CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216387Orig1Orig2s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 118717

MEETING REQUEST-
WRITTEN RESPONSES

Acerta Pharma BV
c/o AstraZeneca
Attention: Marilyn Kiral, PharmD, PhD
Regulatory Affairs Director
One Medimmune Way
Gaithersburg, MD 20878

Dear Dr. Kiral:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for acalabrutinib.

We also refer to your submission dated April 1, 2021, containing a meeting request. The purpose of the requested meeting was to discuss plans for a new tablet formulation of acalabrutinib.

Further reference is made to our Meeting Granted letter dated April 9, 2021, wherein we agreed that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your May 1, 2021 background package.

If you have any questions, please contact Denise Felluca, Regulatory Project Manager, at denise.felluca@fda.hhs.gov or 301-796-4574.

Sincerely,

{See appended electronic signature page}

Yvette Kasamon, MD
Clinical Team Leader
Division of Hematologic Malignancies II
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosure:

- Written Responses

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

WRITTEN RESPONSES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Application Number:	IND 118717
Product Name:	acalabrutinib
Indication:	Treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)
Sponsor Name:	Acerta Pharma B.V.
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act

1.0 BACKGROUND

Calquence (acalabrutinib) was granted accelerated approval October 31, 2017, for the treatment of adult patients with relapsed or refractory mantel cell lymphoma (MCL) and was approved (NDA 210259/S-006 and NDA 210259/S-007) for the treatment of adult patients with CLL and small lymphocytic leukemia (SLL) in November 2019.

The purpose of this pre-NDA meeting is to discuss plans for a new tablet formulation of acalabrutinib. The currently approved Calquence (acalabrutinib) product are capsules.

2.0 QUESTIONS AND RESPONSES

Question 1: *Does the Agency agree that the proposed Table of Contents is appropriate and sufficient to support review of the NDA? (pages 6-8 of the briefing package)*

FDA Response to Question 1:
Yes, your Table of Contents appears reasonable, please use the following guide as a reference when preparing your submission as some required regulatory forms were left out, for example, debarment certification. https://www.fda.gov/media/76444/download

Question 2 *AstraZeneca would like to offer an orientation meeting via teleconference in support of the NDA where AstraZeneca would walk FDA reviewers through the results of the BE study, NDA documentation, drug substance and drug product control strategy, eCRT package, and programming details. Does the Biopharmaceutics and CMC review teams at FDA wish to have such a session, and if so, when during the review period would this be appropriate?*

FDA Response to Question 2:
Yes, the Division of Biopharmaceutics would agree for a CMC-AOM meeting, where the Sponsor/Applicant could walk through the Quality/CMC package including the PBBM Report justifying the proposed dissolution specification and drug substance particle size

specifications. Generally, the Agency will arrange the AOM to occur approximately within 30-45 days following receipt of the NDA.

Question 3: *AstraZeneca will replace the existing capsule product with the acalabrutinib maleate tablet formulation within 3-6 months and retain the current tradename of Calquence to avoid disruption to patients' treatment regimen. Does FDA agree that AZ can retain the Calquence tradename?*

FDA Response to Question 3:
The acceptability of the proprietary name will be a review issue**.** Please submit the proprietary name review request with the NDA submission.

If you require information on submitting a request for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry: *Contents of a Complete Submission for the Evaluation of Proprietary Names* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)

- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022, (https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM511438.pdf)

Please clarify your intention with respect to the capsule formulation.

Additional Clinical Pharmacology Comment

Regarding your proposed NDA submission for the AMT:

1. Submit all SDTM and ADaM datasets and corresponding documentation for your BE Study **D8223C00013**.

3.0 Other Important Meeting Information

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration

are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.[2]

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of

[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

reproductive potential.

- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidance.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[6]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[7]

[6] http://www.fda.gov/ectd
[7] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[8]

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims.*

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial

[8] https://www.fda.gov/media/85061/download

are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[9]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.

- Assessment Aid[10]

Advancing Oncology Decentralized Trials

FDA Oncology requests that applicants submitting data to support NDA/BLA applications to voluntarily add flags to datasets in order to discriminate between REMOTE assessments and TRIAL SITE assessments. The intent is to allow FDA to learn from trials conducted in the COVID-19 pandemic that permitted some aspects of trial conduct to be performed remote from trial sites to reduce potential COVID exposure. The FDA hopes to learn more about the opportunities and challenges of these REMOTE modifications in order to foster use of “decentralize” aspects of clinical trials prospectively in the post-COVID era.

For details please refer to: https://www.fda.gov/about-fda/oncology-center-excellence/advancing-oncology-decentralized-trials

[9] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[10] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

YVETTE L KASAMON
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CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 118717
Request Receipt Date	19 June 2019
Product	Acalabrutinib
Indication	Acalabrutinib as monotherapy for the treatment of adult patients with chronic lymphocytic leukemia
Drug Class/Mechanism of Action	BTK inhibitor (2nd generation)
Sponsor	Acerta Pharma
ODE/Division	Office of Hematology and Oncology Products/ Division of Hematology Products
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	18 August 2019

Note: This document must be uploaded into CDER's electronic document archival system as a ***clinical review: REV-CLINICAL-24 (Breakthrough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes,*** *and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR)****.*** *Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

Indication: Acalabrutinib as monotherapy for the treatment of adult patients with chronic lymphocytic leukemia.

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

3. **Was the BTDR submitted to a PIND?** ☐YES ☒NO
   If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 4a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
☐ Undetermined
☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked "No", BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history.

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

Brief Description of the Drug

Acalabrutinib is a second generation, orally available inhibitor of Bruton's Tyrosine Kinase (BTK). Acalabrutinib irreversibly binds to a cysteine residue in active site and inactivates BTK, which plays a critical role in the B-cell receptor (BCR) signaling pathway. Acalabrutinib has demonstrated selective inhibition of BTK, with inhibition of only two other kinases, bone marrow kinase on X chromosome (BMX) and erb-b2 receptor tyrosine kinase (ERBB4). Acalabrutinib at a dose of 100mg BID provided near complete BTK occupancy over 24 hours at steady state in patients with Chronic Lymphocytic Leukemia (CLL) and was chosen as the dose to further investigate in several B cell malignancies. Acalabrutinib was granted accelerated approval for patients with mantle cell lymphoma who have received at least one prior therapy and is being explored in several B-cell malignancies (non Hodgkin lymphoma, Waldenström macroglobulinemia, CLL, and select solid tumors). There are currently 25 ongoing company sponsored trials in oncology with over 2261 patients exposed in company sponsored trials. An sNDA is planned for Q3/4 2019 for an indication in treatment naïve and relapsed and refractory CLL based the trials included in the two randomized trials ACE-CL-007 (treatment naïve CLL) and ACE-CL-309 (relapsed and refractory CLL) included in this breakthrough request.

Brief Description of the Disease and Intended Population

Patients with CLL represent approximately 27% of all leukemias in the United States, with an incidence of 4.9 per 100,000 persons, and is the most common leukemia in Western countries.[1] CLL is a disease of older adults, majority over 70 years of age, and many present with coexisting health conditions. At diagnosis, around 90% of patients have comorbid conditions and over 40% have at least one major comorbidity that includes cardiopulmonary or vascular disease, diabetes, or a secondary malignancy.[2] The number of estimated deaths from CLL in 2019 is 3,930 (NCI SEER website, 2019). In general, CLL is rarely curable except for the few patients who undergo stem cell transplant. Most patients eventually relapse after initial treatment and prognosis after relapse remains poor.

The landscape for treatment for patients with CLL has evolved in recent years and continues to evolve. There has been trend toward the use of chemotherapy free regimens (molecularly targeted agents either alone or in combination with anti – CD20 therapy).[3,4] Several randomized trials in both the treatment naïve and relapsed and refractory setting have demonstrated a progression free survival advantage of oral molecular targeted therapy in combination with anti-CD20 therapy over standard chemoimmunotherapy.[5]

Treatment naïve CLL:

For "fit" patients, fludarabine, cyclophosphamide, rituximab (FCR) chemoimmunotherapy remains standard frontline therapy. Complete remission (CR) rates with FCR treatment range from 40% to 72% with a median progression-free survival (PFS) of 4.3 to 6.4 years.[6] For patients with treatment naïve CLL who have underlying co-morbidities and are not eligible for FCR therapy, chemotherapy in combination with anti-CD20 therapy or ibrutinib or venetoclax in combination with anti-CD20 therapy are available. Single-agent ibrutinib is also approved in this setting based on randomized trial demonstrating a PFS and OS overall surivival advantage over single agent chlorambucil.[7]

Two recent approvals of ibrutinib in combination with obinutuzumab (iLLUMINATE trial) and venetoclax in combination with obinutuzumab (CLL14 trial) demonstrated superior PFS compared to a comparator arm of chlorambucil-obinutuzumab. For patients with high risk genetic features (17p deletion or unmutated-IGHV), conventional chemoimmunotherapy produces inferior outcomes and based on recent trial results, ibrutinib or venetoclax is indicated for these patients (venetoclax and ibrutinib USPI).[8] Several phase 3 trials are ongoing with novel targeted agents and frontline therapy for CLL will continue to evolve.

Relapsed and Refractory CLL

For patients with relapsed and refractory disease, treatment depends on prior therapy and comorbidities. Given the age and high percentage of comorbidity, chemotherapy free options (targeted agents and anti-CD20 agents) are often pursued. Ibrutinib and venetoclax are approved either alone or in combination with anti-CD20 therapy. Idelalisib an

oral small molecule inhibitor of phosphatidylinositol 3-kinas (PI3K). Idelalisib is approved in combination with rituximab for patients with relapsed CLL in patients for whom rituximab alone would be considered appropriate therapy due to comorbidities.

8. Information related to endpoints used in the available clinical data:

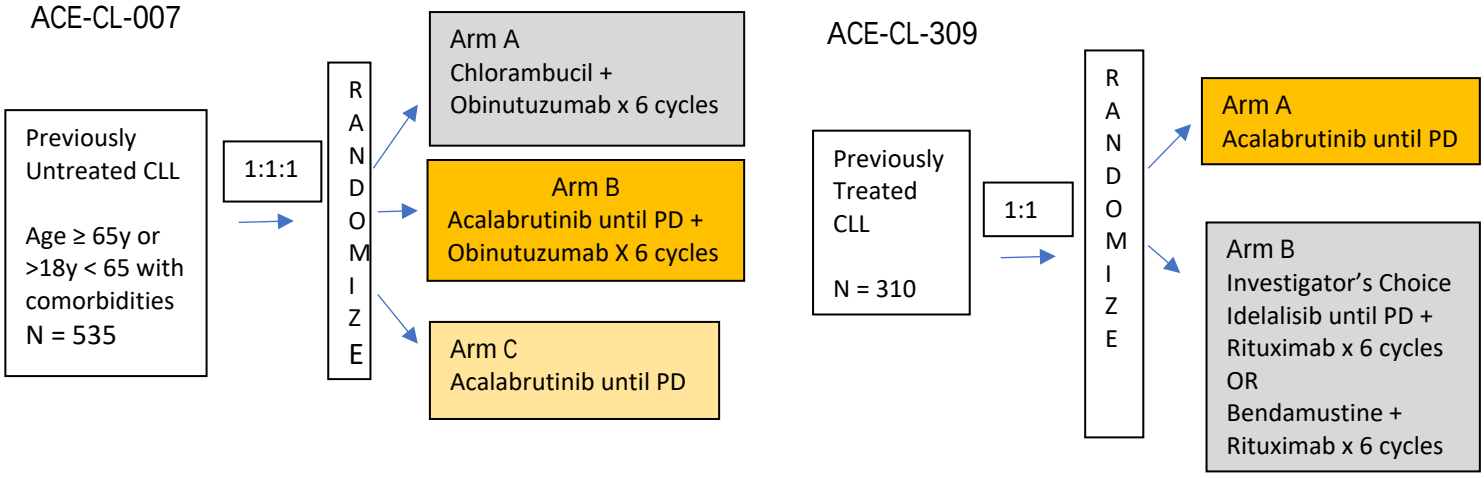
a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The primary efficacy endpoints for both trials supporting the BTDR is PFS per independent review committee (IRC).

Table 1: Summary of Trial Characteristics

	ACE-CL-007 **ELEVATE - TN**	**ACE-CL-309** **ASCEND**
Population	Previously untreated CLL	Previously treated CLL
Treatment Arms	A: Obinutuzumab + Chlorambucil B: Acalabrutinib + Obinutuzumab C: Acalabrutinib Randomized 1:1:1	A: Acalabrutinib B: Investigator Choice of Idelalisib + Rituximab vs. Bendamustine + Rituximab Randomized 1:1
Primary Endpoint	**PFS- IRC assessed** **Arm A vs Arm B**	**PFS- IRC assessed**
Key Secondary Endpoints	PFS- IRC assessed: Arm A vs Arm C ORR by IRC OS Time to Next Treatment	IRC assessed ORR OS TTNT Duration of Response

Figure 1: Trial schemas



b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease.

In patients with untreated CLL, the Division considers the endpoint of IRC-assessed PFS for regular approval. Complete remissnio rate, and overall response rate (ORR) are considered key secondary endpoints to support establishment of clinical benefit for patients with untreated CLL.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

None.

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population.

Treatment Naïve CLL:
The trials supporting the BTDR, the ACE-CL-007, enrolled newly diagnosed patients with CLL with comorbidities, thus the relevant available therapies are those indicated for patients with previously untreated CLL deemed ineligible for intensive therapy. Standard of care regimens include Bendamustine and rituximab (BR) associated with a mPFS of 24-42 months and chlorambucil + obinutuzumab (GC) which has been reported to have a mPFS of 19-29 months in the treatment naïve population.[3,9] Use of venetoclax plus obinutuzumab or ibrutinib plus obinutuzumab is approved for this population based on a demonstration of a PFS advantage compared to obinutuzumab plus chlorambucil. Single-agent ibrutinib is also approved for these patients based on a trial comparing ibrutinib to chlorambucil. Therefore, for treatment naïve patients who are unfit for intensive therapy, venetoclax plus obinutuzumab and ibrutinib plus obinutuzumab are currently recommended therapies.

The table below summarizes the most recently approved therapies for treatment naïve CLL and the results of the randomized trials leading to recent approvals based on IRC-assessed PFS. There is no single agent therapy approved based on the demonstration of an advantage over combination therapy.

Table 2: Available therapy, TN CLL unfit for intensive therapy

Study Year Approved	Regimen	Study population	Patient Number	PFS	HR
RESONATE-2 2016	Ibrutinib vs. Chlorambucil	Untreated CLL ≥ 65 years	N = 136 vs. 133	24-months: 89% vs. 34%	0.12 (0.07, 0.19)
iLLUMINATE 2019	Obinutuzumab + ibrutinib vs. Obinutuzumab + chlorambucil	Untreated CLL ≥ 65 years or CIRS > 6 or CrCl < 70 ml/min	N = 113 vs. 116	30-months: 79% vs. 31%	0.23 (0.14, 0.37)
CLL14 2019	Obinutuzumab + venetoclax vs. Obinutuzumab + chlorambucil	Untreated CLL with CIRS > 6 or CrCl < 70 ml/min	N = 216 vs. 216	24-months: 89% vs. 64%	0.33 (0.22, 0.51)
ACE-CL-007 (included in this BTDR)	Obinutuzumab + Chlorambucil vs. Acalabrutinib + Obinutuzumab	*Untreated* CLL ≥ 65 years or CIRS > 6 or CrCl < 70 ml/min	N =177 vs. 179	30-months: 90% vs 34%	0.1 (0.06, 0.17)
	Obinutuzumab + Chlorambucil vs. Acalabrutinib		N = 177 vs. 179	30 months 82% vs 34%	0.2 (0.13, 0.3)

Previously Treated CLL:

The trials supporting the BTDR, the ACE-CL-309, enrolled patients with CLL who had received at least one prior therapy, and thus the relevant available therapies are those indicated for patients with previously treated CLL. Currently molecularly targeted agents alone or in combination with chemoimmunotherapy are approved in this setting. The trials supporting the approvals of ibrutinib, venetoclax and idelalisib for R/R CLL based on randomized trials with a PFS endpoint are described in the table below. There is no single agent therapy that has been approved based on a comparison to combination therapy.

Table 3: Available Therapy, R/R CLL:

Study Year Approved	Regimen	Study population	Trial Design Randomized	mPFS	PFS HR
RESONATE 2014	Ibrutinib vs. ofatumumab	CLL ≥ with at least one prior therapy	N = 195 vs 196	NE vs. 8.1 months	0.22 (0.15, 0.32)
GS-US-312-0116 2014	Idelalisib + Rituximab vs. Placebo + Rituximab	CLL with at least one prior therapy unable to tolerate standard chemoimmunotherapy	N = 110 vs. 110	19.4 months vs. 6.5 months	HR 0.15 (13.4, 57.5)
HELIOS 2016	Ibrutinib + Bendamustine and Rituximab vs Bendamustine and Rituximab	CLL with at least one prior therapy	N = 289 vs. 289	NE vs 13.3 months	HR 0.2 (0.15, 0.28)
MURANO 2018	Venetoclax + Rituximab vs. Bendamustine + Rituximab	CLL with at least one prior therapy	N = 194 vs. 195	NE (NE, NE) vs. 18.1 months	0.19 (0.13, 0.28)
ACE-CL-309 (Included in this BTDR)	Acalabrutinib vs. Investigator Choice (Idelalisib + Rituximab or Bendamustine + Rituximab)	CLL with at least one prior therapy	N = 155 vs. 155	NR vs 16.5 months	0.31 (0.2, 0.49)

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

Ibrutinib, a first generation BTK inhibitor was granted breakthrough designation for CLL with 17 p deletion in March of 2013.

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

Venetoclax, an oral BCL-2 inhibitor was granted breakthrough designation in February of 2019 in combination with obinutuzumab for the treatment of adult patients with CLL based on the CLL14 trial results and in December of 2015 for patients with relapsed or refractory CLL in combination with rituximab based on the MURANO trial results.

11. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

The BTDR is based on results in patients with CLL from two phase III trials, ACE-CL-007 (Table 3), and ACE-CL-309 (Table 4)

Table 4: ACE – CL - 007

Design	Phase 3, randomized, open-label trial evaluating obinutuzumab plus chlorambucil vs acalabrutinib plus obinutuzumab vs acalabrutinib
Population	Adult patients with previously untreated CLL - ≥ 65 years OR - > 18 years old and < 65 years old with comorbidities - Total Cumulative Illness Rating Scale (CIRS) score > 6 or CrCl 30- 69 mL/min
Treatment plan	Patients were randomized 1:1:1 to receive 28-day cycles in 1 of the following treatment groups: 1. Standard-of-care arm A: Obinutuzumab + Chlorambucil (obino+Clb) for 6 cycles 2. Experimental arm B: Acalabrutinib + Obinutuzumab for 6 cycles then acalabrutinib until PD or toxicity 3. Experimental Arm C: Acalabrutinib continuously until disease progression or toxicity
Treatment duration	Treatment continued until disease progression, unacceptable toxicity, death, or treatment completed
Sample size	535
Primary efficacy endpoint	Progression-free survival per independent review: Arm A vs B
Secondary efficacy endpoints	PFS by IRC: Arm A vs. C, ORR by IRC, OS, TTNT: Arm A vs. B and A vs C,

Table 5: ACE-CL-309

Design	Phase 3, randomized, open-label trial evaluating acalabrutinib vs investigator's choice (idelalisib + rituximab or bendamustine + rituximab)
Population	Adult patients with relapsed or refractory CLL
Treatment plan	Patients were randomized 1:1to receive 1 of the following treatments: 1. Experimental Arm A: Acalabrutinib 100mg PO BID continuously until PD or toxicity 2. Investigator Choice Arm B: Idelalisib + Rituximab x 6 cycles or Bendamustine + Rituximab x 6 cycles
Treatment duration	Acalabrutinib treatment continued until disease progression, unacceptable toxicity, death, or treatment completed
Sample size	310
Primary efficacy endpoint	Progression-free survival per independent review: Arm A vs B
Secondary efficacy endpoints	IRC-assessed ORR, OS, TTNT, DOR, Patient Reported Outcomes (FACIT Fatigue)

[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

Patient Characteristics

In the ACE-CL-007 trial, the median patient age was 70 years (range: 41 to 91 years), 61% were male, and 93% were White. Forty-seven percent of patients had Rai stage III or IV disease, 12% had a CIRS score > 6, and 93% had an ECOG of 0-1. Nine percent of patients had a 17p deletion and 63% had unmutated-IGHV. Demographics and underlying disease characteristics were generally balanced amongst the study arms.

In the ACE-CL-309 trial, the median patient age was 67 years (range: 32-90 years), 67% were male, and 92% were White. Forty-one percent of patients had Rai stage III or IV disease. Sixteen percent of patients had a 17p deletion and 78% had unmutated-IGHV. The median number of therapies was 2, number of prior therapies and types of prior therapies as well as demographics and underlying disease characteristics were generally balanced amongst the study arms.

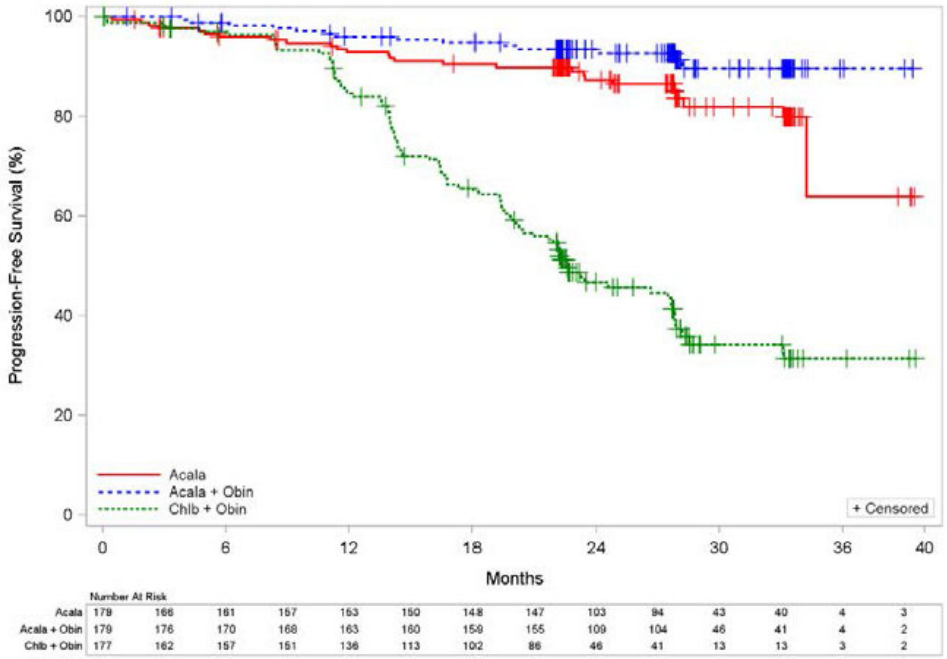
Efficacy

Efficacy was based on PFS per IRC. Other efficacy measures were ORR, and OS although data is immature for OS at the time of the interim analysis.

Kaplan Meier curvers for PFS for the trials displayed in Figure 2 and Figure 3.

In Trial ACE-CL-007, both acalabrutinib in combination with obinutuzumab and acalabrutinib monotherapy demonstrated a statistically significant improvement in PFS compared with obinutuzumab plus chlorambucil, with HR of 0.1 and 0.2 respectively.

Figure 2: Kaplan-Meier Plot for PFS by IRC, ITT population, ACE-CL-007 (Treatment Naïve CLL)



Acala + Obin vs. Chlb + Obin
HR of 0.10
(95% CI 0.06, 0.17;
p < 0.0001

Acala vs. Chlb + Obin
HR: 0.20
(95% CI 0.13, 0.30)
p < 00.0001

Median Follow up: 28.3 months

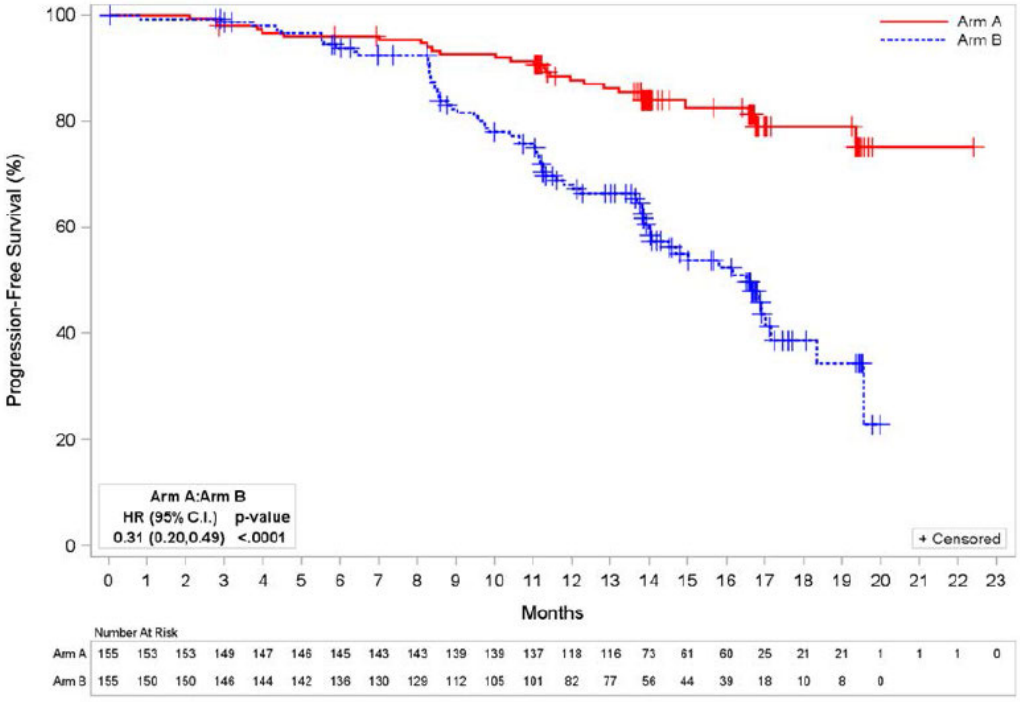
Additionally, in ACE-CL-007, overall response rates were higher in the acalabrutinib arms comparted to the obinutuzumab chlorambucil arm as displayed in the table below.

Table 6: ACE-CL-007 Efficacy Results

Primary and Key Secondary Endpoints	Obinutuzumab + Chlorambucil N = 177	Acalabrutinib + Obinutuzumab N = 179	Acalabrutinib N = 179
Progression-free Survival per IRC			
PFS events, n (%)	93 (53%)	14 (8%) (43.9%)	26 (15%)
Median PFS, months (95% CI)	22.6 (20.2, 28)	NR	NR
Hazard ratio (95% CI) [a]	0.10 (0.06, 0.17)		0.2 (0.13, 0.3)
P-value	<0.0001		<0.0001
Overall Response Rate			
% (95% CI)	79% (72, 84)	94% (89,97)	86% (80,90)
Overall Survival			
Number of deaths, n (%)	17 (9.6%)	9 (5%)	11 (6)
Median OS, months (95% CI)	NE (NE)	NE (NE)	
Hazard ratio (95% CI) [a]	0.47 (0.21, 1.05)		0.6 (0.28, 1.27)
P-value	0.056		0.156
CI: Confidence interval, NE: Not estimable [a] Based on stratified Cox's proportional hazard model			

In Trial ACE-CL-309, both acalabrutinib demonstrated a statistically significant improvement in PFS compared with investiagator choice of either bendamustine plus rituximab or idelalisib plus rituximab HR of 0.31 (05% CI 0.2-0.49), p < 0.0001.

Figure 3: Kaplan Meier PFS by IRC, ITT population ACE-CL-309 (R/R CLL)



Median follow-up 16.1 mo in acalabrutinib and 15.7 mo in IR/BR

Table 7: ACE-CL-309 Efficacy Results

Primary and Key Secondary Endpoints	Acalabrutinib (N=155)	Investigator Choice (N=155)
Progression-free Survival per IRC		
PFS events, n (%)	27 (17.4%)	68 (43.9%)
Median PFS, months (95% CI)	NR	16.5 (14, 17.1
Hazard ratio (95% CI)[a]	0.31 (0.2 0.49)	
P-value[b]	<0.0001	
Overall Response Rate		
% (95% CI)	81% (74, 87)	76% (68, 82)
Overall Survival		
Number of deaths, n (%)	15 (9.7%)	18 (11.6%)
Median OS, months (95% CI)	NE (NE)	NE (NE)
Hazard ratio (95% CI)[a]	0.84 (0.42, 1.66)	
P-value[b]	0.60	

CI: Confidence interval, NE: Not estimable
[a] Based on stratified Cox's proportional hazard model
[b] Based on stratified log-rank test

Safety

In ACE-CL-007, the median duration of exposure of acalabrutinib was 28 months for both acalabrutinib arms, 155 days and 182 days for obinutuzumab and chlorambucil respectively in the comparator arm. There were 4 (2.4%) patient deaths due to AE on the chlorambucil + obinutuzumab arm, 5 (2.8%) on the Acala + Obino arm and 6 (3.4%) on the acalabrutinib arm. The majority of treatment emergent deaths were due to infection (6/15) and other malignancy (4). The rates of discontinuation of treatment due to AE were higher in the comparator arm (14%) than the two study arms (11% acala + obino) and 10% (acalabrutinib). Serious adverse events (SAE) were reported at higher numbers in the acalabrutinib + obinutuzumab (39%) and acalabrutinib (32%) compared to the comparator (23%) arm. The AEs of atrial fibrillation and major hemorrhage, which are known to be associated with BTK inhibitors were reported to be higher in the acalabrutinib arms compared to the control arm. A summary of SAEs and events of clinical interest are displayed in the table below:

ACE-CL-007	Chlorambucil + Obino	Acala + Obino	Acalabrutinib
SAEs	38 (23%)	69 (39%)	57 (32%)
Major hemorrhage	0	3 (1.7)	3 (1.7%)
≥ Grade 3 Atrial fibrillation	0	1 (0.6%)	0
Second Primary Malignancy Excluding non-melanoma skin	6 (4%) 3 (2%))	19 (11%) 10 (6%)	15 (9%) 5 (3%)

In a similar study comparing ibrutinib + obinutuzumab to chlorambucil + obinutuzumab (N = 113 and 115) the rates of ≥ grade 3 atrial fibrillation were 5% (ibrutinib + Obino) vs 0 (Chlorambucil vs obino), suggesting that acalabrutinib may be associated with less off target cardiac toxicity than the 1st generation BTK inhibitor, ibrutinib.

Cytopenias of any type were reported at higher rates in the chlorambucil arm compared to either of the acalabrutinib arms.

In the ACE-CL-309 trial, the median duration of exposure of acalabrutinib was 16 months for acalabrutinib, 11.5 months for idelalisib, and 5.6 months of bendamustine. Medan duration of exposure for rituximab was 5.5 months. There were 6 (4%) patient deaths due to AE on the acalabrutinib arm and 7(5%) on the investigator choice arm. The

rates of discontinuation of treatment due to AE were higher in the comparator arm (44%) than the acalabrutinib arm (10%) supporting tolerability of acalabrutinib. Serious adverse events (SAE) were reported at highest rates in patients receiving idelalisib + rituximab (56%) and were reported in 26% of patients receiving bendamustine + rituximab and 28% of patients receiving acalabrutinib. The most common SAEs in the acalabrutinib arm were pneumonia (5.2%), and atrial fibrillation (1.9%). Second primary malignancies excluding non-melanoma skin were reported in 6.5% of the patients on the acalabrutinib arm and in 3 (2.5% of patients receiving idelalisib + rituximab and 1 (2.9% of patients receiving bendamustine and rituximab.

In summary, the safety profile of acalabrutinib is acceptable for the CLL patient population. The tolerability of the acalabrutinib containing regimens compared to the comparator arms for these trials are supported by the lower discontinuation rates in the study arms. There were no new safety issues identified that offset the PFS advantage of the therapy. Second primary malignancies warrant ongoing follow up, although may be related to underlying risk of SPM in CLL patients and the longer follow up on BTK inhibitor therapy arms. Acalabrutinib monotherapy appears to have a more favorable safety profile compared to chemoimmunotherapy combinations.

12. Division's recommendation and rationale (pre-MPC review):

☒ GRANT:

Provide brief summary of rationale for granting:

The data from the ACE-CL-007 and ACE-CL-309 trials provides evidence of efficacy from two randomized, active-control, phase 3 trials in adult patients with either treatment naïve or previously treated CLL.

The trial in treatment naïve patients randomized 535 patients in a 1:1:1 ratio to receive chlorambucil + obinutuzumab, acalabrutinib + obinutuzumab or acalabrutinib monotherapy. Progression-free survival per IRC was statistically significantly longer in the acalabrutinib + obinutuzumab arm than the chlorambucil + obinutuzumab arm hazard ratio of 0.10 (95% CI: 0.06, 0.17; stratified log-rank test $p<0.0001$ and acalabrutinib compared to chlorambucil + obinutuzumab with HR of 0.2 (95% CI 0.13, 0.3). When compared to recently approved combination therapies (ibrutinib or venetoclax in combination with obinutuzumab) demonstrating a PFS advantage over chlorambucil + obinutuzumab in a similar patient population, this trial provides new data to support the efficacy of monotherapy in this setting. Monotherapy over combination therapy offers less patient burden and removes the AEs of infusion related reactions and additive toxicity of combination therapy.

For relapsed and refractory patients, the ACE-309 trial randomized 310 patients in a 1:1 ratio to receive acalabrutinib monotherapy or investigators choice of idelalisib + rituximab (N = 119) or bendamustine plus rituximab (n = 36). Progression-free survival per IRC was statistically significantly longer in the acalabrutinib arm than the investigator choice arm hazard ratio of 0.31 (95% CI: 0.2, 0.49; stratified log-rank test $p<0.0001$. Compared to recently approved agents (venetoclax or ibrutinib alone or in combination with chemo or immunotherapy), this is the first data from a randomized trial demonstrating a PFS advantage of a monotherapy regimen compared to active combination comparator arm. An effective monotherapy regimen offers patients a reduction in the significant toxicity leading to discontinuations that are associated with combination regimens.

Evaluation of safety revealed a comparable safety profile between acalabrutinib + obinutuzumab or acalabrutinib monotherapy vs the comparator arm of the trials and was consistent with the known safety profile of acalabrutinib and other BTK inhibitors. Importantly the results from these trials demonstrate efficacy of acalabrutinib as monotherapy over an active chemotherapy combination for both the treatment naïve and relapsed and refractory patients. The results of the trials provide statistically significant and importantly, clinically meaningful results that may represent a change to the standard of care for patients with newly diagnosed CLL who are not fit for intensive therapy or relapsed or refractory chronic lymphocytic leukemia.

The Division recommends a revision to the sponsor's proposed indication to specify that breakthrough is granted for acalabrutinib *as monotherapy* for patients with both the treatment naïve and relapsed and refractory CLL.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☐ DENY:

Provide brief summary of rationale for denial:

Not applicable.

13. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The Sponsor is currently planning on submitting an sNDA including the data from the two trials included in this BTDR. Submission is planned starting July 2019 as part of the Oncology Center of Excellence Real-Time Oncology review (RTOR) pilot program with the use of the assessment aid. The final sNDA submission package is planned for October 2019.

14. List references, if any:

1. Noone, A.M., et al., *SEER Cancer Statistics Review, 1975-2015, National Cancer Institute.* 2018. based on November 2017 SEER data submission, posted to the SEER website.
2. Thurmes, P., et al., *Comorbid conditions and survival in unselected, newly diagnosed patients with chronic lymphocytic leukemia.* Leuk Lymphoma, 2008. **49**(1): p. 49-56.
3. Jain, N., *Selecting Frontline Therapy for CLL in 2018.* Hematology Am Soc Hematol Educ Program, 2018. **2018**(1): p. 242-247.
4. Parikh, S. A. (2018). "Chronic lymphocytic leukemia treatment algorithm 2018." Blood Cancer J **8**(10): 93.
5. Fraser, G., et al. (2019). "Updated results from the phase 3 HELIOS study of ibrutinib, bendamustine, and rituximab in relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma." Leukemia **33**(4): 969-980.
6. Eichhorst, B., et al., *First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial.* Lancet Oncol, 2016. **17**(7): p. 928-942.
7. Barr, P., et al., *Updated Efficacy and Safety from the Phase 3 Resonate-2 Study: Ibrutinib As First-Line Treatment Option in Patients 65 Years and Older with Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia.* Blood, 2016. **128**(22): p. 234.
8. O'Brien, S., et al., *Single-agent ibrutinib in treatment-naive and relapsed/refractory chronic lymphocytic leukemia: a 5-year experience.* Blood, 2018. **131**(17): p. 1910-1919.
9. Moreno, C., et al. (2019). "Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial." Lancet Oncol **20**(1): 43-56.

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature:	{See appended electronic signature page}
Team Leader Signature:	{See appended electronic signature page}
Division Director Signature:	{See appended electronic signature page}

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARGRET E MERINO
08/09/2019 10:51:40 AM

ROMEO A DE CLARO
08/09/2019 10:52:49 AM

ANN T FARRELL
08/09/2019 11:16:04 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 118717

MEETING MINUTES

Acerta Pharma, B.V.
c/o Acerta Pharma
Attention: Khanh Nguyen, PharmD
Manager, Regulatory Science
121 Oyster Point Boulevard
South San Francisco, CA 94080

Dear Dr. Nguyen:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for acalabrutinib

We also refer to the telecon between representatives of your firm and the FDA on June 18, 2018. The purpose of the meeting was to discuss the design of the proposed study ACE-CL-311 to support product registration for the proposed indication in frontline chronic lymphocytic leukemia (CLL).

A copy of the official minutes of the telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Ashley Lucci Vaughn, Regulatory Project Manager at (301) 796-5718.

Sincerely,

{See appended electronic signature page}

Yvette Kasamon, MD
Acting Clinical Team Leader
Division of Hematology
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
Sponsor Response to Preliminary Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: June 18, 2018, 1:00-2:00 pm EDT
Meeting Location: Teleconference

Application Number: 118717
Product Name: Acalabrutinib

Indication: Previously untreated CLL
Sponsor/Applicant Name: Acerta Pharma B.V.

Meeting Chair: Yvette Kasamon, MD
Meeting Recorder: Ashley Lucci Vaughn, MS

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products
R. Angelo de Claro, MD, Acting Deputy Director
Yvette Kasamon, MD, Acting Clinical Team Leader
Margret Merino, MD, Clinical Reviewer
Virginia Kwitkowski, MS, ACNP-BC, Associate Director of Labeling
Ashley Lucci Vaughn, MS, Regulatory Health Project Manager

Office of Biostatistics/Division of Biometrics V
Jingjing Ye, PhD, Team Leader
Kallappa Koti, PhD, Reviewer

SPONSOR ATTENDEES
Tara L. Chen, PharmD, BCOP, Clinical Scientist, Clinical Development
Nataliya Chernyukhin, MD, Senior Director, Medical Safety Science
Amanda Roodhouse, Director, Director, Regulatory Science, Acerta Pharma
Melanie M. Frigault, PhD, Head of Translational Science
Steve Kye, MD, MPH, Medical Director, Clinical Development
Dongmei Liu, PhD, MS, Associate Director, Biostatistics, Biometrics
Khanh Nguyen, PharmD, Senior mANAGER, Regulatory Science,
Jennifer Nicholson, MHA, Senior Director, Regulatory Science,
Priti Patel, MD, Executive Director, Head of Clinical Development

1.0 BACKGROUND

Acalabrutinib is a selective inhibitor of Bruton tyrosine kinase that has accelerated approval in previously treated mantle cell lymphoma and is under investigation in previously treated and treatment-naïve chronic lymphocytic leukemia (CLL). On April 11, 2018, the Sponsor submitted a meeting request to discuss the acceptability of the proposed randomized phase 3 study, ACE-CL-311, to support registration of acalabrutinib plus venetoclax, with or without obinutuzumab, for patients with previously untreated CLL.

FDA sent Preliminary Comments to Acerta Pharma B.V. on June 8, 2018.

2.0 DISCUSSION

2.1.

Question 1: Does the Agency agree with the proposed Phase 3 ACE-CL-311 study design, particularly the following aspects:

Question 1a: *Is the proposed patient population adequately defined as per the study eligibility criteria?*

FDA Response to Question 1a: In general, we have no objection to the proposed patient population. However,

- We recommend against the use of the Cumulative Illness Rating Scale (CIRS) for patient selection. CIRS has not been validated for use in CLL or in any cancer setting, and excluding patients with a CIRS score > 6 may exclude a significant number of patients for whom study treatment would be appropriate. Further, because the control arm involves physician choice between an intensive and less intensive chemotherapy regimen (which would not be based on CIRS), the rationale for a CIRS eligibility criterion is unclear. If you choose to use CIRS for patient selection, we recommend that you capture detailed information for all of the components.
- The requirement for a creatinine clearance > 70mL/min may also exclude a significant number of patients for whom study treatment would be appropriate. A lower threshold may be reasonable.

Other comments about the treatment arms: The proposed trial design does not appear to consider information that will be forthcoming from the ongoing trial in frontline CLL, ACE-CL-007.

- The utility of the acalabrutinib monotherapy arm is unclear, as ACE-CL-007 will provide monotherapy data in the same population – previously untreated CLL– for which you seek an indication through ACE-CL-311. In addition, the relatively small sample size in the acalabrutinib monotherapy arm will support only exploratory analyses.
- The value of having both Arms A and B, as opposed to committing to either Arm A or Arm B, is also unclear. The results of the interim analysis of ACE CL 007 may guide the choice of one of these two arms as the comparator to investigator's choice.

Discussion: No further discussion occurred.

Question 1b: *Is the proposed comparator arm (FCR/BR) appropriate to assess the safety and efficacy of acalabrutinib plus venetoclax, with or without obinutuzumab, in the proposed patient population?*

FDA Response to Question 1b: We do not object to the proposed comparator arm of FCR/BR. However,

- As noted in the Preamble, this proposed trial would not, in isolation, be adequate for registrational purposes in CLL because the design does not isolate the treatment effect of acalabrutinib.
- For an investigator choice arm in which the regimens differ in efficacy, as with FCR and BR, a null PFS rate may be challenging to define with accuracy, as this would depend on the proportion of patients who receive FCR vs BR. We also have concern that the null PFS rate may underestimate the performance of the control arm; refer also to the response to Question 1c.
- Differences in safety and efficacy between the two investigator choice arms (BR and FCR) may pose challenges in interpreting the study results. This includes challenges with generalization of the MRD data, given the known differences in MRD negativity rates with FCR as compared to BR.
- Given the interest in chemotherapy-free options for CLL, there may be feasibility issues with excess drop outs from the investigator choice arm, given that cross over is permitted.

Discussion: The Sponsor asked whether Study 311 would suffice as a registrational trial if the acalabrutinib monotherapy arm would be dropped, assuming that Study 007 was successful. The Agency advised that the revised design might be sufficient to support a new efficacy claim, but not with respect to PROs because the design does not isolate the treatment effect of the study drug on PRO endpoints.

Question 1c: *Does the Agency agree with the primary endpoint of PFS per IRC assessment and the proposed secondary endpoints?*

FDA Response to Question 1c: Although we agree with PFS per IRC as the primary endpoint, we have concerns about the timing of the interim and final analysis, including the length of time a PFS event-based analysis will take to complete. An alternative analysis, to allow a time-based analysis in case the treatment effect size of the experimental arm relative to the control arm is better than what was assumed in the protocol, as discussed in a May 15, 2018 written communication regarding trial ACE-CL-007, may be reasonable for an adequately designed trial in frontline CLL. For example, it would trigger the time-driven analysis when a reasonable amount of time elapsed without having the planned PFS events.

We also note that, on the other hand, the current assumption of PFS could be based on an under estimated treatment effect of the control arm. If this happens to be true, your trial could be underpowered. We have concern that the null PFS rate may underestimate the

performance of the control arm, in part because the estimates of median PFS provided do not appear to consider this study's exclusion of patients with 17p deletion. Therefore, not only could the primary efficacy results mature later than anticipated, but the study may be underpowered for the primary endpoint.

Please define PFS and the censoring rule in your SAP. Please be advised that early dropouts should be kept at a minimum.

We are unable to comment on the secondary endpoints without delineation of the key secondary endpoints and the order of testing.

Discussion: The Sponsor inquired as to having one interim analysis wherein the choice of an event-driven analysis versus time-driven analysis (for example at two years) is based on whichever matures first.

The Agency is open to considering this approach, as well as alternative designs. One concern with a time-based analysis at two years is underpowering. In addition, the expectation for such an analysis would be a minimum two-year follow-up for PFS in at least 90% of censored patients. This expectation may change based on review of the details in a revised SAP.

Post-Meeting Comment:
We acknowledge your proposal to perform interim analysis based on either event-driven or time-driven analysis, whichever occurs earlier. We note that it is possible for the interim analysis to occur when only 50% of the total possible information is collected. Early interim analyses can be influenced by random extreme findings that poorly estimate the true treatment effect. FDA generally discourages claiming efficacy based on interim analysis of PFS, especially when the information fraction is as small as 50% because of the increased probability of overly optimistic effect size estimates.

Question 1d: *Does the Agency agree with the proposed interim analysis plan?*

FDA Response to Question 1d: We have no specific objections to the proposed interim analysis plan. However, we have concerns that based on the expected median PFS times for these therapies, this trial will take an excessive time until either a primary or interim event-based analysis. We have the following additional comments:

- Provide clarification on what appears to be a typographical error in the naming of the treatment arms. In Appendix 1, on page 11 of 14, you have explained the sample size determination to compare Arm A and Arm B (see your null and alternative hypotheses). On the following page, you have stated that comparison of Arm A and Arm C will be based on 229 IRC-PFS events.

- Please provide detailed sample size calculation of 880 subjects in the SAP with your assumed dropout rate of 10%.

- Please provide multiple comparison procedures so that the study wise type I error rate is controlled, including primary and secondary comparisons as well as primary and secondary endpoints. Please clarify, if the interim analysis for the primary comparison is significant, how will the secondary comparisons and secondary endpoints will be tested.

- Please provide the expected number of deaths for the OS analysis.

Discussion: The Sponsor plans to address the Agencies concerns included in the preliminary responses and discussed at the June 18, 2018 meeting with a subsequent submission of the SAP for the Study 311.

With respect to PFS estimates both in the experimental and control arms, the Agency reiterated the concern for potential underpowering and advised the Sponsor to consider the effect of excluding the highest risk patients (17p deletion CLL) on projected median PFS estimates.

Question 1e: *Does the Agency agree that this study could support future registration for the treatment of previously untreated CLL patients?*

FDA Response to Question 1e: It is premature to answer this question, particularly when the fundamental trial design is under discussion.

Discussion: No further discussion occurred.

Question 2: *Does the Agency agree with the proposed MRD collection and analysis plan?*

FDA Response to Question 2: Your proposal for MRD collection and analysis appears reasonable.

We have the following additional considerations in defining MRD negativity as a potential endpoint in treatment naïve patients with CLL:

- The optimal site to test for MRD is an unanswered question in the clinical use of MRD analysis in patients with CLL. The definition of MRD negative peripheral blood (PB) or bone marrow (BM) may not be adequate given that therapeutic interventions differentially affect MRD measurements in PB and BM as demonstrated with certain therapeutics (e.g., anti-CD20 antibodies).

- We recommend that you have an analytically validated assay for the purposes of measuring and defining MRD negative CLL and the platform chosen should be fully prespecified (in terms of assay procedure, reagents, and analysis). This information should be included in the protocol. Validation of MRD assays in drug development should encompass the entire assay system from sample collection (e.g., bone marrow aspirate vs. blood) to system output (e.g., decision making threshold for MRD positive vs. negative), and use of relevant clinical samples.

- There are potential disparities between clinical staging and MRD analysis (i.e., PR with MRD negativity) which creates additional uncertainty in defining MRD negativity in newly diagnosed patients with CLL. You should characterize and assess the clinical relevance of MRD data in patients who have residual nodal enlargement but who are MRD negative.

- You will need plans for addressing discrepant MRD results between PB and BM, and for addressing missing results in the MRD analysis. These plans should be prespecified.

- We recommend that you specify how MRD negative results are confirmed and how durability of MRD will be assessed.

- MRD analyses should be based on an ITT population.

Discussion: No further discussion occurred.

Question 3: *Does the Agency agree with the proposed patient-reported outcome (PRO) measurements?*

FDA Response to Question 3: We have no objections to the collection of PRO data, however, because this trial is not designed to isolate the treatment effect of acalabrutinib, PRO endpoints will be viewed as exploratory only. Should this become a registrational trial, the current trial design which does not isolate the treatment effect of acalabrutinib would preclude any PRO labeling claims. Further, there may be some measurement challenges that may be a limitation to PRO data interpretability (e.g., open-label study design, overlap of disease and treatment symptoms, patient attrition).

We have the following comments on the proposed PRO instruments:

FACIT-Fatigue

- FACIT-Fatigue may be a reasonable option to assess fatigue-related symptoms and impacts in the target population, but would not result in labeling claims due to the current trial design. Because you indicated that dyspnea was reported by 12%–49% of patients based on literature, you may also consider using the FACT-Anemia instrument in lieu of the FACIT-Fatigue since it measures both fatigue and shortness of breath. This will allow you to still designate the FACIT-Fatigue subscale score (included in the FACT-Anemia) as a study endpoint and evaluate dyspnea for exploratory purposes. See Additional Comments.

EORTC-QLQ-C30

- It is unclear which subscales will be selected for the PRO analysis. You should plan to designate individual domain(s) from the EORTC-QLQ-C30 that are most relevant to patients and ideally modifiable by treatment.

EORTC item library

- You have proposed to assess a host of disease-related signs and symptoms (e.g., lymphadenopathy, night sweats, bruising, rash, fever, muscle/joint aches, and weight loss). You may want to consider which disease-related signs are more appropriate for clinicians to assess (e.g., bruising, rash, weight loss) and limit these concepts to be evaluated by clinical observation. We do not view recurrent infections to be a disease symptom.

  You do not need to measure an exhaustive list of disease signs and symptoms, but rather the disease-related concepts that are expected to have a meaningful impact on how patients feel or function in daily life. We recommend that your PRO measurement strategy target (1) core disease-related concepts and (2) impacts associated with core disease-related concepts (e.g., interference with activities of daily living, such as physical function). Your planned qualitative work with patients should help inform the concepts that should be measured.

  See Additional Comments for more specific comments on the PRO measurement strategy. Note these comments are more relevant if the trial design is modified to isolate the treatment effect of acalabrutinib.

Additional Comments-Clinical Outcome Assessments:

Comments regarding the PRO measurement strategy

1. In addition to the assessment of disease symptoms and functional impacts, you should also consider the assessment of tolerability. We remain open to assessment of symptomatic adverse events and their descriptive analyses for patients on therapy including impact of treatment on patient's functioning (i.e., physical function). We consider the National Cancer Institute's PRO version of the common terminology criteria for adverse events (PRO-CTCAE) found at http://healthcaredelivery.cancer.gov/pro-ctcae/ to be one acceptable option for assessment of symptomatic adverse events. The GP5 item of the Functional Assessment of Cancer Therapy-General (FACT-G) instrument may also be one reasonable option to assess global side effect impact.

Comments regarding the PRO analysis and clinical trial design considerations:

1. Clearly specify the general analysis plan for your PRO endpoints in the full protocol and statistical analysis plan (SAP). In the SAP, provide the procedures for handling missing values, justification for the endpoint definition and procedures for what constitutes meaningful change. See Additional Comment #5.

2. PRO measurement should be obtained before or shortly after patient withdrawal from treatment should early withdrawal be unpreventable and/or crossover to another treatment arm.

3. PRO assessments will need to be culturally adapted and adequately translated for all intended study populations for use in multinational trials. We refer you to the ISPOR principles for the translation and cultural validation process.[1]

4. The threshold(s) for a meaningful score change in the proposed instruments are unknown. Propose a threshold(s) that would constitute a clinically meaningful score change in the target population for the respective PRO endpoint. We recommend that you explore multiple anchor scales to provide an accumulation of evidence to help interpret a clinically meaningful within-patient score change in the target instruments. This anchor-based approach should be supplemented with both cumulative distribution function and probability density function curves. See Additional Comment #8.

5. Because the FACIT-Fatigue subscale score includes items on both symptoms and impacts, we will review the results of the total score as well as of the individual items to help with the interpretation of the treatment effect. Plan to provide item-level analyses to allow evaluation of whether or not individual items or domains are overly influencing changes observed in the total score.

6. Plan to conduct analyses for the EORTC-QLQ-C30 using both raw and transformed scores to help facilitate data interpretation. If the selected threshold(s) for meaningful score change are based on transformed scores (e.g., linear transformation of a 1-5 raw score scale to a 0-100 score scale), it will be important for you to consider score interpretability of the improvement threshold(s) for both transformed scores and raw scores, i.e. whether the selected threshold(s) based on transformed scores also constitute a clinically meaningful within-patient change for the raw scores. Depending on the proposed score transformation, selected improvement threshold(s) based on transformed scores may reflect less than one category change on the raw score scale, which is not useful for the evaluation and interpretation of clinically meaningful change.

Comments regarding other PRO assessments

1. Include copies of the proposed anchor scale (patient global impression of severity [PGIS]) in your clinical study protocol for review and comment. In addition to the PGIS anchor scale, consider using a patient global impression of change anchor scale and/or well established clinical outcomes as multiple anchors can provide an accumulation of evidence to help interpret a meaningful within-patient score change in the target instrument(s). You will need to provide evidence for what constitutes a meaningful change on the anchor scale(s). Assess the anchor scales at comparable same time points as, but completed after, the target instrument(s).

[1] Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, Erikson P; ISPOR Task Force for Translation and Cultural Adaptation. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health. 2005 Mar-Apr;8(2):94-104.

2. The EQ-5D-5L is a generic preference-based measure intended to provide a single health utility index value for use in economic analyses and lacks evidence of content validity for use in estimating clinical benefit for labeling claims. However, we acknowledge that the EQ-5D-5L may be necessary for other regulatory authorities and/or payers.

Discussion: No further discussion occurred.

3.0 IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that marketing applications for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020 contain reports of molecularly targeted pediatric cancer investigations. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be

submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are

accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:

- A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
- Other significant changes
- Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion

5.0 ACTION ITEMS

There were no action items that identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

Sponsors response to the Agencies preliminary comments.

13 Pages 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/

YVETTE L KASAMON
06/22/2018

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	IND 118717
Request Receipt Date	June 6, 2017
Product	Acalabrutinib
Indication	Treatment of patients with Mantle Cell Lymphoma (MCL) who have received at least one prior therapy
Drug Class/Mechanism of Action	Tyrosine kinase inhibitor
Sponsor	Acerta Pharma B.V.
ODE/Division	OHOP/DHP
Breakthrough Therapy Request Goal Date (within 60 days of receipt)	August 6, 2017

Note: This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Note: Signatory Authority is the Division Director.

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

   Proposed Indication: Treatment of patients with mantle cell lymphoma who have received at least one prior therapy.

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

3. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequeate and sufficiently complete to permit a substantive review?
      - ☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
      - ☐ Undetermined
      - ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

i. Only animal/nonclinical data submitted as evidence ☐
ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked "No", BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If MPC review is not required, email Miranda Raggio and Sandy Benton as soon as this determination is made so that the BTDR can be removed from the MPC calendar.

If 3b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Brief Description of the Drug

Acalabrutinib is a second generation, orally available inhibitor of Bruton's Tyrosine Kinase (BTK). Acalabrutinib selectively and irreversibly binds to BTK, which plays a critical role in the B-cell receptor (BCR) signaling pathway. Acalabrutinib and its active metabolite irreversible bind to a cysteine residue in the BTK active site resulting in inactivation. The 50% inhibitory concentration (IC_{50}) of acalabrutinib is ≤ 5nM. Acalabrutinib has demonstrated selective inhibition of BTK, with inhibition of only two other kinases, bone marrow kinase on X chromosome (BMX) and erb-b2 receptor tyrosine kinase (ERBB4). Acalabrutinib at a dose of 100mg BID provided near complete BTK occupancy over 24 hours at steady state in patients with Chronic Lymphocytic Leukemia(CLL) and was chosen as the dose to further investigate in patients with mantle cell lymphoma. Acalabrutinib is currently not approved for any indication.

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[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

Brief Description of the Disease and intended population

Mantle cell lymphoma is a a serious and life threatening condition with median overall survival of 3-5 years. Mantle Cell lymphoma is a rare subtype of Non-Hodgkin lymphoma (NHL) with a poor prognosis, generally considered incurable with current available therapies. The disease typically affects men with a median age at diagnosis of 64 and occurs in 3000-4000 Americans per year. Mantle cell lymphoma is characterized by the chromosomal translocation t(11;14) with results in constitutive activation of anti-apoptotic pathways.

Ttreatment of newly diagnosed tatients is typically multi-agent chemotherapy regimens (R-CHOP or Hyper – CVAD)[1] and in patients who are eligible, subsequent autologous stem cell transplantation followed by rituximab maintenance therapy. While the majority of patients attain a CR the response is not durable and most patients will eventually relapse. For patients with relapsed and refractory disease, the median overall survival is 1-2 years.[2]

There is no accepted standard of care for patients with relapsed or refractory disease. Therapeutic options include salvage chemotherapy regmens and targeted therapies, but complete response rates are low(< 30%) with very short duration of responses. Bortezomib and lenalidamide are the only approved(regular) treatments for relapsed and refractory MCL and are associated with overall response rate(ORRs) of 31% and 25%, respectively. Ibrutinib (a first generation BTK inhibitor) received accelerated approval in 2013 for relapsed and refractory mantle cell lymphoma based on an ORR of 66% and a confirmatory trial is ongoing with results expected in 2018-19. The intended population for acalabrutinib is patients with relapsed or refractory mantle cell lymphoma who have failed at least 1 prior therapy.

7. Information related to endpoints used in the available clinical data:

a. Endpoints considered by the sponsor as supporting the BTDR:

- Overall response rate (ORR) defined as the percentage of patients as assessed by the investigator achieving a partial response(PR) or complete response(CR) according to the currently accepted Lugano classification of NHL[3]. Secondary endpoints are investigator-assessed duration of response (DOR), progression free survival (PFS), overall survival (OS), and independent review committee (IRC)-assessed ORR, DOR and PFS by Cheson criteria.

b. Endpoints(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease.

- Overall response rate(complete and partial response) and duration of response.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

None

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s)

used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population:

Bortezomib and Lenalidomide are considered available therapy for patients with relapsed or refractory mantle cell lymphoma although there is no accepted standard of care therapy for this group of patients. . Table 1 describes the available therapy and response rates for patients with relapsed or refractory mantle cell lymphoma.

Table 1: Available Therapies for Relapsed or Refractory Mantle Cell Lymphoma

	ORR (95% CI)	CR	Median DOR, mo	Response Criteria used	Approval Status
Bortezomib (N=155)	**31% (24,39)**	**8%**	**9.3**	**Cheson 1999[4]**	**Regular Approval**
Lenalidomide (N=133)	**26% (10,34)**	**7%**	**16.6**	**Cheson 1999[4]**	**Regular Approval**
Ibrutinib (N=111)	**68% (56,75)**	**22%**	**17.5**	**Cheson 2007[5]**	**Accelerated Approval**

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

Ibrutinib is a 1st in class Bruton's tyrosine kinase inhibitor that was granted breakthrough designation for patients with relapsed or refractory mantle cell in 2013 (ORR 68%, 95% CI 56,75). The Sponsor is conducting a randomized phase 3 trial in newly diagnosed mantle cell lymphoma which will serve as the confirmatory trial and final results are expected in 2018-19. Ibrutinib received approval(regular) for several other hematologic conditions: chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma, CLL with 17p deletion, and Waldenstrom's macroglobulinemia

Ibrutinib differs from acalabrutinib in that it is a less selective inhibitor and the binding site is different.

10. Information related to the preliminary clinical evidence:

The Sponsor submitted one clinical trial to support this breakthrough therapy deseignation request. Trial ACE-LY-004 is a phase II, single arm, open-label, multicenter, global study evaluating acalabrutinib as monotherapy in patients with relapsed and refractory mantle cell lymphoma. The study enrolled 124 patients who had received at least one but not more than five prior therapies. Patients received 100mg of acalabrutinib as monotherapy daily until progression or unacceptable drug-related toxicity.

The primary efficacy endpoint is overall response rate defined as CR or PR per the 2014 Lugano classification criteria as assessed by investigator. Secondary endpoints included duration of response, The study completed enrollment in February of 2016 and reported response status with duration of rsponse data for at least 12 months in responders.

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

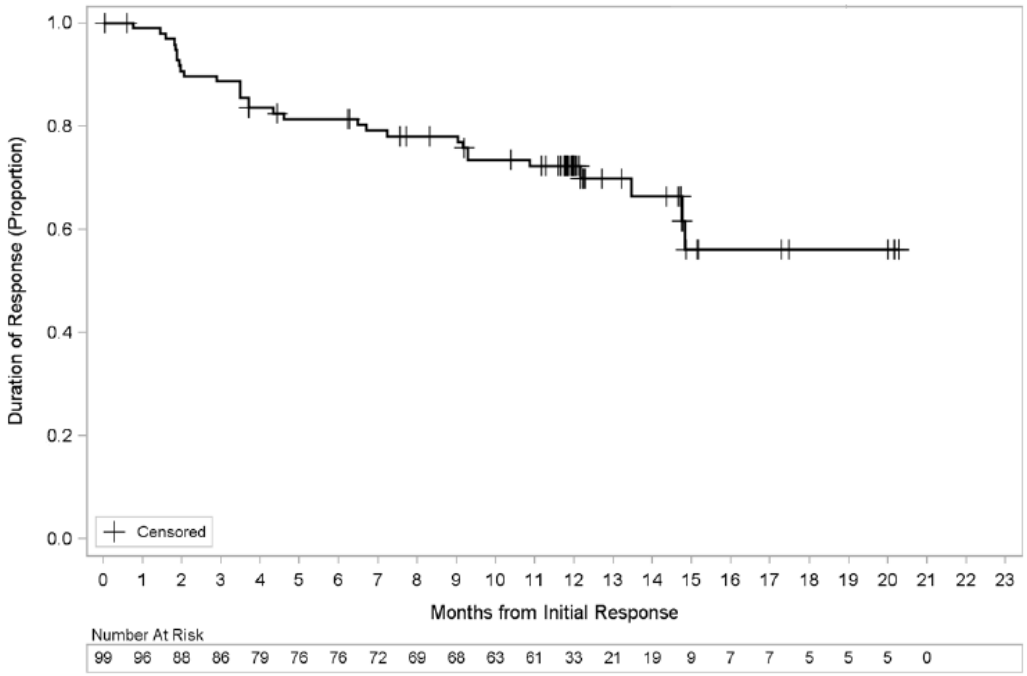
Table 2: Demographics for Study ACE-LY-004

ACE-LY-004 Demographics N=124	
Age (years)	
Median (range)	68 (42,90)
Sex	
Male n (%)	99 (79.8)
Ann Arbor Staging for lymphoma, n(%)	
I	2 (1.6)
II	7 (5.6)
III	22 (17.7)
IV	93 (75)
ECOG Performance Status n (%)	
0	71(57.3)
1	44 (35.3)
2	8 (6.5)
3	1 (0.8)
Number of Prior Regimens	
Median (range)	2 (1,5)
> 3	28 (22.6%)
Refractory Disease at Baseline	
Yes (%)	30 (24.2)

Table 3: Study ACE-LY-004 Efficacy Results

Overall Response and Duration of Response by Investigator per Lugano 2014	**Acalabrutinib (N = 124)**	
	n(%)	**95% CI**
Overall Response Rate(ORR)	**100 (80.6)**	(72,87)
Complete Response(CR)	**49 (39.5)**	(31,49)
Partial Response(PR)	**51 (41.1)**	(32,50)
Stable Disease	11(8.9)	(3,13)
Progressive disease	10 (8.1)	(5,15)
Duration of Response(DOR)(months), median(95% CI)	NR(13.5, NR)	
12-month DOR estimate, %(95% CI)	72%(62,80)	
18-month DOR estimate, %(95% CI)	63(49,74)	
Follow-up,(months), median(range)	**15.2(0.3,23.7)**	

Figure1. Duration of Response in Subjects who Achieved a CR or PR in Study ACE-LY-004



b. Include any additional relevant information. Consider the following in your response:

- ***Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.***

  The overall response rate of acalabrutinib can be considered preliminary clinical evidence of substantial improvement over available therapies. The ORR of 80.6% is ~ 2 fold higher than available therapies of bortezomib and lenalidomide. The CR rate of 40% is 2 fold higher than ibrutinib and 3-5 fold higher than bortezomib and lenalidomide.

Table 4. Response Rates in Available Therapy compared to Acalabrutinib

MCL	**Acalabrutinib N = 124**	**Ibrutinib* N = 111**	**Bortezomib N = 155**	**Lenalidomide N = 134**
Overall Response Rate (ORR) %, 95% CI Complete Response (%) Partial Response (%)	**80.6 (72.6, 87.2)** **40 (31,49)** 41(32,50)	66 (56.2,74.5) 17 (NR 49(NR)	31 (24,39) 8 (4,13) 23(17,31)	26 (18,34) 7 (NR) 19 (NR)
Duration of response (months) Median (95% CI)	NR (13.5, NR)	17.5 (15.8, NR)	9.3 (5.4, 13.8)	16.6 (7.7, 26.7)

- ***Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.***

During an EOP2 meeting in March 2016, the sponsor was asked to provide data on at least 12 month DOR for all responders. This data was provided and demonstrated that 72% of responders remained in response at 12 months.

- ***Safety data:***

  The safety of acalabrutinib has been evaluated in over 610 patients who have taken acalabrutinib at doses between 100mg daily to 400mg daily including 124 patients who received acalabrutinib at a dose of 100mg BID as part of the pivotal study in support of the BTDR and recently submitted NDA. The median duration of treatment for the group of patient with mantle cell lymphoma was 13.8 months. The most frequently reported grade 3 or 4 AEs were neutropenia (10.5%) and anemia (8.9%). Serious Adverse Events (SAEs) were reported in 38.7% of the subjects. In study ACE-LY-004, 5.6% of patients discontinued treatment due to an adverse event. An integrated safety analysis of the 610 patients who have been exposed to acalabrutinib AEs leading to dose delay, dose reduction and treatment discontinuation were reported at 33.4%, 6.1% and 2.5% respectively. Preliminary safety profile appears comparable to first generation BTK inhibitor.

11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT : Grant Breakthrough Designation for the treatment of patients with Mantle Cell Lymphoma who have received at least one prior therapy.

Rationale: Relapsed and refractory mantle cell therapy is a serious and life threatening disease and substantial clinical evidence demonstrated and overall response rate of 80%(95% CI: 72,87) with median duration of response that is not estimable(median follow-up for DOR of 15 months). The 12-month estimate of duration of response in responders is 72%. The demonstration of a 80% response rate is higher than currently available therapy and is clinically meaningful in a population for which no standard approach to 2nd line therapy or beyond has been established. This response is supported by the complete response rate of 40% which is ~2-4 fold higher than available therapies.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

12. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The Sponsor submitted NDA on June 13, 2017 for proposed indication in patients with relaped or refractory Mantle Cell Lymphoma. The Sponsor has initiated a potential confirmatory trial, ACE-LY-308, a phase 3 randomized trial comparing bendamustine and Rituxan versus bendamustine +

rituximab+ acalabrutinib in newly diagnosed patients with mantle cell lymphoma. The primary endpoint is progression free survival(PFS). The Sponsor also has several ongoing trials in other hematologic malignancies(CLL, NHL).

The Division is currently reviewing the submitted NDA under an expedited review timeframe with consideration for an accelerated approval. The Division held a pre-NDA meeting on June 2, 2017 with the objective to reach agreement on the proposed NDA with regards to efficacy and safety data, PK modelling, a 90 day safety update, and data submission. The Division and Sponsor have also had previous meetings to discuss and agree upon the design of the ongoing Phase 3 trial that could potentially serve as confirmatory study.

13. List references, if any:

1. National Comprehensive Cancer Network (NCCN) Guidelines Version 3.2017. March 27, 2017, Mantle Cell Lymphoma. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf

2. Kahl, B.S, et al. *Current Approaches to Mantle Cell Lymphoma: Diagnosis, Prognosis and Therapies.* Am Soc Clin Oncol Educ Book, 2017;**37**: p. 512-525.

3. Cheson, B.D, et al. *Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification.* Journal of Clinical Oncology, 2014. **32**: p. 3059-68.

4. Cheson, B.D, et al. *Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group.* Journal of Clinical Oncology, 1999 **17**(4): p. 1244.

5. Cheson, B.D, et al. *Revised Response Criteria for malignant lymphoma.* Journal of Clinical Oncology, 2007 **25**(5): p. 579-86.

6. Cheah, C.Y, et al. Mantle Cell Lymphoma. Journal of Clinical Oncology, 2016; 34(11) p. 1256-72.

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 1/15/16/M. Raggio

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

/s/

MARGRET E MERINO
07/28/2017

TANYA M WROBLEWSKI
07/28/2017

ANN T FARRELL
07/28/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 118717

MEETING MINUTES

Acerta Pharma B.V.
Attention: William Donaldson, BVSc, PhD
Vice President, Regulatory Affairs
2200 Bridge Parkway, Suite 202
Redwood City, CA 94065

Dear Dr. Donaldson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for acalabrutinib (ACP-196; SCH 2046835/Org 300196-0; SCH 900850).

We also refer to the teleconference between representatives of your firm and the FDA on June 2, 2017. The purpose of the meeting was to determine the adequacy of the Sponsor's clinical dossier based on pivotal study ACE-LY-004 for the proposed New Drug Application (NDA) for accelerated approval in support of the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Beatrice Kallungal, Regulatory Project Manager at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	June 2, 2017, 9 AM to 10 AM EDT
Meeting Location:	via Teleconference
Application Number:	IND 118717
Product Name:	Acalabrutinib (ACP-196; SCH 2046835/Org 300196-0; SCH 900850)
Indication:	For the treatment of patients with mantle cell lymphoma (MCL), who have received at least one prior therapy
Sponsor Name:	Acerta Pharma B.V.
Meeting Chair:	Beatrice Kallungal, MS
Meeting Recorder:	R. Angelo De Claro, MD

FDA ATTENDEES

Center for Drug Evaluation and Research

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products
Ann Farrell, MD, Division Director
R. Angelo de Claro, MD, Medical Officer, Clinical Team Leader
Tanya Wroblewski, MD, Clinical Reviewer
Theresa Carioti, MPH, Chief Project Management Staff
Beatrice Kallungal, MS, Senior Regulatory Project Manager

Office of Biostatistics/Division of Biometrics V
Lei Nie, PhD, Team Leader
Jingjing Ye, PhD, Reviewer

OHOP/Division of Hematology, Oncology, Toxicology
Christopher Sheth, PhD, Team Leader
Brian Cholewa, PhD, Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Bahru Habtemariam, PharmD, Team Leader

Office of Generic Drugs/Office of Research and Standards
Elin Matsson, PhD, ORISE Fellow

SPONSOR ATTENDEES

AstraZeneca
Hesham Abdullah, MD, MSc, RAC, Vice President, Oncology & Immuno-Oncology, GMD

Acerta Pharma
Nataliya Chernyukhin, MD, Senior Director, Medical Safety Science
Davy Chiodin, PharmD, Vice President, Regulatory Science
Xin Huang, PhD, Director, Biostatistics
Naomi Hunder, MD, Vice President, Clinical Development
Jennifer Nicholson, MHA, Senior Director, Regulatory Science
Priti Patel, MD, Senior Medical Director, Clinical Development
Yasameen Qazen, PharmD, Director, Regulatory Science
Iris Roth, PhD, Vice President, Global Medicine Leader
Xiaolin Wang, ScD, Vice President, Biometrics

1.0 BACKGROUND

Acalabrutinib is a Bruton tyrosine kinase (Btk) inhibitor being developed in oncologic and autoimmune indications. Acalabrutinib monotherapy was studied in a single arm, Phase 2 study (ACE-LY-004) in subjects with previously treated mantle cell lymphoma (MCL)..

An End of Phase 2 (EOP2) meeting was held with the Division of Hematology Products on March 21, 2016 to discuss the Sponsor's plans for the clinical development of acalabrutinib in mantle cell lymphoma, including the potential for ACE-LY-004 to serve as the pivotal study for an NDA supporting an indication of previously treated MCL patients for accelerated approval.

On February 1, 2017 the Sponsor received Written Responses for a Type C meeting request to obtain feedback on the content and format of an acalabrutinib New Drug Application (NDA) for accelerated approval in support of the treatment of patients with MCL who have received at least one prior therapy.

On March 1, 2017 a Type B pre-NDA CMC meeting was held where there was agreement on the plan and timing for the stability package to be filed with the MCL NDA submission.

Acalabrutinib received orphan drug designation for the treatment of MCL. The Sponsor plans to submit the NDA for acalabrutinib for the treatment of patients with MCL who have received at least one prior therapy in Q2 2017, with the proposed confirmatory Phase 3 study ACE-LY-308 expected to be initiated by the time of submission.

The purpose of this pre-NDA meeting is to determine the adequacy of the Sponsor's clinical dossier based on pivotal study ACE-LY-004, entitled "*An Open-label, Phase 2 Study of ACP-196 in Subjects with Mantle Cell Lymphoma,*" for the proposed NDA for accelerated approval in

support of the treatment of patients with MCL who have received at least one prior therapy. Further, the Sponsor aims to gain agreement with the Division on the overall content and format, excluding information in Module 3, which was discussed at a Type B, pre-NDA CMC meeting held on March 1, 2017 of the NDA to support the proposed indication.

FDA sent Preliminary Comments to Acerta Pharma on May 26, 2017.

2. DISCUSSION

Clinical

Question 1: Does the Agency agree that the efficacy (as assessed by both IRC and investigator) and safety results of pivotal study ACE-LY-004, along with data from other supportive studies, will support the filing and review of the NDA for accelerated approval in support of the proposed indication?

FDA Response to Question 1:
Based on our current understanding of your topline efficacy and safety data, it appears that they could support an application for the treatment of patients with mantle cell lymphoma who have failed at least 1 prior therapy. The Agency will conduct our own independent analysis of the datasets to confirm the efficacy claims. A decision on filing and subsequent review of the NDA will be made during the filing review.

We note that the study population includes patients with extranodal disease. In the NDA submission, provide assessments of response for all disease compartments [e.g., bone marrow (bone marrow assessments), gastrointestinal(endoscopy), pulmonary). In addition characterization of progressive events for all patients will be important in the review of the application. Provide brief narratives of the progressive events for all patients who progress to include descriptions of new sites of disease progression.
The Division notes that the determination of the accelerated approval pathway is an option based on available therapy at the time of regulatory action of your application. We note that confirmatory studies may be required as part of the accelerated approval pathway and these are usually ongoing at the time of the NDA submission. Provide an update on the status of Study ACE-LY-308 and timeline for submission of your proposed NDA for acalabrutinib.

At the meeting, discuss the proposed timelines for NDA submission, including whether a rolling review would be requested.

Meeting Discussion:
The Sponsor's proposal to provide tabular efficacy summaries per patient in lieu of patient efficacy narratives is acceptable to the Agency. The Agency recommended to include dates of assessment for summary tables included in the tabular efficacy summaries. The Agency also agrees that this component may be submitted within 30 days of the full application submission.

Question 2: Does the Agency suggest the data set and model files for the two PBPK modeling (ie, original and updated) studies be submitted with the original NDA or provided to the clinical pharmacology reviewers separately?

FDA Response to Question 2:
Yes. The data set and model files for the two PBPK modeling studies should be submitted with the original NDA. It is the agency's expectation that the NDA submission should be complete at the time of Original NDA submission. Please refer to the following guidelines regarding general expectations of submitting pharmacometric data and models: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm

Meeting Discussion:
No discussion.

Nonclinical
Question 3: Does the Agency agree with the proposal to submit results of the dose-range finding pre- and postnatal development toxicity study along with the proposed safety update (Question 5)?

FDA Response to Question 3:
The decision on a need to conduct a pre and postnatal development (PPND) toxicity study will be made after our review of the definitive embryofetal development toxicity (EFD) results submitted with the NDA, and if needed, the PPND study could be done post-approval.

Meeting Discussion:
No discussion.

Regulatory

Question 4: Does the Agency agree that the proposed NDA should be considered for priority review?

FDA Response to Question 4:
The decision as to whether to grant priority or standard review will be made during the filing review.

Meeting Discussion:
No discussion.

Question 5: Does the Agency agree with the Sponsor's proposal for the 90-day safety update?

FDA Response to Question 5:
Yes, your proposal is acceptable.

Meeting Discussion:
No discussion.

Question 6: Does the Agency agree that the proposed contents of Modules 1, 2, 4, and 5 are acceptable for the filing and review of the NDA for accelerated approval in support of the proposed indication (see Appendix 5)?

FDA Response to Question 6:
Refer to response to Question 1 regarding filing and review of your proposed application. We reiterate our recommendation provided on January 30, 2017, that you include the following in your NDA application:

1. **Address the following clinical pharmacology questions in Summary of Clinical Pharmacology (Module 2.7.2):**
   a. **What are the exposure-response relationships (dose-response, exposure-response) for efficacy and for safety?**
   b. **What influence do intrinsic and extrinsic factors have on exposure, efficacy, or safety?**
   c. **What dose and administration modifications are recommended for these factors?**
2. **Identify individual subjects with dose reduction, interruption or discontinuation; the time to the first dose reduction, interruption or discontinuation; the reasons for dose reduction, interruption or discontinuation within the exposure-response datasets. Provide the relevant descriptive statistics for each of these variables.**
3. **Provide a table listing of patients with renal or hepatic impairment who have received acalabrutinib, organized by trial number. Include available renal and hepatic function parameters such as SCr, CLCr calculated by the Cockcroft Gault equation (or eGFR calculated by MDRD), AST/ALT, T. Bili, platelet count, etc. for each patient in the listing. Also, provide summaries of the following information for each patient: PK and PD data, safety, and clinical efficacy.**

   It is not clear from the proposed NDA Table of Contents if these recommendations will be addressed.

Meeting Discussion:
No discussion.

Question 7: Does the Agency agree with the Applicant's plan to provide financial disclosure for covered studies ACE-LY-004 and ACE-CL-001?

FDA Response to Question 7:
Yes

Meeting Discussion:
No discussion.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The agency and the sponsor reached agreement on the full submission of the application.

  All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and it was concluded that the Agency will assess the need for REMS during the review of the application. The Sponsor agreed to submit a risk management plan as part of the full application submission.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application: *Tabular efficacy summaries per patient*

  Prominently identify each submission containing your late component with the following wording in bold capital letters at the top of the first page of the submission:

  NDA NUMBER: LATE COMPONENT - CLINICAL

In addition, we note that a chemistry pre-submission meeting was held on March 1, 2017. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

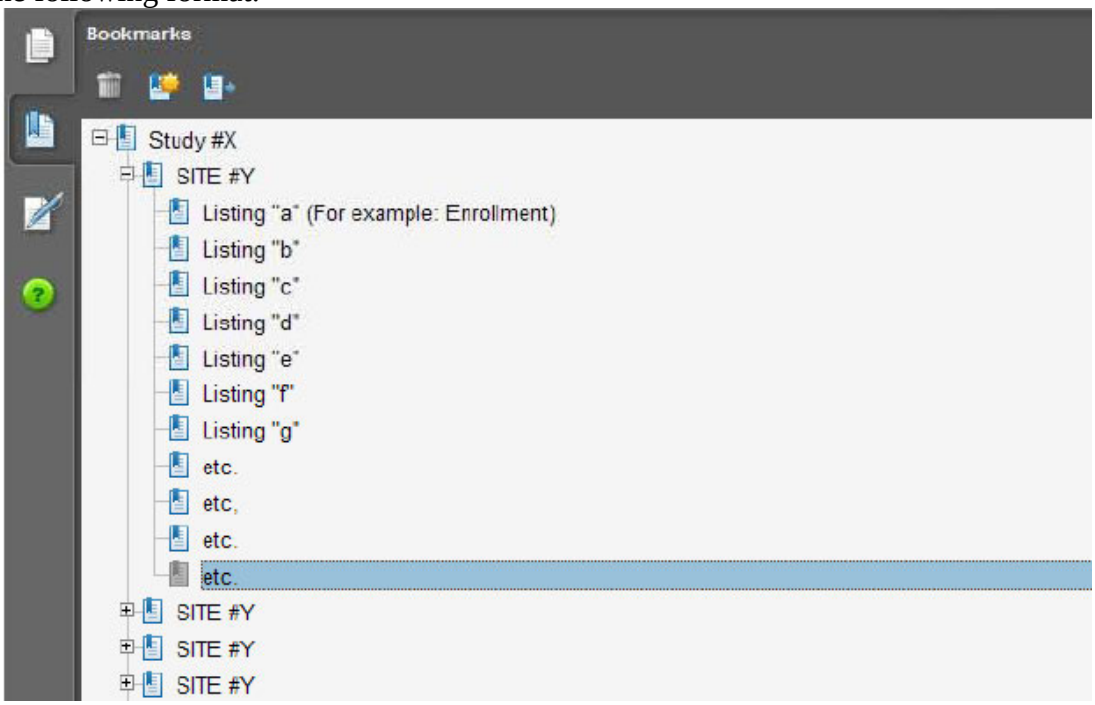
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:

a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
b. Subject listing for treatment assignment (randomization)
c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
f. By subject listing, of AEs, SAEs, deaths and dates
g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to

voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items for this meeting.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor's response to FDA meeting preliminary comments has been appended to the meeting minutes.

24 Pages have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

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/s/

ROMEO A DE CLARO
06/07/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 118717

MEETING MINUTES

Acerta Pharma B.V.
c/o LBR Regulatory & Clinical Consulting Services, Inc.
Attention: Gregory Kelso, PhD
US Agent for Acerta Pharma B.V.
1125 Boone Aire Road
Florence, KY 41042

Dear Dr. Kelso:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for acalabrutinib (ACP-196; SCH 2046835/Org 300196-0; SCH 900850).

We also refer to the meeting between representatives of your firm and the FDA on March 21, 2016. The purpose of the meeting was to obtain regulatory guidance and answers to specific questions on your plans for development of acalabrutinib for the treatment of mantle cell lymphoma (MCL).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Beatrice Kallungal, Regulatory Project Manager, at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase 2
Meeting Date and Time:	March 21, 2016; 9:30 AM – 10:30 AM EDT
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1419 Silver Spring, Maryland 20903
Application Number:	IND 118717
Product Name:	Acalabrutinib (ACP-196)
Indication:	Patients with mantle cell lymphoma (MCL) who have received at least one prior therapy
Meeting Chair:	R. Angelo de Claro, MD
Meeting Recorder:	Beatrice Kallungal, BS

FDA ATTENDEES

Office of Hematology and Oncology Products/Division of Hematology Products
Edvardas Kaminskas, MD, Deputy Director
R. Angelo de Claro, MD, Clinical Team Leader
Tanya Wroblewski, MD, Clinical Reviewer

Office of Biostatistics/Division of Biometrics V
Lei Nie, PhD, Team Leader
Yun Wang, PhD, Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Stacy Shord, PharmD, Reviewer

SPONSOR ATTENDEES

Hesham A Abdullah, MD, MSc, RAC, Vice President, Global Regulatory Affairs, Oncology & Immuno-Oncology, GMD, AstraZeneca
William Bushnell, MSc, Senior Director & Biometrics Team Leader, GMD, AstraZeneca
Flavia Borellini, PhD, CEO, Acerta Pharma
William Donaldson, BVSc, PhD, VP Regulatory Affairs, Acerta Pharma
Jane Huang, MD, VP Clinical Science, Acerta Pharma
Sandeep Inamdar, MD, BS, Sr. Medical Director, Acerta Pharma

Raquel Izumi, PhD, Executive VP Clinical Development, Acerta Pharma
Priti Patel, MD, Senior Medical Director, Clinical Operations, Acerta Pharma
Greg Slatter, PhD, VP DMPK, Clinical Pharmacology, Acerta Pharma
Michael Wang, MD, Professor, Department of Lymphoma/Myeloma,
Division of Cancer Medicine, The University of Texas MD Anderson Cancer
Xiaolin Wang, ScD, VP of Biometrics, Acerta Pharma

1.0 BACKGROUND

Acalabrutinib is a covalent Bruton tyrosine kinase (Btk) inhibitor being developed in oncologic and autoimmune indications. Acalabrutinib monotherapy is currently being studied in a single-arm, Phase 2 study (ACE-LY-004) in subjects with previously treated mantle cell lymphoma (MCL), which completed enrollment and is now closed to enrollment.

The purpose of the meeting is to reach agreement on the development program for acalabrutinib in treatment of patients with MCL and discuss the acceptability of the proposed Phase 3 studies ACE-LY-309 (previously treated MCL) and ACE-LY-308 (previously untreated MCL) for registration in the respective indications. The Sponsor would like to also discuss the potential acceptability of results from the Phase 2 study (ACE-LY-004) to support accelerated approval with ACE-LY-308 serving as the confirmatory study for traditional approval.

FDA sent Preliminary Comments to Acerta on March 16, 2016.

2.0 DISCUSSION

Question 1: Does the Agency agree the study design for ACE-LY-106 is adequate to determine the safety of the acalabrutinib dosage to be evaluated in combination with BR in study ACE-LY-308?

FDA Response:
Your proposed Phase 1b study appears adequately designed to determine a dose to be used in combination with bendamustine and rituximab (BR).

Meeting Discussion:
No Discussion

Question 2: Does the Agency agree with the overall study design (b) (4)
(b) (4)

FDA Response:
No, we have several issues with your trial design.

It is unclear (b) (4)
(b) (4)

[redacted]. **Describe how this issue will be addressed in the protocol and statistical analysis plan.**

Clarify if you intend to enroll subjects with the blastoid or pleomorphic variant of mantle cell lymphoma. Clarify the expected proportion of subjects with these variants in the overall population.

We recommend that you also include measurement of Minimal Residual Disease (MRD) as an exploratory endpoint in your proposed trial.

Meeting Discussion:
No Discussion

Question 3: Does the Agency agree that positive results from study ACE-LY-308 may support the proposed indication of "Acalabrutinib in combination with bendamustine and rituximab is indicated for the treatment of patients with previously untreated mantle cell lymphoma?"

FDA Response:
It is too early to discuss a proposed indication for acalabrutinib based on the Study ACE-LY-308.

Meeting Discussion:
No Discussion

Question 4: Does the Agency agree with the proposed statistical methods [redacted]?

FDA Response:
We disagree [redacted].
Please also refer to additional statistical comments.

Meeting Discussion:
Regarding [redacted]***, the Agency provided feedback regarding concerns*** [redacted]***. The Sponsor may submit revisions to the protocol for Agency feedback.***

Question 5: Does the Agency agree that previously treated MCL constitutes an unmet medical need in the context of determining eligibility for Accelerated Approval in accordance with FDA guidance on Expedited Programs for Serious Conditions?

FDA Response:
We agree that relapsed or refractory mantle cell lymphoma is a serious condition. Eligibility for an accelerated approval pathway involves meeting all the qualifying criteria to include demonstrating a meaningful advantage over available therapies. Consideration for an accelerated approval of acalabrutinib for your proposed indication in previously treated MCL will be based on available therapy at the time of regulatory action.

Question 6: Does the Agency agree that should study ACE-LY-004 demonstrate sufficient magnitude of benefit (in terms of overall response rate (ORR) and duration of response (DOR)) that the data may be considered for Accelerated Approval of acalabrutinib in the proposed indication?

FDA Response:
An important consideration will be the durability of response. We recommend a minimum follow-up of 12 months for all responders for trial ACE-LY-004.

The Agency notes that the therapeutic landscape for the treatment of mantle cell lymphoma is rapidly evolving. The determination if an accelerated approval pathway is an option will be based on available therapy at the time of regulatory action of your application.

Meeting Discussion:
The Sponsor proposes their target for NDA submission in Q4 2016, based on a June 2016 data cutoff date with an estimated 8-month median duration of follow-up. The Agency emphasized the importance of 12-month follow-up for safety and efficacy data in the proposed population in order to support a breakthrough designation request (BTDR) and an application submission. For efficacy data, the Agency clarified minimum of 12-months follow-up for responders, which would start from the onset of response.

The Agency also explained that, as per PDUFA V regulations, applications must be complete at the time of submission. Late submissions may be allowed, but late submissions are inappropriate for data that are critical for the evaluation of safety and efficacy.

The Sponsor clarified that patients who are refractory to ibrutinib were not enrolled in trial ACE-LY-004.

Question 7: Does the Agency agree (b) (4) (b) (4)

FDA Response:
No, we have several issues regarding the trial design (b) (4) (b) (4)**.**

(b) (4) (b) (4)**. We recommend to redesign the trial to adequately isolate the treatment effect of acalabrutinib compared to ibrutinib.**

Lastly, the decision for an accelerated approval pathway for acalabrutinib in a previously treated MCL lymphoma population will be based on available therapy at the time of regulatory action of the application. See response to question 5.

Meeting Discussion:
The Sponsor proposes to submit a revised protocol (b) (4) ***, which the Agency will review and provide feedback.***

The Sponsor inquired regarding the possibility of analysis of a subset of patients in trial ACE-LY-004 for duration of response. The Agency can review a proposal that is submitted by the Sponsor.

Additional comments:

Clinical Pharmacology
For study ACE-LY-309:

- (b) (4) (b) (4) **You need to clarify if patients with mild hepatic impairment will be dose adjusted for ibrutinib or exclude patients with total bilirubin > 1.5xULN.**

Statistical:
For study ACE-LY-004:

- **Time-to-event endpoints, such as PFS and overall survival (OS), are not interpretable in this single-arm trial.**
- **Results on duration of response, in additional to overall response rate, are important in evaluating treatment effect in single-arm study.**

For study ACE-LY-309:

- (b) (4) (b) (4) **. This assessment schedule may cause measurement bias in PFS.**
- **Your study design cannot isolate the treatment effect of acalabrutinib.**
- **You mentioned in study protocol Section 11.2 that the follow-up time is assumed to be approximately 29 months after the first subject has been randomized. We have the concern this will not provide sufficient follow-up for reliably evaluating time-to-event endpoints. In addition, this is not consistent with your projection of study duration of 48 months after the first subject has been randomized.**

For study ACE-LY-308 and ACE-LY-309:

- **Your proposed disease assessment schedules are not consistent.** (b) (4) (b) (4) **We recommend you revise the disease assessment schedules to every 12 weeks no matter the subject is on or off treatment.**

- **We discourage [redacted] (b) (4), because those analysis results may be unreliable and overestimate actual treatment effect.**
- **In the absence of a statistically significant result for the primary analysis of the primary endpoint, results based on secondary endpoints, subgroups, or further analysis of the primary endpoints cannot result in (either singly or in combination) an efficacy claim. In the event that there is a statistically significant result for the primary analysis of the primary endpoint, those secondary endpoints that are significant after proper adjustment for multiplicity may be included in the label. Please include in a future submission, any secondary endpoints for which claims may be included in the labeling and how adjustments will be made for multiplicity to guarantee a study-wise 1-sided type I error rate of 0.025.**
- **All patients should be followed for PFS until a PFS event occurs (progression or death) or until the data cutoff. Missing data/assessments of progression should be kept at a minimum. A substantial amount of missing data could undermine confidence in the PFS results of the trial and may prevent a labeling claim on PFS. Sensitivity analyses, using different censoring mechanisms, should be performed to assess the robustness of the result of the primary analysis of PFS.**

3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at

301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017,** the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is

intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

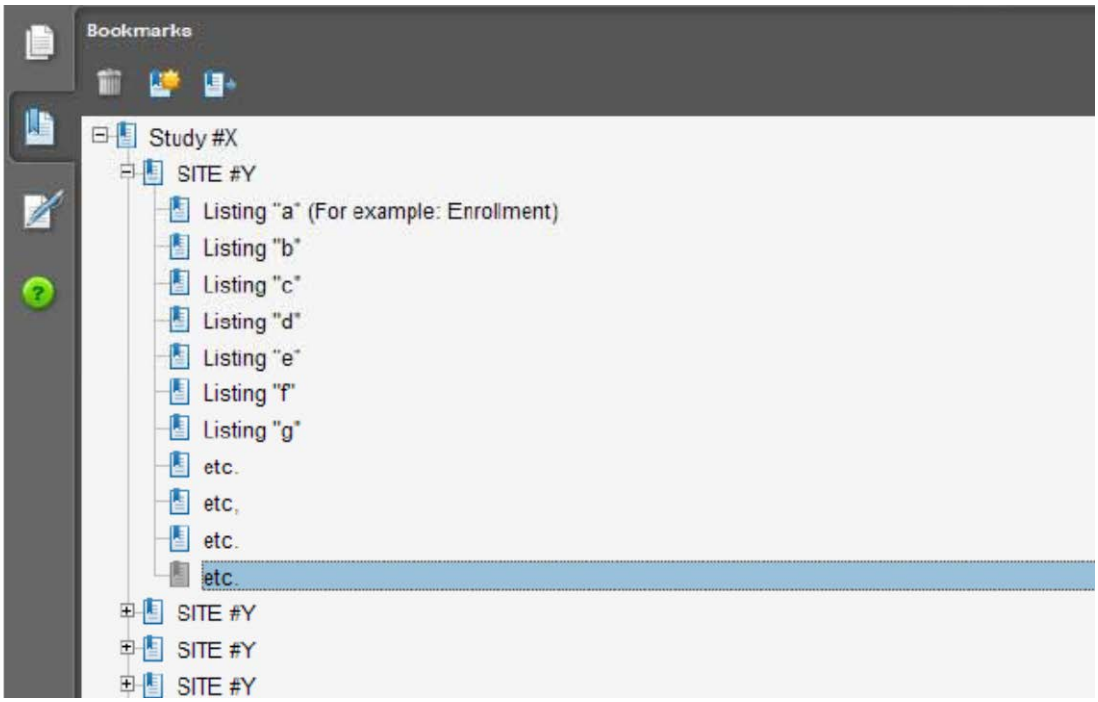
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry "*Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning*" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items for this meeting.

6.0 ATTACHMENTS AND HANDOUTS

The handouts used for this meeting has been appended to the meeting minutes.

6 Pages have been Withheld in Full as B4(CCI/TS)
Immediately Following this Page

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

/s/

ROMEO A DE CLARO
03/25/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 118717

MEETING MINUTES

Acerta Pharma B.V.
c/o LBR Regulatory & Clinical Consulting Services, Inc.
Attention: Gregory L. Kelso, PhD
US Agent for Acerta Pharma B.V.
7000 Houston Road, Suite 18
Florence, KY 41042

Dear Dr. Kelso:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ACP-196 (SCH 2046835/Org 300196-0; SCH 900850).

We also refer to the meeting between representatives of your firm and the FDA on August 27, 2015. The purpose of the meeting was to obtain regulatory guidance and answers to specific questions regarding an Accelerated Approval approach for ACP-196 treatment in patients with previously treated chronic lymphocytic leukemia (CLL) and who are intolerant of ibrutinib.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Beatrice Kallungal, Regulatory Project Manager at (301) 796-9304.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase 2
Meeting Date and Time:	August 27, 2015; 1:00 PM – 2:00 PM (ET)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1313 Silver Spring, Maryland 20903
Application Number:	IND 118717
Product Name:	ACP-196 (SCH 2046835/Org 300196-0; SCH 900850)
Proposed Indication:	Treatment of chronic lymphocytic leukemia in patients who are intolerant of ibrutinib therapy (b) (4)
Sponsor/Applicant Name:	Acerta Pharma B.V.
Meeting Chair:	R. Angelo de Claro, MD
Meeting Recorder:	Beatrice Kallungal, BS

FDA ATTENDEES

Division of Hematology Products
Edvardas Kaminskas, MD, Deputy Division Director
R. Angelo de Claro, MD, Medical Officer, Clinical Team Leader
Tanya Wroblewski, MD, Clinical Reviewer

Office of Biostatistics/Division of Biometrics V
Yun Wang, PhD, Reviewer

SPONSOR ATTENDEES

John Byrd, MD, D. Warren Brown Chair of Leukemia Research, Director of Hematology and Oncology, The Comprehensive Cancer Center, Arthur G James Cancer Hospital
William Donaldson, BVSc, PhD, VP Regulatory Affairs, Acerta Pharma
Maria Fardis, PhD, Chief Operating Officer, Acerta Pharma
Jane Huang, MD, VP Clinical Sciences
Raquel Izumi, PhD, Executive VP Clinical Development, Acerta Pharma
Dave Johnson, Chief Executive Officer, Acerta Pharma
Jesse McGreivy, MD, Chief Medical Officer, Acerta Pharma
Roger Ulrich, PhD, Chief Scientific Officer, Acerta Pharma

Xiaolin Wang, ScD, VP of Biometrics, Acerta Pharma
Elsa Johnson, MBA, PMP, Sr. Director, Program Management, Acerta Pharma

1.0 BACKGROUND

ACP-196 is a small molecule covalent Bruton tyrosine kinase (Btk) inhibitor, currently being evaluated as a single agent and in combination with other agents in several hematologic malignancies and solid tumors. The requested meeting will focus on ACP-196 as single-agent treatment for patients with previously treated chronic lymphocytic leukemia (CLL) who are intolerant of ibrutinib and have no available therapy options. The objectives of this meeting are to reach agreement on the design of the proposed (b) (4) (b) (4)

FDA sent Preliminary Comments to Acerta on August 25, 2015.

2. DISCUSSION

Preamble: The Division discourages your development proposal (b) (4) (b) (4)

The Division recommends conducting randomized controlled trial(s).

Question 1: Does the Agency agree (b) (4) (b) (4)?

FDA Response:
No, we do not agree (b) (4) (b) (4)

Meeting Discussion:
See meeting discussion under question 6.

Question 2: Does the Agency agree with the proposed definition (b) (4) (b) (4) (b) (4)?

FDA Response:
While your proposed definition [redacted] appears reasonable, we do not agree with the design [redacted] Refer to Preamble and response to question 1.

Meeting Discussion:
No discussion

Question 3: Does the Agency agree with the overall design of the proposed study [redacted]

FDA Response:
No, see Preamble and response to question 1.

Meeting Discussion:
No discussion

Question 4: Does the Agency agree with the Sponsor's proposed [redacted]

FDA Response:
No, see Preamble and response to question 1.

Meeting Discussion:
No discussion

Question 5: Does the Agency agree [redacted]

FDA Response:
No, see Preamble and responses to questions 1 and 4.

Meeting Discussion:
No discussion

Question 6: Does the Agency agree [redacted]

FDA Response:
No. The Division does not agree with your development proposal. [redacted]

Meeting Discussion:
The Agency reiterated concerns with a development approach (b) (4)
(b) (4)

Question 7: Does the Agency agree (b) (4)
(b) (4)

FDA Response:
We do not agree (b) (4)
(b) (4)

Meeting Discussion:
No discussion

Question 8: Does the Agency agree (b) (4)
(b) (4)

FDA Response:
No, see Preamble.

Meeting Discussion:
No discussion

3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format.

This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note

that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.

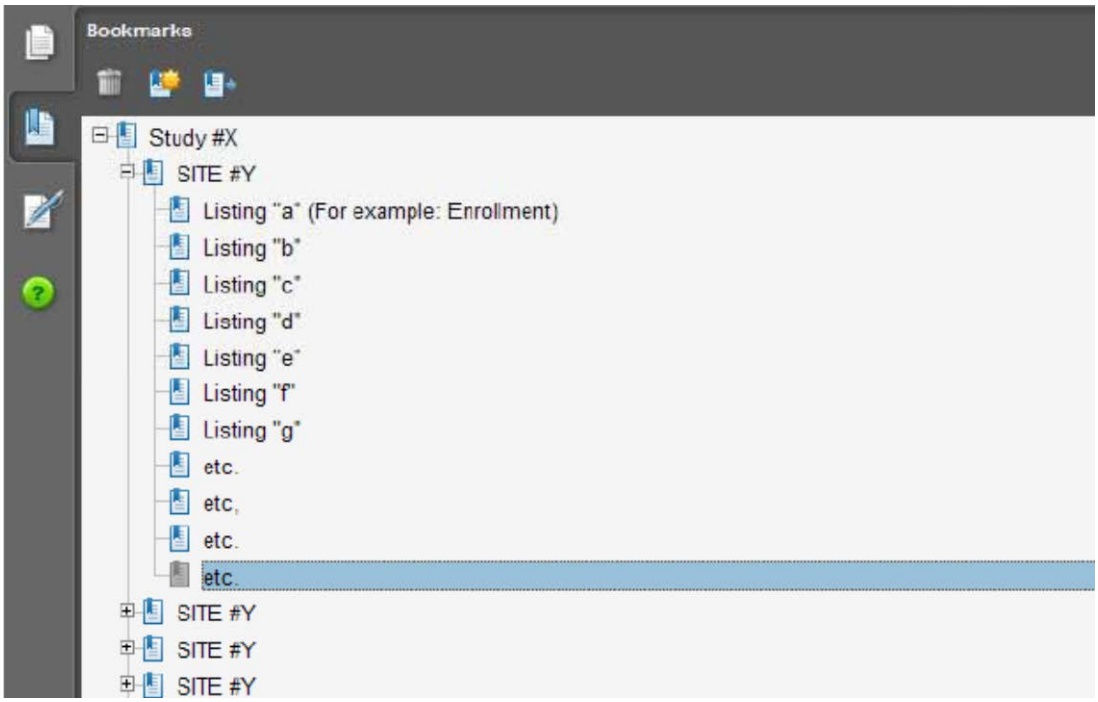
c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry *Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning* (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items from this meeting.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor's response to the Agency's preliminary meeting comments has been appended to these meeting minutes.

3 Pages 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/

ROMEO A DE CLARO
08/31/2015