeutic oral doses of ACP-196.
3. To describe changes in other electrocardiogram (ECG) parameters including PR and RR intervals, QRS duration, T wave morphology, presence of U waves, and outlier assessment.

4. To explore the relationship between the pharmacokinetics (PK) of ACP-196 and corresponding QTc intervals.

4.2.4 Study Description

4.2.4.1 Design

This is a single-dose, randomized, double-blind, double dummy, placebo- and positive-controlled, 4-period, balanced crossover study under fasting conditions.

4.2.4.2 Controls

The Applicant used both placebo and positive (moxifloxacin) controls.

4.2.4.3 Blinding

The applicant used double dummy administered test drug and moxifloxacin.

4.2.5 Treatment Regimen

4.2.5.1 Treatment Arms

Subjects were randomized to 1 of 4 treatment sequences selected from a Latin Square: ABCD, BDAC, CADB, or DCBA. The treatments were as follows:

Treatment A: 100 mg ACP-196 (1 x 100 mg capsule), ACP-196 matching placebo (3 × 100 mg matching placebo capsules), and moxifloxacin matching placebo (1 x 400 mg matching placebo tablet) at Hour 0 on Day 1 after an overnight fast.

Treatment B: 400 mg ACP-196 (4 × 100 mg capsules) and moxifloxacin matching placebo (1 × 400 mg matching placebo tablet) at Hour 0 on Day 1 after an overnight fast.

Treatment C: 400 mg moxifloxacin (1 × 400 mg tablet) and ACP-196 matching placebo (4 × 100 mg matching placebo capsules) at Hour 0 on Day 1 after an overnight fast.

Treatment D: ACP-196 matching placebo (4 × 100 mg matching placebo capsules) and moxifloxacin matching placebo (1 × 400 mg matching placebo tablet) at Hour 0 on Day 1 after an overnight fast.

Total duration of the study was 14 days after the last study drug (or placebo) administration and last check for AE. The washout period was 7 days.

4.2.5.2 Sponsor's Justification for Doses

A 100-mg single therapeutic oral dose of ACP-196 was selected for this study since this dose has been used in previous patient and healthy subject studies and was well tolerated with no safety concerns. The 100-mg twice daily (BID) dose has produced objective responses in subjects with CLL and represents a clinically therapeutic dose. No accumulation of ACP-196 is apparent after 8 days of dosing; therefore, a single-dose design was proposed for this study.

A 400 mg single supratherapeutic oral dose of ACP-196 has been selected for this study. The PK parameters of ACP-196 have been characterized in CLL patients over a dose range of 100, 175, 250, and 400 mg daily for a period of 8 days. The steady-state $AUC_{0\text{-inf}}$ on Day 8 was 2310 and 1870 ng*h/mL for ACP-196 doses of 250 and 400 mg, respectively. In a similar manner, the plasma C_{max} values were 1350 and 902 ng/mL for ACP-196 doses of 250 and 400 mg, respectively. Therefore, in patients after administration of daily doses of ACP-196 for 8 days, the plasma C_{max} and $AUC_{0\text{-inf}}$ did not increase as the dose of ACP-196 was increased from 250 to 400 mg, suggesting that a plateau of exposure had been reached at daily doses of up to 400 mg for 8 days. The 400-mg dose also represents a factor of 2 over the expected oncology dosage (ie, 100-mg BID resulting in 200 mg total daily dose) which fully saturates BTK for a period of 24 hours after administration. The observed PD of BTK inhibitor action, in particular changes in B cell trafficking between lymphoid organs and peripheral blood, suggest that a single administration of a fully saturating dose may cause temporary alterations in circulating B cells. However, the rate of BTK resynthesis in humans has been studied, and regeneration of circulating lymphocytes with unbound BTK was expected to occur within 24 to 48 hours of a single saturating dose.

The side effect profile observed in the healthy volunteers treated with saturating doses of ACP-196 (ie, 50 mg BID, 100 mg QD) alone or in combination with strong inhibitors of CYP3A4, suggests that the temporary effects on B cell recirculation do not compromise host resistance. In ACE-CL-001, daily administration of 400 mg for a period of 28 days was well tolerated. A similar incidence and grade of AEs was observed at this dose level, compared with those in the cohorts receiving 100 mg QD, during the 28-day, dose-limiting toxicity (DLT) period.

Reviewer's Comment: Acceptable. The 100 mg BID is the proposed therapeutic dosing regimen and there is no accumulation with BID dosing. The 400 mg supratherapeutic dose represents a factor of 2 over the proposed oncology dosage (i.e., 200 mg daily) and is the highest dose explored to date in patients. Substantial increase in exposure is unlikely for doses higher than 400 mg because of observed similar exposure between 250 and 400 mg at the steady state. The C_{max} with 400 mg dose is 3.6-fold of that with 100 mg dose. The worst case scenario is DDI with itraconazole (strong CYP3A and P-gp inhibitor) which results in 3.7-fold increase in C_{max} of ACP-196.

4.2.5.3 Instructions with Regard to Meals

Water (except water provided with dosing) was restricted 1 hour before and 1 hour after each study drug administration, but was allowed ad libitum at all other times.

Subjects fasted overnight for ≥ 10 hours before each study drug administration. On Day 1 of each period, subjects continued the fast for ≥ 4 hours postdose.

Standard lunch, dinner, and an evening snack were scheduled to be completed ≥ 60 minutes before any scheduled Holter-extracted ECG time. Standard meals and a snack were provided to all subjects on Day 1 at approximately 4, 10, and 12 to 13 hours postdose, respectively.

Subjects were not required to consume meals in their entirety. When confined in the CRU, subjects were required to fast from all food and drink except water between meals and snacks.

Meals were to be consumed after or completed ≥ 60 minutes before any Holter extracted ECG.

Reviewer's Comment: Acceptable. In the presence of food, the mean plasma ACP-196 C_{max} values decreased to ~27% of the values observed in the fasted state.

4.2.5.4 ECG and PK Assessments

See Appendix 6.2 for ECG and PK assessments. Briefly,

ECG: -1, -0.75, -0.5, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h post-dose.

PK: Before dosing (0 hour) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h post-dose in each period.

Continuous 12-lead Holter monitoring was conducted during each treatment period for approximately 25 hours starting on Day 1 (approximately 1 hour before dosing) up to Day 2 (approximately 24 hours postdose). Triplicate 10-second, 12-lead ECG recordings were extracted from the Holter monitor data on Day 1 within a 5-minute time window around the scheduled timepoints.

Reviewer's Comment: Acceptable. The timing of ECG/PK sampling is appropriate to capture potential effects at T_{max} (~0.75-1.5 h) and delayed effects over 24 h.

4.2.5.5 Baseline

Applicant used an average of QTc predose measurements at -1, -0.75, and -0.5 hour as baselines.

4.2.6 ECG Collection

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

4.2.7 Sponsor's Results

4.2.7.1 Study Subjects

Forty-eight (48) healthy adult non-tobacco using men and women enrolled and 41 (85.4%) subjects completed the study. Subject disposition is presented below in Table 2.

Table 2: Subject Disposition

Disposition	ABCD	BDAC	CADB	DCBA	Overall
Randomized	12 (100%)	12 (100%)	12 (100%)	12 (100%)	48 (100%)
Completed the Study	12 (100%)	10 (83%)	9 (75%)	10 (83%)	41 (85%)
Discontinued from the Study	0 (0%)	2 (17%)	3 (25%)	2 (17%)	7 (15%)
Reasons for Discontinuation					
Failed Drug/Alcohol Laboratory	0 (0%)	0 (0%)	1 (8%)	0 (0%)	1 (2%)
Personal Reason	0 (0%)	1 (8%)	0 (0%)	0 (0%)	1 (2%)
Other	0 (0%)	1 (8%)	2 (17%)	2 (17%)	5 (10%)

Acerta Project No.: ACE-HV-005
Source: Table 14.1.1

Treatment A: 100 mg ACP-196 (therapeutic dose)
Treatment B: 400 mg ACP-196 (supratherapeutic dose)
Treatment C: 400 mg moxifloxacin (positive control)
Treatment D: Placebo

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4.2.7.2 Statistical Analyses

4.2.7.2.1 Primary Analysis

The primary endpoint was baseline-adjusted mean differences between ACP-196 (100 mg and 400 mg) and placebo in ΔQTcF. For analysis the sponsor used the method of analysis of covariance (ANCOVA). The model included sequence, period, sex, time, treatment and treatment-by-time as fixed effects, subject within sequence as random effect and baseline as covariate. The results of this analysis are presented in Table 3. The results show that the upper bounds of the 90%, 2-sided CI of the LSM difference in QTcF change from baseline for both 100 mg ACP-196 and 400 mg ACP-196 were < 10 ms at all 12 postdose timepoints over 24 hours, with results ranging from 0.699 ms to 3.527 ms for 100 mg ACP-196, and from 1.757 ms to 4.181 ms for 400 mg. The sponsor concluded that there were no significant effect of ACP-196 on QTc prolongations at either the therapeutic or supratherapeutic dose.

Table 3: Sponsor's ΔQTcF and ΔΔQTcF for ACP-196 100 mg and 400 mg

		LS Means							
Parameter dQTcF (msec)	Scheduled Hour	A	B	C	D	Diff* (A-D)	90% 2-sided CI	Diff* (B-D)	90% 2-sided CI
	0.25	-1.459	-0.411	-0.284	-0.400	-1.059	(-2.817, 0.699)	-0.011	(-1.779, 1.757)
	0.50	-2.527	-2.387	3.116	-2.911	0.384	(-1.457, 2.225)	0.523	(-1.328, 2.375)
	0.75	0.109	0.147	7.383	-1.422	1.531	(-0.464, 3.527)	1.569	(-0.437, 3.576)
	1.00	0.359	0.217	9.650	0.356	0.003	(-1.969, 1.976)	-0.139	(-2.122, 1.844)
	1.50	0.927	2.124	11.334	1.245	-0.317	(-2.048, 1.414)	0.880	(-0.861, 2.620)
	2.00	-0.482	0.799	12.827	-0.022	-0.460	(-2.244, 1.325)	0.821	(-0.974, 2.615)
	3.00	-0.073	0.403	13.272	0.089	-0.162	(-1.950, 1.626)	0.314	(-1.484, 2.112)
	4.00	-0.141	2.078	14.516	1.267	-1.408	(-3.185, 0.369)	0.811	(-0.976, 2.598)
	6.00	-1.868	-0.225	8.627	-0.400	-1.468	(-4.461, 1.525)	0.175	(-2.835, 3.185)
	8.00	-4.595	-2.155	5.516	-3.711	-0.884	(-3.494, 1.725)	1.556	(-1.069, 4.181)
	12.00	-3.232	-1.434	6.938	-2.711	-0.521	(-3.016, 1.975)	1.277	(-1.233, 3.787)
	24.00	-4.459	-3.806	2.450	-4.022	-0.437	(-2.459, 1.586)	0.216	(-1.818, 2.250)

LS = Least-squares, CI = Confidence interval
*Diff=Difference between the LS mean for ACP-196 and placebo.
The upper limit of the 95% one-sided CI is the upper limit of the 90% 2-sided CI.
The statistical model includes sequence, period, sex, time, treatment, and the interaction between time and treatment as fixed effects. The repeated variable was the time point at which the interval was measured. Subject within sequence was included as a random effect and the baseline value was included as a covariate.
Treatment A: 100 mg ACP-196 (therapeutic dose)
Treatment B: 400 mg ACP-196 (supratherapeutic dose)
Treatment C: 400 mg moxifloxacin (positive control)
Treatment D: Placebo
Source: Tables 14.2.1.2.3
Program: /CA15129/sas_prg/pksas/pd/adam_intext_statsmixed.sas 02SEP2016 14:45

Source: Clinical Study Report ACE-HV-005, Table 11-3, Pages 58/300

Reviewer's Comments: We provided our independent analysis in Section 5.2. Our ΔΔQTcF results are similar to those reported by the sponsor.

4.2.7.2.2 Assay Sensitivity

The sponsor used the same ANCOVA model to analyze the ΔQTcF effect for moxifloxacin. The results are presented in Table 4. The assay was adequately sensitive to test for prolongation as the lower bounds of the 97.5% 2-sided CI were > 5 ms at Hours 1 through 4 for dQTcF least-squares means (LSM) differences between moxifloxacin and placebo, with results ranging from 6.6564 to 10.788 ms.

Table 4: Sponsor's ΔQTcP and ΔΔQTcP for Moxifloxacin (Per-Protocol Population)

		LS Means			
Parameter	Scheduled Hour	C	D	Diff%n(C-D)	2-sided 97.5% CI for difference of LS means
dQTcF (msec)	1.0	9.652	0.455	9.197	(6.564, 11.831)
	2.0	12.830	0.077	12.753	(10.256, 15.249)
	3.0	13.274	0.188	13.086	(10.635, 15.538)
	4.0	14.519	1.366	13.153	(10.788, 15.517)

LS = Least-squares, CI = Confidence interval
Diff = Difference between the LS mean for moxifloxacin and placebo.
The study has the ability to detect an effect of 5 msec if the lower confidence limit (LCL) of the two-sided 97.5% CIs (one-sided alpha
error level or 0.0125 [0.05/4] using Bonferroni adjustment for at least 1 time point is greater than 5 ms.)
The statistical model includes sequence, period, sex, time, treatment, and the interaction between time and treatment as fixed effects. The
repeated variable was the time point at which the interval was measured. Subject within sequence was included as a random effect and
the baseline value was included as a covariate.
Treatment C: 400 mg moxifloxacin (positive control)
Treatment D: Placebo
Source: Table 14.2.1.2.4
Program: /CA15129/sas_prg/pksas/pd/adam_stats_pd_assay_intext.sas 02SEP2016 14:38

Source: Clinical Study Report ACE-HV-005, Table 11-4, Pages 60/300

Reviewer's Comments: We provided our independent analysis in Section 5.2. Our ΔΔQTcF results of moxifloxacin are similar to those reported by the sponsor.

4.2.7.2.3 Categorical Analysis

Categorical analysis was used to summarize in the categories of QTc ≤450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and >500 ms, and changes from baseline QTc ≤30 ms, between 30 and 60 ms, and >60 ms. No subject's absolute QTcF >480 ms or ΔQTcF > 60 ms.

Table 5: Sponsor's Categorical Analysis

Parameter (unit)	Category	D N=45 n %	A N=44 n %	B N=43 n %	C N=45 n %
QT (msec)	<= 450	43 (96%)	38 (86%)	40 (93%)	32 (71%)
	>450 to <=480	2 (4%)	6 (14%)	3 (7%)	13 (29%)
	>480 to <=500	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	>500	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Change: <= 30	43 (96%)	44 (100%)	43 (100%)	41 (91%)
	Change: >30 to <=60	2 (4%)	0 (0%)	0 (0%)	4 (9%)
	Change: >60	0 (0%)	0 (0%)	0 (0%)	0 (0%)
QTcF (msec)	<= 450	44 (98%)	44 (100%)	43 (100%)	42 (93%)
	>450 to <=480	1 (2%)	0 (0%)	0 (0%)	3 (7%)
	>480 to <=500	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	>500	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Change: <= 30	45 (100%)	44 (100%)	43 (100%)	44 (98%)
	Change: >30 to <=60	0 (0%)	0 (0%)	0 (0%)	1 (2%)
	Change: >60	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PR (msec)	<200	39 (87%)	39 (89%)	36 (84%)	41 (91%)
	>=200	6 (13%)	5 (11%)	7 (16%)	4 (9%)
	>=220	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Change: <25%	45 (100%)	44 (100%)	43 (100%)	45 (100%)
	Change: >=25%	0 (0%)	0 (0%)	0 (0%)	0 (0%)
QRS (msec)	>110 to <120	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	>=120	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Change: <25%	45 (100%)	44 (100%)	43 (100%)	45 (100%)
	Change: >=25%	0 (0%)	0 (0%)	0 (0%)	0 (0%)
HR (bpm)	<30	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	<40	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	<50	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	>90	1 (2%)	0 (0%)	0 (0%)	0 (0%)
	>100	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Change: <30%	38 (84%)	40 (91%)	34 (79%)	35 (78%)
	Change: >=30%	7 (16%)	4 (9%)	9 (21%)	10 (22%)

Note: N is the total number of subjects in the treatment and n is the number of subjects with maximum post-baseline value in the categories specified and % is calculated as n/N*100.
Outliers are based on the triplicate averages and change-from-baseline values.
Treatment A: 100 mg ACP-196 (therapeutic dose) Treatment B: 400 mg ACP-196 (supratherapeutic dose)
Treatment C: 400 mg moxifloxacin (positive control) Treatment D: Placebo

Source: Clinical Study Report ACE-HV-005, Table 11-5, Pages 61/300

Reviewer's Comments: We provided our independent analysis in Section 5.2. Our categorical results are similar to those reported by the sponsor.

4.2.7.2.4 Additional Analyses

No subject HR>100 bpm and QRS >=120 ms (see Table 5). Twelve subjects PR>=200 ms.

4.2.7.3 Safety Analysis

No deaths, SAEs, or subject discontinuations due to AEs in this study.

There was 1 ECG finding reported as an AE in this study.

- Subject 28 (a 36-year-old male; Treatment Sequence ABCD) experienced a Grade 1 abnormal electrocardiogram ST-T segment (verbatim term: non-specific ST and T wave abnormality – inferior leads) approximately 6 hours after dosing with 100 mg ACP-196. The subject had no reported medical history and screening ECG, vital signs, and laboratory assessments were within normal limits. The subjects' safety ECG assessments were noted to be normal throughout all study periods, with sinus arrhythmia noted only on the check-in safety ECG assessment for Period 3. There were no remarkable findings in the post treatment vital sign or laboratory assessments for this subject in Period 1. The abnormality was observed on the Holter assessed ECGs on Day 1 from Hours 6 through 24, with the accompanying comment: non-specific ST and T wave abnormality – may be due to ischemia. Values for HR, RR, PR, QRS, QT, and QTcF parameters were noted to be within normal limits for these assessments. Holter monitoring assessments for this subject in Periods 2, 3, and 4 were within normal limits. The event lasted 6 hours and was considered by the PI to be related to the study treatment. No cardiac enzymes were performed at the time of this event and the subject did not report any symptoms and had no other AEs on the study.

Five (5) subjects were discontinued from treatment on the study due to out-of-range ECG parameters; these were noted at check-in assessments and were not considered by the PI to be clinically significant.

- Subject 18 (a 52-year-old male; Treatment Sequence BDAC) was discontinued before dosing on Day 1 of Period 3 due to intraventricular conduction delay (IVCD) that was noted at the Day -1 check-in ECG. The QRS interval was 126 msec, with a recheck result of 116 msec. At all prior assessments including baseline and screening, the QRS interval ranged from 102 to 108 msec.
- Subject 23 (a 42-year-old female; Treatment Sequence DCBA) was discontinued before dosing on Day 1 of Period 3 due to sinus bradycardia (< 50 bpm) and elevated QTcF intervals (> 450 msec) that were noted at the Day -1 check-in ECG. The QTcF result was 454 msec with a HR of 49 bpm. On recheck, results were QTcF 451 msec and HR 48 bpm, and QTcF 459 msec and HR 56 bpm. Screening and baseline ECG results were within normal limits.
- Subject 31 (a 60-year-old male; Treatment Sequence CADB) was discontinued before dosing on Day 1 of Period 3 due to an elevated QTcF interval (> 450 msec) that was noted at the Day -1 check-in ECG. The QTcF interval was 460 msec, and upon rechecks, were 463 and 454 msec. Screening and baseline QTcF interval values were within normal limits.
- Subject 34 (a 40-year-old male; Treatment Sequence CADB) was discontinued before dosing on Day 1 of Period 3 due to low HR (< 50 bpm) and IVCD that was noted at the Day -1 check-in ECG. The subject had a low HR of 48 bpm. Upon recheck, the HR was within normal limits (62 bpm) but the QRS interval was increased at 112 msec and with a further recheck remained at 112 msec.

Screening and baseline ECG assessments were within normal limits for these parameters.

- Subject 45 (a 55-year-old female; Treatment Sequence DCBA) was discontinued before dosing on Day 1 of Period 2 due to first degree atrioventricular (AV) block (PR interval > 220 msec), with sinus arrhythmia that was noted at the Day -1 check-in ECG. The PR interval was 226 msec and on recheck was 230 msec. Screening and baseline ECG assessments were within normal limits for these parameters.

There were 3 abnormal laboratory values reported as AEs: increased AST (100 mg ACP-196) and increased neutrophil count and WBC count (400 mg ACP-196). All laboratory values reported as AEs were reported as Grade 1 in intensity and considered by the PI to be unrelated to the study treatments, although the reported event of increased AST (which occurred in a subject after drinking 12 beers, and occurred with an AST:ALT ratio of approximately 2:1 consistent with an alcohol effect) met CTCAE 4.03 criteria for Grade 3.

A total of 66 AEs were experienced by 26 (54%) subjects. Subject incidence and number of AEs reported was similar for 100 mg ACP-196, moxifloxacin, and placebo, but were higher for the supratherapeutic dose, 400 mg ACP-196 particularly for events of headache, nausea, and diarrhea. These were the most common events reported across the study, and occurred as non-serious Grade 1 events except for one event of diarrhea which was non-serious Grade 2. Sixty-three (63) AEs were Grade 1 (mild) in intensity and 3 were Grade 2 (moderate).

Reviewer's Comment: There is no evidence in the brief narratives that the baseline ECG abnormalities that caused 5 subjects to discontinue treatment were drug related. There was no pattern between treatment sequence and the period of the baseline abnormal ECGs. The study drug has a short elimination half-life (~2 hours) and after a 7-day washout drug concentrations were negligible prior to dosing for each study period. Furthermore, there are no detectable drug effects on any of the ECG parameters (QTc, PR, QRS and HR).

4.2.7.4 Clinical Pharmacology

4.2.7.4.1 Pharmacokinetic Analysis

The mean drug concentration-time profile is illustrated in Figure 1 and the PK parameters are presented in Table 6. The geometric mean C_{max} and $AUC_{0\text{-}inf}$ values in the thorough QT study were 3.6-fold (1672 vs. 466 ng/mL) and 7-fold (4653 vs 663 ng*h/mL) higher following administration of 400 mg (supratherapeutic dose) compared to the administration of 100 mg (therapeutic dose) ACP-196. T_{max} for ACP-196 concentration were 1.5 and 0.75 h for 400 mg and 100 mg dose, respectively.

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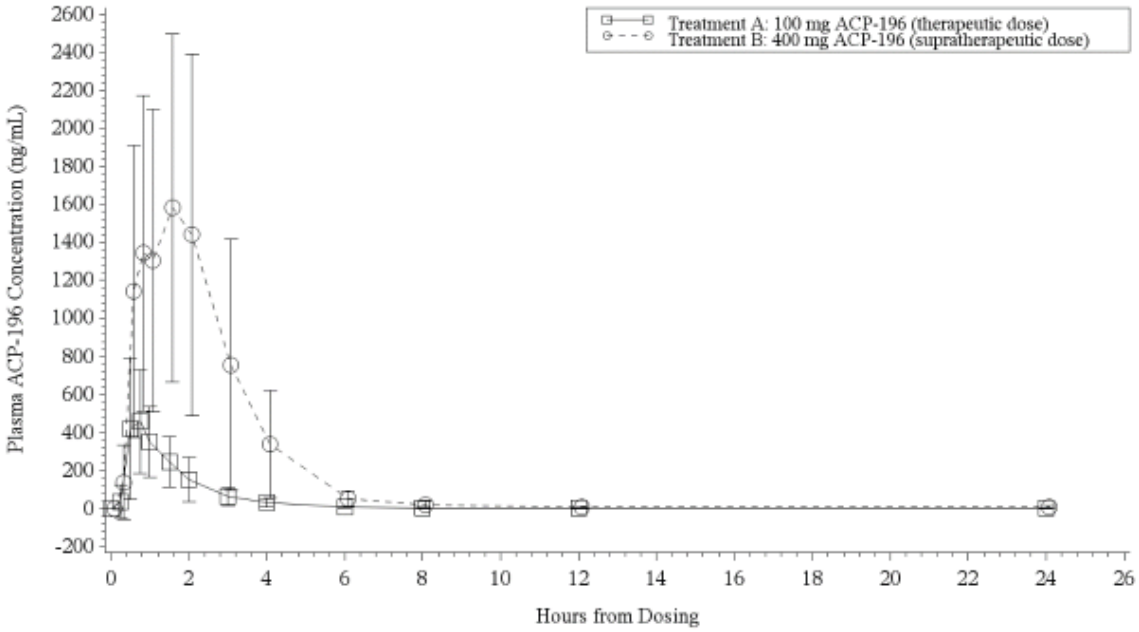
Figure 1: Mean (SD) Plasma ACP-196 Concentration-Time Profile



Source: Clinical Study Report ACE-HV-005, Figure 11-1, Pages 47/300

Table 6: Plasma ACP-196 PK Parameters Following Administration of 100 mg and 400 mg of ACP-196

	Treatment A (100 mg ACP-196)		Treatment B (400 mg ACP-196)	
Pharmacokinetic Parameters	**Geometric Mean (Geom. CV%)**	**n**	**Geometric Mean (Geom. CV%)**	**n**
AUC0-last (ng*hr/mL)	677.48 (50.5)	44	3965.5 (60.4)	43
AUC0-inf (ng*hr/mL)	662.53 (47.7)	38	4652.9 (51.9)	31
AUC%extrap (%)	1.7016 ± 3.2520	38	0.44140 ± 0.58351	31
Cmax (ng/mL)	465.87 (83.2)	44	1672.3 (64.5)	43
Tmax (hr)	0.7507 (0.50, 3.05)	44	1.5006 (0.50, 4.00)	43
t1/2 (hr)	2.6442 ± 2.7156	38	3.5127 ± 2.6253	31

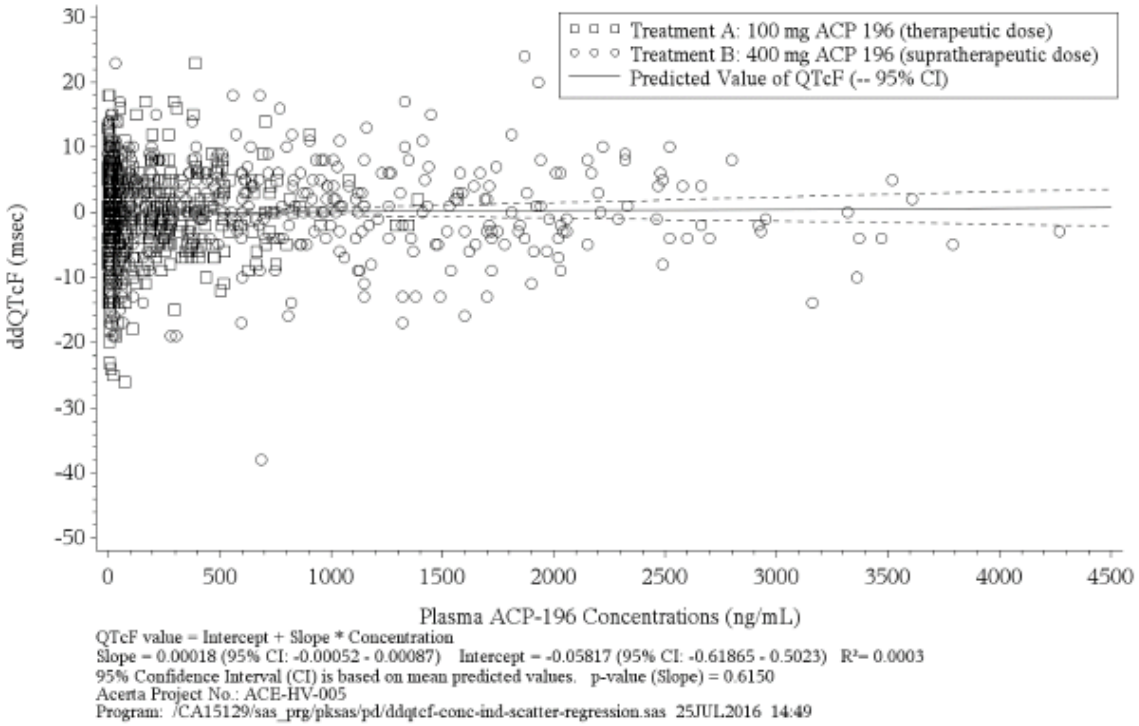
Treatment A: 100 mg ACP-196 (therapeutic dose)
Treatment B: 400 mg ACP-196 (supratherapeutic dose)
Tmax is presented as Median (Minimum, Maximum)
AUC%extrap and t1/2 are presented as Mean ± SD

Source: Clinical Study Report ACE-HV-005, Table 11-2, Pages 49/300

4.2.7.4.2 Exposure-Response Analysis

Placebo-corrected changes from baseline in QTcF (ddQTcF) versus plasma ACP-196 concentrations are presented in Figure 2. The estimated slope for ACP-196 was 0.00018 msec/ng/mL. No relationship between ddQTcF versus plasma ACP-196 concentrations was observed. The predicted value (90% 2-sided confidence limits) of ddQTcF at the geometric mean value of C_{max} for 100 mg ACP-196 was 0.025 msec (-0.369, 0.419) and for 400 mg ACP-196 was 0.240 msec (-0.579, 1.059). The upper limit of the 90% 2-sided CI of the predicted ddQTcF at C_{max} was < 10 msec for both treatments.

Figure 2: Placebo-Corrected Change From Baseline in QTcF Versus Plasma ACP-196 Concentrations (E-R Model)



Source: Clinical Study Report ACE-HV-005, Figure 11-10, Pages 63/300

Reviewer's Analysis: A plot of ΔΔQTc vs. drug concentrations with the reviewer's analysis is presented in Section 5.3. The results confirm that there is no statistically significant slope for the concentration-QTc relationship.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

QTcF was used for the primary statistical analysis and other analyses. There were no significant heart rate effects with the drug.

5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for ACP-196

The statistical reviewer used a mixed effect model to analyze the ΔQTcF effect. The model includes treatment, period, time, and treatment-by-time as fixed effects, subject as random effect, and baseline values as a covariate. The analysis results are listed in Table 7. The largest upper bounds of the 2-sided 90% CI for the mean differences between ACP-196 100 mg and placebo, and ACP-196 400 mg and placebo is 3.7 ms for both dose levels.

Table 7: **Analysis Results of ΔQTcF and ΔΔQTcF for ACP-196 100 mg and ACP-196 400 mg**

		Treatment Group							
	Placebo	ACP-196 100 mg				ACP-196 400 mg			
	ΔQTcF	ΔQTcF		ΔΔQTcF		ΔQTcF		ΔΔQTcF	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.25	-0.6	44	-1.5	-0.8	(-2.8, 1.2)	43	-0.5	0.1	(-1.9, 2.1)
0.5	-3.1	44	-2.6	0.5	(-1.5, 2.5)	43	-2.4	0.7	(-1.3, 2.7)
0.75	-1.7	44	0.0	1.7	(-0.3, 3.7)	43	0.0	1.7	(-0.3, 3.7)
1	0.1	44	0.3	0.2	(-1.8, 2.1)	43	0.1	-0.0	(-2.0, 2.0)
1.5	1.0	44	0.8	-0.1	(-2.1, 1.9)	43	2.0	1.0	(-1.0, 3.0)
2	-0.3	44	-0.5	-0.2	(-2.2, 1.7)	43	0.7	1.0	(-1.0, 3.0)
3	-0.1	44	-0.1	0.0	(-2.0, 2.0)	43	0.3	0.4	(-1.6, 2.4)
4	1.0	44	-0.2	-1.2	(-3.2, 0.8)	43	1.9	1.0	(-1.0, 3.0)
6	-0.6	44	-1.9	-1.3	(-3.3, 0.7)	43	-0.4	0.3	(-1.7, 2.2)
8	-3.9	44	-4.6	-0.7	(-2.7, 1.3)	43	-2.2	1.7	(-0.3, 3.7)
12	-3.0	44	-3.3	-0.3	(-2.3, 1.7)	43	-1.6	1.4	(-0.6, 3.4)
24	-4.3	44	-4.5	-0.2	(-2.2, 1.8)	43	-3.9	0.3	(-1.7, 2.3)

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data as she used to analyze the QTc data. The results are presented in Table 8. The largest unadjusted 90% lower confidence interval is 11.4 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 10.7 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin could be detected from the study.

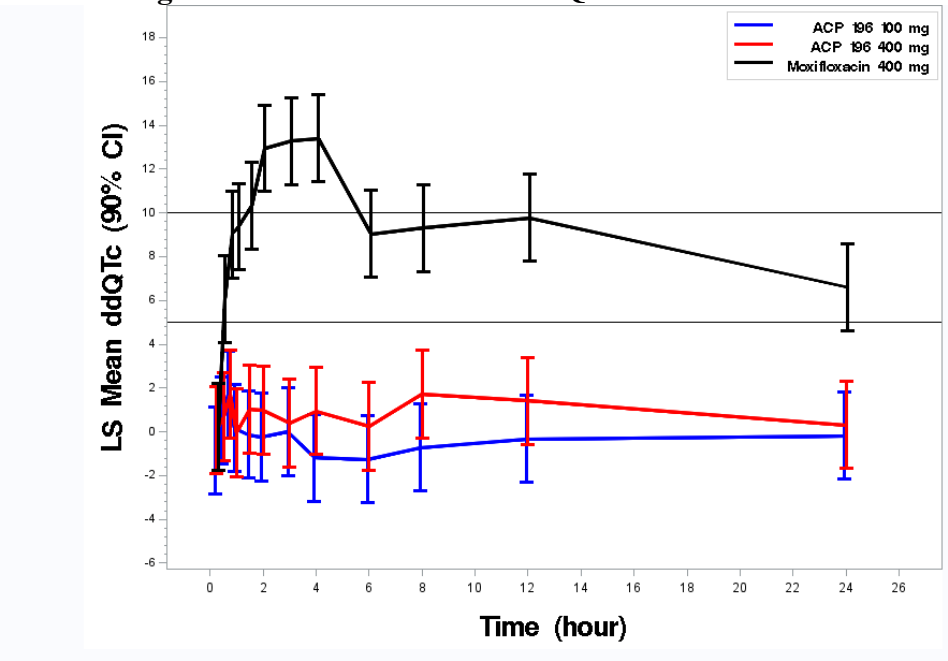
Table 8: Analysis Results of ΔQTcF and ΔΔQTcF for Moxifloxacin 400 mg

Treatment Group						
	Placebo	Moxifloxacin 400 mg				
	ΔQTcF	ΔQTcF		ΔΔQTcF		
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	Adj. 90% CI
0.25	-0.6	45	-0.4	0.2	(-1.7, 2.2)	(-2.5, 2.9)
0.5	-3.1	45	2.9	6.1	(4.1, 8.0)	(3.4, 8.8)
0.75	-1.7	45	7.3	9.0	(7.0, 11.0)	(6.3, 11.7)
1	0.1	45	9.5	9.4	(7.4, 11.4)	(6.7, 12.1)
1.5	1.0	44	11.3	10.3	(8.3, 12.3)	(7.6, 13.0)
2	-0.3	45	12.7	12.9	(11.0, 14.9)	(10.3, 15.6)
3	-0.1	45	13.2	13.3	(11.3, 15.3)	(10.6, 16.0)
4	1.0	45	14.4	13.4	(11.4, 15.4)	(10.7, 16.1)
6	-0.6	45	8.4	9.0	(7.1, 11.0)	(6.3, 11.7)
8	-3.9	45	5.4	9.3	(7.3, 11.3)	(6.6, 12.0)
12	-3.0	45	6.8	9.8	(7.8, 11.8)	(7.1, 12.5)
24	-4.3	45	2.3	6.6	(4.6, 8.6)	(3.9, 9.3)

5.2.1.3 Graph of ΔΔQTcF Over Time

The following figure displays the time profile of ΔΔQTcF for different treatment groups.

Figure 3: Mean and 90% CI ΔΔQTcF Time Profile



5.2.1.4 Categorical Analysis

Table 9 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and >500 ms. No subject's QTcF was above 480 ms.

Table 9: Categorical Analysis for QTcF

Treatment Group	Total N	Value<=450 ms	450 ms<Value<=480 ms	480 ms<Value<=500 ms	Value>500
ACP 196 100 mg	44	44 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ACP 196 400 mg	43	43 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Placebo	45	44 (97.8%)	1 (2.2%)	0 (0.0%)	0 (0.0%)
moxifloxacin 400 mg	45	42 (93.3%)	3 (6.7%)	0 (0.0%)	0 (0.0%)

Table 10 lists the categorical analysis results for ΔQTcF. No subject's change from baseline was above 60 ms.

Table 10: Categorical Analysis of ΔQTcF

Treatment Group	Total N	Value<=30 ms	30 ms<Value<=60 ms	60 ms<Value<=90 ms	Value>90 ms
ACP 196 100 mg	44	44 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ACP 196 400 mg	43	43 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Placebo	45	45 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
moxifloxacin 400 mg	45	44 (97.8%)	1 (2.2%)	0 (0.0%)	0 (0.0%)

5.2.2 HR Analysis

The statistical reviewer used a mixed model to analyze the ΔHR effect. The analysis results are listed in Table 11. The largest upper bounds of the 2-sided 90% CI for the mean differences between ACP-196 100 mg and placebo, and ACP-196 400 mg and placebo are 2.6 bpm and 4.8 bpm, respectively. Table 12 presents the categorical analysis of HR. No subject in the ACP-196 group experienced HR greater than 100 bpm.

Table 11: Analysis Results of ΔHR and ΔΔHR for ACP-196 100 mg and ACP-196 400 mg

		Treatment Group							
	Placebo	ACP-196 100 mg				ACP-196 400 mg			
	ΔHR	ΔHR		ΔΔHR		ΔHR		ΔΔHR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.25	1.5	44	0.7	-0.8	(-2.2, 0.6)	43	0.5	-1.0	(-2.4, 0.4)
0.5	0.9	44	0.8	-0.1	(-1.5, 1.3)	43	1.2	0.3	(-1.1, 1.7)
0.75	0.8	44	1.5	0.7	(-0.7, 2.1)	43	2.1	1.3	(-0.1, 2.7)
1	0.4	44	1.6	1.2	(-0.2, 2.6)	43	1.7	1.3	(-0.1, 2.7)
1.5	0.1	44	1.0	0.9	(-0.5, 2.3)	43	2.3	2.3	(0.9, 3.7)
2	-0.3	44	0.6	0.8	(-0.6, 2.2)	43	3.1	3.4	(2.0, 4.8)
3	-0.3	44	0.3	0.6	(-0.8, 2.0)	43	2.3	2.6	(1.2, 4.0)
4	0.6	44	0.2	-0.4	(-1.8, 1.0)	43	2.0	1.4	(0.0, 2.8)
6	10.1	44	8.6	-1.5	(-2.9, -0.1)	43	10.1	-0.0	(-1.4, 1.4)
8	7.2	44	6.1	-1.1	(-2.5, 0.3)	43	7.8	0.7	(-0.7, 2.1)
12	8.4	44	8.2	-0.2	(-1.6, 1.2)	43	9.7	1.3	(-0.1, 2.7)
24	3.7	44	3.2	-0.5	(-1.8, 0.9)	43	3.8	0.2	(-1.2, 1.6)

Table 12: Categorical Analysis for HR

Treatment Group	Total N	HR <= 100 bpm	HR >100 bpm
ACP 196 100 mg	44	44 (100%)	0 (0.0%)
ACP 196 400 mg	43	43 (100%)	0 (0.0%)
Placebo	45	45 (100%)	0 (0.0%)
moxifloxacin 400 mg	45	45 (100%)	0 (0.0%)

5.2.3 PR Analysis

The statistical reviewer used a mixed model to analyze the ΔPR effect. The analysis results are listed in Table 13. The largest upper bounds of the 2-sided 90% CI for the mean differences between ACP-196 100 mg and placebo, and ACP-196 400 mg and placebo are 3.4 ms and 2.5 ms, respectively. Table 14 presents the categorical analysis of PR. Twelve subjects in the ACP-196 group (13.8%) experienced PR > 200 ms, which is similar to the percentage of subjects in the placebo group (13.3%).

Table 13: Analysis Results of ΔPR and ΔΔPR for ACP-196 100 mg and ACP-196 400 mg

		Treatment Group							
		ACP-196 100 mg				ACP-196 400 mg			
	ΔPR	ΔPR		ΔΔPR		ΔPR		ΔΔPR	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.25	-0.5	44	-1.3	-0.7	(-2.5, 1.0)	43	-0.5	0.0	(-1.7, 1.8)
0.5	0.6	44	-0.7	-1.2	(-2.9, 0.5)	43	0.1	-0.4	(-2.2, 1.3)
0.75	1.3	44	-0.1	-1.3	(-3.1, 0.4)	43	1.5	0.3	(-1.5, 2.0)
1	0.0	44	0.2	0.2	(-1.5, 2.0)	43	0.8	0.8	(-1.0, 2.5)
1.5	-0.6	44	-0.4	0.2	(-1.5, 2.0)	43	0.0	0.6	(-1.1, 2.4)
2	0.6	44	0.5	-0.1	(-1.9, 1.6)	43	-0.5	-1.2	(-2.9, 0.6)
3	0.1	44	-0.0	-0.1	(-1.9, 1.6)	43	-1.9	-2.0	(-3.8, -0.3)
4	-0.5	44	-0.5	-0.0	(-1.8, 1.7)	43	-1.9	-1.5	(-3.2, 0.3)
6	-4.0	44	-3.4	0.6	(-1.2, 2.3)	43	-4.3	-0.3	(-2.1, 1.4)
8	-5.0	44	-4.4	0.6	(-1.2, 2.3)	43	-6.2	-1.2	(-3.0, 0.6)
12	-2.9	44	-1.3	1.6	(-0.1, 3.4)	43	-5.2	-2.3	(-4.0, -0.5)
24	-0.1	44	-0.2	-0.1	(-1.8, 1.6)	43	-0.9	-0.8	(-2.6, 0.9)

Table 14: Categorical Analysis for PR

Treatment Group	Total N	PR <= 200 ms	PR >200 ms
ACP 196 100 mg	44	39 (88.6%)	5 (11.4%)
ACP 196 400 mg	43	36 (83.7%)	7 (16.3%)
Placebo	45	39 (86.7%)	6 (13.3%)
moxifloxacin 400 mg	45	41 (91.1%)	4 (8.9%)

5.2.4 QRS Analysis

The statistical reviewer used a mixed model to analyze the ΔQRS effect. The analysis results are listed in Table 15. The largest upper bounds of the 2-sided 90% CI for the mean differences between ACP-196 100 mg and placebo, and ACP-196 400 mg and placebo are 2.0 ms and 1.5 ms, respectively. Table 16 presents the categorical analysis of QRS. No subject in the ACP-196 group experienced QRS greater than 110 ms.

Table 15: Analysis Results of ΔQRS and ΔΔQRS for ACP-196 100 mg and ACP-196 400 mg

		Treatment Group							
		ACP 196 100 mg				ACP 196 400 mg			
	ΔQRS	ΔQRS		ΔΔQRS		ΔQRS		ΔΔQRS	
Time (h)	LS Mean	N	LS Mean	LS Mean	90% CI	N	LS Mean	LS Mean	90% CI
0.25	0.0	44	-0.2	-0.2	(-0.9, 0.5)	43	-0.1	-0.1	(-0.8, 0.7)
0.5	-0.1	44	-0.2	-0.0	(-0.8, 0.7)	43	0.2	0.3	(-0.4, 1.0)
0.75	-0.3	44	0.1	0.4	(-0.3, 1.1)	43	0.5	0.8	(0.0, 1.5)
1	-0.1	44	-0.1	0.0	(-0.7, 0.7)	43	0.3	0.4	(-0.3, 1.1)
1.5	-0.2	44	0.3	0.6	(-0.2, 1.3)	43	0.1	0.4	(-0.4, 1.1)
2	0.3	44	0.4	0.1	(-0.7, 0.8)	43	0.5	0.2	(-0.6, 0.9)
3	-0.0	44	0.2	0.3	(-0.5, 1.0)	43	0.5	0.5	(-0.2, 1.3)
4	0.2	44	0.2	0.0	(-0.7, 0.7)	43	0.2	0.0	(-0.7, 0.8)
6	1.0	44	1.8	0.8	(0.1, 1.5)	43	1.1	0.1	(-0.6, 0.8)
8	-0.3	44	1.0	1.3	(0.5, 2.0)	43	0.3	0.5	(-0.2, 1.3)
12	-0.7	44	0.2	0.9	(0.2, 1.6)	43	-0.5	0.3	(-0.5, 1.0)
24	-0.3	44	-0.2	0.1	(-0.6, 0.9)	43	-0.8	-0.5	(-1.2, 0.3)

Table 16: Categorical Analysis for QRS

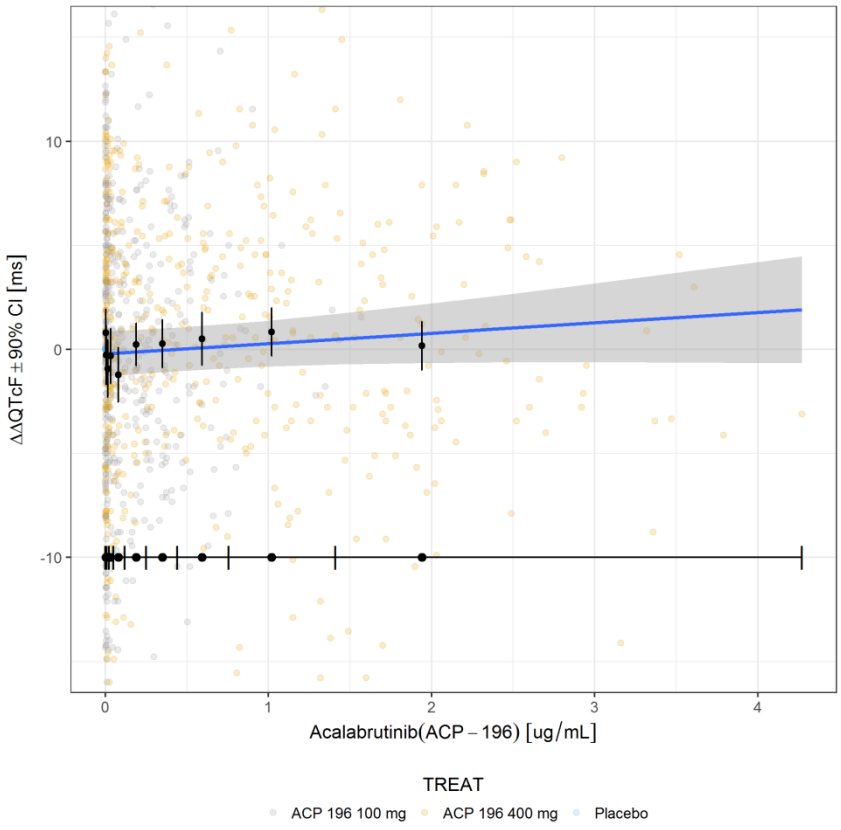
Treatment Group	Total N	QRS <= 110 ms	QRS > 110 ms
ACP 196 100 mg	44	44 (100%)	0 (0.0%)
ACP 196 400 mg	43	43 (100%)	0 (0.0%)
Placebo	45	45 (100%)	0 (0.0%)
moxifloxacin 400 mg	45	45 (100%)	0 (0.0%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean drug concentration-time profile is illustrated in Figure 1.

The relationship between ΔΔQTcF and acalabrutinib (ACP-196) concentrations was investigated by linear mixed-effects modeling. The relationship is visualized in Figure 4 with no statistically significant slope (0.0005 ms per ng/mL, p=0.2) for exposure-response relationship. The mean (90% CI) predicted ΔΔQTcF at the acalabrutinib C_{max} of 1672 ng/mL for supratherapeutic dose (400 mg) is 0.6 ms with upper bound of 90% CI of 1.9 ms. The upper bound is below the 10 ms regulatory threshold.

Figure 4: ΔΔQTcF vs. Acalabrutinib (ACP-196) Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

No clinically relevant effects on PR and QRS intervals.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	Total daily dose of 200 mg per day administered either as 200 mg once per day or 100 mg twice per day is currently proposed for oncology indications. Acerta has also [redacted] (b) (4)	
Maximum tolerated dose	The maximum tolerated dose has not been reached with ACP-196. 400 mg QD is the highest dose explored to date and no DLTs or drug-related SAEs occurred at this dose level or below in subjects with CLL.	
Principal adverse events	To date, ACP-196 has been well tolerated at all dose levels evaluated in the ongoing first-in-human study (ACE-CL-001 [NTC02029443]) in subjects with CLL. As mentioned above, no DLTs have occurred at any dose level from 100 to 400 mg QD and 100 mg BID in ACE-CL-001. No study-drug related SAEs have occurred at any dose level. The MTD was not reached in this study; however, per the protocol, dose escalation was stopped once a plateau in exposure was observed on repeat dosing (ie, between 250 and 400 mg). ACP-196 has also been evaluated in a PK/PD, food-effect, and drug-drug interaction study in healthy volunteers (ACE-HV-001). The highest single dose evaluated in the healthy volunteer study was 100 mg. No drug-related toxicities were evident in the healthy volunteer study. This table provides brief summaries of the results of that study.	
Maximum dose tested	Single Dose	400 mg in oncology subjects 100 mg in healthy volunteers
	Multiple Dose	400 mg daily. Median days on study = 62 (range 55-77 days) as of 16 Sept 2014
Exposures Achieved at Maximum Tested Dose	Single Dose	*Mean (%CV) exposure for 400 mg dose in CLL patients:* C_{max} = 2090 ng/mL (48.5%) $AUC_{0\text{-}inf}$ = 5320 ng*hr/mL (41.8%) Mean (%CV) exposure for 100 mg dose in normal healthy volunteers: C_{max} = 580 ng/mL (25.8%) $AUC_{0\text{-}inf}$ = 633 ng*hr/mL (29.7%)
	Multiple Dose	Mean (%CV) exposure for 400 mg dose in CLL patients: C_{max} = 940 ng/mL (46.7 %) $AUC_{0\text{-}inf}$ = 2120 ng*hr/mL (49.8%)
Range of linear PK	As mentioned above a single dose PK study has been completed in healthy volunteers. Briefly, the pharmacokinetics of ACP-196 are approximately linear over a range of 2.5 to 100 mg in healthy volunteers. Mean $AUC_{0\text{-}24}$ or AUC_{INF} values increased in a dose proportional manner based on the increases of the total dose administered. Between the 5.0 mg (2.5 mg BID, Cohort 1) dose and the 100 mg (50 mg BID or 100 mg QD, Cohort 4 or 5) doses administered, mean AUC values increased between 16- to 23-fold over the 20-fold increase in dose. Between the 5.0 (2.5 mg BID, Cohort 1) to 10 mg (5.0 mg BID, Cohort 2) and the 50 mg (25 mg BID, Cohort 3) to 100 mg (50 mg BID or 100 mg QD, Cohort 4 or 5) increases in dose, the increases in AUC were close to	

	proportional to the increase in dose. Mean C_{max} values increased in a greater than dose proportional manner, based on the increases of the single dose administered Between the 2.5 mg BID dose (Cohort 1) and the 100 mg QD dose (Cohort 5) administered, mean C_{max} values increased 163-fold over the 40-fold increase in dose. However, this reflected some non-linearity in PK at the lower doses (2.5mg) due to the covalent nature of the interaction of ACP-196 with Btk. Preliminary PK data from the first-in-human study shows ACP-196 displayed approximately linear PK in CLL patients over a dose range of 100 - 400 mg as a single dose. On repeat dose administration of ACP-196 to CLL patients the exposure (AUC and C_{max}) to ACP-196 on day 8 did not increase as the dose was increased from 250 to 400 mg.	
Accumulation at steady state	The half-life of ACP-196 in humans ranges from 1-2.3 hours. As a consequence, there is no accumulation of ACP-196 with administration of doses of 100 mg BID and up to 400 mg daily in CLL patients.	
Metabolites	The major metabolic pathway for ACP-196 involves conjugation of ACP-196 with glutathione and subsequent elimination as glutathione, cysteine or N-acetylcysteine conjugates. This pathway involves inactivation of the butynamide electrophile by conjugation with the cysteinyl-thiol of glutathione. Therefore, these metabolites will no longer be electrophiles and are not expected to have significant biological activity against Btk. The profile of metabolites of ACP-196 in systemic circulation in humans will be evaluated as part of the ongoing development program.	
Absorption	Absolute/ Relative Bioavailability	The absolute bioavailability of ACP-196 in humans will be evaluated in ACE-HV-003 protocol that will initiate in 4Q2014. The absolute bioavailability of ACP-196 in preclinical species ranges from 9.9% to 53% with a mean bioavailability of 25%.
	Tmax	• Median (range) for parent: 0.5 hr (0.5 to 1 hr) • Median (range) for metabolites: The pharmacokinetics of metabolites of ACP-196 have not been evaluated in humans.
Distribution	Vd/F or Vd	Mean (%CV) in healthy volunteers: Vd/F ranges from 515 to 233 L over a 2.5 mg to 100 mg dose, respectively. The %CV over the same dose levels ranged from 38 to 26 %, respectively.
	% bound	Mean (%CV): ACP-196 demonstrated 97.5% (CV=0.2%) and 91.9% (CV=1.2%) binding to human plasma proteins at 1 and 10 µM, respectively.
Elimination	Route	A formal human ADME study will be conducted as part of the clinical development program for ACP-196. In rat, following IV administration, 85% of the dose was recovered; the primary route of elimination was biliary secretion (69% of dose) with a smaller component of renal elimination (16% of dose).

	Terminal t½	• Mean (%CV) for parent in healthy volunteers: Terminal half-life ranges from 2.14 to 0.965 h over a 2.5 mg to 100 mg dose, respectively. The %CV over the same dose levels ranged from 34 to 18%, respectively. • Mean (%CV) for parent in CLL patients: Terminal half-life ranges from 0.8 to 2.27 h after 8 days of daily dosing for 100 mg and 400 mg dose levels, respectively. The %CV for the same dose levels was 21 to 43%, respectively. • Mean (%CV) for metabolites: The pharmacokinetics of metabolites of ACP-196 have not been defined
	CL/F or CL	Mean (%CV): CL/F ranges from 165 to 170 L/h over a 2.5 mg to 100 mg dose, respectively. The %CV over the same dose levels ranged from 8 to 29 %, respectively.
Intrinsic Factors	Age	The PK of a 100 mg dose of ACP-196 has been studied in a population of CLL patients, median age = 59.5 (range 55 – 84), and in healthy volunteers, median age = 47 (range 24 – 56). The mean C_{max} values were similar for both populations. Single dose PK parameters for CLL Patients (N=9): C_{max} = 623 ng/mL (CV= 77.5%) $AUC_{0\text{-}inf}$ = 1090 ng*hr/mL (CV= 59.4%) Single dose PK parameters for healthy volunteers (N=6): C_{max} = 580 ng/mL (CV=29.7%) $AUC_{0\text{-}inf}$ = 633 ng*hr/mL (CV= 29.7%)
	Sex	There is no effect of sex on the PK of a 75 mg dose of ACP-196. Men (N=6): C_{max} = 404 ng/mL (CV= 56.6%) $AUC_{0\text{-}inf}$ = 455 ng*hr/mL (CV=22.9%) Women (N=6): C_{max} = 503 ng/mL (CV=58%) $AUC_{0\text{-}inf}$ = 538 ng*hr/mL (CV=49.2%)
	Race	The effect of race has not been evaluated
	Hepatic & Renal Impairment	The effect of renal impairment has not been evaluated. The effect of hepatic impairment will be evaluated in ACE-HI-001 protocol that will be initiated in 4Q2014
Extrinsic Factors	Drug interactions	The effect of itraconazole (a strong CYP3A4 and P-gp inhibitor) on the PK of ACP-196 has been evaluated in healthy volunteers (ACE-HV-001). Plasma ACP-196 C_{max} values increased 3.7-fold in the presence of itraconazole. The mean plasma ACP-196 $AUC_{(0\text{-}\infty)}$ values increased by 5-fold in the presence of itraconazole. The effect of calcium carbonate, omeprazole and rifampin on the PK of ACP-196 will be evaluated in ACE-HV-004 protocol that will be initiated in 4Q2014.

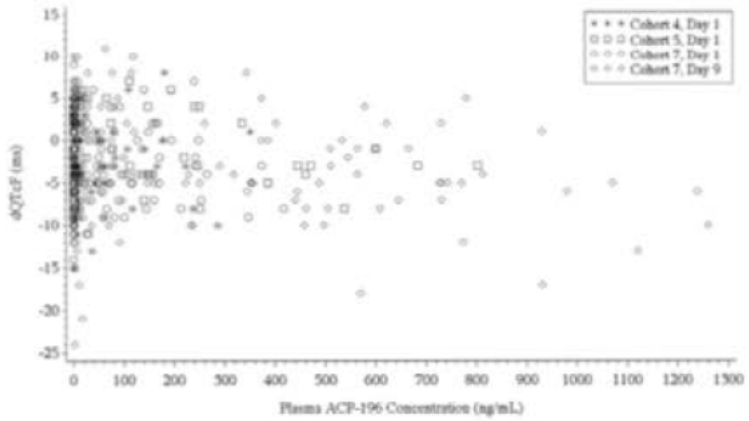
	Food Effects	The effect of a high fat meal on the oral pharmacokinetics of ACP-196 has been evaluated in 6 male and 6 female healthy volunteers (ACE-HV-001). In the presence of food, the mean plasma ACP-196 C_{max} values decreased to 27.3% of the values observed in the fasted state. The mean plasma $AUC_{(0-t)}$, $AUC_{(0-24)}$, and $AUC_{(0-\infty)}$ values remained relatively unchanged with the fed state values being 89.9% to 91.2% compared to the fasted state.
Expected High Clinical Exposure Scenario	The high clinical exposure scenario may occur with a 200 mg dose of ACP-196 in CLL patients in the presence of a strong CYP3A and p-glycoprotein inhibitor, such as itraconazole or ketoconazole, or in Richter's syndrome where patients are currently treated with a 200 mg BID dose of ACP-196. Plasma ACP-196 C_{max} values increased 3.7-fold for a 50 mg dose of ACP-196 in the presence of itraconazole. The mean plasma ACP-196 $AUC_{(0-\infty)}$ values increased by 5-fold in the presence of itraconazole. The expected exposures for a 200 mg single dose of ACP-196 in the presence of itraconazole are as follows: C_{max} = 3104 ng/mL and $AUC_{(0-\infty)}$ = 5360 ng*hr/mL with a linear extrapolation of exposure from a 50 mg dose to a 200 mg dose of ACP-196. For a twice daily dose of 200 mg of ACP-196 with itraconazole the C_{max} value will be similar to the projected single dose C_{max} (3104 ng/mL) and the projected $AUC_{(0-\infty)}$ will be 10,720 ng*hr/mL. (b) (4)	
Preclinical Cardiac Safety	ACP-196 was examined in vitro for effects on the human ether-a-go-go related gene (hERG) channel activity, at concentrations up to 10 µM under GLP. At a concentration of 10 µM, ACP-196 showed an inhibition of 25.1 ± 1.3% of the hERG tail current in stably transfected HEK-293 cells. A GLP cardiovascular safety study was conducted in conscious radiotelemetry-instrumented male Beagle dogs to assess the potential acute effects of oral gavage administration of ACP-196 on arterial blood pressure, heart rate, body temperature, and lead II electrocardiogram (ECG). Mean blood concentrations of 188, 679, and 3442 ng/mL ACP-196 were noted at 3 hours post-dosing following administration of 3, 10, and 30 mg/kg, respectively. Heart rate, arterial blood pressure (systolic, diastolic, and mean arterial pressure), pulse pressure, body temperature, and ECG waveforms (from which the ECG intervals PR, QRS, RR, QT, and heart rate-corrected QT [QTcV] were derived), or physical condition of the animals were not affected by a single oral gavage dose of 3, 10, or 30 mg/kg ACP-196.	

Clinical Cardiac Safety

ACE-HV-001: A Phase 1, Single-center, Open-label, Sequential Dose-Escalation Study of ACP-196 in Healthy Subjects to Evaluate Safety, Pharmacokinetics, Pharmacodynamics, Food Effects, and Drug-Drug Interactions. This trial is completed with 59 subjects. The study explored a range of doses from 2.5 BID to 100 mg QD of ACP-196 in Part 1 and doses of 75 mg in Part 2 and doses of 50 mg administered with itraconazole in Part 3.

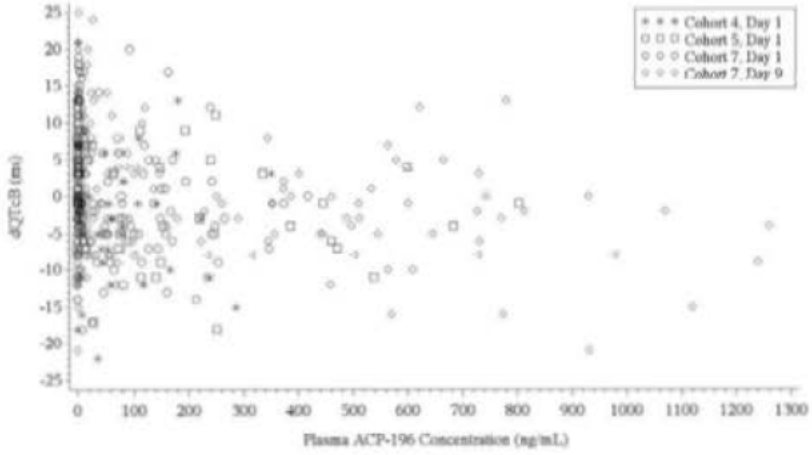
		Part 1					Part 2	Part 3
	Overall	Cohort 1 2.5 mg BID	Cohort 2 5 mg BID	Cohort 3 25 mg BID	Cohort 4 50 mg BID	Cohort 5 100 mg QD	Cohort 6 75 mg QD	Cohort 7 50 mg QD
Enrolled	59	6	6	6	6	6	12	17
Safety Population	59	6	6	6	6	6	12	17
Evaluable Population	58	6	6	6	6	6	12	16
Completed Study	58	6	6	6	6	6	12	16
Did Not Complete Study	1	0	0	0	0	0	0	1
Discontinued due to:								
Adverse Event	1	0	0	0	0	0	0	1

A complete analysis of the cardiac results from the Holter monitor/PK evaluations for Cohort 4, Cohort 5, and Cohort 7 was performed and is available as a separate report (ACE-HV-001 Cardiology Report). The results of these analyses show no correlation between ACP-196 exposure and change in QTc whether using the Fridericia (QTcF: Figure 1) or Bazett (QTcB: Figure 2) correction. In addition, no effect of ACP-196 was observed on heart rate and 12-lead ECG parameters.



BLQ concentrations are treated as 0

Figure 1: Change From Baseline in QTcF (dQTcF) Versus Time-Matched Plasma ACP-196 Concentrations



BLQ concentrations are treated as 0

Figure 2: Change From Baseline in QTcB (dQTcB) Versus Time-Matched Plasma ACP-196 Concentrations

ACE-CL-001: A Phase 1, Multicenter, Open-label, and Dose-escalation Study of ACP-196 in Subjects with Chronic Lymphocytic Leukemia.

A dose-escalation study of ACP-196 in subjects with CLL (ACE-CL-001) has enrolled 49 subjects as of 17 September 2014. The dosages have ranged from 100 to 400 mg QD and also included 100 to 200 mg twice per day (BID). Subjects treated with 100, 175, 250 and 400 mg QD and 5 subjects treated with 100 mg BID have completed the dose-limiting toxicity (DLT) review period. No DLTs occurred at these dose levels. No serious adverse events (SAEs) related to study drug have occurred in any of the subjects treated to date. No deaths have occurred on study. No study-drug related AEs have led to discontinuation of subjects from the study. Below lists each of the cohorts and average time on study as of 17 September 2014:

Cohort #/Name	Dosage	N	Mean (Range) Days on Study
1	100 mg QD	9	181 (7-226))
2	175 mg QD	8	156 (84-174)
3	250 mg QD	7	123 (119-127)
4a	400 mg QD	6	65 (56-78)
2b	100 mg BID	10	38 (1-78)
Ibrutinib Intolerant	200 mg QD	2	4 (2-6)_
Treatment naive	200 mg QD	6	11 (1-22)
Richter's Syndrome	200 mg BID	1	13 (13-13)

BID = twice per day; QD = once per day

This study includes central ECG monitoring with the following schedule:

Study Segment	Day	ECG Acquisition Times
Screening	--	Triplicate at least 1 min apart
Cycle 1	1-2	Single ECG predose, and 1, 2, 4, 6, and 24 h (before Day 2 dose) after 1st dose; window for ECGs at 1, 2, 4, 6 h is ±10 min. The 24 h ECG must be predose on Day 2.
Cycle 1	8	Single ECG predose, and 1, 2, 4, and 6 h after 8th dose; window for ECGs at 1, 2, 4, 6 h is ±10 min
Cycle 1	15, 22, 28	Single ECG 1 h (±10 min) postdose
Cycle 2	15, 28	Single ECG anytime during the visit
Cycles 3 to 6	28	Single ECG anytime during the visit
30-day follow up	--	Single ECG anytime during the visit

Based on the review of the ECG data from 12 September 2014, no clinically significant QTc prolongation has been observed on the study. Two subjects (01-003/100 mg QD and 01-010/250 mg QD) have experienced Grade 1 syncope. Both events were reported as unrelated to ACP-196 by the investigator. One subject (03-001/175 mg QD) experienced myopericarditis (Grade 2) and tachycardia (Grade 1) associated with the myopericarditis. Both the myopericarditis and tachycardia were reported as unrelated to ACP-196 by the investigator. No cardiac AEs related to study drug have been reported to date.

6.2 TABLE OF ASSESSMENTS

Study Procedures[a]	S[b]	Periods 1, 2, 3, and 4[c]																FU[d]
Study Days →		-1	1														2	
Hours →		C-I[e]	-1	-0.75	-0.5	0	0.25	0.5	0.75	1	1.5	2	3	4	6	8	12	24	
Administrative Procedures																			
Informed Consent	x																		
Inclusion/Exclusion Criteria	x	x																	
Medical History	x																		
Safety Evaluations																			
Physical Examination[f]	x	x																x[g]	
Height	x																		
Weight	x	x																	
Safety 12-Lead ECG	x		x[h]															x	
Vital Signs (HR, BP, Resp.R, & T)	x		x[h]								x							x	
Hematology, Serum Chemistry, and Urinalysis	x[i]	x[j]																x[j,g]	
Serum TSH	x																	x[g]	
Serum Pregnancy Test (♀ only)	x	x																x[g]	
Serum FSH (postmenopausal ♀ only)	x																		
Helicobacter pylori Breath Test		x																	
Urine Drug and Alcohol Screen	x	x																	
Urine Cotinine Screen	x																		
HIV/Hepatitis Screen	x																		
Adverse Events Monitoring		x																	x
Concomitant Medication Monitoring	x	x																	
Study Drug Administration / ECG / PK																			
Study Drug Administration						x													
Holter Extracted ECG Sampling			x	x	x		x	x	x	x	x	x	x	x[k]	x	x	x[k]	x	
Blood for PK					x		x	x	x	x	x	x	x	x[k]	x	x	x[k]	x	
Other Procedures																			
Standard meal														x			x		
Confinement in the CRU		x																	
Visit	x																		

a. For details on Procedures, refer to Section 11 of the protocol (Appendix 16.1.1).
b. Within 28 days before the first study drug administration.
c. The washout period was ≥ 5 days between each dose.
d. The clinic attempted to contact subjects using their standard procedures approximately 14 days after the last study drug administration to determine if any AE had occurred since the last dose of study drug(s). Subjects who terminated the study early were contacted if the PI deemed it necessary.
e. Subjects were admitted to the CRU the day before dosing, at the time indicated by the CRU.
f. A full physical examination was performed at screening, each check-in and before check-out in Period 4 or before early termination from the study. A symptom-driven physical examination may have been performed at other times at the PI's discretion.
g. Performed at the end of Period 4 or before early termination from the study.
h. Performed within 24 hours before dosing.
i. Samples for serum chemistry at screening were obtained after a fast of ≥ 12 hours. Samples for fasting cholesterol, triglycerides, amylase, and lipase were collected only at screening.
j. On-study samples for serum chemistry (including check-in) were obtained after a fast of ≥ 8 hours, however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours before the serum chemistry sample was taken.
k. Collected before the meal.

Abbreviations: ♀ = women, AE = adverse event, BP = blood pressure, C-I = check-in, CRU = Clinical Research Unit, ECG = electrocardiogram, FSH = follicle-stimulating hormone, FU = follow-up, HIV = human immunodeficiency virus, HR = heart rate, PI = Principal Investigator, PK = pharmacokinetic, Resp.R = respiratory rate, S = screening, T = temperature, TSH = thyroid-stimulating hormone.

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/s/

MOH JEE NG
10/12/2017

QIANYU DANG
10/12/2017

DHANANJAY D MARATHE
10/12/2017

MICHAEL Y LI
10/12/2017

CHRISTINE E GARNETT
10/12/2017

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

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

Memorandum

Date: October 11, 2017

To: Ashley Lucci Vaughn, Regulatory Project Manager
Division of Hematology Products (DHP)

Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Nisha Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Davis, Team Leader, OPDP

Subject: OPDP Labeling Comments for CALQUENCE® (acalabrutinib) capsules, for oral use

NDA: 210259

In response to DHP's consult request dated June 19, 2017, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for the original NDA submission for CALQUENCE® (acalabrutinib) capsules, for oral use (Calquence).

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI emailed to OPDP on October 6, 2017, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Nisha Patel at (301) 796-3715 or nisha.patel@fda.hhs.gov.

Package Insert

Section	Statement from draft	Comment
Highlights, Warnings and Precautions 6 Adverse Reactions	**Atrial Fibrillation**: Monitor for atrial fibrillation and manage as appropriate (emphasis added). **Atrial Fibrillation** (emphasis added)	We note that the Warnings and Precautions section of the full PI includes the header, "5.5 Atrial Fibrillation **and Flutter**" (emphasis added). OPDP recommends revising the Highlights, Warnings and Precautions section of the PI and Adverse Reactions section of the full PI to include "flutter."
Highlights, Drug Interactions	CYP3A Inhibitors: Avoid co-administration with strong CYP3A inhibitors. Dose adjustments may be recommended.	We note that the Drug Interactions section of the full PI states, "When CALQUENCE is co-administered with moderate CYP3A inhibitors, reduce acalabrutinib dose to 100 mg once daily." Should this information/concept be added to the Highlights, Drug Interactions section of the PI?
1 Indications and Usage	Continued approval for this indication may be contingent upon verification and description of clinical benefit in **confirmatory trials** (emphasis added).	We note that the Highlights, Indications and Usage section of the PI states, "Continued approval for this indication may be contingent upon verification and description of clinical benefit in **a confirmatory trial**" (emphasis added). OPDP recommends revising the Indications and Usage section of the full PI for consistency with the Highlights, Indications and Usage section of the PI.
5 Warnings and Precautions, 5.2 Infection	Monitor patients for signs and symptoms of infection and treat as medically appropriate.	We note that the Highlights, Warnings and Precautions section of the PI states, (b) (4) Should "monitor for fever" be added to the Warnings and Precautions section of the full PI?
5 Warnings and Precautions, 5 (b) (4) Cytopenias	In the CALQUENCE clinical trial LY-004, patients' complete blood counts were assessed monthly during treatment.	We note that the Highlights, Warnings and Precautions section of the PI states, "Monitor complete blood counts monthly during treatment." Should this statement be added to the Warnings and Precautions section of the full PI?
5 Warnings and Precautions		Should the full PI include an "Embryo-Fetal Toxicity" section?

Section	Statement from draft	Comment
17 Patient Counseling Information	<u>Hemorrhage</u> Inform patients to report signs or symptoms of severe bleeding. <u>Infections</u> Inform patients to report signs or symptoms suggestive of infection.	Should the signs and symptoms of these warnings and precautions be added to the Patient Counseling Information section of the full PI?
17 Patient Counseling Information	Advise patients that CALQUENCE capsules should be swallowed whole with a glass of water, **without being** (b) (4) **or chewed** (emphasis added).	We note that the Dosage and Administration section of the full PI states, "Advise patients not to open, break or chew the capsules." OPDP recommends revising the Patient Counseling Information section of the full PI to include "opened" and "broken" versus " (b) (4)

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

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/s/

NISHA PATEL
10/11/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	October 05, 2017
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 210259
Product Name and Strength:	Calquence (acalabrutinib) Capsules, 100 mg
Applicant/Sponsor Name:	Single-Ingredient
Submission Date:	September 27, 2017
OSE RCM #:	2017-1197-1
DMEPA Safety Evaluator:	Leeza Rahimi, Pharm.D.
DMEPA Team Leader:	Hina Mehta, Pharm.D.

1 PURPOSE OF MEMO

Division of Hematology Products (DHP) requested that we review the revised container labels and Professional Sample labels for Calquence (acalabrutinib) 100 mg capsules (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] We note that the Applicant now intends to supply only bottles of the 60 count capsules. Per the Applicant a business decision has been made not to package the (b) (4)-count bottles in one carton. Therefore, there are no labels for the carton to review.

2 CONCLUSION

The revised container labels for Calquence are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Rahimi, L. Label and Labeling Review for Calquence (NDA 210259). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 SEP 12. RCM No.: 2017-1197.

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/s/

LEEZA RAHIMI
10/10/2017

HINA S MEHTA
10/10/2017

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

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: NDA 210259

Application Type: New NDA

Drug Name(s)/Dosage Form(s): acalabrutinib (ACP-196), hard shell capsule

Applicant: Acerta Pharma B.V.

Receipt Date: 06/13/2017

Goal Date: 10/31/2017

1. Regulatory History and Applicant's Main Proposals

Pursuant to Section 505(b)(1) of the Food, Drug and Cosmetic Act and 21 CFR 314.50, Acerta Pharma B.V. (Acerta) has submitted a New Drug Application (NDA 210259) for acalabrutinib 100 mg oral capsules for the treatment of patients with mantel cell lymphoma (MCL) who have received at least one prior therapy.

Acalabrutinib (ACP-196) is an orally bioavailable, covalent inhibitor of Bruton tyrosine kinase (BTK). Acalabrutinib forms a covalent bond with Cys481 in the BTK adenosine triphosphate (ATP) pocket, permanently inactivating the enzyme and resulting in the inhibition of proliferation and survival signals in malignant B cells.

On September 21, 2015, acalabrutinib received Orphan Drug Designation for the treatment of mantle cell lymphoma. Acalabrutinib was recently granted Breakthrough Therapy Designation for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy on July 31, 2017.

Acalabrutinib is a new molecular entity being review under the PDUFA V Program.

As part of this NDA submission, the Applicant also submitted the proposed US Prescribing Information (USPI) in Microsoft Word format.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements of Prescribing Information (SRPI)" checklist (see Section 4 of this review).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies, see Section 4 of this review.

All SRPI format deficiencies of the PI will be conveyed to the applicant during labeling negotiations. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format.

4. Selected Requirements of Prescribing Information

The Selected Requirement of Prescribing Information (SRPI) is a 41-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Highlights

See Appendix for a sample tool illustrating Highlights format.

HIGHLIGHTS GENERAL FORMAT

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

Comment:

YES 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select "NO" unless a waiver has been granted.

Comment:

YES 3. A horizontal line must separate:

- HL from the Table of Contents (TOC), **and**
- TOC from the Full Prescribing Information (FPI).

Comment:

YES 4. All headings in HL (from Recent Major Changes to Use in Specific Populations) must be **bolded** and presented in the center of a horizontal line. (Each horizontal line should extend over the entire width of the column.) The HL headings (from Recent Major Changes to Use in Specific Populations) should be in UPPER CASE letters. See Appendix for HL format.

Comment:

NO 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix for HL format.

Comment: *There appears to be white space between HL heading and HL Limitation Statement. But there is no space before product title (per appendix for HL format).*

YES 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

YES 7. Headings in HL must be presented in the following order:

Heading	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 five labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

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

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

YES 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

YES 11. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

N/A 12. All text in the BW must be **bolded**.

Comment: *Box Warning missing.*

N/A 13. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. Even if there is more than one warning, the term "**WARNING**" and not "**WARNINGS**" should be used. For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings. The BW title should be centered.

Comment: *BW is missing from the appropriate section.*

N/A 14. The BW must always have the verbatim statement "***See full prescribing information for complete boxed warning***." This statement must be placed immediately beneath the BW title, and should be centered and appear in *italics*.

Comment:

N/A 15. The BW must be limited in length to 20 lines. (This includes white space but does not include the BW title and the statement "***See full prescribing information for complete boxed warning.****"*)

Comment:

Recent Major Changes (RMC) in Highlights

N/A 16. RMC pertains to only five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. Labeling sections for RMC must be listed in the same order in HL as they appear in the FPI.

Comment:

N/A 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(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, "Warnings and Precautions, Acute Liver Failure (5.1) --- 8/2015."

Comment:

N/A 18. A changed section must be listed under the RMC heading for at least one year after the date of the labeling change and must be removed at the first printing subsequent to the one year period. (No listing should be one year older than the revision date.)

Comment:

Dosage Forms and Strengths in Highlights

YES 19. For a product that has more than one dosage form (e.g., capsules, tablets, injection), bulleted headings should be used.

Comment:

Contraindications in Highlights

YES 20. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

Comment:

Selected Requirements of Prescribing Information

Adverse Reactions in Highlights

YES 21. 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 which should be a toll-free number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**"

Comment:

Patient Counseling Information Statement in Highlights

YES 22. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

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

- **See 17 for PATIENT COUNSELING INFORMATION**

If a product **has (or will have)** 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:

Revision Date in Highlights

YES 23. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015** ").

Comment:

Contents: Table of Contents (TOC)

See Appendix for a sample tool illustrating Table of Contents format.

YES 24. The TOC should be in a two-column format.

Comment:

YES 25. The following heading must appear at the beginning of the TOC: **"FULL PRESCRIBING INFORMATION: CONTENTS."** This heading should be in all UPPER CASE letters and **bolded**.

Comment:

N/A 26. The same title for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

YES 27. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

YES 28. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (for, of, to) and articles (a, an, the), or conjunctions (or, and)].

Comment:

YES 29. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

YES 30. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."

Comment:

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

YES 31. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

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 Lactation (if not required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, use "**Labor and Delivery**")
8.3 Females and Males of Reproductive Potential (if not required to be in PLLR format, use "**Nursing Mothers**")
8.4 Pediatric Use
8.5 Geriatric Use
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 32. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, *"[see Warnings and Precautions (5.2)]*."

Comment:

N/A 33. For each RMC listed in HL, the corresponding new or modified text in the FPI must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

YES 34. The following heading "**FULL PRESCRIBING INFORMATION"** must be **bolded,** must appear at the beginning of the FPI, and should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

N/A 35. All text in the BW should be **bolded**.

Comment:

N/A 36. The BW must have a title in UPPER CASE, following the word "**WARNING**" and other words to identify the subject of the warning. (Even if there is more than one warning, the term, "**WARNING**" and not "**WARNINGS**" should be used.) For example: "**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**". If there is more than one warning in the BW title, the word "and" in lower case can separate the warnings.

Comment:

CONTRAINDICATIONS Section in the FPI

YES 37. If no Contraindications are known, this section must state "None."

Comment:

ADVERSE REACTIONS Section in the FPI

YES 38. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection), the following verbatim statement (or appropriate modification) should precede the presentation of adverse reactions from clinical trials:

> "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 practice."

Comment:

N/A 39. When postmarketing adverse reaction data are included (typically in the "Postmarketing Experience" subsection), 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:

Selected Requirements of Prescribing Information

PATIENT COUNSELING INFORMATION Section in the FPI

YES 40. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION). The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:

- Advise the patient to read the FDA-approved patient labeling (Patient Information).
- Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide).
- Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Comment:

YES 41. FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide) must not be included as a subsection under Section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix: Highlights and Table of Contents Format

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (non-proprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/201Y
Section Title, Subsection Title (x.x) M/201Y

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use: Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/201Y

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

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/s/

ASHLEY S LUCCI VAUGHN
10/10/2017

THERESA A CARIOTI
10/10/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	September 12, 2017
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 210259
Product Name and Strength:	Calquence (acalabrutinib) Capsules, 100 mg
Product Type:	Single-Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Acerta Pharma B.V.
Submission Date:	June 13, 2017
OSE RCM #:	2017-1197
DMEPA Safety Evaluator:	Leeza Rahimi, Pharm.D.
DMEPA Team Leader:	Hina Mehta, Pharm.D.

1 REASON FOR REVIEW

Acerta Pharmaceutical submitted NDA 210259 for Calquence (acalabrutinib) 100 mg capsules for the treatment of patients with mantle cell lymphoma (MCL) that have received at least one prior therapy on June 13, 2017. The application was requested as and granted a priority review designation.

The Division of Hematology Products (DHP) requested that we review the Prescribing Information (PI), carton, and container labels of the product for the areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factor Review	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA evaluated the submitted PI, carton and container labels for areas of vulnerability in regards to medication error. Our review identified areas in the labels and labeling that can be improved to increase readability and prominence of important information.

We provide our recommendations in Sections 4.1 and 4.2 and recommend their implementation prior to approval of this application.

4 CONCLUSION & RECOMMENDATIONS

We identified areas on the PI, container label and carton labeling that can be improved to increase clarity and prominence of important information to promote the safe use of this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Highlights of Prescribing Information (HPI) and Full Prescribing Information (FPI):

1) Replace "Tradename" with the conditionally acceptable proprietary name throughout the HPI and FPI.

B. Highlights of Prescribing Information: Dosage and Administration

1) Add "approximately 12 hours apart" at the end of the first bullet to ensure this important information is not overlooked.

2) Add statement "Do not break, open, or chew capsule." to second bullet to ensure this important information is not overlooked.

C. Full Prescribing Information (FPI):

1) Section 2 Dosage And Administration:

a) Revise the statement with administration instructions as follows: "Swallow the capsules whole with water. Do not break, open, or chew the capsules."

b) Consider revising the heading for section 2.2 to read: "Dose Modification for Adverse Reaction" to enhance the prominence of the provided dosing information for the adverse reactions.

c) Under section 2.2 Table 1: Recommended Dose Modification for Adverse Reactions, revise numbers 1st, 2nd, 3rd, and 4th to read "first", "second", "third", and "fourth" respectively.

2) Section 3 Dosage Forms And Strengths:

a) Remove the information following "100 mg capsules" as the description of the capsule should be in section 16 How Supplied.

3) Section 16 How Supplied/Storage And Handling:

a) In the storage section, add the temperature unit after each numerical temperature reading. For example, "Store at 20°C- 25°C (68°F-77°F); excursions permitted to 15°C - 30°C (59°F - 86°F) [see USP Controlled Room Temperature]

4.2 RECOMMENDATIONS FOR ACERTA PHARMA

We recommend the following be implemented prior to approval of this NDA:

A. Carton Label:

1) Please replace the term "TRADENAME" with the conditionally acceptable proprietary name.

2) Relocate the net quantity statement (60 capsules) away from the product strength (100 mg), such as to the bottom of the principal display panel. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement. Draft Guidance: Container and Carton, April 2013 (lines 461-463).

3) As currently presented, there is no space allotted for the lot number and expiration. The lot number statement is required on the container and carton labeling when there is sufficient space per 21 CFR 201.10(i)(1). Please ensure the lot number is clearly differentiated from the expiration date. In addition, please ensure that there are no other numbers located in close proximity to the expiration date where it can be mistaken as the expiration date.

4) As currently presented the NDC is denoted by a placeholder. Replace with NDC number and submit for Agency review.

5) Revise the storage information to add the temperature unit after each numerical temperature reading. For example, "Store at 20°C- 25°C (68°F-77°F); excursions permitted to 15°C - 30°C (59° - 86°F) [see USP Controlled Room Temperature].

B. Container Labels ((b) (4) Capsules and 60 Capsules) and Professional Sample:

1) See A.1, A.4, and A.5.

C. Container Label (60 Capsules):

1) See A-3.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Calquence that Acerta submitted on June 13, 2017 and June 16, 2017.

Table 2. Relevant Product Information for Calquence	
Initial Approval Date	N/A
Active Ingredient	acalabrutinib
Indication	For the treatment of patients with mantle cell lymphoma (MCL) that have received at least one prior therapy
Route of Administration	oral
Dosage Form	Capsules
Strength	100 mg
Dose and Frequency	1 capsule twice daily
How Supplied	Bottles of (b) (4) count and 60 count
Storage	Store at 20°C- 25°C (68°F-77°F); excursions permitted to 15°C - 30°C (59°F - 86°F) [see USP Controlled Room Temperature]

APPENDIX B. PREVIOUS DMEPA REVIEWS

On August 01, 2017, we searched DMEPA's previous reviews using the terms, acalabrutinib.

Our search identified zero labeling reviews.

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

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

/s/

LEEZA RAHIMI
09/12/2017

HINA S MEHTA
09/13/2017

CLINICAL INSPECTION SUMMARY

Date	August 18, 2017
From	Anthony Orencia M.D., F.A.C.P., GCPAB Medical Officer Janice Pohlman M.D., M.P.H., GCPAB Team Leader, for Kassa Ayalew, M.D., M.P.H., GCPAB Branch Chief Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Margret Merino, M.D., Medical Officer Tanya Wroblewski, M.D., Clinical Team Leader Ashley Lucci Vaughn, Regulatory Project Manager Division of Hematology Products
NDA	210259
Applicant	Acerta Pharma
Drug	acalabrutinib
NME	Yes
Therapeutic Classification/Status	Bruton's tyrosine kinase (BTK) inhibitor
Proposed Indication	Treatment of patients with mantle cell lymphoma who have (b) (4) at least one prior therapy
Consultation Request Date	June 20, 2017
Summary Goal Date	September 18, 2017
Action Goal Date	October 31, 2017
PDUFA Date	February 13, 2018 [Breakthrough-Priority review]

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites (Drs. Wang and Goy) were selected by the Division of Hematology Products (DHP) for inspection of conduct of Study ACE-LY-004 submitted in support of NDA 210259. Acerta Pharma, the sponsor of the study was also inspected. The study data from these clinical sites as reported by the sponsor are considered to be reliable in support of the requested indication.

The preliminary regulatory classification for Drs. Wang and Goy is No Action Indicated (NAI). The preliminary regulatory classification for the inspection of Acerta Pharma is Voluntary Action Indicated (VAI).

2. BACKGROUND

Acalabrutinib is an irreversible second-generation Bruton's tyrosine kinase (BTK) inhibitor. This new molecular entity is proposed for the treatment of patients with mantle cell lymphoma who had received at least one prior therapy.

The Division of Hematology Products (DHP), requested two domestic clinical sites and sponsor for inspection for this application. The selected clinical sites (particularly Dr. Wang's site), had high enrollment with the potential to have substantial impact on efficacy outcome.

Study ACE-LY-004

Study ACE-LY-004 is a Phase 2, multicenter, open-label, single arm study. The primary study objective is to determine the activity of acalabrutinib in subjects with relapsed or refractory mantle cell lymphoma. The secondary objective is to characterize the safety profile.

Patients received 100 mg of acalabrutinib twice daily continuously, in repeated 28-day cycles, until disease progression or unacceptable treatment-related adverse event(s) occurred. Positron-emission tomography and computed tomography scans were performed at Cycle 2 (within 7 days) and Cycle 6 to confirm complete response or as clinically indicated. Subjects with confirmed complete response did not undergo further PET or CT imaging unless there was probable progressive disease.

The primary endpoint was overall response rate (ORR) as assessed by the clinical investigators per Lugano classification for Non-Hodgkins Lymphoma (NHL). The ORR was defined as the proportion of study subjects achieving a partial or a complete response. The Division of Hematology Products requested that the sponsor include 12 months of follow up from all treatment responders as well as assessment of response for all disease compartments. The study is on-going.

This multicenter study was conducted at over 40 centers internationally in nine countries including Western Europe, Australia and the U.S. There were 124 study subjects who enrolled in the study. The sponsor claimed an 80% treatment response, which is higher than currently available therapies for mantle cell lymphoma.

3. RESULTS (by site):

Name of Clinical Investigator/Sponsor Address	Protocol #/ Site #/# Subjects	Inspection Dates	Classification
Michael Wang, M.D. M.D. Anderson Cancer Center 1515 Holcombe Blvd. Houston, TX 77030	Protocol ACE-LY-004 Site #34 28 total	July 31 to August 4, 2017	Pending: Preliminary NAI
Andre Goy, M.D. 92 Second Street Hackensack, New Jersey 07601	Protocol ACE-LY-004 Site #35 6 total	July 25 to 26, 2017	Pending: Preliminary NAI

Name of Clinical Investigator/Sponsor Address	Protocol #/ Site #/# Subjects	Inspection Dates	Classification
Acerta Pharma 2200 Bridge Parkway, Suite 101 Redwood City, CA 94065	Sponsor of: Protocol ACE-LY-004	August 1 to 15, 2017	Pending: Preliminary VAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data are unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Investigator

1. Michael Wang, M.D./Study ACE-LY-004

The inspection was conducted from July 31 to August 4, 2017. A total of 31 subjects were screened, and 28 subjects were enrolled. There were 14 study subjects who developed progressive disease or disease-related deaths. The study is ongoing for 14 patients. A comprehensive review of 15 subjects' records enrolled at this site was conducted. Partial review for various source records was completed for all the enrolled study subjects.

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.

Source documents for enrolled 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. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practice. No Form FDA 483 (Inspectional Observations) was issued.

2. Andre Goy, M.D./Study ACE-LY-004

The inspection was conducted from July 25 to 26, 2017. A total of six subjects were screened, and six subjects were enrolled. The study is ongoing for the six subjects. An audit of all the subjects' records enrolled at this site 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.

Source documents for enrolled 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. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection. No Form FDA 483 was issued.

Sponsor

3. Acerta Pharma

This inspection was conducted from August 1 to 15, 2017.

The sponsor inspection included review of the following: clinical site set up, site management and monitoring, financial disclosures, and trial master file.

Monitoring plans and monitoring visit reports were reviewed. Review of the monitoring reports conducted by the contract research organization (CRO) for 20 clinical sites demonstrated that the sites received adequate periodic monitoring. IRB approvals, clinical site protocol deviations, and serious adverse event reporting were adequate.

A Form FDA 483 was issued at the end of the inspection for failure of the sponsor to ensure proper monitoring of the study. Specifically:

a. The sponsor's monitors failed to ensure that all revised protocol versions were submitted to the IRB or Ethics Committee within a reasonable time period for approval, at six of 20 clinical sites reviewed. Delay from release of a revised protocol version and submission to the IRB or Ethics Committee ranged from 4 to 11 months.
b. The sponsor monitors failed to provide training documentation that the Clinical Investigators or Sub-Investigators were trained on Protocol ACE-LY-004.

GCPAB Reviewer comments:
The NDA submission contains the original version of this Phase 2 protocol, along with six amended versions of the protocol. Amended versions of the protocol provided updated safety information based on ongoing nonclinical and other clinical study experience. The most recent version of the protocol in the application is Version 6.0 dated July 19, 2016, however a newer version was available at the sponsor (Version 7.0 dated April 8, 2017). Based on review of summary of changes for each version, it appears that edits made to amended versions were primarily for clarity, rather than change in procedures. Amendment 3 did increase the frequency of pregnancy testing for women of childbearing potential. Amendments 5 and 6 decreased the overall number of PET/CT scans being performed (therefore decreasing radiation exposure), as well as providing more flexibility in scheduling. Pending more details regarding clinical sites and specific protocol versions involved, it seems likely that some revisions of the protocol should have been more promptly reviewed by the IRB, however the revisions themselves did not seem to enhance the safety risk that subjects would have been exposed to.

These observations were shared with DHP who did not consider these observations to be critical, in terms of reliability of the data.

The sponsor otherwise appeared to maintain adequate oversight of the clinical trial.

{See appended electronic signature page}

Anthony Orencia, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Janice Pohlman, M.D., M.P.H.
Team Leader, Good Clinical Practice Assessment Branch, for
Kassa Ayalew, M.D., M.P.H., Branch Chief
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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

/s/

ANTHONY J ORENCIA
08/18/2017

JANICE K POHLMAN
08/18/2017

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 # 210259 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: Calquence (TBD) Established/Proper Name: acalabrutinib (ACP-196) Dosage Form: Hard shell capsule Strengths: 100 mg Route(s) of Administration: oral form		
Applicant: Acerta Pharma B.V. Agent for Applicant (if applicable):		
Date of Application: June 13, 2017 Date of Receipt: June 13, 2017 Date clock started after Unacceptable for Filing (UN):		
PDUFA Goal Date: February 13, 2018	Action Goal Date (if different): October 31, 2017	
Filing Date: August 12, 2017	Date of Filing Meeting: July 18, 2017	
Chemical Classification (original NDAs only) : ☒ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☐ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): **Treatment of patients with mantel cell lymphoma who have recieved at least one prior therapy**		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2)NDA/NDA Supplement: Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.***		☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***		☐ 351(a) ☐ 351(k)

Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)
☐ Fast Track Designation ☒ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☒ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): **IND 118717**	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in electronic archive? ***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 electronic archive.***	☒	☐		

Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***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*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***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 from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☐ Paid ☒ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
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. Contact the User Fee Staff. If appropriate, send UN letter.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☐ Yes ☐ No

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted questions below:	☐	☒		
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☐	X	

• 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)].**	☐	☐	X	
• 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)]?** ***If you answered yes to any of the above bulleted 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 for advice.***	☐	☐	X	
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☐	X	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, 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 and GAIN exclusivity will extend both of the timeframes in this provision by 6 months and five years, respectively. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

• If FDA has approved one or more pharmaceutically equivalent (PE) products in one or more NDAs before the submission date of the original 505(b)(2) application, did the applicant identify one such product as a listed drug (or an additional listed drug) relied upon and provide an appropriate patent certification or statement **[see 21 CFR 314.50(i)(1)(i)(C) and 314.54]**? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If no,** include template language in the 74-day letter. ***Failure to identify a PE is an approvability issue but not a filing issue [see 21 CFR 314.125(b)(19)]*** ***Note: Pharmaceutical equivalents** are drug products in identical dosage forms and route(s) of administration that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.*	☐	☐	X	

Exclusivity	YES	NO	NA	Comment
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug 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)(14)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: **5 Years** ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☒	☐	☐	
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
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)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note****: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ 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).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.	☒	☐		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	
Forms and Certifications				
***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 (3397/3792), 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.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	

[1] http://www fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf

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)?	☒	☐	☐	
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)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☒	☐		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***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].*** ***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…"*	☒	☐	☐	
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? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
For NMEs: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* For non-NMEs: *Date of consult sent to Controlled Substance Staff* :	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
PREA Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]*** ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), 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 reviewed by PeRC prior to approval of the application/supplement.*	☒	☐		**Orphan drug designation**
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☒	Orphan drug designation
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☐	☐	☐	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required[3]***	☐	☒		

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☒ Other (specify) Investigator Brochure			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in Physician Labeling Rule (PLR) format?[4]	☒	☐		
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? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☒	☐ ☐	☐ ☐	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR 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? ***If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.***	☐	☐	☒	

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576 htm

Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	☒	☐	☐	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***	☐	☐		
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:*** ***DDMAC, 06/19/17*** ***DMPP-Patient Labeling, 06/19/17*** ***DRISK, 06/20/17*** ***OSI, 06/20/17*** ***DMEPA, 06/22/17***	☒	☐	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** March 21, 2016	☒	☐	N/A	
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** June 02, 2017	☒	☐		

Any Special Protocol Assessments (SPAs)? **Date(s):**	☐	☒		

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 18, 2017

BACKGROUND: Pursuant to Section 505(b)(1) of the Food, Drug and Cosmetic Act and 21 CFR 314.50, Acerta Pharma B.V. (Acerta) submitted a New Drug Application (NDA) for acalabrutinib 100 mg oral capsules for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. All modules to this application were submitted on June 13, 2017.

Acalabrutinib (ACP-196) is an orally bioavailable, covalent inhibitor of Bruton tyrosine kinase (BTK). Acalabrutinib forms a covalent bond with Cys481 in the BTK adenosine triphosphate (ATP) pocket, permanently inactivating the enzyme and resulting in the inhibition of proliferation and survival signals in malignant B cells.

On September 21, 2015, acalabrutinib received Orphan Drug Designation for the treatment of mantle cell lymphoma. Acalabrutinib was recently granted Breakthrough Therapy Designation for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy on July 31, 2017.

Acalabrutinib is a new molecular entity being review under the PDUFA V Program.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Ashley Lucci Vaughn	Y
	CPMS/TL:	Theresa Carioti	Y
Cross-Discipline Team Leader (CDTL)	Tanya Wroblewski		Y
Division Director/Deputy	Al Deisseroth		Y
Office Director/Deputy	Richard Pazdur		N
Clinical	Reviewer:	Margret Merino	Y
	TL:	Tanya Wroblewski	Y
Clinical Pharmacology	Reviewer:	Vicky Hsu	Y
	TL:	Bahru Habtemariam	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:	Yuan Xu	Y
	TL:	Jiang Liu	Y
Biostatistics	Reviewer:		

	TL:		
Nonclinical Pharmacology/Toxicology)	Reviewer:	Brenda Gherke	N
	TL:	Chris Sheth	Y
Statistics (carcinogenicity)	Reviewer:	Jingjing Ye	Y
	TL:	Lei Nie	Y
Product Quality (CMC) Review Team:	ATL:	Sherita McLamore	Y
	RBPM:		
• Drug Substance	Reviewer:		
• Drug Product	Reviewer:		
• Process	Reviewer:		
• Microbiology	Reviewer:		
• Facility	Reviewer:		
• Biopharmaceutics	Reviewer:	Yang Zhao/ Okpo Eradiri	Y
• Immunogenicity	Reviewer:		
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)			
OMP/OMPI/DMPP (MedGuide, PPI, IFU)	Reviewer:	Sharon Mills	Y
	TL:	Barbera Fuller	
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labeling)	Reviewer:	Nisha Patel	Y
	TL:		
OSE/DMEPA (proprietary name, carton/container labeling)	Reviewer:	Leeza Rahimi	Y
	TL:		
OSE/DRISK (REMS)	Reviewer:	Ingrid Chapman	Y
	TL:	Elizabeth Everhart	
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		

Other reviewers/disciplines			
OSI/Clinical Inspections	Reviewer:	Anthony Orencia	Y
	TL:	Janice Pohlman	
Other attendees			
	*For additional lines, right click here and select "insert rows below"		

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues: ○ 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? Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable ☒ No comments

CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an NME NDA or original BLA, include the reason. For example:*** ○ ***this drug/biologic is not the first in its class*** ○ ***the clinical study design was acceptable*** ○ ***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***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:
• 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? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CONTROLLED SUBSTANCE STAFF • Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
New Molecular Entity (NDAs only) • Is the product an NME?	 ☒ YES ☐ NO
Environmental Assessment • Categorical exclusion for environmental assessment EA) requested? **If no**, was a complete EA submitted? **Comments**:	 ☒ YES ☐ NO ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? **Comments**:	☐ Not Applicable ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review (BLAs only) **Comments**:	☐ Review issues for 74-day letter
APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)	☐ N/A
• 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?	☒ YES ☐ NO
• If so, were the late submission components all submitted within 30 days?	☒ YES ☐ NO
• What late submission components, if any, arrived after 30 days?	N/A
• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?	☒ YES ☐ NO
• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?	☒ YES ☐ NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Ann T. Farrell, MD **Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in "the Program" PDUFA V): August 18, 2017 **21st Century Review Milestones (see attached)** (listing review milestones in this document is optional): **Comments**:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. Review Classification: ☐ Standard Review ☒ Priority Review
ACTION ITEMS	
☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
☐	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
☐	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.
☒	If priority review, notify applicant in writing by day 60 (see CST for choices)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☒	Update the PDUFA V DARRTS page (for applications in the Program)
☐	Other

Annual review of template by OND ADRAs completed: April 2016

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

/s/

ASHLEY S LUCCI VAUGHN
08/01/2017

THERESA A CARIOTI
08/01/2017