CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213312Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 125669

MEETING PRELIMINARY COMMENTS

Aadi Bioscience, Inc.
Attention: Mitchall G. Clark, BPharm (Hons), MRPharmS
Sr. Vice President, Regulatory Affairs and Quality Assurance
17383 Sunset Blvd, Suite A250
Pacific Palisades, CA 90272

Dear Mr. Clark:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ABI-009.

We also refer to your February 28, 2020, correspondence, received February 28, 2020, requesting a meeting to discuss and obtain feedback on the contents and format of your proposed 505(b)(2) New Drug Application (NDA) for ABI-009 for the treatment of advanced (metastatic or locally advanced) malignant PEComa.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

[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.

If you have any questions, call me at 301-796-4803.

Sincerely,

{See appended electronic signature page}

Stacie Woods, Pharm.D.
Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases 2
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:

- Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: Tuesday, May 12, 2020, 12:00 PM – 1:00 PM ET
Meeting Location: Teleconference

Application Number: 125669
Product Name: ABI-009

Indication: Treatment of advanced (metastatic or locally advanced) malignant PEComa
Sponsor Name: Aadi Bioscience, Inc.
Regulatory Pathway: 505(b)(2)

FDA ATTENDEES (tentative)

Office of Oncologic Diseases (OOD)
Jessica Boehmer, M.B.A., Regulatory Scientist
Division of Oncology 2 (DO2)
Harpreet Singh, M.D., Division Director
Denise Casey, M.D., Clinical Reviewer
Suzanne Demko, P.A.-C. Clinical Team Leader

Division of Hematology Oncology Toxicology (DHOT)
Sachia Khasar, Ph.D., Nonclinical Reviewer
Whitney Helms, Ph.D., Nonclinical Team Leader

Office of Scientific Investigations (OSI)
Max Ning, M.D., Reviewer
Michele Fedowitz, M.D., Reviewer

Office of Biostatistics (OB)
Division of Biostatistics V (DBV)
Pourab Roy, Ph.D., Statistical Reviewer
Pallavi Mishra-Kalyani, Ph.D., Statistical Reviewer Team Leader

Office of Clinical Pharmacology (OCP)
Division of Cancer Pharmacology (DCPII)
Vicky Hsu, Ph.D., Clinical Pharmacology Reviewer
Jeanne Fourie-Zirkelbach, Ph.D., Clinical Pharmacology Team Leader

Office of Product Quality (OPQ)
Hailin Wang, Ph.D., Product Quality Reviewer
Quamrul Majumder, Ph.D., Product Quality Reviewer
Xing Wang, Ph.D., Product Quality Team Leader

Office of Regulatory Operations (ORO)/Oncologic Disease (OD)
Stacie Woods, Pharm.D., Regulatory Health Project Manager

SPONSOR ATTENDEES
Mitchall Clark, B.Pharm, MRPharmS, Sr. VP Regulatory Affairs and Quality Assurance, Aadi Bioscience, Aadi Bioscience
Neil Desai, Ph.D., CEO, Aadi Bioscience
Mark Dickson, M.D., Medical Oncologist, Memorial Sloan Kettering Cancer Center
Berta Grigorian, B.S., VP, Clinical Operations, Aadi Bioscience
(b) (4)
Shihe Hou, Ph.D., Director, Regulatory Science and Quality Assurance, Aadi Bioscience
Nicole Hsu, BScPhm, MS, Director, Regulatory Affairs, Aadi Bioscience
Nancy Jorgesen, M.S., MBA, VP, Project Leadership, Aadi Bioscience
Erik Kratzer, M.S., Sr., Director Manufacturing Operations, Aadi Bioscience
(b) (4)
Anita Schmid, Ph.D. , Director, Clinical Research & Development, Aadi Bioscience
Andrew J. Wagner, M.D., Ph.D., Medical Oncologist, Dana Farber Cancer Institute
Assistant Professor, Medicine, Harvard Medical School

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference meeting scheduled for May 12, 2020, 12:00 PM – 1:00 PM ET, between Aadi Biosciences, Inc. and the Division of Oncology Products 2. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

BACKGROUND

Regulatory

On June 11, 2015, a pre-IND meeting was held to discuss the development program for ABI-009 for patients with advanced malignant perivascular epithelioid tumors (PEComa). Key points of the discussion are as follows:

- FDA stated that a single, adequate and well-conducted study demonstrating unequivocal evidence of an important treatment effect (e.g., overall response rate (ORR) of sufficient magnitude and durability) that reflects substantial evidence of clinical benefit in a well- defined patient population could be supportive of an application seeking regular approval. FDA additionally stated that if Aadi chose to seek regular approval rather than accelerated approval based on the results of a single study (PEC001), a postmarketing study to collect additional safety data in the malignant PEComa population would likely be required.

- FDA advised that a detailed definition of 'advanced malignant PEComa' that specifically addresses the minority of patients who do not have distant metastases at the time of enrollment be provided in the protocol submitted to the IND.

- FDA agreed with the proposal to include patients with metastatic and locally advanced and unresectable disease in the trial planned to support registration; however, FDA recommended that exploratory subgroup analyses based on disease stage be incorporated into the statistical analysis plan (SAP) as these patients may respond differently to treatment.

- During the discussion of the adequacy of the proposed statistical analysis plan, FDA stated that an estimation study with a primary endpoint of ORR that excludes 14.7% from the lower bound of the 95% confidence interval could be an acceptable design. Assuming that a 30% response rate is observed, a sample size of at least 30 patients with advanced malignant PEComa might be sufficient for results of this trial to support a marketing application.

- FDA agreed that the estimated safety database of a maximum of 30 patients with advanced malignant PEComa who will have been treated for at least six months with the intended dose of ABI-009, in conjunction with the safety database from Study CA401 (N=26), and the safety data available for the listed drugs Rapamune and Torisel might be sufficient to support a marketing application provided that no unusual toxicities are identified in patients with malignant PEComa.

On October 16, 2018, FDA and Aadi held a teleconference to discuss the preliminary efficacy data from Study PEC-001. FDA recommended that Aadi submit a request for BTD based on the preliminary response and duration of response data included in the Fast Track Designation request.

On December 10, 2018, a Type C meeting was held to discuss Aadi's regulatory strategy in preparation for the submission of a 505(b)(2) NDA for ABI-009. Key points of the discussion are as follows:

- Aadi requested a waiver from the requirement to submit the source and analysis data from Study CA401 in CDISC SDTM and ADaM format and proposed submission of legacy format datasets based on SAS transport files along with a data definition file and annotated CRF. FDA stated that this was acceptable and requested that Aadi provide raw and analysis (derived) datasets in SAS v5 XPORT transport format (XPT files); a data definition table for raw and analysis datasets (define.pdf) including the source derivation for each variable in the datasets and hypertext links from the define.pdf to the XPT files and the annotated Case Report Form (CRF); and annotated CRFs in pdf format. FDA further states that Module 5 of the NDA should include SAS programs that can be used to reproduce the efficacy and safety results in the Clinical Study Report and the proposed labeling and a document (.pdf) that provides the description of analyses in the submitted SAS programs.

- Aadi proposed (b) (4) (b) (4); however, FDA did not agree to this approach (b) (4) (b) (4). FDA advised that Aadi conduct the primary safety analysis on Study PEC-001, a pooled safety analysis that includes studies of ABI-009 conducted under Aadi Bioscience sponsored INDs and that Aadi include a side-by-side presentation of adverse event results occurring in Study PEC-001 and in the pooled analysis with a discussion of any notable differences between the two groups. FDA also stated that Aadi should include a side-by-side summary of safety from patients enrolled in non-oncology clinical studies in the NDA.

- FDA recommended that Aadi submit the NDA based on the study protocol's planned primary analysis (i.e., when all patients have had the opportunity to have been followed for six months following initiation of ABI-009) and that proposals for submission of updated efficacy information during the review could be discussed during the pre-NDA meeting.

- FDA agreed with Aadi's proposal to include CRFs and narratives for all patients who died, had other serious adverse events, or who discontinued ABI-009 for adverse events. FDA stated that if there are adverse events of special interest (AESI) that Aadi is following across the ABI-009 development program, that the CRFs and patient narratives for AESI that are grade 3 or greater in severity should also be submitted.

- FDA stated that the final indication would be based on review of the data for the overall PEC-001 study population and for the disease subgroups included in the NDA.

- FDA states that product labeling should describe treatment emergent AE data regardless of causality (either investigator- or sponsor-determined) given that the safety data is derived from a single arm trial with no internal control.

Designations

On December 21, 2017, ABI-009 was granted orphan designation for treatment of PEComa.

On October 24, 2018, fast track designation was granted for ABI-009, for the treatment of patients with advanced (metastatic or locally advanced) malignant PEComa.

On December 12, 2018, breakthrough therapy designation was granted for ABI-009, for the treatment of patients with advanced (metastatic or locally advanced) malignant PEComa.

Nonclinical

AB-009 is a human albumin-bound rapamycin, an mTOR inhibitor and immunosuppressive agent. To support the submission of a 505(b)(2) NDA, Aadi provided a summary of a single-dose GLP-compliant nonclinical PK comparison study with limited toxicological endpoints in Sprague-Dawley rats to support the scientific bridge between ABI-009 and the listed drug as well as tabular listings of other pharmacology and pharmacokinetic studies conducted to support the activity, safety, and distribution of AB-009 alone or compared to sirolimus.

Clinical

Disease Background
PEComas are a collection of rare mesenchymal tumors composed of perivascular epithelioid cells distinguished by melanocytic (HMB-45) and smooth muscle (desmin and actin) positivity using immunohistochemistry. Most PEComas are benign and do not recur after complete surgical resection. A small subset of PEComas demonstrate malignant behavior including development of local recurrences and distant metastases. The incidence of these advanced malignant PEComas is approximately 50-80 patients per year in the U.S. Malignant PEComas are characterized by tumor suppressor gene 2 (TSC2) mutations, have a female preponderance, and present in various locations including the gastrointestinal tract, uterus, and retroperitoneum. Metastatic disease can develop in any organ. Most patients with locally advanced or recurrent disease develop metastatic disease within one year from diagnosis. The literature is scarce given the rarity of the condition; however, the median overall survival (OS) in limited case series

of locally advanced or inoperable or metastatic PEComa is reported as 14-16 months. There are no systemic therapies approved for patients with malignant PEComa. Cytotoxic chemotherapy used as an off-label treatment has not been shown to have antitumor effects or improve outcomes. Radiation therapy has not been shown to be effective.

Development of ABI-009 in malignant PEComa is based on the pathogenesis of PEComa involving the loss of TSC2, or more rarely TSC1. Inactivating mutations in TSC1 or 2 lead to overactivation of mTOR, a regulatory protein kinase that serves as a regulator of cell survival, proliferation, stress, and metabolism. Additionally, multiple small retrospective case series report antitumor activity with other mTOR inhibitors (e.g., everolimus, sirolimus) in patients with malignant PEComa.

ABI-009 Clinical Development Program
The clinical development program for ABI-009 includes Aadi- or investigator-sponsored studies in various cancer and nononcology indications. Aadi proposes to use the efficacy results from a single study, PEC-001, to support a 505(b)(2) NDA for ABI-009 for the treatment of patients with advanced (metastatic or locally advanced) malignant PEComa. Study PEC-001 is a multi-center, single-arm study of ABI-009 100 mg/m2 IV administered on days 1 and 8 of a 21-day cycle in patients with advanced malignant PEComa. The patient population included patients with locally advanced disease for which surgery was not a recommended option and patients with metastatic disease. All patients had measurable disease and were naïve to prior mTOR inhibitor therapy at enrollment. The primary endpoint of the trial was ORR determined by independent radiologic assessment using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Duration of response (DOR) is a key secondary endpoint. The primary efficacy and safety analyses were to be conducted when all enrolled patients had had the opportunity to be treated for at least 6 months.

Thirty-four patients received ABI-009 in Study PEC-001. The primary efficacy analysis was performed using data from 31 (26 with metastatic disease and 5 with locally advanced disease with no surgical option) evaluable patients who received at least one dose of ABI-009 and had one post baseline response evaluation. As of the data cutoff May 22, 2019, the centrally-assessed ORR in 31 patients was 39% (95% CI: 22, 58). All responses were partial responses. For the subset of 26 patients with metastatic disease, the ORR was 46% (95% CI: 27, 67) and for the subset of 5 patients with locally advanced and inoperable disease, there were no objective responses. According to the briefing package, during the post-treatment follow-up, 2 of the 5 patients with locally advanced disease were able to undergo surgery to remove the tumor and remained disease-free at the data-cut off 2-2.5 years following treatment. For the 12 patients who experienced an objective response, the median duration of response was not reached, and 10 (83%) of the responding patients had ongoing responses six months or longer and 5 (42%) had ongoing responses of 12 months or longer.

The primary safety data in the NDA will be from Study PEC-001. Supportive safety data will be from Studies CA401, GBM-007, COLO-007, and PAH-001 (see Table 4 in briefing document). The topline safety results from Study PEC-001 indicate that 44% of patients had at least 1 SAE including 2 patients (6%) who died from SAEs considered unrelated to ABI-009: upper gastrointestinal hemorrhage and atelectasis. The most frequent (≥30%) treatment-related adverse events were stomatitis/mucositis, fatigue, anemia, nausea, diarrhea, weight and appetite loss, peripheral edema, hypokalemia, hyperglycemia, vomiting, dysgeusia, cough, and rash.

SPONSOR QUESTIONS AND FDA RESPONSES

Chemistry, Manufacturing and Controls

1. An overview of the CMC development program is provided in Section 1.15.1. During the February 25, 2020 Type B CMC meeting, the Agency requested that the development of critical manufacturing steps be described. The requested information was not provided in the meeting information package for the February 25, 2020 meeting. Summaries of the formulation and manufacturing process development studies are provided in Section 1.15.1.3 and Section 1.15.1.6 of the current meeting package, respectively. Does the FDA agree that the ABI-009 formulation and manufacturing process development program is complete?

   FDA Response: Based on the information provided in the submission, the manufacturing formula and manufacturing process development program appears appropriate. A final determination on completeness of the manufacturing process development and/or process optimization will be made at the time of NDA review when all the information is available.

2. During the February 25, 2020 Type B CMC meeting, the Agency requested that process changes be identified. Two process changes occurred during the clinical development of ABI-009. Section 1.15.1.7 provides a summary of process changes and the studies conducted to support the changes. Please confirm the adequacy of our approach to supporting these process changes.

   FDA Response: Studies conducted (b) (4) seems acceptable. However, we could not find a comparative CQA (specifically, protein-bound particles (b) (4)) analysis of your drug product made with new and initial processes in the submission. The adequacy of these process changes will be made at the time of NDA review when all the information is available.

3. Aadi will retain the required samples for method validation purposes; the samples are described in Section 1.15.1.9 of this meeting package. Please confirm that the choice of method validation samples is appropriate.

FDA Response: The proposed plan appears appropriate. In addition to Lot C349-001 as indicated in the meeting package, reserve samples from two other planned registration batches. A final determination on the need for method validation and sample request will be made during NDA review based on quality assessment.

Nonclinical

4. As requested in the December 10, 2018 Type C meeting, the Agency agreed in principle that the nonclinical program appeared adequate to support a 505(b)(2) NDA for ABI-009. Since that time, the GLP single-dose nonclinical pharmacokinetic (PK) comparison Study 1291.01 required to bridge to the RLD has been completed and a summary of the results is provided in Appendix B. An overall summary of the program is described at a high level in Section 1.15.2. Details on the program were provided in the meeting package for the December 10, 2018 Type C Meeting (submitted October 23, 2018, Serial No. 0024).

    a. Please confirm Aadi's proposal to rely on the nonclinical studies identified in Table 24 that were previously conducted for the RLD but for which the Sponsor does not have a right of reference is acceptable to support the ABI-009 505(b)(2) NDA.

        FDA Response: As previously stated in the minutes of the meeting of December 10, 2018, the nonclinical program appears adequate to support a 505(b)(2) NDA for AB-009; however, the acceptability of data from these studies will be determined during the review of all data included in the NDA submission.

    b. Please confirm that the level of detail provided in the representative tabular summaries in Appendix C is sufficient.

        FDA Response: The level of detail provided in the representative tabular summaries in Appendix C appears sufficient.

5. Toxicology studies to support the ABI-009 505(b)(2) NDA started prior to December 17, 2016, the implementation date for the SEND data policy according to the FDA Data Standards Catalog. The FDA Study Data Technical Conformance Guide (October 2019) limits the scope of the SEND Implementation Guide V3.0 requirements to single-dose general toxicology, repeat-dose general toxicology, and carcinogenicity studies. Due to the timing of Aadi's toxicology studies to support the NDA relative to the timing of implementation of the SEND data policy, Aadi is not planning to submit SEND files for these studies. Additionally, at FDA's request and to support the submission of a 505(b)(2) NDA, Aadi has conducted a single-dose GLP

nonclinical PK comparison Study 1291.01 with limited toxicological endpoints to support the scientific bridge between ABI-009 and the RLD. Aadi considers that this is primarily a PK study and is therefore not planning to submit SEND files for this study.

a. Please confirm that Aadi's proposal to not submit SEND files in the 505(b)(2) NDA for toxicology studies, based on study start dates referenced in the SEND data policy, is acceptable.

FDA Response: Aadi's proposal to not submit SEND files in the 505(b)(2) NDA for toxicology studies is acceptable.

b. Please confirm the proposal to not submit SEND files in the 505(b)(2) NDA for the single-dose GLP nonclinical PK comparison study (Report 1291.01), based on it being primarily a PK study, is acceptable.

FDA Response: Aadi's proposal to not submit SEND files in the 505(b)(2) NDA for the single-dose GLP nonclinical PK comparison study is acceptable.

Clinical Pharmacology

6. At the December 10, 2018 Type C meeting, FDA requested that pre-specified Clinical Pharmacology information be provided in tabular format at the time of the pre-NDA meeting. The completed Highlights of Clinical Pharmacology information is provided in Question 6 Supporting Data, Table 27. Please note that no independent Clinical Pharmacology studies were completed, thus only the relevant table is provided. In addition, a general description of the kinetics of ABI-009 and a proposal for language for the Prescribing information is further described in Question 6 Supporting Data.

a. Please confirm the Clinical Pharmacology table provided at the request of the Agency is sufficient.

FDA Response: Yes, the Highlights of Clinical Pharmacology Table provided in the meeting package appears sufficient.

b. The pharmacokinetics of ABI-009 administered at the recommended dose of 100 mg/m2 were modeled after combining PK information from PEC-001 in PEComa patients and CA401 in patients with solid tumors. Does the FDA agree with Aadi's approach to its selection of PK parameters to be included in the Prescribing Information?

FDA Response: Yes, FDA agrees with Aadi Bioscience's proposed approach; however, the acceptance of the PK parameters to be included in the PI will be determined during the NDA review.

Clinical/Statistics

7. At the December 10, 2018 Type C Meeting, FDA indicated it did not object to Aadi's proposal to amend the SAP for the registrational clinical trial (Protocol PEC-001) to evaluate all secondary endpoints for all evaluable patients combined over disease types in addition to analyzing patients by subgroup of disease (metastatic vs. locally advanced). This proposal was made because there were fewer than expected patients enrolled in the study with locally advanced disease compared to those with metastatic disease. None of the additional changes to the statistical analysis plan (SAP) were considered substantive. FDA requested that a list of changes between versions of the SAP be provided in the NDA submission. The most current version of the SAP (V4.0) along with summaries of changes are provided in Appendix D and an overview is provided in Question 7 Supporting Data.

   All analyses in accordance with the current version of the SAP (V4.0) are complete. Please confirm that no additional analyses are required in the original NDA.

   FDA Response: The proposed analyses appear reasonable. Although no other analyses are required at this time, FDA may request additional analyses after submission of the NDA to assist the review of the application.

8. A list of the tables, listings, and figures (TLFs) and key select examples of the TLFs that will be included in the clinical study report (CSR) for the pivotal Phase 2 clinical study, PEC-001, are provided in Appendix E.

   Does the Agency agree that the list of tables, listings, and figures for the pivotal Phase 2 clinical study (PEC-001) is complete? Does the Agency recommend additional presentations of the study data to assist in the review of the NDA?

   FDA Response: The proposed list of TLFs to be included in the PEC-001 CSR appears to be complete. FDA may request submission of additional analyses during the NDA review.

9. The demonstration of the efficacy of ABI-009 in PEComa is based on the Phase 2 open-label clinical study designed to evaluate the efficacy and safety in patients with advanced malignant PEComa (PEC-001). The PEC-001 study completed enrollment on November 12, 2018 (35 adult patients, with 31 centrally confirmed PEComa) and the milestone for the primary analysis was met on April 16, 2019 when all patients had the opportunity to be treated with ABI-009 for 6

months. Accordingly, the primary analysis has been conducted and the PEC-001 trial has met its primary efficacy endpoint (ORR by 6 months based on independent central radiology review), as well as demonstrated clinically meaningful duration of response (a key secondary endpoint). In addition, the safety data showed an acceptable safety profile in this patient population generally consistent with the safety profile of the RLD, with manageable adverse events. Results of the PEC-001 study are summarized below in the data to support Question 9 Supporting Data.

Please confirm that the results from the PEC-001 trial are sufficient to support a 505(b)(2) NDA filing.

FDA Response: The results from Study PEC-001 appear sufficient to support a 505(b)(2) NDA filing.

10. In the December 10, 2018 Type C Meeting, Aadi requested that it be permitted to not submit an integrated summary of safety (ISS) because the key safety and efficacy data in PEComa patients is derived from a single study in approximately 30 patients. The Agency denied the request and requested a pooled analysis of safety data from all patients exposed to any dose of IV ABI-009 across all ongoing or completed studies in cancer indications across the ABI-009 development program be included in the NDA to permit a larger sample size for assessing common and rare safety events. FDA also requested a side-by-side summary of safety from patients enrolled in non-oncology clinical studies. In terms of the presentation of the pooled analysis, FDA stated that the summary of clinical safety may be sufficient for the narrative of the integrated summary, but TLFs supporting an integrated safety dataset should be provided in Module 5. Aadi subsequently submitted an SAP on February 19, 2019 (Serial No. 0032) that prospectively described the analysis of the pooled safety datasets for FDA comment. The FDA also confirmed in their April 19, 2019 advice that the primary efficacy analysis from PEC-001 and supporting information from CA401 could be summarized in the summary of clinical efficacy and no integrated summary of efficacy was required.

Aadi has integrated the safety data as requested. Aadi's interpretation of ABI-009 safety data in PEComa patients (Study PEC-001) in comparison to all patients exposed to any dose of IV ABI-009, either monotherapy or in combination, across all ongoing and completed studies in oncology and non-oncology studies, is provided in Question 10 Supporting Data. Key tables planned for inclusion in the 2.7.4 Summary of Clinical Safety are provided in Appendix F. Additionally, a copy of the SAP for the ISS is available in Appendix G. A table of contents for the integrated safety TLFs, and a few examples of ISS tables planned for inclusion in Module 5 are provided in Appendix H.

a. Please confirm that the list of tables and listings is complete and in agreement with the Agency's correspondence dated April 19, 2019.

FDA Response: The list of tables and listings to be included in the Summary of Clinical Safety as outlined in the Appendix appears acceptable.

b. Please confirm that the integrated safety analysis conducted as described in the provided SAP and the proposed presentation of data in the Tables and Listings, along with the key in-text tables is sufficient and meets the Agency's expectations. If not, please clarify.

FDA Response: The proposed analyses for the ISS as outlined in Appendix G appear acceptable. While FDA agrees with the safety data for the pooled oncology patients being presented in a side-by-side manner for Study PEC-001 (N=34), the total oncology pool (N=76) and the oncology pool without PEC-001 (N=42), it is unnecessary to include additional columns in the side-by-side safety tables for the specific oncology studies other than PEC-001 as these sample sizes are too small to draw reliable conclusions regarding differing safety profiles per study populations.

11. In the June 2015 Pre-IND meeting, FDA recommended that Aadi perform exploratory-response analyses for efficacy and safety with the data obtained from the proposed trial (i.e., Protocol PEC-001) and other trials. Aadi subsequently reached agreement with FDA on the design and analysis plan for the proposed population PK analyses, Study ADI0101, on data from Study PEC-001s and Phase 1 Study CA401 at the December 10, 2018 Type C meeting; a copy of the Type C meeting minutes is provided in Appendix A.

The SAP and an executive summary of the Study ADI0101 results are provided in Appendix I. The modeling processes used to establish the population PK model demonstrated a final two compartment model with saturable binding that was then used to simulate blood sirolimus concentrations for ABI-001. The exposure-response analysis revealed that:

- Baseline laboratory values for low platelets, low hemoglobin, and elevated aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were associated with increased risk for thrombocytopenia, anemia, and recurrence of elevated AST and ALT, respectively.
- Sirolimus exposure (Cavg) showed a positive relationship for the incidence of thrombocytopenia.
- No significant trends were observed between increasing incidence or severity of other adverse effects and sirolimus exposure, including anemia, mucositis, rash, pneumonitis, elevated AST, elevated ALT, neutropenia, hypokalemia, hyperglycemia, dehydration, hypertriglyceridemia, and diarrhea.

- For covariates in the population PK model, age and/or sex had various associations with AEs of thrombocytopenia, anemia, mucositis, elevated AST, and pneumonitis. However, given the small sample size of the subsets and the relative low frequency of events, no dose modifications are recommended based on age and sex.
- A positive relationship for the probability of response was observed for sirolimus exposure.
- Based on the above population PK modeling, elevated baseline AST and ALT were associated with increased risk of AST and ALT elevation. Hence, dose adjustments for patients with hepatic impairment are suggested in the labelling for ABI-009.

Does the Agency agree that the population PK analyses are sufficient to inform the review of the ABI-009 505(b)(2) NDA and that no further analyses are needed to support the application?

FDA Response: Yes, Aadi Bioscience's proposed population PK analyses appear sufficient to support a 505(b)(2) NDA filing; however, FDA may request Aadi Bioscience to perform further analyses if identified during the NDA review.

Regulatory Affairs

12. At the December 10, 2018 Type C meeting, FDA requested that a tabular summary be provided for information in the proposed 505(b)(2) application "that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature." The tabular summary is provided in Question 12 Supporting Data, Table 39.

    Does FDA agree that the information listed as being essential to the approval of ABI-009 that is being provided by reliance on the FDA's previous finding of safety and effectiveness for the RLD, or by reliance on published literature, is sufficient to support filing and review of the 505(b)(2) NDA?

    FDA Response: The summary table (Table 39 in the meeting package) listing the information to be provided by reliance on the FDA's previous finding of safety and effectiveness for the proposed listed drugs appears acceptable. Whether the information provided is sufficient will be determined during review of the NDA.

    Please also refer to additional information under the subsection titled "505(b)(2) Regulatory Pathway," below.

13. At the December 10, 2018 Type C meeting, FDA recommended that Aadi submit the NDA for ABI-009 based on the planned primary analysis of the PEC-001 study (i.e., when all patients had the opportunity to be treated for 6 months following initiation of ABI-009). The last patient in the PEC-001 trial had the

opportunity to be treated for 6 months on April 16, 2019 and the NDA will therefore contain, in accordance with FDA's recommendation, data through this date with a cut-off of May 22, 2019 for Study PEC-001. Similarly, the ISS will contain data through April 30, 2019 for all ongoing studies. Given ABI-009 has been granted Breakthrough Therapy Designation, and the PEC-001 trial has met its primary endpoint in a life-threatening condition, Aadi is planning to request priority review. The proposed scope of the safety update provided to the FDA during the review of the NDA is limited to the PEC-001 study, as this is the only relevant study conducted in the proposed indication, advanced malignant PEComa. Safety information collected from all other studies are in other indications and utilize dose regimens and treatment combinations that do not reflect the recommended monotherapy dose schedule for the population in the label.

a. Should priority review be granted, when, during the shortened review period, would a safety update of the PEC-001 trial be expected?

FDA Response: A safety update report is required to be submitted within 120 days from submission of a complete application; however, it is helpful to have the safety update report submitted for review by 90 days from the NDA submission given the shortened review timeline.

b. Aadi is planning to provide a safety update solely for the PEC-001 trial during the review period, and not the ongoing studies in other indications. Please confirm this is acceptable.

FDA Response: The proposal to only include safety data from Study PEC-001 in the safety update report is acceptable; however, Aadi must inform FDA of any new or unexpected safety signals observed across the ABI-009 global development program during the NDA review as these may impact the overall risk assessment of ABI-009 in the intended use population.

14. A Target Product Profile (TPP) is provided (Appendix J) as a tool to communicate how the data generated with ABI-009, as well as information from the RLD, will be presented in the proposed prescribing information in the NDA.

Does the Agency concur that the Target Product Profile provided is acceptable to use as a basis for the prescribing information that will be submitted in the 505(b)(2) NDA?

FDA Response: In general, prescribing information will be a review issue to be negotiated during review of the NDA. The provided Target Product Profile appears acceptable as a basis for the prescribing information to be submitted in the NDA. FDA suggests that Aadi also examine the prescribing information from

a related drug (e.g., Torisel®) to inform the format and content of the ABI-009 labeling submitted in the NDA.

15. Consistent with the FDA's advice during the December 10, 2018 Type C Meeting, Aadi has focused the proposed safety section of the label on treatment-emergent adverse events (TEAEs) due to the single arm design of the pivotal Study PEC-001. (b) (4) Aadi considers safety experience with other studies (Phase 1 CA401, other oncology and non-oncology studies) supportive, and while the sponsor intends to utilize this information to detect any differences in safety signals from the PEC-001 study, the key safety information for prescribers is in patients with advanced malignant PEComa.

Two separate summary tables of all TEAEs reported in at least 10% (>3 patients) of patients who received ABI-009 in the PEC-001 study are planned for the prescribing information: one for hematologic and laboratory abnormalities and another for nonhematologic events (Appendix J, TPP, Section 6 Adverse Reactions). The proposed cut-off of 10% is consistent with other labels within the mTOR inhibitor class of drugs and follows the example on page 2 of the 2006 FDA Guidance Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format. Adverse events of special interest (AESIs) were preidentified at the start of the study based on class effects of mTOR inhibitors (Sivendran, 2014; Martins, 2013; Aapro, 2014) and/or were more frequent in the first-in-human dose-finding safety study (CA401). Their related preferred terms were grouped together into a single combined term to avoid diluting or obscuring the true effect in the label (e.g., (b) (4) is treated as a group term that includes aphthous ulcer, mouth ulceration, esophageal ulcer, and stomatitis). These AESI group terms are presented in both the hematologic/laboratory and nonhematologic event summary tables and the preferred terms constituting the AESIs were footnoted. Grouped terms are also defined in Appendix E, Listing 16.2.7.8 for Study PEC-001.

The proposed ABI-009 prescribing information will describe in narrative form the most common treatment-emergent adverse reactions occurring at 30% or higher in the PEC-001 study, with events split into general, hematological, and laboratory abnormality categories (Appendix J, TPP, Section 6 Adverse Reactions). This cut-off for the narrative description of common events was based in part on precedence from other mTOR inhibitor labels, as well as on an assessment of the threshold beyond which key clinically meaningful events (including all AESIs, except for dermatitis, pneumonitis, and dehydration) consistent with the drug class occurred in the PEC-001 Study, further described in Question 15 Supporting Data. Any adverse events of special interest that fell

below this cut-off but were considered clinically significant were included in the warnings and precautions (e.g., pneumonitis).

The selection of terms to elevate to the Warnings and Precautions section of the label (Appendix J, TPP, Section 5 Warnings and Precautions) relies primarily on an assessment of the safety data collected in the PEC-001 study and for language considered class labeling from the RLD Rapamune. The methodology is described in Question 15 Supporting Data.

a. Does the Agency agree that the scope of the safety information proposed for the label is appropriately limited to the PEC-001 safety population?

FDA Response: No. While the focus of labeling is the intended population of use, the purpose of safety labeling is to describe all adverse reactions and safety hazards that may be serious or clinically important as they have implications for prescribing decisions and patient management. The Study PEC-001 safety data alone may not permit a reliable assessment of risk for rare but serious adverse reactions to ABI-009 that are not adequately represented in the 34 patient database. Particularly for Section 5, FDA strongly recommends that all safety data from clinical studies of ABI-009 be analyzed, in addition to considering safety data for the RLD and drug class effects, as a strategy to develop and sufficiently inform each of the subsections under Warning and Precautions. Further, Aadi should include in the NDA a thoughtful rationale for the ABI-009 safety population selected to inform Section 5 of the package insert. For Section 6.1 Clinical Trials Experience, the focus should be a description of the adverse reactions that occurred at the dose intended for use in the recommended indication.

b. Does the Agency agree with the proposed cut-off of 10% for the 2 tabular summaries of treatment-emergent adverse reactions in the Adverse Reaction section of the label?

FDA Response: In general, the cut-off for presentation of toxicities in the label should adequately inform prescribers of the risks associated with use of the drug. The proposed thresholds of 30% for the narrative description and 10% for the tabular presentations of common adverse reactions in Section 6 may be acceptable; however, a final determination will depend on review of the safety data in the application. The complete content of product labeling will be negotiated during the review of the NDA.

c. Does the Agency agree with the proposed cut-off of 30% for the narrative descriptions of common adverse reaction in the Adverse Reaction section of the label?

FDA Response: See FDA Response to 15b.

d. Does the Agency agree with the proposed terms in the Warnings and Precautions in the label?

FDA Response: The proposed terms in the TPP may be acceptable; however, the final list of warnings will depend on review of the safety data in the application. See Response to 15a.

16. Aadi has not conducted independent clinical studies in patients with hepatic and renal impairment, nor in geriatric populations (however, 15 of 34 enrolled patients were 65 years of age or older). Sirolimus tablets and oral solution (Rapamune) are the referenced listed drugs for this NDA. Aadi will rely on information specific to special populations developed by the sponsor of Rapamune but to which it does not have the right of reference.

The safety and efficacy of sirolimus in these populations was described in the original NDA for the RLD for these populations, and guidance for dosing these populations is provided in the package insert for Rapamune. The following is a summary of Aadi's approach to each of these patient populations:

a. Patients with Renal Impairment: The effect of renal impairment on the pharmacokinetics of sirolimus is not known. However, labeling for the RLD indicates there is minimal (2.2%) renal excretion of the drug or its metabolites in healthy volunteers. Consistent with the RLD, in a nonclinical study (BTC P0606001), ABI-009 was excreted primarily through the fecal route (approximately 90% of total excretion), with a minor contribution from the renal route. Therefore, as with the RLD, no dosing modifications will be recommended for ABI-009.

Does the Agency agree with Aadi's approach to addressing dosing recommendations for renally impaired patients?

FDA Response: Yes, Aadi Bioscience's proposed dosing recommendation in patients with renal impairment appears reasonable.

b. Patients with Hepatic Impairment: Independent studies in hepatically impaired patients have not been conducted with ABI-009. Aadi's proposed recommendation for use in patients with hepatic impairment is provided in Question 16 Supporting Data: Hepatic Impairment Patients.

Does the Agency concur with Aadi's approach for dosing in hepatically impaired patients?

FDA Response: Aadi Bioscience's proposed dosing recommendations in patients with hepatic impairment appear reasonable; however, the final determination will be made during the NDA review.

c. Geriatric Use: The phase 2 registrational trial in patients with advanced malignant PEComa (PEC-001), an ultra-rare disease, had a relatively small sample size. Although the age groups were generally balanced (56% <65 years vs 44% ≥65) along with the adverse events across the age groups, PEC-001 did not include a sufficient number of patients aged 65 and over to definitively determine whether elderly patients respond differently from younger patients, and other reported clinical experience has not identified differences. The "Geriatric Use" subsection will include a statement consistent with 21 CFR 201.57(c)(9)(v). Further data and rational are provided in Question 16 Supporting Data: Geriatric Patients.

Does the Agency agree with Aadi's proposed labeling language for Geriatric Use?

FDA Response: The proposed labeling language for Geriatric Use appears reasonable and the content of product labeling will be negotiated during the review of the NDA. See the following FDA Guidance on Content and Format for Geriatric Labeling available at https://www.fda.gov/media/72141/download

17. ABI-009 has been granted orphan drug designation and is therefore exempt from Pediatric Research Equity Act. Additionally, while mTOR is listed as a "relevant" molecular target in association with the FDARA 2017 Race for Children Act, the NDA is being planned for submission in the second quarter of 2020, prior to the August 18, 2020 implementation date. Aadi is therefore not planning to conduct pediatric studies at this time in PEComa.

(b) (4)

(b) (4). Aadi notes the FDA's January 2020 Q&A on Pediatric Study Plan for Oncology Drugs: Transitional Information Until Full Implementation of FDARA Section 504 encourages sponsors to address molecularly targeted pediatric

cancer investigations in their development plans even if sponsors are planning to submit their applications prior to August 18, 2020.

ABI-009 was granted Fast Track and Breakthrough Therapy designations on October 24, 2018 and December 12, 2018 respectively, and expects to file a rolling submission shortly after the pre-NDA meeting on May 12, 2020.

a. Please confirm that an agreed-upon initial Pediatric Study Plan (iPSP) is not required for the ABI-009 505(b)(2) NDA submission if the first component of a rolling submission is submitted prior to August 18, 2020, and the last component is submitted within 6 months of the first component.

FDA Response: An agreed-upon initial Pediatric Study Plan (iPSP) is not required for the ABI-009 505(b)(2) NDA submission if the first component of a rolling submission is submitted prior to August 18, 2020. If the NDA submission is not initiated prior to August 18, 2020, FDA recommends that Aadi submit an iPSP that describes a plan to develop ABI-009 in a pediatric oncology population (b) (4) and that includes a request for deferral of pediatric assessments if necessary. Please see the following guidance for Pediatric Study Plans available at https://www.fda.gov/media/86340/download

b. Although we anticipate filing the NDA prior to August 18, 2020, unanticipated events such as the ongoing COVID-19 pandemic have the potential to delay the NDA beyond this timepoint. It is our intent to submit an iPSP requesting a waiver for pediatric studies in patients with advanced malignant PEComa, (b) (4) at the time of initial NDA filing. If the Agency does not agree with our proposal in (a) above, given that we have Breakthrough Therapy designation and have demonstrated clinical benefit for ABI-009 in the treatment of patients with advanced malignant PEComa, a rare disease with an unmet medical need, may we submit the NDA if the iPSP is not approved at the time the final component of the rolling NDA is submitted?

FDA Response: See Response to 17a.

18. A proposed table of contents of Modules 1, 2, 3, 4, and 5 of the NDA that reflect current guidance and the outcome of the December 10, 2018 and February 25, 2020 Type B meetings is provided in Appendix K.

Does the Agency have any comments regarding this proposal for the format and content of the NDA? Based on the Agency's current knowledge of the

development program and plans for the 505(b)(2) NDA for ABI-009, does the Agency have any additional requests for information that will facilitate the review?

FDA Response: The proposed table of contents provided in Appendix K appears acceptable.

19. Aadi has prepared a Bioresearch Monitoring (BIMO) package for the PEC-001 study that includes the required elements described in FDA's Bioresearch Monitoring Technical Conformance Guide (February 2018).

Study PEC-001 is the pivotal study that provides the safety and efficacy claims in the PEComa population in the proposed label for this NDA. Aadi notes the BIMO package applies to "all major (i.e., pivotal) studies used to support safety and efficacy claims in new drug applications (NDAs)" per the FDA's Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018).

A representative example of the PDF subject-level data line listing, and a depiction of how the BIMO package will be submitted in module 5 is provided in Appendix L.
Please confirm the BIMO package contains the expected elements in the proper format and that this information is expected for the PEC-001 study only.

FDA Response: Your proposal appears to be acceptable as an example of the format for subject-level data line listings. Please note that for Study PEC-001, complete subject-level data line listings by study site should be submitted to the NDA. For additional details, please also refer to Pages 2-4 and Appendix 2 of the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications *[see link below, Office of Scientific Investigations (OSI) Requests].*

20. At the December 10, 2018 Type C meeting, FDA confirmed the acceptability of Aadi's request for a waiver from the requirement to submit the source and analysis data from Phase 1 legacy study CA401 in CDISC SDTM and ADaM format given its legacy status (study completion in June 2011). While FDA did not object to the proposal that datasets would not be provided in CDISC-compliant format for the CA401 study, the Agency did request the datasets and supportive information be provided as follows:

- Raw and analysis (derived) datasets in SAS v5 XPORT transport from (XPT files);
- Data definition table for raw and analysis datasets (define.pdf) including the source derivation for each variable in the datasets. The hypertext link

will also be provided from the define.pdf to the XPT files and the annotated Case Report Form (CRF); and
- Annotated CRFs in pdf format.

In addition, FDA requested the following be included in Module 5 of the NDA submission:

- SAS programs that can be used to reproduce the efficacy and safety results in the CSR and the proposed labeling.
- A document (.pdf) that provides the description of analyses in the submitted SAS programs. The document should include the names of datasets and variables that were used in the analyses.

The eCTD Module 5 folder table of contents for the CA401 legacy study is provided in Appendix M.

Does the Agency agree that the structure and content of the datasets and supportive information for the CA401 study is acceptable? Does the Agency have any additional requests for information that will facilitate the review?

FDA Response: The proposed content and structure of the datasets and supportive information for CA4010 appears acceptable. You may also consider including a reviewer's guide to facilitate the review of your data.

21. The data packages for the PEC-001 study and the ISS will be submitted in CDISC compliant SDTM and ADaM format consistent with FDA's Study Data Technical Conformance Guide (March 2018) located in FDA's Guidance for Industry titled "Providing Regulatory Submissions in Electronic Format – Standardized Study Data."

The eCTD module 5 folder table of contents for both the PEC-001 study and the ISS are provided in Appendix N and Appendix O, respectively. All SDTM datasets, ADaM datasets, and programs for the ADaM datasets for both the PEC-001 study and ISS TLFs are planned for inclusion in the NDA. Consistent with the FDA Guidance Study Data Technical Conformance Guide (March 2019), only a subset of programs that code for the key PEC-001 and the ISS TLFs are proposed for inclusion in the NDA. Further details are provided in Question 21 Supporting Data.

Does the Agency agree that the structure and content of the datasets and supportive information for the PEC-001 study and the ISS are acceptable? Does the Agency have any additional requests for information that will facilitate the review?

FDA Response: The proposed tables of contents for Study PEC-001 and for the ISS are acceptable.

Additional Comments

22. The Oncology Center for Excellence has developed an Assessment Aid to facilitate FDA's assessment of NDA/BLA applications (including supplements). The Assessment Aid is based on the FDA Multidisciplinary Review template with most sections divided into two parts, clearly delineated to emphasize ownership of each position as either the Applicant's position or the FDA's position. The applicant fills in their positions in the relevant sections; these should be concise and only include critical information (e.g., should generally be no longer than 100 pages).

    The Agency would like to offer you the use of the Assessment Aid for your planned NDA for ABI-009 for the treatment of patients with metastatic or locally advanced malignant PEComa. If you choose to participate, FDA would expect receipt of the completed Assessment Aid within 30 days of submission of the final module of the NDA.

    Included below are the Assessment Aid instructions and Assessment Aid template for your reference, as well as the FDA website describing this program. The AA instructions and template are attached. Your review should not exceed 100 pages.

    https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

Clinical Pharmacology

Take the following recommendation about labeling into your consideration:

23. FDA recommends the content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application be consistent with FDA Guidance for Industry, "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" (available at https://go.usa.gov/xn4qB). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

Address the following questions in the Summary of Clinical Pharmacology:

24. What is the basis for selecting the doses and dosing regimen used in the trials intended to support your marketing application? Identify individuals who required

dose modifications, and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.

25. What are the exposure-response relationships for efficacy, safety and biomarkers?

26. What is the effect of ABI-009 on the QT/QTc interval?

27. What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?

28. How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure, efficacy, or safety? What dose modifications are recommended?

Apply the following advice in preparing the clinical pharmacology sections of the original submission:

29. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.

30. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with minimum and maximum values as appropriate.

31. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.

    - Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

    - Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.

32. Submit the following for the population pharmacokinetic analysis reports:

    - Standard model diagnostic plots

- Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line
- Model parameter names and units in tables.
- Summary of the report describing the clinical application of modeling results. Refer to the following pharmacometric data and models submission guidelines at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.

33. Submit the following information and data to support the population pharmacokinetic analysis:

- SAS transport files (*.xpt) for all datasets used for model development and validation.
- A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets
- Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

34. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and toxicity) relationships in the targeted patient population. Refer to Guidance for Industry at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf for population PK, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf for exposure-response relationships, and http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm for pharmacometric data and models submission guidelines.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our March 10, 2020, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor

application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[2]

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))

[2] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

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.[3]

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 FDA's Guidance on Formal Meetings Between the FDA and Sponsors or Applicants[4] to ensure open lines of dialogue before and during their drug development process.

[3] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[4] See the guidance for industry *"Formal Meetings Between the FDA and Sponsors or Applicants."*

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.[5]

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[6] and Pregnancy and Lactation Labeling Final Rule[7] 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.

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,

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

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 guidances.

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.[8]

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.[9]

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."

[8] http://www.fda.gov/ectd
[9] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

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)				

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999).[10] In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at Regulations.gov.[11]

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate.

[10] 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.
[11] http://www.regulations.gov

You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
(1) Example: Published literature	*Nonclinical toxicology*
(2) Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
(3) Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
(4)	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

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* (February 2018) and the associated *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*.[12]

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 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[13]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- AssessmentAid[14]

[12] https://www.fda.gov/media/85061/download
[13] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[14] 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/

STACIE A WOODS
05/06/2020 11:57:44 AM

IND 125669

MEETING PRELIMINARY COMMENTS

Aadi Bioscience Inc
Attention: Mitchall G. Clark, BPharm (Hons), MRPharmS
Sr. VP Regulatory Affairs and Quality Assurance
17383 Sunset Blvd Suite A250
Pacific Palisades, CA 90272

Dear Mr. Clark:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ABI-009 (sirolimus).

We also refer to the meeting between representatives of your firm and the FDA on February 25, 2020. The purpose of the meeting was to discuss and receive feedback on questions and proposals regarding aspects of the CMC regulatory strategy and requirements for selected Chemistry, Manufacturing and Control (CMC) topics in preparation for the submission of a 505(b)(2) NDA for ABI-009.

A copy of the official minutes of the meeting/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 Kristine Leahy, Regulatory Business Process Manager, at (240) 402-5834.

Sincerely,

{See appended electronic signature page}

Anamitro Banerjee, Ph.D.
Branch Chief, Branch 1
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

[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.

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: February 25, 2020, 1:00p.m. – 2:00p.m.
Meeting Location: WO Building 22, Conference Room 1315

Application Number: 125669
Product Name: sirolimus (formerly rapamycin) albumin-bound nanoparticles for injectable suspension; Company Codes ABI-009, nab-sirolimus

Indication: Malignant Perivascular Epithelioid Cell Tumor (PEComa), a rare form of sarcoma that has Orphan Drug Designation (DRU-2017-6162).

Sponsor Name: Aadi Bioscience, Inc.

Meeting Chair: Anamitro Banerjee
Meeting Recorder: Kristine Leahy

FDA ATTENDEES (tentative)
Anamitro Banerjee, Ph.D., Branch Chief, Branch 1, OPQ/ONDP
Xing Wang, Ph.D., Quality Assessment Lead, OPQ/ONDP
Sheena Wang, Ph.D., Drug Product Reviewer, OPQ/ONDP
Soumya Mitra, Ph.D., Drug Substance Reviewer, OPQ/ONDP
Mei Ou, Ph.D., Biopharmaceutics Reviewer, OPQ/ONDP
Banu Zolnik, Ph.D., Biopharmaceutics Team Lead, OPQ/ONDP
Lisa Ashmore, Ph.D., Product Quality Microbiology Reviewer, OPQ/OPMA
Quamrul Majumder, Ph.D., OPMA Reviewer, OPQ/OPMA
Rakhi Shah, Ph.D., Branch Chief, OPQ/OPMA
Kristine Leahy, RPh., Regulatory Business Process Manager, OPQ/OPRO

SPONSOR ATTENDEES
Mitchall Clark, B.Pharm, MRPharmS, Sr. VP Regulatory Affairs and Quality Assurance, Aadi Bioscience
Neil Desai, PhD, President and CEO, Aadi Bioscience
Shawn Hou, PhD, Director, Regulatory Science and Quality Assurance, Aadi Bioscience
Nancy Jorgesen, MS, MBA, VP, Project Leadership, Aadi Bioscience
Julie Cheng, Director, Global Quality and Analytical Services, Celgene Corporation
Erik Kratzer, Principal Engineer - Commercial Product Development, Celgene Corporation

1.0 BACKGROUND

The purpose of this request is to receive feedback on questions and proposals regarding aspects of the CMC regulatory strategy and requirements for selected Chemistry, Manufacturing and Control (CMC) topics in preparation for the submission of a 505(b)(2) NDA for ABI-009.

Aadi has addressed outstanding issues raised during the December 12, 2018 Type B CMC meeting with the FDA and is initiating the preparation of the NDA. The primary objective of this meeting is to determine if the data generated in response to the issues raised during the Type B (has breakthrough designation granted December 12, 2018) meeting adequately address the FDA's comments and questions. It is anticipated that the 505(b)(2) NDA will be filed in the second quarter of 2020.

Specifically, the development of ABI-009 is progressing as planned and the registrational clinical study Protocol PEC-001 closed to enrollment and database locked in May 2019. It is anticipated that the 505(b)(2) NDA will be filed in the second quarter of 2020. Aadi wishes to specifically update the FDA regarding the issues raised in the December 2018 Type B CMC meeting and seek confirmation that the CMC development program appears complete.

2. DISCUSSION

Question 1:

Please confirm that the stability protocol for the ongoing testing of stability lots, and future validation and commercial lots, is complete and does not require a test for sirolimus associated with nanoparticles, (b) (4) (b) (4) ?

FDA Response to Question 1:

Yes, we agree. Based on the information provided in your submission, it appears that it is reasonable to not include a test for sirolimus associated nanoparticles (b) (4) in the DP stability specification. You should however add in process controls for (b) (4) your manufacturing process.

You should also provide a risk assessment (b) (4) (b) (4) during stability storage (b) (4) and include a test for (b) (4) release and stability specifications or other control strategy as necessary.

Meeting Discussion 1:

The sponsor requested further F2f discussion on FDA's aspects of our responses to ***Questions 1, 3b, 3d, 3f, and our additional comments*** *regarding the solubility of rapamycin and in-vitro release testing. Slides were presented.*

The FDA stated that risk assessment and justifications [redacted] should be included in P.2 of the NDA submission. Characterization data of the registration batch samples prepared from the final selected manufacturing process should be provided. In absence of entire process development report or batch data (sirolimus associated with nanoparticles [redacted]) made [redacted], we are unable to comment on the need for such in-process test in future validation and commercial lots. A final determination will be made at the time of NDA review.

Question 2:

Based on the data presented in Section 2.15.2 (Question 2), does the FDA agree that it has been adequately demonstrated [redacted] that the study [redacted] adequately addresses the question of the nature of binding of sirolimus and human albumin?

FDA Response to Question 2:

Yes, we agree. The data provided appears to be sufficient to support the understanding of nature of binding of sirolimus and human albumin. You should include this information in the proposed NDA.

Question 3

3a) Regarding an identity test for Human Albumin in ABI-009

Please confirm the adequacy of this response.

FDA Response to Question 3a:

The proposed ID test for HSA in ABI-009 appears to be reasonable. A final determination will be made at the time of NDA review.

3b) Regarding impurities from Human Albumin

Please confirm the adequacy of this response.

FDA Response to Question 3b:

No, we do not agree. [redacted]

(b) (4)

Therefore, you should include a test of HSA oligomeric status in the DP release and stability specification or provide additional data to justify its non-inclusion.

3c) Regarding a test for Container Content per USP <697>
Please confirm the adequacy of this response.

FDA Response to Question 3c:
Your proposal of not including container content test in the DP release specification appears to be reasonable based on the results provided for the withdrawn volume study. A final determination will be made at the time of NDA review.

3d) Regarding tests which establish the amount of (b) (4) sirolimus and (b) (4) Human Albumin
The analysis demonstrates consistency across a variety of clinical and experimental lots. Does the agency concur that the sirolimus and albumin components have been adequately characterized and do not need to be part of the product specification?

FDA Response to Question 3d:
Yes, we agree. Analysis of the drug content across various clinical and experimental batches provided in your submission indicates that most of the drug in the formulation (b) (4) was associated with the nanoparticle and the (b) (4) form of sirolimus (b) (4) was largely associated with soluble albumin. In your NDA, you should provide the analysis for production batches manufactured using the final selected manufacture process (b) (4) and components.

In addition, you should also evaluate and report in the NDA, the impact of different level of (b) (4) sirolimus on physical stability of the reconstituted suspension (b) (4) to support the proposed in-use condition. Large particle characterization by Laser Diffraction or filtration recovery study of the reconstituted solution is recommended.

Meeting Discussion 3d:
The FDA clarified that the since analysis of clinical and experimental batches had shown that (b) (4) of the sirolimus drug content may be (b) (4), it's important to demonstrate the physical stability of the reconstituted suspension prepared from these samples can be consistently maintained for the proposed in-use condition.
Due to light obscuration requirement for the Laser Diffraction measurement, the samples may need to be diluted in the suspending media which does not represent the actual in-use state of the sample, therefore, the filtration recovery is still

recommended to characterize the reconstituted solution before and after the in-use storage.

3e) Regarding a test for Elemental Impurities per USP <232> and <233>
Please confirm the adequacy of this response.

FDA Response to Question 3e:
It appears to be acceptable to not to include a test for elemental impurities in the drug product specification. In your NDA, you should include a risk assessment for the elemental impurities consistent with the recommendations of ICH Q3D.

3f) Regarding a test for an in vitro drug release method (b) (4) (b) (4) of measuring drug release

Based on these data, Aadi has confirmed that there is minimal release of sirolimus from ABI-009 nanoparticles at concentrations above the solubility level of sirolimus. (b) (4) (b) (4) (b) (4) **The studies by** (b) (4) **on behalf of Aadi confirmed that variations around the target for manufacturing processing parameters, or age of the samples, have no impact on the in vitro drug release or dissolution characteristics. Aadi therefore proposes there is no value gained by the addition of an in vitro release test to the release or stability specifications for the drug product to the control of the manufacturing process or quality control of ABI-009. The experimentation and results will be presented in the characterization section of the NDA (Module 3.2.P.2.2.). Based on the characterization data generated, does the FDA agree with Aadi's proposal?**

FDA Response to Question 3f:
(b) (4) (b) (4) that in vitro drug release method is not needed (b) (4) is not adequately justified (b) (4) (b) (4) Before we can agree that the in vitro drug release method is not needed, please clarify how (b) (4) sirolimus contribute to the efficacy of the drug product.

Please also clarify if the role of albumin [redacted] has interaction/complexation with sirolimus so that albumin is essential for efficacy. Meanwhile, in the absence of the above information, FDA's recommendation for development of an appropriate in vitro drug release method for quality control purpose remains. The in vitro drug release method should be capable of evaluating sirolimus released from both soluble albumin associated sirolimus, and albumin-nanoparticle associated sirolimus. We recommend you evaluate the in vitro drug release with regards to the changes of the following (but not limit to) drug loading, particle size distribution, albumin oligomeric status, etc.

Please refer to the *Additional FDA Comments* regarding the in vitro drug release method development and setting the acceptance criterion/criteria.

Meeting Discussion 3f:

[redacted] *The FDA stated that the results of the* [redacted] *test and all additional data should be included in the NDA* [redacted]. *The Sponsor also stated that they will include additional modeling data to support their justification that in vitro drug release method is not needed as a QC test for the finished drug product. The FDA recommended the Sponsor to include all the supporting data in the NDA and stated that their justification will be reviewed in the NDA.*

Question 4:

Please confirm that the study supports the requirement for an analytical comparison of the RLD with ABI-009 for the purpose of the proposed 505(b)(2) NDA.

FDA Response to Question 4:

The study appears to support the assay and impurities comparison of listed drug with ABI-009 for the purpose of the proposed 505(b)(2) NDA. This information should be included in the NDA for review.

Question 5:

a) **Does the FDA agree with the selection of the proposed executed batch record for inclusion in the NDA?**

FDA Response to Question 5:
No, the agency does not agree. Submit all the executed batch records for the primary stability batches and recently manufactured drug product batches in NDA. In the NDA, provide a comparative evaluation of all the changes proposed for the commercial process as compared to the clinical batches and demonstrate that these changes have no impact on the product quality.

Question 6:
Please confirm that our understanding of the guidance is correct with specific reference to the transfer of ABI-009 from [redacted] (b) (4)

FDA Response to Question 6:
No, the agency cannot confirm that your understanding of the guidance is correct with respect to site change request. Manufacturing site changes will require a facility evaluation proposed in a Comparability Protocol (CP) and may not justify a reporting category other than a Changes Being Effected in 30 days (CBE-30) or Prior Approval Supplement (PAS).

We will evaluate whether the facility impacted by the change should be subject to a pre-approval inspection at the time that the site change or other change(s) are to be made. And if we determine that a pre-approval inspection is needed within the 30 days after receipt of a CBE 30 submission for a site change, a PAS will be necessary to gain approval for the new site and any associated process changes.

Question 7: **(See comments a-k.)** ***Please confirm that the approaches to addressing the issues arising out of the Type B CMC meeting as summarized above are adequate.***

FDA Response to Question 7: For Question 7.f, the overall approach appears reasonable. Based on the Table of Contents for the Type V DMF provided in Attachment 5, it appears that some sections in the DMF may not be applicable for manufacture of the proposed drug product [redacted] (b) (4).
In the NDA, provide any product-specific information that will direct the reviewer to relevant DMF sections applicable for manufacture of the proposed drug product [redacted] (b) (4)

Question 8:
Does the FDA have additional questions regarding whether the particle size test is measuring sirolimus albumin-bound particles, or [redacted] (b) (4) **albumin?**

FDA Response to Question 8:
We do not have additional questions at this time.

Question 9:
Provided in Attachment 3 is the content plan for the drug product NDA Module 3 which has been updated since last presented in the December 12, 2018 pre-meeting information package. Please confirm that the plan is acceptable to support a 505(B)(2) NDA.

FDA Response to Question 9:
The proposed content plan for NDA Module 3 appears to be adequate to support a 505(B)(2) submission.

Additional FDA Comments:

1) While solubility dependent dissociation of nanoparticles upon dilution is expected, solubility of sirolimus in this protein bound nanosuspension system is not fully characterized. Provide solubility characterization of the clinical lots and future production lots in different solvents (e.g. saline and diluted HSA solution) to demonstrate that product with the comparable solubility profile/apparent solubility can be consistently manufactured. In addition, evaluate whether immediate release/dissociation of the suspension product can be achieved based on comparison of the apparent solubility of sirolimus and estimated product concentration upon infusion.
2) Include Type II DMF letter of authorization(s) (LOA) for sirolimus (API) in your NDA application from API manufacturer(s).

3) FDA has the following recommendation for the in vitro drug release method development:

A. A detailed description of the in vitro drug release method being proposed for the evaluation of your drug product and the development parameters (e.g., the selection of the equipment/apparatus, in vitro release media, agitation, pH, sink condition, etc.) used to select the proposed in vitro release method as the optimal method for your product. The testing conditions used for each test should be clearly specified. The drug release profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. FDA recommends the use of at least twelve samples per testing variable. The in vitro drug release method should be capable of measuring the drug release with respect to free drug concentration only.

Meeting Discussion:
None.

B. Provide the complete in vitro release profile data (individual, mean, SD, profiles) for the product. The data should be reported as the cumulative percentage of drug released with time (the percentage is based on the product's label claim at 5, 10, 15, 30, 45 minutes, 1, 2, 3, 4, 6, 8, 12, 24, 36, 72 hours, etc.).

C. Provide data to support the discriminating ability of the selected in vitro drug release method. In general, the testing conducted to demonstrate the discriminating ability of the selected drug release method should compare the in vitro release profiles of the target product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical material attributes (CMAs) and critical formulation variables (CFVs).

D. For the selection of the in vitro drug release acceptance criterion of the product, FDA recommends use of the drug release profile data from the clinical batches and primary (registration) batches (throughout the stability program) for setting the acceptance criterion. The in vitro drug release profile should encompass the timeframe over which at least 85% of the drug is released, or where the plateau of drug release is reached if incomplete drug release occurs. The acceptance criterion(a) should be based on average in vitro drug release data (n = 12). A minimum of three time points is recommended to set the specification. These time points should cover the early, middle (~40-60%), and late stages of the drug release profile. The last time point should be the time point where at least 80% of drug is released.

E. Please note that the acceptability of the in vitro drug release method and acceptance criterion(a) will be determined during the NDA review cycle. However, you have the option of submitting the in vitro drug release method development and validation report for FDA's review and comments under your IND. If you decide to submit it, please include in the cover letter of the Amendment that you are seeking FDA's feedback, specifically from the Division of Biopharmaceutics and notify OPQ RBPM of this amendment for timely review and feedback within three months of the submission.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No Issues requiring further discussion

5.0 ACTION ITEMS

No Action Items

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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/

KRISTINE F LEAHY
03/24/2020 11:28:57 AM

ANAMITRO BANERJEE
03/24/2020 11:43:55 AM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 125669
Request Receipt Date	October 23, 2018
Product	ABI-009
Indication	Advanced malignant perivascular epithelial cell tumors (PEComa)
Drug Class/Mechanism of Action	Nab-rapamycin; mTOR inhibitor
Sponsor	Aadi Bioscience, INC.
ODE/Division	OHOP/DOP2
Breakthrough Therapy Request(BTDR) Goal Date (within 60 days of receipt)	December 22, 2018

Note: This document must be uploaded into CDER's electronic document archival system as a ***clinical review: REV-CLINICAL-24 (Breakthough 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):**

   ABI-009 is intended for the treatment of patients with advanced (metastatic or locally advanced) malignant perivascular epithelial cell tumors (PEComa).

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:

   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

[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

☐ 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.

Disease Background

Perivascular epithelial cell tumors (PEComas) are a collection of rare mesenchymal tumors composed of perivascular epithelioid cells distinguished by melanocytic (HMB-45) and smooth muscle (desmin and actin) positivity using immunohistochemistry. Most PEComas are benign and do not recur after complete surgical resection. A small subset of PEComas demonstrate malignant behavior including development of local recurrences and distant metastases. The incidence of these advanced malignant PEComas is approximately 50-80 patients per year in the U.S. Malignant

[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

PEComas are characterized by tumor suppressor gene 2 (TSC2) mutations, have a female preponderance, and present in various locations including the gastrointestinal tract, uterus, and retroperitoneum. Metastatic disease can develop in any organ, but most commonly occurs in the lungs, bones and brain. Most patients with locally advanced or recurrent disease develop metastatic disease within one year from diagnosis. The literature is scarce given the rarity of the condition; however, the median overall survival (OS) in limited case series of locally advanced and inoperable or metastatic PEComa is reported as 14-16 months despite use of chemotherapy or radiation (Wagner 2010; Bleeker 2012).

Regulatory History

A pre-IND meeting was held on June 11, 2015, to discuss the development program for ABI-009 for patients with advanced malignant PEComa. Key points of the discussion are listed below:

- AADi stated their intention to submit an NDA seeking accelerated approval if Study PEC001 meets the proposed endpoints; however, given that malignant PEComa is an extremely rare and serious condition with no known cure and no current FDA-approved treatments, FDA told AADi that a single, adequate and well-conducted study demonstrating unequivocal evidence of an important treatment effect (i.e., ORR of sufficient magnitude and durability) that reflects substantial evidence of clinical benefit in a well-defined patient population could be supportive of an application seeking regular approval. FDA additionally stated that if AADi chooses to seek regular approval rather than accelerated approval based on the results of a single study (PEC001), a postmarketing study to collect additional safety data in the malignant PEComa population will likely be required. The design of this study would be discussed at the preNDA meeting.

- FDA advised that a detailed definition of 'advanced malignant PEComa' that specifically addresses the minority of patients who do not have distant metastases at the time of enrollment be provided in the eligibility criteria in the protocol submitted to the original IND.

- FDA agreed with the proposal to include patients with metastatic and locally advanced and unresectable disease in the trial planned to support registration; however, FDA recommended that subgroup analyses based on disease stage be incorporated into the statistical analysis plan (SAP) as these patients may respond differently to treatment. FDA acknowledged that these analyses would be exploratory.

- During the discussion of the adequacy of the proposed statistical analysis plan, FDA stated that an estimation study with a primary endpoint of ORR that excludes 14.7% from the lower bound of the 95% confidence interval would be an acceptable design. Assuming that a 30% response rate is observed, a sample size of at least 30 patients with advanced malignant PEComa could be sufficient for results of this trial to support a marketing application.

- FDA agreed that the estimated safety database of a maximum of 30 patients with advanced malignant PEComa who will have been treated for at least six months with the intended dose of ABI-009, in conjunction with the safety database from Study CA401 (N=26), and the safety data available for the listed drugs Rapamune and Torisel could be sufficient to support a marketing application provided that no unusual toxicities are identified in patients with malignant PEComa.

On August 26, 2018, Aadi requested Fast Track Designation for ABI-009. Aadi was able to provide the same preliminary efficacy data from Study PEC-001 that is included in the BTDR. FDA granted ABI-009 Fast Track Designation on October 24, 2018.

On October 16, 2018, FDA and Aadi had a teleconference to discuss the preliminary efficacy data from Study PEC-001. FDA recommended that Aadi submit a request for BTD based on the preliminary response and duration of response data and Aadi agreed.

On October 23, 2018, Aadi submitted the BTDR for ABI-009.

ABI-009 Mechanism of Action and Clinical Development Program

ABI-009 is a lyophilized nanoparticle formulation of rapamycin (b) (4) with human serum albumin. Rapamycin inhibits the mammalian target of rapamycin (mTOR), a regulatory protein kinase that serves as a regulator of cell survival, proliferation, stress, and metabolism. Rapamycin and its analogs (rapalogs) function as allosteric inhibitors of mTORC1 and are currently used in the treatment of advanced renal cell carcinoma and other tumors. ABI-009 development in PEComa is based on the pathogenesis of PEComa involving the loss of TSC2, or more rarely TSC1, and inactivating mutations in TSC1 and 2 lead to overactivation of mTOR. Therefore, mTOR inhibition with ABI-009 may be a strategy for treating PEComa. Multiple small retrospective case series report antitumor activity with other mTOR inhibitors (e.g., everolimus, sirolimus) in patients with malignant PEComa (Wagner 2010; Dickson 2014).

The clinical development program for ABI-009 includes 11 completed or ongoing Aadi- or investigator-sponsored studies in various cancer indications, pulmonary arterial hypertension, or refractory epilepsy. Study CA401 is a completed dose-finding study in patients with advanced solid tumors conducted under IND 74610. In this study, twenty-six patients were treated with ABI-009 administered IV at doses between 45 and 150 mg/m^2 per week for three weeks, followed by one week of rest (28-day cycle). Dose-limiting toxicities included grade 3 aspartate aminotransferase elevation, grade 4 thrombocytopenia, grade 3 suicidal ideation, and grade 3 hypophosphatemia. The maximum tolerated dose was established at 100 mg/m^2. Common adverse events (AEs) were mucositis, fatigue, rash, diarrhea, nausea, thrombocytopenia, hypokalemia, anemia, and neutropenia.

The safety data from Study CA401 supported initiation of Study PEC-001 under IND 125669. Study PEC-001 is a multi-center, single-arm study of ABI-009 given at 100 mg/m^2 IV administered on days 1 and 8 of a 21-day cycle in patients with advanced malignant PEComa. The patient population includes patients with locally advanced disease for which surgery is not a recommended option and patients with metastatic disease. The primary endpoint of the trial is ORR determined by independent radiologic assessment using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Duration of response (DOR) is a key secondary endpoint. The planned sample size of 30 patients allows for the lower bound of the 95% confidence interval (CI) to exceed 14.7% assuming an observed ORR of 30%. The primary efficacy and safety analyses will be conducted when all enrolled patients have had the opportunity to be treated for at least 6 months.

The sponsor intends to submit a 505(b)(2) NDA for ABI-009 because it contains the same active ingredient as rapamycin (rapamune, NDA 021083).

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.

Aadi considers durable ORR to be a clinically meaningful endpoint supporting the BTDR. DOR is a secondary endpoint. ORR and DOR according to RECISTv1.1 were assessed for patients participating in Study PEC-001, and these results will be independently reviewed prior to the preNDA meeting. The investigator-reviewed data are provided to support the BTDR.

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*

- *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*

- *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

DOP2 agrees that demonstration of a meaningful effect size on durable ORR according to RECIST would be clinically meaningful and reasonably likely to predict clinical benefit of a drug in patients with malignant PEComa and could support an application for marketing approval in this ultrarare patient population.

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. Consider the following in your response:

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*

- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

There are no FDA-approved therapies and no known curative treatments for patients with malignant PEComa that is unresectable or metastatic. There is evidence in the literature that malignant PEComa that is resected with negative margins can be cured with surgery alone. For patients with recurrent or metatastic disease and for patients with localized tumors that are inoperable, chemotherapy and/or radiation have not been shown to be effective. In recent years, multiple small case series have been published reporting response rates with mTOR inhibitors used for inoperable disease or in the neoadjuvant setting as a bridge to surgery in patients with high risk malignant PEComa. There have been no prospective studies of mTOR inhibition in patients with PEComa. The following table summarizes the case series (or case reports) in the literature reporting antitumor activity with mTOR inhibition:

Reference	Patients	Treatment and Outcomes
Italiano, 2010	N=2	• Neoadjuvant temsirolimus for lung met following resection of primary uterine PEComa. CR followed by lobectomy. • Temsirolimus following progression on chemotx for metastatic dz; PR then PD after 22 weeks
Wagner, 2010	N=3	Sirolimus for 3 patients, one PR and two prolonged SD
Dickson, 2013	N=5	4 responses in 5 patients with abdominal PEComa treated with sirolimus/everolimus, CR=2, PR=2, PD=1; one patient with PR had surgical resection and remains in remission at 6 months post op.
Benson, 2014	N=10	5 of 7 patients with evaluable metastatic PEComa experienced PR to sirolimus or temsirolimus. No DOR data. Median OS = 2.4 yrs.
Bergamo, 2014	N=1	Neoadjuvant sirolimus for malignant PEComa of liver allowed complete surgical resection after tumor shrinkage.
Fletcher, 2016	N=1	Everolimus following resection of brain mets in patient with small intestine PEComa led to prolonged stable disease.

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

None.

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 data supporting the BTDR for ABI-009 comes from Study PEC-001. This is an ongoing multicenter, single arm study of ABI-009 100 mg/m^2 IV administered on Days 1 and 8 of a 21 day cycle in 30 patients with advanced malignant PEComa defined as patients with localized tumors that are inoperable and patients with metastatic disease. The primary endpoint is confirmed ORR, as determined by an independent review committee (IRC). An analysis was performed using data from the first 29 patients who have received at least one dose of ABI-009 and have had one post baseline response evaluation (data cutoff of September 14, 2018). The ORR was 41% (95% CI: 24, 61). The following table copied from Aadi's briefing document summarizes the investigator-assessed and confirmed ORR as of the data cutoff date.

Table 1. Objective Response by the Investigator using RECIST v1.1, Efficacy Evaluable Patients

Variable	All patients (N = 29)	Metastatic (N = 23)	Locally Advanced [1] (N = 6)
Patient with a Complete or Partial Response, n (%) [2]	12 (41)	11 (48)	1 (17)
Confirmed, n	11	10	1
Unconfirmed, n	1	1	0
95% CI (exact binomial confidence interval)	(23.5, 61.1)	(26.8, 69.4)	(0.4, 64.1)
Stable Disease, n (%) [3]	9 (31)	5 (22)	4 (67)
Progressive Disease, n (%)	5 (17)	5 (22)	0 (0)
Not Evaluable, n (%) [4]	3 (10)	2 (9)	1 (17)

[1] Locally advanced with no option for surgery
[2] All PR. For the patient with unconfirmed response, confirmation is pending
[3] One patient had a complete resection after 10 cycles of therapy and a reduction of 11.5% of the tumor burden
[4] Three patients were recently enrolled and post-baseline tumor assessment was not available as of the data cut-off of Sep-14-2018. Note however, that these patients are included in the efficacy evaluable patients (i.e., included in the denominator for response calculations)

For the 12 patients who experienced an objective response, the range of DOR from the onset of response was 0 to 19.4 months at the time of data cutoff. The median duration of response was not reached, and eight (67%) of the responding patients had ongoing responses six months or longer. Additionally, most responders (9/12, 75%) responded after the first two cycles of treatment (at first restaging evaluation). The DOR data is summarized in the table copied from the BTDR briefing document below.

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

Table 2. Listing of Duration of Response for Patients with a Response as Assessed by the Investigator

Disease Subtype	Patients with a Partial Response, Subject ID	Duration of Response (months) [1]	Confirmed Response Status	Ongoing Response and Treatment
Metastatic	(b) (6)	19.4+	Yes	Yes
Metastatic		12.5+	Yes	Yes
Metastatic		11.1+	Yes	Yes
Metastatic		9.7+	Yes	Yes
Metastatic		7.0	Yes	No
Locally Advanced, Unresectable		6.2	Yes	No
Metastatic		5.6+	Yes	Yes
Metastatic		5.6	Yes	No
Metastatic		3.9+	Yes	Yes
Metastatic		1.5	Yes	No
Metastatic		1.4+	Yes	Yes
Metastatic		0.0+	Pending	Yes

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 .*
- *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.*
- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

DOP2 considers the objective response and duration of response data from patients with advanced malignant PEComa treated with ABI-009 in Study PEC-001 to be preliminary evidence of a substantial improvement over cytotoxic chemotherapy that has not been shown to demonstrate any objective responses in this tumor type.

To further support the BTDR, Aadi conducted a benefit-risk assessment by comparing and reviewing the available safety data for ABI-009 from PEC-001 with those reported in the first-in-human Study CA401 and with the Rapamune Prescribing Information in the context of the preliminary efficacy data from PEC-001. Based on Aadi's assessment and summary data presented in the BTDR briefing document, the safety of ABI-009 appears consistent with reported events for Rapamune (oral sirolimus) and other rapalogs. The serious adverse events that are reported for rapamune include allergic reactions, edema, elevations in cholesterol and triglycerides, increased risk of infection, including viral infections, and secondary malignancies. The registration study in patients with advanced malignant PEComa is ongoing and safety data is still being collected. Of the 31 patients with advanced malignant PEComa treated in Study PEC-001 at data cut off, most AEs were low grade, and common (> 20%) treatment-related AEs included myelosuppression, mucositis, diarrhea, and rash. Serious AEs occurred in 7 patients and included pancytopenia, acute coronary syndrome, abdominal pain, diarrhea, enteritis, dehydration and acute kidney injury. Aadi states that two DSMB meetings have evaluated the safety of ABI-009 at specified times during the PEC-001 trial to date and recommended continuation of the clinical trial.

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

☒ GRANT :

Provide brief summary of rationale for granting:

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

There are no systemic therapies approved for patients with malignant PEComa. Cytotoxic chemotherapy used as an off label treatment has not been shown to have antitumor effects or improve outcomes. Radiation therapy has not been shown to be effective. There are multiple small retrospective case series of patients who have had a response to other drugs with a similar mechanism of action (mTOR inhibition), and this provided rationale for prospective evaluation of ABI-009 in PEComa. DOP2 considers the effect size on response rate of 41% together with the durability of responses (67% of responders having at least 6 months duration) in patients treated to date in Study PEC-001 to be preliminary evidence of a substantial improvement over alternative treatment options. DOP2 has also considered the relatively favorable safety profile of ABI-009 in the context of a life threatening disease with a poor prognosis.

☐ 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:

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):

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

DOP2 will continue to communicate with Aadi and provide regulatory guidance to facilitate the development program for ABI-009 for the treatment of patients with advanced malignant PEComa. A preNDA meeting has been requested and scheduled. DOP2 will advise on the planned 505(b)(2) approval pathway, options for expanded access programs, and the design of appropriate post-marketing clinical studies to further evaluate the safety and effectiveness of ABI-009 in this population.

14. List references, if any:

1. Wagner AJ, Malinowska-Kolodziej I, Morgan JA, et al, Clinical Activity of mTOR Inhibition With Sirolimus in Malignant Perivascular Epithelioid Cell Tumors: Targeting the Pathogenic Activation of mTORC1 in Tumors, 2010, JCO, 28 (5):835-840.
2. Bleeker JS, Quevedo JS, Folpe AL, "Malignant" Perivascular Epithelioid Cell Neoplasm: Risk Stratification and Treatment Strategies, 2012, Sarcoma ID: 541626.
3. Dickson MA, Schwartz GK, Antonescu CR, et al, Extrarenal perivascular epithelioid cell tumors (PEComas)

respond to mTOR inhibition: clinical and molecular correlates. 2014, Int J Cancer 132(7): 1711-1717.

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}

Revised 10/3/18/M. Raggio

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/

DENISE A CASEY
12/11/2018

SUZANNE G DEMKO
12/12/2018

PATRICIA KEEGAN
12/12/2018