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APPLICATION NUMBER:

213312Orig1s000

INTEGRATED REVIEW

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	NDA
Application Number	213312
Priority or Standard	Priority
Submit Date	5-28-2021
Received Date	5-28-2021
PDUFA Goal Date	11-26-2021
Division/Office	DO2/OOD
Review Completion Date	11-22-2021
Established Name	sirolimus protein-bound particles for injectable suspension (albumin-bound)
(Proposed) Trade Name	FYARRO
Pharmacologic Class	mTOR inhibitor
Code name	ABI-009
Applicant	Aadi Bioscience Inc.
Formulation	protein-bound particles for injectable suspension (albumin-bound)
Dosing Regimen	100 mg/m ² administered as an intravenous (IV) infusion over 30 minutes on Days 1 and 8 of each 21-day cycle
Applicant Proposed Indication	Treatment of advanced (metastatic or locally advanced) malignant perivascular epithelioid cell tumor (PEComa)
Recommendation on Regulatory Action	Approval
Recommended Indication	Treatment of adult patients with locally advanced unresectable or metastatic malignant perivascular epithelioid cell tumor (PEComa)

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OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

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OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BEV	bevacizumab
BIMO	Bioresearch Monitoring Program
BLA	Biologics License Application
BMI	body mass index
BOR	best overall response
BUN	blood urea nitrogen
BSA	body surface area
C _{avg}	average concentration
C _{max}	maximum concentration
CBC	complete blood count
CCNU	lomustine
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
ClinRO	clinician reported outcome
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COA	clinical outcome assessment
CR	complete response

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CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DCR	disease control rate
DDI	drug-drug interaction
DEPI	Division of Epidemiology
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DMEPA	Division of Medication Error Prevention and Analysis
DNA	deoxyribonucleic acid
DOR	duration of response
DRISK	Division of Risk Management
E-R	exposure-response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	end of treatment
ER	estrogen receptor
FAS	Full Analysis Set
FDA	Food and Drug Administration
FD&C	Food Drug and Cosmetic
FISH	fluorescence in situ hybridization
FOB	functional observation battery
GBM	glioblastoma multiforme
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
HERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus

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HNSTD	highest non-severely toxic dose
hpf	high powered field
HSA	human serum albumin
ICH	International Council for Harmonisation
IND	Investigational New Drug
ISS	integrated summary of safety
IT	intrathecal
IV	intravenous
LAM	lymphangioleiomyomatosis
LDH	lactate dehydrogenase
LLC	limited liability corporation
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
mFOLFOX6	modified regimen of 5 fluorouracil, leucovorin, and oxaliplatin
min	minimum
MRI	magnetic resonance imaging
MRZ	marizomib
MTD	maximum tolerated dose
mTOR	mechanistic target of rapamycin kinase
n	number of patients in the category
N	number of patients
<i>nab</i>	nanoparticle albumin-bound
NCI	National Cancer Institute
NDA	New Drug Application
NME	new molecular entity
NOAEL	no-observed-adverse-effect level
ObsRO	observer reported outcome
OPDP	Office of Prescription Drug Promotion
OPQ	Office of Pharmaceutical Quality

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ORR	overall response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
P-gp	P-glycoprotein
PAH	pulmonary arterial hypertension
PD	progressive disease
PEComa	perivascular epithelioid-cell tumors
PerfO	performance outcome
PFS	progression-free survival
PI	principal investigator
PK	pharmacokinetics
PO	<i>per os</i> (oral)
PP	Per Protocol
PR	partial response <i>or</i> progesterone receptor
PRO	patient reported outcome
PT	Preferred Term
qw2/3	weekly for 2 weeks, followed by a week of rest
qw3/4	weekly for 3 weeks, followed by a week of rest
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	risk evaluation and mitigation strategy
RLD	Reference Listed Drug
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	stable disease <i>or</i> standard deviation
SLD	sum of lengths of tumor diameters

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SMC	smooth muscle cell
SOC	System Organ Class
STS	soft-tissue sarcoma
$t_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
TEAESI	treatment-emergent adverse events of special interest
TERAE	treatment-emergent related adverse event
TERSAE	treatment-emergent related serious adverse event
TESAE	treatment-emergent serious adverse event
TFL	tables, figures, and listings
TMZ	temozolomide
TTR	time to response
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
V _c	central volume of distribution
VEGF	vascular endothelial growth factor
V _p	peripheral volume of distribution
WHO	World Health Organization

1 Executive Summary

1.1. Product Introduction

Sirolimus protein-bound particles for injectable suspension (also called ABI-009, nab-sirolimus, or Fyarro, hereafter referred to as ABI-009) is sirolimus formulated as albumin-bound nanoparticles. ABI-009 is an inhibitor of mechanistic target of rapamycin kinase (mTOR), which controls key cellular process such as cell survival, growth, and proliferation. The mTOR pathway is frequently dysregulated in malignant perivascular epithelioid cell tumors (PEComas). At the time of application submission, ABI-009 was not approved for any indication.

The current New Drug Application (NDA) for ABI-009 was submitted pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.

The Applicant proposed the following indication for ABI-009:

Treatment of advanced (metastatic or locally advanced) malignant perivascular epithelioid cell tumor (PEComa)

The recommended dosage for the proposed indication is 100 mg/m² administered as an intravenous (IV) infusion over 30 minutes on Days 1 and 8 of each 21-day cycle until disease progression or unacceptable toxicity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The FDA review teams for all disciplines have recommended that regular approval be granted for ABI-009 for the following indication:

For the treatment of adult patients with locally advanced unresectable or metastatic malignant perivascular epithelioid cell tumor (PEComa)."

Malignant PEComa is considered an “ultra-rare” soft tissue sarcoma, with an incidence ≤ 1 per 1,000,000 (Stacchiotti, 2021) with no FDA-approved available therapies. Malignant PEComa is a serious and life-threatening condition. Patients with this disease have a poor prognosis; although not well characterized, median survival is reported to range between 16-30 months (Bleeker, 2012; Sanfilipo, 2019). Response rates reported for chemotherapy agents and vascular endothelial growth factor (VEGF) receptor inhibitors used off-label are low (3-22%) (Sanfilippo, 2019).

The recommendation for approval is supported by results from Study PEC-001, a multi-center single-arm trial that included 34 patients with malignant PEComa with either locally advanced unresectable or metastatic disease. Three patients were excluded because the diagnosis of PEComa was not confirmed by central pathology review, resulting in a primary efficacy population of 31 patients. The major efficacy outcomes were ORR and duration of response (DOR) as determined by blinded independent central review (BICR) according to the response Evaluation Criteria in Solid Tumors (RECIST) v 1.1. The confirmed ORR in the primary efficacy population is 39% (95% confidence interval [CI]: 22, 58) and although median DOR was not reached, 58% of responders had a response lasting greater than 24 months. Most patients had received prior treatment (including surgery, radiation, or systemic therapy) for malignant PEComa; ninety-four percent of patients in the primary efficacy population had prior surgery, 19% had prior radiation therapy, and 13% had prior systemic therapy. The effects on ORR and DOR observed in PEC-001 are clinically meaningful. The information provided by the Applicant provides substantial evidence of the effectiveness of ABI-009 for the treatment of patients with locally advanced unresectable or metastatic malignant PEComa. The submitted evidence meets the statutory evidentiary standard for approval, demonstrating a robust and clinically meaningful effect on overall response rate (ORR) that is durable. The FDA also concluded that the overall benefit:risk assessment for ABI-0009 is favorable for the indicated patient population. The results represent a direct clinical benefit for patients with this rare, life-threatening cancer for which there were no FDA-approved drugs prior to this indication being granted.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

-Malignant PEComa is considered an “ultra-rare” soft tissue sarcoma, with an incidence ≤ 1 per 1,000,000 (Stacchiotti, 2021). Survival outcomes for malignant PEComa are poorly characterized with median survival reported between 16-30 months (Bleeker, 2012; Sanfilipo, 2019). There are currently no FDA-approved available therapies for malignant PEComa. Prior experience with systemic therapies has demonstrated limited responses with anthracycline- and gemcitabine-based chemotherapies, as well as vascular endothelial growth factor (VEGF) receptor inhibitors (ORR 10%; 95% CI: 3-22%)(Sanfilipo, 2019).

Genetic alterations in the mechanistic target of rapamycin kinase (mTOR) pathway have been identified in the majority of malignant PEComas (Akumalla, 2021), including mutations in the *TSC1* and *TSC2* genes. ABI-009 is an albumin-bound injectable formulation of sirolimus. Sirolimus is known to bind to FK Binding Protein-12 (FKBP-12) to generate a complex that binds to and inhibits the activation of mTOR (Brown, 1994). Study PEC-001 was a multi-center, single-arm trial of ABI-009 in 34 patients with malignant PEComa with either locally advanced unresectable or metastatic disease. This was the first prospective clinical trial for patients with malignant PEComa. Three patients were excluded after central pathology review, resulting in a primary efficacy population of 31 patients. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR) as determined by blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. The primary efficacy population demonstrated a confirmed ORR of 39% (95% CI: 22, 58). Among responders, 58% had a response lasting greater than 24 months.

ABI-009 has an acceptable safety profile when assessed in the context of a life-threatening disease with no available therapies. The primary safety dataset included 34 patients in Study PEC-001 that received ABI-009 at the recommended dose. The most common ($\geq 30\%$) adverse reactions were stomatitis, fatigue, rash, infection, nausea, edema, diarrhea, musculoskeletal pain, decreased weight, decreased appetite and cough, vomiting and dysgeusia. One patient experienced Grade 1 hypersensitivity. The most common ($\geq 6\%$) Grade 3 to 4 laboratory abnormalities observed with Fyarro were decreased lymphocytes, increased glucose, decreased potassium, decreased phosphate, decreased hemoglobin, and increased lipase. Serious adverse reactions occurred in 14 (41%) patients who received Fyarro. Serious adverse reactions in occurring $> 5\%$ of patients included infection (4 patients) and abdominal pain, dehydration, and upper gastrointestinal hemorrhage (each in 2 patients). Permanent discontinuation of ABI-009 due to an adverse reaction occurred in 3 (9%) patients. Adverse reactions which resulted in

permanent discontinuation of Fyarro included pneumonitis, anemia, and noninfective cystitis. Fatal adverse reactions occurred in 2 (6%) patients who received ABI-009, including respiratory failure in 1 (2.9%) patient and upper gastrointestinal hemorrhage in 1 (2.9%) patient. Review of the safety data from an additional 42 patients with cancer who received ABI-009 in clinical trials did not identify additional safety signals. Given the size of the primary safety database, the risks of hypersensitivity and infusion-related reactions remain incompletely characterized. The safety of ABI-009 in patients with moderate and severe hepatic impairment was not assessed in PEC-001. Analysis of the drug product at release and in storage conditions revealed the presence of albumin dimers and oligomers, however the immunogenicity of these protein aggregates remains unknown.

Postmarketing requirements will include the submission of safety data from additional clinical trial(s), an evaluation of ABI-009 in patients with hepatic impairment, and an evaluation of the potential for QT prolongation. Finally, a post-marketing commitment will evaluate the levels of albumin dimers and oligomers in the product in comparison with other FDA-approved albumin-bound products.

The review team concluded that this application provided substantial evidence of the effectiveness of ABI-009 through demonstration of a clinically meaningful ORR according to BICR accompanied by a compelling DOR in patients with unresectable or metastatic malignant PEComa. In the setting of a serious and life-threatening illness without any approved treatment options, these results represent a direct clinical benefit for patients with this extremely rare cancer. The safety profile is acceptable in the context of this serious and life-threatening condition; the toxicities observed in PEC-001 are commonly managed by oncologists. Therefore, the risk: benefit assessment for ABI-009 is favorable for the treatment of adult patients with locally advanced unresectable or metastatic, malignant perivascular epithelioid cell tumor.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Malignant PEComa is a rare soft tissue sarcoma with an incidence of 1 per 1,000,000 (Stacchiotti, 2021). • Median survival for malignant PEComa has been reported between 16 and 30 months in retrospective studies (Bleeker, 2012; Sanfilipo, 2019).	Locally advanced unresectable or metastatic, malignant PEComa is a life-threatening disease with poor survival.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	- No FDA-approved therapies are currently available for malignant PEComa. - To date, only limited retrospective data has been reported on systemic therapies for malignant PEComa. These include anthracycline- and gemcitabine-based chemotherapies, as well as vascular endothelial growth factor (VEGF) receptor inhibitors with limited (ORR 10%, 95% CI: 3-22%).	There is an unmet medical need for patients with locally advanced unresectable or metastatic, malignant PEComa. This conclusion is based on limited clinical experience with systemic therapy for malignant PEComa documenting poor response rates and the limited life expectancy of patients with this disease.
Benefit	- The primary efficacy data supporting this NDA are from patients with locally advanced unresectable or metastatic malignant PEComa enrolled in Study PEC-001, a multi-center, single-arm trial. - Among 31 patients in the primary efficacy population, the confirmed ORR by BICR was 39% (95% CI 22, 58). All responses were partial as of the final data cut-off, however 2 responses converted to complete in follow-up analyses. The median DOR was not reached. Among responders, 58% experienced a response lasting greater than 24 months.	The submitted evidence meets the statutory evidentiary standard for regular approval. The observed ORR and durable responses are clinically meaningful in the context of the poor prognosis of the disease and limited available approved therapies. Randomized-controlled trials in this setting would be infeasible due to the rarity of the disease, lack of an established standard of care to serve as a control arm, and concerns regarding equipoise given the magnitude of response observed in PEC-001.
Risk and Risk Management	The primary safety database for this NDA includes 34 patients from Study PEC-001. The most common ($\geq 30\%$) adverse reactions were stomatitis, fatigue, rash, infection, nausea, edema, diarrhea, musculoskeletal pain, decreased weight, decreased appetite, cough, vomiting, and dysgeusia. Data from 42 patients with other cancers	While ABI-009 can cause severe toxicities, these toxicities are generally manageable and safety concerns are adequately addressed by information in the Warnings and Precautions section and the dose modification

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	who received ABI-009 in clinical trials were used to support the safety review. No additional safety signals were identified in this supplementary population. • Serious adverse reactions occurred in 14 (41%) patients, including infection in 4 (12%) patients and 2 (6%) patients each with abdominal pain, dehydration, and upper gastrointestinal hemorrhage. • Permanent discontinuation of Fyarro due to an adverse reaction occurred in 3 (9%) patients, including pneumonitis, anemia, and noninfective cystitis. • Fatal adverse reactions occurred in 2 (6%) patients, including respiratory failure in 1 (2.9%) patient and upper gastrointestinal hemorrhage in 1 (2.9%) patient. • Stomatitis, myelosuppression, infections, hypokalemia, hyperglycemia, interstitial lung disease/non-infectious pneumonitis, hypersensitivity reactions, hemorrhage, embryofetal toxicity, and male infertility are included as warnings in the product label. Immunizations and risks associated with live vaccines, and risk of transmission of infectious agents with human albumin, are also addressed in Section 5 of the product label.	recommendations in product labeling. The observed safety profile of ABI-009 is acceptable when assessed in the context of the treatment of a life-threatening disease. The review team did not believe a Risk Evaluation and Mitigation Strategy (REMS) was warranted to ensure the safe use of the product given the information included in the product label Postmarketing requirements will be issued for data from clinical trials to further characterize known safety risks, the safety in patients with hepatic impairment, and the risk for QT prolongation.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
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☐	Clinical outcome assessment (COA) data, such as	[e.g., Section 6.1 Study endpoints]
☐	Patient reported outcome (PRO)	
☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Section 2.1 Analysis of Condition]
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify)	
☐	Patient experience data that was not submitted in the application, but was considered in this review.	

No patient experience data was submitted or reviewed in support of this Application.

X

Diana Bradford, M.D.
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

The serine-threonine kinase mammalian target of rapamycin (mTOR) plays a key role in the regulation of cell growth and metabolism. Consistent with its role in cell proliferation, abnormal activation of the mTOR pathway occurs in proliferative disease conditions including various human cancers ([Gonzalez-Angulo 2013](#)), such as perivascular epithelioid-cell tumors (PEComas) ([Martignoni 2010](#)), colorectal cancer ([Wu 2015](#)), glioblastoma ([Chakravarti 2004](#)), and thus the mTOR pathway is considered to be an attractive target for anti-cancer therapy ([Meric Bernstam 2009](#)).

Malignant perivascular epithelioid-cell tumors are very rare aggressive diseases with no FDA-approved treatment options. They are defined by the World Health Organization (WHO) as 'mesenchymal tumors composed of distinctive cells that show a focal association with blood vessels and usually express both melanocytic and smooth muscle markers', and are a rare subset of soft-tissue sarcomas with an undefined cell of origin ([Fletcher 2013](#)). Malignant PEComas may arise in almost any body site (typically the uterus, retroperitoneum, lung, kidney, liver, genitourinary, and gastrointestinal tract) and can have an aggressive clinical course including distant metastases and ultimate death ([Martignoni 2008](#)).

Malignant PEComas have been shown to frequently harbor mutations in the *TSC1* and/or *TSC2* genes that result in activation of mTORC1 pathway. Hence, mTORC1 signaling presents a promising therapeutic target for malignant PEComas ([Wagner 2010](#)). Malignant PEComas represent an unmet medical need, as cytotoxic chemotherapies typically used for sarcomas show minimal benefit and there are currently no drugs approved for this disease. Aadi Biosciences has developed a novel mTOR inhibitor, ABI-009, measuring its effects in a registrational clinical trial (Study PEC-001), the first prospective study in advanced malignant PEComa.

The FDA's Assessment:

The FDA generally agrees with Aadi's position. Malignant PEComas are considered to be "ultra-rare" soft tissue sarcomas with an incidence ≤ 1 per 1,000,000 (Stacchiotti, 2021). The majority of malignant PEComas harbor genetic alterations in the mechanistic target of rapamycin kinase (mTOR) pathway including alterations in *TSC2* (32.3%), *TSC1* (9.6%), *TFE3* (16.1%), and *FLCN* (6.4%) (Akumalla, 2021).

2.2. Analysis of Current Treatment Options

The Applicant's Position:

Currently, no effective medical treatment has been approved for patients with malignant PEComa. Therefore, treatment of PEComa represents a clear unmet medical need and requires the development of effective therapeutic interventions.

The primary treatment option for patients with localized malignant PEComa is surgery. The majority (~70%) of patients with localized primary malignant PEComas develop metastatic disease over a median follow-up of 1 year (Bleeker 2012, Tirumani 2014), and nearly one-fifth of the patients have metastatic disease at presentation (Tirumani 2014). Lung, liver, peritoneum, and bones were the most common sites of metastases in an observational study with 36 patients (Tirumani 2014). There is no curative therapy once the disease has spread and it is usually fatal with a median survival of 16 months (Bleeker 2012).

While there have been no prospective clinical trials in patients with advanced or metastatic PEComa, in a retrospective analysis assembled from isolated case reports of 18 patients with unresectable or metastatic malignant PEComas, the median overall survival (OS) was 16 months (range: 4 to 30 months) (Bleeker 2012). Chemotherapy and radiotherapy have not been shown to provide significant clinical benefit (Bleeker 2012). Neoadjuvant treatment has been utilized in a small number of cases usually reporting either progression or minimal evidence of efficacy in the resected tumor. The role of adjuvant therapy is also unclear (Bleeker 2012). In the metastatic setting, systemic chemotherapy has shown little efficacy, as there were no objective responses reported with the use of cytotoxic drugs, including doxorubicin, ifosfamide, paclitaxel, carboplatin, and epirubicin (Bleeker 2012, Scheppach 2013).

In metastatic soft tissue sarcoma in general, cytotoxic therapy remains a standard treatment in both chemotherapy-naïve and previously treated patients, and single-agent doxorubicin is still an appropriate first-line chemotherapy option. As a single agent it resulted in an overall response rate (ORR) of 5–18% and median OS of 7.0–12.0 months independent of the schedule of administration (Borden 1987, Bramwell 2000, Judson 2001). Several randomized trials compared doxorubicin-based combinations including high dose ifosfamide, imidazole carboxamide and/or gemcitabine versus doxorubicin single-agent. Response rates with combination were better than with single-agent doxorubicin (18–25% compared to 5–18%) (Omura 1983, Borden 1987, Lorigan 2007, Judson 2014). There were conflicting results in terms of PFS (2 to 8 months), only some trials reporting a benefit with the combination compared to doxorubicin alone, especially when high doses of both doxorubicin and ifosfamide were used (Judson 2014). However, overall survival was not significantly improved but severity of adverse events (AEs) was significantly increased with the combination therapies (Judson 2014). Targeted therapies, such as ridaforolimus, imatinib, and pazopanib did not provide higher response rates in general soft-tissue sarcomas (ORR 1.9%, 2.2%, and 6.3%, respectively) (Chugh 2009, Sleijfer 2009, Chawla 2012). Thus, despite its modest activity, doxorubicin has

remained the drug used either in monotherapy or combination in adult soft tissue sarcomas for several years.

The mTOR pathway, which is inhibited by *TSC1/TSC2* complex, is frequently deregulated in PEComas, making it a promising target for treatment. The activity of oral mTOR inhibitors both in lymphangioleiomyomatosis (LAM) and in malignant PEComas have been reported (Bissler 2008, Wagner 2010, Dickson 2013). A more recent retrospective chart review of 39 patients with PEComa treated between 2000 and 2018 at 5 European centers reports an ORR of 41% with mTOR inhibitors (oral sirolimus, everolimus, temsirolimus), with a median progression-free survival (PFS) of 9 months, although the response assessment frequency is unknown and likely highly variable across centers (Sanfilippo 2019). The response rate produced by the mTOR inhibitors were in stark contrast to the relatively low responses (8%) produced by vascular endothelial growth factor (VEGF) inhibitors (pazopanib, sorafenib, sunitinib), anthracycline-based chemotherapy (13%), and gemcitabine-based chemotherapy (20%). In particular, the majority (80%) of the mTOR-related responses occurred in extra-uterine primary tumors, along with a nonsignificant trend toward a worse PFS for patients with uterine versus extra-uterine, indicating efficacy of oral mTORs may be limited to a subset of patients (Sanfilippo 2019). While the efficacy results are supportive of mTOR use in patients with advanced PEComa patients, results of prospectively designed clinical studies cannot be appropriately compared with retrospective analyses or cases studies given inherent differences in the rigor of data collection, such as selection and observation bias, less rigorous analytic requirements (eg, imaging frequency), and incomplete information (eg, lack of safety data to make clinical benefit vs risk comparison), and prospectively designed clinical studies are warranted.

Although other mTOR inhibitors have been used off-label for treatment of advanced malignant PEComa, the ABI-009 AMPECT study (Study PEC-001) is the first prospective study in this disease and provides evidence that nanoparticle albumin-bound (*nab*)-sirolimus offers an important benefit in a rare and aggressive sarcoma for which there are no approved therapies.

The FDA's Assessment:

The FDA agrees with the Applicant's description of available therapies for patients with locally advanced unresectable or metastatic malignant PEComa. Study PEC-001 is the first prospective clinical trial for patients with malignant PEComa. Limited responses have been observed in retrospective reviews of patients with malignant PEComa who received anthracycline-based chemotherapy (ORR 13%, 95% CI 3-33.6%), gemcitabine-based chemotherapy (ORR 20%, 95% CI 4-48.1%), and VEGF receptor inhibitors (ORR 8.3%, 95% CI 0.2-38.5%)(Sanfilippo, 2019).

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

ABI-009 (sirolimus albumin-bound nanoparticles for injectable suspension), is an investigational drug product, with completed and ongoing clinical trials in the United States (US). ABI-009 is not currently registered or approved in the US or in any other country.

The FDA's Assessment:

ABI-009 was granted Orphan Drug designation on December 21, 2017. ABI-009 received Fast Track Designation on October 24, 2018 for the treatment of patients with advanced (metastatic or locally advanced) malignant PEComa to demonstrate clinically important effects on objective response rate (ORR) and duration of response (DOR). The FDA granted Breakthrough Therapy Designation for the treatment of patients with advanced (metastatic or locally advanced) malignant PEComa on December 12, 2018.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

The initial Investigational New Drug (IND) application for ABI-009 was submitted by the original sponsor, Abraxis BioScience on 22 December 2006 to support a Phase 1 dose escalation, safety, and pharmacokinetics (PK) study in patients with solid tumors (Protocol CA401 A Phase 1 Trial of ABI-009 (*nab*-rapamycin) Administered Weekly in Patients with Advanced Non-hematologic Malignancies), NCT00635284. Abraxis held a pre-IND meeting via teleconference with the Agency on 31 August 2006 to discuss the nonclinical and clinical development plan for ABI-009. During this meeting, it was agreed that the development program for ABI-009 should be designed to suit the requirements to file a New Drug Application (NDA) pursuant to Section 505(b)(2) of the Food Drug and Cosmetic Act (FD&C) [a '505(b)(2)' NDA]. The nonclinical program therefore focused on studies to compare ABI-009 to the approved formulation of sirolimus (Rapamune® Tablets and Oral Solution; NDA 21083 and NDA 21110) and to confirm that the different formulation, dose, and route of administration has not negatively impacted the safety, pharmacokinetics, and efficacy of sirolimus in nonclinical models.

In October 2010, Abraxis was acquired by Celgene Corporation, and Abraxis became a wholly owned subsidiary of Celgene. Clinical Study CA401 was completed in 2011, but development of ABI-009 was put on hold by Celgene. In 2014, Aadi Bioscience (formerly Aadi Limited Liability Corporation [LLC]) was granted an exclusive license by Celgene to continue the development of ABI-009. The IND was transferred to Aadi, after which Aadi submitted new INDs to support the development of the product in (b) (4)

(b) (4)
 (b) (4) PEComa (NCT02494570). Recently, Celgene was acquired by Bristol Meyers Squibb in October 2019.

Key interactions with the Agency since the submission of the original IND for PEComa are summarized below in [Table 1](#).

Table 1: Summary of Presubmission and Submission Regulatory Activities

Date	Type	Description and Key Agreements
11 June 2015	Pre-IND Meeting	2 clinical studies sufficient for 505(b)(2) NDA filing: a single arm registrational Phase 2 Study PEC-001 in advanced malignant PEComa with at least 30 evaluable patients, and Phase 1 dose-finding Study CA401 in solid tumors - Study PEC-001 registrational study: - ORR accepted as primary endpoint with duration of response (DOR) as a key secondary endpoint - Sample size of at least 30 patients (Assuming an observed ORR by 6 months of 30% and a sample size of 30, the lower bound of the 95% confidence interval [CI] for the estimated ORR by 6 months would exclude values less than 14.7%.) - Post-marketing safety study would likely be required, to be discussed at pre-NDA meeting - A nonclinical pharmacokinetic (PK) study with limited toxicology assessments recommended to bridge to the Reference Listed Drug (RLD) Rapamune - An exploratory exposure-response (E-R) analyses for efficacy and safety was recommended
21 December 2017	Orphan Designation	Orphan Drug designation granted for treatment of perivascular epithelioid cell tumors (PEComa).
16 October 2018	Breakthrough Therapy Designation	During teleconference to review Fast Track Designation Request, FDA recommended Aadi pursue Breakthrough designation.
24 October 2018	Fast Track Designation	Fast Track Designation granted for treatment of patients with advanced (metastatic or locally advanced) malignant PEComa.
10 December 2018	Type C Meeting – Clinical/Nonclinical	A pre-NDA meeting request submitted 01 October 2018 was addressed with a recommendation by the FDA to split the Clinical/Nonclinical topics into a separate meeting from the chemistry, manufacturing, and controls (CMC) meeting. Confirmed PK Bridging Study design (1291.01) and overall nonclinical program appeared adequate to support 505(b)(2) NDA.

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Date	Type	Description and Key Agreements
		- Confirmed exposure-response study design (Study ADI0101) using data from Study PEC-001 and Study CA401. Population PK analysis also recommended for intrinsic/extrinsic factors. - Integrated Summary of Safety requested, limited to Aadi-sponsored studies with intravenous (IV) infusion route of administration. Pooled safety data from oncology studies, side-by-side with non-oncology studies to be presented in Module 5 and described in narrative format in Module 2 Clinical Summary of Safety. - FDA recommended submission of the NDA after all patients have had the opportunity to be followed for 6 months. - FDA requested that Aadi address the impact of hepatic impairment on the PK and safety of <i>nab</i>-rapamycin to provide adequate dosing recommendations in this population.
12 December 2018	Type B Meeting – CMC	CMC meeting split from Clinical/Nonclinical topics per FDA recommendation. Key points from this meeting included: - At the time of submission, the NDA may be filed with 1 batch of ABI-009 with 36 months of stability data and 2 batches with 6 months of data. - Provide data confirming the number of sirolimus molecules binding albumin. - Information supporting the CMC and specifically the safety evaluation for adventitious agents in human albumin may be addressed by reference to the suppliers approved BLA. - Provide studies supporting the adequacy of analytical methods to measure intended attributes such as (b) (4) (b) (4) drug substance and human albumin - Include additional test to enhance the specification - The proposed strategy for bridging ABI-009 and the RLD is acceptable. - Evaluate if the manufacturing process leads to new impurities or degradants from human albumin.
12 December 2018	Breakthrough Therapy Designation	Breakthrough Therapy Designation granted for treatment of patients with advanced (metastatic or locally advanced) malignant PEComa.
09 April 2019	Advice Letter – ISS SAP	- FDA agreed with proposed analyses and planned presentation for the integrated summary of safety (ISS) as described in the statistical analysis plan (SAP) were acceptable - Confirmed that efficacy analyses from Study PEC-001 and Study CA401 could be summarized in the Module 2 Clinical Summary of Efficacy – no Module 5 Integrated Summary of Efficacy was required

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FYARRO (sirolimus protein-bound particles for injectable suspension) (albumin-bound)

Date	Type	Description and Key Agreements
25 February 2020	Type B Meeting – CMC	- The nature of binding of sirolimus and human albumin has been adequately addressed - A test for human serum albumin (HSA) oligomeric status should be included in the release and stability specification - Conduct a filtration recovery study on in-use stability samples - Aadi to include all supporting data to justifying its position that an in-vitro release test is not necessary for ABI-009 - Executed batch records for all primary stability batches and recently manufactured drug product batches - The NDA content plan appears to be adequate - Provide solubility characterization of clinical batches and future production batches
02 March 2020	Proprietary Name Conditional Acceptance	The FDA conditionally accepted the proprietary name “Fyarro”.
06 May 2020	Pre-NDA Meeting Request Preliminary Comments	In response to Aadi’s Pre-NDA Meeting request dated 28 February 2020, the FDA provided the following feedback: Clinical - Confirmed that topline data from PEC-001 with a cutoff date of 22 May 2019 are sufficient to support a NDA. - Confirmed planned statistical analyses and TFL presentations for registrational Study PEC-001 and supporting safety studies are acceptable - Confirmed that the proposed technical data packages supporting the PEC-001 clinical study, integrated summary studies, and Bioresearch Monitoring Program (BIMO) are acceptable - Pediatric Study Plan not required if the first component of our rolling submission is filed before 18 August 2020. Chemistry, Manufacturing and Controls - Clarified batches to provide in Methods Validation Package - Reiterated previous advice to provide specific characterization to support manufacturing process changes Nonclinical - Confirmed nonclinical development program appears complete

The FDA’s Assessment:

The FDA agrees with the Applicant’s position.

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

4.1. Office of Scientific Investigations (OSI)

Three clinical investigators were selected for on-site clinical inspection: Drs. Wagner (Site 001), Ravi (Site 004), and Ganjoo (Site 007). The central radiology imaging center was also selected for inspection. The inspections revealed no significant findings; there was no evidence of underreporting of serious adverse events or significant protocol deviations. Based on the results of these inspections, Study PEC-001 appears to have been conducted adequately and the data generated by the inspected entities appear to be reliable.

Details regarding inspections can be found in the dedicated review by the Office of Scientific Investigations.

4.2. Product Quality

The product quality review team completed an Integrated Quality Assessment; the team determined that the Applicant provided sufficient information to assure the identity, strength, purity, quality, and bioavailability of the proposed drug product and that product labeling includes adequate quality information to ensure safe use. All associated manufacturing, testing, and packaging facilities were deemed acceptable. Please see the Integrated Quality Assessment for full details.

4.3. Clinical Microbiology

There were no issues identified in the microbiology review. See the Integrated Quality Assessment for full details.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The FDA's Assessment:

The Applicant [Aadi Bioscience, Inc. (Aadi)] submitted NDA 213312 under the 505(b)(2) pathway for ABI-009 for the treatment of patients with advanced (metastatic or locally advanced) malignant Perivascular Epithelioid Cell carcinoma (PEComa). ABI-009 (nab-sirolimus) is sirolimus formulated as albumin-bound nanoparticles for injectable suspension with an established pharmacological class of mTOR inhibitor. Sirolimus, a macrocyclic lactone produced by *Streptomyces hygroscopicus*, is an allosteric inhibitor of mechanistic target of rapamycin kinase (mTOR, previously known as mammalian target of rapamycin), a protein kinase that controls cell growth and proliferation and is downstream of PI3K-AKT in the signal transduction pathway controlling many pathophysiological phenomena. mTOR exists in 2 distinct complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). Sirolimus binds to immunophilin, the 12-kDa FK506-binding protein 12 (FKBP12), and the complex directly inhibits mTORC1 (Saxton, 2017). Inhibition of mTOR by sirolimus suppresses cytokine-driven T-cell proliferation, inhibiting the progression from the G1 to the S phase of the cell cycle (Smolewski, 2006). PEComa is often linked to overactivation of the mTOR pathway (Dickson, 2013). ABI-009 contains the same active pharmaceutical ingredient (API; i.e., sirolimus) as the reference listed drug (RLD) Rapamune, which is approved as tablets and as an oral solution for: 1) the prophylaxis of organ rejection in patients ≥ 13 years old receiving renal transplants, and 2) the treatment of lymphangioleiomyomatosis.

Although the Applicant conducted some nonclinical studies with ABI-009, since ABI-009 was submitted under the 505(b)(2) pathway, the Applicant is relying on FDA's findings of safety for the listed drug (Rapamune) for much of the nonclinical data needed to support approval of ABI-009 (Fyarro) in the current indication, including chronic toxicology, genotoxicity, carcinogenicity, and reproductive and development toxicity studies. These nonclinical studies were conducted with an oral formulation of sirolimus. It is appropriate to rely on these data because sirolimus is the active ingredient in both Fyarro and Rapamune. Thus, based on the Rapamune label, the Fyarro label contains warnings for embryo-fetal toxicity and male infertility; recommends that females of reproductive potential and males with female partners of reproductive potential use effective contraception during treatment with Fyarro and for 12 weeks after the last dose; and advises patients not to breastfeed during treatment with Fyarro and for 2 weeks after the last dose. Due to the different routes of administration (oral vs. IV) and a lack of relevant exposure data, the nonclinical team did not include cross-species dose or exposure comparisons in the Fyarro label.

The Applicant did not conduct in vitro pharmacology studies to support the mechanism of action of ABI-009. Rather, since ABI-009 and Rapamune contain the same active ingredient (sirolimus), the Applicant is relying on the mechanism of action of the API sirolimus demonstrated in NDA 21083 (Rapamune Oral Solution) and NDA 21110 (Rapamune Tablets). Given that there are no available animal models of PEComa, and mTOR overexpression is seen in PEComa, the Applicant evaluated the in vivo anti-tumor activity of IV ABI-009 in numerous xenograft models exhibiting activation of the mTOR pathway. Across multiple studies, IV administration of 40 mg/kg ABI-009 three times a week (120 mg/kg/week; 360 mg/m²/week) for 4 weeks induced in vivo anti-tumor activity in mice bearing human xenograft tumors with mTOR pathway activation. In mice bearing phosphatase and tensin homolog (PTEN)-null human UMUC3 bladder cancer xenografts, IV administration of 15 mg/kg/week ABI-009 resulted in higher sirolimus concentrations in the plasma and tumor compared to administration of oral formulations of sirolimus or everolimus at the same weekly total dose, which correlated with greater suppression of downstream mTOR activity and tumor growth inhibition (TGI) with IV ABI-009.

To support the scientific bridge between IV administration of ABI-009 and oral administration of the RLD (Rapamune), the Applicant conducted a GLP-compliant comparative pharmacokinetic (PK) bridging study between ABI-009 and the oral formulation of sirolimus (Rapamune), in which male and female Sprague-Dawley rats were treated with IV ABI-009 or oral Rapamune at single doses of 0.5 and 17 mg/kg. Following IV administration of ABI-009, all animals demonstrated systemic exposure to sirolimus and its major metabolite, secorapamycin, and exposures increased with increasing dose. Mean sirolimus and secorapamycin exposures were <2-fold higher in males compared to females. Following administration of an oral solution of Rapamune, there was inconsistent exposure to sirolimus or secorapamycin at the 0.5 or 17 mg/kg dose levels. Thus, sirolimus AUC for most animals and terminal elimination parameters for all animals could not be calculated following administration of the Rapamune oral solution. In general, exposure to sirolimus and secorapamycin from ABI-009 IV was higher than from oral Rapamune at the same sirolimus dose level. These results correlate with pharmacology data demonstrating that IV administration of ABI-009 resulted in greater tumor growth inhibition compared to administration of an oral formulation of sirolimus at the same total weekly dose.

In safety pharmacology studies, ABI-009 inhibited in vitro hERG potassium currents with an IC₅₀ value of 61 μM, suggesting a low potential for prolongation of QTc and correlating with a lack of clinically relevant QT interval prolongation in patients who received ABI-009 at the recommended dose of 100 mg/m². Further, single IV doses of ABI-009 up to 90 mg/kg had no effect on open field behavior of rats, indicating a lack of central nervous system toxicity in this study.

The Applicant conducted a GLP-compliant 28-day toxicology study in Sprague-Dawley rats

evaluating once daily IV administration of up to 120 mg/kg ABI-009 on Days 1, 5, and 9 followed by a 28-day recovery period. There were 2/20 mortalities at the 120 mg/kg (720 mg/m²) dose level, which is higher than the recommended clinical dose of 100 mg/m² IV on Days 1 and 8 of a 21-day cycle. Target organs of ABI-009 toxicity included the heart, liver, lung, thymus, and reproductive organs. Overall, the 28-day toxicology study did not identify any new toxicities associated with ABI-009 compared to an oral formulation of sirolimus (Rapamune).

There are no outstanding issues from a pharmacology/toxicology perspective for this 505(b)(2) application that would prevent the approval of Fyarro for the treatment of adult patients with locally advanced unresectable or metastatic malignant PEComa.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

Aadi is seeking approval of an NDA for ABI-009 for the treatment of patients with advanced (metastatic or locally advanced) malignant PEComa under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act, using Rapamune Tablets (NDA 021110) and Rapamune Oral Solution (NDA 021083) as the Reference Listed Drug (RLD). This 505(b)(2) NDA contains full reports of investigations of safety, pharmacokinetics, and effectiveness, with some of the information required for approval coming from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference.

Other approved mTOR inhibitors similar to sirolimus include temsirolimus and everolimus. Temsirolimus (Torisel®, Pfizer Inc, New York, NY, USA) is a sirolimus prodrug that has been approved for the treatment of advanced renal cell carcinoma (RCC) ([Torisel Prescribing Information](#)). Everolimus (Afinitor®, Novartis Pharmaceutical Corporation, East Hanover, NJ, USA) is a sirolimus analog that has been approved for the treatment of multiple tumor types including advanced RCC, breast cancer, neuroendocrine tumors of pancreatic origin, renal angiomyolipoma, and subependymal giant cell astrocytoma ([Afinitor Prescribing Information](#)). Although not used as RLDs in the 505(b)(2) NDA for ABI-009, the safety and efficacy information of temsirolimus and everolimus is referenced in the NDA when relevant to provide background information on known class effects of mTOR inhibitors.

In determining which nonclinical studies were necessary to support a 505(b)(2) NDA for ABI-009 for the treatment of patients with advanced malignant PEComa, an advanced disease with limited therapeutic options, Aadi considered the International Conference on Harmonization S9 Guideline titled "Nonclinical Evaluation for Anticancer Pharmaceuticals (dated October 29, 2009)". Differences in formulation, dose, and routes of administration between ABI-009 and the RLD Rapamune were also taken into consideration. Of note, Rapamune is administered orally (PO) at a clinical dose of 2 mg daily (following a 6 mg loading dose) formulated as solution

and tablets for oral administration, compared to a recommended weekly dose (cycle: 2 weeks on, 1 week off) of 100 mg/m² for ABI-009 formulated as albumin-bound nanoparticles for IV administration.

5.3. Pharmacology

Primary pharmacology

The Applicant's Position:

The in vitro and in vivo primary pharmacodynamics for ABI-009 are described in Module 2.4.1.1. In vitro pharmacodynamic studies were not conducted with ABI-009 because sirolimus is a known active substance with a well-known mechanism of action as an mTOR inhibitor to support its basic pharmacology as a chemotherapy.

Clinically, PEComa is often linked to overactivation of mTOR pathway, possibly through a combination of genetic alterations in *TSC1* or *TSC2* and pS6-S235/236 activation ([Dickson 2013](#)). There is no available animal model for PEComa; however, given that mTOR overexpression is known in PEComa, the antitumor activity of ABI-009 administered IV has been evaluated in tumor types where the activation of the mTOR pathway has been demonstrated. ABI-009 showed significantly higher tumor accumulation of sirolimus, inhibition of the mTOR target pS6 in the tumor and tumor growth inhibition compared to orally administered sirolimus at the same total dose (Module 2.6.2 Section 2.2.16). Seventeen non-Good Laboratory Practice (GLP) in vivo pharmacology studies were conducted in various human tumor xenograft models. In studies across all mTOR driven tumor types tested, ABI-009 was well tolerated and exhibited potent antitumor activity as a single agent and in combination with other therapeutic agents.

The FDA's Assessment:

*Generally, Assessment Aids provided by Applicants should not contain an Applicant's Position for the Primary Pharmacology section. This reviewer made an exception in this case as the summary provided by the Applicant is brief but accurate.

In general, the FDA agrees with the Applicant's assessment that ABI-009 had activity against mTOR-driven tumors. Across multiple studies, IV administration of 40 mg/kg ABI-009 three times a week for 4 weeks induced in vivo anti-tumor activity in mice bearing human xenograft tumors with mTOR pathway activation, including MX-1 (breast cancer cells that lack the expression of PTEN, a tumor suppressor gene that negatively regulates mTOR pathway), HCT-116 (colon cancer cells with mTORC1/mTORC2 overexpression), HT29 (colon cancer), SK-OV-3 (ovarian cancer), and MDA-MB-231 (human breast cancer cells with mTOR pathway overexpression).

In Study #CA-AAD-2, the Applicant evaluated in vivo anti-tumor activity, drug concentration in tumors and whole blood, and mTOR target suppression in tumors following treatment with ABI-009 (nab-sirolimus), sirolimus, or the mTOR inhibitor everolimus in athymic nude mice bearing subcutaneous PTEN-null human bladder cancer (UMUC3) xenografts. Tumor-bearing mice (tumor volume ~150-250 mm³ for PK assessment and ~60 to 160 mm³ for TGI assessment) were treated with either:

- **Sirolimus** at 15 or 80 mg/kg/week (3 or 16 mg/kg, given once daily [qd]×5) orally (PO)
- **ABI-009** at 15, 40 or 80 mg/kg/week (7.5, 20 or 40 mg/kg, given 2×/week) IV
- **Everolimus** at 15 or 80 mg/kg/week (3 or 16 mg/kg, given qd×5) PO

For PK/PD assessment, whole blood and tumor samples were collected from 3 mice/group at 1, 24, and 168 hours post-dose on Day 1 and 1 hour post-dose on Day 4, followed by analysis of sirolimus and everolimus concentrations using liquid chromatography with tandem mass spectrometry (LC-MS/MS). Matching tumor samples from the other flank were analyzed for suppression of downstream mTOR signaling by measuring the levels of phosphorylated ribosomal protein 6 (pS6) with immunohistochemistry (IHC). The Applicant also assessed the effect on tumor growth using 5 mice/group. An IV saline group was included as a negative control, and mice were treated for 5 weeks. Body weight and tumor measurements were recorded every Monday, Wednesday, and Friday and signs of distress were assessed daily for all mice. Treatment with IV ABI-009, oral sirolimus, or oral everolimus resulted in greater tumor growth inhibition (TGI) compared to the saline control group (Table 2) without inducing substantial body weight loss (data not shown). At the dose of 15 mg/kg/week, enhanced TGI and improved survival were seen with ABI-009 IV compared to equivalent oral doses of sirolimus and everolimus. At the high dose of 80 mg/kg/week, ABI-009 (IV) and everolimus (PO) exhibited similar TGI and survival, whereas oral sirolimus resulted in lower TGI/survival. All ABI-009-treated groups (15, 40, and 80 mg/kg/week) induced similar TGI, suggesting the lack of a dose response (Table 2). All mice dosed with ABI-009 survived for the duration of the study.

Table 2: Effect of Sirolimus, Everolimus, and ABI-009 on Tumor Growth and Survival (FDA Table)

Group	Treatment	Treatment and Schedule (N=5)	TGI (%)	Animal survival	
				Median (Days)	Number surviving
1	Saline	Saline (10 mL/kg IV 2x/week for 5 weeks)	0	19	0/5
2	Sirolimus	15 mg/kg/week for 5 weeks	24	21	1/5
3		80 mg/kg/week PO for 5 weeks	50	28	1/5
4	ABI-009	15 mg/kg/week IV for 5 weeks	70	NR	5/5
5		40 mg/kg/week IV for 5 weeks	64		5/5
6		80 mg/kg/week IV for 5 weeks	64		5/5

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7	Everolimus	15 mg/kg/week PO for 5 weeks	36	19	1/5
8		80 mg/kg/week PO for 5 weeks	68	NR	5/5

NR – Not recorded (Median survival not reached)

At the dose of 15 mg/kg/week, PK analysis demonstrated that exposure to sirolimus from ABI-009 (IV) was much higher in plasma and tumor tissue than from an oral formulation of sirolimus or everolimus (Table 3). Further, IV administration of ABI-009 resulted in greater suppression of mTOR activity at the 15 mg/kg/week dose level as measured by a reduction in S6 phosphorylation (Table 4). Overall, IV administration of ABI-009 resulted in higher sirolimus concentrations in the tumor compared to oral administration of sirolimus or everolimus, thus resulting in greater mTOR inhibition and TGI.

Table 3: Drug Concentration in Tumor and Blood on Days 1, 4, and 7 (FDA Table)

Treatment (N=3)	Dose (mg/kg/wk)	Tumor Conc (ng/g)				Blood Conc (ng/mL)	
		D1 – 1h	D1 - 24 h	D4 – 1h	D7	D4 – 1h	D7
Sirolimus (PO)	15	0	15.2	6.3	29.4	79.3	0.8
			(58)	(68)	(20)	(27)	(5)
ABI-009/Sirolimus	80	48.5	350	228.0	588	1513	6.8
		(55)	(2)	(6)	(0.8)	(2)	(1)
ABI-009 (IV)	15	1080	888	427	595	2173	3.9
	40	1490	786	1430	706	2373	5.4
	80	2652	744	1386	471	2593	6.0
Everolimus (PO)	15	18.5	48.6	68.7	28.7	271	1.9
		(58)	(18)	(6)	(20)	(8)	(2)
		577	433	860	150	2383	10.0
ABI-009/Everolimus	80	(4.6)	(1.7)	(1.6)	(3)	(1)	(0.6)

Blue numbers in parenthesis (X) are fold ABI-009 compared to sirolimus or everolimus; wk - week.

Table 4: Phosphorylated S6-Positive Percent Area Following Treatment with ABI-009, Sirolimus, or Everolimus (FDA Table)

Time (N=3/time point)	pS6 Positive Tumor Area Percent (%)								
	ABI-009 15 mg/kg/week			Sirolimus 15 mg/kg/week			Everolimus 15 mg/kg/week		
	Viable	Necrotic	Total	Viable	Necrotic	Total	Viable	Necrotic	Total
D1 - 1h	1.72	1.28	1.72	18.48	N/A	18.48	32.45	10.90	31.94
D1 – 24h	1.13	0.02	1.12	18.92	0.03	18.92	13.08	7.48	12.50
D7	1.14	0.21	1.06	9.79	0.14	8.29	11.17	0.09	9.16
	ABI-009 80 mg/kg/week			Sirolimus 80 mg/kg/week			Everolimus 80 mg/kg/week		
D1 - 1h	1.51	0.43	1.50	4.21	3.26	4.17	3.67	0.02	3.66
D1 – 24h	0.84	0.07	0.84	0.77	0.02	0.76	0.83	N/A	0.83

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D7	1.73	0.88	1.72	1.10	0.06	1.03	4.75	0.03	4.70
D – Day; h – hour; N/A – Not applicable									

In Study #CA-AB-11, the anti-tumor activity of IV ABI-009 in mice bearing HT29 colon cancer xenografts was not improved significantly at higher dose levels of 60 mg/kg or 80 mg/kg IV 3 times a week for 4 weeks, 1 week on/1 week off compared to 40 mg/kg 3 times a week for 4 weeks.

The Applicant also evaluated the in vivo anti-tumor activity of ABI-009 alone or in combination with erlotinib (EGFR inhibitor), suberoylanilide hydroxamic acid (SAHA; HDAC inhibitor), cetuximab (anti-EGFR antibody), perifosine (AKT inhibitor), doxorubicin, or oxaliplatin in the mTOR-activated MDA-MB-231 human breast tumor xenograft model. Each female athymic nude mouse (5 per group) was implanted subcutaneously with MDA-MB-231 breast tumor cells into the right and left flanks. Dosing was initiated when tumors reached a size of ~100 mm³. Treatment with 40 mg/kg ABI-009 IV 3 times a week for 4 weeks induced 75% TGI compared to saline control without inducing body weight loss or mortality. Combined treatment with ABI-009 and erlotinib, perifosine, doxorubicin, or SAHA improved anti-tumor activity compared to ABI-009 alone; however, these combinations also resulted in increased toxicity as assessed by weight loss and mortality.

Secondary Pharmacology

The Applicant's Position:

In addition to activity in tumor cells, the secondary pharmacodynamics of antiproliferative activity of sirolimus against vascular smooth muscle cells and myofibroblasts have been well established in the literature (eg, [Gasper 2013](#)). In addition to cancer, mTOR activation also plays essential roles in the proliferation of lymphocytes, vascular smooth muscle cells (SMCs), and endothelial cells ([Costa 2005](#)), in the proliferation of endothelium and smooth muscle of the pulmonary arteries ([Waxman 2013](#)), and in metabolic diseases caused by abnormal mitochondrial metabolism ([Eldar-Finkelman 2011](#), [Zheng 2016](#)). mTOR inhibition by sirolimus resulted in strong antiproliferative activity, particularly in vascular SMCs ([Krymskaya 2011](#), [Houssaini 2013](#), [Goncharov 2014](#)). Multiple in vitro studies ([Krymskaya 2011](#), [Goncharov 2014](#)), animal models ([Paddenbergh 2007](#), [Goncharov 2014](#)), and new translational data using human pulmonary arterial hypertension (PAH) patient samples ([Goncharov 2014](#)) demonstrate that sirolimus can prevent and reverse PAH.

The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment. According to the second sentence of the Applicant, *In addition to cancer, mTOR activation also plays essential roles in the*

proliferation of lymphocytes, vascular smooth muscle cells (SMCs), etc. These physiologic effects are triggered by activation of mTOR, and can be attenuated by mTOR inhibition. Thus, this section appears to be related to the primary pharmacology of mTOR.

Safety Pharmacology

The Applicant's Position:

Sirolimus is a well-known active pharmaceutical ingredient. Therefore, Aadi conducted two GLP safety pharmacology studies with ABI-009, including a cardiovascular safety pharmacology study and an in vivo central nervous system (CNS) safety pharmacology study, and is relying on known respiratory safety pharmacology information for the RLD ([Rapamune Prescribing Information](#)). The ABI-009 cardiovascular safety pharmacology study was conducted in vitro and demonstrated potential for a low potency human ether-à-go-go-related gene (HERG) channel blocking effect. The CNS safety pharmacology study showed that ABI-009 as a single IV dose of 30, 60, or 90 mg/kg (equivalent to 180, 360, or 540 mg/m² human dose, up to 5.4 times of 100 mg/m² clinical dose) administered to rats did not result in changes in any of the functional observation battery (FOB) parameters evaluated in the study. Overall, the CNS safety pharmacology of Rapamune and ABI-009 nonclinical CNS safety pharmacology studies did not indicate CNS toxicity as a concern.

The FDA's Assessment:

The FDA generally agrees with the assessment of the Applicant. The IC₅₀ for ABI-009-induced inhibition of in vitro hERG potassium currents was 61 μM.

5.4. ADME/PK

The Applicant's Position:

ABI-009 IV administration resulted in significantly higher maximum concentration observed (C_{max}) and AUC (area under the concentration-time curve) compared with oral sirolimus of the RLD. Substantial and prolonged distribution of sirolimus is observed following ABI-009 IV, intrathecal (IT), and subcutaneous (SC) administration. ABI-009 IV results in significantly higher tumor drug accumulation compared with equal dose of oral sirolimus and oral everolimus. The metabolism of ³H-sirolimus when administered IV as ABI-009 is consistent with the published literature for sirolimus, which indicates that sirolimus is extensively metabolized by cytochrome P450 3A4 (CYP3A4) enzymes in human liver and small intestine through O-demethylation and/or hydroxylation ([Christians 1992](#), [Streit 1996](#), [Lampen 1998](#)). Consistent with previous results with the RLD oral sirolimus, fecal excretion represented the major route of elimination with 68.57 and 69.99% radioactivity of IV administered *nab*-³H-sirolimus for male

and female rats, respectively. Renal excretion was a minor route of elimination, representing 7.73 to 8.84% of the administered doses.

The FDA's Assessment:

In general, the FDA agrees with the assessment of the Applicant. In addition to the data summarized by the Applicant, sirolimus has an equipotent metabolite (secorapamycin) which was also detected at higher concentrations from ABI-009 (IV) than the oral formulation of sirolimus.

In Study #1291.01, the Applicant compared the PK parameters of sirolimus and the major active metabolite secorapamycin in 5 Sprague-Dawley rats/sex/group following single IV administration of 0.5 or 17 mg/kg ABI-009 and single oral administration of 0.5 or 17 mg/kg Rapamune (oral formulation of rapamycin). Blood was collected at pre-dose; 5, 15, and 30 minutes post-dose; and 1, 3, 8, 24, 72, and 120 hours post-dose. Whole blood samples were analyzed for sirolimus and secorapamycin using a validated LC-MS/MS analytical method. There were no mortalities or drug-related clinical signs following IV ABI-009 or oral rapamycin at single doses up to 17 mg/kg. Following IV administration of ABI-009, all animals demonstrated systemic exposure to sirolimus and its major metabolite, secorapamycin, and exposures (C_{max} and AUC_{inf}) increased with increasing dose (Table 5). Sirolimus C_{max} increased greater than dose proportionally, whereas sirolimus AUC increased less than dose proportionally. Mean exposures for sirolimus and secorapamycin were higher in males compared to females, however, the differences were less than 2-fold. Following administration of an oral solution of Rapamune, there was inconsistent exposure to sirolimus or secorapamycin at the 0.5 or 17 mg/kg dose levels. Thus, sirolimus AUC for most animals and terminal elimination parameters for all animals could not be calculated following administration of the Rapamune oral solution. As shown in Table 5, exposure to sirolimus and secorapamycin were higher in rats given IV ABI-009 compared to those given oral Rapamune at the same sirolimus dose level. Specifically, sirolimus and secorapamycin C_{max} were approximately 16- to 508-fold and 432- to 1072-fold higher, respectively, following IV administration of ABI-009 compared to oral administration of Rapamune.

Table 5: Pharmacokinetic Parameters of Sirolimus and Secorapamycin in Rats (FDA Table)

Pharmacokinetic Parameters of Sirolimus after IV ABI-009 or Oral Rapamune in Rats						
Test Article/ Dose level (mg/kg)	Male			Female		
	C_{max} (ng/mL)	AUC_{∞} (h*ng/mL)	T_{max} (h)	C_{max} (ng/mL)	AUC_{∞} (h*ng/mL)	T_{max} (h)
ABI-009/ 0.5	72.4	1020	0.083	45.2	559	0.083
ABI-009/ 17	3990	9130	0.083	3720	7960	0.083
Rapamune/ 0.5	3.84	NC	1	2.76	NC	1

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Rapamune/ 17	7.85	NC	8.2	8.76	NC	28.0
Pharmacokinetic Parameters of Secorapamycin after IV ABI-009 or Oral Rapamune in Rats						
ABI-009/ 0.5	11.3	9.95	0.083	4.05	NC	0.083
ABI-009/ 17	686	1450	0.083	566	1290	0.083
Rapamune/ 0.5	NC	NC	NC	NC	NC	NC
Rapamune/ 17	0.640	NC	40	1.31	NC	48
NC = Not calculated (or no data available) due to values below lower limit of detection (2 ng/mL)						

5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position:

In single dose and repeat-dose nonclinical toxicology studies, the no-observed-adverse-effect level (NOAEL) for ABI-009 administered IV was not established. The maximum tolerated dose (MTD) of ABI-009 in rats was determined to be 78.9 mg/kg (equivalent to 473.4 mg/m² human dose, 4.7 times higher than the 100 mg/m² MTD and clinical dose of ABI-009). Toxicities observed in these toxicology studies include signs of respiratory toxicity, increases in glucose, cholesterol, and triglycerides, which are consistent with known toxicities of sirolimus and the class effect of mTOR inhibitors. Histopathological analysis revealed that target organs affected by ABI-009 were the heart, lungs, thymus, and male reproductive organs. Studies conducted in mouse, rat, dog, and monkey during the development of RLD identified the major target organ toxicities for sirolimus are heart, lungs, thymus, pancreatic islet cells, male reproductive organs, ovary, and bones. No new target organ toxicities were identified in the ABI-009 single dose and repeat-dose studies conducted by Aadi. The nonclinical toxicity studies did not identify any new areas of risk for the IV administration of ABI-009.

The FDA's Assessment:

FDA agrees with the assessment of the Applicant and that no new target organs of toxicity were identified with IV ABI-009. The GLP-compliant 28-day repeat-dose toxicology study in rats with ABI-009 (Study #SNBL.119.08) was reviewed by Dr. Shwu-Luan Lee under the original IND submission. Rats received 0, 20, 40, 90, or 180/120 mg/kg ABI-009 IV on Days 1, 5, and 9 with terminal necropsy on Day 16 (5 rats/sex/group) and recovery cohort necropsy on Day 37 (5 rats/sex/group). The STD₁₀ of ABI-009 in rats was 120 mg/kg (720 mg/m²) IV on Days 1, 5, and 9. Bone toxicity was not observed at ABI-009 doses up to 120 mg/kg. This study did not include an assessment of toxicokinetics.

5.5.2. Genetic Toxicology

The Applicant's Position:

The standard battery of genotoxicity studies per International Council for Harmonisation (ICH) S2(R1) were not conducted for ABI-009 because sufficient information regarding the potential for genotoxicity is available from studies reported in the prescribing information for the RLD Rapamune ([Rapamune Prescribing Information](#)). Sirolimus was not genotoxic in the in vitro bacterial reverse mutation assay (NDA 021083, Study GTR 18811), the Chinese hamster ovary cell chromosomal aberration assay (NDA 021083, Study GTR 22683), the mouse lymphoma cell forward mutation assay (NDA 021083, Study GTR 25495), and the in vivo mouse micronucleus assay (NDA 021083, Study GTR 25481). In a non-GLP Ames test (Study CEREP 11585) conducted for sirolimus by Aadi, sirolimus was not mutagenic in Salmonella strains TA98 and TA100 both in the presence and absence of S9 metabolic activation, at concentrations tested (5, 10, 50, 100 µM). Similarly, everolimus and temsirolimus were not genotoxic in a battery of in vitro assays ([Afinitor Prescribing Information](#), [Torisel Prescribing Information](#)).

The FDA's Assessment:

In general, the FDA agrees with the assessment of the Applicant. The mini Ames assay conducted by the Applicant was sufficient to support this application because the Applicant also relied on genotoxicity data reported in the prescribing information for the RLD, Rapamune.

5.5.3. Carcinogenicity

The Applicant's Position:

Carcinogenicity evaluation is not required for anticancer agents in accordance with ICH S1A and ICH S9. Additionally, the potential carcinogenicity of sirolimus following chronic exposure has been well documented; therefore, no studies have been conducted to assess the carcinogenicity potential of ABI-009. Carcinogenicity studies of sirolimus were conducted in mice and rats. In an 86-week female mouse study (NDA 021083, Study GTR-32267) at sirolimus oral doses of 12.5 to 50 mg/kg (30 to 120 times higher than the 2 mg daily clinical dose, adjusted for body surface area, equivalent to 37.5 to 150 mg/m² human dose, comparable to ABI-009 clinical dose), there was a statistically significant increase in malignant lymphoma at all dose levels compared with controls. In a second mouse study at dosages that were approximately 3 to 16 times the clinical dose (adjusted for body surface area), hepatocellular adenoma and carcinoma in males were considered sirolimus-related. In the 104-week rat study (NDA 021083, Study GTR 32266) with sirolimus at 0.2 mg/kg (equal to or lower than the clinical dose of 2 mg daily, adjusted for body surface area), there were no significant findings ([Rapamune Prescribing Information](#)).

The FDA's Assessment:

FDA agrees with the assessment of the Applicant. Although carcinogenicity studies were previously conducted with the RLD, carcinogenicity studies are not needed to support the use of ABI-009 in the currently proposed indication per ICH S9.

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

This NDA was filed under Section 505(b)(2) of the US regulations, using Rapamune as the RLD. Therefore, no reproductive and developmental toxicity studies were performed with ABI-009. Per ICH S9, studies on fertility and early embryonic development, and pre- and postnatal toxicology are not required to support marketing of pharmaceuticals for the treatment of advanced cancer. In addition, sufficient information is available regarding the RLD Rapamune, which showed toxic effects in male and female reproductive organs, diminished fertility, and embryo and fetal toxicities. Rapamune is an anti-proliferative drug and affects rapidly dividing cells like the germ cells. Rapamune can cause fetal harm when administered to a pregnant woman. Azoospermia or oligospermia may be observed ([Rapamune Prescribing Information](#)). Since ABI-009 is delivered IV at a higher weekly dose compared with the RLD oral Rapamune (180 mg vs 14 mg), it is expected that ABI-009 will cause the same type of reproductive and development toxicities. Aadi proposes to adopt the same warnings and precaution in the United States Prescribing Information (USPI) as for the RLD Rapamune and requires effective contraception for male and female patients with childbearing potential to minimize the risk of developmental defects.

The FDA's Assessment:

FDA generally agrees with the assessment of the Applicant that it is appropriate to rely on FDA's findings of reproductive and developmental toxicity for Rapamune.

5.5.5. Other Toxicology Studies

The Applicant's Position:

For local tolerance, ABI-009 was biocompatible with blood and did not cause hemolysis with the highest ABI-009 concentration of 5 mg/mL mixed with rat blood at the ratio of 1:1. No risks were identified that would prevent the IV administration of ABI-009.

The batches of ABI-009 used in the studies conducted to support the nonclinical program have comparable levels of the impurities to the batches used in the phase 1 and phase 2 clinical studies. The main impurity identified in ABI-009 is seco-rapamycin (also known as seco-

rapamycin A), a ring-opened isomer and in vivo metabolite of sirolimus. The limit for this impurity in the drug product specification is not more than (b) (4)%. Further information regarding seco-rapamycin A is provided in Module 3.2.P.5.5. Seco-rapamycin A showed less than (b) (4)% of the potency of sirolimus in a thymocyte proliferation assay (Wang 1994). In a previous 28-day repeat-dose toxicity study with sirolimus (NDA 021083, Study GTR-27897), sirolimus containing (b) (4)% seco-rapamycin A did not impact the toxicological profile of sirolimus. Therefore, seco-rapamycin A is not likely to contribute significantly to the pharmacological activity and toxicity of sirolimus.

The FDA's Assessment:

The FDA generally agrees with the assessment of the Applicant.

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X

Sachia Khasar, Ph.D.
Primary Reviewer

Emily Wearne, Ph.D.
Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant submitted this 505(b)(2) NDA to obtain marketing approval for ABI-009 (sirolimus protein-bound particles for injectable suspension) for the treatment of patients with locally advanced, unresectable or metastatic, malignant perivascular epithelioid cell tumor (PEComa). The proposed dosing regimen is 100 mg/m² administered as an IV infusion over 30 minutes on Days 1 and 8 of 21-day cycles until disease progression or unacceptable toxicity. Fyarro is formulated as a lyophilized powder containing 100 mg of sirolimus as albumin-bound particles in single-dose vial for reconstitution.

In Applicant's pivotal Phase 2 single-arm clinical trial **PEC-001** in patients with advanced malignant PEComa (N=34), ABI-009 at the proposed recommended dosage resulted in an overall response rate (ORR) of 39%, all of which were partial responses. The most common (≥30%) adverse reactions were stomatitis, fatigue, rash, infection, nausea, edema, diarrhea, musculoskeletal pain, decreased weight, decreased appetite and cough.

The listed drug (LD) is Rapamune® (sirolimus), which is formulated as tablets or oral solution for oral administration. ABI-009 has very limited exposure overlap with the LD as its maximum concentration (C_{max}) is 170 -fold higher than that of the LD's. The Applicant relies on clinical pharmacology data of the RLD on the data of pharmacokinetics (PK), specific populations, and drug-drug interactions (DDIs) of the LD.

The Clinical Pharmacology package to support this NDA included analyses of the proposed dosing regimen, PK data, and use in specific populations and DDIs. The exposure-response (E-R) analysis for efficacy suggests a positive relationship between exposure and best overall response (BOR) in the pivotal study **PEC-001**; however, these results need to be interpreted with caution given the limited number of patients with a response (12/31) included in the analysis. A positive E-R relationship for safety was identified for thrombocytopenia and rash but not for neutropenia, hypokalemia, hyperglycemia, dehydration, hypertriglyceridemia, or diarrhea using the data from study **PEC-001** and the dose finding study **CA401** (N=60).

Because the proposed recommended dosage is close to the maximum tolerated dose (MTD), a post-marketing requirement (PMR) will be issued that requires the Applicant to conduct a dedicated hepatic impairment (HI) trial to evaluate the PK and safety of ABI-009 in subjects with mild, moderate, and severe HI (based on NCI criteria). A PMR will also be issued to require the Applicant to assess the potential QT interval prolongation risk for ABI-009 as the higher

exposures observed with ABI-009 compared to the LD and the QT interval prolongation potential for ABI-009 has not been adequately evaluated.

Recommendations

The Office of Clinical Pharmacology has reviewed the information and data contained in NDA 213312. This NDA is approvable from a Clinical Pharmacology perspective.

REVIEW ISSUE	RECOMMENDATIONS / COMMENTS
Pivotal or supportive evidence of effectiveness	Based on study PEC-001 , treatment with ABI-009 resulted in an ORR of 39%.
General dosing instructions	The proposed dosing regimen is 100 mg/m ² administered as an IV infusion over 30 minutes on Days 1 and 8 of 21-day cycles. Population PK and exposure-response (E-R) analyses support the proposed dosing regimen.
Dosing in patient subgroups (intrinsic and extrinsic factors)	The following dosage modifications are recommended for patients with hepatic impairment (HI, based on NCI criteria): ▪ Severe HI: avoid use ▪ Moderate HI: reduce dose to 56 mg/m² ▪ Mild HI: reduce dose to 75 mg/m² The following dosage modifications are recommended for the following drug-drug interactions (DDI): ▪ Strong CYP3A4 inhibitor and/or P-gp inhibitors: avoid use ▪ Strong CYP3A4 inducers and/or P-gp inducers: avoid use ▪ Moderate or weak CYP3A4 inhibitors: reduce dose to 56 mg/m²
Labeling	Overall, the proposed labeling recommendations are acceptable upon the Applicant's agreement to the FDA revisions to the labeling.
Initial bridge between the to-be-marketed and clinical trial formulations	N/A (the Applicant notes that there have been no changes in the formulation or processing aids throughout the development of ABI-009).

Post-Marketing Requirements (PMR) or Commitments (PMC)

Clinical Pharmacology PMR #1

The Applicant proposed dosage modifications for patients with HI per LD Rapamune® (sirolimus) labeling. FDA is requiring that the Applicant conduct the following trial as a PMR to evaluate the PK and safety of Fyarro in subjects with mild, moderate, and severe HI (based on NCI criteria).

Conduct a hepatic impairment clinical trial to evaluate the pharmacokinetics and safety of Fyarro in subjects with mild, moderate, and severe hepatic impairment (based on NCI criteria) and determine the magnitude of increase in exposure and

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appropriate dosage. Design and conduct the trial in accordance with the FDA Guidance for Industry titled: *“Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”*

Draft Analysis Plan Submission: 03/2022
Final Analysis Plan Submission: 06/2022
Study Completion: 10/2023
Final Report Submission: 03/2024

Provide the datasets with the final report.

The decision to issue a PMR for HI trial was based on the following factors:

- Lack of clinical data in patients with moderate or severe HI
- Non-linear PK of ABI-009 above a dose of 100 mg/m²
- The recommended dose of 100 mg/m² is near the MTD
- The HI data from Rapamune cannot be relied upon due to significantly higher exposures achieved following IV administration of ABI-009 than that achieved following administration of Rapamune and differences between hepatic impairment classification systems (Rapamune used Child-Pugh criteria, ABI-009 will be using NCI criteria)

Clinical Pharmacology PMR #2

FDA is requiring that the Applicant assess the QT interval prolongation potential of ABI-009 as a PMR.

Conduct a clinical trial to assess the potential risk of QT interval prolongation and the effect of Fyarro on the QT interval. Design and conduct the trial in accordance with the ICH E14 Guidance for Industry titled: *“E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.”*

Draft Analysis Plan Submission: 03/2022
Final Analysis Plan Submission: 06/2022
Study Completion: 03/2025
Final Report Submission: 06/2025

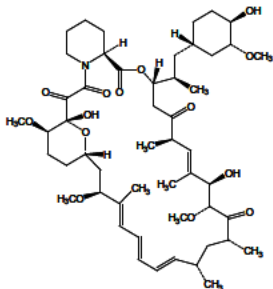
Provide the datasets with the final report.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

Table 6: Highlights of ABI-009 Clinical Pharmacology

General Information	
Chemical structure and major physical and chemical properties	 Molecular formula: C₅₁H₇₉NO₁₃ Molecular weight: 914.2 g/mol
Indication	Treatment of patients with advanced (metastatic or locally advanced) malignant perivascular epithelioid cell tumor (PEComa).
Route of administration and formulation type and strengths	Route of Administration: ABI-009 is administered as an intravenous (IV) infusion over 30 minutes following reconstitution with 0.9% sodium chloride injection. Formulation Type: ABI-009 is supplied as lyophilized cake containing 100 mg of sirolimus and approximately 850 mg of human albumin formulated as albumin-bound nanoparticles in a (b) (4) vial for reconstitution with 20 mL of 0.9% saline to an injectable suspension containing 5 mg/mL sirolimus. There have been no changes in the formulation or processing aids throughout the development of ABI-009; the same formulation has been used in all clinical trials.
Maximum tolerated dose	The CA401 study established that ABI-009 has a MTD of 100 mg/m² IV infused over 30 minutes in cycles of once weekly administration for 3 weeks followed by a one-week break. The recommended therapeutic dosing regimen, studied in the registrational PEC-001 study in patients with PEComa, was 100 mg/m² IV for 2 weeks out of 3, rather than the 3 weeks out of 4 in the CA401 study. The highest non-severely toxic dose (HNSTD) and the no-observed-adverse-effect level (NOAEL) were not determined, as serious adverse events occurred at lowest evaluated dose level in the oncology setting, 45 mg/m². Adverse events requiring permanent dose reductions were observed at the 10 mg/m² IV dose in the non-oncology setting in Study PAH-001 (patients with pulmonary arterial hypertension[PAH]). These were low-grade persistent events in a different patient population (PAH) and with a different risk profile compared to the PEComa population.

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Major adverse events	Adverse events are summarized below from the registrational Phase 2 Study PEC-001. The population described is the Safety Analysis set (n = 34), ie, all patients that received at least one dose of ABI-009 in Study PEC-001. <u>Most Common Events</u> Overall, the most common treatment-emergent adverse events (TEAEs; defined as occurring in $\geq 30\%$ of patients) reported were: mucositis (79%, 27/34), fatigue and rash (68% each, 23/34), infections (59%, 20/34), anemia (56%, 19/34), nausea (50%, 17/34), weight decreased (47%, 16/34); diarrhea, decreased appetite, and hyperglycemia (44% each, 15/34), peripheral edema and hypokalemia (41% each, 14/34), hypertriglyceridemia (35%, 12/34), and cough, dysgeusia, hypercholesterolemia, thrombocytopenia, and vomiting (32% each, 11/34). The most common treatment-emergent related adverse events (TERAEs) (defined as occurring in $\geq 30\%$ of patients) reported were: mucositis (79%, 27/34), fatigue (59%, 20/34), rash (56%, 19/34), anemia and nausea (47% each, 16/34), diarrhea and weight decreased (38% each, 13/34), hyperglycemia (35%, 12/34), and decreased appetite, hypercholesterolemia, hypertriglyceridemia, and thrombocytopenia (32% each, 11/34). For the above two lists of most common events, mucositis, rash, infections, anemia, hyperglycemia, hypertriglyceridemia, hypercholesterolemia, and thrombocytopenia were group terms comprised of several preferred terms mapping into the relevant special interest AEs, as described in Study PEC-001 CSR, Listing 16.2.7.8. For example, “mucositis” is treated as a group term that includes aphthous ulcer, mouth ulceration, esophageal ulcer, and stomatitis. Adverse events of special interest (AESIs) were preidentified at the start of the study based on class effects of mTOR inhibitors (Martins 2013, Aapro 2014, Sivendran 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. <u>CTCAE Grade of Events</u> Treatment-emergent adverse events were predominantly Grade 1 or Grade 2 (1008/1099 [92%] events). Grade 3 TEAEs were reported in 24/34 (71%) patients, and Grade 4 TEAEs were reported in 3/34 (9%) patients. When the Investigator’s assessment of relationship to study drug was taken into account, Grade 3 TERAEs were reported in 18/34 (53%) patients, with no patients experiencing a Grade 4 or 5 TERAE. There was no apparent relationship between incidence of Grade 3 and Grade 4 events and the treatment cycle (ie, study drug exposure). Treatment-emergent adverse events were tolerable and manageable, with most being Grade 1 or Grade 2 events. Eighty percent of TEAEs resolved; two-thirds (64%) of them without action taken and approximately one-third (36%) were managed with dose reductions and study drug interruption. <u>Dose Modifications, Interruptions, and Discontinuations</u> Twelve (35%) patients experienced TEAEs that required study drug dosage reductions, which were also considered related by the Investigator. The most common TEAEs associated with reductions in study drug were stomatitis and pneumonitis in 3 (9%) patients each. All other TEAEs resulting in study drug dose reductions occurred in a single patient each. All dose reductions occurred in Cycles 2–5; 11 (32%) patients had 1 dose reduction, and 2 (6%) patients had 2 dose reductions (12 patients with dose reduction for TEAE and 1 patient due to Investigator decision).
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Twenty-two (65%) patients experienced TEAEs that required study drug interruptions (ie, a delayed or missed dose), which were considered TERAEs by the Investigator in 20 (59%) patients. The most common TEAEs associated with study drug interruptions were stomatitis in 6 (18%) patients; anemia and pneumonitis in 5 (15%) patients each; and thrombocytopenia, dehydration, and dermatitis acneiform in 2 (6%) patients each. All other TEAEs resulting in study drug interruptions occurred in a single patient each. The most common TERAEs associated with study drug interruptions were stomatitis in 6 (18%) patients; pneumonitis in 5 (15%) patients; anemia in 3 (9%) patients; and thrombocytopenia, dehydration, and dermatitis acneiform in 2 (6%) patients each. All other TERAEs resulting in study drug interruptions occurred in a single patient each. Most dose delays occurred after Cycle 3. Adverse events were rarely the reason for study drug discontinuation; 2 (6%) patients experienced TERAEs that required permanent discontinuation of study drug: anemia and cystitis noninfective in 1 (3%) patient each.																															
Pharmacokinetic (PK) Features																															
Dose or exposure range tested in clinical trials	Single Dose	Pharmacokinetic data were collected in the Phase 1 dose escalation, safety, and PK Study CA401 in patients with advanced solid tumors. Patients received ABI-009 IV weekly for 3 weeks followed by a rest week (28-day cycles) until disease progression or unacceptable toxicity occurred, at dose levels ranging from 45 to 150 mg/m²; higher dose levels of 125 mg/m² and 150 mg/m² produced dose limiting toxicities (DLTs). Aadi notes that the 3 of 4 weeks dosing regimen differs from the recommended proposed schedule of 100 mg/m² IV weekly for 2 weeks, followed by a week of rest. While no independent single dose PK study was conducted, relevant single dose PK data are available from Study CA401 and the calculated PK parameters from observed PK data are provided below. Blood samples were obtained only for the first dose of ABI-009 from all patients from pre-dose up to 168 hours after infusion, essentially providing single-dose PK data. Specifically, blood samples were obtained during Cycle 1 from patients receiving ABI-009 pre-dose, at 15 minutes and 30 minutes (immediately prior to the termination of the infusion) during dosing; and post infusion (0.25, 0.5, 1.0, 1.5, 2, 4, 6, 8, 24, 48, 72, 96, and 168 hours after infusion of the first dose of ABI-009). Summary of Study CA401 PK Parameters <table><tr><th rowspan="2">PK Parameters</th><th colspan="5">ABI-009 Dose (mg/m²)</th></tr><tr><th>45 (n = 7)</th><th>56.25 (n = 3)</th><th>100 (n = 7)</th><th>125 (n = 7)</th><th>150 (n = 2)</th></tr><tr><td>C_{max} (ng/mL)</td><td>1640 (46.0)</td><td>2740 (41.8)</td><td>3020 (41.9)</td><td>3980 (42.1)</td><td>2800 (173)</td></tr><tr><td>AUC_{0-inf} (ng×h/mL)</td><td>24200 (17.1)</td><td>24500 (34.6)</td><td>38700 (39.8)</td><td>26500 (21.0)</td><td>68600 (1.93)</td></tr><tr><td>t_½ (hour)</td><td>38.6 (23.7)</td><td>44.8 (34.4)</td><td>56.8 (39.5)</td><td>53.7 (23.7)</td><td>90.7 (5.42)</td></tr></table> Abbreviations: AUC_{0-inf} = area under the concentration-time curve from time 0 to infinity; C_{max} = maximum drug concentration; n = number of patients;	PK Parameters	ABI-009 Dose (mg/m ²)					45 (n = 7)	56.25 (n = 3)	100 (n = 7)	125 (n = 7)	150 (n = 2)	C _{max} (ng/mL)	1640 (46.0)	2740 (41.8)	3020 (41.9)	3980 (42.1)	2800 (173)	AUC _{0-inf} (ng×h/mL)	24200 (17.1)	24500 (34.6)	38700 (39.8)	26500 (21.0)	68600 (1.93)	t _½ (hour)	38.6 (23.7)	44.8 (34.4)	56.8 (39.5)	53.7 (23.7)	90.7 (5.42)
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	45 (n = 7)	56.25 (n = 3)	100 (n = 7)	125 (n = 7)	150 (n = 2)																										
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	PK = pharmacokinetic; $t_{1/2}$ = terminal elimination half-life; %CV = percent coefficient of variation. Note: Data are presented as the geometric mean (geometric %CV) Source: Study CA401 CSR. A summary of PK parameters across all dose groups at the recommended dose of 100 mg/m² with arithmetic and geometric means and medians is provided in Module 2.7.2 Section 3.4.										
Multiple Dose	Data from 2-dose sparse PK sampling in the registrational phase 2 Study PEC-001, in which patients were treated with ABI-009 at 100 mg/m² (weekly for 2 weeks followed by a week of rest in a 21-day cycle) were combined for a population PK model with single-dose PK data from the Phase 1 dose-finding PK Study CA401, in which patients were treated with ABI-009 at doses ranging from 45 mg/m² to 150 mg/m² (weekly for 3 weeks followed by a week of rest in a 28-day cycle). Blood samples in Study PEC-001 were obtained during Cycle 1 on Days 1 and 8 at pre-dose and at 0.5, 1, 2, 4 hours post-dose, and a 2-week trough sample was taken pre-dose on Cycle 2 Day 1. Blood samples in Study CA401 were obtained during Cycle 1 at pre-dose, at 15 minutes and 30 minutes (immediately prior to the termination of the infusion) during dosing; and post infusion (0.25, 0.5, 1.0, 1.5, 2, 4, 6, 8, 24, 48, 72, 96, and 168 hours [prior to Cycle 1 Day 8, ie, 1 week trough] after infusion of the first dose of ABI-009). Pharmacokinetic parameters from the combined dataset were modeled for each dose level. Data from patients treated at the 100 mg/m² dose level in the 2 studies were merged, totaling 41 patient data (Study PEC-001: n = 34, and Study CA401: n = 7). The estimates of the geometric mean (%CV) are below. Pharmacokinetic Parameters for ABI-009 Clinical Dose of 100 mg/m² <table border="1"> <tr> <td>Dose (mg/m²)</td><td>100</td></tr> <tr> <td>N</td><td>41</td></tr> <tr> <td>C_{max} (ng/mL)</td><td>2590 (30.0)</td></tr> <tr> <td>AUC_{0-inf} (ng×h/mL),</td><td>22100 (50.3)</td></tr> <tr> <td>$t_{1/2}$ (hour)</td><td>58.9 (41.3)</td></tr> </table> Abbreviations: AUC_{0-inf} = area under the concentration-time curve from time 0 to infinity; C_{max} = maximum drug concentration; N = number of patients; $t_{1/2}$ = terminal elimination half-life; %CV = percent coefficient of variation. Note: Data are presented as the geometric mean (%CV) Source: Study ADI0101 Report Table 6, Table 8, Table 9.	Dose (mg/m ²)	100	N	41	C _{max} (ng/mL)	2590 (30.0)	AUC _{0-inf} (ng×h/mL),	22100 (50.3)	$t_{1/2}$ (hour)	58.9 (41.3)
Dose (mg/m ²)	100										
N	41										
C _{max} (ng/mL)	2590 (30.0)										
AUC _{0-inf} (ng×h/mL),	22100 (50.3)										
$t_{1/2}$ (hour)	58.9 (41.3)										
Range of linear PK	After IV administration of ABI-009 at doses from 45–150 mg/m², there were dose-proportional increases in C_{max}. Drug exposure in the first 4 hours (AUC₀₋₄) increased in a largely dose-proportional and predictable manner, whereas terminal elimination phases were largely indistinguishable when comparing across dose groups. Total systemic exposure as measured by area under the concentration-time curve from time 0 to infinity (AUC_{0-inf}) did not increase in a dose-proportional manner over the dose range 45–150 mg/m².										
Accumulation at steady state	No specific studies have been conducted that are sufficient to establish PK measures in humans at steady state. The weekly IV administration of ABI-009 is not intended to achieve a steady blood sirolimus level. In Study PEC-001, the mean trough blood sirolimus level 1 week after dosing was 21.9 ng/mL and less than 1% of C_{max} following ABI-009										

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	administration, indicating that there is no significant sirolimus accumulation in blood with weekly multiple dose administration of ABI-009.
Metabolism	Seco-rapamycin A, a metabolite and degradation product of sirolimus, is the major circulating metabolite in blood following ABI-009 IV infusion, with seco-rapamycin A C_{max} >10% of sirolimus C_{max} immediately after infusion in Study PEC-001 (Study PEC-001 CSR). Seco-rapamycin A showed less than 4% of the potency of sirolimus in a thymocyte proliferation assay (Wang 1994). The metabolism of ABI-009 was not studied in clinical studies. Information on metabolism comes from the RLD, Rapamune, for studies involving sirolimus metabolites. Sirolimus is extensively metabolized by CYP3A4 in vivo. Seven major metabolites, including hydroxy, demethyl, and hydroxydemethyl sirolimus, were identifiable in whole blood (Leung 2006).

The Applicant's Position:

ABI-009 pharmacokinetics consist of C_{max} at the end of infusion (30 minutes), followed by a lengthy elimination phase, with a dose-proportional increase of C_{max} with increasing dose over the dose range 45–150 mg/m², based on data from clinical studies Study CA401 and Study PEC-001. The rapid time to C_{max} was followed by relatively slow terminal elimination phase, which did not vary considerably across dose groups, and may account for the non-dose-proportionality of $AUC_{0-\infty}$. Drug exposure in the first 4 hours (AUC_{0-4}) increased in a largely dose-proportional and predictable manner, whereas terminal elimination phases are largely indistinguishable when comparing across dose groups. Total systemic exposure, as measured by $AUC_{0-\infty}$, did not increase in a dose-proportional manner over the dose range 45–150 mg/m². However, within the clinically relevant dose range up to the MTD (45–100 mg/m²), $AUC_{0-\infty}$ increased in a predictable manner.

The difference in PK profile between ABI-009 and Rapamune is attributable to the difference in the route of administration (IV vs oral, respectively) and dosage (maximum of 100 mg/m² [170 mg for a typical adult] vs maximum 40 mg, respectively). Following administration of Rapamune Oral Solution, the mean time to peak concentration (t_{max}) of sirolimus were approximately 1 hour and 2 hours in healthy subjects and renal transplant patients, respectively, while it was immediately following the end of infusion for ABI-009. The bioavailability of sirolimus is low and was estimated to be approximately 14% after the administration of Rapamune Oral Solution ([Rapamune Prescribing Information](#)).

The weekly IV administration of ABI-009 is not expected to achieve a steady blood sirolimus level. In Study PEC-001, the mean trough blood sirolimus level 1 week after dosing was 21.9 ng/mL, representing less than 1% of C_{max} following ABI-009 administration, indicating that there is no significant sirolimus accumulation in blood with weekly multiple dose administration of ABI-009.

The FDA's Assessment:

The FDA generally agrees with Applicant's position. However, the FDA notes that in the above Highlights of ABI-009 Clinical Pharmacology table, under the Range of Linear PK, the Applicant states that there were dose-proportional increases in C_{max} after administration of ABI-009 at IV doses from 45-150 mg/m². The Applicant also states that drug exposure in the first 4 hours (AUC₀₋₄) increased in a largely dose-proportional and predictable manner, whereas terminal elimination phases were largely indistinguishable when comparing across dose groups. The FDA disagrees as the data and popPK analysis suggest that C_{max} could be less than dose proportional and there is insufficient data to support the statement that drug exposure in the first 4 hours (AUC₀₋₄) increased in a largely dose-proportional and predictable manner.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:

In the oncology setting, the starting clinical dose and dose regimen to be supported by the nonclinical program was 45 mg/m² per week, approximately 1/10 of the maximum tolerated repeat-dose in rat (Module 2.4.4.2), which was the starting dose in the first-in-human dose-finding study CA401. The CA401 study established that ABI-009 has a MTD of 100 mg/m² IV infused over 30 minutes in cycles of once weekly administration for 3 weeks followed by a one-week break. The highest non-severely toxic dose (HNSTD) and the NOAEL were not determined, as serious adverse events occurred at the lowest evaluated dose level in the oncology setting, 45 mg/m². Adverse events requiring permanent dose reductions were observed at the 10 mg/m² IV dose in the non-oncology setting in Study PAH-001 (PAH). These were low-grade persistent events in a different patient population (ie, PAH) and with a different risk profile compared to the PEComa population.

In Study PEC-001, the planned dose and schedule was 100 mg/m²/week ABI-009 administered via IV infusion over 30 (±10) minutes weekly for 2 weeks, followed by a week of rest (ie, a 21-day cycle). This schedule is different from the one evaluated in Study CA401, which administered ABI-009 weekly for 3 weeks, followed by a week of rest (ie, a 28-day cycle). In Study CA401, 19.4% of doses were missed at doses ≤100 mg/m², and most of the missing doses (83%) occurred at Day 15 of a cycle, corresponding to the third administration within a cycle. The modified schedule used for Study PEC-001 allowed the patients to have 1 week of rest during the third week, when most of the toxicities occurred on the schedule used in Study CA401. This schedule resulted in 16 ABI-009 administrations over a 6-month (24-week) period per protocol versus the 18 administrations during the same period in Study CA401 (representing a global dose intensity reduction of 11% when comparing the 2 schedules). In Study PEC-001, adverse events were tolerable and manageable, indicating that the dose and schedule is optimal.

The Applicant's Position:

The recommended therapeutic dosing regimen, studied in the registrational PEC-001 study, was 100 mg/m² IV for 2 weeks out of 3.

The FDA's Assessment:

The FDA agrees with the Applicant's position. The proposed dosing regimen of ABI-009 100 mg/m² administered as an IV infusion over 30 minutes on Days 1 and 8 of 21-day cycles presents an acceptable benefit-risk profile in the intended patient population.

6.2.2.2. Therapeutic Individualization

Data:

Pharmacokinetic drug interaction studies were not performed with ABI-009 in animals because the potential drug interactions with sirolimus are well understood in humans and are described in the approved package insert for Rapamune. Sirolimus is known to be a substrate for both CYP3A4 and P-gp and is extensively metabolized by the CYP3A4 isozyme in the intestinal wall and liver ([Rapamune Prescribing Information](#)). Potential drug interactions may occur with inducers or inhibitors of CYP3A4 and P-gp.

The labeling for the RLD indicates that drug interaction studies have not been conducted with drugs other than those described in the Rapamune Prescribing Information. The labeling for Rapamune also advises that 'Care should be exercised when drugs or other substances that are substrates and/or inhibitors or inducers of CYP3A4 are administered concomitantly with Rapamune. Co-administration of Rapamune with other known strong inhibitors or inducers of CYP3A4 and/or P-gp is not recommended. In patients in whom strong inhibitors or inducers of CYP3A4 are indicated, alternative therapeutic agents with less potential for inhibition or induction of CYP3A4 should be considered' ([Rapamune Prescribing Information](#)).

Aadi has not conducted independent clinical studies in patients with hepatic and renal impairment, nor in geriatric populations. However, in Study PEC-001, 15 of 34 enrolled patients were 65 years of age or older.

In Study PEC-001, 13/34 treated patients had at least 1 dose reduction (to 75 mg/m²) and 2/13 had 2 dose reductions (75 mg/m² then 56 mg/m²) without compromising efficacy. Four patients with a dose reduction achieved a partial response (PR) and continued responding (2/4 were ongoing at the time of data cutoff). Additionally, 6/13 patients had a confirmed SD (ie, SD ≥12 weeks), 2/6 had 2 dose reductions.

In addition to doses studied in PEC-001, in Study CA401 the starting dose was 45 mg/m², which showed evidence of activity, with 1 patient in the 45 mg/m² cohort (diagnosed with adenocarcinoma of the kidney and with bone and intrathoracic metastases) achieving a confirmed PR (target lesion reduced by 35.1% and the duration of response lasted 183 days).

The Applicant's Position:

Based on doses studied in PEC-001 and CA401, the dose reduction recommendations from 100 mg/m² are 75, 56, and 45 mg/m² to manage adverse reactions.

Because the active ingredient is the same in both the RLD and ABI-009, drug interaction information as provided in the labeling of the RLD will be adopted in the labeling for ABI-009. The recommendations for ABI-009 are presented below, based on information in the labeling for the RLD.

No formal drug interaction studies have been conducted with ABI-009; however, coadministration of ABI-009 with other known strong inhibitors of CYP3A4 and/or P-gp (such as ketoconazole, voriconazole, itraconazole, erythromycin, clarithromycin, or HIV protease inhibitors) or other known strong inducers of CYP3A4 and/or P-gp (such as rifampin or rifabutin) is not recommended. In patients in whom strong inhibitors or inducers of CYP3A4 are indicated, alternative therapeutic agents with less potential for inhibition or induction of CYP3A4 should be considered.

Care should be exercised when drugs or other substances that are substrates and/or inhibitors or inducers of CYP3A4 are administered concomitantly with ABI-009.

In patients with mild hepatic impairment, a precautionary reduction of the recommended dose to 75 mg/m² is proposed in the labeling for ABI-009. For patients with moderate hepatic impairment, a reduction to 56 mg/m² is recommended. Because no data for ABI-009 are available in patients with severe hepatic impairment, dosing of these patients with ABI-009 is not recommended.

The FDA's Assessment:

The FDA generally agrees with Applicant's position. Regarding hepatic impairment evaluation, refer to FDA's Assessment under Section 6.3.2.3.

6.2.2.3. Outstanding Issues

Data:

None.

The Applicant's Position:

None.

The FDA's Assessment:

Sirolimus is metabolized by the liver. Study **PEC-001** did not enroll patients with moderate or severe hepatic impairment (HI) and enrolled few patients with mild MI. The approved labeling will recommend that ABI-009 should be avoided in patients with severe HI and recommend a

lower dosage for patients with mild or moderate HI based on the available information from the LD. The safety profile of ABI-009 in patients with moderate or severe HI is unknown. Given the higher exposures observed with ABI-009 compared to the LD, a clinical trial is needed to determine the exposure of sirolimus in patients with HI, assess safety in this patient population, and determine an appropriate starting dosage in this patient population.

A PMR will be issued for a dedicated HI trial to evaluate the PK and safety of ABI-009 in subjects with mild, moderate, and severe HI (based on NCI criteria).

A PMR will also be issued to assess the potential QT interval prolongation risk for ABI-009 as the QT interval prolongation potential for ABI-009 has not been sufficiently evaluated given the higher exposures observed with ABI-009 compared to the LD.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

See Table 2 above.

The Applicant's Position:

An overview of the ABI-009 ADME properties, clinical pharmacokinetics, and drug-drug interaction (DDI) potential is summarized below.

Absorption, Distribution, Metabolism and Elimination (ADME)

Following IV administration, sirolimus is released immediately from the ABI-009 nanoparticles at concentrations below the limit of solubility of sirolimus (eg, 30 to 40 µg/mL in plasma) and therefore, the bioavailability of sirolimus (primarily in its bound form to human albumin) from ABI-009 entering the blood stream is 100%. Sirolimus binds with high affinity to human albumin; (b) (4)

(b) (4) Following the immediate dissolution of the ABI-009 nanoparticles during a 30-minute infusion, sirolimus is transported to the site of action in the form of soluble albumin-bound sirolimus (b) (4).

In vitro studies with ABI-009 demonstrated >99% binding to human serum albumin. Oral sirolimus from the RLD is known to be extensively bound to human plasma proteins (approximately 92%, and mainly to serum albumin [97%], α1-acid glycoprotein, and lipoproteins), and is reported to partition into red blood cells following administration of the

reference listed drug (RLD; [Rapamune Prescribing Information](#)). In a population PK analysis for ABI-009, the central volume of distribution (V_c) and peripheral volume of distribution (V_p) were 17.9 and 43.1 L, respectively.

Metabolism studies were not performed for ABI-009. Studies on the RLD have shown that sirolimus is a substrate for both CYP3A4 and P-glycoprotein (P-gp). Inducers of CYP3A4 and P-gp may decrease sirolimus concentrations, whereas inhibitors of CYP3A4 and P-gp may increase sirolimus concentrations.

Sirolimus is extensively metabolized by O-demethylation and/or hydroxylation in the intestinal wall and liver. Seven major metabolites of RLD sirolimus have been identified in whole blood, including hydroxy, demethyl, and hydroxydemethyl metabolites; some are also detectable in plasma, feces, and urine. Seco-rapamycin A, the ring-opened isomer of sirolimus, is a degradation product formed in liver microsomes and was detected in plasma after sirolimus administration in human subjects ([Leung 2006](#)). Glucuronide and sulfate conjugates of sirolimus were not present in any of the biologic matrices.

After a single dose of ^{14}C -sirolimus oral solution in healthy volunteers, the majority (91%) of radioactivity was recovered from the feces, and only a minor amount (2.2%) was excreted in urine ([Rapamune Prescribing Information](#)). These clinical study results are in good agreement with a nonclinical study of nab - ^3H -sirolimus administered as a single IV dose to male and female rats, where the majority of nab - ^3H -sirolimus-derived radioactivity (68.57% and 69.99%, respectively) was excreted in the feces between 8 and 24 hours after dosing and 8.84% and 7.73%, respectively was excreted via the urine.

Clinical Pharmacokinetics

ABI-009 PK consist of an early and immediate peak followed by a lengthy elimination phase, with a dose-proportional increase of $C_{\max}$ with increasing dose, based on data from Study CA401 and Study PEC-001. After ABI-009 IV infusion, sirolimus immediately enters a period of rapid elimination from the blood within the first few hours. As noted above, sirolimus binds with high affinity to human albumin; (b) (4)

(b) (4). This saturable binding effect is thought to drive the latter/terminal portion of elimination, which is similar across dose groups. The saturable binding is thought to result in the observed area under the concentration-time curve from time 0 to infinity ($\text{AUC}_{0-\infty}$) values across the dose ranges that are not dose proportional. The variation in clinical effect of ABI-009 across the dose ranges studied (45–150 mg/m^2) is therefore thought to be most associated with the peak concentration and exposure achieved by ABI-009 in the first 4 hours following IV infusion.

Drug-Drug Interactions

See [Section 6.2.2.2](#).

The FDA's Assessment:

The FDA agrees with Applicant's position.

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

Yes. The modeling processes used to establish the population PK model demonstrated a final two-compartment model with saturable binding. This model was then used to simulate blood sirolimus concentrations for ABI-009. The exposure-response analysis revealed that a positive relationship for the probability of response was observed for sirolimus exposure.

Data:

Data from sparse PK sampling in the registrational Phase 2 Study PEC-001, in which patients with advanced malignant PEComa were treated with ABI-009 at 100 mg/m² were combined for a population PK model with data from the Phase 1 dose-finding PK Study CA401, in which patients with advanced solid tumors were treated with ABI-009 at doses ranging from 45 mg/m² to 150 mg/m². A total of 60 patients with 709 observations from both Study CA401 and Study PEC-001 were included in the data set used for modeling. There were 22 males and 38 females, the majority of which were Caucasian. The median age of the patients at baseline was 60 years old, and median weight was 79.1 kg. In addition, blood chemistries for the patients were all within normal ranges at baseline.

For exposure-response efficacy analysis, source data provided for Study PEC-001 had a total of 31 patients in the data set. There were 6 males and 25 females; there were 17 patients below the age of 65 and 14 patient 65 years old or above. The analysis population for efficacy exposure-response consisted of all patients in Study PEC-001 with available response values for BOR, DOR, PFS, and longitudinal observations of tumor growth.

The efficacy endpoints of best overall response (BOR), DOR, PFS, and Tumor Growth were based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria.

Best Overall Response

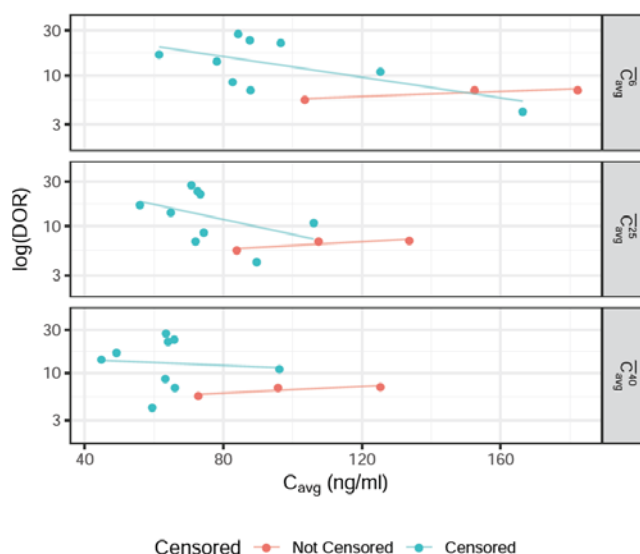
For the efficacy response analysis, three exposure metrics of the average model-predicted concentrations (C_{avg}) through Day 6 (C_{6avg}), Day 25 (C_{25avg}), and Day 40 (C_{40avg}) were used, with demographic and baseline laboratory values considered as additional covariates. Positive

relationships were shown for the probability of the BOR response for all three exposure metrics (C_{6avg} , C_{25avg} , and C_{40avg}) by age, gender, and Eastern Cooperative Oncology Group (ECOG) score.

Duration of Response

As shown in Figure 1, there were only 3 patients with non-censored values. A relationship with the log(DOR) could not be determined as most responders did not show progression and were still on treatment at the time of analysis.

Figure 1: Duration of Response to ABI-009 for Sirolimus Average Concentrations



Abbreviation: C_{avg} = average concentration; C_{6avg} = average model-predicted concentrations through Day 6; C_{25avg} = average model-predicted concentrations through Day 25; C_{40avg} = average model-predicted concentrations through Day 40.

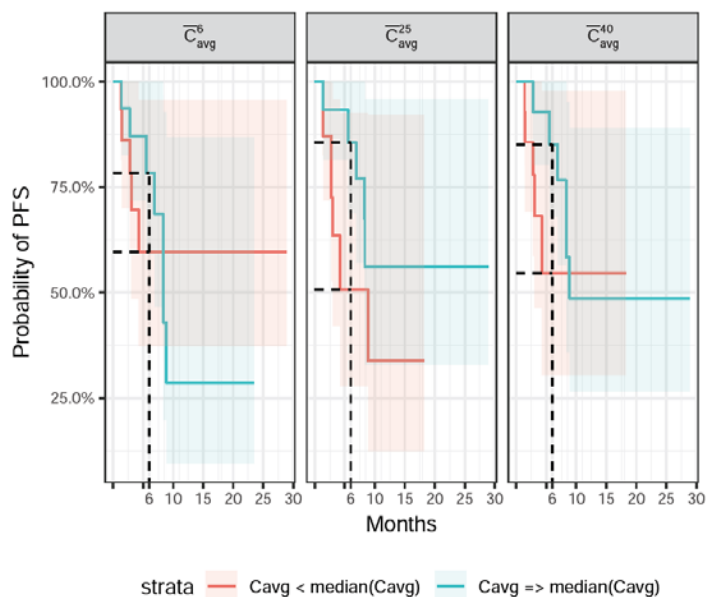
Note: The solid lines represent a linear fit for each subgroup of patients.

Source: Study ADI0101 Population PK Report, Figure 114.

Progression-Free Survival

Figure 2 suggests evidence of an increase of probability of PFS in patients with higher exposure. This observation is consistent for each candidate summary exposure statistic. This relationship is also consistent at 6 months (as represented by the dashed lines).

Figure 2: Kaplan-Meier Progression-Free Survival for Sirolimus Average Concentrations Above and Below the Median for ABI 009



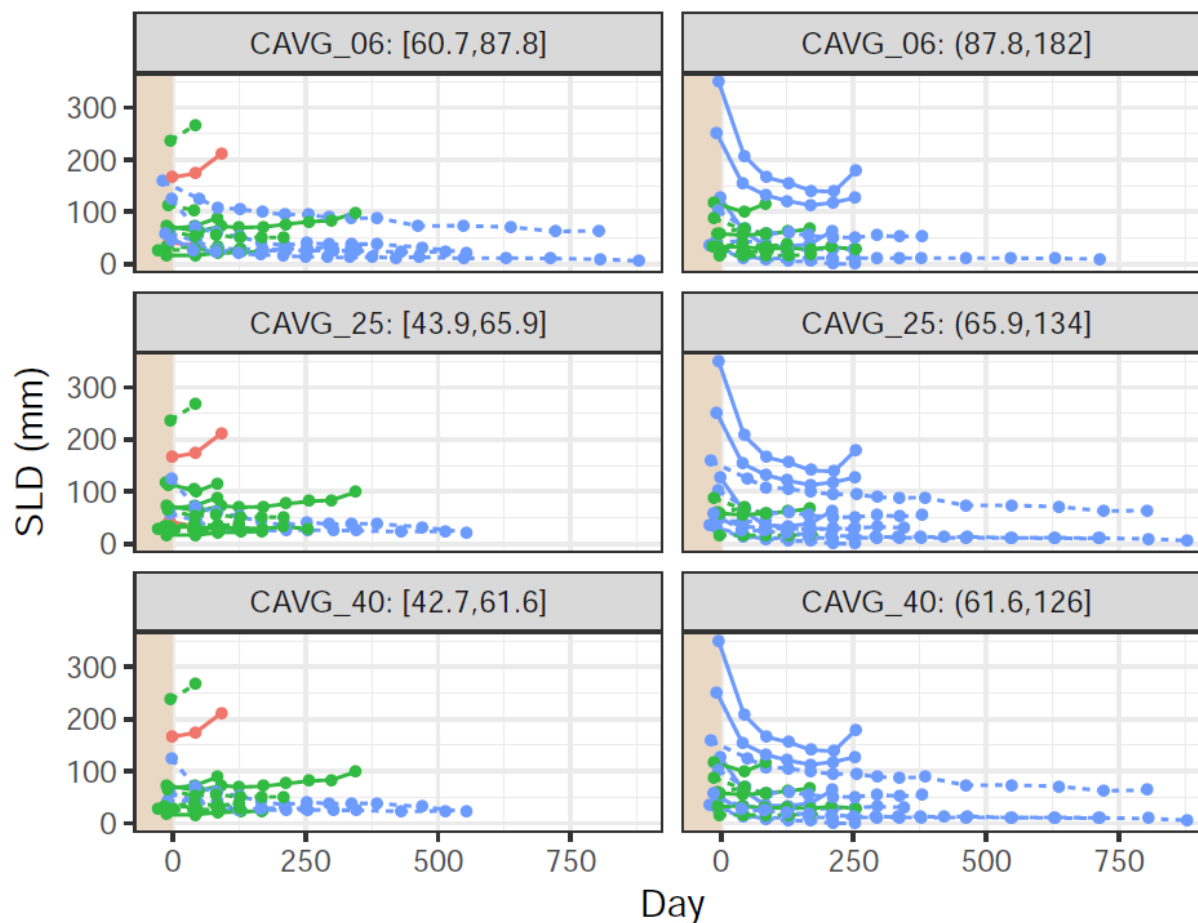
Abbreviations: C_{avg} = average blood sirolimus concentration; C_{6avg} = average model-predicted concentrations through Day 6; C_{25avg} = average model-predicted concentrations through Day 25; C_{40avg} = average model-predicted concentrations through Day 40; PFS = progression-free survival. Note: The colored lines indicate strata, the ribbons (shaded areas) represent the 95% confidence intervals, and the dashed lines represent 6-month data. Source: Study ADI0101 Population PK Report, Figure 115.

Tumor Size

As shown in Figure 3, there is no suggestive evidence of a relationship between longitudinal measurements of tumor growth and exposure. This finding is consistent within low and high exposure groups for each of the candidate summary exposure statistics.

The relationship between age and BOR may be partially confounded by baseline tumor burden, as shown in Figure 4.

Figure 3: Summary of Length of Diameters for Tumors for Lower and Upper Median Average Sirolimus Concentrations by Study Day

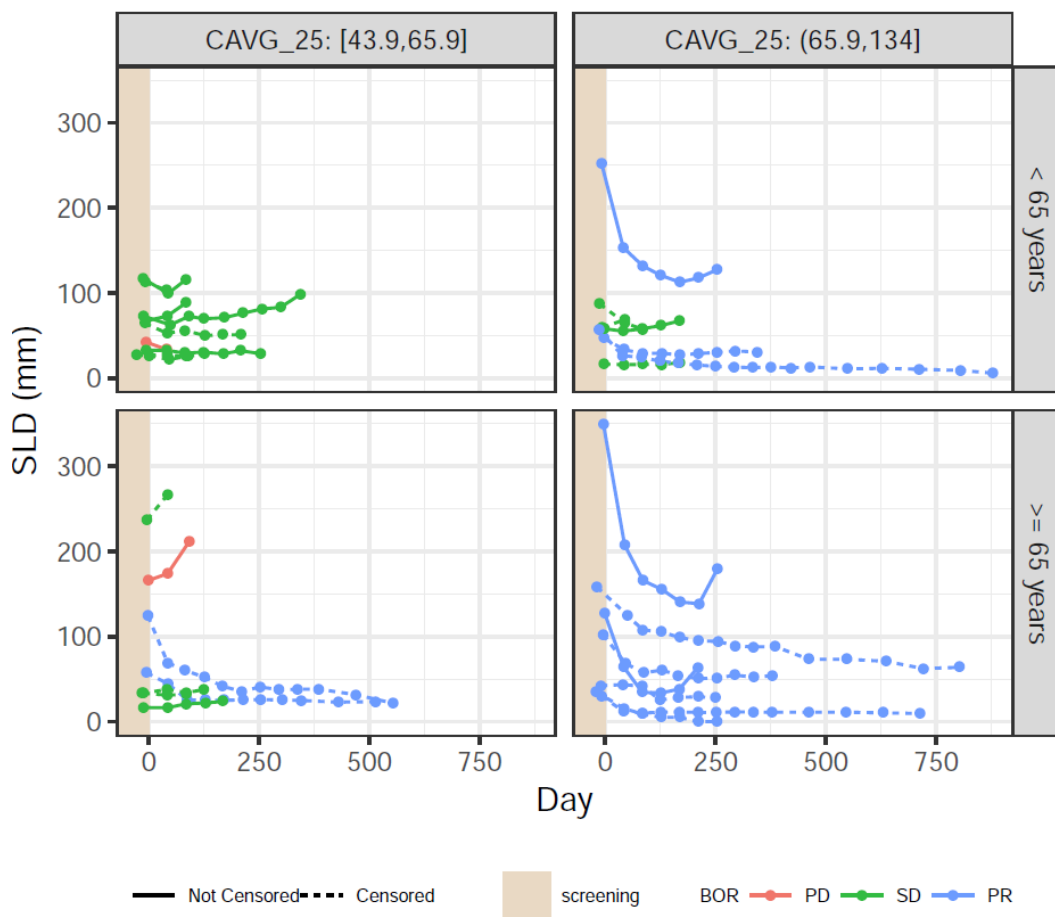


Abbreviations: BOR = best overall response; C_{6avg} = average model-predicted concentrations through Day 6; C_{25avg} = average model-predicted concentrations through Day 25; C_{40avg} = average model-predicted concentrations through Day 40; SLD = sum of lengths of tumor diameters.

Note: Lines = a patient's tumor size as a function of study days; colors = the category of BOR assigned to the patient; line type = if the patient was censored (dashed) or not censored (solid); the solid brown area = screening period.

Source: Study ADI0101 Population PK Report, Figure 116.

Figure 4: Summary of Length of Diameters by Study Day and Average Sirolimus Concentrations for Patients <65 or ≥65 Years of Age



Abbreviations: BOR = best overall response; C_{25avg} = average model-predicted concentrations through Day 25; PD = progressive disease; PR = partial response; SD = stable disease; SLD = sum of lengths of tumor diameters.

Source: Study ADI0101 Population PK Report, Figure 117.

The FDA's Assessment:

The Applicant's analysis is reasonable. However, the results need to be interpreted with caution due to the limited number of patients included in the analysis. E-R analyses based on DOR, PFS, and tumor size have limitations. Please refer to Section 19.4 for more details on E-R analysis.

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

The Applicant's Position:

Yes. The proposed ABI-009 dosing regimen—100 mg/m²/week administered via IV infusion over 30 (±10) minutes weekly for 2 weeks, followed by a week of rest (ie, a 21-day cycle)— is appropriate based on efficacy and safety results from Study PEC-001 and supported by the dose-finding first-in-human study, CA401. Study PEC-001 clinical efficacy results demonstrated a high response rate with durable responses. The emerging safety profile of ABI-009 in the treatment of patients with advanced malignant PEComa shows consistent safety signals compared with the known safety profile for Rapamune, Afinitor, or Torisel, and that seen in the first-in-human clinical study of ABI-009.

Data:

The following nonclinical, pharmacokinetic, and clinical information was used to select the dose and schedule for the registrational Study PEC-001.

Nonclinical toxicology studies of ABI-009 showed no new or unexpected toxicity compared to what is already known for sirolimus and other mTOR inhibitors, despite higher dose with ABI-009 and different route of administration. The data from a GLP toxicology study indicate that the MTD of ABI-009 with no mortality was at the nominal dose level of 90 mg/kg (78.9 mg/kg actual dose, equivalent to 473.4 mg/m² human dose) in rat. The original starting clinical dose and dose regimen to be supported by the nonclinical program was 45 mg/m² per week, approximately 1/10 of the maximum tolerated repeat-dose in rat, which was the starting dose in the first-in-human dose-finding Study CA401.

As noted in [Sections 6.2.1](#) and [6.2.2](#), it can be concluded that the pharmacokinetics within the clinically relevant dose range of 45–100 mg/m² are predictable.

The MTD was established in Study CA401 when (in the standard 3 + 3 design) there were 2 DLTs in the 150 mg/m² group (dose administered weekly for 3 weeks with a 1-week break). In Study CA401 protocol amendment 4, additional patients were enrolled and treated at a dose level of 125 mg/m² to better define the MTD, and 2 DLTs were observed at this level; thus, ABI-009 at 100 mg/m² was determined as the MTD.

Disease control (defined as SD for ≥16 weeks, and confirmed overall complete response [CR] or PR in Study CA401) was observed in all CA401 dose groups, providing preliminary evidence of efficacy in patients with advanced tumors treated with ABI-009.

In Study PEC-001, the planned dose and schedule was 100 mg/m²/week ABI-009 administered

via IV infusion over 30 (± 10) minutes weekly for 2 weeks, followed by a week of rest (ie, a 21-day cycle). This schedule is different from the one evaluated in Study CA401, which administered ABI-009 weekly for 3 weeks, followed by a week of rest (ie, a 28-day cycle). During Study CA401, 19.4% of doses were missed at doses ≤ 100 mg/m². Most of the missing doses (83%) occurred at Day 15 of a cycle, corresponding to the third administration within a cycle. The modified schedule used for Study PEC-001 allowed the patients to have 1 week of rest during the third week, when most of the toxicities occurred on the schedule used in Study CA401. This schedule resulted in 16 ABI-009 administrations over a 6-month (24-week) period per protocol versus the 18 administrations during the same period in Study CA401 (representing a global dose intensity reduction of 11% when comparing the 2 schedules).

The FDA's Assessment:

The FDA agrees with Applicant's position. The proposed dosing regimen of ABI-009 100 mg/m² administered as an IV infusion over 30 minutes on Days 1 and 8 of 21-day cycles presents an acceptable benefit-risk profile in the intended patient population.

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

The Applicant's Position:

No. Dose adjustments for ABI-009 are not recommended in older patients, based on gender or race, or in patients with renal impairment. Given that sirolimus is metabolized primarily in the liver, dose adjustments are proposed for mild and moderate hepatic impairment. Because no data for ABI-009 are available in patients with severe hepatic impairment, treatment of these patients with ABI-009 is not recommended.

Data:

Based upon data from Study PEC-001 and pooled oncology data (with or without Study PEC-001), there is no evidence that older patients (ie, those ≥ 65 years) with PEComa have a different safety profile after receiving ABI-009 than patients < 65 years, or that there is a difference in the non-PEComa study populations. This is consistent with the [Rapamune Prescribing Information](#) regarding geriatric use; therefore no dose adjustments are recommended in older patients.

Based upon data from Study PEC-001, which examined TEAEs by race, there was no evidence that race has an influence on the ABI-009 safety profile, consistent with the Rapamune Prescribing Information. Analysis of safety data by race or gender was not conducted for the pooled oncology data (with or without Study PEC-001). The race of patients enrolled was overwhelmingly Caucasian, providing too few non-Caucasian patients in the pooled data for an analysis. Study PEC-001 enrolled primarily females, while the other

oncology studies' enrollments were heavily skewed towards males; this gender imbalance, combined with the differences in study design (ie, disease conditions, concomitant antineoplastic study drugs, dosing regimens), precluded a meaningful analysis of safety data by gender. No dose adjustments are recommended for the RLD based on race or gender. Therefore, as with the RLD, there will be no recommendations for ABI-009 dose adjustments based on gender or race.

Patients with renal impairment (serum creatinine ≥ 1.5 mg/dL and/or creatinine clearance ≥ 60 mL/min) were not included in the Phase 1 Study CA401. Labeling for the RLD indicates there is minimal (2.2%) renal excretion of the drug or its metabolites in healthy volunteers (Leung 2006). Consistent with the RLD (Rapamune Prescribing Information), 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 modification is recommended for ABI-009.

The influence of hepatic impairment (bilirubin > the upper limit of normal [ULN], or to patients with serum glutamic oxaloacetic transaminase and/or serum glutamic pyruvic transaminase > $1.5 \times$ ULN) on the PK of ABI-009 has not been formally evaluated. An informal analysis was conducted on the safety profiles of patients with hepatic impairment. Aadi acknowledges the limitations of such a post-hoc analysis in the limited number of patients and considers this assessment exploratory.

No patients enrolled in Study PEC-001 fell into the moderate or severe categories of hepatic impairment. A summary of safety events in the mild hepatically impaired patients in Study PEC-001 demonstrates that patients with mild hepatic impairment experienced TEAEs consistent with the safety profile of sirolimus, managed successfully with dose delays and in some cases dose reductions, similar to how patients without hepatic impairment were managed. Instructions on managing TEAEs consistent with the protocol are provided in the proposed Prescribing Information in Section 2. Dosing and Administration. No conclusive differences in the safety profile of these patients is noted from PEComa patients without hepatic impairment, although Aadi acknowledges the limitation in sample size.

Because no data for ABI-009 are available in patients with severe hepatic impairment, and sirolimus is metabolized primarily in the liver, dosing of these patients with ABI-009 is not recommended. Section 12.3 Pharmacokinetics in the proposed ABI-009 Prescribing Information for hepatic impairment follows the FDA Guidance on Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling: (US Food and Drug Administration 2003), Option 3 for extensive (>20 percent) hepatic elimination, wide therapeutic range.

The FDA's Assessment:

In response to FDA's information request, the Applicant provided the results of a data analysis

comparing the clearance and observed steady-state average ABI-009 concentrations based on the following subgroups: hepatic impairment (HI, based on NCI criteria), renal impairment (RI), geriatric vs. non-geriatric age, sex, and race (**Table 7**):

Table 7: Applicant analysis on covariate subgroups of intrinsic factors (reported as mean and 95% CI)

Subgroup	Mean Clearance (L/h) (95% CI)	Mean Observed steady state average ABI-009 concentration ^a (ng/mL) (95% CI)
Hepatic Impairment^b		
Normal (n=29) AST ≤ ULN TB < ULN	116 (103-129.5)	106 (94.9-118)
Mild (n=5) AST > ULN TB ≤ 1.5 x ULN	104 (67.9-141)	121 (73-169)
Moderate (n=0) TB > 1.5-3.0 x ULN	N/A	N/A

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Severe (n=0) TB > 3.0-10. x ULN	N/A	N/A
Renal Impairment^c		
Normal (n=15) > 90 mL/min	111 (88.2-133.8)	116 (95.3-137)
Mild (n=13) 60 – 89 mL/min	115 (97.1-132.5)	107 (88.7-124)
Moderate (n=6) 30 – 59 mL/min	123 (96.5-149.6)	95.5 (78-113)
Severe (n=0) 15 – 29 mL/min	N/A	N/A
Age		
Geriatric (n=13) < 65 years	119 (104-133.7)	103 (89.5-117)
Non-Geriatric (n=21) > 65 years	112 (94.5-129.7)	112 (95.7-129)
Sex		
Male (N=6)	113 (76.1-150.4)	115 (73-157)
Female (n=28)	115 (102-128.1)	107 (95.6-119)
Race		
White (n=22)	115 (101-130.1)	109 (94.1-124)
Non-white (n=12)	113.1 (89.8-136.4)	108 (89.4-128)

Abbreviations: AST, aspartate aminotransferase; CI, confidence interval; N/A, not applicable (no patients in this subgroup); TB, total bilirubin; ULN, upper limit of normal

^aDerived as AUC_{0-∞}/tau

^bBased on NCI criteria for hepatic impairment

^cBased on Cockcroft-Gault formula

Source: Table 1 from Applicant's Response to FDA information request (dated 9-17-21).

The FDA agrees with the Applicant's position that there are no clinically significant differences in the PK of ABI-009 based on age (18 to 78 years), sex, and mild or moderate RI. However, the effects of race (non-white races), severe RI, moderate and severe HI on the PK of ABI-009 are unknown.

The exposures in patients with mild HI appeared generally comparable to those with normal hepatic function; however the sample size is limited (n=5 with mild HI). There is no data on the use of ABI-009 in patients with moderate or severe hepatic impairment. In consideration of the current treatment landscape for patients with advanced PEComa, the FDA agrees with the following dosage modifications proposed by the Applicant (despite the limited HI data) based on the recommendation in the RLD:

- **Severe HI:** avoid use
- **Moderate HI:** reduce dose to 56 mg/m²
- **Mild HI:** reduce dose to 75 mg/m²

Patients with HI should be closely monitored for adverse reactions and follow the prescribed

labeling for dose modifications for adverse reactions.

While the FDA agrees with the proposed dosage modifications for patients with HI, the FDA is also requiring that the Applicant conduct a dedicated HI trial as a PMR to evaluate the PK and safety of Fyarro in subjects with mild, moderate, and severe HI (based on NCI criteria). The decision to issue a PMR for HI trial was based on the following factors:

- Lack of clinical data in patients with moderate or severe HI
- Non-linear PK of ABI-009 above a dose of 100 mg/m²
- The recommended dose of 100 mg/m² is near the MTD
- The HI data from Rapamune cannot be relied upon due to significantly higher exposures achieved following administration for ABI-009 than that achieved following administration of Rapamune and differences between HI classification systems (Rapamune used Child-Pugh criteria, ABI-009 will be using NCI criteria)

Note that due to the limited elimination of sirolimus in the urine (2%), evaluation of the effect of severe renal impairment is not needed.

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

The Applicant's Position:

No formal drug interaction studies have been conducted with ABI-009. However, co-administration of ABI-009 with other known strong inhibitors of CYP3A4 and/or P-gp (such as ketoconazole, voriconazole, itraconazole, erythromycin, clarithromycin, or HIV protease inhibitors) or other known strong inducers of CYP3A4 and/or P-gp (such as rifampin or rifabutin) is not recommended. In patients in whom strong inhibitors or inducers of CYP3A4 are indicated, alternative therapeutic agents with less potential for inhibition or induction of CYP3A4 should be considered.

Data:

Pharmacokinetic drug interaction studies were not performed with ABI-009 in animals because the potential drug interactions with sirolimus are well understood in humans and are described in the approved package insert for Rapamune. Sirolimus is known to be a substrate for both CYP3A4 and P-gp and is extensively metabolized by the CYP3A4 isozyme in the intestinal wall and liver ([Rapamune Prescribing Information](#)). Potential drug interactions may occur with inducers or inhibitors of CYP3A4 and P-gp.

The PK interaction between sirolimus and concomitantly administered drugs is discussed below. The labeling for the RLD indicates that drug interaction studies have not been conducted with drugs other than those described in the sections below. The labeling for

Rapamune also advises that ‘Care should be exercised when drugs or other substances that are substrates and/or inhibitors or inducers of CYP3A4 are administered concomitantly with Rapamune. Co-administration of Rapamune with other known strong inhibitors or inducers of CYP3A4 and/or P-gp is not recommended. In patients in whom strong inhibitors or inducers of CYP3A4 are indicated, alternative therapeutic agents with less potential for inhibition or induction of CYP3A4 should be considered’ ([Rapamune Prescribing Information](#)).

Because the active ingredient is the same in both the RLD and ABI-009, drug interaction information as provided in the labeling of the RLD will be adopted in the labeling for ABI-009.

Sirolimus in ABI-009 is known to be a substrate for both CYP3A4 and P-gp. Inducers of CYP3A4 and P-gp may decrease sirolimus concentrations whereas inhibitors of CYP3A4 and P-gp may increase sirolimus concentrations. In patients in whom strong inhibitors or inducers of CYP3A4 are indicated, alternative therapeutic agents with less potential for inhibition or induction of CYP3A4 should be considered.

Care should be exercised when drugs or other substances that are substrates and/or inhibitors or inducers of CYP3A4 are administered concomitantly with ABI-009.

Drugs Which May be Co-Administered Without Dose Adjustment

Clinically significant PK drug-drug interactions with sirolimus were not observed in studies of drugs listed below. Therefore, ABI-009 and these drugs may be co-administered without dose adjustments ([Rapamune Prescribing Information](#), [Zimmerman 2004](#)).

- Acyclovir
- Atorvastatin
- Digoxin
- Glyburide
- Nifedipine
- Norgestrel/ethinyl estradiol (Lo/Ovral®)
- Prednisolone
- Sulfamethoxazole/trimethoprim (Bactrim®)

Other Drug-Food Interactions

Grapefruit juice reduces CYP3A4-mediated drug metabolism ([Cohen 2012](#)). The following information is provided in the labeling for the RLD: ‘Grapefruit juice must not be taken with or used for dilution of Rapamune’. Therefore, grapefruit juice must not be taken with ABI-009 treatment.

Drug-Herb Interactions

St. John’s Wort (*Hypericum perforatum*) induces CYP3A4 and P-gp ([Mannel 2004](#)). The following information is provided in the labeling for the RLD: ‘since sirolimus is a substrate for both cytochrome CYP3A4 and P-gp, there is the potential that the use of

St. John's Wort in patients receiving Rapamune could result in reduced sirolimus concentrations.

The FDA's Assessment:

FDA generally agrees with Applicant's position. Regarding DDIs, the FDA agrees with the following dosage modifications:

- **Strong CYP3A4 inhibitor and/or P-gp inhibitors:** avoid use
- **Strong CYP3A inducers and/or P-gp inducers:** avoid use
- **Moderate or weak CYP3A4 inhibitors:** reduce dose to 56 mg/m²

Note that the use of moderate or weak CYP3A4 inducers with ABI-009 may result in decreased efficacy.

Refer to final labeling regarding DDIs and associated management strategies.

X

X

Wenchi (Vicky) Hsu, Ph.D.
Primary Reviewer

Hong Zhao, Ph.D.
Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

The Applicant's Position:

Data:

The clinical development program for ABI-009 spans a number of oncology and non-oncology indications in studies sponsored by Aadi as well as investigator-sponsored studies. The primary studies supporting the efficacy and safety of ABI-009 in the NDA are registrational Phase 2 Study PEC-001 in the proposed indication for approval, advanced malignant PEComa, and Phase 1 dose-finding Study CA401 in metastatic solid tumors, which provides supporting information. As agreed in the 10 December 2018 Type C Meeting with the FDA (Module 1.6.3), the studies included in the integrated summary of safety (Module 2.7.4 Table 3) were limited to

those studies where ABI-009 was administered via IV infusion, and to studies sponsored by Aadi.

The status of each of these studies is summarized in [Table 8](#), which includes four oncology studies:

- Study PEC-001, a Phase 2 open-label study to assess clinical safety and efficacy of single-agent ABI-009 in patients with advanced malignant (either metastatic or locally advanced disease and ineligible for surgery) PEComa. This study has completed enrollment, with the last patient enrolled on 12 November 2018 and the preplanned primary analysis conducted when all patients had an opportunity to be treated for 6 months. At the time of the 22 May 2019 data cut-off for the analysis, 10 patients were still on treatment and the study is still ongoing.
- Study CA401, a completed first-in-human Phase 1 open-label, dose-finding study to assess the safety, tolerability, and PK of single-agent ABI-009 in patients with metastatic solid tumors. The last patient last visit occurred on 04 June 2011.
- Study GBM-007, a Phase 2 open-label study of the safety and efficacy of ABI-009 as a single agent or in combination with standard of care in patients with recurrent high-grade glioma, and in patients with newly diagnosed glioblastoma multiforme (GBM). This study is ongoing and currently enrolling patients. At the time of the 30 April 2019 data cut-off, 9 patients were treated.
- Study COLO-007, a Phase 1/2 multi-center study to identify the recommended Phase 2 dose (RP2D) and determine the efficacy and safety profile of ABI-009 administered as first-line therapy in combination with modified regimen of 5 fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) and bevacizumab in patients with advanced or metastatic colorectal cancer. This study is ongoing and currently enrolling patients. At the time of the 30 April 2019 data cut-off, 7 patients were treated.

Summary safety data is also provided from a non-oncology clinical study in PAH:

- Study PAH-001, a Phase 1 study to evaluate the safety and efficacy of ABI-009 in patients with severe progressive PAH on maximal currently available standard of care therapy. This study is ongoing and currently enrolling patients. At the time of the 30 April 2019 data cut-off, 9 patients were enrolled on study.

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Table 8: Completed and Ongoing Clinical Studies Included in NDA

Trial Identity	NCT Number	Trial Design	Regimen / Schedule / Route	Study Endpoints	Treatment Duration / Follow-up	Number of Patients Enrolled	Study Population	Number of Centers & Countries
PEC-001	NCT02494570	Phase 2, open-label study to determine efficacy and safety in patients with advanced malignant PEComa (no control arm)	ABI-009 at 100 mg/m ² qw2/3 (30-minute IV infusion)	ORR by 6 months as determined by RECIST v1.1 (primary endpoint). Secondary endpoints are DOR, PFS, OS, safety/ tolerability, as well as exploratory pharmacodynamics using various tumor biomarkers.	Treatment until disease progression or unacceptable toxicity	35 enrolled, 34 treated, 31 efficacy evaluable; data cut off 22-May-2019	Patients with advanced malignant PEComa	9 centers; United States
CA401	NCT00635284	Phase 1, open-label dose-finding study to determine MTD, PK, safety in patients with metastatic solid tumor (no control arm)	ABI-009 at 45–150 mg/m ² qw3/4 (30-minute IV infusion)	MTD and DLT of ABI-009; characterize the toxicities of ABI-009; determine the PK parameters when given on a weekly schedule.	Treatment until disease progression or unacceptable toxicity	27 enrolled, 26 treated; data cut-off 06-Oct-2011	Patients with metastatic solid tumor	2 centers; United States
GBM-007	NCT03463265	Phase 2, open-label study to determine efficacy and safety of single agent ABI-009 or in combination, in naïve patients with recurrent high-grade glioma (Arm A) and patients with newly diagnosed glioblastoma (Arm B) (no control arm)	<u>Arm A</u> ABI-009 ABI-009 + TMZ ABI-009 + BEV ABI-009 + CCNU ABI-009 + MRZ	<u>Arm A</u> Investigate the safety and efficacy of ABI-009 administered as single agent or in combination with TMZ, or BEV, or CCNU.	Treatment until disease progression or unacceptable toxicity	Up to 114 planned; 10 enrolled, 9 treated; data cut-off 30-Apr-2019 (No patients enrolled in Arm B at the time of data cut-off)	<u>Arm A</u> Naïve patients with recurrent high-grade glioma (WHO Grade III or IV)	3 centers; United States

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Trial Identity	NCT Number	Trial Design	Regimen / Schedule / Route	Study Endpoints	Treatment Duration / Follow-up	Number of Patients Enrolled	Study Population	Number of Centers & Countries
			<u>ABI-009 Dose:</u> Single agent ABI-009 at 100 mg/m², and at 60 mg/m² as a combination agent <u>ABI-009 Schedule:</u> • qw3/4 with TMZ, BEV, and MRZ • qw2/3 with CCNU (30-minute IV infusion) <u>Arm B</u> ABI-009 at 60 mg/m² weekly for 4 weeks, then ABI-009 at 60 mg/m² qw3/4 + TMZ + radiation therapy (30-minute IV infusion)	<u>Arm B</u> Evaluate the efficacy of ABI 009 in patients with newly diagnosed glioblastoma who have enhancing tumors after surgery and have not previously received any local or systemic therapy.			<u>Arm B</u> Patients with newly diagnosed glioblastoma	

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FYARRO (sirolimus protein-bound particles for injectable suspension) (albumin-bound)

Trial Identity	NCT Number	Trial Design	Regimen / Schedule / Route	Study Endpoints	Treatment Duration / Follow-up	Number of Patients Enrolled	Study Population	Number of Centers & Countries
COLO-007	NCT03439462	Phase 1/2, open-label dose-finding study to determine RP2D, determine efficacy and safety of combination in patients with metastatic colorectal cancer (no control arm)	ABI-009 at 20–30 mg/m ² at qw3/4 or every 2 weeks (30-minute IV infusion) + mFOLFOX6 + BEV	MTD and DLT of ABI-009; DCR, PFS, ORR, progression free rate at 6 months, safety and tolerability, exploratory biomarkers.	Treatment until disease progression or unacceptable toxicity	Up to 55 planned; 8 enrolled, 7 treated; data cut-off 30-Apr-2019	Patients with metastatic colorectal cancer, for first-line treatment	6 centers; United States
PAH-001	NCT02587325	Phase 1/1b, open-label dose-finding study to determine MTD, DLT, RP2D, in patients with severe PAH WHO Functional Class II or III (no control arm)	ABI-009 at 1–10 mg/m ² (short ~3-minute infusion) weekly for 16 weeks + standard of care therapy Optional up to 32 weeks of weekly maintenance + standard of care	MTD and DLT of ABI-009; secondary endpoints include various pulmonary function measurements.	16 weeks + optional 32 weeks of maintenance	Up to 18 planned; 9 enrolled and treated; data cut-off 30-Apr-2019	Patients with severe PAH WHO Functional Class II or III	6 centers; United States

Abbreviations: BEV = bevacizumab; CCNU = lomustine; DCR = disease control rate; DLT = dose-limiting toxicity; DOR = duration of response; IV = intravenous; mFOLFOX6 = modified regimen of 5-fluorouracil, leucovorin, and oxaliplatin; MRZ = marizomib; MTD = maximum tolerated dose; ORR = overall response rate; OS = overall survival; PAH = pulmonary arterial hypertension; PEComa = perivascular epithelioid cell tumor; PFS = progression-free survival; PK = pharmacokinetic; qw2/3 = weekly for 2 weeks, followed by a week of rest; qw3/4 = weekly for 3 weeks, followed by a week of rest; RP2D = recommended Phase 2 dose; TMZ = temozolomide; WHO = World Health Organization.

The Applicant's Position:

The clinical studies listed above are sufficient to support the application for the orphan indication of advanced malignant PEComa.

The evidence for the efficacy of ABI-009 100 mg/m² administered as an IV infusion over 30 minutes on Days 1 and 8 of a 21-day cycle for the treatment of advanced (metastatic or locally advanced) malignant PEComa is provided primarily by a single arm Phase 2 study (Study PEC-001), supported by a Phase 1 study in patients with metastatic solid tumors (Study CA401). Efficacy results for each study are presented separately and considered inappropriate for pooling due to differences in patient populations and dosing regimens.

The safety and tolerability of ABI-009 have been evaluated in 4 completed or ongoing Aadi-sponsored, oncology clinical trials in which ABI-009 was administered by IV infusion (further details on these studies are provided in Module 2.5 Section 1.3). As agreed in the 10 December 2018 Type C Meeting with the FDA (Module 1.6.3), the studies planned for inclusion in the integrated summary of safety were limited to those studies where ABI-009 was administered via IV infusion, and to studies sponsored by Aadi. In accordance with agreements reached in the above-mentioned meeting, Module 2.7.4 Summary of Clinical Safety presents the integrated safety summary required by the regulations (21CFR 314.50(d)(5)(vi)(a).

The Agency requested a side-by-side comparison of results from Study PEC-001 and the pooled oncology data in which ABI-009 was administered intravenously (solid tumors, colorectal cancer, glioblastoma), and a side-by-side comparison of the pooled oncology safety data with safety data from patients enrolled in Aadi-sponsored non-oncology protocols (pulmonary arterial hypertension) in which ABI-009 was administered intravenously. These contain the columns of greatest relevance (Study PEC-001 alone [n = 34], total oncology pool [N = 76; with Study CA401 (n = 26), Study GBM-007 (n = 9), and Study COLO-007 (n = 7) in addition to Study PEC-001], the oncology pool without Study PEC-001 [n = 42], and the non-oncology Study PAH-001 [N = 9]). The supportive tables and listings from this integrated analysis are provided in Module 5.3.5.3.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the clinical studies included in this application. Refer to Section 8.2 for a description of the safety population considered in FDA's review.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

The Applicant's Position:

The efficacy evaluation for this submission is based primarily on the efficacy data from the registration Study PEC-001 (AMPECT).

The FDA's Assessment:

The FDA agrees with the Applicant's position.

8.1.1. Study PEC-001 (AMPECT)

The Applicant's Description:

Trial Design

Evidence for the efficacy of ABI-009 100 mg/m² administered as an IV infusion over 30 minutes on Days 1 and 8 of a 21-day cycle for the treatment of advanced (either metastatic or locally advanced disease for which patients are not eligible for surgery, and for which there are currently no approved therapies) malignant PEComa is provided by a registrational, Phase 2 prospective, single-arm, open-label, multi-center study to assess clinical safety and efficacy of ABI-009 in patients with malignant PEComa (Study PEC-001).

Investigators and Study Centers

The study was conducted in the US by the following investigators:

Andrew J. Wagner, MD, PHD	Dana-Farber Cancer Institute, Boston, MA
Mark Dickson, MD	Memorial Sloan-Kettering, New York, NY
Erlinda Maria Gordon, MD	Sarcoma Oncology Research Center, Santa Monica, CA
Vinod Ravi, MD	University of Texas, MD Anderson Cancer Center, Houston, TX
Rashmi Chugh, MD	University of Michigan, Ann Arbor, MI
Richard F. Riedel, MD	Duke University Medical Center/Duke Cancer Center, Durham, NC
Kristen N. Ganjoo, MD	Stanford Medicine, Stanford, CA
Lee D. Cranmer, MD, PhD	Seattle Cancer Care Alliance, Seattle, WA
Brian Van Tine, MD, PhD	Washington Univ. School of Medicine/Siteman Cancer Center, St. Louis, MO

Key Inclusion/Exclusion Criteria

Patients with advanced (metastatic or locally advanced) malignant PEComa, who had not been previously treated with an mTOR inhibitor were eligible for this study. Patients were required to have measurable disease (as determined by RECIST v1.1 guidelines).

Methodology

Following baseline evaluations, eligible patients received ABI-009 100 mg/m² IV infusion (over 30 minutes) weekly for 2 weeks followed by a week of rest (21-day cycles).

Imaging and efficacy assessments were performed at the following frequency:

- ≤4 weeks prior to Cycle 1 Day 1 (during screening)
- every 6 weeks (±3 days) after Day 1 of every treatment cycle for the first 1 year
- every 12 weeks (±7 days) thereafter until disease progression

The end of treatment (EOT) visit computed tomography/magnetic resonance imaging (CT/MRI) was performed only for those patients who discontinued treatment for a reason other than disease progression.

Determination of disease progression for clinical management of patients on study was assessed at the local site. If an initial observation of objective response (CR or PR) is made, a confirmation scan was to be performed 6 weeks after initial observation. If CR or PR was confirmed, the event was considered to occur on the date that the initial observation was made. Scans were submitted to an independent central imaging laboratory for assessment by RECIST v1.1. Details regarding independent central radiology review are included within the Imaging Review Charter in Appendix 16.1.13.

Throughout the study, patients were routinely assessed for toxicities, the need for dose modifications, and response assessments. Patients remained on treatment until they experienced PD or unacceptable toxicity, withdrew consent, started another anticancer therapy, or (in the opinion of the treating physician) it was no longer in the patient's best interest to continue on treatment, at which time EOT evaluations were completed.

Patients who discontinued treatment completed EOT evaluations and entered the on-study Follow-up period. Post-treatment survival time and any subsequent anticancer therapy information status was monitored in the Follow-up period approximately every 12 (±3) weeks from the EOT visit or more frequently as needed, until death, withdrawal of consent, or study closure, whichever was earliest. This evaluation could be by record review and/or telephone contact.

Selection of Dose

The MTD and DLTs of ABI-009 were previously evaluated in patients with advanced solid tumors (Study CA401). Based on that study, the dose of ABI-009 was selected to be 100 mg/m², administered as once-weekly 30 (±10) minute IV infusions for 2 weeks followed by a week of rest (Days 1 and 8 of a 21-day cycle).

Study Administrative Structure

Table 9: Study Administrative Structure

Study Administrative Structure	
Sponsor	Aadi Bioscience, Inc. 17383 Sunset Boulevard Suite A250 Pacific Palisades, CA 90272 USA
Clinical Supplies Managed by	(b) (4)
Clinical Supplies Manufactured by	
Data Management	
Bioanalytical Analysis	
Monitored by	
Medical Monitor	

Study Administrative Structure		
Medical Writer(s)		(b) (4)

Study Endpoints

The primary endpoint was ORR by 6 months determined by independent central readers using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Secondary efficacy endpoints were DOR, PFS, and OS, as well as pharmacodynamics using tumor biomarkers. Exploratory endpoints included ORR from the time of study treatment initiation until disease progression as of the data cut-off (determined by both the independent central readers' and Investigators' RECIST assessments); DOR and PFS as determined by Investigator evaluation; and the disease control rate (DCR; defined as the percentage of patients with a confirmed response or with SD of ≥ 12 weeks' duration determined by both the independent central readers' and Investigators' RECIST assessments).

Statistical Analysis Plan and Amendments

The planned analysis is documented in the Statistical Analysis Plan (SAP) v4.0, dated 15 February 2019 (Study PEC-001 CSR Appendix 16.1.9). Previous versions of the SAP (all prior to database lock and data analysis) are included within the CSR appendix, along with descriptions of the changes between versions.

Analysis Populations

The Full Analysis Set (FAS) consisted of all enrolled patients who received any amount of ABI-009. The Safety Analysis Set was identical to the FAS. This analysis set was used for patient disposition, exposure, and safety analyses.

The Efficacy Analysis Set included all enrolled patients with measurable tumor per RECIST v1.1 at baseline who received at least 1 dose of ABI-009 and who have a confirmed diagnosis of PECOma. This analysis set was used for all primary and secondary efficacy analyses.

The Per Protocol (PP) Analysis Set included all enrolled patients who did not have any prospectively defined major protocol deviation. A prospectively defined list of important protocol violations or deviations categorized as major or minor deviations has been compiled and was finalized prior to the clinical database lock. The PP Analysis Set

was defined when the list of major protocol and minor protocol violations or deviations was finalized. A sensitivity analysis of the primary and secondary efficacy endpoints (DOR, PFS) as well as time to response (TTR), was performed using the PP Analysis Set.

The PK Analysis Set included all enrolled patients who received any amount of ABI-009 and had an adequate number of concentration determinations for PK calculations.

Power and Sample Size

Sample size estimation was based on the primary efficacy endpoint, confirmed ORR by 6 months: proportion of patients who achieve an objective response.

The sample size was targeted to be approximately 30 patients in order to provide a reasonably precise estimate of the true ORR by 6 months. Assuming an observed ORR of 30% and a sample size of 30, the lower bound of the 95% CI for the estimated ORR by 6 months would exclude values less than 14.7%. A sample size of 30 patients is expected to result in the half width of the 95% CI for the estimated ORR by 6 months of no more than 18.7%.

Efficacy Analyses

The primary analysis for this study was planned after all patients had an opportunity to be treated for 6 months. Patients who were still active at the time of the primary analysis could continue on study until disease progression or medication intolerance was observed.

Primary Endpoint: Overall Response Rate by 6 Months

The Efficacy Analysis Set was used in the analysis of the primary efficacy endpoint. Patients without response assessment after baseline were accounted for in the denominator when calculating the response rate (ie, these patients were counted as patients without response). The number and proportion of patients with ORR by 6 months was reported together with exact binomial 95% CI using Clopper and Pearson procedure ([Clopper 1934](#)).

Sensitivity analyses of the primary endpoint was performed using the PP Analysis Set.

In addition to the presentation of all data by metastatic versus locally advanced disease and ineligible for surgery, if there were sufficient numbers of patients (at least $n = 5$) by subgroups, ORR and its 95% CI could be reported by subgroups (sex, age at enrollment [<65 vs 65 years and over], baseline ECOG [0 vs 1], median time lapsed from initial diagnosis to treatment, and prior treatment for PEComa [naïve vs treated]).

Sensitivity Analysis of the Primary Endpoint

In addition to the analysis of the main primary efficacy endpoint using the Efficacy Analysis Set, the primary efficacy endpoint was analyzed using the PP Analysis Set as a sensitivity analysis.

Secondary Efficacy Endpoints

The secondary efficacy endpoints included DOR, median PFS, PFS rate at 6 months (PFS6), and median OS.

Only patients achieving an objective confirmed response were included in the analysis of DOR. Duration of response was defined as the time from when criteria of response (CR or PR) was first met until the first observation of disease progression per RECIST v1.1 or death due to any cause. Patients without these events were censored at their last evaluable tumor assessment. Duration of response (in months) was calculated as the difference between date of confirmed disease progression or death (or date of last evaluable tumor assessments for those with no events) minus date of confirmed CR or PR plus 1 with difference divided by 30.4. Time to response was analyzed and defined as time between initial report of CR/PR and time of first dose + 1 divided by 30.4.

Progression-free survival was defined as the time from the first dose date to the first observation of a disease progression or death due to any cause. If a patient had not progressed or died by the data cut-off date, the PFS time was censored at the time of the last evaluable assessment. Time to disease progression (in months) was calculated as the difference between date of confirmed disease progression (or date of death, whichever came first) or date of last evaluable assessment minus first dose date + 1 with difference divided by 30.4.

Progression-free survival rate at 6 months was defined the same way as PFS, except all patients who had not progressed within the 6-month interval after first dose were censored.

The number of treatment cycles at which best response occurred was also summarized descriptively.

Overall survival was defined as the time from the first dose date to the date of death due to any cause + 1 with difference divided by 30.4. If a patient was lost to follow-up before the data cut-off date or still alive by the data cut-off date the OS time was censored at the last contact date. The last contact date was the last documented visit date or the date of the last phone contact when the patient was known to be alive.

Exploratory Efficacy Analyses

The independently-assessed ORR was also reported including any response that occurred during the study (ie, responses that occurred from first dose through data

cut-off, rather than during the first 6 months of treatment per the primary endpoint).

The investigator-assessed efficacy endpoint of ORR by 6 months, secondary efficacy endpoints of DOR, and PFS, and exploratory post-hoc efficacy endpoint of disease control rate (DCR; defined as the percentage of patients with a confirmed response or with SD of ≥ 12 weeks' duration), as well as TTR, were reported and their exact 95% CIs were reported for the Efficacy Analysis Set.

The analysis of other exploratory endpoints including results of molecular analysis of cell-free deoxyribonucleic acid (DNA) assay, and tumor biopsy results from exome sequencing, fluorescence in situ hybridization (FISH), and immunohistochemistry will be analyzed and reported separately by the assay/tumor biopsy vendor. However, the presence/absence of biomarkers based on blood samples was presented by visit. In addition, the presence/absence of biomarkers could be cross-tabulated with patients' tumor responses.

Safety Analyses

Treatment Exposure

Exposure to ABI-009 as recorded in each patient's drug administration form was summarized by cycles and type of disease. The summary included the number of cycles, total planned and actual cumulative dose, duration of dosing, and dose relative intensity.

The total actual (planned) cumulative dose was calculated as the sum of the actual (planned) doses administered divided by the patient's body surface area (BSA). Duration of dosing was calculated as the average dosing per cycle; this was 30 minutes per dosing if there was no interruption. Dose relative intensity was calculated as the ratio of the cumulative actual total dose averaged per week divided by the cumulative planned total dose averaged per week. The counts and percentages of patients who had dosing interrupted or discontinued ABI-009 permanently, and reasons for drug discontinuation, were also reported.

Drug exposure by cycle and type of disease were listed.

Treatment-Emergent Adverse Events

Adverse event summary tables were produced are provided in Module 2.7.4.

The treated population (Safety Analysis Set) was the analysis set for all safety analyses. The Investigator was to assess all AEs and serious adverse events (SAEs) and record each on the appropriate case report form or Serious Adverse Event Report Form. Treatment-emergent adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA version 21.0) and grouped by their System Organ Class

(SOC) and Preferred Term (PT). The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 was used to grade severity of AEs and laboratory toxicities.

Adverse events of special interest (AESIs) were preidentified at the start of the study based on class effects of mTOR inhibitors 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 (eg, mucositis is treated as a group term that includes aphthous ulcer, mouth ulceration, esophageal ulcer, and stomatitis). These AESIs are listed in Table 5 of the protocol (Study PEC-001 CSR Appendix 16.1.1) and include NCI CTCAE toxicity grading. Other AESIs include those listed in Section 7.2.2 of the protocol (Study PEC-001 CSR Appendix 16.1.1), and in Study PEC-001 CSR Appendix 16.2.7, Listing 16.2.7.8.

Laboratory Assessments

Laboratory test results (including hematology, coagulation, serum chemistry, urinalysis, thyroid function tests, human immunodeficiency virus (HIV), hepatitis tests, and fasting lipid tests) and abnormal laboratory values were presented in data listings.

Summaries of actual values and changes from baseline were presented for each assessment time point, beginning with the Screening visit. Shift tables summarizing the counts and percentages of patients who were normal at baseline with their worst post-baseline value or worst toxicity grade were also displayed.

Vital Signs

Vital signs (eg, blood pressure, pulse, respiration rate, temperature) together with weight and BSA were collected at screening, and Day 1 and Day 8 of every treatment cycle and at the EOT visit. Summaries of actual values and changes from baseline will be presented for each assessment time point, beginning with Cycle 1 Day 1.

Vital signs deemed abnormal were listed.

Weight changes from baseline were graphically presented and listed.

Physical Examination

Physical examination of body systems will be performed at screening, Day 1 of every cycle and at the EOT visit. Categories of findings (normal, abnormal, not evaluated) on physical examination were summarized as counts and percentages by body systems within visit. Whether abnormal findings were clinically significant was also reported.

Shift as well as changes in ECOG score together with the worst post-baseline changes were summarized.

Protocol Amendments

The original protocol dated 16 June 2015 was amended twice:

- Amendment 1, dated 09 August 2015

In brief, Amendment 1:

- o clarified the use of the tumor biopsy tissue
- o clarified contraceptive requirements and pregnancy testing
- o excluded patients with active gastrointestinal (GI) bleeding
- o clarified vital signs collection
- o clarified laboratory testing (HIV, fasting lipids, thyroid function)
- o clarified that FISH analysis of TFE3 would be performed in a central Clinical Laboratory Improvement Amendments (CLIA) laboratory
- o specified that the primary efficacy analysis would be performed using the Efficacy Analysis Set and the Full Analysis Set
- o clarified summarization of the time-to-event endpoints.

- Amendment 2, dated 11 December 2015

In brief, Amendment 2:

- o clarified the purpose and collection of the tumor biopsy samples
- o added Cycle 4 Day 1 blood sample for biomarker assessment
- o added exclusions for HIV and Hepatitis B and C and clarified their testing
- o clarified the BSA calculation frequency
- o clarified the schedule of scans
- o clarified the window for ECG testing
- o clarified the PK sampling schedule
- o clarified the dose reduction sequence and dose reduction rules
- o clarified the dosing time window and catheter flushing procedure

The protocol and all amendments are provided in Study PEC-001 CSR Appendix 16.1.1. Descriptions of the changes for each protocol version are included within the appendix.

As both amendments were implemented prior to patient enrollment, the changes have not impacted the trial integrity or interpretation of the results.

The FDA's Assessment:

The FDA agrees with the Applicant's description and consideration for the design of trial PEC-001. The primary endpoint of ORR was assessed after all patients were treated for 6 months. In this review, FDA will refer to primary endpoint as ORR. In addition, the FDA

agrees with the description of the secondary endpoints, statistical analysis plan, and efficacy analysis population. Of note, time-to-event endpoints such as PFS and OS are not interpretable in a single arm trial and are considered exploratory. The FDA reviewed the final version of the SAP and summary of changes from previous versions and found them to be acceptable.

8.1.2. Study Results

The Applicant's Position:

Compliance with Good Clinical Practices

Data:

The following investigator sites (Table 10) and service provider (Table 11) audits were conducted by Aadi Bioscience, Inc. to assess compliance with Good Clinical Practice (GCP) and the registrational Study PEC-001. Audit certificates are available in the Clinical Study Report for PEC-001, Section 16.1.8.

Table 10: Study PEC-001 Investigator Site Audits

Investigator	Site No.	Audit Location	Audit Dates
Kristen Ganjoo, MD	Site 007	Cancer Clinical Trials Office, Sarcoma & Thoracic Oncology Group 777 Welch Rd, Suite G-101 Palo Alto, CA 94304	29-30 October 2018
Richard Riedel, MD	Site 006	Duke Cancer Institute 20 Duke Medicine Circle Durham, NC 27710	05-06 November 2018
Brian Van Tine, MD	Site 008	Washington University School of Medicine in St. Louis Mid Campus Center (MCC) 4590 Children's Place, 10th Floor St. Louis, MO 63110	29-30 November 2018
Vinod Ravi, MD	Site 004	MD Anderson Cancer Center 1515 Holcome Blvd. Houston, TX 77030	12-13 December 2018

Table 11: Study PEC-001 Service Provider Audits

Service Provider	Function	Audit Location	Audit Dates
(b) (4)			

The study was conducted in full conformance with the ethical principles of GCP and the Declaration of Helsinki. The conduct of all aspects of the study, including methods for obtaining informed consent, were also in accordance with principles enunciated in the Declaration, the ICH GCP, and applicable regional regulations/guidelines.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Financial Disclosure

The Applicant's Position:

The financial disclosure documentation for study PEC-001 is summarized in Section 19.2. One investigator in this study submitted FDA Form 3455 declaring positive financial interest with attachments detailing the amount of financial interest and steps taken to minimize bias. It is unlikely that the positive financial disclosures biased the PEC-001 study results, as the primary efficacy analysis was performed by a blinded independent review committee. This investigator did not enroll patients into this study.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Patient Disposition

The Applicant's Position: The data cutoff for this NDA provided sufficient data maturity to assess the efficacy and safety of the therapy in patients with malignant PEComa.

Data:

Patient disposition is summarized in Table 12. Of the 41 patients who entered screening, 35 were enrolled in the study (ie, signed consent and met all eligibility criteria), and 34 were treated.

The last patient enrolled on 12 November 2018 and the preplanned data cut-off occurred on 22 May 2019, when all patients had a chance to be treated for 6 months. Twenty-four (71%) patients had discontinued from treatment, and 13 (38%) had discontinued from the study. Reasons for discontinuation from treatment include 15 (44%) patients for disease progression, 5 (15%) for withdrawal of consent, 2 (6%) for

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an AE, and 1 (3%) each for initiation of new therapy and for death. Reasons for discontinuation from the study include 5 (15%) patients for death, and 4 (12%) each for withdrawal of consent and for disease progression.

Table 12: Patient Disposition

Disposition Status, n (%)	Metastatic (N = 35)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 41)
Number Signed Informed Consent and Screened ^a	35	5	41
Number Enrolled ^b	30 (86)	5 (100)	35 (85)
Not Treated	1 (3)	0	1 (3)
Treated ^c	29 (97)	5 (100)	34 (97)
Discontinued from the Treatment	19 (66)	5 (100)	24 (71)
Adverse Event	1 (3)	1 (20)	2 (6)
Disease Progression	14 (48)	1 (20)	15 (44)
Began New Therapy	0	1 (20)	1 (3)
Withdrew Consent from Study Treatment	4 (14)	1 (20)	5 (15)
Death	0	1 (20)	1 (3)
Discontinued from the Study	11 (38)	2 (40)	13 (38)
Patient Withdrawal of Consent from Study	3 (10)	1 (20)	4 (12)
Disease Progression	4 (14)	0	4 (12)
Death	4 (14)	1 (20)	5 (15)

Abbreviations: N = number of patients; n = number of patients in the category.

Note: Percentages in each group for the number Enrolled are based on the number Screened. Percentages in each group for Not Treated and Treated patients are based on the number of patients in the Enrolled Analysis Set while the rest is based on the number of patients in the Safety (Treated) Analysis Set.

a. Patient (b) (6) dropped from site 001 and was enrolled/treated at site 002 later. There are no duplicate records on this patient.

b. Enrolled patients signed informed consent and met eligibility criteria.

c. Enrolled and treated population will be the denominators for any rows below.

Source: Study PEC-001 CSR Table 14.1.1.1.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position with the exception of patient disposition due to adverse events and withdrawal of consent. The FDA review of patients who were categorized as having withdrawn consent by the Applicant identified one patient (b) (6) with previous adverse reaction of grade 2 non-infectious

pneumonitis who “withdrew consent from Study PEC-001 after discussing concerns of adverse events and the possibility of recurrent pneumonitis with the investigator”. The FDA determined this to represent a discontinuation due to an adverse event.

The Applicant provided an updated table of patient disposition based on the 90-day safety update for Study PEC-001. This has been modified to reflect the additional discontinuation due to an adverse event described above.

Table 13: Patient Disposition (FDA Analysis)

Disposition Status, n (%)	Primary Safety Population (N = 34)
Discontinued from the Treatment	29 (85)
Adverse Event	3 (9)
Disease Progression	19 (56)
Began New Therapy	1 (3)
Withdrew Consent from Study Treatment	5 (15)
Death	1 (3)
Discontinued from the Study	24 (71)
Patient Withdrawal of Consent from Study	5 (15)
Lost to Follow-up	3 (9)
Disease Progression	4 (12)
Death	11 (32)
Other: Patient entered hospice care	1 (3)

Abbreviations: N = number of patients; n = number of patients in the category.
Source: Module 5.3.5.2 Safety Update Report (90-day)

Protocol Violations/Deviations

The Applicant’s Position:

The prospectively defined important protocol deviations, categorized as major or minor deviations, are summarized in [Table 14](#). A total of 26 (74%) patients had 109 deviations, of which 4 major deviations in 4 (11%) patients were considered major, and 105 in 25 (71%) patients were considered minor.

Patients with major deviations were excluded from the Efficacy Analysis Set and/or the

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Per Protocol Analysis Set, as applicable.

Table 14: Protocol Deviations (Enrolled Analysis Set)

Deviation Category	Metastatic (N = 30)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 35)
Patients with Any Deviations, n (%)	24 (80)	2 (40)	26 (74)
Patients with Major Deviations, n (%)	3 (10)	1 (20)	4 (11)
Uncontrolled Serious Medical/Psychiatric Illness	2 (7)	0	2 (6)
Administering Expired Investigational Product	0	1 (20)	1 (3)
Did Not Provide Tissue for Central Histological Confirmation of Malignant PEComa (Inclusion Criterion #2)	1 (3)	0	1 (3)
Patients with Minor Deviations, n (%)	23 (77)	2 (40)	25 (71)
ECG out of Window	14 (47)	1 (20)	15 (43)
<2 Missed, Consecutive Safety Labs – Chemistry, Hematology, Lipids	12 (40)	2 (40)	14 (40)
≤2 Missed PK Samples Within a Cycle	6 (20)	1 (20)	7 (20)
Missing Data After End of Treatment	4 (13)	0	4 (11)
≥21 Day Window Between Doses Unless Approved by the Medical Monitor	2 (7)	0	2 (6)
Scan Collected out of Window	2 (7)	0	2 (6)
Dosing Given outside of ±2 Day Window	1 (3)	0	1 (3)
Single Missed Dose Within 1 Cycle After First 6 Months	1 (3)	0	1 (3)
Uncontrolled Diabetes Mellitus	0	1 (20)	1 (3)
Total Number of Deviations			
All	94	15	109
Major	3	1	4
Minor	91	14	105

Abbreviations: ECG = electrocardiogram; N = number of patients; n = number of patients in the category; PK = pharmacokinetic.

Note: Percentages are based on the number of patients in the Enrolled Analysis Set in each group.

Source: Study PEC-001 CSR Table 14.1.1.3.

Patients without a confirmed diagnosis of PEComa were excluded from the Efficacy

Analysis Set (includes all enrolled patients with measurable tumor per RECIST v1.1 at baseline who received at least one dose of ABI-009, and have a confirmed diagnosis of PECOma).

Table 15: Sensitivity Analysis of Primary Endpoint

Category	(CR + PR)/N	ORR, % ^a	95% Exact CI ^b
Efficacy Analysis Set ^c	(0+12)/31	38.7	[21.8, 57.8]
Per Protocol Analysis Set ^d	(0+12)/28	42.9	[24.5, 62.8]

Abbreviations: CI = confidence interval; CR = complete response; N = number of patients; ORR = overall response rate; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.

a. ORR = (CR + PR)/N, with N being the total number of patients in the analysis set.

b. CI based on Clopper-Pearson exact test for binomial data.

c. The Efficacy Analysis Set includes all enrolled patients with measurable tumor per RECIST v1.1 as assessed by the Principal Investigator at baseline who received at least one dose of ABI-009, and have a confirmed diagnosis of PECOma.

d. The Per Protocol (PP) Analysis Set includes Enrolled Analysis Set who do not have any prospectively defined major protocol violation or deviation.

Source: Study PEC-001 CSR Table 14.2.1.2.

To explore the sensitivity of the primary efficacy analysis, the population of patients without any major protocol deviations by 6 months (PP Analysis Set) was used to analyze ORR by 6 months (Table 15). The ORR by 6 months was similar between the Efficacy and PP Analysis Sets (38.7% and 42.9%, respectively), with overlapping 95% CIs. Time to response was identical to that using the Efficacy Analysis Set (Study PEC-001 CSR Table 14.2.1.7). The sensitivity analysis excluding those patients with major protocol deviations did not demonstrate a substantial impact on the overall interpretation of efficacy results for this study.

The FDA's Assessment:

The FDA agrees with the Applicant's description in the protocol deviation/violation section. The sensitivity analysis excluding those patients with major protocol deviations showed a similar treatment effect as the primary efficacy analysis. Details of FDA's assessment of ORR is in the Efficacy Results – Primary Endpoint section.

Table of Demographic Characteristics

The Applicant's Position:

Patient demographics are summarized in Table 16. Patients ranged in age from 27 to 78 years, with a median age of 59.5 years. The majority were female (82%), White (71%), of non-Hispanic/Latino ethnicity (82%), and with a baseline ECOG score of 0 in 26 (76%) patients and a score of 1 in 8 (24%) patients.

Table 16: Patient Demographic and Baseline Characteristics (Safety Analysis Set)

Characteristic	Metastatic (N = 29)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 34)
Age (years)			
n	29	5	34
Mean (SD)	57.8 (12.54)	58.6 (15.21)	57.9 (12.71)
Median	59.0	60.0	59.5
Min, Max	27, 78	34, 73	27, 78
Age Category, n (%)			
<65 years	16 (55)	3 (60)	19 (56)
≥65 years	13 (45)	2 (40)	15 (44)
<75 years	27 (93)	5 (100)	32 (94)
≥75 years	2 (7)	0	2 (6)
Sex, n (%)			
Male	5 (17)	1 (20)	6 (18)
Female	24 (83)	4 (80)	28 (82)
Ethnicity, n (%)			
Hispanic or Latino	5 (17)	0	5 (15)
Not Hispanic or Latino	23 (79)	5 (100)	28 (82)
Not Reported	1 (3)	0	1 (3)
Race, n (%)			
White	21 (72)	3 (60)	24 (71)
Black or African American	2 (7)	1 (20)	3 (9)
Asian	2 (7)	1 (20)	3 (9)
Native Hawaiian or Other Pacific Islander	1 (3)	0	1 (3)
Other	1 (3)	0	1 (3)
Not Reported	2 (7)	0	2 (6)
ECOG Performance Status, n (%)			
0	22 (76)	4 (80)	26 (76)
1	7 (24)	1 (20)	8 (24)
Height (cm)			
n	29	5	34
Mean (SD)	163.37 (10.509)	163.36 (9.622)	163.37 (10.243)

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Characteristic	Metastatic (N = 29)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 34)
Median	162.00	160.20	162.00
Min, Max	144.8, 188.0	156.0, 180.0	144.8, 188.0
Weight (kg)			
n	29	5	34
Mean (SD)	71.39 (20.019)	81.52 (6.129)	72.88 (18.917)
Median	67.60	83.32	72.80
Min, Max	45.2, 117.9	71.7, 86.5	45.2, 117.9
Body Mass Index (kg/m ²)			
n	29	5	34
Mean (SD)	26.49 (6.072)	30.79 (4.058)	27.12 (5.972)
Median	26.34	32.72	26.47
Min, Max	19.3, 43.3	24.6, 34.2	19.3, 43.3
Body Surface Area (m ²)			
n	29	5	34
Mean (SD)	1.78 (0.281)	1.89 (0.095)	1.79 (0.264)
Median	1.80	1.89	1.82
Min, Max	1.4, 2.4	1.8, 2.0	1.4, 2.4

Abbreviations: ECOG = Eastern Cooperative Oncology Group; Max = maximum; Min = minimum; N = number of patients; n = number of patients in the category; SD = standard deviation.

Note: Percentages are based on the number of patients in the Safety Analysis Set in each group.

Source: Study PEC-001 CSR Table 14.1.2.1.

Demographics and baseline characteristics for this patient population were as expected during the development of the protocol.

The FDA's Assessment:

The primary efficacy population included 31 patients with diagnosis of malignant PEComa confirmed by central pathology review. Patient demographics for this population are described in the table below.

Table 17: Patient Demographic and Baseline Characteristics (Efficacy Analysis Set)

Characteristic	All Patients (N = 31)
Age (years)	
Mean (SD)	58.7 (11.8)
Median	60
Min, Max	34, 78
Age Category, n (%)	
<65 years	17 (55)
≥65 years	14 (45)
<75 years	29 (94)
≥75 years	2 (6)
Sex, n (%)	
Male	6 (19)
Female	25 (81)
Ethnicity, n (%)	
Hispanic or Latino	4 (13)
Not Hispanic or Latino	26 (84)
Not Reported	1 (3)
Race, n (%)	
White	23 (74)
Black or African American	3 (10)
Asian	2 (6)
Native Hawaiian or Other Pacific Islander	1 (3)
Not Reported	2 (6)
ECOG Performance Status, n (%)	
0	25 (81)
1	6 (19)
Height (cm)	
Mean (SD)	163.4 (9.4)
Median	162.00
Min, Max	148.5, 188.0
Weight (kg)	
Mean (SD)	73.3 (19.0)
Median	71.8

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213312
FYARRO (sirolimus protein-bound particles for injectable suspension) (albumin-bound)

Characteristic	All Patients (N = 31)
Min, Max	45.8, 117.9
Body Mass Index (kg/m ²)	
Mean (SD)	27.3 (6.2)
Median	26.5
Min, Max	19.3, 43.3
Body Surface Area (m ²)	
Mean (SD)	1.8 (0.26)
Median	1.8
Min, Max	1.4, 2.4

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Patient cancer history is summarized in [Table 18](#). Median time from initial diagnosis to time of informed consent was 9.21 months for patients with metastatic disease, and 17.34 months for patients whose disease was locally advanced and ineligible for surgery. There were 3 patients in the metastatic group who did not have histologically confirmed PEComa (1 patient with unclassified pleomorphic sarcoma of left broad ligament mass, and 1 with malignant glomus tumor of the left kidney; the third patient did not provide tissue for central pathology confirmation); these were excluded from the Efficacy Analysis Set. The anatomic regions of primary tumor diagnosis were pelvic (15 [44%] patients), abdominal (13 [38%] patients), thoracic (5 [15%] patients), and head and neck (1 [3%] patient). The anatomic regions of metastatic sites were thoracic (21 [62%] patients), abdominal (16 [47%] patients), pelvic (7 [21%] patients), and bone, unspecified (2 [6%] patients).

Table 18: Cancer History (Safety Analysis Set)

Characteristic	Metastatic (N = 29)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 34)
Time Since Initial Diagnosis to Informed Consent (months) ^a			
n	27	5	32
Mean (SD)	23.41 (33.990)	21.26 (23.210)	23.08 (32.235)

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213312
FYARRO (sirolimus protein-bound particles for injectable suspension) (albumin-bound)

Characteristic	Metastatic (N = 29)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 34)
Median	9.21	17.34	9.21
Min, Max	0.3, 139.0	0.9, 56.2	0.3, 139.0
Histologically Confirmed PEComa, n (%)			
Yes	26 (90)	5 (100)	31 (91)
No	3 (10)	0	3 (9)
Number of Metastatic Sites, n (%)			
1	11 (38)	-	-
2	9 (31)	-	-
3	7 (24)	-	-
>3	2 (7)	-	-
Reason Patient was Not Amenable to Surgery, n (%)			
Morbidity Exceeds Benefit	-	1 (20)	-
Patient not Fit for Surgery	-	1 (20)	-
Tumor Location Unsafe to Operate	-	2 (40)	-
Other: Patient Refused Nephrectomy	-	1 (20)	-
Reason Patient was Not Amenable to Radiation Treatment, n (%)			
Morbidity Exceeds Benefit	-	1 (20)	-
Patient not Fit for Radiation Therapy	-	0	-
Tumor Location not Fit for Radiation	-	3 (60)	-
Other	-	1 (20)	-
N/A	-	1 (20)	-
Anatomic Region of Primary Tumor(s), n (%)			
Abdominal Region	12 (41)	1 (20)	13 (38)
Bone, Unspecified	0	0	0
Head and Neck	0	1 (20)	1 (3)
Pelvic Region	14 (48)	1 (20)	15 (44)
Thoracic Region	3 (10)	2 (40)	5 (15)
Anatomic Region of Metastatic Site(s), n (%)			
Abdominal Region	16 (55)	-	16 (47)
Bone, Unspecified	2 (7)	-	2 (6)

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213312
FYARRO (sirolimus protein-bound particles for injectable suspension) (albumin-bound)

Characteristic	Metastatic (N = 29)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 34)
Head and Neck	0	-	0
Pelvic Region	7 (24)	-	7 (21)
Thoracic Region	21 (72)	-	21 (62)

Abbreviations: Max = maximum; Min = minimum; N = number of patients; n = number of patients in the category; SD = standard deviation.

Note: Percentages are based on the number of patients in the Safety Analysis Set in each group. Patients (b) (6) were treated but excluded from the Efficacy Analysis Set because they did not have or could not be diagnosed with PEComa. Patients with multiple metastatic sites within the same body region are counted only once in the region.

a. (Date of informed consent – date of initial PEComa diagnosis + 1)/30.4.

Source: Study PEC-001 CSR Table 14.1.2.2 and Table 14.1.2.3.

History of prior cancer therapies for PEComa is summarized in Table 19, prior systemic therapies for PEComa in Table 20, prior radiation therapy for PEComa in Table 21, and prior PEComa-related surgeries in Table 22.

The majority of patients (32 [94%]) received prior therapy (systemic therapy, radiotherapy, or surgery) for PEComa. There were 6 (18%) patients who received systemic therapy (4 of 6 patients had prior treatment for advanced disease), 7 (21%) received radiotherapy, and 32 (94%) underwent surgery. Of the patients with metastatic disease, median time from last systemic therapy to the first ABI-009 dose was 11.35 months. Median time from last radiotherapy to first ABI-009 dose was 9.87 months for the metastatic group and 21.64 months for the single patient with prior radiotherapy in the locally advanced and ineligible for surgery group.

Table 19: History of Prior Cancer Therapies for PEComa (Safety Analysis Set)

Prior Cancer Therapy Category, n (%)	Metastatic (N = 29)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 34)
No Previous Treatment	1 (3)	1 (20)	2 (6)
With Any Previous Treatment	28 (97)	4 (80)	32 (94)
Any Systemic Therapy	6 (21)	0	6 (18)
Any Radiation	6 (21)	1 (20)	7 (21)
Any Surgery	28 (97)	4 (80)	32 (94)
Combination			

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213312
FYARRO (sirolimus protein-bound particles for injectable suspension) (albumin-bound)

Prior Cancer Therapy Category, n (%)	Metastatic (N = 29)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 34)
Systemic Therapy and Radiation	4 (14)	0	4 (12)
Systemic Therapy and Surgery	6 (21)	0	6 (18)
Systemic Therapy, Radiation, and Surgery	4 (14)	0	4 (12)

Abbreviations: N = number of patients; n = number of patients in the category.

Note: Percentages are based on the number of patients in the Safety Analysis Set in each group.

Source: Study PEC-001 CSR Table 14.1.2.1.

Table 20: Prior Cancer Systemic Therapy for PEComa (Safety Analysis Set – Metastatic Group)

Prior Cancer Systemic Therapy Category	Metastatic (N = 29)
No Prior Cancer Systemic Therapy ^a , n (%)	23 (79)
With Any Prior Cancer Systemic Therapy ^a , n (%)	6 (21)
Line of Therapy, n (%)	
First	6 (100)
Second	3 (50)
Third	1 (17)
Fourth	1 (17)
Fifth	1 (17)
Type of Therapy, n (%)	
Chemotherapy	6 (100)
Antibody	1 (17)
Therapy Setting, n (%)	
Neoadjuvant	1 (17)
Adjuvant	4 (67)
Therapeutic ^b	4 (67)
Time between Last Dose of Previous Treatment and First Dose of ABI-009 (months)	
n	5
Mean (SD)	32.67 (56.917)
Median	11.35

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213312
FYARRO (sirolimus protein-bound particles for injectable suspension) (albumin-bound)

Prior Cancer Systemic Therapy Category	Metastatic (N = 29)
Min, Max	1.1, 134.0
Number of Cycles	
n	6
Mean (SD)	4.2 (2.14)
Median	4.0
Min, Max	2, 7
Best Response, n (%)	
Stable Disease	3 (50)
Progressive Disease	3 (50)
Not Evaluable	1 (17)
Not Applicable	2 (33)
Reason Therapy was Discontinued, n (%)	
Progressive Disease	2 (33)
Completed Regimen	3 (50)
Adverse Event	1 (17)
Unknown	1 (17)

Abbreviations: Max = maximum; Min = minimum; N = number of patients; n = number of patients in the category; SD = standard deviation.

Note: Patients in the locally advanced and ineligible for surgery subgroup did not report any prior cancer systemic therapy.

a. Percentage is based on the number of patients in the Safety Analysis Set with metastatic disease, while percentages in the rest of the table are based on the number of patients with any prior cancer systemic therapy.

b. Therapeutic setting is considered treatment for advanced disease (n = 6).

Source: Study PEC-001 CSR Table 14.1.2.6.

Table 21: Prior Cancer Radiation Therapy for PEComa (Safety Analysis Set)

Prior Cancer Radiation Therapy Category	Metastatic (N = 29)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 34)
No Prior Cancer Radiation Therapy ^a , n (%)	23 (79)	4 (80)	27 (79)
With Any Prior Cancer Radiation Therapy ^a , n (%)	6 (21)	1 (20)	7 (21)
Type of Radiation Therapy, n (%)			
External Beam	6 (100)	1 (100)	7 (100)
Site of Radiation, n (%)			

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213312
FYARRO (sirolimus protein-bound particles for injectable suspension) (albumin-bound)

Prior Cancer Radiation Therapy Category	Metastatic (N = 29)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 34)
Breast	1 (17)	0	1 (14)
Lung	1 (17)	0	1 (14)
Retroperitoneum	1 (17)	0	1 (14)
Soft Tissue	1 (17)	0	1 (14)
Other	3 (50)	1 (100)	4 (57)
Chest wall	1 (17)	0	1 (14)
Left Hip	1 (17)	0	1 (14)
Pelvis	1 (17)	0	1 (14)
Spine	0	1 (100)	1 (14)
Radiation Therapy Setting, n (%)			
Neoadjuvant	1 (17)	0	1 (14)
Adjuvant	4 (67)	1 (100)	5 (71)
Therapeutic ^b	2 (33)	0	2 (29)
Time between Last Dose of Previous Treatment and First Dose of ABI-009 (months)			
n	6	1	7
Mean (SD)	31.55 (41.899)	21.64 (----)	30.14 (38.432)
Median	9.87	21.64	10.07
Min, Max	5.5, 111.8	21.6, 21.6	5.5, 111.8
Total Dose (Gy)			
n	6	0 ^c	6
Mean (SD)	2098.2 (3179.80)	-	2098.2 (3179.80)
Median	54.5	-	54.5
Min, Max	30, 6400	-	30, 6400

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213312
FYARRO (sirolimus protein-bound particles for injectable suspension) (albumin-bound)

Prior Cancer Radiation Therapy Category	Metastatic (N = 29)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 34)
Best Response, n (%)			
Complete Response	2 (33)	0	2 (29)
Stable Disease	1 (17)	0	1 (14)
Not Evaluable	2 (33)	1 (100)	3 (43)
Not Applicable	3 (50)	0	3 (43)

Abbreviations: Max = maximum; Min = minimum; N = number of patients; n = number of patients in the category; SD = standard deviation.

- Percentage is based on the number of patients in the Safety Analysis Set in each group, while percentages in the rest of the table are based on the number of patients with prior cancer radiation therapy (n = 7). A patient may have received more than 1 prior radiation therapy.
- Therapeutic setting is considered treatment for advanced disease.
- One patient in the locally advanced and ineligible for surgery group received radiation therapy, but no radiation dose information was recorded.

Source: Study PEC-001 CSR Table 14.1.2.7.

Table 22: Prior Cancer Related Surgeries for PEComa (Safety Analysis Set)

Prior Cancer Related Surgeries Category	Metastatic (N = 29)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 34)
No Prior Cancer Related Surgery ^a , n (%)	1 (3)	1 (20)	2 (6)
With Any Prior Cancer Related Surgery ^a , n (%)	28 (97)	4 (80)	32 (94)
Number of Cancer Related Surgeries	78	6	84
Surgery Description, n (%)			
Biopsy	15 (54)	3 (75)	18 (56)
Tumor Resection	21 (75)	2 (50)	23 (72)
Other	12 (43)	0	12 (38)
Curative	6 (21)	0	6 (19)
Diagnostic	3 (11)	0	3 (9)
Palliative	2 (7)	0	2 (6)
Re-excision for Positive Margins	1 (4)	0	1 (3)
Reconstruction	1 (4)	0	1 (3)

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213312
FYARRO (sirolimus protein-bound particles for injectable suspension) (albumin-bound)

Prior Cancer Related Surgeries Category	Metastatic (N = 29)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 34)
Other	4 (14)	0	4 (13)
Unknown	3 (11)	0	3 (9)
Site of Cancer Related Surgery, n (%)			
Brain	0	1 (25)	1 (3)
Head and Neck	1 (4)	0	1 (3)
Abdomen-Other	8 (29)	0	8 (25)
Pelvis	9 (32)	2 (50)	11 (34)
Other	11 (39)	1 (25)	12 (38)
Intent of Cancer Related Surgery, n (%)			
Curative	18 (64)	1 (25)	19 (59)
Diagnostic/Staging	20 (71)	3 (75)	23 (72)
Palliative	6 (21)	0	6 (19)
Re-excision for Positive Margins	1 (4)	0	1 (3)
Reconstruction	1 (4)	0	1 (3)
Unknown	3 (11)	0	3 (9)
Other	5 (18)	0	5 (16)
Outcome of Cancer Related Surgery, n (%)			
Normal	20 (71)	2 (50)	22 (69)
Abnormal, Clinically Significant	13 (46)	2 (50)	15 (47)
Malignant PEComa	1 (4)	1 (25)	2 (6)
Both Aspirates and Core Biopsies Demonstrate a Poorly Differentiated Malignant Neoplasm	1 (4)	0	1 (3)
Consistent with Metastatic Disease	1 (4)	0	1 (3)
Identification of Tumor	1 (4)	0	1 (3)
Low Grade Endometrial Stromal Sarcoma	1 (4)	0	1 (3)
Malignant Perivascular Epithelioid Cell Tumor	1 (4)	0	1 (3)
Malignant TFE3 Translocation Associated Perivascular Epithelioid Cell Neoplasm (PEComa), 9 cm	1 (4)	0	1 (3)
Metastatic Epithelioid Tumor, with Associated Pigment	1 (4)	0	1 (3)
Moderate Mitotic Activity Later Confirmed to be Malignant PEComa	1 (4)	0	1 (3)

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213312
FYARRO (sirolimus protein-bound particles for injectable suspension) (albumin-bound)

Prior Cancer Related Surgeries Category	Metastatic (N = 29)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 34)
Path Showed a 6.9 cm Tumor with 37 Mitosis per 10 hpf (Tumor was ER Positive and PR Negative)	1 (4)	0	1 (3)
Pathology Most Consistent with Malignant Perivascular Epithelioid Cell Neoplasm	1 (4)	0	1 (3)
Pathology Revealed Malignant PEComa	1 (4)	0	1 (3)
Pathology Review Felt Consisted with Lipoma	1 (4)	0	1 (3)
Pathology Showed Involvement by Malignant Perivascular Epithelioid Cell Tumor	1 (4)	0	1 (3)
Patient Demonstrated PEComa	1 (4)	0	1 (3)
PEComa	1 (4)	0	1 (3)
Positive for Malignancy	1 (4)	0	1 (3)
Positive for Metastasis	1 (4)	0	1 (3)
Positive for PEComa	1 (4)	0	1 (3)
Report Showed Atrophy	1 (4)	0	1 (3)
Residual Disease	1 (4)	0	1 (3)
Right Nephrectomy, Diagnosed with PEComa	1 (4)	0	1 (3)
Sarcoma with Smooth Muscle Differentiation	1 (4)	0	1 (3)
Spindle Cell Neoplasm Consistent with PEComa	0	1 (25)	1 (3)
Splenic Biopsy Showed Metastatic PEComa	1 (4)	0	1 (3)
Other	4 (14)	0	4 (13)
Bronchoscopy was Negative.	1 (4)	0	1 (3)
Insufficient Tissue for Diagnosis	1 (4)	0	1 (3)
Metastatic Lesion of the Right Iliac Bone	1 (4)	0	1 (3)
Pathology Felt Consistent with Undifferentiated Uterine Sarcoma	1 (4)	0	1 (3)
Recurrent PEComa	1 (4)	0	1 (3)
Resection of Recurrent Disease	1 (4)	0	1 (3)
Unknown About Pathology	1 (4)	0	1 (3)
With Residual Disease, n (%)			
Yes	19 (68)	3 (75)	22 (69)
No	13 (46)	1 (25)	14 (44)

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213312
FYARRO (sirolimus protein-bound particles for injectable suspension) (albumin-bound)

Prior Cancer Related Surgeries Category	Metastatic (N = 29)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 34)
Unknown	9 (32)	0	9 (28)

Abbreviations: ER = estrogen receptor; hpf = high powered field; Max = maximum; Min = minimum; N = number of patients; n = number of patients in the category; PR = progesterone receptor; SD = standard deviation.

a. Percentages are based on the number of patients in the Safety Analysis Set in each group, while percentages in the rest of the table are based on the number of patients with a prior cancer related surgery in each group.

Source: Study PEC-001 CSR Table 14.1.2.8.

Previous and ongoing medical history in >1 patient is summarized in Table 23.
The majority of patients (31 [91%]) reported an ongoing medical condition. The most frequently reported ongoing medical condition was hypertension in 14 (41%) patients.
All other medical conditions were reported in <30% of patients.

Table 23: Previous and Ongoing Medical History in >1 Patient by Body System and Medical Condition (Safety Analysis Set)

Body System Medical Condition, n (%)	Previous Medical Conditions (N = 34)	All Ongoing Medical Conditions (N = 34)
Patients with Any Medical Condition	21 (62)	31 (91)
Blood and lymphatic system disorders		
Anaemia	0	5 (15)
Cardiac disorders		
Sinus bradycardia	0	2 (6)
Endocrine disorders		
Hypothyroidism	0	6 (18)
Eye disorders		
Dry eye	2 (6)	0
Gastrointestinal disorders		
Abdominal pain	1 (3)	2 (6)
Constipation	0	9 (26)
Diarrhoea	2 (6)	0
Gastroesophageal reflux disease	0	5 (15)
Haemorrhoids	0	2 (6)
Nausea	1 (3)	6 (18)

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213312
FYARRO (sirolimus protein-bound particles for injectable suspension) (albumin-bound)

Body System Medical Condition, n (%)	Previous Medical Conditions (N = 34)	All Ongoing Medical Conditions (N = 34)
General disorders and administration site conditions		
Fatigue	1 (3)	10 (29)
Pain	0	2 (6)
Immune system disorders		
Drug hypersensitivity	1 (3)	5 (15)
Seasonal allergy	0	2 (6)
Infections and infestations		
Herpes zoster	2 (6)	0
Investigations		
Alanine aminotransferase increased	0	2 (6)
Aspartate aminotransferase increased	0	2 (6)
Metabolism and nutrition disorders		
Decreased appetite	0	5 (15)
Diabetes mellitus	0	3 (9)
Hypercholesterolaemia	0	4 (12)
Hyperglycaemia	0	2 (6)
Hyperlipidaemia	3 (9)	2 (6)
Hypertriglyceridaemia	1 (3)	2 (6)
Type 2 diabetes mellitus	0	2 (6)
Musculoskeletal and connective tissue disorders		
Back pain	0	3 (9)
Muscular weakness	0	2 (6)
Musculoskeletal pain	0	3 (9)
Neck pain	1 (3)	2 (6)
Osteopenia	0	2 (6)
Osteoporosis	0	2 (6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Tumour pain	0	3 (9)
Uterine leiomyoma	4 (12)	2 (6)
Nervous system disorders		
Headache	0	2 (6)

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213312
FYARRO (sirolimus protein-bound particles for injectable suspension) (albumin-bound)

Body System Medical Condition, n (%)	Previous Medical Conditions (N = 34)	All Ongoing Medical Conditions (N = 34)
Neuropathy peripheral	0	3 (9)
Psychiatric disorders		
Anxiety	0	5 (15)
Depression	1 (3)	6 (18)
Insomnia	0	4 (12)
Renal and urinary disorders		
Chronic kidney disease	0	2 (6)
Reproductive system and breast disorders		
Pelvic pain	0	2 (6)
Respiratory, thoracic and mediastinal disorders		
Cough	0	2 (6)
Dyspnoea	0	2 (6)
Sleep apnoea syndrome	2 (6)	0
Vascular disorders		
Hypertension	1 (3)	14 (41)

Abbreviations: N = number of patients; n = number of patients in the category.

Note: Percentages are based on the number of patients in the Safety Analysis Set. Reported are medical conditions that are not related to PEComa diagnosis. Medical history terms are coded using WHODrug Format C March 2019.

Source: Study PEC-001 CSR Table 14.1.2.4.

Surgical history (ie, surgeries not related to PEComa diagnosis) in >1 patient overall is summarized in Table 24. The most common surgical procedures were hysterectomy in 9 (26%) patients and cholecystectomy in 4 (12%) patients.

Table 24: Surgical History in >1 Patient Overall by Body System and Surgical Procedure (Safety Analysis Set)

Body System Surgical Procedure, n (%)	Metastatic (N = 29)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 34)
Patients with Any Surgical Procedure	21 (72)	3 (60)	24 (71)
Investigations			
Colonoscopy	2 (7)	1 (20)	3 (9)
Surgical and medical procedures			

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213312
FYARRO (sirolimus protein-bound particles for injectable suspension) (albumin-bound)

Body System Surgical Procedure, n (%)	Metastatic (N = 29)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 34)
Appendicectomy	2 (7)	0	2 (6)
Breast Conserving Surgery	3 (10)	0	3 (9)
Bunion Operation	2 (7)	0	2 (6)
Cataract Operation	1 (3)	1 (20)	2 (6)
Cholecystectomy	3 (10)	1 (20)	4 (12)
Female Sterilisation	3 (10)	0	3 (9)
Hip Arthroplasty	2 (7)	0	2 (6)
Hysterectomy	7 (24)	2 (40)	9 (26)
Hysterosalpingo-Oophorectomy	1 (3)	1 (20)	2 (6)
Knee Arthroplasty	2 (7)	0	2 (6)
Myomectomy	2 (7)	0	2 (6)
Salpingo-Oophorectomy Bilateral	3 (10)	0	3 (9)
Skin Neoplasm Excision	2 (7)	0	2 (6)
Splenectomy	2 (7)	0	2 (6)
Tonsillectomy	2 (7)	0	2 (6)
Uterine Dilation and Curettage	3 (10)	0	3 (9)

Abbreviations: N = number of patients; n = number of patients in the category.

Note: Percentages are based on the number of patients in the Safety Analysis Set in each group. Surgical history not related to PEComa diagnosis is reported. Surgical history terms are coded using WHODrug Format C March 2019.

Source: Study PEC-001 CSR Table 14.1.2.5.

The Applicant's Position:

Disease characteristics, prior treatments (systemic therapy, radiation therapy, surgeries), prior and ongoing medical history, and surgical history were as expected for this patient population.

The FDA's Assessment:

The FDA agrees with the Applicant's position that disease characteristics and prior and ongoing medical history were as expected for the patient population.

FDA analysis of prior therapies included patients in the primary efficacy population of Study PEC-001 (N=31). These included:

- 29 patients (94%) who underwent prior surgery

- 6 patients (19%) who underwent prior radiation therapy
- 4 patients (13%) who underwent prior systemic therapy

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Data:

Study medication administration occurred under the supervision of clinic personnel. A total of 34 patients received at least 1 dose of ABI-009 (Table 25). Patients in the metastatic group received a median of 9.0 treatment cycles (17.0 infusions) over 5.56 months. Patients in the locally advanced and ineligible for surgery group received a median of 5.0 treatment cycles (8.0 infusions) over 3.98 months. Overall, patients received a median of 8.5 treatment cycles (16.5 infusions) over 5.43 months.

Table 25: Number of Cycles Administered, Treatment Duration, and Number of Infusions (Safety Analysis Set)

Characteristic	Metastatic (N = 29)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 34)
Number of Cycles of ABI-009 Administered			
n	29	5	34
Mean (SD)	13.0 (12.05)	6.8 (4.71)	12.1 (11.44)
Median	9.0	5.0	8.5
Minimum, Maximum	2, 46	1, 13	1, 46
Treatment Duration (months) ^a			
n	29	5	34
Mean (SD)	8.67 (8.544)	4.34 (3.228)	8.03 (8.100)
Median	5.56	3.98	5.43
Minimum, Maximum	0.7, 31.3	0.3, 8.2	0.3, 31.3

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FYARRO (sirolimus protein-bound particles for injectable suspension) (albumin-bound)

Characteristic	Metastatic (N = 29)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 34)
Number of Infusions			
n	29	5	34
Mean (SD)	24.8 (23.79)	12.0 (8.60)	22.9 (22.59)
Median	17.0	8.0	16.5
Minimum, Maximum	3, 91	2, 22	2, 91

Abbreviations: N = number of patients; n = number of patients in the category; SD = standard deviation.

a. Treatment duration = (Date of last dose date minus date of first dose + 1)/30.4.

Source: Study PEC-001 CSR Table 14.1.3.2.

At least 1 dose interruption occurred in 25 (74%) patients, with a median 1.0 interruption ([Table 26](#)). Dose reductions (13 [38%] patients) and dose rate reductions (1 [3%] patient) occurred less frequently. Interruptions and dose reductions were mainly due to AEs. Data for interruptions, dose reductions, and rate of dose reductions by cycle are summarized in Study PEC-001 CSR Table 14.1.3.1.

Table 26: Number of Patients with at Least One Interruption, Dose Reduction, or Rate of Dose Reduction, and Number of Interrupted Infusions (Safety Analysis Set)

Category, n (%)	Metastatic (N = 29)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 34)
Patients with ≥1 Incident of Drug Interrupted ^a	21 (72)	4 (80)	25 (74)
Adverse Event	18 (62)	4 (80)	22 (65)
Non-compliance	2 (7)	0	2 (6)
Other	8 (28)	2 (40)	10 (29)
Number of Incidents of Drug Interrupted			
1	7 (24)	1 (20)	8 (24)
2	7 (24)	1 (20)	8 (24)
3	5 (17)	1 (20)	6 (18)
5	0	1 (20)	1 (3)
6	1 (3)	0	1 (3)
11	1 (3)	0	1 (3)

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Category, n (%)	Metastatic (N = 29)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 34)
Patients with ≥ 1 Incident of Dose Reduced ^a	10 (34)	3 (60)	13 (38)
Adverse Event	9 (31)	3 (60)	12 (35)
Principal Investigator Decision	1 (3)	0	1 (3)
Number of Incidents of Dose Reduced			
1	9 (31)	2 (40)	11 (32)
2	1 (3)	1 (20)	2 (6)
Patients with ≥ 1 Incident of Dose Rate Reduced ^a	1 (3)	0	1 (3)
Other	1 (3)	0	1 (3)
Number of Incidents of Dose Rate Reduced			
1	1 (3)	0	1 (3)
Number of Interrupted Infusions ^a			
N	1	0	1
Mean (SD)	1.0 (----)	-	1.0 (----)
Median	1.0	-	1.0
Minimum, Maximum	1, 1	-	1, 1

Abbreviations: N = number of patients; n = number of patients in the category; SD = standard deviation.

b. Dosing-related incidents consist of drug interrupted (dose missed or dose delayed), dose reduced, or dose rate reduced (infusion interruption). Infusion interruption implies infusion was stopped and then restarted.

Source: Study PEC-001 CSR Table 14.1.3.2, Table 14.1.3.3.

The median cumulative dose received during the study was 1600.0 mg/m² for patients in the metastatic group, and 800.0 mg/m² for patients in the locally advanced and ineligible for surgery group (Table 27). The median dose intensity of ABI-009 received was 62.16 mg/m²/week for patients in the metastatic group, 44.08 mg/m²/week for patients in the locally advanced and ineligible for surgery group, and 61.62 mg/m²/week overall. The median percentage of protocol-specified ABI-009 dose was 93.20% for patients in the metastatic group, 66.09% for patients in the locally advanced and ineligible for surgery group, and 93.28% overall. The majority of patients (55%) in the metastatic group received >90% of the protocol-specified dose, while 3 of the 5 patients in the locally advanced and ineligible for surgery received <70% of the protocol-specified dose.

Table 27: Actual Dose per Patient, Cumulative Dose per Patient, Average Dose Intensity, and Percentage of Protocol Dose (Safety Analysis Set)

Category	Metastatic (N = 29)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 34)
Cumulative Actual ABI-009 Dose/Patient, mg ^a			
n	29	5	34
Mean (SD)	3993.7 (4018.71)	1634.2 (930.17)	3646.7 (3811.48)
Median	2560.0	1520.0	2218.5
Minimum, Maximum	645, 17719	400, 2833	400, 17719
Cumulative Actual ABI-009 Dose/Patient, mg/m ² ^a			
n	29	5	34
Mean (SD)	2355.1 (2375.24)	909.2 (569.11)	2142.5 (2257.52)
Median	1600.0	800.0	1450.0
Minimum, Maximum	300, 9100	200, 1675	200, 9100
Average ABI-009 Dose Intensity, mg/m ² /week ^b			
n	29	5	34
Mean (SD)	57.53 (9.701)	48.49 (15.071)	56.20 (10.859)
Median	62.16	44.08	61.62
Minimum, Maximum	30.2, 66.7	31.3, 66.7	30.2, 66.7
Percentage of Protocol ABI-009 Dose ^c			
n	29	5	34
Mean (SD)	86.25 (14.544)	72.71 (22.596)	84.26 (16.281)
Median	93.20	66.09	92.38
Minimum, Maximum	45.3, 100.0	46.9, 100.0	45.3, 100.0
Percentage of Protocol ABI-009 Dose Category, n (%) ^c			
≥90%	16 (55)	2 (40)	18 (53)
80 to <90%	4 (14)	0	4 (12)
70 to <80%	5 (17)	0	5 (15)
<70%	4 (14)	3 (60)	7 (21)

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Abbreviations: N = number of patients; n = number of patients in the category; SD = standard deviation.

- Cumulative ABI-009 dose per patient in mg or mg/m² is sum of administered doses across all dosing time points.
- Average ABI-009 dose intensity is cumulative ABI-009 dose divided by the number of dosing between last and first doses accounting for rest week between cycles.
- Percentage of protocol ABI-009 dose is calculated as the average dose intensity divided by the protocol initial average dose intensity of 66.7 mg/m² per week within a dosing cycle in percent.

Source: Study PEC-001 CSR Table 14.1.3.2.

The Applicant's Position:

Overall, patients received a median of 8.5 treatment cycles (16.5 infusions) over 5.43 months. The median dose intensity of 61.62 mg/m² represents 92.4% of the possible maximum in the regimen, indicating high treatment compliance.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Concomitant Medications

Data:

Concomitant medications are summarized by WHO therapeutic main group in [Table 28](#). All patients took at least one concomitant medication while participating in the study. The most common WHO therapeutic main group of concomitant medications were antibacterials for systemic use and antiemetics and antinauseants (26 [76%] patients each); analgesics (24 [71%] patients); corticosteroids (dermatological preparations), mineral supplements, and stomatological preparations (20 [59%] patients each); psycholeptics (19 [56%] patients); antihistamines for systemic use, antithrombotic agents, and lipid modifying agents (14 [41%] patients each); blood substitutes and perfusion solutions, drugs for acid related disorders, and vitamins (12 [35%] patients each); and anesthetics, antidiarrheals (intestinal antiinflammatory/antiinfective agents), and drugs for constipation (11 [32%] patients each). All other therapeutic main groups of concomitant medications were reported in <30% of patients. Concomitant medications by chemical therapeutic subgroup and preferred term are summarized in post-text Table 14.4.4.1. Two patients received a prohibited medication (Appendix 16.2.9, Listing 16.2.10.2): Patient (b) (6) received a fentanyl-containing medication for chest pain for a 6-week period, and Patient (b) (6) received a single dose of fentanyl during an endoscopy procedure.

Concomitant procedures are summarized by body site and procedure in [Table 29](#). Approximately half (18 [53%]) of the patients had a concomitant procedure performed

while on study.

Table 28: Incidence of Concomitant Medications in >1 Patient Overall by WHO Therapeutic Main Group (Safety Analysis Set)

WHO Therapeutic Main Group, n (%)	Metastatic (N = 29)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 34)
Patients with at Least 1 Concomitant Medication	29 (100)	5 (100)	34 (100)
Antibacterials for Systemic Use	22 (76)	4 (80)	26 (76)
Antiemetics and Antinauseants	21 (72)	5 (100)	26 (76)
Analgesics	19 (66)	5 (100)	24 (71)
Corticosteroids, Dermatological Preparations	17 (59)	3 (60)	20 (59)
Mineral Supplements	17 (59)	3 (60)	20 (59)
Stomatological Preparations	18 (62)	2 (40)	20 (59)
Psycholeptics	15 (52)	4 (80)	19 (56)
Antihistamines for Systemic Use	12 (41)	2 (40)	14 (41)
Antithrombotic Agents	12 (41)	2 (40)	14 (41)
Lipid Modifying Agents	13 (45)	1 (20)	14 (41)
Blood Substitutes and Perfusion Solutions	10 (34)	2 (40)	12 (35)
Drugs for Acid Related Disorders	9 (31)	3 (60)	12 (35)
Vitamins	9 (31)	3 (60)	12 (35)
Anesthetics	9 (31)	2 (40)	11 (32)
Antidiarrheals, Intestinal Antiinflammatory/Anti-infective Agents	10 (34)	1 (20)	11 (32)
Drugs for Constipation	9 (31)	2 (40)	11 (32)
Corticosteroids for Systemic Use	9 (31)	1 (20)	10 (29)
Diuretics	10 (34)	0	10 (29)
Psychoanaleptics	9 (31)	1 (20)	10 (29)
Antiinflammatory and Antirheumatic Products	7 (24)	2 (40)	9 (26)
Drugs Used in Diabetes	6 (21)	3 (60)	9 (26)
Agents Acting on the Renin-Angiotensin System	7 (24)	1 (20)	8 (24)
Beta Blocking Agents	7 (24)	0	7 (21)
Cough and Cold Preparations	6 (21)	1 (20)	7 (21)
Calcium Channel Blockers	5 (17)	1 (20)	6 (18)

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WHO Therapeutic Main Group, n (%)	Metastatic (N = 29)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 34)
Drugs for Functional Gastrointestinal Disorders	5 (17)	1 (20)	6 (18)
Nasal Preparations	4 (14)	1 (20)	5 (15)
Antibiotics and Chemotherapeutics for Dermatological Use	4 (14)	0	4 (12)
Antifungals for Dermatological Use	4 (14)	0	4 (12)
Drugs for Obstructive Airway Diseases	4 (14)	0	4 (12)
Ophthalmologicals	4 (14)	0	4 (12)
Thyroid Therapy	2 (7)	2 (40)	4 (12)
Antianemic Preparations	2 (7)	1 (20)	3 (9)
Antimycotics for Systemic Use	3 (10)	0	3 (9)
Antipruritics, Including Antihistamines, Anesthetics, etc.	3 (10)	0	3 (9)
Antivirals for Systemic Use	3 (10)	0	3 (9)
Emollients and Protectives	3 (10)	0	3 (9)
General Nutrients	3 (10)	0	3 (9)
Muscle Relaxants	2 (7)	1 (20)	3 (9)
Other Alimentary Tract and Metabolism Products	3 (10)	0	3 (9)
Other Nervous System Drugs	2 (7)	1 (20)	3 (9)
Vaccines	3 (10)	0	3 (9)
Anti-Acne Preparations	2 (7)	0	2 (6)
Antigout Preparations	2 (7)	0	2 (6)
Cardiac Therapy	1 (3)	1 (20)	2 (6)
Drugs for Treatment of Bone Diseases	2 (7)	0	2 (6)
Sex Hormones and Modulators of the Genital System	2 (7)	0	2 (6)
Topical Products for Joint and Muscular Pain	2 (7)	0	2 (6)
Unspecified Herbal and Traditional Medicine	2 (7)	0	2 (6)
Urologicals	2 (7)	0	2 (6)

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WHO Therapeutic Main Group, n (%)	Metastatic (N = 29)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 34)
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Abbreviations: N = number of patients; n = number of patients in the category; WHO = World Health Organization.

Note: Percentages are based on the total number of patients in the Safety Analysis Set in each group. Concomitant medications are coded using WHODrug Format C March 2019. Therapeutic levels are ordered based on largest total frequency, with each patient counted once per level. Concomitant medications are medications patients took after signing the informed consent form.

Source: Study PEC-001 CSR Table 14.4.4.1.

Table 29: Incidence of Concomitant Procedures (Safety Analysis Set)

Body Site Procedure, n (%)	All Patients (N = 34)
Patients with Any Concomitant Procedures	18 (53)
Head and neck	
Cataract correction surgery	1 (3)
Cauterization	1 (3)
Dental procedure (crown replacement)	1 (3)
Root canal	1 (3)
Tooth extraction	1 (3)
Ultrasound left neck	1 (3)
Ultrasound head neck soft tissue	1 (3)
Abdomen, other	
Paracentesis	1 (3)
Ureter stents removed	1 (3)
X-ray abdomen	1 (3)
Limb, lower	
Biopsy by shave technique	1 (3)
Compression stocking	1 (3)
Cryotherapy	1 (3)
Lung	
Computed tomography chest	1 (3)
Ultrasound guided thoracentesis of the left lung	1 (3)
Ventilation-perfusion scan	1 (3)
Heart	

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Body Site Procedure, n (%)	All Patients (N = 34)
Echocardiogram	1 (3)
Port placement	1 (3)
Mediastinum	
Central line with infusion port placement	1 (3)
Other	
2 units packed red blood cells	1 (3)
Cataract surgery	1 (3)
Central port placement	1 (3)
Colonoscopy	2 (6)
Computed tomography abdomen pelvis	1 (3)
Computed tomography abdomen pelvis with contrast	1 (3)
Endoscopy	1 (3)
Esophagogastroduodenoscopy	1 (3)
Lithotripsy removal of renal stone	1 (3)
Magnetic resonance imaging	1 (3)
Port-a-cath replacement	1 (3)
Urethral stent placement	1 (3)

Abbreviations: N = number of patients; n = number of patients in the category.

Note: Percentages are based on the number of patients in the Safety Analysis Set. Concomitant procedures are those that occurred after the signing of the informed consent form.

Source: Study PEC-001 CSR Table 14.4.4.2.

The Applicant's Position:

Concomitant medication usage and concomitant procedures are as expected for this patient population.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Rescue Medication Use

The Applicant's Position:

Utilization of rescue medication is not applicable to Study PEC-001.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Primary Endpoint: ORR by 6 Months, by Confirmed Central Reader Assessment

For the primary efficacy endpoint of ORR by 6 months confirmed by independent central reader assessment (Table 30), 12 (38.7%) patients were responders by 6 months (95% CI: 21.8, 57.8). Of the metastatic patients, 12 (46.2%) were responders (95% CI: 26.6, 66.6); all of the locally advanced and ineligible for surgery patients had stable disease as the best response by 6 months.

Responses occurred early (Table 31); of those patients who were responders, 8 (67%) had an initial response by 6 weeks, with an additional 3 (25%) by 12 weeks, and 1 (8%) at 24 weeks. The median number of cycles prior to confirmed response was 2.00 (ie, 6 weeks). Median TTR was 1.4 months (95% CI: 1.3, 1.4). A swimmer plot of response based on central reader assessment is presented in [Figure 5](#).

As a note, imaging scans were performed every 6 weeks for the first year, then every 12 weeks thereafter without adjustment for treatment cycles that may have shifted due to dose interruptions or other delays. Although the data tables express the interval in cycles, times to response are expressed in number of elapsed weeks per the imaging schedule (eg, end of Cycle 2 = end of 6 weeks, end of Cycle 4 = end of 12 weeks, etc).

Table 30: Overall Response Rate by 6 Months Based on Confirmed Central Readers' RECIST Assessments (Efficacy Analysis Set)

Category	Metastatic (N = 26)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 31)
Overall Response Rate (ORR) ^a	(0+12)/26 = 46.2%	(0+0)/5 = 0%	(0+12)/31 = 38.7%
95% Exact CI for ORR	[26.6, 66.6]	-	[21.8, 57.8]
Best Overall Objective Response (confirmed), n (%)			
Complete Response (CR)	0	0	0
95% Exact CI	-	-	-
Partial Response (PR)	12 (46.2)	0	12 (38.7)
95% Exact CI	[26.6, 66.6]	-	[21.8, 57.8]

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Category	Metastatic (N = 26)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 31)
Stable Disease (SD)	11 (42.3)	5 (100.0)	16 (51.6)
95% Exact CI	[23.4, 63.1]	[47.8, 100.0]	[33.1, 69.8]
Progressive Disease (PD)	3 (11.5)	0	3 (9.7)
95% Exact CI	[2.4, 30.2]	-	[2.0, 25.8]

Abbreviations: CI = confidence interval; N = number of patients; n = number of patients in the category; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: 95% CI obtained from Clopper-Pearson exact test for binomial data. The primary efficacy endpoint is based on the confirmed best overall response during the first 6 months of ABI-009 treatment, or earlier among patients who discontinued the study or had progressive disease within 6 months after the first ABI-009 dose.

a. ORR = (CR + PR)/N, N is the total number of patients in the Efficacy Analysis Set.

Source: Study PEC-001 CSR Table 14.2.1.1.

Table 31: Number of Treatment Cycles Prior to Response and Time to Response Based on Confirmed Central Readers' RECIST Assessments (Efficacy Analysis Set)

Category	Metastatic (N = 26)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 31)
Patients with a Confirmed Response	12	0	12
Patients with No Response	14	5	19
Treatment Cycle at which Response Initially Observed ^a , n (%)			
2	8 (67)	0	8 (67)
4	3 (25)	0	3 (25)
6	1 (8)	0	1 (8)
Treatment Cycles Prior to Confirmed Response ^b			
Mean (SD)	2.8 (1.34)	-	2.8 (1.34)
Median	2.00	-	2.00
Min, Max	2, 6	-	2, 6
Time to Response (TTR) ^a (months)			
Number at Risk	12	-	12
With Events	12	-	12
Censored	0	-	0
Quartiles and 95% CI of TTR			

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Category	Metastatic (N = 26)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 31)
25 th	1.4 [1.3, 1.4]	-	1.4 [1.3, 1.4]
Median	1.4 [1.3, 2.8]	-	1.4 [1.3, 2.8]
75 th	2.8 [1.4, 4.1]	-	2.8 [1.4, 4.1]
Minimum, Maximum	1.3, 4.1	-	1.3, 4.1

Abbreviations: CI = confidence interval; CR = complete response; N = number of patients; n = number of patients in the category; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = standard deviation.

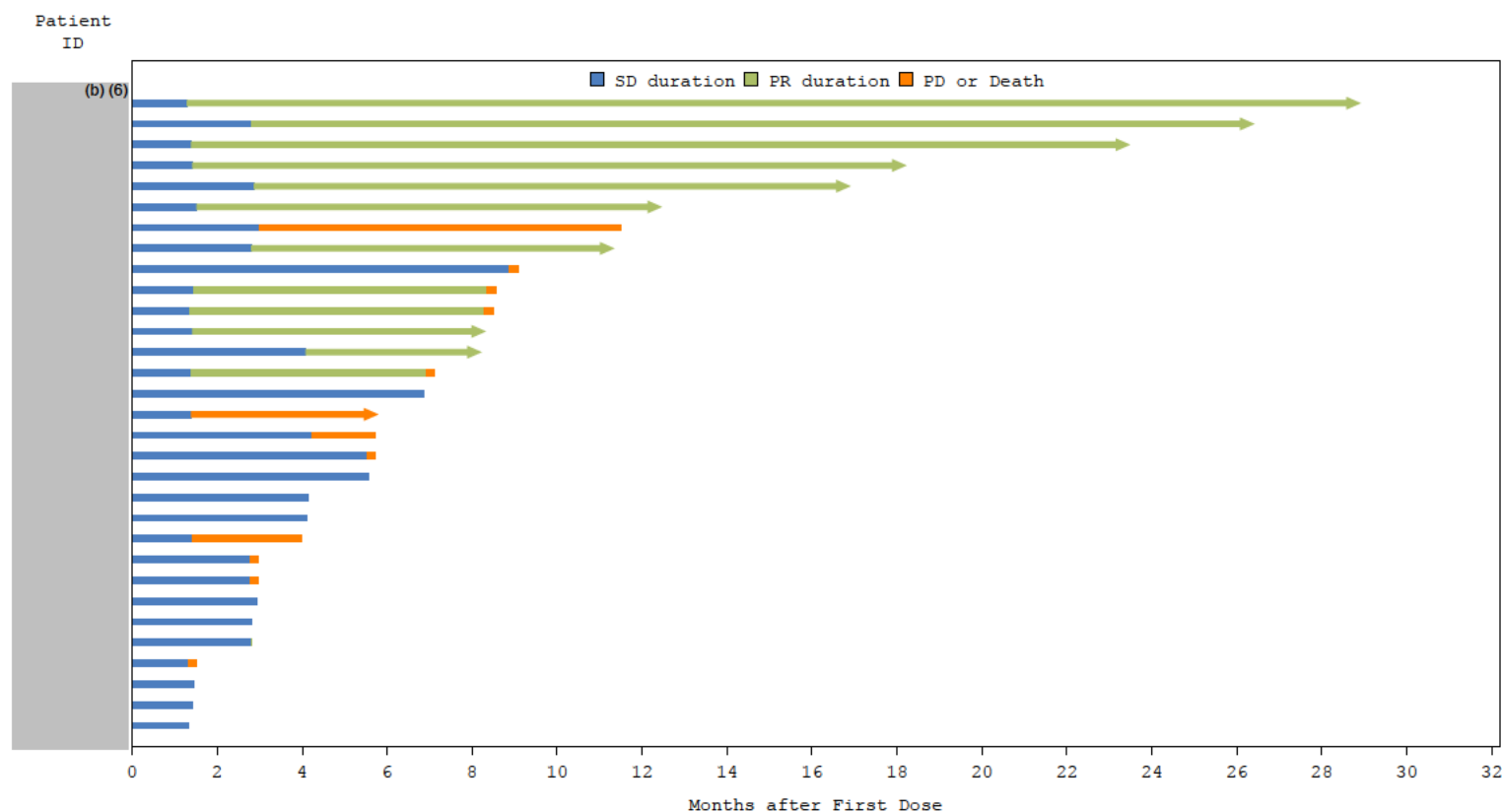
Note: Quartile estimates are obtained from Kaplan-Meier survival curves. Patients (b) (6) were treated but excluded from the Efficacy Analysis Set because they did not have or could not be diagnosed for PEComa. No patient had complete response as of the last imaging date prior to the data cut-off on 22 May 2019

b. Percentages and summary statistics reported using only patient with confirmed CR or PR.

c. This analysis includes partial responders only. Time to response = (Date confirmed CR or PR was first reported – date of first dose + 1)/30.4.

Source: Study PEC-001 CSR Table 14.2.1.4, Table 14.2.1.6.

Figure 5: Swimmer Plot of Response Based on Central Readers' Assessment (Efficacy Analysis Set)



Abbreviations: PD = progressive disease; PR = partial response; SD = stable disease.

Note: * indicates a patient of locally advanced disease and ineligible for surgery, all other patients are metastatic disease. Central readers did not have access to Investigators' imaging assessments and clinical data.

Source: Study PEC-001 CSR Figure 14.2.1.4.1.

Sensitivity Analysis

To explore the sensitivity of the primary efficacy analysis, the population of patients without any major protocol deviations by 6 months (PP Analysis Set) was used to analyze ORR by 6 months (Table 15). The ORR by 6 months was similar between the Efficacy and PP Analysis Sets (38.7% and 42.9%, respectively), with overlapping 95% CIs. Time to response was identical to that using the Efficacy Analysis Set (Study PEC-001 CSR Table 14.2.1.7).

Subgroup Analysis

In addition to the subgroups of patients with metastatic disease versus those with locally advanced disease and ineligible for surgery, subgroup analysis of the primary efficacy endpoint of ORR by 6 months confirmed by central reader assessment is summarized in Table 32. Patients ≥65 years of age had a higher response rate than those <65 years of age (9/14 [64.3%] vs 3/17 [17.6%], respectively), with 2 patients ≥75 years of age, both achieving a response. Other subgroups examined (gender, ECOG performance status at baseline, history of prior cancer therapies, or time from initial PEComa diagnosis to first ABI-009 dose) showed little difference between the subgroups.

Table 32: Subgroup Analysis of Overall Response Rate by 6 Months Based on Confirmed Central Readers' RECIST Assessments (Efficacy Analysis Set)

Category	(CR + PR)/n	ORR, % ^a	95% Exact CI ^b
Efficacy Evaluable Patients	(0+12)/31	38.7	[21.8, 57.8]
Sex			
Male	(0+2)/6	33.3	[4.3, 77.7]
Female	(0+10)/25	40.0	[21.1, 61.3]
Age at Baseline, years			
<65	(0+3)/17	17.6	[3.8, 43.4]
≥65	(0+9)/14	64.3	[35.1, 87.2]
<75	(0+10)/29	34.5	[17.9, 54.3]
≥75	(0+2)/2	100.0	-
ECOG Performance Status at Baseline			
0	(0+10)/25	40.0	[21.1, 61.3]
1	(0+2)/6	33.3	[4.3, 77.7]

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Category	(CR + PR)/n	ORR, % ^a	95% Exact CI ^b
Race			
White	(0+12)/23	52.2	[30.6, 73.2]
Not White	(0+0)/6	0	[0, 45.9]
Not Reported	(0+0)/2	0	-
History of Prior Cancer Therapies			
No Previous Treatment	(0+1)/2	50.0	-
Any Prior Treatment	(0+11)/29	37.9	[20.7, 57.7]
Time from Initial PEComa Diagnosis to First ABI-009 Dose, months			
Below Median ^c	(0+5)/15	33.3	[11.8, 61.6]
At or Above Median	(0+6)/14	42.9	[17.7, 71.1]
Unknown Date of Initial PEComa Diagnosis	(0+1)/2	50.0	-

Abbreviations: CI = confidence interval; CR = complete response; ECOG = Eastern Cooperative Oncology Group; N = number of patients; n = number of patients in the category; ORR = overall response rate; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: The primary efficacy endpoint is based on the confirmed best overall response during the first 6 months of ABI-009 treatment, or study discontinuation/progressive disease within 6 months after the first dose of the investigational product. Percentage is based on the number of patients in the subgroup in the Efficacy Analysis Set. Confidence interval estimates are provided for subgroups with at least 5 patients.

d. ORR = (CR + PR)/n, with n being the total number of patients in the subgroup.

e. CI based on Clopper-Pearson exact test for binomial data.

f. Based on median of 7.4 months among 29 patients with reported date for initial PEComa diagnosis.

Source: Study PEC-001 CSR Table 14.2.1.3.

The Applicant's Position:

This registrational trial met its primary endpoint demonstrating the efficacy of ABI-009 in PEComa. The independently-assessed ORR by 6 months was 38.7% (95% CI: 21.8, 57.8).

The majority (26/31, 83.9%) of the efficacy evaluable patients had metastatic disease, and 12/26 (46.2%) patients had a response during treatment with ABI-009.

The 5 locally advanced and ineligible for surgery patients had SD as their best response on treatment (0% PD), and their 3-month and 6-month PFS rate was 100% each.

Although the subgroup patient populations are small for definitive conclusions, the results provide evidence that patients benefitted from treatment with ABI-009 regardless of age or gender. In particular, patients ≥65 years of age benefitted from treatment, with 9/14 (64.3%) achieving a partial response. Six patients had a previous line of therapy; of the 4 evaluable for response, 3 (75.0%) had a PR, suggesting that ABI-009 may be efficacious in previously treated patients.

In patients with primary uterine PEComa, a hard-to-treat subset ([Sanfilippo 2019](#)), there was a high response rate (42.9%).

The FDA's Assessment:

The FDA agrees the Applicant's description of the primary endpoint results. ORR was 38.7% (95% CI: 21.8%, 57.8%) in the 31 patients who received at least 1 dose of ABI-009 and who have a confirmed diagnosis of PEComa. All responders (n=12) had metastatic disease.

The FDA agrees with the Applicant's description that the subgroup analyses results were generally consistent with the primary efficacy analysis, but notes that these subgroup analyses should be interpreted with caution given the very small sample sizes in the efficacy population and subgroups.

The FDA also notes some minor errors in presentation of the ORR 95% CI for some subgroups in Table 25. The 95% CI for ORR for the "Not White" subcategory for race was not estimable. For the subgroups of patients with "No Previous Treatment" and "Unknown Date of Initial PEComa Diagnosis", the 95% CI was [1.26, 98.7].

PFS rates at 3 and 6 months are not interpretable in a single arm study and are not considered to be adequate endpoints for a marketing application review.

Data Quality and Integrity

Data:

The ABI-009 clinical sites were monitored by clinical research associates following study-specific monitoring plans for consistency. Data were queried per study-specific data management plans. Additionally, a Data Monitoring Committee (DMC) reviewed safety data for Study PEC-001.

The Applicant's Position:

No issues were identified with the data quality or integrity from Study PEC-001 which could affect the efficacy results.

The FDA's Assessment:

The FDA agrees that there were no data integrity concerns with this application.

Efficacy Results – Secondary and other relevant endpoints

Data:

Overall Response Rate (ORR) by 6 Months, by Investigators' Assessment (Exploratory Efficacy Endpoint)

The exploratory endpoint of ORR by 6 months by Investigators' RECIST assessments is summarized in Table 33. Results are similar to the ORR by 6 months by central review. Time to response by Investigators' assessments was also similar to TTR by central review (post-text Table 14.2.1.13).

Table 33: Overall Response Rate by 6 Months Based on Investigators' RECIST Assessments (Efficacy Analysis Set)

Category	Metastatic (N = 26)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 31)
Overall Response Rate (ORR) ^a	(0+12)/26 = 46.2%	(0+1)/5 = 20.0%	(0+13)/31 = 41.9%
95% Exact CI for ORR	[26.6, 66.6]	[0.5, 71.6]	[24.5, 60.9]
Best Overall Objective Response (confirmed), n (%)			
Complete Response (CR)	0	0	0
95% Exact CI	-	-	-
Partial Response (PR)	12 (46.2)	1 (20.0)	13 (41.9)
95% Exact CI	[26.6, 66.6]	[0.5, 71.6]	[24.5, 60.9]
Stable Disease (SD)	11 (42.3)	4 (80.0)	15 (48.4)
95% Exact CI	[23.4, 63.1]	[28.4, 99.5]	[30.2, 66.9]
Progressive Disease (PD)	3 (11.5)	0	3 (9.7)
95% Exact CI	[2.4, 30.2]	-	[2.0, 25.8]

Abbreviations: CI = confidence interval; N = number of patients; n = number of patients in the category; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: 95% CI obtained from Clopper-Pearson exact test for binomial data. The exploratory efficacy endpoint is based on the confirmed best overall response during the first 6 months of ABI-009 treatment, or earlier among patients who discontinued the study or had progressive disease within 6 months after the first ABI-009 dose.

a. ORR = (CR + PR)/N, N is the total number of patients in the Efficacy Analysis Set.

Source: Study PEC-001 CSR Table 14.2.1.11.

Duration of Response (DOR) Based on Central Reader Assessment (Secondary Efficacy Endpoint)

The secondary endpoint of DOR based on central readers' RECIST assessments is summarized in Table 34. Median DOR had not been reached, as 9/12 (75%) responding patients were still on treatment at the time of the analysis; when censoring was ignored, the range was 4.2+ to 27.7+ months. The median duration of treatment for the responders was 14.9 months (range: 6.5 – 31.3+). The 25th percentile of 7.0 months (95% CI: 5.6, --) indicates that patients achieved a durable response, with 10 (83%), 6 (50%), and 5 (42%) patients having a response of >6, >9, and >12 months duration, respectively.

Table 34: Duration of Response Based on Confirmed Central Readers' RECIST Assessments (Efficacy Analysis Set)

Category	Metastatic (N = 26)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 31)
Patients with a Partial Response	12	0	12
Patients with No Response	14	5	19
Duration of Response (DOR) ^a (months)			
Number at Risk	12	-	12
With Events	3	-	3
Censored	9	-	9
Quartiles and 95% CI of DOR			
25 th	7.0 [5.6, --]	-	7.0 [5.6, --]
Median	-- [6.9, --]	-	-- [6.9, --]
75 th	-- [--, --]	-	-- [--, --]
Descriptive Statistics with Censoring Ignored			
Minimum, Maximum	4.2+, 27.7+	-	4.2+, 27.7+
Patients with DOR, n (%)			
>6 Months	10 (83)	-	10 (83)
>9 Months	6 (50)	-	6 (50)
>12 Months	5 (42)	-	5 (42)

Abbreviations: CI = confidence interval; CR = complete response; N = number of patients; n = number of patients in the category; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: Quartile estimates are obtained from Kaplan-Meier survival curves. Patients (b) (6) were treated but excluded from the Efficacy Analysis Set because they did not have or could not be

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Category	Metastatic (N = 26)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 31)
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diagnosed for PEComa. No patient had complete response as of the last imaging date prior to the data cut-off on 22 May 2019.

a. This analysis includes partial responders only. Duration of response = (Date of disease progression or death – date confirmed CR or PR was first reported + 1)/30.4.

Source: Study PEC-001 CSR Table 14.2.1.4.

Overall Response Rate (ORR) as of Data Cut-Off by Confirmed Central Reader Assessment (Exploratory Efficacy Endpoint)

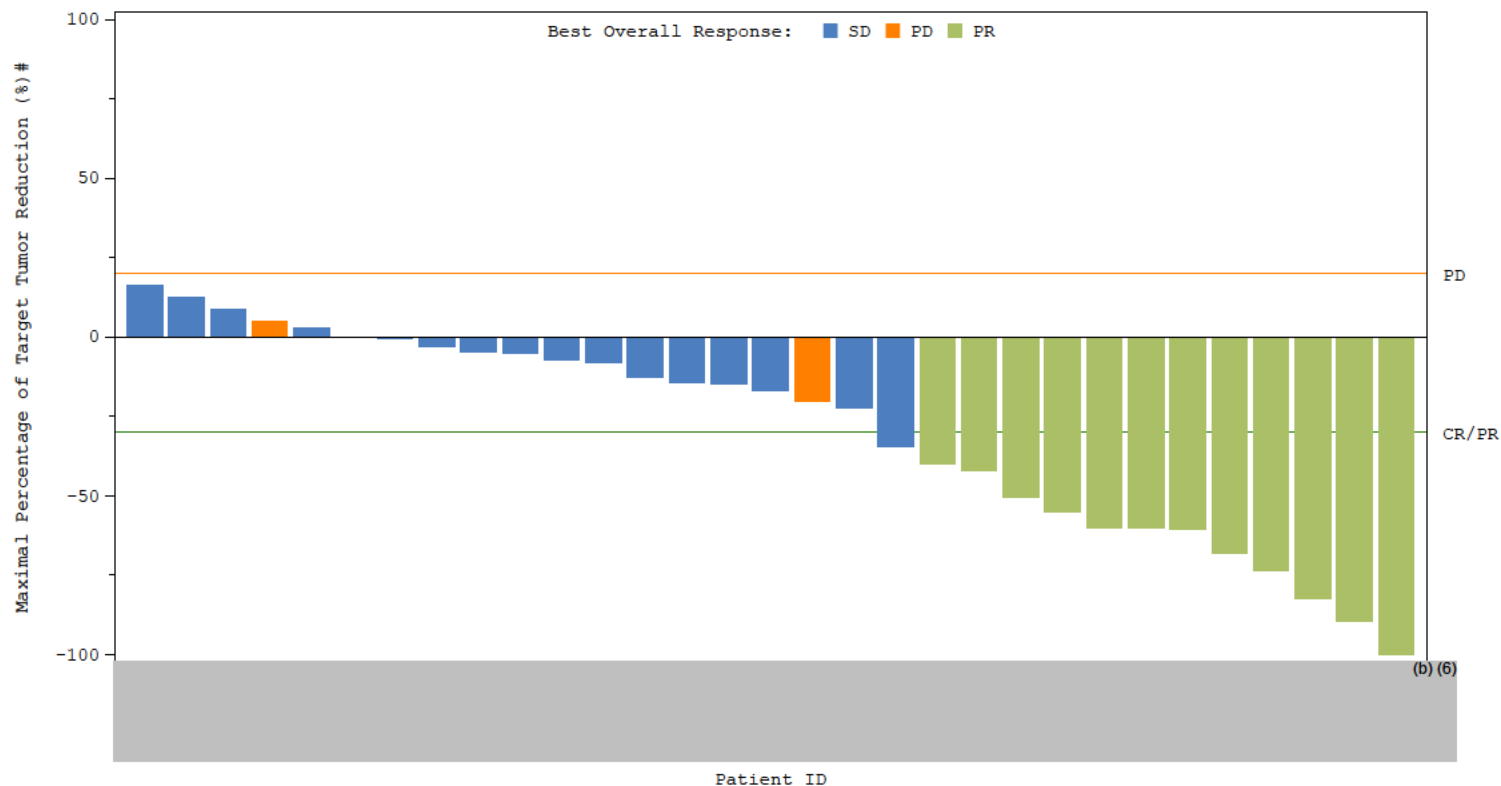
The exploratory endpoint of ORR as of data cut-off confirmed by central reader assessment is summarized in Study PEC-001 CSR Table 14.2.1.9, and is identical to the primary efficacy analysis in Table 30. Best overall response is illustrated in [Figure 6](#).

Responses did not appear to be related to primary tumor site; the 12 responses were observed in 6 types of primary sites (uterine [3 patients], kidney [3 patients], retroperitoneal [2 patients], pelvis [2 patients], liver [1 patient], and small bowel [1 patient]).

Of note, in patients with primary uterine PEComa, a hard-to-treat subset ([Sanfilippo 2019](#)), there was a high response rate (3/7 [42.9%] patients) (Study PEC-001 CSR Appendix 16.2.4, Listing 16.2.4.1.3.1; and Appendix 16.2.6, Listing 16.2.6.2.1.1).

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Figure 6: Best Overall Response as of Data Cut-Off (Efficacy Analysis Set)



Abbreviations: PD = progressive disease; PR = partial response; SD = stable disease.

Note: * indicates a patient of locally advanced disease and ineligible for surgery, all other patients are metastatic disease. # Maximal percentage of tumor reduction is defined as the minimum percent change in the sum of diameters from baseline based on all target lesions across all post-baseline assessments for each patient whose best overall response was not PD. Patient (b) (6) had no baseline target tumor.

Source: Study PEC-001 CSR Appendix 16.2.6, Figure 16.2.6.1.5.5.1.

Overall Response Rate (ORR) as of Data Cut-Off by Investigators' Assessment (Exploratory Efficacy Endpoint)

The exploratory endpoint of ORR as of data cut-off confirmed by Investigators' RECIST assessments is summarized in Study PEC-001 Table 14.2.1.12, and is identical to Investigator's assessment by 6 months.

During long-term survival follow-up, it was reported that 2 patients with locally advanced disease and who were ineligible for surgery (Patient (b) (6) and Patient (b) (6)) were subsequently able to undergo surgery to remove the locally advanced tumor after treatment with ABI-009. Patient (b) (6) experienced a 7.9% reduction in target lesions after 1 cycle, and Patient (b) (6) had a 22.3% reduction in target lesions after 10 cycles (Appendix 16.2.6, Listing 16.2.6.2.1.1). Both patients remained in long-term survival follow-up (2.5 and 2 years, respectively) as of the 22 May 2019 data cut-off for the primary analysis.

Sensitivity Analysis of Secondary Efficacy Endpoint Duration of Response (DOR) Based on Central Reader Assessment

To explore the sensitivity of the secondary efficacy endpoint, the population of patients without any major protocol deviations (PP Analysis Set) was used to analyze DOR (Table 35). Duration of response was identical to the analysis using the Efficacy Analysis Set.

Table 35: Sensitivity Analysis of Duration of Response Based on Confirmed Central Readers' RECIST Assessments (Per Protocol Analysis Set)

Category	Metastatic (N = 24)	Locally Advanced, Ineligible for Surgery (N = 4)	All Patients (N = 28)
Patients with a Partial Response	12	0	12
Patients with No Response	12	4	16
Duration of Response (DOR) ^a (months)			
Number at Risk	12	-	12
With Events	3	-	3
Censored	9	-	9

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Category	Metastatic (N = 24)	Locally Advanced, Ineligible for Surgery (N = 4)	All Patients (N = 28)
Quartiles and 95% CI of DOR			
25 th	7.0 [5.6, ----]	-	7.0 [5.6, ----]
Median	---- [6.9, ----]	-	---- [6.9, ----]
75 th	---- [----, ----]	-	---- [----, ----]
Descriptive Statistics with Censoring Ignored			
Minimum, Maximum	4.2+, 27.7+	-	4.2+, 27.7+
Patients with DOR, n (%)			
>6 Months	10 (83)	-	10 (83)
>9 Months	6 (50)	-	6 (50)
>12 Months	5 (42)	-	5 (42)

Abbreviations: CI = confidence interval; CR = complete response; N = number of patients; n = number of patients in the category; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: Quartile estimates are obtained from Kaplan-Meier survival curves. Patients (b) (6) were treated but excluded from the Efficacy Analysis Set because they did not have or could not be diagnosed for PEComa. No patient had complete response as of the last imaging date prior to the data cut-off on 22 May 2019.

a. This analysis includes partial responders only. Duration of response = (Date of disease progression or death – date confirmed CR or PR was first reported + 1)/30.4.

Source: Study PEC-001 CSR Table 14.2.1.7.

Duration of Response (DOR) Based on Investigators' Assessment (Exploratory Efficacy Endpoint)

The exploratory endpoint of DOR based on Investigators' RECIST assessments is summarized in Table 36. Results are similar to the DOR by central review.

Table 36: Duration of Response Based on Investigators' RECIST Assessments (Efficacy Analysis Set)

Category	Metastatic (N = 26)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 31)
Patients with a Partial Response	12	1	13
Patients with No Response	14	4	18

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Category	Metastatic (N = 26)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 31)
Duration of Response (DOR) ^a (months)			
Number at Risk	12	1	13
With Events	3	1	4
Censored	9	0	9
Quartiles and 95% CI of DOR			
25 th	7.0 [5.6, --]	6.2 [--, --]	6.9 [5.6, --]
Median	-- [5.6, --]	6.2 [--, --]	-- [6.2, --]
75 th	-- [--, --]	6.2 [--, --]	-- [--, --]
Descriptive Statistics with Censoring Ignored			
Minimum, Maximum	1.5, 27.7+	6.2, 6.2	1.5, 27.7+
Patients with DOR, n (%)			
>6 Months	9 (75)	1 (100)	10 (77)
>9 Months	6 (50)	-	6 (46)
>12 Months	5 (42)	-	5 (38)

Abbreviations: CI = confidence interval; CR = complete response; N = number of patients; n = number of patients in the category; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: Quartile estimates are obtained from Kaplan-Meier survival curves. Patients (b) (6) were treated but excluded from the Efficacy Analysis Set because they did not have or could not be diagnosed for PEComa. No patient had complete response as of the last imaging date prior to the data cut-off on 22 May 2019.

a. This analysis includes partial responders only. Duration of response = (Date of disease progression or death – date confirmed CR or PR was first reported + 1)/30.4.

Source: Study PEC-001 CSR Table 14.2.1.13.

Progression-Free Survival (PFS) Based on Central Reader Assessment (Secondary Efficacy Endpoint)

The secondary endpoints of PFS and PFS rate at 6 months based on central readers' RECIST assessments are summarized in Table 37. Median PFS was 8.9 months (95% CI: 5.5, --), while the PFS rate at 6 months was 69.5% (95% CI: 47.6, 83.7). A Kaplan-Meier plot of PFS based on central reader assessment is presented in [Figure 7](#).

Table 37: Progression-Free Survival Based on Confirmed Central Readers' RECIST Assessments (Efficacy Analysis Set)

Progression-free Survival (PFS) ^a	Metastatic (N = 26)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 31)
Number at Risk	26	5	31
With Events	11	1	12
Censored	15	4	19
Quartiles and 95% CI of PFS (months)			
25 th	4.2 [1.4, 8.3]	8.9 [--, --]	4.2 [1.4, 8.4]
Median	8.4 [4.2, --]	8.9 [--, --]	8.9 [5.5, --]
75 th	-- [8.4, --]	8.9 [--, --]	-- [8.9, --]
3-Month Rate and 95% CI	75.3 [52.9, 88.2]	100.0	78.7 [58.5, 89.9]
6-Month Rate and 95% CI	65.3 [42.0, 81.1]	100.0	69.5 [47.6, 83.7]
9-Month Rate and 95% CI	47.1 [24.0, 67.3]	--	45.4 [22.6, 65.7]
12-Month Rate and 95% CI	47.1 [24.0, 67.3]	--	45.4 [22.6, 65.7]

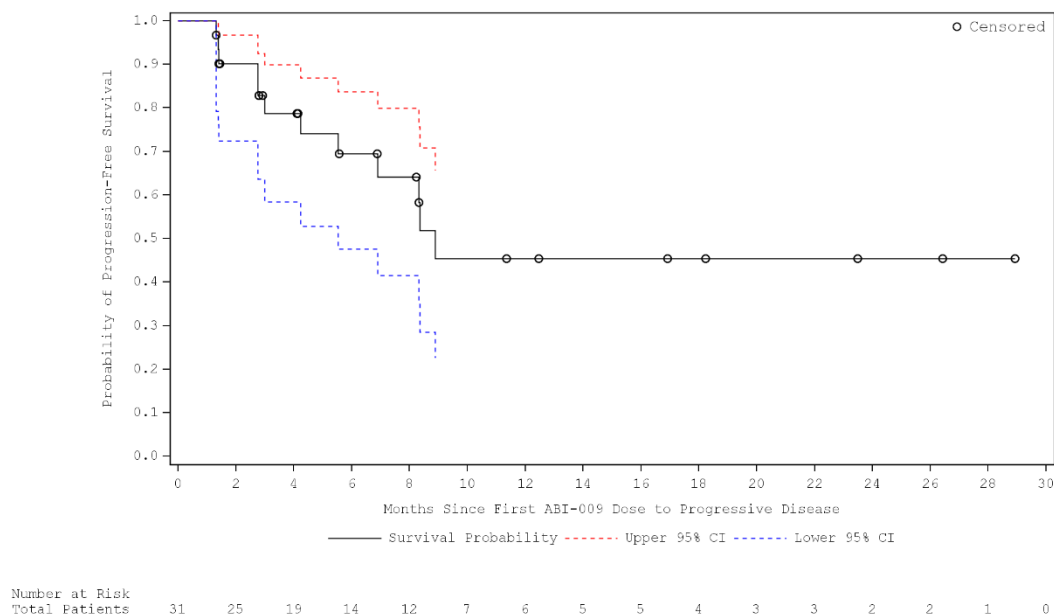
Abbreviations: CI = confidence interval; N = number of patients; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: Quartile and rate estimates are obtained from Kaplan-Meier survival curves. Unstable estimates for confidence intervals due to few patients among those with locally advanced disease and ineligible for surgery are excluded for reporting. Patients (b) (6) were treated but excluded from the Efficacy Analysis Set because they did not have or could not be diagnosed for PEComa.

a. PFS = (Date of disease progression or death – first dose date + 1)/30.4. Censored events comprise of patients who have not experienced progressive disease as of the last imaging date prior to the data cut-off on 22 May 2019. Months for censored events are as of the last imaging date.

Source: Study PEC-001 CSR Table 14.2.1.5.

Figure 7: Kaplan-Meier Plot of Progression-Free Survival Based on Confirmed Central Readers' RECIST Assessments (Efficacy Analysis Set)



Abbreviations: CI = confidence interval; RECIST = Response Evaluation Criteria in Solid Tumors.

Source: Study PEC-001 CSR Figure 14.2.1.5.1.

Sensitivity Analysis of Secondary Efficacy Endpoint Progression-Free Survival (PFS) Based on Central Reader Assessment

To explore the sensitivity of the secondary efficacy endpoints, the population of patients without any major protocol deviations (PP Analysis Set) was used to analyze PFS (Table 38). Median PFS and 95% CIs were identical to the analysis using the Efficacy Analysis Set, and the PFS rate at 6 months was similar at 70.8% (95% CI: 47.7, 85.1).

Table 38: Progression-Free Survival Based on Confirmed Central Readers' RECIST Assessments (Per Protocol Analysis Set)

Progression-free Survival (PFS) ^a	Metastatic (N = 26)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 31)
Number at Risk	24	4	28
With Events	10	1	11
Censored	14	3	17

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Progression-free Survival (PFS) ^a	Metastatic (N = 26)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 31)
Quartiles and 95% CI of PFS (months)			
25 th	4.2 [1.3, 8.3]	8.9 [--, --]	5.5 [1.4, 8.4]
Median	8.4 [4.2, --]	8.9 [--, --]	8.9 [5.5, --]
75 th	-- [8.4, --]	8.9 [--, --]	-- [8.9, --]
3-Month Rate and 95% CI	78.3 [55.3, 90.4]	100.0	80.9 [60.0, 91.6]
6-Month Rate and 95% CI	67.9 [43.8, 83.4]	100.0	70.8 [47.7, 85.1]
9-Month Rate and 95% CI	49.0 [24.9, 69.3]	--	46.2 [22.8, 66.8]
12-Month Rate and 95% CI	49.0 [24.9, 69.3]	--	46.2 [22.8, 66.8]

Abbreviations: CI = confidence interval; N = number of patients; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: Quartile and rate estimates are obtained from Kaplan-Meier survival curves. Unstable estimates for confidence intervals due to few patients among those with locally advanced disease and ineligible for surgery are excluded for reporting. Excluded from the Per Protocol Analysis Set are patients who did not have or could not be diagnosed for PEComa (b) (6), patients with uncontrolled serious medical/mental condition (b) (6), and one patient administered expired ABI-009 (b) (6).

a. PFS = (Date of disease progression or death – first dose date + 1)/30.4. Censored events comprise of patients who have not experienced progressive disease as of the last imaging date prior to the data cut-off on 22 May 2019. Months for censored events are as of the last imaging date.

Source: Study PEC-001 CSRTTable 14.2.1.8.

Progression-Free Survival (PFS) Based on Investigator's Assessment (Exploratory Efficacy Endpoint)

The exploratory endpoints of PFS and PFS rate at 6 months based on Investigators' RECIST assessments are summarized in Table 39. Median PFS was 8.4 months (95% CI: 5.5, --), while the PFS rate at 6 months was 61.1% (95% CI: 40.6, 76.4).

Table 39: Progression-Free Survival Based on Investigators' RECIST Assessments (Efficacy Analysis Set)

Progression-free Survival (PFS) ^a	Metastatic (N = 26)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 31)
Number at Risk	26	5	31
With Events	14	2	16
Censored	12	3	15

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	Metastatic (N = 26)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 31)
Progression-free Survival (PFS) ^a			
Quartiles and 95% CI of PFS (months)			
25th	3.0 [1.4, 6.9]	4.1 [4.1, 8.9]	4.1 [1.4, 6.9]
Median	8.4 [5.5, ----]	8.9 [4.1, 8.9]	8.4 [5.5, ----]
75th	---- [8.4, ----]	8.9 [4.1, 8.9]	---- [8.9, ----]
3-Month Rate and 95% CI	76.7 [55.3, 88.8]	100.0	79.8 [60.4, 90.4]
6-Month Rate and 95% CI	59.9 [38.1, 76.1]	66.7	61.1 [40.6, 76.4]
9-Month Rate and 95% CI	45.2 [24.5, 63.9]	-----	42.5 [22.9, 60.9]
12-Month Rate and 95% CI	39.6 [19.5, 59.1]	-----	37.2 [18.3, 56.2]

Abbreviations: CI = confidence interval; N = number of patients; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: Quartile and rate estimates are obtained from Kaplan-Meier survival curves. Unstable estimates for confidence intervals due to few patients among those with locally advanced disease and ineligible for surgery are excluded for reporting. Patients (b) (6) were treated but excluded from the Efficacy Analysis Set because they did not have or could not be diagnosed for PEComa.

a. PFS = (Date of disease progression or death – first dose date + 1)/30.4. Censored events comprise of patients who have not experienced progressive disease as of the last imaging date prior to the data cut-off on 22 May 2019.

Source: Study PEC-001 CSR Table 14.2.1.14.

Overall Survival (OS)

The secondary endpoint of OS is summarized in Table 40. Median OS had not been reached as 29 of 34 treated patients were still alive, with OS rate at 6 months of 93.2% (95% CI: 75.5, 98.3). Median time on study (ie, from first dose to date of last contact) was 11.5 months (Study PEC-001 CSR Table 14.1.1.1).

Table 40: Overall Survival (Safety Analysis Set)

	Metastatic (N = 29)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 34)
Overall Survival (OS) ^a			
Number at Risk	29	5	34
With Events	4	1	5
Censored	25	4	29
Quartiles and 95% CI of OS (months)			
25 th	22.2 [3.8, --]	-- [8.9, --]	22.2 [8.9, --]
Median	-- [18.0, --]	-- [8.9, --]	-- [22.2, --]
75th	-- [--, --]	-- [8.9, --]	-- [--, --]

	Metastatic (N = 29)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 34)
Overall Survival (OS) ^a			
6-Month Rate and 95% CI	92.0 [71.6, 97.9]	100.0 [100.0, 100.0]	93.2 [75.5, 98.3]
9-Month Rate and 95% CI	92.0 [71.6, 97.9]	75.0 [12.8, 96.1]	88.8 [68.7, 96.3]
12-Month Rate and 95% CI	92.0 [71.6, 97.9]	75.0 [12.8, 96.1]	88.8 [68.7, 96.3]

Abbreviations: CI = confidence interval; N = number of patients.

Note: Quartile estimates are obtained from Kaplan-Meier survival curves.

a. OS = (Date of death among those who died or date last known alive – first dose date + 1)/30.4.

Source: Study PEC-001 CSR Table 14.2.1.16.

Disease Control Rate (DCR) Based on Central Reader Assessment (Post-hoc Analysis of Exploratory Efficacy Endpoint)

The post-hoc exploratory endpoint of disease control rate (DCR; defined as the percentage of patients with a confirmed response or with SD of ≥ 12 weeks' duration) based on central readers' RECIST assessments is summarized in Table 41. The DCR was 71.0% (95% CI: 52.0, 85.8).

Table 41: Disease Control Rate Based on Confirmed Central Readers' RECIST Assessments (Efficacy Analysis Set)

Category	Metastatic (N = 26)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 31)
Disease Control Rate (DCR) ^a , n (%)	18 (69.2)	4 (80.0)	22 (71.0)
95% Exact CI	[48.2, 85.7]	[28.4, 99.5]	[52.0, 85.8]
Confirmed Partial Response (PR)	12 (46.2)	0	12 (38.7)
95% Exact CI	[26.6, 66.6]	-	[21.8, 57.8]
Stable Disease (SD) of ≥ 12 Weeks' Duration	6 (23.1)	4 (80.0)	10 (32.3)
95% Exact CI	[9.0, 43.6]	[28.4, 99.5]	[16.7, 51.4]

Abbreviations: CI = confidence interval; N = number of patients; n = number of patients in the category; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: 95% CI obtained from Clopper-Pearson exact test for binomial data. The exploratory efficacy endpoint is the percentage of patients with either confirmed partial response or stable disease with at least 12 weeks duration.

a. DCR = (PR + SD)/N, N is the total number of patients in the Efficacy Analysis Set.

Source: Study PEC-001 CSR Table 14.2.1.10.

Disease Control Rate (DCR) Based on Investigator's Assessment (Post-hoc Analysis of

Exploratory Efficacy Endpoint)

The post-hoc exploratory endpoint of DCR based on Investigators' RECIST assessments is summarized in Table 42. The DCR based on Investigator's review was similar to the DCR based on central readers' review, at 74.2% (95% CI: 55.4, 88.1).

Table 42: Disease Control Rate Based on Investigators' RECIST Assessments (Efficacy Analysis Set)

Category	Metastatic (N = 26)	Locally Advanced, Ineligible for Surgery (N = 5)	All Patients (N = 31)
Disease Control Rate (DCR) ^a , n (%)	19 (73.1)	4 (80.0)	23 (74.2)
95% Exact CI	[52.2, 88.4]	[28.4, 99.5]	[55.4, 88.1]
Confirmed Partial Response (PR)	12 (46.2)	1 (20.0)	13 (41.9)
95% Exact CI	[26.6, 66.6]	[0.5, 71.6]	[24.5, 60.9]
Stable Disease (SD) of ≥12 Weeks' Duration	7 (26.9)	3 (60.0)	10 (32.3)
95% Exact CI	[11.6, 47.8]	[14.7, 94.7]	[16.7, 51.4]

Abbreviations: CI = confidence interval; N = number of patients; n = number of patients in the category; RECIST = Response Evaluation Criteria in Solid Tumors.

Note: 95% CI obtained from Clopper-Pearson exact test for binomial data. The exploratory efficacy endpoint is the percentage of patients with either confirmed partial response or stable disease with at least 12 weeks duration.

a. DCR = (PR + SD)/N, N is the total number of patients in the Efficacy Analysis Set.

Source: Study PEC-001 CSR Table 14.2.1.15.

Biomarkers

Select immunohistochemistry tumor biomarkers and OncoPanel findings at baseline versus best overall response based on central readers' RECIST assessments are summarized in Table 43, while [Figure 8](#) illustrates the maximum percent of target lesion reduction versus pS6 expression status and *TSC1/TSC2* mutational status. Expression of pS6 was associated with response ($p = 0.008$), while lack of pS6 expression was a negative predictor of response. Patients with a *TSC2* mutation were significantly more likely to have a response to ABI-009 treatment (8/9 [89%] patients; $p < 0.001$), and all patients with a *TSC2* mutation had a target lesion response. Responses were also seen in patients with *TSC1* mutations (20%) or no *TSC1* or *TSC2* mutations (9%), although at much lower frequency than for *TSC2* mutations, indicating that ABI-009 is active regardless of mutational status. Of note, 91% of patients with no *TSC1* or *TSC2* mutations had a stable disease as best response, which further supports the clinical benefit of ABI-009 regardless of mutational status. Patients with a *TSC2* mutation were more likely to express pS6 (7/9 [77.8%] patients, [Figure 8](#)).

Table 43: Immunohistochemistry Tumor Biomarkers and OncoPanel Findings at Baseline versus Best Overall Response Based on Confirmed Central Readers' RECIST Assessments (Efficacy Analysis Set)

Biomarker	Complete/ Partial Response (N = 12)	Stable Disease (N = 16)	Progressive Disease (N = 3)
Immunohistochemistry (n = 25)			
pS6 status			
Negative (n = 8)	0	8/8 (100)	0
Positive (n = 17)	10/17 (59)	4/17 (24)	3/17 (18)
	p = 0.008 ^a		
Unknown pS6 status (n = 6)	2/6 (33)	4/6 (67)	0
OncoPanel for Mutational Status (n = 25)			
TSC1 mutation (n = 5)	1/5 (20)	3/5 (60)	1/5 (20)
TSC2 mutation (n = 9)	8/9 (89)	1/9 (11)	0
Neither TSC1 nor TSC2 (n = 6)	1/11 (9)	10/11 (91)	0
	p < 0.001 ^b		
Unknown mutational status (n = 6)	2/6 (33)	4/6 (67)	0

Abbreviations: N = number of patients; n = number of patients in the category; RECIST = Response Evaluation Criteria in Solid Tumors.

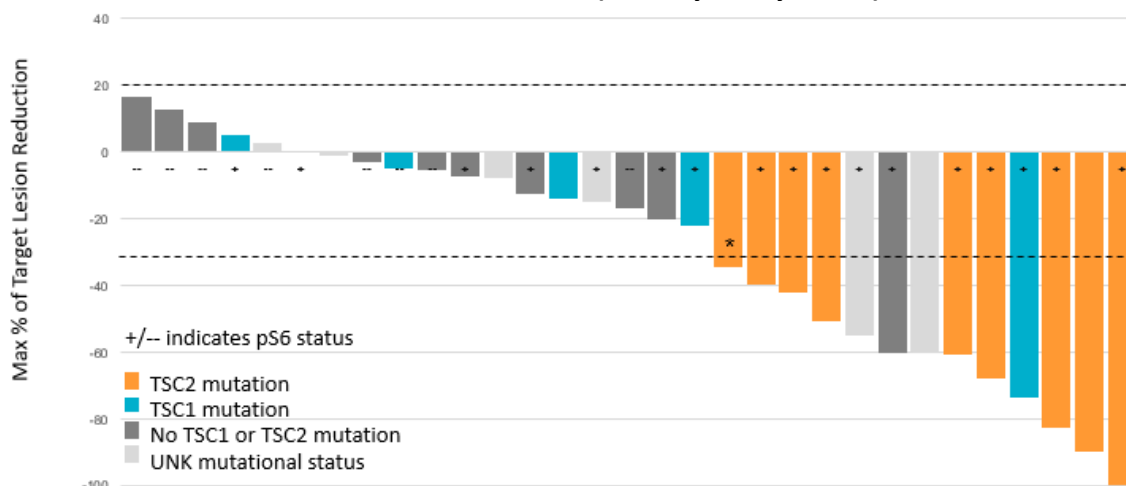
Note: Percentages are based on number of patients with positive, negative, or unevaluable biomarker status at screening.

a. 2x2 Fisher test.

b. Chi square test.

Source: Study PEC-001 CSR Table 14.2.3.2, Wagner 2019.

Figure 8: Maximum Percent Target Lesion Reduction versus pS6 Expression Status and TSC1/TSC2 Mutational Status (Efficacy Analysis Set)



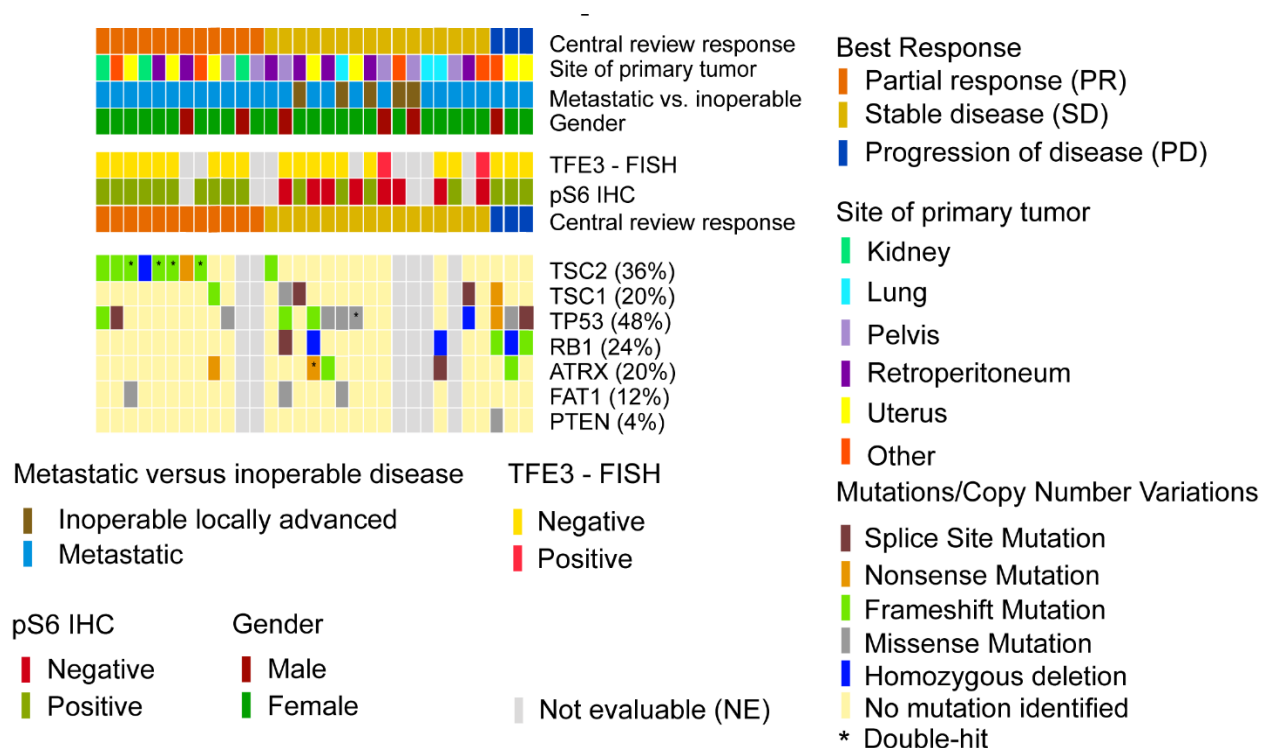
Abbreviations: Max = maximum; RECIST = Response Evaluation Criteria in Solid Tumors; UNK = unknown.

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Note: Each bar represents the maximum percentage of target lesion reduction for each individual patient in the Efficacy Analysis Set. Dashed lines represent the limit of target lesion stable disease, per RECIST.
* 1 patient with TSC2 mutation had an unconfirmed partial response, and thus best response is stable disease.
Source: Wagner 2019.

Figure 9 is a CoMut plot of the Efficacy Analysis Set, showing best overall response based on central readers' RECIST assessments, site of primary tumor, metastatic disease/locally advanced disease, gender, pS6 immunohistochemistry status, and mutations/copy number variations for each patient. No trend emerged for primary tumor site versus response, with responses observed in 7 types of primary tumor. Of note, 3/7 (42.9%) patients with uterine tumors, a hard-to-treat primary tumor type (Sanfilippo 2019), had a response. TFE3 translocation (2/22, both patients with SD) was infrequent and mutations in other genes (ATRX, RB1, FAT1, PTEN) were not associated with tumor response.

Figure 9: CoMut Plot for Efficacy Analysis Set



Abbreviations: FISH = fluorescence in situ hybridization; IHC = immunohistochemistry; NE = not evaluable; PD = progressive disease, PR = partial response, SD = stable disease.

Note: Each column represents a different patient.

Source: Wagner 2019.

The Applicant's Position:

This registrational trial met its primary endpoint demonstrating the efficacy of ABI-009 in PEComa. The independently-assessed ORR by 6 months was 38.7% (95% CI: 21.8, 57.8) with durable responses and an acceptable safety profile. There was a high degree of concordance between investigator and independent review of response.

The secondary endpoint of 6-month PFS rate of 69.5% (95% CI: 47.6, 83.7) , assessed by central review, compares favorably to historic reference points for potentially active therapeutics used in the treatment of sarcomas (>14% at 6 months) ([Penel 2011](#)). The 3-month PFS Rate of 78.7% (95% CI: 58.5, 89.9) compares favorably to the historical reference in sarcomas of ≥40% for an active regimen ([Penel 2011](#)).

Rapid responses were observed (median time to response 1.4 months), and although median DOR was not reached, the 25th percentile of 7.0 months (95% CI: 5.6, --) indicates that patients achieved a durable response, with 10 (83%), 6 (50%), and 5 (42%) patients having a response of >6, >9, and >12 months duration, respectively. As of the 22 May 2019 data cut-off for the primary analysis, 9/12 (75%) of responders were still on treatment.

The majority (26/31, 83.9%) of the efficacy evaluable patients had metastatic disease, and 12/26 (46.2%) patients had a response during treatment with ABI-009.

The 5 locally advanced and ineligible for surgery patients had SD as their best response on treatment (0% PD), and their 3-month and 6-month PFS rate was 100% each.

Although the subgroup patient populations are small for definitive conclusions, the results provide evidence that patients benefitted from treatment with ABI-009 regardless of age or gender. In particular, patients ≥65 years of age benefitted from treatment, with 9/14 (64.3%) achieving a PR. Six patients had a previous line of therapy; of the 4 evaluable for response, 3 (75.0%) had a PR, suggesting that ABI-009 may be efficacious in previously treated patients.

In patients with primary uterine PEComa, a hard-to-treat subset ([Sanfilippo 2019](#)), there was a high response rate (3/7 patients; 42.9%).

The disease control rate (confirmed CR + PR or SD ≥12 weeks) of 71.0% (95% CI: 52.0, 85.8) demonstrated clinical benefit in the majority of patients.

As of the data cut-off date, 27/34 treated patients were alive; median OS had not been reached, with OS rate at 6 months of 93.2% (95% CI: 75.5, 98.3), and an OS rate at 12 months of 88.8% (95% CI: 68.7, 96.3). Median time on study (ie, from first dose to date of last contact) was 11.5 months.

The FDA's Assessment:

The FDA received the updated DOR data on October 7th, 2021 with data cut off date (DCO) of June 30, 2021, which reflected 25 months of follow-up after the primary analysis date and approximately 2.5 years after the last patient initiated treatment. See Table 44 below for updated DOR results. The median DOR was not reached with a range of 5.6 to 55.5+ months. Four of 12 responders were still receiving treatment as of June 30, 2021. Assessment of DOR is based on patients who responded within the efficacy analysis set (N=31). All other DOR analyses based on different analysis populations are considered exploratory.

Table 44: Duration of response (DOR) with data cut off June 30, 2021

Duration of Response (DOR)	(N=12)
Median (95% CI) in months	NR (6.5, NE)
Range in months	5.6, 55.5+
% with duration ≥ 6 months	92%
% with duration ≥ 12 months	67%
% with duration ≥ 24 months	58%

Sensitivity analyses of ORR and DOR per investigator assessment, different data cut offs, and different analysis populations were generally consistent with the primary analyses for ORR and DOR.

FDA also notes that time-to-event endpoints (e.g., PFS and OS) are not interpretable in a single arm trial and are considered exploratory. FDA also does not consider DCR as an interpretable efficacy endpoint for single-arm studies because it incorporates stable disease, which is dependent upon underlying tumor biology and other intrinsic factors which may vary from patient to patient.

Although no objective responses were noted among patients with locally-advanced unresectable tumors, 2 patients with unresectable tumors at the time of enrollment were subsequently able to undergo resection following treatment with ABI-009.

The majority of responders harbored genetic alterations in *TSC2* (8 of 10 patients), and all responders demonstrated pS6 positivity on immunohistochemistry. Given the small sample size of these subgroups, FDA considers these biomarker analyses to be exploratory.

Dose/Dose Response

Data:

The PEC-001 study was conducted at a single dose. While CA401 evaluated multiple doses, it was not designed as an efficacy study. It is notable that CA401 did provide evidence of efficacy response to ABI-009 in patients with solid tumors.

The Applicant's Position:

Because the one study conducted in PEComa patients, PEC-001, evaluated a single dose level of ABI-009, evaluation of dose/dose response was not applicable to this program.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Durability of Response

Data:

See above described Efficacy Results – Secondary and other relevant endpoints.

The Applicant's Position:

At the time of data cut-off for the NDA, the median DOR was not reached. However, the 25th percentile of 7.0 months (95% CI: 5.6, --) indicates that patients achieved a durable response, with 10 (83%), 6 (50%), and 5 (42%) patients having a response of >6, >9, and >12 months duration, respectively. As of the 22 May 2019 data cut-off for the primary analysis, 9/12 (75%) of responders were still on treatment.

The FDA's Assessment:

The FDA agrees with the Applicant's position. See above information regarding updated duration of response data from the June 30, 2021 data cut-off.

Persistence of Effect

Data:

See above in the section for Efficacy Results – Secondary and other relevant endpoints.

The Applicant's Position:

There have been no prior prospective trials in patients with advanced malignant PEComa. However, across a majority of clinical trials in soft-tissue sarcoma (STS), response rates are low and typically below 20% ([Bramwell 2000](#), [Chugh 2009](#), [Garcia del Muro 2016](#), [Tap 2016](#), [Comandone 2017](#)), indicating that the 39% observed ORR is clinically meaningful in PEComa, a rare type of STS.

The median TTR was 1.4 months (95% CI: 1.3, 1.4). Median DOR had not been reached as of the 22 May 2019 data cut off, as 9/12 (75%) responding patients were still on treatment at the time of the analysis; when censoring was ignored, the range was 4.2+ to 27.7+ months. The 25th percentile for DOR of 7.0 months (95% CI: 5.6, --) indicates that patients achieved a clinically meaningful benefit with rapid and durable responses, with 10 (83%), 6 (50%), and 5 (42%) patients having a response of >6, >9, and >12 months duration, respectively. Notably, one patient with a primary renal PEComa that metastasized to the lungs and lymph nodes had a PR for 9.7 months that converted to a CR, and is ongoing treatment at 23.3+ months. Eight of the 9 patients are responders (1 CR and 7 PR), indicating that patients have continued benefit, and that ABI-009 is tolerable as long-term treatment and produces durable responses. Of note, as of 22 May 2020, 7 responding patients remain on treatment and when censoring was ignored, the range for DOR was 5.6 to 42.4+ months) suggestive of highly durable responses.

While none of the patients in the locally advanced and ineligible for surgery group achieved responses, all 5 patients achieved stable disease. The median duration of treatment was 3.98 months, ranging from 0.3–8.2 months. The range of maximum percent change in target tumor reduction was 2.8–22.3%. Patient (b) (6) experienced a 7.9% reduction in target lesions after 1 cycle, and Patient (b) (6) had a 22.3% reduction in target lesions after 10 cycles. During the post-treatment long-term survival follow-up, it was reported that these 2 patients (40%) were able to undergo surgery to remove the locally advanced tumor following ABI-009 treatment. Both patients remained in long-term survival follow-up (2 and 2.5 years, respectively) as of the 22 May 2019 data cut-off for the primary analysis. Of note, both of these patients were disease-free at the time of data cut-off as reported by the investigators, and had not initiated any additional therapy. During the on-study follow-up, Patients (b) (6) were last confirmed to be alive and without recurrence on 16 April 2020 and 05 March 2020, respectively.

Median PFS was 8.9 months (95% CI: 5.5, --); the PFS rate at 3 months was 78.7% (95% CI: 58.5, 89.9) and the PFS rate at 6 months was 69.5% (95% CI: 47.6, 83.7), both of which compare favorably to the 'potentially active' historical rates of ≥40% at 3 months and ≥14% at 6 months for an active therapy in advanced sarcoma ([Penel 2011](#)).

Median OS had not been reached, with OS rate at 6 months of 93.2% (95% CI: 75.5, 98.3), and rate at 12 months of 88.8% (95% CI: 68.7, 96.3).

The DCR (defined as the percentage of patients with a confirmed response or with SD of ≥ 12 weeks' duration) was 71.0% (95% CI: 52.0, 85.8), demonstrating clinical benefit for the majority of patients.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position. See above information regarding updated duration of response data from the June 30, 2021 data cut-off. FDA reiterates that time to event endpoints such as PFS and OS are not interpretable in a single arm study.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

No PRO data were collected in Study PEC-001.

The Applicant's Position:

Patient-reported endpoints were not included or evaluated in Study PEC-001.

The FDA's Assessment:

The FDA acknowledges no COA (PRO) data was collected in Study PEC-001.

Additional Analyses Conducted on the Individual Trial

Data:

No other analyses were planned or conducted in Study PEC-001.

The Applicant's Position:

No additional analyses were identified as appropriate for Study PEC-001.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

Study PEC-001 was an open-label, single-arm trial that enrolled 31 evaluable patients with locally advanced, unresectable, or metastatic malignant PEComa. Patients were required to have measurable disease at baseline with centrally confirmed diagnosis by pathology of malignant PEComa. Patients received ABI-009 at a dose of 100 mg/m² on Days 1 and 8 of 21-day cycles until disease progression or unacceptable toxicity. Among the 31 evaluable patients, the ORR was 38.7% (95% CI: 21.8%, 57.8%). All responses were partial responses and all responding patients had metastatic disease; two patients with partial responses later converted to complete responses. Subgroup analyses showed consistent results across several pre-specified subgroups. Based on the data cut-off date of June 30, 2021, the median DOR was not reached, with a range of 5.6 to 55.5+ months. The FDA considers the efficacy results described above to be clinically meaningful and a direct clinical benefit to patients with this rare, life-threatening cancer.

8.1.4. Assessment of Efficacy Across Trials

Primary Endpoints

Data:

A single study to evaluate efficacy of ABI-009 in PEComa patients was conducted. Therefore, assessment of efficacy across trials was not applicable to this population.

The Applicant's Position:

The efficacy of ABI-009 100 mg/m² administered as an IV infusion over 30 minutes on Days 1 and 8 of a 21-day cycle for the treatment of advanced (metastatic or locally advanced) malignant PEComa is provided primarily by a single arm Phase 2 study in PEComa patients (Study PEC-001), supported by evidence of efficacy from a dose-finding Phase 1 study in patients with metastatic solid tumors (Study CA401). Efficacy results for these two studies are presented separately and are considered inappropriate for pooling due to differences in patient populations and dosing regimens.

The FDA's Assessment:

The FDA agrees with the Applicant's description that only efficacy results from PEC-001 were used to provide primary evidence of efficacy.

Secondary and Other Endpoints

Data:

A single efficacy study (PEC-001) was performed in patients with malignant PEComa.

The Applicant's Position:

Because only a single efficacy study was performed in patients with malignant PEComa, comparison of secondary and other efficacy endpoints across ABI-009 trials was not considered appropriate.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Subpopulations

Data:

A single efficacy study (PEC-001) was performed in patients with malignant PEComa.

The Applicant's Position:

Because only a single efficacy study was performed in patients with malignant PEComa, comparison of efficacy across subpopulations in ABI-009 trials was not considered appropriate.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Additional Efficacy Considerations

The FDA's Assessment:

Not applicable.

8.1.5. Integrated Assessment of Effectiveness

Data:

A single efficacy study (PEC-001) was performed in patients with malignant PEComa.

The Applicant's Position:

Because only a single efficacy study was performed in patients with malignant PEComa, integration of efficacy data was not considered appropriate.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

8.2. Review of Safety

The Applicant's Position:

The safety and tolerability of ABI-009 have been evaluated in 4 completed or ongoing Aadi-sponsored, oncology clinical trials in which ABI-009 was administered by IV infusion (further details on these studies are provided in Section 7). As agreed in the 10 December 2018 Type C Meeting with the FDA (Reference ID: 4354943), the studies planned for inclusion in the integrated summary of safety were limited to those studies where ABI-009 was administered via IV infusion, and to studies sponsored by Aadi. In accordance with agreements reached in the above-mentioned meeting, Module 2.7.4 Summary of Clinical Safety presents the integrated safety summary required by the regulations [21 CFR 314.50(d)(5)(vi)(a)]. The Agency requested a side-by-side comparison of results from Study PEC-001 and the pooled oncology data in which ABI-009 was administered intravenously (solid tumors, colorectal cancer, glioblastoma), and a side-by-side comparison of the pooled oncology safety data with safety data from patients enrolled in Aadi-sponsored non-oncology protocols (pulmonary arterial hypertension) in which ABI-009 was administered intravenously. For the integrated safety, tables summarized data in side-by-side columns (provided in Module 5.3.5.3; also see Module 2.7.4 Table 10):

- Study PEC-001 alone (N = 34)
- Oncology pool with PEC-001 (N = 76)
 - Study PEC-001 (n = 34)
 - Study CA401 (n = 26)
 - Study GBM-007 (n = 9)
 - Study COLO-007 (n = 7)
- Oncology pool without Study PEC-001 [N = 42]
 - Study CA401 (n = 26)
 - Study GBM-007 (n = 9)
 - Study COLO-007 (n = 7)
- Non-oncology Study PAH-001 [N = 9]].

The FDA's Assessment:

The FDA agrees with the Applicant's position.

8.2.1. Safety Review Approach

The Applicant's Position:

The safety and tolerability of ABI-009 have been evaluated in 4 completed or ongoing Aadi-sponsored, oncology clinical trials in which ABI-009 was administered by IV infusion (further details on these studies are provided in Section 7).

Study PEC-001 is the Phase 2 pivotal clinical study to support approval of ABI-009 for the treatment of patients with advanced malignant PEComa. Study CA401 was the first-in-human Phase 1 dose-finding study of ABI-009 in patients with metastatic solid tumors and was completed in 2011. Study GBM-007 and Study COLO-007 are 2 additional ongoing, Aadi-sponsored oncology clinical studies in which no new safety signals have been identified to date.

Study PAH-001 is an ongoing study evaluating the safety of ABI-009 as a novel, targeted, systemic therapy for PAH in combination with standard of care treatment, and are summarized herein. No new safety signals have been identified in this PAH study.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position. During review of the pooled oncology population without Study PEC-001 and the non-oncology population (Study PAH-001), FDA determined that only 4 additional patients were treated with ABI-009 as a single agent at the recommended dosage. An assessment of safety among patients receiving combination therapy would be confounded by the concomitant drugs, and because patients treated at lower doses of ABI-009 may not exhibit the same toxicities, FDA's approach to safety review included only patients in Study PEC-001 in the primary safety analysis. Safety data from patients enrolled on Study CA401, Study GBM-007, Study COLO-007, and Study PAH-001 were considered supportive in the review.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

An overview of the 85 patients who received at least 1 dose of ABI-009 are summarized in integrated summary of safety (ISS) Table 4.1.1 and ISS Table 4.1.3 (additional data summarized in Module 2.7.4 Table 9), presented as pooled oncology data (with or without Study PEC-001), at the time of the data cut-off, as well as the individual non-oncology and the oncology studies.

In Study PEC-001, 10 (29%) of the 34 patients were still on treatment. Exposure for the other studies is lower, due to differences in study design, dosing, or maturity of data.

In particular, Study CA401 was a dose-escalation study starting at lower doses. The other oncology studies (COLO-007 and GBM-007) used lower doses of ABI-009 (20–60 mg/m²) in combination with standard of care. These studies were initiated more recently, with 50% (8/16) of patients still on treatment.

The Applicant's Position:

Overall in Study PEC-001, patients received a median of 8.5 treatment cycles (16.5 infusions) over 5.43 months. The median dose intensity of 55.56 mg/m² represents 83.29% of the possible maximum in the regimen, indicating high treatment compliance.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Relevant characteristics of the safety population:

Data:

Demographic and baseline characteristics are summarized in ISS Table 2.1 and ISS Table 2.3. In general, the demographic and baseline characteristics were similar across the studies with regard to median age, race, ethnicity, baseline body mass index (BMI), and body surface area (BSA). The pooled oncology data (without Study PEC-001) was weighted toward male patients (69.0%), while Study PEC-001 and Study PAH-001 had a higher percentage of female patients (82.4% and 88.9%, respectively), which is consistent with known epidemiology.

Disease characteristics at baseline are summarized in ISS Table 3.1 and ISS Table 3.3. Diagnosis at baseline for patients enrolled into Study CA401 varied, as this study enrolled patients with metastatic solid tumors. The other studies limited enrollment to high-grade (Grade 3 and 4) glioblastoma/anaplastic astrocytoma/anaplastic oligodendroglioma for Study GBM-007, metastatic colorectal cancer for Study COLO-007, advanced malignant PEComa for Study PEC-001, and pulmonary arterial hypertension with WHO Functional Class II–III for Study PAH-001. The sites of primary lesion site or disease were brain (categorized as Head and Neck) for Study GBM-007, colorectal for Study COLO-007, and lung/thoracic Study PAH-001, and varied for Study CA401 and Study PEC-001 as summarized in ISS Table 3.1 and ISS Table 3.3.

The Applicant's Position:

Integration of safety data from the oncology studies was considered appropriate, with similar results with and without the PEComa population. Due to differences in disease characteristics, the PAH safety data were not pooled with safety data from the oncology studies. The demographic characteristics of patients in the PAH study were similar to the oncology studies,

despite the differences in disease characteristics.

Demographics and baseline disease characteristics were as expected for the populations in the ABI-009 studies included in the integrated summary of safety. In general, the demographic and baseline characteristics were similar across the studies with regard to median age, race, ethnicity, baseline body mass index (BMI), and body surface area (BSA). The pooled oncology data (without Study PEC-001) was weighted toward male patients (69.0%), while Study PEC-001 and Study PAH-001 had a higher percentage of female patients (82.4% and 88.9%, respectively), which is consistent with known epidemiology. Patients in Study PEC-001 mostly were older (mean age, 59.5 years; range, 27 to 78 years), and PEComa is known to be more common in older adults.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position. Baseline characteristics for the 34 patients comprising the primary safety population in Study PEC-001 are listed in the table below:

Table 45: Demographic characteristics of patients enrolled in Study PEC-001

Characteristic	Study PEC-001 (N = 34)
Age (years)	
n	34
Mean (SD)	57.9 (12.71)
Median	59.5
Min, Max	27, 78
Age Category, n (%)	
<65 years	19 (56)
≥65 years	15 (44)
<75 years	32 (94)
≥75 years	2 (6)
Sex, n (%)	
Male	6 (18)
Female	28 (82)
Ethnicity, n (%)	
Hispanic or Latino	5 (15)
Not Hispanic or Latino	28 (82)
Not Reported	1 (3)

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Characteristic	Study PEC-001 (N = 34)
Race, n (%)	
White	24 (71)
Black or African American	3 (9)
Asian	3 (9)
Native Hawaiian or Other Pacific Islander	1 (3)
Other	1 (3)
Not Reported	2 (6)
ECOG Performance Status, n (%)	
0	26 (76)
1	8 (24)
Height (cm)	
n	34
Mean (SD)	163.37 (10.243)
Median	162.00
Min, Max	144.8, 188.0
Weight (kg)	
n	34
Mean (SD)	72.88 (18.917)
Median	72.80
Min, Max	45.2, 117.9
Body Mass Index (kg/m ²)	
n	34
Mean (SD)	27.12 (5.972)
Median	26.47
Min, Max	19.3, 43.3
Body Surface Area (m ²)	
n	34
Mean (SD)	1.79 (0.264)
Median	1.82
Min, Max	1.4, 2.4

Abbreviations: ECOG = Eastern Cooperative Oncology Group; Max = maximum; Min = minimum;
N = number of patients; n = number of patients in the category; SD = standard deviation.

Note: Percentages are based on the number of patients in the Safety Analysis Set in each group.

Source: Study PEC-001 CSR Table 14.1.2.1.

Adequacy of the safety database:

The Applicant's Position:

PEComa is a rare disease, and in the ABI-009 clinical program the database of patients with advanced malignant PEComa in Study PEC-001 is supplemented by patients with solid tumors in completed Study CA401 who had similar demographic characteristics and exposure to ABI-009, as well as patients in the ongoing GBM-007 and COLO-007 studies. Thus, as presented in the ISS, the ABI-009 safety database consists of over 70 oncology patients. As of the 22 May 2019 data cut-off date, 10 patients continued on therapy in the PEC-001 study and additional patients were continuing treatment in the ongoing oncology (n = 8) and nononcology (n = 7) programs, providing additional safety data.

The reported safety data are consistent with the known safety profile of sirolimus, the RLD.

In response to Aadi's Pre-NDA Meeting request dated 28 February 2020, the FDA provided the following feedback regarding the adequacy of the safety review plan:

- Confirmed that topline data from PEC-001 with a cutoff date when all patients had an opportunity to be treated for 6 months (occurred on 22 May 2019) are sufficient to support an NDA.
- Confirmed planned statistical analyses and tables, figures, and listings (TFLs) presentations for registrational Study PEC-001 and supporting safety studies are acceptable
- Confirmed that the proposed technical data packages supporting the PEC-001 clinical study, integrated summary studies, and BIMO plan are acceptable

Demographic and baseline characteristics of patients treated with 100 mg/m²/week ABI-009 administered via IV infusion over 30 (±10) minutes weekly for 2 weeks, followed by a week of rest (ie, a 21-day cycle) were generally representative of the PEComa population. Treated patients varied with respect to age, sex, race, and ethnicity. The duration of treatment in Study PEC-001 is adequate to provide assessment of adverse reactions.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position. Additional data from the 90-day safety update (data cut-off January 30, 2021) were used to support the safety review.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:

Data monitoring, in addition to site and vendor audits, ensured the accuracy and completeness of clinical safety data collected in the ABI-009 program.

The Applicant's Position:

No issues were identified regarding data integrity or submission quality that had an effect on the clinical safety review.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Categorization of Adverse Events

Data:

In the ABI-009 clinical program, similar safety data categorization methods were used across all clinical studies to capture AEs, physical examination results, vital signs (inclusive of electrocardiogram [ECG] results), concomitant medication records, and the results of clinical laboratory sample evaluations. Adverse events, AESIs (relevant to mTOR inhibitors) and SAEs were coded using the MedDRA reporting system. Adverse events were graded according to the NCI CTCAE version 4.03.

Detailed methods for individual studies are provided in each respective protocol. The safety data categorization methods are summarized in Table 46.

Table 46: Safety Data Categorization Methods

Data Categorization Parameter	Method for Data Categorization
Adverse Event (AE) Definitions and Data Categorization Procedures	For all studies, AEs were collected continuously beginning with the signing of informed consent until 28 days (PEC-001, GBM-007, COLO-007, PAH-001) or 30 days (CA401) after the patient's last dose of ABI-009. CA401 Adverse events included: • an exacerbation of a pre-existing illness • an increase in frequency or intensity of a pre-existing episodic event or condition • a condition detected or diagnosed after protocol drug administration even though it may have been present prior to the start of the protocol

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Data Categorization Parameter	Method for Data Categorization
	- continuously persistent disease or symptoms that were present at baseline and worsened following the start of the protocol PEC-001, GBM-007, COLO-007, PAH-001 Adverse events are any noxious, unintended, or untoward medical occurrence that may appear or worsen in a patient during the course of a protocol, and include: - new intercurrent illness - worsening concomitant illness - an injury - any concomitant impairment of the patient's health - any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) - a diagnosis or syndrome - abuse, withdrawal, sensitivity, or toxicity to the study drug - any sequela of an accidental or intentional overdose of the study drug The Investigator was to assess all AEs and serious adverse events (SAEs) and record each on the appropriate case report form or Serious Adverse Event Report Form. Events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 9 (CA401, updated to version 21), version 20 (PAH-001, updated to version 21), or version 21 (PEC-001, GBM-007, COLO-007).
AE Severity	The Investigator assessed severity for each AE and SAE reported during the study, using the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0 (CA401), version 4.03 (PEC-001, PAH-001), or version 5.0 (GBM-007, COLO-007). Maximum intensity was assigned using one of the severity grades as outlined in the CTCAE. If the AE is not specifically listed in CTCAE, the following grades were to be used: - Grade 1: mild - Grade 2: moderate - Grade 3: severe - Grade 4: life-threatening or disabling - Grade 5: death
Assessment of Causality	The Investigator's assessment of causality was provided for all AEs (serious and non-serious) as outlined in the CA401, PEC-001, GBM-007, COLO-007, and PAH-001 protocols. An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the study drug caused or contributed to an AE. Clinical failure without evidence of study drug toxicity was to be considered unrelated to study drug. These criteria, in addition to good clinical judgment, was to be used as a guide for determining the causal assessment.

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Data Categorization Parameter	Method for Data Categorization
Deaths, Other Serious AEs, and Other Significant AEs	Serious, life-threatening, and unexpected AEs were identified and handled in accordance with the United States Code of Federal Regulations (21 CFR §312.32) or in accordance with the International Council for Harmonisation (ICH) guidance document E2A “Clinical Safety Data Management: Definitions and Standards for Expedited Reporting”. These events were recorded on the AE case report form. All unresolved SAEs (“ongoing” at the final study visit) were followed by the study staff until resolution or deemed stable.
Other Safety Assessments	Physical examinations, vital signs measurements, 12-lead ECGs, and clinical laboratory assessments were performed at the Screening visit and throughout the study as indicated in the Schedule of Activities of the CA401, PEC-001, GBM-007, COLO-007, and PAH-001 protocols. Clinically significant findings were recorded as medical history or AEs.
Concomitant Medications	Concomitant medications were collected throughout the study and recorded in the case report form, including (but not limited to) indication, total daily dose, route, and time/duration of administration.

The Applicant’s Position:

Adverse event and other safety data were collected and categorized in accordance with accepted standards as defined in regulations and guidance and according to clinical practice. Adverse events, AESIs, and SAEs were coded using the MedDRA reporting system and were graded according to NCI CTCAE version 4.03. Categorization and collection methods were prespecified in the clinical protocols and meaningful deviations from protocols were identified.

The FDA’s Assessment:

The FDA agrees with the Applicant’s position. Recorded adverse events included all treatment-emergent adverse events.

Routine Clinical Tests

Data:

The protocols prespecified the various clinical laboratory evaluations to be performed before study entry, throughout the study, and at the follow-up evaluation. Hematology tests included a complete blood count (CBC) including, but not limited to white blood cell count with differential, hemoglobin, hematocrit, and platelet count. Chemistry tests included albumin, alkaline phosphatase, amylase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), lipase, magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, and total protein.

The Applicant's Position:

The two studies with CSRs (CA401 and PEC-001) revealed little to no effect of ABI-009 on laboratory values in addition to those identified as part of the AESI terms. The 60 patients in these two studies represent the total enrollment in the single-agent oncology studies, and present a view of the effect of ABI-009 on laboratory assessments not confounded by toxicities from other drugs in the combination-agent oncology studies' dosing regimens. The addition of clinical laboratory data from the combined-agent oncology studies would confound those from ABI-009 monotherapy oncology studies, and would be of little additional value and were therefore not included in the integrated safety tables.

The FDA's Assessment:

The FDA disagrees with the Applicant that review of Study CA401 and PEC-001 "revealed little to no effect of ABI-009 on laboratory values." For more information see the results of FDA's review of laboratory abnormalities, described in Section 8.2.4 below.

8.2.4. Safety Results

Deaths

Data:

Patients with outcome of death are summarized in ISS Table 6.8.1 and ISS Table 6.8.3.

There were 3 fatal TEAEs identified in the safety database. In Study PEC-001, Patient (b) (6) died from upper gastrointestinal hemorrhage, and Patient (b) (6) died from atelectasis, both considered by the Investigator to be unrelated to ABI-009. In Study CA401, Patient (b) (6) died of dyspnea, considered by the Investigator to be possibly related to ABI-009.

In addition, 3 patients in Study CA401 died from progressive disease during the study's reporting period.

Median time from initiation of treatment to death was 29.1 weeks for the 2 patients who had a fatal TEAE in Study PEC-001, and 10.5 weeks for the 4 patients who died in Study CA401 for.

The Applicant's Position:

There were 3 fatal TEAEs: 2 for Study PEC-001 both of which were considered by the Investigator to be unrelated to study treatment (upper gastrointestinal hemorrhage, and atelectasis), and 1 for Study CA401 (dyspnea), which was considered by the Investigator to be possibly related to ABI-009. The two patient deaths on Study PEC-001 were both likely related to disease progression. The patient death on CA401 with the event term of dyspnea occurred in a patient who had been noted to have pulmonary infiltrates by chest computed tomography

in (b) (6) with worsening at the time of the adverse event report of (b) (6). To further assess the dyspnea SAE, we reviewed the frequency of similar AEs and SAEs and note that the rate of dyspnea grade ≤ 3 across both studies was 11/76 (14.5%); the rate of respiratory failure $\leq$ grade 3 was 0. Among SAEs, dyspnea was reported as 2/76 (2.6%) and respiratory failure, 1/76 (1.3%). These rates and severity of dyspnea are not unexpected given that the patients all had advanced malignancies. We also reviewed the incidence of GI bleeding or upper GI bleeding. The rate was 0 for grade ≤ 3 and among SAEs, the rate was 2/76 (2.6%) and 1/76 (1.3%), respectively. These rates of GI bleeding SAEs also are not unexpected given the debility of the safety population. Thus, Aadi concludes that the 3 SAEs resulting in death were not associated with a safety signal for ABI-009.

The FDA's Assessment:

The FDA disagrees with the Applicant's position as our review identified one death as being associated with the safety signal of hemorrhage. No additional safety signals were identified in this review.

There were two deaths in Study PEC-001:

Patient (b) (6) had a history of chronic obstructive pulmonary disease and pulmonary hypertension with metastatic malignant PEComa of the left latissimus dorsi. Treatment with ABI-009 was initiated on (b) (6), and the last dose was administered on (b) (6). On (b) (6), follow-up imaging revealed disease progression and the end of treatment visit was on (b) (6). On (b) (6), the patient was admitted to the hospital after a fall. Imaging revealed continued disease progression including lung metastases. On (b) (6), the patient died of respiratory failure, with a reported preferred term of atelectasis. FDA considered this event to be related to disease progression, and therefore this event was not described in Section 6 of the product label.

Patient (b) (6) had a history of gastritis and advanced malignant PEComa of the right bronchus. Treatment with ABI-009 was initiated on (b) (6), and the last dose was administered on (b) (6). The first dose of Cycle 13 was held due to decreased hemoglobin (8.1 g/dL) on (b) (6). Platelets were within normal limits. On the evening of (b) (6), the patient experienced massive hematemesis at home, which was followed by cardiac arrest and death. The contribution of ABI-009 to this case of fatal hemorrhage could not be ruled out; in addition, a significant proportion of patients (24%) experienced bleeding of any Grade in a pooled term analysis, providing further evidence to support a possible causative role of ABI-009. Therefore, this death was considered a fatal adverse reaction and was described in Section 6 of the product label. Refer to Section 8.2.11 regarding the risk of hemorrhage and corresponding Warning in the product label.

There were 4 additional deaths in Study CA401:

Three deaths were determined to be related to disease progression. An additional death occurred in a 65 year old male patient with esophageal carcinoma with lung metastases who developed possible community acquired pneumonia and died of respiratory failure 17 days after his last dose of ABI-009. After review of the case, and in light of an identified safety signal for infection observed with ABI-009, the contribution of ABI-009 to this death could not be ruled out. The risk of serious infections, including pneumonia, is communicated in the Warnings and Precautions section (5.3) of labeling for ABI-009.

Serious Adverse Events

Data:

Treatment-emergent serious adverse events (TESAEs) are summarized in ISS Table 6.2.1, ISS Table 6.2.3, ISS Table 6.7.1 and ISS Table 6.7.3, and treatment-emergent related serious adverse events (TERSAEs) are summarized in ISS Table 6.4.1 and ISS Table 6.4.3.

Treatment-emergent serious adverse events occurred in 14 (41.2%) patients in Study PEC-001 with a TESAE incidence rate (per 100 person-weeks) of 2.6, with similar incidence percentages in the pooled oncology data (with and without Study PEC-001). Most SAEs (ie, individual event terms) occurred in only ≤ 1 patient in each study, with 3 events in Study PEC-001 occurring in 2 patients each (abdominal pain, upper gastrointestinal hemorrhage, dehydration); TESAEs occurring in ≥ 2 patients in the pooled oncology data (with Study PEC-001) included: abdominal pain and failure to thrive (3 [3.9%] patients each); upper gastrointestinal hemorrhage, pyrexia, pneumonia, dehydration, dyspnea (2 [2.6%] patients each).

Treatment-emergent serious adverse events occurred in 2 (22.2%) patients in Study PAH-001 with a TESAE incidence rate (per 100 person-weeks) of 1.2. No individual event term occurred in >1 patient.

Treatment-emergent related serious adverse events occurred in 8 (23.5%) patients in Study PEC-001, with similar incidence percentages in the pooled oncology data (with Study PEC-001). Incidence rates of TERSAEs were lower in the other oncology studies, resulting in a lower percentage in the pooled oncology data (without Study PEC-001). Most TERSAEs (ie, individual event terms) occurred in only ≤ 1 patient in each study, with dehydration occurring in 2 patients in Study PEC-001; TERSAEs occurring in ≥ 2 patients in the pooled oncology data (with Study PEC-001) included: dehydration and failure to thrive (2 [2.6%] patients each). No distribution pattern of TERSAEs was apparent across the oncology studies.

Treatment-emergent related serious adverse events occurred in 1 (11.1%) patient in Study PAH-001. No individual event term occurred in >1 patient.

The Applicant's Position:

In reviewing the treatment-emergent, related SAEs, within each SOC, most TERSAEs were single events by preferred term. For those SOCs with more than one event (e.g., cardiac [n = 2], gastrointestinal [n = 4], and metabolic [n = 4]), no clear pattern was discerned as each of these SOCs represent events common among those with advanced metastatic cancer (e.g., failure to thrive, dehydration, acute coronary syndrome), or among those receiving mTOR inhibitors related to class effect (eg, vomiting, enteritis, diarrhea) as described in the Rapamune package insert.

The FDA's Assessment:

The FDA agrees with the Applicant's position. Because of the small sample size of the primary safety population and single-arm design of PEC-001, all treatment-emergent serious adverse events were considered as possible adverse reactions regardless of assessed relatedness. All SAEs observed in PEC-001 are described in the table below. The most common SAE in PEC-001 was infection (in 12% of patients). This risk of infections is included as a warning and precaution in the product label.

Table 47: Treatment-Emergent Serious Adverse Events in Study PEC-001

SAE	Study PEC-001 N = 34	
	Grade 1-5 n (%)	Grade 3-4 n (%)
Any SAE	14 (41)	10 (29)
Gastrointestinal disorders		
Abdominal Pain (GT)	2 (6)	1 (2.9)
Diarrhoea (GT)	2 (6)	1 (2.9)
Intestinal obstruction	1 (2.9)	1 (2.9)
Infections and infestations		
Infection (GT)	4 (12)	3 (9)
Pneumonia (GT)	1 (2.9)	1 (2.9)
General disorders and administration site conditions		
Oedema (GT)	1 (2.9)	1 (2.9)
Pyrexia (GT)	1 (2.9)	0

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SAE	Study PEC-001 N = 34	
	Grade 1-5 n (%)	Grade 3-4 n (%)
Metabolism and nutrition disorders		
Dehydration	2 (6)	2 (6)
Hypoglycaemia	1 (2.9)	1 (2.9)
Cardiac disorders		
Acute coronary syndrome	1 (2.9)	1 (2.9)
Bradycardia	1 (2.9)	0
Injury, poisoning and procedural complications		
Comminuted fracture	1 (2.9)	0
Fall	1 (2.9)	0
Musculoskeletal and connective tissue disorders		
Musculoskeletal Pain (GT)	3 (9)	1 (2.9)
Blood and lymphatic system disorders		
Pancytopenia	1 (2.9)	1 (2.9)
Renal and urinary disorders		
Acute Kidney Injury (GT)	1 (2.9)	1 (2.9)
Respiratory, thoracic and mediastinal disorders		
Haemothorax	1 (2.9)	1 (2.9)
Atelectasis	1 (2.9)	0
Vascular disorders		
Haemorrhage (GT)	3 (9)	1 (2.9)
Hypotension (GT)	1 (2.9)	1 (2.9)

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FYARRO (sirolimus protein-bound particles for injectable suspension) (albumin-bound)

SAE	Study PEC-001 N = 34	
	Grade 1-5 n (%)	Grade 3-4 n (%)

Source: adae.xpt, adsl.xpt. Variables used: USUBJID, APOP, TRTEMFL, AEDECOD, AEBODSYS, ATOXGRN, AESER.

Note: Custom grouped terms are designated by '(GT)'.

Abdominal Pain (GT) includes: Abdominal pain.

Acute Kidney Injury (GT) includes: Acute kidney injury.

Diarrhoea (GT) includes: Diarrhoea, and Enteritis.

Dyspnoea (GT) includes: Dyspnoea.

Haemorrhage (GT) includes: Gastrointestinal haemorrhage, Post procedural haemorrhage, and Upper gastrointestinal haemorrhage.

Hypotension (GT) includes: Hypotension.

Infection (GT) includes: Cellulitis, Clostridium difficile infection, Enteritis infectious, Gangrene, Gastroenteritis viral, Influenza, Pneumonia, Pyelonephritis, Sepsis, Staphylococcal sepsis, Upper respiratory tract infection, and Urinary tract infection.

Musculoskeletal Pain (GT) includes: Arthralgia, Arthritis, Musculoskeletal chest pain, and Non-cardiac chest pain.

Oedema (GT) includes: Oedema.

Pneumonia (GT) includes: Pneumonia.

Pyrexia (GT) includes: Pyrexia.

Rash (GT) includes: Rash.

Urinary Tract Infection (GT) includes: Urinary tract infection.

Vomiting (GT) includes: Vomiting.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

In Study PEC-001, 3 (8.8%) patients experienced TEAEs leading to ABI-009 withdrawal. The percentages for the pooled oncology data (with or without Study PEC-001) were similar (ISS Table 6.6.1 and ISS Table 6.6.3). In non-oncology Study PAH-001, 2 (22.2%) patients experienced TEAEs leading to ABI-009 withdrawal. No pattern to these TEAEs was apparent.

Of note, Study PEC-001 Patient (b) (6) has 2 reasons listed for ABI-009 withdrawal: progressive disease and having TEAEs leading to ABI-009 withdrawal. The 6-week post-dose imaging performed on (b) (6) showed disease progression (she was removed from the study on (b) (6)) which is listed as the primary reason for treatment discontinuation. As such, she is included in the summary statistics as discontinued for disease progression (see narrative in Study PEC-001 CSR Section 14.3.3). However, the patient experienced the onset of 5 TEAEs (Grade 1 abdominal distension, fatigue, decreased appetite, muscular weakness; and Grade 2 anemia) on (b) (6); these are erroneously coded

with action taken in ISS Listing 5.0 as “drug withdrawn”. The investigator confirmed post data cut-off that the unrelated TEAEs were due to disease progression and should have not been identified as reason for treatment withdrawal. Therefore, the TEAE data in ISS Table 6.6.1 and ISS Table 6.6.3 for those preferred terms, system organ classes, and number of overall patients in Study PEC-001 and the pooled oncology data (with Study PEC-001) should be decremented accordingly.

The Applicant’s Position:

The incidence of TEAEs leading to ABI-009 withdrawal in Study PEC-001 was 3 (8.8%) patients; the percentages for the pooled oncology data (with or without Study PEC-001) were similar. No pattern to these TEAEs was apparent. Despite the higher dose of mTOR inhibitor with ABI-009 as compared to Rapamune and other similar agents, adverse events and tolerability were similar, and tolerability as manifest by drug discontinuation rates was acceptable.

The FDA’s Assessment:

The FDA review of patients who were categorized as having withdrawn consent by the Applicant identified that one patient (b) (6) with previous adverse reaction of grade 2 non-infectious pneumonitis “withdrew consent from Study PEC-001 after discussing concerns of adverse events and the possibility of recurrent pneumonitis with the investigator.” The FDA determined this to represent a discontinuation due to an adverse event.

Adverse reactions leading to ABI-009 withdrawal in Study PEC-001 occurred in 3 (9%) of patients. Adverse reactions that resulted in permanent discontinuation included non-infectious pneumonitis, anemia, and non-infective cystitis in one patient each.

Dose Interruption/Reduction Due to Adverse Effects

Data:

Treatment-emergent adverse events of special interest leading to ABI-009 withdrawal or dose modification are summarized in ISS Table 8.1.1 and ISS Table 8.1.3.

In Study PEC-001, 22 (64.7%) patients experienced at least 1 TEAESI leading to ABI-009 withdrawal or dose modification. The percentages for the pooled oncology data (with or without Study PEC-001) were slightly lower. No individual TEAESI leading to ABI-009 withdrawal or dose modification in Study PEC-001 occurred in $\geq 30\%$ of patients.

No individual TEAESI leading to ABI-009 withdrawal or dose modification occurred in $\geq 30\%$ of patients in the pooled oncology data (with Study PEC-001). In the pooled oncology data (without Study PEC-001), thrombocytopenia leading to ABI-009 withdrawal or dose modification occurred in 15 (35.7%) patients.

In Study PEC-001 (Study PEC-001 CSR Section 12.3.1.3.4), mucositis was the most common nonhematologic AE; the majority of cases (44/50 [88.0%] mucositis events) resolved. Approximately one-third of the resolved mucositis events (16/44 [36.4%]) needed no action taken, and 28/44 (63.6%) resolved with drug interruptions and/or concomitant medications (most commonly steroid mouthwash). The majority of anemia events were Grade 1 or Grade 2 (62/68 [91.2%] anemia events), and 60/68 (88.2%) events resolved. The majority of the resolved anemia events (45/60 [75.0%]) needed no action taken, and 15/60 (25.0%) resolved with drug interruptions and/or concomitant medications. All events of thrombocytopenia were Grade 1 or Grade 2 (22/23 [95.7%] thrombocytopenia events) other than a single Grade 3 event; all resolved other than a single Grade 1 event. The majority of resolved events (16/22 [72.7%]) needed no action taken, and 6/22 (27.3%) resolved with dose modifications. Pneumonitis occurred in 6/34 (17.6%) patients, with all being Grade 1 and Grade 2 events, and all (100%) resolved. Most (10/13 [76.9%] pneumonitis events) were managed by dose modifications and/or concomitant medications, and 23.1% needed no action taken (all Grade 1).

In the pooled oncology data including Study PEC-001, mucositis was also the most common nonhematologic AESI; the majority of cases (71/84 [84.5%] mucositis events) resolved. Most of the resolved mucositis events (60/71 [84.5%]) needed no action taken for ABI-009, and 11/71 (15.5%) resolved with dose reductions and/or drug interruptions. The majority of anemia events were Grade 1 or Grade 2 (78/88 [88.6%] anemia events), and 74/88 (84.1%) events resolved. The majority of the resolved anemia events (64/74 [86.5%]) needed no action taken for ABI-009, and 10/74 (13.5%) resolved with drug interruptions. The majority of thrombocytopenia events were Grade 1 or Grade 2 (76/89 [85.4%] thrombocytopenia events), and 83/89 (93.3%) events resolved. Approximately one-third of resolved thrombocytopenia events (32/83 [38.6%]) needed no action taken for ABI-009, and 51/83 (61.4%) resolved with dose reductions, drug interruptions, or withdrawal. Pneumonitis occurred in 6/76 (7.9%) patients, with all being Grade 1 and Grade 2 events, and all (100%) pneumonitis events resolved. Slightly less than half of the resolved pneumonitis events (6/13 [46.2%]) needed no action taken for ABI-009, and 7/13 (53.8%) were managed by dose reductions and/or drug interruptions.

In the pooled oncology data excluding Study PEC-001, mucositis was again the most common nonhematologic AESI; the majority of cases (27/34 [79.4%] mucositis events) resolved. Most of the resolved mucositis events (24/27 [88.9%]) needed no action taken for ABI-009, and 3/27 (11.1%) resolved with drug interruptions. The majority of anemia events were Grade 1 or Grade 2 (16/20 [80.0%] anemia events), and 14/20 (70.0%) events resolved. The majority of the resolved anemia events (12/14 [85.7%]) needed no action taken for ABI-009, and 2/14 (14.3%) resolved with drug interruptions. The majority of thrombocytopenia events were Grade 1 or Grade 2 (54/66 [81.8%] thrombocytopenia events), and 61/66 (92.4%) events resolved. Approximately one-quarter of resolved thrombocytopenia events (16/61 [26.2%]) needed no action taken for ABI-009, and 45/61 (73.8%) resolved with dose reductions,

drug interruptions, or withdrawal.

In non-oncology Study PAH-001, 4 (44.4%) patients experienced at least 1 TEAESI leading to ABI-009 withdrawal or dose modification. No individual TEAESI leading to ABI-009 withdrawal or dose modification occurred in $\geq 30\%$ of patients. All thrombocytopenia events were Grade 1 (8/8 [100.0%] thrombocytopenia events), and 7/8 (87.5%) events resolved. Most resolved thrombocytopenia events (4/7 [57.1%]) needed no action taken for ABI-009, and 3/7 (42.9%) resolved with drug interruptions.

The Applicant's Position:

The current scheme for management of ABI-009 dose adjustments for AEs is appropriate. Adverse events were manageable and generally consistent with those known for sirolimus. Treatment-emergent AEs were tolerable and manageable, with most being Grade 1 or Grade 2 events. Approximately 77% (1157/1494) of TEAEs resolved; 10% (143/1494) of TEAEs required dose modifications, and 87% (125/143) of TEAEs requiring dose modifications resolved, indicating that per-protocol dose modifications were appropriate.

The FDA's Assessment:

The FDA's analysis of TEAEs that led to drug interruption or withdrawal included all TEAEs and was not limited to AEs of special interest.

Dosage interruptions of ABI-009 due to an adverse reaction occurred in 22 (65%) patients. Adverse reactions which required dosage interruption in $> 5\%$ of patients included stomatitis in 6 (18%) patients with stomatitis, 5 (15%) patients with pneumonitis in 5 (15%) patients, anemia in 3 (9%) patients with anemia, and 2 (6%) patients each with dehydration, dermatitis acneiform, and thrombocytopenia in 2 (6%) patients each.

Table 48: Treatment-Emergent Adverse Events Resulting in Study Drug Interruptions

	Study PEC-001 N = 34 n (%)
Dose interrupted - y - due to AEs	22 (65)
Stomatitis (GT)	6 (18)
Anaemia	5 (15)
Pneumonitis (GT)	5 (15)
Dehydration	2 (6)
Rash (GT)	2 (6)
Thrombocytopenia	2 (6)

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	Study PEC-001 N = 34 n (%)
Abdominal Pain (GT)	1 (2.9)
Acute Coronary Syndrome	1 (2.9)
Acute Kidney Injury (GT)	1 (2.9)
Amylase Increased	1 (2.9)
Blepharitis	1 (2.9)
Bradycardia	1 (2.9)
Comminuted Fracture	1 (2.9)
Fatigue (GT)	1 (2.9)
Haemoglobin Decreased	1 (2.9)
Haemothorax	1 (2.9)
Hypoaesthesia Oral	1 (2.9)
Hypotension (GT)	1 (2.9)
Influenza	1 (2.9)
Intestinal Obstruction	1 (2.9)
Lipase Increased	1 (2.9)
Localised Infection	1 (2.9)
Musculoskeletal Pain (GT)	1 (2.9)
Neutropenia	1 (2.9)
Pancytopenia	1 (2.9)
Tooth Abscess	1 (2.9)

Group Stomatitis (GT) includes PT terms STOMATITIS, APHTHOUS ULCER, MOUTH ULCERATION, GLOSSITIS,
Group Fatigue (GT) includes PT terms FATIGUE, ASTHENIA,
Group Rash (GT) includes PT terms RASH MACULO-PAPULAR, DERMATITIS ACNEIFORM, RASH PRURITIC, RASH
ERYTHEMATOUS, RASH, PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME, RASH PAPULAR, SKIN
EXFOLIATION, RASH MACULAR,
Group Abdominal Pain (GT) includes PT terms ABDOMINAL PAIN, EPIGASTRIC DISCOMFORT, ABDOMINAL PAIN
UPPER,
Group Pneumonitis (GT) includes PT terms PNEUMONITIS,
Group Musculoskeletal Pain (GT) includes PT terms NECK PAIN, BACK PAIN, MYALGIA, NON-CARDIAC CHEST PAIN,
PAIN IN EXTREMITY, MUSCULOSKELETAL CHEST PAIN, ARTHRALGIA,
Group Acute Kidney Injury (GT) includes PT terms ACUTE KIDNEY INJURY,
Group Hypotension (GT) includes PT terms HYPOTENSION,
Source: ADSL (Subject-Level Analysis Dataset) - 2020-07-28, ADAE (Adverse Events) - 2020-07-28. Variables used:
USUBJID, TRT01A, FASFL, TRTEMFL, AEDECOD, AETOXGRN, DOSEINFL, DOSERDFL, AEBODSYS, AESER

Dose reductions of ABI-009 due to an adverse reaction occurred in 12 (35%) patients. Adverse reactions which required dose reductions in > 5% of patients included stomatitis and pneumonitis in 3 (9%) patients each with stomatitis and pneumonitis.

Table 49: Treatment-Emergent Adverse Events Resulting in Study Drug Dose Reduction

	Study PEC-001 N = 34 N (%)
Dose reduced - y - due to AEs	12 (35)
Pneumonitis (GT)	3 (9)
Stomatitis (GT)	3 (9)
Abdominal Pain (GT)	1 (2.9)
Acute Coronary Syndrome	1 (2.9)
Alanine Aminotransferase Increased	1 (2.9)
Aspartate Aminotransferase Increased	1 (2.9)
Blood Creatinine Increased	1 (2.9)
Dehydration	1 (2.9)
Fatigue (GT)	1 (2.9)
Hyperglycaemia	1 (2.9)
Thrombocytopenia	1 (2.9)

Group Stomatitis (GT) includes PT terms STOMATITIS, MOUTH ULCERATION, APHTHOUS ULCER, GLOSSITIS,

Group Fatigue (GT) includes PT terms FATIGUE, ASTHENIA,

Group Abdominal Pain (GT) includes PT terms ABDOMINAL PAIN, EPIGASTRIC DISCOMFORT, ABDOMINAL PAIN UPPER,

Group Pneumonitis (GT) includes PT terms PNEUMONITIS,

Source: ADSL (Subject-Level Analysis Dataset) - 2020-07-28, ADAE (Adverse Events) - 2020-07-28. Variables used: USUBJID, TRT01A, FASFL, TRTEMFL, AEDECOD, AETOXGRN, DOSEINFL, DOSERDFL, AEBODSYS, AESER

Significant Adverse Events

Data:

Adverse Events of Special Interest

Adverse events of special interests (AESIs) were predefined at the start of the study based on class effects of mTOR inhibitors ([Martins 2013](#), [Aapro 2014](#), [Sivendran 2014](#)) and/or were events seen 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 (eg, Mucositis is treated as a group term that includes aphthous ulcer, mouth ulceration, esophageal ulcer, and stomatitis). Grouped terms are also defined in Study PEC-001 CSR Appendix 16.2.7, Listing 16.2.7.8.

Treatment-emergent adverse events of special interest (TEAESI) are summarized in ISS Table 6.7.1, ISS Table 6.7.3, ISS Table 7.1.1, and ISS Table 7.1.3. All oncology study patients (76 [100%]) in the Safety Analysis Population reported at least 1 TEAESI through the date of data cut-off.

The TEAESI incidence rate (per 100 person-weeks) was 32.3 for Study PEC-001, and is slightly lower than the incidence rate observed in the other oncology studies which range from 41.6–43.9%.

In Study PEC-001, the most common TEAESIs (in $\geq 30\%$ of patients) reported were: mucositis (27 [79.4%] patients); rash (23 [67.6%] patients); infection (20 [58.8%] patients); anemia (19 [55.9%] patients); diarrhea and hyperglycemia (15 [44.1%] patients each); hypokalemia (14 [41.2%] patients); hypertriglyceridemia (12 [35.3%] patients); hypercholesterolemia and thrombocytopenia (11 [32.4%] patients each).

In the pooled oncology data (with Study PEC-001), the most common TEAESIs (in $\geq 30\%$ of patients) reported were: mucositis (48 [63.2%] patients); infection (40 [52.6%] patients); rash and thrombocytopenia (34 [44.7%] patients each); anemia (32 [42.1%] patients); diarrhea (28 [36.8%] patients); hypokalemia (25 [32.9%] patients).

In the pooled oncology data (without Study PEC-001), the most common TEAEs (in $\geq 30\%$ of patients) reported were: thrombocytopenia (23 [54.8%] patients); mucositis (21 [50.0%] patients); infection (20 [47.6%] patients); diarrhea and anemia (13 [31.0%] patients each).

The differences are likely due to differences in study designs, treatment regimens (single agent vs in combination with standard of care), and patient populations enrolled in the oncology studies.

All patients with PAH (9 [100%]) in the Safety Analysis Population reported at least 1 TEAESI through the date of data cut-off. The TEAESI incidence rate (per 100 person-weeks) was 25.4 for Study PAH-001, and is slightly lower than the oncology studies which range from 32.3–43.9%. In Study PAH-001, the most common TEAESIs (in $\geq 30\%$ of patients) reported were: diarrhea and infection (5 [55.6%] patients each); rash and thrombocytopenia (4 [44.4%] patients each); dermatitis and hypertriglyceridemia (3 [33.3%] patients each).

Treatment-Emergent Adverse Events of Special Interest Grade ≥ 3

Treatment-emergent adverse events of special interest Grade ≥ 3 are summarized in ISS Table 9.1.1 and ISS Table 9.1.3.

Treatment-emergent adverse events of special interest Grade ≥ 3 were experienced by 17 (50.0%) patients in Study PEC-001, which is slightly higher than the rates in the pooled oncology data (with or without Study PEC-001). No individual TEAEs Grade ≥ 3 occurred in $\geq 30\%$ of patients in any individual oncology study or the pooled oncology data (with or without Study PEC-001).

In non-oncology Study PAH-001, treatment-emergent adverse events of special interest Grade ≥ 3 were experienced by 1 (11.1%) patient.

The Applicant's Position:

Results to date with ABI-009 show a consistent safety profile between the Phase 1 and Phase 2 studies. All AEs observed in this study are consistent with the known class-effects of the related mTOR inhibitors. The toxicities of ABI-009 are both familiar to and manageable by oncologists. The risk profile is consistent across mTOR inhibitors, and there are no special considerations for the management of risk after consideration of the known class effects of mTOR inhibitors.

The FDA's Assessment:

In addition to the TEAEs of special interest reported above, hemorrhage was noted in 8 (24%) patients, including 1 Grade 5 and 1 Grade 3 upper gastrointestinal hemorrhage. Four patients experienced epistaxis, including three Grade 1 TEAE and one Grade 2 TEAE. Additional cases of hemorrhage included mouth hemorrhage, hemorrhoidal hemorrhage, and post-procedural hemorrhage (all Grade 1). Analysis of the temporal relationship with thrombocytopenia revealed that no patients had thrombocytopenia at the time of hemorrhage. One patient (b) (6) experienced thrombocytopenia ($90 \times 10^9/L$) 3 weeks prior to the onset of hemorrhage, however thrombocytopenia had recovered to $147 \times 10^9/L$ just prior to the episode of epistaxis. Given the relatively number of patients experiencing bleeding in the absence of thrombocytopenia and the occurrence of severe and fatal cases, the review team assessed that hemorrhage should be added as a Warning in the product label. See Section 8.2.11 and Section 11.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

The tables presented here limit the data included to that occurring by preferred term in $\geq 10\%$ of the pooled oncology (with Study PEC-001) population. This incidence level was chosen to minimize non-clinically relevant data appearing in the tables for this summary; however, all data is present within the source data tables and listings (Module 5.3.5.3).

The in-text discussion of the most common TEAEs is limited to events occurring in $\geq 30\%$ of patients, which is similar to the method utilized in the Prescribing Information for Rapamune and for other mTOR inhibitors.

Overview of Adverse Events

For all studies, AEs were collected continuously beginning with the signing of informed consent until 28 days (PEC-001, GBM-007, COLO-007, PAH-001) or 30 days (CA401) after the patient's last dose of ABI-009.

An overview of TEAEs for the Safety Analysis Population is summarized in ISS Table 5.1 and ISS Table 5.3. All oncology study patients (76 [100%]) in the Safety Analysis Population reported at least 1 TEAE through the date of data cut-off, with all patients but 1 (in Study CA401) reporting at least 1 treatment-emergent related adverse event (TERAE).

The most prevalent maximum severity of TEAEs in the pooled oncology data (with Study PEC-001) was Grade 3 (46 [60.5%] patients), followed by Grade 2 in 21 (27.6%) patients, Grade 4 in 5 (6.6%) patients, and Grade 1 in 1 (1.3%) patient. The breakdown by grade in Study PEC-001 and in the pooled oncology data (without Study PEC-001) were similar to the pooled oncology data (with Study PEC-001).

One clinical study reported in this NDA is an ongoing study in patients with PAH, a non-oncology indication (Study PAH-001). All non-oncology study patients (9 [100%]) in the Safety Analysis Population reported at least 1 TEAE through the date of data cut-off, with all patients reporting at least 1 TERAE (ISS Table 5.1 and ISS Table 5.3). The most prevalent maximum severity of TEAEs in patients with PAH was Grade 2 (6 [66.7%] patients), followed by Grade 3 in 2 (22.2%) patients, and Grade 1 in 1 (11.1%) patient.

Most Common Treatment-Emergent Adverse Events

Treatment-emergent adverse events (using the threshold of TEAEs occurring in $\geq 10\%$ of the pooled oncology patients [with Study PEC-001]) for the Safety Analysis Population are summarized in ISS Table 6.1.1, ISS Table 6.1.3, ISS Table 6.7.1, ISS Table 6.7.3, ISS Table 6.9.1, and ISS Table 6.9.3

In Study PEC-001, the most common TEAEs (in $\geq 30\%$ of patients) reported were: stomatitis (24 [70.6%] patients); fatigue (23 [67.6%] patients); anemia (19 [55.9%] patients); nausea (17 [50.0%] patients); weight decreased (16 [47.1%] patients); diarrhea and decreased appetite (15 [44.1%] patients each); edema peripheral and hypokalemia (14 [41.2%] patients each); hyperglycemia (12 [35.3%] patients); vomiting, dysgeusia, cough, and maculo-papular rash (11 [32.4%] patients each).

In the pooled oncology data (with Study PEC-001), the most common TEAEs (in $\geq 30\%$ of patients) reported were: fatigue (39 [51.3%] patients); anemia and stomatitis (32 [42.1%] patients each); diarrhea and nausea (28 [36.8%] patients each); hypokalemia (26 [34.2%] patients); weight decreased (25 [32.9%] patients); decreased appetite (23 [30.3%] patients).

In the pooled oncology data (without Study PEC-001), the most common TEAEs (in $\geq 30\%$

of patients) reported were: thrombocytopenia and fatigue (16 [38.1%] patients each); mucosal inflammation (14 [33.3%] patients); anemia and diarrhea (13 [31.0%] patients each). The difference in incidence of adverse events among the studies is likely due to the patient populations enrolled in the individual oncology studies, and if ABI-009 was administered as single agent (Study PEC-001, Study CA401) or in combination with other therapies (Study COLO-007, Study GBM-007).

Individual TEAE data is presented in ISS Listing 5.0. In Study PEC-001, 79.6% of the TEAEs were resolved at the time of the data cut-off, indicating that adverse events were manageable. Of those events which resolved, 64.1% resolved without action taken, and 35.9% were managed with dose modifications (drug interruptions or dose reductions) and/or concomitant medications (Study PEC-001 CSR Section 12.2.1). In the pooled oncology data (with Study PEC-001), 75.1% of the TEAEs were resolved at the time of the data cut-off. Of those events which resolved, 89.2% resolved without action taken for ABI-009, and 10.8% were managed with dose modifications (drug interruptions or dose reductions) and/or drug withdrawal. In the pooled oncology data (without Study PEC-001), 67.1% of TEAEs resolved. Of those events which resolved, 80.8% resolved without action taken for ABI-009, and 19.2% were managed with dose modifications (drug interruptions or dose reductions) and/or drug withdrawal.

In non-oncology Study PAH-001, the most common TEAEs (in $\geq 30\%$ of patients) reported were: headache (7 [77.8%] patients); diarrhea (5 [55.6%] patients); nausea (4 [44.4%] patients); fatigue, epistaxis, and alopecia (3 [33.3%] patients each). In Study PAH-001, 59.5% of TEAEs were resolved at the time of the data cut-off. Of those events which resolved, 84.6% resolved without action taken for ABI-009, and 15.4% were managed with dose modifications (drug interruptions or dose reductions) and/or drug withdrawal.

Treatment-Emergent Adverse Events Grade ≥ 3

Treatment-emergent adverse events Grade ≥ 3 (using the threshold of TEAEs occurring in $\geq 10\%$ of the pooled oncology patients [with Study PEC-001]) are summarized in ISS Table 6.5.1 and ISS Table 6.5.3.

Treatment-emergent adverse events Grade ≥ 3 were experienced by 24 (70.6%) patients in Study PEC-001, with similar rates in the pooled oncology data (with or without Study PEC-001). No individual TEAE Grade ≥ 3 occurred in $\geq 30\%$ of any individual oncology study or the pooled oncology data (with or without Study PEC-001).

Treatment-emergent adverse events Grade ≥ 3 were experienced by 2 (22.2%) patients in non-oncology Study PAH-001, with no individual Grade ≥ 3 event occurring in >1 patient.

Treatment-Emergent Adverse Events by Relationship to ABI-009

Treatment-emergent adverse events related to ABI-009 (using the threshold of TEAEs occurring in $\geq 10\%$ of the pooled oncology patients [with Study PEC-001]) are summarized in

ISS Table 6.3.1 and ISS Table 6.3.3.

In Study PEC-001, the most common TERAEs (in $\geq 30\%$ of patients) reported were: stomatitis (24 [70.6%] patients); fatigue (20 [58.8%] patients); anemia and nausea (16 [47.1%] patients each); diarrhea and weight decreased (13 [38.2%] patients each); decreased appetite (11 [32.4%] patients).

In the pooled oncology data (with Study PEC-001), the most common TERAEs (in $\geq 30\%$ of patients) reported were: fatigue (32 [42.1%] patients); stomatitis (31 [40.8%] patients); anemia and nausea (25 [32.9%] patients each); diarrhea (24 [31.6%] patients).

In the pooled oncology data (without Study PEC-001), the most common TEAEs (in $\geq 30\%$ of patients) reported were: thrombocytopenia (16 [38.1%] patients); mucosal inflammation (14 [33.3%] patients).

As with the TEAEs as a whole, the difference in incidence of TERAEs is likely due to differences in study designs, treatment regimens (single agent vs in combination with standard of care), and patient populations enrolled in the oncology studies.

In non-oncology Study PAH-001, the most common TERAEs (in $\geq 30\%$ of patients) reported were: headache (6 [66.7%] patients); diarrhea (5 [55.6%] patients); nausea and fatigue (3 [33.3%] patients each)

The Applicant's Position:

Treatment-emergent adverse events observed in ABI-009 studies to date show a consistent safety profile between the Phase 1 and Phase 2 studies. All AEs observed in studies of ABI-009 are consistent with the known class effects of the mTOR inhibitors and are both familiar to and manageable by oncologists. The risk profile is consistent across mTOR inhibitors. Therefore, Aadi believes that the risks can be adequately managed through the proposed prescribing information as well as through post-marketing surveillance.

The FDA's Assessment:

Although the entire safety database was analyzed, the FDA's review of adverse reactions focused on patients who received ABI-009 in Study PEC-001. The most common adverse reactions ($\geq 30\%$) were stomatitis in 27 (79%) patients, fatigue and rash in 23 (68%) patients, infection in 20 (59%) patients, nausea and edema in 17 (50%) patients, diarrhea, musculoskeletal pain and decreased weight in 16 (47%) patients, decreased appetite in 15 patients (44%), cough in 12 (35%) patients, and vomiting and dysgeusia in 11 (32%) patients.

Given the frequency and severity of stomatitis in Study PEC-001, this adverse reaction was included in the warnings and precautions section of the product label. This included 18% of patients with Grade 3 events. Infections occurred in 59% of patients and were Grade 3 in 12%

of patients. Because the relationship between myelosuppression and infection could not be definitively established, infection was listed as a separate warning in the product label. Pneumonitis occurred in 18% of patients in Study PEC-001 with no Grade 3 events, however given the clinical significance of this adverse reaction, this was included as a warning in the product label. Furthermore, these three adverse reactions are known risks associated with other FDA-approved mTOR inhibitors, which supports the causal role of ABI-009 in myelosuppression, infection, and pneumonitis.

Supplementary analysis of adverse reactions in an additional 42 patients treated with ABI-009 for oncology indications did not reveal additional safety signals. In general, the incidence of adverse reactions was greater in Study PEC-001 than in these other trials. Exposure to ABI-009 was lower in these non-PEComa trials possibly resulting in a lower incidence of adverse reactions.

Table 50: Treatment-Emergent Adverse Events in ≥10% in Patients in PEC-001

TEAE	Study PEC-001 (N=34)	
	All Grades (%)	Grade 3 to 4* (%)
Gastrointestinal		
Stomatitis ^a	79	18
Nausea	50	0
Diarrhea ^b	47	2.9
Vomiting	32	2.9
Abdominal Pain ^c	29	6
Constipation	24	2.9
Dry Mouth	15	0
Hemorrhoids	12	0
General disorders		
Fatigue	68	2.9
Edema ^d	50	2.9
Pyrexia	24	0
Infections		
Infections ^e	59	12
Investigations		
Weight decreased	47	0
Metabolism and nutrition		
Decreased appetite	44	0

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Dehydration	15	6
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain ^f	47	2.9
Nervous system		
Dysgeusia	32	0
Headache	29	0
Peripheral neuropathy ^g	15	0
Dizziness ^h	12	0
Psychiatric disorders		
Insomnia	21	2.9
Respiratory, thoracic, and mediastinal disorders		
Cough ⁱ	35	0
Pneumonitis	18	0
Dyspnea ⁱ	12	0
Skin and subcutaneous tissue disorders		
Rash ^k	68	0
Pruritus	18	0
Alopecia	24	0
Dry Skin	12	0
Nail disorder	12	0
Vascular disorders		
Hypertension	29	2.9
Hemorrhage ^l	24	2.9
Eye disorders		
Vision blurred	12	0

Grading according to NCI CTCAE Version 4.03

^aIncludes stomatitis, aphthous ulcer, mouth ulceration, esophageal ulcer.

^bIncludes diarrhea and enteritis

^cIncludes abdominal pain, abdominal pain upper, and epigastric discomfort

^dIncludes face edema, generalized edema, edema, edema peripheral, and periorbital edema

^eIncludes all reported infections, including but not limited to, upper respiratory tract infection, urinary tract infection, sinusitis, skin infection, folliculitis, nasopharyngitis, pharyngitis, pharyngitis streptococcal, pneumonia, vaginal infection.

^fIncludes arthralgia, back pain, musculoskeletal chest pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity

^gIncludes dysesthesia, hypoesthesia, neuropathy peripheral, paresthesia, and peripheral sensory neuropathy

^hIncludes dizziness, dizziness postural, and vertigo

ⁱIncludes cough, productive cough, and upper-airway cough syndrome

^jIncludes dyspnea and dyspnea exertional

^kIncludes dermatitis acneiform, palmar-plantar erythrodysesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, and skin exfoliation

^lIncludes epistaxis, hemorrhoidal hemorrhage, mouth hemorrhage, post procedural hemorrhage, and upper

gastrointestinal hemorrhage. Includes one fatal adverse reaction of upper GI hemorrhage

*No Grade 4 reactions were reported.

The FDA did not independently verify the TEAEs reported to be treatment-related as attribution of AEs is difficult to assess in non-randomized trials without a control arm.

Laboratory Findings

Data:

The two completed clinical studies with final clinical study reports (CSRs; CA401 and PEC-001) revealed little to no effect of ABI-009 on laboratory values in addition to those identified as part of the AESI terms. The 60 patients in these two studies represent the total enrollment in the single-agent oncology studies, and present a view of the effect of ABI-009 on laboratory assessments not confounded by toxicities from other drugs in the combination-agent oncology studies' dosing regimens. The addition of clinical laboratory data from the combined-agent oncology studies would confound those from ABI-009 monotherapy oncology studies, and would be of little additional value.

Study CA401 Laboratory Findings

Clinically significant hematology and chemistry values are summarized in Table 51 and Table 52, respectively.

Clinically significant hematology values were observed for neutrophils (Grade 3: 1 [4%] patient in the 45 mg/m² dose group), platelets (Grade 3: 4 [15%] patients, 1 in the 45 mg/m² dose group, 2 in the 125 mg/m² dose group, and 1 in the 150 mg/m² dose group), and lymphocytes (Grade 3: 4 [15%] patients, 1 in each of the following dose groups: 45 mg/m² [14%], 56.5 mg/m² [33%], 100 mg/m² [14%], and 125 mg/m² [14%]; and Grade 4: 1 [4%] patient in the 45 mg/m² dose group).

The maximal degrees of myelosuppression observed were Grade 3 white blood cells (1 [4%] patient in the 125 mg/m² dose group) and Grade 3 hemoglobin (2 [8%] patients, 1 in the 100 mg/m² dose group, and 1 in the 125 mg/m² dose group).

Table 51: Incidence of Clinically Significant Hematology Values that Occurred After the Start of Treatment (Study CA401 Treated Population)

Parameter, n (%)	Grade ^a	Dose mg/m ²					Total (N = 26)
		45 (N = 7)	56.25 (N = 3)	100 (N = 7)	150 (N = 2)	125 (N = 7)	
Neutrophils (ANC)	L3	1 (14)	0	0	0	0	1 (4)
WBC	L3	0	0	0	0	1 (14)	1 (4)

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Hemoglobin	L3	0	0	1 (14)	0	1 (14)	2 (8)
Platelets	L3	1 (14)	0	0	1 (50)	2 (29)	4 (15)
Lymphocytes	L3	1 (14)	1 (33)	1 (14)	0	1 (14)	4 (15)
	L4	1 (14)	0	0	0	0	1 (4)

Abbreviations: ANC = absolute neutrophil count; N = number of patients; n = number of patients in the category; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; WBC = white blood cells.

Note: Patients with both Grade 3 and 4 values for a specific parameter were tabulated as Grade 4.

a. NCI CTCAE Grade was used.

Source: Study CA401 CSR post-text Table 9.0.

The clinically significant chemistry values that occurred after the start of treatment were observed for total bilirubin (Grade 3; 1 [4%] patient in the 125 mg/m² dose group), glucose (Grade 3 hyperglycemia; 6 [23%] patients, 2 in the 45 mg/m² dose group, 1 in the 56.25 mg/m² dose group, and 3 in the 100 mg/m² dose group), potassium (Grade 3 hypokalemia; 5 [19%] patients, 4 in the 45 mg/m² dose group, and 1 in the 100 mg/m² dose group), and sodium (Grade 3 hyponatremia; 3 [12%] patients, 1 in the 56.25 mg/m² dose group, 1 in the 100 mg/m² dose group, and 1 in the 150 mg/m² dose group).

Table 52: Incidence of Clinically Significant Clinical Chemistry Values that Occurred After the Start of Treatment (Study CA401 Treated Population)

Parameter, n (%)	Grade ^a	Dose mg/m ²					Total (N = 26)
		45 (N = 7)	56.25 (N = 3)	100 (N = 7)	150 (N = 2)	125 (N = 7)	
Total Bilirubin (hyperbilirubinemia)	H3	0	0	0	0	1 (14)	1 (4)
Glucose (hyperglycemia)	H3	2 (29)	1 (33)	3 (43)	0	0	6 (23)
Potassium (hypokalemia)	L3	4 (57)	0	1 (14)	0	0	5 (19)
Sodium (hyponatremia)	L3	0	1 (33)	1 (14)	1 (50)	0	3 (12)

Abbreviations: N = number of patients; n = number of patients in the category; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Patients with both Grade 3 and 4 values for a specific parameter were tabulated as Grade 4.

a. NCI CTCAE Grade was used.

Source: Study CA401 CSR post-text Table 10.1.

The majority of patients experienced no toxicities as defined by the liver and kidney function parameters of alkaline phosphatase, ALT, AST, total bilirubin, and creatinine (Study CA401 CSR post-text Table 10.0). Of the toxicities that did occur, most were mild or moderate (Grades 1 and 2, respectively). One patient in the 125 mg/m² experienced a severe increase (Grade 3) in

total bilirubin.

Study PEC-001 Laboratory Findings

As the registrational trial, Study PEC-001 enrolled patients with advanced malignant PEComa. As such, its laboratory findings represent expected toxicities in the post-approval population to be treated with ABI-009.

Grade 3 or higher hematology results were confined to a single instance of decreased hemoglobin during Cycle 20, and decreased lymphocytes occurring in 1–3 patients at various times throughout the study (Study PEC-001 CSR Table 14.3.4.1.3). Grade 3 or higher serum chemistry results occurred in 1–4 patients for different analytes at various times throughout the study (Study PEC-001 CSR Table 14.3.4.2.3). No pattern was observed by treatment cycle, suggesting that the events did not represent any cumulative toxicity of the study drug.

Lipid results did not show any apparent treatment effect (Study PEC-001 CSR Table 14.3.4.3).

There were no shifts from baseline for hematology or chemistry that were notable (Study PEC-001 CSR Table 14.3.4.1.2 and Table 14.3.4.2.2, respectively), however select analytes that are associated with prospectively-defined AESI are presented in Table 53. Shifts to Grade 3 or higher were infrequent and manageable with dose reductions or treatment delays.

Table 53: Select Hematology and Serum Chemistry Toxicity Grade Shifts (Study PEC-001 Safety Analysis Set)

Analyte, n (%)	Baseline		Maximal Toxicity Grade During the Study ^a				
	Grade	Patients	0	1	2	3	4
Hemoglobin	0	19 (56)	3 (9)	9 (26)	6 (18)	1 (3)	0
	1	10 (29)	0	4 (12)	6 (18)	0	0
	2	5 (15)	0	0	4 (12)	1 (3)	0
	Total	34 (100)	3 (9)	13 (38)	16 (47)	2 (6)	0
Platelets	0	33 (97)	22 (65)	11 (32)	0	0	0
	1	1 (3)	0	0	1 (3)	0	0
	Total	34 (100)	22 (65)	11 (32)	1 (3)	0	0
Alanine aminotransferase	0	29 (85)	13 (38)	13 (38)	2 (6)	1 (3)	0
	1	5 (15)	1 (3)	4 (12)	0	0	0
	Total	34 (100)	14 (41)	17 (50)	2 (6)	1 (3)	0

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Analyte, n (%)	Baseline		Maximal Toxicity Grade During the Study ^a				
	Grade	Patients	0	1	2	3	4
Aspartate aminotransferase	0	29 (85)	18 (53)	9 (26)	1 (3)	1 (3)	0
	1	5 (15)	2 (6)	3 (9)	0	0	0
	Total	34 (100)	20 (59)	12 (35)	1 (3)	1 (3)	0
Glucose	0	33 (97)	26 (76)	3 (9)	0	3 (9)	1 (3)
	1	1 (3)	1 (3)	0	0	0	0
	Total	34 (100)	27 (79)	3 (9)	0	3 (9)	1 (3)

Abbreviations: CTCAE = Common Toxicity Criteria for Adverse Events; n = number of patients in the category; NCI = National Cancer Institute

Note: Numbers in parentheses are percentages of patients with non-missing grades at both baseline and post baseline. Unscheduled visits are taken into account for maximal toxicity grade.

a. Toxicity is graded with NCI CTCAE version 4.03: 0 = Normal, 1 = Mild, 2 = Moderate; 3 = Severe; 4 = Life-threatening, 5 = Death.

Source: Study PEC-001 CSR Table 14.3.4.1.2 and Table 14.3.4.2.2.

The Applicant's Position:

Laboratory abnormalities in Study CA-401 and Study PEC-001 did not reveal any additional safety signals and were consistent with an advanced malignancy patient population. Specific dosing recommendations for patients with hepatic impairment are detailed in Module 1.14.1.3 Draft Labeling Text.

The FDA's Assessment:

FDA review of laboratory abnormalities focused on those which worsened from baseline, as summarized in Table 54 below. This differed from the Applicant's analysis, which was based on adverse reaction terms. The most common laboratory Grade 3 to 4 abnormalities ($\geq 6\%$) were decreased lymphocytes in 7 (21%) patients, increased glucose and decreased potassium in 4 (12%) patients, decreased phosphate in 3 (9%) patients, and decreased hemoglobin and increased lipase in 2 (6%) patients. This analysis revealed clinically-significant laboratory abnormalities based on the type of abnormality and the incidence of severe (Grade 3 to 4) abnormalities that worsened from baseline. These included anemia, neutropenia, and thrombocytopenia, which were grouped as myelosuppression and included in the warnings and precautions section of the product label. Finally, Grade 3 laboratory abnormalities of hypokalemia and hyperglycemia occurred in 12% of patients in the primary safety population. Given the clinical significance of these abnormalities, hypokalemia and hyperglycemia were included in the warnings and precautions section of the product label.

Table 54: Laboratory Abnormalities $\geq 10\%$ That Worsened from Baseline in PEC-001

	Study PEC-001 ² (N=34)	
Laboratory Abnormality ¹	All Grades (%)	Grades 3 to 4 (%)
Hematology		
Decreased lymphocytes	82	21
Decreased hemoglobin	68	6
Decreased leukocytes	41	0
Decreased neutrophils	35	0
Decreased platelets*	35	0
Chemistry		
Increased creatinine	82	0
Increased triglycerides	52	0
Increased cholesterol	48	3
Increased alanine aminotransferase (ALT)	47	2.9
Decreased potassium	44	12
Decreased magnesium	42	0
Decreased albumin	35	2.9
Increased aspartate transaminase (AST)	32	2.9
Increased alkaline phosphatase	29	0
Decreased sodium	24	2.9
Decreased calcium	15	0
Decreased glucose	15	0
Decreased phosphate	15	9
Increased lipase	12	6
Increased glucose	12	12
Increased sodium	12	0
¹ Grading according to NCI CTCAE Version 4.03 ² The denominator used to calculate the rate varied from 33 to 34 based on the number of patients with a baseline value and at least one post-treatment value.		

Vital Signs

The Applicant's Position:

An evaluation of patients in completed studies PEC-001 and CA-401 revealed no notable effect of ABI-009 on vital signs, physical findings, and other observations related to safety. The 60 patients in these two studies represent the total enrollment in the single-agent oncology studies, and present a view of the effect of ABI-009 on vital signs, physical findings, and other observations related to safety not confounded by toxicities from other drugs in the combination-agent oncology studies' dosing regimens. The addition of data from those studies may have obscured ABI-009's effect on these parameters and would be of little additional value.

The FDA's Assessment:

The FDA agrees with the Applicant's position. The FDA's review of vital sign data did not identify any safety signals measured by an effect of ABI-009 on vital signs in the primary safety population. In the 34 patients in Study PEC-001 the following median values and corresponding ranges for each vital sign is listed below:

- Median Systolic Blood Pressure (SBP):
 - Baseline: 129 mmHg (range 101, 159)
 - End of Treatment: 129 mmHg (range 96, 158)
- Median Diastolic Blood Pressure (DBP):
 - Baseline: 74 mmHg (range 53, 94)
 - End of Treatment: 74 mmHg (range 59, 88)
- Median Heart Rate:
 - Baseline: 79 beats per minute (range 40, 115)
 - End of Treatment: 81 beats per minute (range 56, 110)
- Median Respiratory Rate:
 - Baseline: 18 breaths per minute (range 16, 20)
 - End of Treatment: 18 breaths per minute (range 14, 20)
- Median Temperature:
 - Baseline: 36.6 degrees Celsius (range 35.9, 37.7)
 - End of Treatment: 36.7 degrees Celsius (range 36.1, 37.4)
- Median Weight:
 - Baseline: 72 kilograms (range 46, 113)
 - End of Treatment: 74 kilograms (range 40, 108)

Electrocardiograms (ECGs)

Data:

In Study PEC-001, ECG cardiac monitoring was conducted on Day 1 and Day 8 of Cycle 1 and thereafter on Day 1 of every treatment cycle. In each case, ECG was monitored during infusion around the 30 minute time point after the start of infusion to coincide with the end of the infusion period which lasted 30 ($\pm$ 10) minutes. Based on the results from ECG monitoring, ABI-009 did not result in adverse cardiac effects. At the time of the primary analysis, there

were no clinically significant effects observed on cardiac function, including QTc interval. No Grade 2 or heart failure events occurred during the study. Additionally, there were no effects on renal function. Based on these results, ABI-009 did not result in any cardiac effects requiring additional monitoring or management. There were no clinically relevant changes in ECGs in Study CA401.

The Applicant's Position:

Overall, ABI-009 showed no remarkable effects on cardiac function, consistent with the known safety profile of sirolimus.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

QT

Data:

At the time of the primary analysis, there were no clinically significant effects observed on cardiac function, including QTc interval. Two patients had Grade 1 mild QTc elevations (>450 msec male or >470 msec female). No dose interruptions or dose modifications were required to manage these asymptomatic low grade QTc prolongations.

The Applicant's Position:

ABI-009 showed no clinically significant effects on QTc interval, consistent with the known safety profile of sirolimus.

The FDA's Assessment:

The FDA agrees with the Applicant's position. As noted in the nonclinical review, in safety pharmacology studies, ABI-009 inhibited *in vitro* hERG potassium currents with an IC₅₀ value of 61 µM, suggesting a low potential for prolongation of QTc. Please refer to the Clinical Pharmacology review in Section 6 and Section 13 (Postmarketing Requirements and Commitments) for further discussion of the QT-prolonging potential of ABI-009 and the post-marketing requirement for further evaluation of QT prolongation.

Immunogenicity

Data:

There were no data from the ABI-009 clinical trials suggesting immunogenicity in the trial populations. Rash is a known class effect of mTOR inhibitors and events of rash were reported in the ABI-009 clinical program. In Study PEC-001, rash was reported in 23 (67.6%) patients, and in the pooled oncology data in 34 (44.7%) patients. In Study PAH-001, rash was reported in 4 (44.4%) patients. In the exposure-response adverse event analysis in Study ADI0101, no significant trends were observed between increasing incidence or severity of rash and sirolimus exposure.

The Applicant's Position:

No immunogenic effects were observed for ABI-009 except for rash, which is a known class effect for mTOR inhibitors. However, ABI-009 contains human albumin and, thus, there is a remote potential for an immunogenic reaction (ie, hypersensitivity) to human albumin, which will be included in the product label.

The FDA's Assessment:

The FDA review of the primary safety population identified one case of hypersensitivity and one case of infusion-related reaction in Study PEC-001. Assessment of the immunogenicity of ABI-009 was limited by the sample size and will be addressed by a post-marketing requirement to more adequately characterize the risk of serious adverse events including hypersensitivity and infusion-related reaction.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1 [Name Safety Issue]

Data:

Not applicable.

The Applicant's Position:

The safety profile of sirolimus is well understood and reported in the prescribing information for approved mTor inhibitors. No new potential safety issues were identified as a result of the safety review of ABI-009.

The FDA's Assessment:

See Section 8.2.4 and 8.2.11. FDA identified hemorrhage as a potential new safety issue during review of safety data from Study PEC-001.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data:

Not applicable

The Applicant's Position:

Section is not applicable.

The FDA's Assessment:

The FDA agrees that this section is not applicable.

8.2.7. Safety Analyses by Demographic Subgroups

Data:

Intrinsic Factors – Age

Treatment-emergent adverse events (using the threshold of TEAEs occurring in $\geq 10\%$ of the pooled oncology patients [with Study PEC-001]) for the Safety Analysis Population are summarized by age category (<65 years, ≥ 65 years) in ISS Table 6.1.1a and ISS Table 6.1.2a; and ISS Table 6.1.1b and ISS Table 6.1.2b, respectively.

Study PEC-001

All patients in Study PEC-001 experienced at least 1 TEAE. In the Safety Analysis Population of patients who received at least 1 dose of ABI-009 (N = 34), 56% of patients were <65 years and 44% were ≥ 65 years.

In Study PEC-001, in general, TEAEs tended to be similar between the age groups of <65 and ≥ 65 years, with a few exceptions. The TEAEs that were >20% lower for patients <65 years versus patients ≥ 65 years were: anemia (42% vs 73%), thrombocytopenia (5% vs 33%), diarrhea (32% vs 60%), edema peripheral (26% vs 60%), weight decreased (32% vs 67%), dysgeusia (16% vs 53%), cough (21% vs 47%), pneumonitis (5% vs 33%), and pruritic rash (0% vs 33%). Of note, a few TEAEs were higher in patients <65 years than those ≥ 65 years, albeit none exceeded 20% difference. The TEAEs that were >15% higher in patients <65 years were: stomatitis (79% vs 60%), pyrexia (32% vs 13%), AST increased (32% vs 13%), and decreased lymphocyte count (26% vs 7%).

The number of TESAEs were also similar between the age groups: 8/19 (42%) versus 6/15 (40%) of the <65 and ≥ 65 years cohorts, respectively (Module 2.7.4 Table 14 and Table 15).

Pooled Oncology Data (with Study PEC-001)

All patients across all studies, including CA401, GBM-007, COLO-007, PEC-001, and PAH-001, had at least 1 TEAE. When all oncology protocols were pooled (N = 76), 66% were <65 years and 34% were ≥65 years.

In the pooled oncology data (with Study PEC-001), results were similar to the above. In general, TEAEs tended to be similar between the age groups of <65 and ≥65 years, with a few exceptions. The TEAEs that were >20% lower for patients <65 years versus patients ≥65 years were: diarrhea (30% vs 50%), edema peripheral (18% vs 39%), weight decreased (22% vs 54%), dysgeusia (12% vs 35%), and cough (18% vs 39%).

The number of TESAEs were also similar between the age groups: 23/50 (46%) versus 11/26 (42%) of the <65 and ≥65 years cohorts, respectively (Module 2.7.4 Table 14 and Table 15).

Non-Oncology Study PAH-001

The small population size of the age category ≥65 years precludes a meaningful analysis of the effect of age on TEAE incidence in Study PAH-001.

The Applicant's Position:

Age

Based upon data from Study PEC-001 and pooled oncology data (with or without Study PEC-001), there is no evidence that older patients (ie, those ≥65 years) with PEComa have a different safety profile after receiving ABI-009 than patients <65 years, or that there is a difference in the non-PEComa study populations. This is consistent with the Rapamune Prescribing Information regarding geriatric use; therefore no dose adjustments are recommended in older patients.

Gender & Race

Based upon data from Study PEC-001 CSR Table 14.3.1.4 which examined TEAEs by race, there was no evidence that race has an influence on the ABI-009 safety profile, consistent with the Rapamune Prescribing Information. Analysis of safety data by race or gender was not conducted for the pooled oncology data (with or without Study PEC-001). The race of patients enrolled was overwhelmingly Caucasian, providing too few non-Caucasian patients in the pooled data for an analysis. Study PEC-001 enrolled primarily females, while the other oncology studies' enrollments were heavily skewed towards males; this gender imbalance, combined with the differences in study design (ie, disease conditions, concomitant antineoplastic study drugs, dosing regimens), precluded a meaningful analysis of safety data by gender.

As with RLD, there will be no recommendations for ABI-009 dose adjustments based on gender or race.

The FDA's Assessment:

The FDA agrees with the Applicant's position. The risk of TEAEs was balanced between patients under 65 years old and patients 65 years or older in the table below. Because of the small number of patients in the male subgroup by gender and non-white subgroups by race, it is not possible to draw definitive conclusions on whether there are differences in the safety profile of ABI-009 by gender or race.

Table 55: Treatment-emergent adverse events by age in Study PEC-001

	Study PEC-001, Age < 65 years N = 19 N (%)	Study PEC-001, Age ≥ 65 years N = 15 N (%)
All-Grade TEAEs	19 (100)	15 (100)
Grade 3-5 TEAEs	13 (68)	11 (73)
Grade 3-4 TEAEs	12 (63)	10 (67)
Grade 3	9 (47)	10 (67)
Grade 4	3 (16)	0 (0.0)
Grade 5 (Deaths due to TEAEs)	1 (5)	1 (7)
Serious TEAEs (SAEs)	8 (42)	7 (47)

Source: ADSL (Subject-Level Analysis Dataset) - 2020-07-28, ADAE (Adverse Events) - 2021-08-06. Variables used: USUBJID, TRT01A, FASFL, TRTEMFL, AETOXGRN, AESER, AGEGR1

Table 56: Treatment-emergent adverse events by gender in Study PEC-001

	Study PEC-001, Female gender N = 28 N (%)	Study PEC-001, Male Gender N = 6 N (%)
All-Grade TEAEs	28 (100)	6 (100)
Grade 3-5 TEAEs	20 (71)	4 (67)

	Study PEC-001, Female gender N = 28 N (%)	Study PEC-001, Male Gender N = 6 N (%)
Grade 3-4 TEAEs	19 (68)	3 (50)
Grade 3	17 (61)	2 (33)
Grade 4	2 (7)	1 (17)
Grade 5 (Deaths due to TEAEs)	1 (3.6)	1 (17)
Serious TEAEs (SAEs)	11 (39)	3 (50)

Source: ADSL (Subject-Level Analysis Dataset) - 2020-07-28, ADAE (Adverse Events) - 2020-07-28. Variables used: USUBJID, TRT01A, FASFL, TRTEMFL, AETOXGRN, AESER, SEX

8.2.8. Specific Safety Studies/Clinical Trials

Data:

An integrated assessment of ABI-009 safety in clinical trials is provided in Module 2.7.4. Additional safety studies of ABI-009 were not conducted.

The Applicant's Position:

No new safety information is provided in the current submission.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

No studies have been conducted to assess the carcinogenic potential of ABI-009. However, sirolimus was carcinogenic in mice and rats, and increased tumor incidences were observed for lymphoma, hepatocellular adenoma and carcinoma, and testicular adenoma ([Rapamune Prescribing Information](#)). Detailed information is summarized in Module 2.6.6.5. Sirolimus is known to cause embryo/fetal toxicity in animal models (Rapamune Prescribing

Information). Detailed nonclinical information is summarized in Module 2.6.6.6. (b) (4)

The FDA's Assessment:

The FDA disagrees with the Applicant's position. Review of the nonclinical safety data for the listed drug (Rapamune) supports that females of reproductive potential and males with female partners of reproductive potential use effective contraception during treatment with ABI-009 and for 12 weeks after the last dose. As the Applicant is relying on FDA's findings of safety for the listed drug for much of the nonclinical data needed to support approval of ABI-009 in the current indication, including chronic toxicology, genotoxicity, carcinogenicity, and reproductive and development toxicity studies, this recommendation is consistent with the Rapamune label.

Human Reproduction and Pregnancy

The Applicant's Position:

The risks of ABI-009 administration during pregnancy have not been evaluated. Sirolimus is associated with embryo and fetal toxicity in rats, and is excreted in trace amounts in milk of lactating rats ([Rapamune Prescribing Information](#)). Detailed nonclinical information is summarized in Module 2.6.6.6. Consistent with the [Rapamune Prescribing Information](#), ABI-009 should not be administered to pregnant women. (b) (4)

Adverse effects on male reproductive organs have been observed for both sirolimus ([Rapamune Prescribing Information](#)) and ABI-009 (Module 2.4.4.5 and Module 2.6.6.3) in animals. Both male and female study patients receiving ABI-009 are recommended to use effective contraceptive methods prior to, during, and until 6 months after completing treatment.

The FDA's Assessment:

The FDA disagrees with the Applicant's position as in Section 8.2.9 above. Consistent with the product label for the listed drug (Rapamune), it is recommended for patients not to breastfeed during treatment with Fyarro and for 2 weeks after the last dose.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

ABI-009 is being studied in ongoing Investigator Sponsored Studies (pediatric solid tumors and pediatric epilepsy). No reports of serious adverse events in these studies were reported as of the 22 May 2019 data cut-off date for the NDA submission. Aadi-sponsored studies have not examined ABI-009 in pediatric patients <18 years of age, and ABI-009 is not recommended for

use in this population to treat PEComa.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

There is no known antidote for ABI-009 overdose. In case of overdose, vital signs should be monitored closely, and as appropriate, general supportive measures should be followed.

Possible complications may include thrombocytopenia, anemia, hypokalemia, hypercholesterolemia, hyperlipidemia, hypertension, arthralgia, diarrhea, and rash.

No evidence of psychological or physical dependence effects to ABI-009 has been demonstrated in nonclinical or clinical studies.

No evidence of psychological or physical withdrawal or rebound effects to ABI-009 has been demonstrated in nonclinical or clinical studies.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data:

Not applicable.

The Applicant's Position:

ABI-009 is not approved for marketing in any region.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Expectations on Safety in the Postmarket Setting

Data:

Not applicable.

The Applicant's Position:

Treatment-emergent adverse events observed in ABI-009 studies to date show a consistent safety profile between the Phase 1 and Phase 2 studies. All AEs observed in studies of ABI-009 are consistent with the known class-effects of the mTOR inhibitors and are both familiar to and manageable by oncologists. The risk profile is consistent across mTOR inhibitors. Therefore, Aadi believes that the risks can be adequately managed through the proposed prescribing information as well as through post-marketing surveillance.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

A comprehensive plan was developed and implemented to evaluate safety associated with the use of ABI-009 that ensured the maintenance of an acceptable benefit-risk balance for patients during the conduct of clinical trials. In accordance with the 10 December 2018 Type C Meeting with the FDA, the studies planned for inclusion in the integrated summary of safety were limited to those studies where ABI-009 was administered via IV infusion, and to studies sponsored by Aadi. In accordance with agreements reached in the above mentioned meeting, this summary of clinical safety presents the integrated safety summary required by the regulations (21CFR 314.50(d)(5)(vi)(a)). Similar data collection methods were used across all clinical studies to capture demographic and baseline characteristics of study participants as well as AEs, physical examination results, vital signs (inclusive of ECG results), concomitant medication records, and the results of clinical laboratory sample evaluations. In accordance with advice provided by the FDA in a Type C Meeting on 10 December 2018 with Aadi, the Summary of Clinical Safety includes a pooled analysis of 4 Aadi-sponsored oncology protocols in which ABI-009 was administered by intravenous infusion and summary of a single non-oncology study in PAH.

An assessment of the benefit-risk of ABI-009 in the treatment of advanced malignant PEComa was approached by a two-step process: 1) comparing and reviewing the available safety data from Study PEC-001 with those reported in the Phase 1 Study CA401 and with the RLD, rapamycin (Rapamune Prescribing Information) and other relevant mTOR inhibitors (everolimus and temsirolimus; [Afinitor Prescribing Information](#) and [Torisel Prescribing Information](#), respectively), and 2) evaluating the benefit-risk dimensions taking into consideration all available efficacy data from Study PEC-001 and literature review of the disease and treatment options.

The emerging safety profile of ABI-009 in the treatment of patients with advanced malignant PEComa is consistent with the known safety profiles for Rapamune and other mTOR inhibitors including Afinitor and Torisel. Most of the events have also been reported in the [Rapamune Prescribing Information](#) as a warning or precaution, although the grade was not specified. While a few events that occurred in Study PEC-001 are not described in the [Rapamune Prescribing Information](#), they have been noted for everolimus and temsirolimus ([Afinitor Prescribing Information](#),), except for amylase increase and hemothorax.

The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment of the safety of ABI-009, with the exceptions described in the preceding FDA sections. Notably, upon review of the application, FDA considered the relevant safety population to be the patients enrolled on Study PEC-001 rather than the pooled population described by the Applicant. In addition, while the FDA review considered the toxicities associated with other products in the same drug class, the application does not formally rely upon safety data derived from experience with other products. Despite the size of the safety database, it is considered appropriate for the current indication given extreme rarity and serious nature of malignant PEComa, and the demonstrated safety profile of ABI-009 based on the results of Study PEC-001. In addition, there is ample clinical experience with drugs in the same class such that the profile of adverse reactions and their management is well-understood. The FDA agreed with the Applicant's identification of significant and serious safety signals of stomatitis, myelosuppression, infections, hypokalemia, hyperglycemia, and non-infectious pneumonitis. Immunizations and risks associated with live vaccines, and risk of transmission of infectious agents with human albumin, are also addressed in Section 5 of the product label. Additionally, FDA identified an additional safety risk of hemorrhage. Given the need to further characterize serious risks associated with ABI-009, safety data from additional clinical trial(s) will be required as a post-marketing requirement. An evaluation of ABI-009 in patients with hepatic impairment, and of the risk for QTc prolongation will also be required as PMRs. FDA considers the agreed-upon product labeling and PMRs adequate to address safety concerns associated with the use of ABI-009.

Overall, the toxicity profile of ABI-009 is considered acceptable when considering the observed treatment effect in patients with this serious and life-threatening condition. The major safety risks of ABI-009 are toxicities that oncologists frequently manage.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

In general, there were no major statistical issues with the study design, statistical analysis plan,

or efficacy results for Study PEC-001. No inferential procedures were used to evaluate results from this single arm study. Instead, the FDA evaluated efficacy based on the magnitude of ORR per blinded independent central review by RECIST V1.1 and durability of responses. Time-to-event endpoints such as PFS, and OS are not interpretable in this single arm study, and these results were considered exploratory.

The results of Study PEC-001 demonstrated an ORR of 38.7% (12/31), with a 95% CI of 21.8%, 57.8%. All responders had a partial response and had metastatic disease. Based on a subsequent DCO date of June 30, 2021, the median DOR was not reached (range: 5.6, 55.5+ months).

8.4. Conclusions and Recommendations

The FDA's Assessment:

Malignant PEComa is considered an “ultra-rare” soft tissue sarcoma, with an incidence ≤ 1 per 1,000,000 (Stacchiotti, 2021). Survival outcomes for malignant PEComa are poorly characterized with median survival reported between 16-30 months (Bleeker, 2012; Sanfilipo, 2019). There are currently no FDA-approved therapies for malignant PEComa. Limited antitumor activity has been reported with anthracycline- and gemcitabine-based chemotherapies, as well as vascular endothelial growth factor (VEGF) receptor inhibitors (ORR 10%, 95% CI 3-22%)(Sanfilipo, 2019).

Substantial evidence of the effectiveness of ABI-009 for patients with locally advanced or metastatic malignant PEComa was demonstrated by the results of Study PEC-001. Study PEC-001 is a multi-center single-arm trial that enrolled 34 patients with malignant PEComa who had locally advanced unresectable or metastatic disease. Three patients were excluded after central pathology review, resulting in a primary efficacy population of 31 patients. The major efficacy outcomes were ORR and DOR as determined by blinded independent central review according to RECIST v1.1. ORR in the primary efficacy population was 39% (95% CI: 22, 58). The median DOR was not reached; however, 58% of responders had a response lasting greater than 24 months. Randomized-controlled trials in this setting would be infeasible due to the extreme rarity of this cancer, lack of an established standard of care to serve as a control arm, and concerns regarding equipoise given the responses observed in PEC-001.

ABI-009 has an acceptable safety profile for the intended population of patients, who have a life-threatening disease with no FDA-approved alternative treatments. Safety signals identified in Study PEC-001 included stomatitis, myelosuppression, infections, hypokalemia, hyperglycemia, non-infectious pneumonitis, and hemorrhage. Given the limited size of the safety database, the risks of hypersensitivity and infusion-related reactions could not be adequately assessed. Safety data from additional clinical trial(s), an evaluation of ABI-009 in patients with hepatic impairment, and an evaluation of the risk of QT prolongation will be

required as post-marketing requirements. The clinical reviewers do not recommend a REMS be implemented for ABI-009 given the current safety profile and experience of the oncologists in managing the expected toxicities associated with ABI-009. Risk management based on labeling and routine pharmacovigilance will be employed to ensure the safe and effective use of ABI-009 in patients with PEComa. Overall, the safety database is considered appropriate for the current indication given the rarity of this life-threatening disease, the tolerability of ABI-009 in the context of Study PEC-001, and the established prior experience with drugs in the same class that have demonstrated a manageable safety profile.

In conclusion, the benefit:risk assessment for ABI-009 is favorable, and the review team unanimously recommends approval of this NDA for ABI-009 for the treatment of adult patients with locally advanced unresectable or metastatic malignant perivascular epithelioid cell tumor (PEComa). The results of Study PEC-001 demonstrated a clinically meaningful overall response rate accompanied by a compelling DOR; as such, these results represent a direct clinical benefit patients with this rare, life-threatening cancer. We therefore recommend regular approval for this application.

X

X

Ting-Yu (Jeff) Chen, Ph.D.
Primary Statistical Reviewer

Mallorie Fiero, Ph.D.
Statistical Team Leader

X

X

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Primary Clinical Reviewer

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Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

The FDA did not refer this application to an advisory committee as no significant efficacy or

safety issues were identified during the review that required external input for the proposed indication.

10 Pediatrics

The Applicant's Position:

The safety and efficacy of ABI-009 in pediatric patients have not been established.

ABI-009 is being studied in ongoing Investigator-sponsored studies by the Children's Oncology Group (COG) in pediatric solid tumors (NCT02975882, or ADVL1514) and in pediatric epilepsy (NCT03646240). As of the NDA data cutoff of 22 May 2019, no SAEs have been reported in either study (pediatric patients with solid tumors, n = 18; pediatric epilepsy study, n = 6). These ongoing studies have treated additional patients since the NDA data cutoff, and as of the latest safety data review (04 September 2020), none of the 20 treated patients in the COG study had an SAE and 2/9 patients in the pediatric epilepsy study had a total of 5 SAEs (nervous system, GI disorders), none of which were considered related to study drug. Of note, 3/20 patients in the COG study discontinued treatment due to an AE (anemia, neutropenia, and/or thrombocytopenia).

The FDA's Assessment:

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. ABI-009 was granted orphan designation on December 21, 2017, and was therefore exempt from the requirements of PREA. The requirements under the RACE Act were not triggered by this NDA because the first component of the rolling application was submitted prior to August 18, 2020. Additionally, the active ingredient of ABI-009, sirolimus, is not a new active ingredient.

11 Labeling Recommendations

Data:

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	Applicant's Proposed Labeling	FDA's proposed Labeling
HIGHLIGHTS OF PRESCRIBING INFORMATION	(b) (4)	Highlights were revised based on the agreed upon full prescribing information. The product title was edited in accordance with the guidance Product Title and Initial US Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products to: FYARRO™ (sirolimus protein-bound particles for injectable suspension) (albumin-bound), for intravenous use.

1 INDICATIONS AND USAGE	(b) (4)	Specified that the indication is for “adult” patients and reworded for clarity: <i>For the treatment of adult patients with locally advanced unresectable or metastatic malignant perivascular epithelioid cell tumor (PEComa).</i>
2 DOSAGE AND ADMINISTRATION		Section 2.1: The dosage and administration was clarified such that treatment should continue until disease progression or unacceptable toxicity. Section 2.2: Extensive edits were made to dosage modifications for adverse reactions to reflect the severity of each adverse reaction and known clinical experience from Study PEC-001. Section 2.4: Specific dose modifications for hepatic impairment were added. Section 2.5 (previous): (b) (4) text was deleted, given no actionable information. Section 2.5: The title: Preparation and Administration was re-ordered and in accordance with current labeling practice, (b) (4) was edited to hazardous, (b) (4) was edited to powder, and text was edited for clarity and brevity.
3 DOSAGE FORMS AND STRENGTH		Removed (b) (4) as this may be perceived as promotional. In accordance with current labeling practice, edited (b) (4) to

	(b) (4)	powder.
5 WARNINGS AND PRECAUTIONS	(b) (4)	was changed to stomatitis for specificity. Thrombocytopenia, neutropenia, and anemia were grouped as myelosuppression to better characterize toxicity. Hypersensitivity, male infertility and immunizations were added to highlights. The title (b) (4) was edited to: Interstitial Non-Infectious Lung Disease / Non-Infectious Pneumonitis. The title Immunizations was edited to: Immunizations and Risks Associated with Live Vaccines to better characterize the issue and for consistency with other oncology labeling. The title Human Albumin was edited to: Risk of Transmission of Infectious Agents with Human Albumin to better characterize the issue and for consistency with other oncology labeling. Specific recommendations were provided for observation for hypersensitivity.

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213312
FYARRO (sirolimus protein-bound particles for injectable suspension) (albumin-bound)

		(b) (4) A new warning for Hemorrhage was added for safety. Adverse reaction rates were edited for consistency with Section 6. Statements related to the practice of medicine were removed.
6 ADVERSE REACTIONS	Standard information on Adverse Reactions was included.	Edited for clarity, reordered information for consistency with oncology labeling practices. Included information about serious adverse reactions, discontinuations, interruptions and dosage reductions. FDA verified and edited percentages per Applicant provided datasets.
7 DRUG INTERACTIONS	Strong and moderate/weak inhibitors/inducers of CYP3A4, as well as grapefruit juice, were listed separately.	7.1, 7.2 and 7.3 were combined under a new title “Effect of Other Drugs on FYARRO” consistent with current labeling practices.
8 USE IN SPECIFIC POPULATIONS 8.1 Pregnancy	Standard information was included, including a section on Patients with Renal Impairment.	Edited for brevity. Inclusion of rabbit study that resulted in fetal deaths and decreases in maternal weight. Section 8.5 text was edited for compliance with 21 CFR 201.57(c)(9)(v)(1) (b) (4)

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213312
FYARRO (sirolimus protein-bound particles for injectable suspension) (albumin-bound)

10 OVERDOSAGE	 (b) (4)	Section deleted, due to lack of actionable information.
11 DESCRIPTION	Standard information was provided.	Edited for clarity and brevity.
12 CLINICAL PHARMACOLOGY	Standard information was provided including a statement that FYARRO did not result in clinically significant adverse cardiac effect.	Edited for consistency with other oncology labels. A statement was added to reflect that: The effect of FYARRO on the QTc interval has not been adequately characterized.
13 NONCLINICAL TOXICOLOGY	Standard information was provided.	Edited for clarity and brevity.

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213312
FYARRO (sirolimus protein-bound particles for injectable suspension) (albumin-bound)

14 CLINICAL STUDIES 14.1 Perivascular Epithelioid Cell Carcinoma (PEComa)	Demographic information on 34 patients in AMPECT was provided.	Edited for clarity, brevity and consistency with current labeling practice. Demographic information edited to include only the 31 patients in efficacy population. DOR data were updated and information on two CRs noted at an additional data cutoff was included.
16 HOW SUPPLIED/ STORAGE AND HANDLING	The product title was listed as: (b) (4) 	Edited for clarity and consistency with current labeling practice. The product title was updated to: FYARRO (sirolimus protein-bound particles for injectable suspension) (albumin-bound)
17 PATIENT COUNSELING INFORMATION	Standard information corresponding to adverse reactions described in Section 5 was included.	Edited for clarity and brevity, and consistent with changes to Warnings and Precautions.

The Applicant's Position:

Based on efficacy and safety findings from Study PEC-001 in patients with PEComa, with supportive safety results from Study CA401 in patients with solid tumors, the Applicant is proposing the language above for the Fyarro label.

The FDA's Assessment:

This section was completed by the Applicant and initially included the entire original labelling text in the column "Applicant's Proposed Labeling." For clarity and brevity, this text was removed and high-level changes to the proposed labelling have been summarized. The proposed prescribing information was edited for safety, accuracy, clarity, and brevity in accordance with 21 Code of Federal Regulations (CFR), final and draft labeling guidances and current labeling practices to ensure safe and effective use of Fyarro.

12 Risk Evaluation and Mitigation Strategies (REMS)

The Applicant's Position:

As described in the Guidance for Industry entitled "REMS: FDA's Application of Statutory Factors in Determining When a REMS is Necessary", Aadi carefully assessed the six factors used by the FDA in determining whether to require a REMS. Based on the benefit-risk profile of ABI-009 for the proposed indication, Aadi believes that the risks can be adequately managed through the proposed prescribing information as well as through post-marketing surveillance.

The FDA's Assessment:

The risks of ABI-009 are acceptable in the indicated patient population with a serious and life-threatening condition; the safe use of ABI-009 can be adequately implemented in the post-marketing setting through product labeling and routine pharmacovigilance. No additional risk management strategies are recommended.

13 Postmarketing Requirements and Commitments

The FDA's Assessment:

The following post-marketing requirements and post-marketing commitment will be issued for this application:

PMR #1

Conduct an integrated safety analysis to assess the serious risk of infusion related reactions and to further characterize the risks of severe adverse reactions including myelosuppression, hypokalemia, hyperglycemia, non-infectious pneumonitis, hypersensitivity, and their sequelae in a sufficient number of patients exposed to Fyarro; and to identify risk factors for development of these adverse reactions. The study should include appropriate monitoring and risk mitigation strategies.

Draft Analysis Plan Submission:	03/2022
Final Analysis Plan Submission:	06/2022
Study Completion:	03/2025
Final Report Submission:	06/2025

Clinical PMR Rationale

The safety assessment of nab-sirolimus evaluated in Trial PEC-001 (A phase 2 multi-center investigation of efficacy of ABI-009 [nab-rapamycin] in patients with advanced malignant perivascular epithelioid cell tumors) was limited to only 34 patients. An infusion-related reaction occurred in a single patient, but given the small size of the safety database, the risk of infusion-related reactions in patients receiving ABI-009 is not well characterized. Additionally, among the 34 patients in the primary safety population, the incidence of adverse reactions of anemia, thrombocytopenia, neutropenia, hypokalemia, hyperglycemia, non-infectious pneumonitis, and hypersensitivity with nab-sirolimus were 65%, 35%, 35%, 45%, 12%, 18%, and 2.9%, respectively. Insufficient data is available to adequately characterize and assess the incidences of these risks. Cases of pneumonitis led to treatment interruptions and discontinuations. Given the small size of the safety database and rarity of PEComa, postmarketing data outside of a clinical trial is unlikely to address these deficiencies. The goal of this PMR is to provide further information to better characterize the risk of serious adverse reactions including infusion-related reactions, myelosuppression, hypokalemia, hyperglycemia, non-infectious pneumonitis, and hypersensitivity.

PMR #2

Conduct a hepatic impairment clinical trial to evaluate the pharmacokinetics and safety of Fyarro in subjects with mild, moderate, and severe hepatic impairment (based on NCI criteria) and determine the magnitude of increase in exposure and appropriate dosage. Design and conduct the trial in accordance with the FDA Guidance for Industry titled: "[Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.](#)"

Draft Protocol Submission:	03/2022
Final Protocol Submission:	06/2022
Study Completion:	10/2023
Final Report Submission:	03/2024

Clinical PMR Rationale

Fyarro (nab-sirolimus) is metabolized by the liver. Trial PEC-001 did not evaluate Fyarro (nab-sirolimus) in patients with moderate and severe hepatic impairment and current labeling recommends that Fyarro should not be used in patients with severe hepatic impairment. The safety profile in patients with hepatic impairment is unknown. A clinical trial is needed to determine if there is an increased exposure of nab-sirolimus in patients with hepatic impairment resulting in an increase in toxicity and to determine an appropriate starting dosage in this patient population.

PMR #3

Conduct a clinical trial to assess the potential risk of QT interval prolongation and the effect of Fyarro on the QT interval. Design and conduct the trial in accordance with the ICH E14 Guidance for Industry titled: "*E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.*"

Draft Protocol Submission:	03/2022
Final Protocol Submission:	06/2022
Trial Completion:	03/2025
Final Report Submission:	06/2025

Provide the datasets with the final report.

Clinical Pharmacology PMR Rationale

The QT interval prolongation potential for Fyarro has not been sufficiently evaluated. ABI-009 has very limited exposure overlap with the listed drug RAPAMUNE as its maximum concentration (C_{max}) is 170-fold higher than that of RAPAMUNE. Therefore, the Applicant is required to assess the QT interval prolongation potential for Fyarro as a PMR.

PMC #1

In Trial PEC-001, adverse reactions of hypersensitivity have occurred with infusion of FYARRO.

Because (b) (4) of the risk of immunogenicity and hypersensitivity with therapeutic proteins, further information is required to characterize the risk of immunogenicity and hypersensitivity in FYARRO. Submit side by side test results of albumin dimer/oligomer levels for FYARRO and any approved products containing albumin as an excipient with an established safety profile (b) (4) to support the proposed limit of albumin dimer/oligomer levels in FYARRO. A CBE-30 supplement will be submitted to propose an update to the drug product specifications if justified based on the results of this study. (b) (4)

Final Protocol Submission: 03/2022

Study Completion: 03/2023

Final Report Submission: 06/2023

CMC PMC Rationale

Human albumin is known to be prone to dimerization/oligomerization under denatured condition due to disulfide scrambling/exchange. Batch analysis and stability data showed a (b) (4)

(b) (4). The registration/clinical batch data provided (see table below) did not support the upper specification limit of (b) (4)% for dimer + unnamed oligomer. The level of albumin species should be controlled as critical product quality attributes (b) (4)

(b) (4). The literature reference provided by the Applicant and summary of hypersensitivity observed in clinical trial in relation to %dimer/oligomer in the clinical batch, was insufficient to support the proposed upper limit of (b) (4)% due to potential immunogenicity concern.

APPEARS THIS WAY ON ORIGINAL

14 Division Director (OCP)

X

15 Division Director (OB)

X

16 Division Director (Clinical) and Designated Signatory Authority

I have reviewed this application and agree with the approval recommendation by the FDA review teams.

X

Martha Donoghue, MD
Deputy Division Director, Division of Oncology 2
Office of Oncologic Disease

17 Appendices

17.1. References

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17.2. Financial Disclosure

The Applicant's Position:

Studies PEC-001, CA401, PAH-001, COLO-007, and GBM-007 are the covered clinical studies for the ABI-009 program. The financial disclosure documentation provided reflects the investigator information gathered across all covered studies where safety or efficacy data is included in the NDA, up to the data cutoff utilized in the NDA: 22 May 2019 for the PEC-001 study, and 30 April 2019 for the ongoing studies PAH-001, COLO-007, GBM-007. Study CA401 was completed in October 2011, and was also included. Of these five studies, two investigators (one from Study PEC-001 and one from GBM-007) had financial disclosures, which Aadi considers unlikely to have biased study results, and one subinvestigator had missing information:

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213312
FYARRO (sirolimus protein-bound particles for injectable suspension) (albumin-bound)

Study	Investigator / Role	Issue	Comments
PEC-001	(b) (6) - subinvestigator for Site (b) (6)	Positive disclosure	FDA Form 3455 declaring positive financial interest was signed, and attachments detail the amount of financial interests, and steps taken to minimize bias. Only one patient (b) (6) was treated at this site, who originally enrolled at Site (b) (6) subsequently transferred to Site (b) (6). Treating 1 patient was well under the 20% cap specified for his site. This represents minimal contribution of the site where (b) (6) was involved to study data as a whole.
CA401	(b) (6) - subinvestigator for Site (b) (6)	Missing disclosure	Form FDA 3454 was provided along with details of 7 attempts to follow up via phone and email. This a legacy study completed under previous ownership.
GBM-007	(b) (6) - principal investigator for Site (b) (6), and subinvestigator for Sites (b) (6)	Positive disclosure	FDA Form 3455 declaring positive financial interest was signed for each site that (b) (6) participated in as an investigator. The attachments describe (b) (6) specific financial disclosures, and steps taken to minimize bias.

In Study PEC-001, the primary efficacy analysis was performed by a blinded independent review committee, and the contribution of efficacy and safety data to Study GBM-007 from a site with a single subinvestigator with the positive financial disclosure was a single patient in a supportive non-registrational study. The sites with principal investigator (PI) involvement who had a positive disclosure were monitored regularly, and the PI did not participate in data analysis for the NDA.

It is unlikely that the positive financial disclosures biased the PEC-001 study results, as the primary efficacy analysis was performed by a blinded independent review committee.

Study GBM-007 was included in the NDA as a supporting study to broaden the safety data provided to the FDA. The sites (b) (6) with PI involvement who had a positive disclosure were monitored regularly, and (b) (6) did not participate in data analysis for the NDA.

The FDA's Assessment:

Covered Clinical Study (Name and/or Number):* PEC-001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>82</u>		

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

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

17.3. Nonclinical Pharmacology/Toxicology

Data:

See [Section 5](#) above.

The Applicant's Position:

See [Section 5](#) above.

The FDA's Assessment:

The FDA agrees that there is no additional information to add here. See Section 5 for the FDA

nonclinical review.

17.4. OCP Appendices (Technical documents supporting OCP recommendations)

17.4.1. Bioanalytical review

The FDA's Assessment:

Regarding PK samples in the pivotal Phase 2 Study **PEC-001**, the Applicant used a validated bioanalytical method for quantitation of sirolimus and secorapamycin (a thermal degradation product and human metabolite of sirolimus) in K₂EDTA human whole blood. The method used a liquid extraction followed by liquid chromatography with tandem mass spectrometry instrumental analysis.

Details of the validated method are provided below. The Applicant's bioanalytical method is acceptable for the intended purpose.

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213312
FYARRO (sirolimus protein-bound particles for injectable suspension) (albumin-bound)

Table 57: Applicant's bioanalytical sample analysis summary

Sponsor Protocol Number	PEC-001
Protocol Title	A phase 2 multi-center investigation of efficacy of ABI-009 (nab-rapamycin) in patients with advanced malignant perivascular epithelioid cell tumors (PEComa)
Sponsor Contact Information	Berta Grigorian 818-416-8378 bgrigorian@aadiobio.com
PI Contact Information	(b) (4)
Regulatory Requirements	Clinical
Sponsor or (b) (4) SOPs	(b) (4)
Analytes Determined	Rapamycin and Secorapamycin
Internal Standards	Rapamycin- ¹³ CD ₃ and Secorapamycin- ¹³ CD ₃
Matrix and Anticoagulant	K ₂ EDTA human whole blood
Dates Samples Received at (b) (4)	28-Apr-2016, 12-May-2016, 14-Jun-2016, 8-Jul-2016, 16-Jul-2016, 22-Jul-2016, 5-Aug-2016, 11-Aug-2016, 19-Aug-2016, 8-Sep-2016, 13-Sep-2016, 15-Sep-2016, 20-Sep-2016, 4-Oct-2016, 6-Oct-2016, 12-Oct-2016, 19-Oct-2016, 25-Oct-2016, 27-Oct-2016, 8-Nov-2016, 11-Nov-2016, 17-Nov-2016, 1-Dec-2016, 13-Jan-2017, 20-Jan-2017, 9-Feb-2017, 24-Feb-2017, 2-Mar-2017, 3-Mar-2017, 8-Mar-2017, 17-Mar-2017, 21-Mar-2017, 28-Mar-2017, 18-Apr-2017, 26-Apr-2017, 2-Jun-2017, 1-Sep-2017, 8-Sep-2017, 20-Sep-2017, 12-Oct-2017, 27-Oct-2017, 10-Nov-2017, 17-Nov-2017, 1-Dec-2017, 7-Dec-2017, 28-Dec-2017, 14-Feb-2018, 16-Feb-2018, 21-Feb-2018, 23-Feb-2018, 7-Mar-2018, 8-Mar-2018, 21-Mar-2018, 10-May-2018, 18-May-2018, 6-Jun-2018, 12-Jun-2018, 27-Jun-2018, 19-Jul-2018, 26-Jul-2018, 7-Aug-2018**, 10-Aug-2018, 23-Aug-2018**, 27-Aug-2018, 4-Oct-2018, 10-Oct-2018, 17-Oct-2018, 26-Oct-2018, 30-Oct-2018, 6-Nov-2018, 21-Nov-2018, 26-Nov-2018**, 4-Dec-2018, 6-Dec-2018, 12-Dec-2018, 18-Dec-2018 ** – Samples received thawed
Total Number of Samples Received	342
Condition on Receipt	Frozen on dry ice, unless otherwise noted
Sample Storage Conditions and Locations	Frozen (-80°C), BEQ.1063, BEQ.1303, BEQ.1402
(b) (4) Experimental Start Date	6-Apr-2017
(b) (4) Experimental Completion Date	4-Jan-2019
Analytical Method Version	BAM.0307.07 (effective date: 17-May-2018)
Methodology	Supported liquid extraction and LC-MS/MS instrumental analysis
Method Validation Report Numbers	BIO.VR.0194-1583.01 and BIO.VR.0194-1583.02
Calibration Curve Range	1.00 to 400 ng/mL
Duration of Matrix Stability Required	Rapamycin: 764 days at -80°C Secorapamycin: 764 days at -80°C
Duration of Matrix Stability Established	Rapamycin: 764 days at -80°C Secorapamycin: 544 days at -80°C
Total Number of Samples Assayed	334 samples for each analyte (see Table 12 and Table 13 for additional information)
Notice of Withdrawal of Consent	(b) (4) received no notification of withdrawal of consent for any clinical subjects.
Number of Analytical Runs (Total)	26

NDA/BLA Multi-disciplinary Review and Evaluation NDA 213312
FYARRO (sirolimus protein-bound particles for injectable suspension) (albumin-bound)

Number of Rejected Analytical Runs	6 runs rejected for rapamycin, 7 runs rejected for secorapamycin	
Inter-run Accuracy	Rapamycin Low QC (3.00 ng/mL): 0.7% Middle QC (30.0 ng/mL): -2.7% High QC (300 ng/mL): -1.7% Over-Range QC (800 ng/mL): -8%	Secorapamycin Low QC (3.00 ng/mL): 7.7% Middle QC (30.0 ng/mL): 6.3% High QC (300 ng/mL): 7% Over-Range QC (800 ng/mL): 3.9%
Inter-run Precision	Rapamycin Low QC (3.00 ng/mL): 8.9% Middle QC (30.0 ng/mL): 6.5% High QC (300 ng/mL): 5.7% Over-Range QC (800 ng/mL): 7.5%	Secorapamycin Low QC (3.00 ng/mL): 6.5% Middle QC (30.0 ng/mL): 2.9% High QC (300 ng/mL): 2.1% Over-Range QC (800 ng/mL): 6.2%
Samples Reanalysis SOP	BIO.PDN.SOP.002	
Incurred Sample Reproducibility SOP	BIO.PDN.SOP.003	

Source: From Applicant's Determination of Rapamycin and Secorapamycin in K2EDTA Human Whole Blood by LC-MS/MS report.

Table 58: Applicant's bioanalytical validation summary

Methodology	Supported-liquid extraction and LC-MS/MS instrumental analysis	
Matrix and Anticoagulant	K ₂ EDTA human whole blood	
Calibration Curve Range	1.00 to 400 ng/mL	
Analytes	Rapamycin	Secorapamycin
Internal Standards	Rapamycin- ¹³ CD ₃	Secorapamycin- ¹³ CD ₃
Results from Original Validation (Reported in BIO.VR.0194-1583.01)		
Inter-run Accuracy	LLOQ QC (1.00 ng/mL): -4.4% Low QC (3.00 ng/mL): 1% Middle QC (30.0 ng/mL): 1.7% High QC (300 ng/mL): -0.3%	LLOQ QC (1.00 ng/mL): -6.4% Low QC (3.00 ng/mL): -7.3% Middle QC (30.0 ng/mL): -3% High QC (300 ng/mL): -1%
Inter-run Precision	LLOQ QC (1.00 ng/mL): 7% Low QC (3.00 ng/mL): 3.7% Middle QC (30.0 ng/mL): 2.6% High QC (300 ng/mL): 3.3%	LLOQ QC (1.00 ng/mL): 3.7% Low QC (3.00 ng/mL): 7.2% Middle QC (30.0 ng/mL): 2.7% High QC (300 ng/mL): 3.1%
Dilution Integrity	Over-range VS: 800 ng/mL diluted 50-fold accuracy bias: -3.9%, precision: 2%	Over-range VS: 800 ng/mL diluted 50-fold accuracy: -3.6%, precision: 2.1%
Selectivity	No interferences in 10 lots of matrix	
Spiked Selectivity	For 10 lots spiked to contain 3.00 ng/mL accuracy: 3.3%, precision: 3.0%	For 10 lots spiked to contain 3.00 ng/mL accuracy: -12.0%, precision: 3.6%
Recovery	54.2-64.9% for rapamycin and 58.9-68.5% for rapamycin- ¹³ CD ₃	57.6-73.2% for secorapamycin and 72.1-85.1% for secorapamycin- ¹³ CD ₃
Matrix Effects (ISTD normalized matrix factor)	Low level: 0.949, 1.5% CV High level: 0.927, 0.7% CV	Low level: 1.020, 1.6% CV High level: 0.974, 1.1% CV
Benchtop Stability	At least 4 hours at room temperature for both analytes	
Freeze/Thaw Stability	3 cycles at -20°C and -80°C. Although rapamycin met acceptance criteria for both temperatures, secorapamycin did not pass at either temperature due to negative bias. Stored QCs were thawed once from -80°C storage for use in Runs 24 and 25 in which secorapamycin met acceptance criteria.	
Long-Term Stability	At least 5 days at -20°C and -80°C.	At least 5 days at -80°C only. Secorapamycin demonstrated instability at -20°C when stored for 5 days.
Extract Stability	At least 22 hours for samples maintained at 2-8°C until injection	

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FYARRO (sirolimus protein-bound particles for injectable suspension) (albumin-bound)

Reinjection Reproducibility	At least 4 hours for samples already injected and then maintained at 2-8°C	
Stock Solution Stability	At least 317 days in MeOH, when stored at -30 to -10°C, for 200 µg/mL conc.	At least 319 days in MeOH, when stored at -30 to -10°C, for 200 µg/mL conc.
Interference Assessments	Acceptable for both analytes	
Results from Partial Validation (To be reported in BIO.VR.0194-1583.02)***		
Intra-run Accuracy	LLOQ QC (1.00 ng/mL): -3.4% Low QC (3.00 ng/mL): -3% Middle QC (30.0 ng/mL): 5.3% High QC (300 ng/mL): 2.3%	LLOQ QC (1.00 ng/mL): -6.6% Low QC (3.00 ng/mL): -0.3% Middle QC (30.0 ng/mL): 1.3% High QC (300 ng/mL): 1%
Intra-run Precision	LLOQ QC (1.00 ng/mL): 4.2% Low QC (3.00 ng/mL): 3.2% Middle QC (30.0 ng/mL): 2.5% High QC (300 ng/mL): 1.8%	LLOQ QC (1.00 ng/mL): 10.4% Low QC (3.00 ng/mL): 2.3% Middle QC (30.0 ng/mL): 1.1% High QC (300 ng/mL): 1.5%
Selectivity	No interferences in 10 lots of matrix	
Spiked Selectivity	For 10 lots spiked to contain 3.00 ng/mL accuracy: -4.3%, precision: 6.5%	For 10 lots spiked to contain 3.00 ng/mL accuracy: -5.7%, precision: 5.3%
Recovery	73.1-76.7% for rapamycin and 69.4-75.5% for rapamycin- ¹³ CD ₃	76.4-81.0% for secorapamycin and 78.7-81.6% for secorapamycin- ¹³ CD ₃
Matrix Effects (ISTD normalized matrix factor)	Low level: 0.989, 2.9% CV High level: 0.980, 3.5% CV	Low level: 0.992, 2.0% CV High level: 0.988, 1.3% CV
Benchtop Stability	At least 24 hours at room temperature	5 hours at room temperature
Freeze/Thaw Stability	At least 6 cycles at -80°C	At least 6 cycles at -80°C
Long-Term Stability	At least 146 days at -20°C At least 764 days at -80°C	At least 544 days at -80°C
Extract Stability	At least 54 hours for samples maintained at 2-8°C until injection	
Reinjection Reproducibility	At least 23 hours for samples maintained at 2-8°C until injection	

Source: From Applicant's Determination of Rapamycin and Secorapamycin in K2EDTA Human Whole Blood by LC-MS/MS report.

17.4.2. Pharmacometrics Review:

Executive Summary:

The applicant submitted this 505(b)(2) NDA to obtain marketing approval for ABI-009 in the treatment of patients with locally advanced, unresectable or metastatic, malignant perivascular epithelioid cell tumor (PEComa).

The proposed dosing regimen is 100 mg/m² administered as an IV infusion over 30 minutes on Days 1 and 8 of 21-day cycles until disease progression or unacceptable toxicity. ABI-009 is formulated as a lyophilized powder containing 100 mg of sirolimus formulated as albumin-bound particles in single-dose vial for reconstitution.

The listed drug is Rapamune® (sirolimus), as tablets or oral solution for oral administration. ABI-009 has very limited exposure overlap with the listed drug as its C_{max} is 170-fold of the list drug's C_{max} level. The proposed indication was not approved for the listed drug.

Considering the current recommended dosing regimen is close to the MTD, a PMR is to be issued for a dedicated hepatic impairment trial to evaluate the PK and safety of ABI-009 in subjects with mild, moderate, and severe HI (based on NCI criteria).

The analysis of exposure-response relationship for efficacy consisted of 31 patients in pivotal study PEC-001 with available response values for best overall response (BOR). There were 12 responders in study PEC-001. A positive relationship of exposure with BOR could be identified. However, the result needs to be interpreted with caution due to the limited number of patients.

Analyses of exposure response (E-R) relationships for safety were performed using a population of 60 patients in pooled data from pivotal study PEC-001 and dose finding study CA401. A positive relationship was identified for thrombocytopenia and rash. There is no positive E-R relationship for neutropenia, hypokalemia, hyperglycemia, dehydration, hypertriglyceridemia or diarrhea.

17.4.2.1 Population PK Analysis

The Applicant's Position:

A population pharmacokinetic (PK) model for sirolimus in PEComa patients was developed using data from 2 studies: 1) sparse PK sampling in the registrational phase 2 trial (PEC-001) in PEComa patients were combined with 2) data from the phase 1 dose-finding PK/PD study (CA401) with full PK sampling in patients with advanced solid tumors. A total of 60 patients with 709 observations from both studies PEC-001 (N = 34) and CA401 (N = 26) were included in the Population PK Analysis data set. The population PK modeling was a 2-compartment model with saturable binding in the central compartment.

Exposures demonstrated that sirolimus C_{max} increases with increasing dose (45 to 150 mg/m²), and a similar dose-relationship was observed for AUC during the first 4 hours after infusion (AUC₀₋₄), but less of a dose-relationship for AUC from time zero to infinity, AUC_{0-inf}. This is consistent with the observed data, in which increasing the dose results in higher concentrations for the first few hours after dosing, but drug was rapidly eliminated. Terminal elimination phases were largely indistinguishable across dose groups.

Given the low shrinkage value for clearance random effects, predicted exposures derived from the population PK model were deemed appropriate for subsequent efficacy and safety analyses.

The covariate analysis suggested little effects of body weight, suggesting that no adjustments for weight would be necessary for the adult population at the 100 mg/m² dose level.

Sirolimus undergoes extensive *hepatic* metabolism, largely via the cytochrome P450 system. Clinically meaningful changes in sirolimus exposure were not observed with elevated hepatic

function in this analysis, likely due to the small number of subjects available and limited range of hepatic impairment in these subjects. Additionally, clinical studies PEC-001 and CA401 were not designed to definitively characterize effects of hepatic function on sirolimus disposition. Therefore, dose adjustments are likely warranted in patients with reduced hepatic function.

In Section 2.4 Patients with Hepatic Impairment, of the proposed USPI for FYARRO, dose adjustments to 75 mg/m² and 56 mg/m² are included for patients with mild and moderate hepatic impairments, respectively. FYARRO is not recommended for use in patients with severe hepatic impairment.

Population PK Summary Table

General Information		
Study Included		CA401, PEC-001
Dose(s) Included		45, 56.25, 100, 125, and 150 mg/m ²
Population Included		Patients with untreatable advanced nonhematologic malignancies; Patients with perivascular epithelioid cell tumors
Population Characteristics (Table XX)	General	Age 60 (18-78) years; Weight 79.1 (42.3-118) kg; 22 Male (36.7%); 38 Female (63.3%); Caucasian 43 (71.7%)
	Organ Impairment	ALT 19 (0-61) (U/L); (Median (range)) AST 22.5 (10-73) (U/L); (Median (range)) Bilirubin 0.4 (0-1.20) (mg/dL); (Median (range)) Hematocrit 37.2 (26.9-44.9) (%); (Median (range))
	Pediatrics	none
No. of Patients, PK Samples, and BLQ		60 subjects, 667 observations, 6 BLQ records
Sampling Schedule	Rich Sampling	CA401: Blood samples from 26 treated patients (16 males and 10 females) were collected during Cycle 1 Day 1 at predose, 15min, 30min 1, 1.5, 2, 4, 6, 24, 48, 72, 96, and 168 hours after the start of infusion (ie, trough sample just prior to Cycle 1 Day 8 dose).
	In ITT Population	PEC-001: Sparse blood samples for sirolimus concentrations were taken on Cycle 1 Days 1 and 8 predose, and at 30 min and then at 1, 2, and 4 hours after the start of the infusion and a 2-week trough sample was taken predose before Cycle 2 Day 1.
Covariates Evaluated	Static	Weight, AST, ALT, Bili, RBC

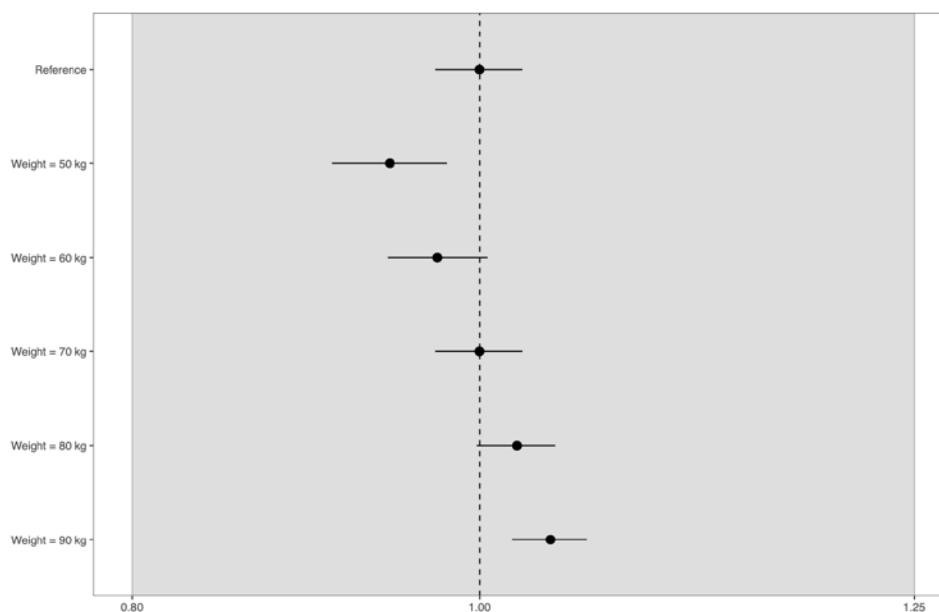
Final Model	Summary
Software and Version	NONMEM v. 7.4.3
Model Structure	<i>Two-compartment model with linear clearance and saturable binding in the central compartment. Inter-individual random effects modeled for CL, Vc, and Vp. Proportional model was used to describe the residual error.</i>
Model Parameter Estimates	Table 59
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	<i>All parameters were estimated with adequate precision. IIV was of a reasonable magnitude on CL and Vc and large on Vp; shrinkage was below 10% for all IIV parameters. The performance of these metrics was adequate for the PK objectives.</i>
BLQ for Parameter Accuracy	<i>All BLQ values were excluded; The percentage of BLQ values was sufficiently low to not have any impact on parameter estimation</i>
Significant Covariates and Clinical Relevance	<i>No covariates were deemed clinically relevant; Figure 10.</i>

Table 59: Parameter Estimates from Final Population PK Model.

Parameter	Estimate	%RSE	CI (95%)	Units
CL	93.8	9.48	(77.9, 113)	L/h
Vc	17.9	8.14	(15.2, 20.9)	L
Q	106	17.6	(75.0, 149)	L/h
Vp	42.6	13.0	(33.0, 55.0)	L
RMAX	7.53	5.62	(6.75, 8.41)	mcmol
KD	0.0148	15.9	(0.0109, 0.0202)	mcmol
CL and Q WT effect	0.160	2.40	(0.152, 0.167)	
Vc and Vp WT effect	0.441	0.600	(0.435, 0.446)	
Interindividual variability				
ω_{CL}	0.161	25.3	(0.0809, 0.240)	Var
ω_{Vc}	0.133	27.1	(0.0624, 0.204)	Var
ω_{Vp}	1.62	27.0	(0.760, 2.47)	Var
Residual error				
$\sigma_{Proportional}$	0.0621	11.0	(0.0486, 0.0755)	Var

Source: Study ADI0101 Report, Table 4

Figure 10: Covariate Forest Plot for Sirolimus Clearance.



Source: Study ADI0101 Report, Figure 44. The point ranges represent the median and 95% CI of the CL at the given covariate value normalized to the median reference CL. The shaded region represents normalized CL from 0.8 to 1.25.

The FDA's Assessment for population PK model:

1. Sponsor's population PK model was acceptable with limitations.
A nonlinear PK relationship between dosing level of 45-150 mg/m² was observed in dose finding study CA401. Due to limited patient number in overall and dose finding studies, no more improvement was required but model extrapolation needs to be taken with caution.

Table 60: Summary of Pharmacokinetics Parameters (Treated Population Study CA401)

PK Parameters	Dose (mg/m ²)				
	45 (n = 7)	56.25 (n = 3)	100 (n = 7)	125 (n = 7)	150 (n = 2)
C _{max} (ng/mL)	1640 (46.0)	2740 (41.8)	3020 (41.9)	3980 (42.1)	2800 (173)
t _{max} (h)	0.5 [0.15, 0.50]	0.5 [0.34, 0.5]	0.5 [0.25, 0.50]	0.25 [0.25, 0.5]	1.1 [0.53, 1.67]
AUC _{0-∞} (ng×h/mL)	24200 (17.1)	24500 (34.6)	38700 (39.8)	26500 (21.0)	68600 (1.93)
t _{1/2} (h)	38.6 (23.7)	44.8 (34.4)	56.8 (39.5)	53.7 (23.7)	90.7 (5.42)
CL (L/h)	7.35 (27.8)	6.37 (25.8)	4.96 (47.4)	2.67 (24.7)	4.61 (23.4)

Source: table 2 of study CA401 CSR

2. Body Weight is the significant covariate for clearance and volume of distribution. This justified a body surface area (BSA) proportional dosing regimen of the Applicant's final selected dosing regimen.
3. Sirolimus undergoes extensive hepatic metabolism, largely via the cytochrome P450 system. Clinically meaningful changes in sirolimus exposure were not observed with elevated hepatic function in this analysis, likely due to the small number of subjects available and limited range of hepatic impairment in these subjects. Considering the current recommended dosing regimen is close to MTD, a PMR is to be issued for a dedicated hepatic impairment trial to evaluate the PK and safety of ABI-009 in subjects with mild, moderate, and severe HI.

17.4.2.2 Exposure-Response Analysis for Efficacy

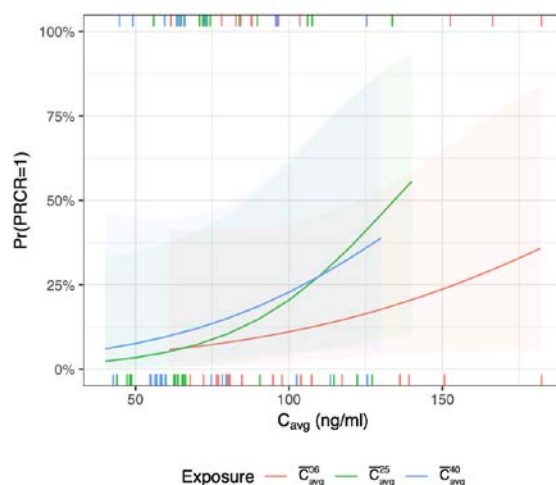
The Applicant's Position:

The analysis population for graphical evaluation of efficacy exposure-response consisted of all patients in Study PEC-001 with available response values for best overall response (BOR). A positive relationship for the probability of response (partial of confirmed as per RECIST v1.1) was observed for sirolimus exposure from ABI-009.

ER Efficacy Summary Table

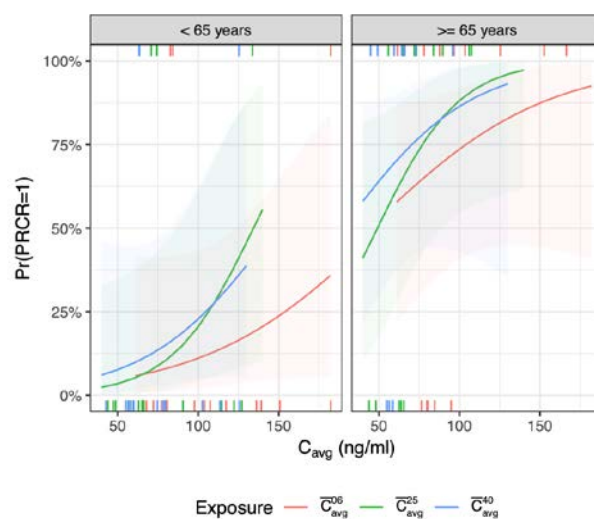
General Information		
Goal of ER analysis		<i>Evaluate the relationship between exposure and efficacy</i>
Study Included		<i>PEC-001</i>
Endpoint		<i>Best overall response (BOR)</i>
No. of Patients (total, and with individual PK)		<i>31</i>
Population Characteristics (Table XX)	General	<i>17 age < 65 years; 14 age ≥ 65 years. 25 active baseline ECOG; 6 restricted baseline ECOG. 25 female; 6 male.</i>
	Pediatrics (if any)	<i>none</i>
Dose(s) Included		<i>100 mg/m²</i>
Exposure Metrics Explored (range)		<i>Average concentration through 6, 24, and 40 days following dosing (C_{avg}^6, C_{avg}^{25}, C_{avg}^{40}).</i>
Covariates Evaluated		<i>Sex, age, baseline ECOG</i>
Visualization of E-R relationships		<i>Figure 11- Figure 14</i>

Figure 11: Exposure Response Relationship for Efficacy (BOR)



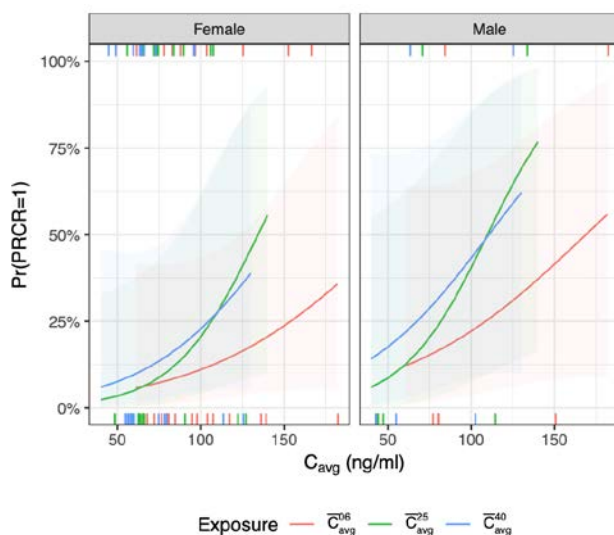
Source: Study ADI0101 Report, Figure 110. Holding discrete covariate values constant at reference levels: AGE GROUP < 65 years, SEX = Female and ECOG = Active. The tick marks indicate observed response outcomes.

Figure 12: Exposure Response Relationship for Efficacy in Different Age Groups



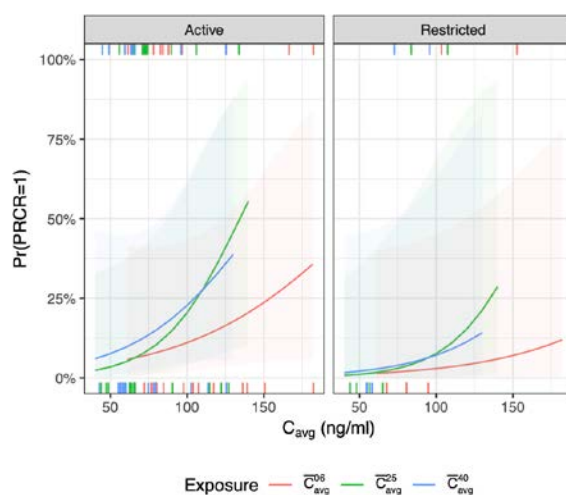
Source: Study ADI0101 Report, Figure 111. Holding discrete covariate values constant at reference levels: SEX = Female and ECOG = Active. The tick marks indicate observed response outcomes.

Figure 13: Exposure Response Relationship for Efficacy Stratified by Sex



Source: Study ADI0101 Report, Figure 112. Holding discrete covariate values constant at reference levels: AGEGROUP < 65 years and ECOG = Active. The tick marks indicate observed response outcomes.

Figure 14: Exposure Response Relationship for Efficacy Stratified by baseline ECOG



Source: Study ADI0101 Report, Figure 113. Holding discrete covariate values constant at reference levels: SEX = Female and AGEGROUP < 65 years. The tick marks indicate observed response outcomes.

The FDA's Assessment:

The Applicant's analysis is reasonable. However, the results need to be interpreted with caution due to the limited overall patient number.

17.4.2.3 Exposure-Response Analysis for Safety

The Applicant's Position:

Graphical analysis was used to evaluate the relationship between sirolimus clearance and aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (BILI), hematocrit (HCT), and red blood cells (RBC). The exposure and safety measures were evaluated via formal model-based analysis (as well as evaluated graphically for trends) for 7 preselected adverse events (AEs): anemia, thrombocytopenia, AST, ALT, mucositis, rash, pneumonitis. The most common AEs corresponded to the AEs from both studies that were identified in advance for model-based analysis. Additionally, exposure and safety measures were analyzed via graphical analysis to identify trends for neutropenia, hypokalemia, hyperglycemia, dehydration, hypertriglyceridemia, and diarrhea.

Graphical analysis suggests a strong relationship between lower levels of baseline platelet count and hemoglobin and the incidence of thrombocytopenia and anemia, respectively. There was a statistically significant positive relationship between exposure and incidence of thrombocytopenia; while a small positive nonsignificant positive relationship was observed for anemia.

There was a statistically significant positive relationship between elevated AST and ALT incidence and baseline AST and ALT. Graphically, no trends were observed between increasing incidence or severity of elevated AST and elevated ALT and sirolimus exposure.

Based on a formal model, a small negative nonsignificant relationship was observed between drug exposure and mucositis or pneumonitis; while a positive but nonsignificant relationship was observed between drug exposure and rash. Graphically, no trends were observed between increasing incidence or severity of mucositis, rash, or pneumonitis and sirolimus exposure.

Graphical evaluation of other AEs, including neutropenia, hypokalemia, hyperglycemia, dehydration, hypertriglyceridemia, and diarrhea showed no relationship between incidence and exposure, or AE severity and exposure.

Baseline lab values are predictive of adverse event incidence for anemia, thrombocytopenia, elevated AST, and elevated ALT.

Although the patient sample size is small, modeling and simulation results do not indicate that a starting dose different than the MTD of 100 mg/m² would be beneficial with regards to safety.

ER Safety Summary Table

General Information		
Goal of ER analysis		<i>Evaluate the relationship between exposure and safety measures using model-based analysis</i>
Study Included		CA401, PEC-001
Population Included		<i>Patients with untreatable advanced nonhematologic malignancies; Patients with perivascular epithelioid cell tumors</i>
Endpoint		<i>Thrombocytopenia, anemia, mucositis, rash, elevated AST, elevated ALT, and pneumonitis</i>
No. of Patients (total, and with individual PK)		60
Population Characteristics (Table XX)	General	<i>Age 60 (18-78) years; (Median (range)) Weight 79.1 (42.3-118) kg; (Median (range)) 22 Male (36.7%); 38 Female (63.3%); Caucasian 43 (71.7%)</i>
	Organ impairment	<i>ALT 19 (8-61) (U/L); (Median (range)) AST 23 (11-69) (U/L); (Median (range))</i>
	Pediatrics (if any)	<i>none</i>
	Geriatrics (if any)	<i>Age 69 (65 – 78) years, 37% subj $\geq$65 yr, 12% subj $\geq$75 yr 7 (23%) male</i>
Dose(s) Included		<i>45, 56.25, 100, 125, and 150 mg/m²</i>
Exposure Metrics Explored (range)		<i>Daily C_{avg}⁶ (61.5 – 182 ng/mL)</i>
Covariates Evaluated		<i>age, sex, baseline platelet count, baseline hemoglobin, baseline AST, baseline ALT</i>
Final Model Parameters		Summary
Model Structure		<i>Bernoulli GLM model with a complementary log-log link and offset from the log of time at risk</i>
Model Parameter Estimates		Table 61- Table 67
Covariates and Clinical Relevance		<i>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. 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.</i>

Visualization of E-R relationships	<i>Figure 15</i>
Overall Clinical Relevance for ER	<i>Although the patient sample size is small, modeling and simulation results do not indicate that a starting dose different than the maximum tolerated dose (MTD) of 100 mg/m² would be beneficial with regards to efficacy or safety.</i>

Table 61: Parameter Estimates from Final ER Model of Thrombocytopenia

Parameter	Description	Estimate	95% CI
θ_0	Intercept	0.511	(-2.73, 3.76)
θ_1	Average Concentration (ng/mL)	0.0109	(0.00148, 0.0203)
θ_2	Age (Years)	-0.0493	(-0.0855, -0.0132)
θ_3	Male	1.45	(0.332, 2.57)
θ_4	Baseline Platelet Count (10 ⁹ /L)	-0.0204	(-0.0302, -0.0107)

Source: Study ADI0101 Report, Table 16

Table 62: Parameter Estimates from Final ER Model of Anemia

Parameter	Description	Estimate	95% CI
θ_0	Intercept	-2.82	(-5.36, -0.291)
θ_1	Average Concentration (ng/mL)	0.000151	(-0.0104, 0.0107)
θ_2	Age (Years)	-0.0460	(-0.0828, -0.00917)
θ_3	Male	-0.916	(-1.96, 0.126)
θ_4	Baseline Hemoglobin (g/dL) - Linear	-9.58	(-14.0, -5.20)
θ_5	Baseline Hemoglobin - Quadratic	-4.93	(-9.39, -0.462)

Source: Study ADI0101 Report, Table 18

Table 63: Parameter Estimates from Final ER Model of Mucositis

Parameter	Description	Estimate	95% CI
θ_0	Intercept	-3.18	(-5.21, -1.15)
θ_1	Average Concentration (ng/mL)	-0.000293	(-0.00920, 0.00861)
θ_2	Age (Years)	-0.0290	(-0.0575, -0.000560)
θ_3	Male	0.152	(-0.676, 0.980)

Source: Study ADI0101 Report, Table 19

Table 64: Parameter Estimates from Final ER Model of Rash

Parameter	Description	Estimate	95% CI
θ_0	Intercept	-7.33	(-10.1, -4.54)
θ_1	Average Concentration (ng/mL)	0.00571	(-0.00400, 0.0154)
θ_2	Age (Years)	0.0244	(-0.0149, 0.0637)
θ_3	Male	-0.469	(-1.41, 0.476)

Source: Study ADI0101 Report, Table 20

Table 65: Parameter Estimates from Final ER Model of elevated AST

Parameter	Description	Estimate	95% CI
θ_0	Intercept	-1.18	(-4.48, 2.12)
θ_1	Average Concentration (ng/mL)	-0.0136	(-0.0344, 0.00716)
θ_2	Age (Years)	-0.0846	(-0.132, -0.0374)
θ_3	Male	0.0263	(-1.37, 1.42)
θ_4	Baseline AST (U/L)	0.0243	(-0.0171, 0.0657)

Source: Study ADI0101 Report, Table 21

Table 66: Parameter Estimates from Final ER Model of elevated ALT

Parameter	Description	Estimate	95% CI
θ_0	Intercept	-5.76	(-9.71, -1.81)
θ_1	Average Concentration (ng/mL)	-0.00571	(-0.0248, 0.0133)
θ_2	Age (Years)	-0.0364	(-0.0843, 0.0116)
θ_3	Male	0.554	(-0.838, 1.95)
θ_4	Baseline ALT (U/L)	0.0540	(0.00804, 0.0999)

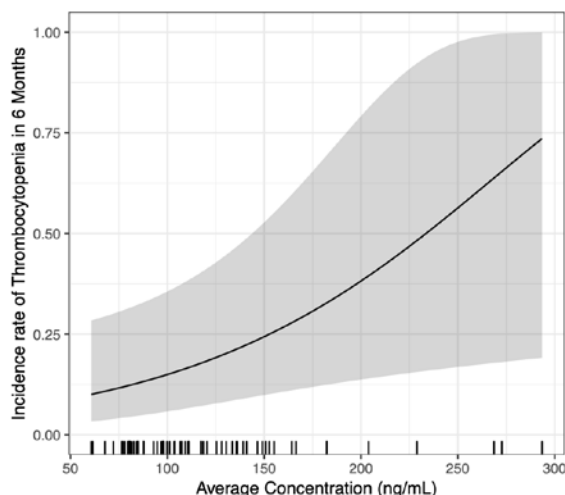
Source: Study ADI0101 Report, Table 22

Table 67: Parameter Estimates from Final ER Model of Pneumonitis

Parameter	Description	Estimate	95% CI
θ_0	Intercept	-14.2	(-22.9, -5.49)
θ_1	Average Concentration (ng/mL)	-0.0162	(-0.0484, 0.0160)
θ_2	Age (Years)	0.130	(0.00513, 0.254)

Source: Study ADI0101 Report, Table 23

Figure 15: Exposure Response Analysis for Thrombocytopenia



Source: Study ADI0101 Report, Figure 54. Predicted probability of thrombocytopenia within 6 months for a typical subject (58 year-old woman with baseline platelet count of $281 \times 10^9/L$). Grey ribbon indicates 90% confidence interval. Marks along x-axis indicate simulated exposure values used in modeling.

The FDA's Assessment:

The Applicant's analysis is acceptable.

17.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

See Section 8.2 for FDA's assessment of safety.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Sachia Khasar	OOD/DHOT	Section 5	<u>X</u> Authored <u> </u> Approved
	Signature: Gabriel S. Khasar -S Digitally signed by Gabriel S. Khasar -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000595653, cn=Gabriel S. Khasar -S Date: 2021.11.17 09:50:56 -05'00'			
Nonclinical Team Leader	Emily Wearne	OOD/DHOT	Section 5	<u>X</u> Authored <u>X</u> Approved
	Signature: Emily F. Wearne -S Digitally signed by Emily F. Wearne -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001296929, cn=Emily F. Wearne -S Date: 2021.11.15 15:59:35 -05'00'			
Nonclinical Team Division Director	John Leighton	OOD/DHOT	Section 5	Authored <u>X</u> Approved
	Signature: John K. Leighton -S Digitally signed by John K. Leighton -S Date: 2021.11.16 07:22:56 -05'00'			
Clinical Pharmacology Reviewer	Wenchi (Vicky) Hsu	OCP/DCPI	Sections 6, 17.4	<u>X</u> Authored <u> </u> Approved
	Signature: Vicky Hsu -S Digitally signed by Vicky Hsu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Vicky Hsu -S, 0.9.2342.19200300.100.1.1=2000996657 Date: 2021.11.15 17:25:44 -05'00'			
Clinical Pharmacology Team Leader	Hong Zhao	OCP/DCPII	Sections 6, 17.4	<u>X</u> Authored <u>X</u> Approved
	Signature: Hong Zhao -S Digitally signed by Hong Zhao -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Hong Zhao -S, 0.9.2342.19200300.100.1.1=1300136450 Date: 2021.11.17 08:19:40 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED / APPROVED
Clinical Pharmacology Division Director	Nam Atiqur Rahman	OCP/DCPII	Sections 6, 17.4	Authored <u>X</u> Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nam A. Rahman -S, 0.9.2342.19200300.100.1.1=1300072597 Date: 2021.11.15 16:14:52 -05'00'			
Pharmacometrics Reviewer	Yuan Xu	OCP/DPM	Sections 6, 17.4	<u>X</u> Authored Approved
	Signature: Yuan Xu -S Digitally signed by Yuan Xu -S Date: 2021.11.17 10:33:39 -05'00'			
Pharmacometrics Team Leader	Jiang Liu	OCP/DPM	Sections 6, 17.4	<u>X</u> Authored <u>X</u> Approved
	Signature: Jiang Liu -S Digitally signed by Jiang Liu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jiang Liu -S, 0.9.2342.19200300.100.1.1=2000348510 Date: 2021.11.17 09:29:10 -05'00'			
Clinical Reviewer	Gautam Mehta	OOD/DO2	Sections 1, 2, 3, 7, 8, 9, 10, 11, 12, 13, 17.1, 17.2	X Authored ____ Approved
	Signature: Gautam Mehta Digitally signed by Gautam Mehta DN: cn=Gautam Mehta, o=Food and Drug Administration, ou=Division of Oncology 2, email=Gautam.Mehta@fda.hhs.gov, c=US Date: 2021.11.15 17:56:30 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader and CDTL	Diana Bradford	OOD/DO2	Sections: All	<u>X</u> Authored <u>X</u> Approved
	Signature: Diana L. Bradford -S Digitally signed by Diana L. Bradford S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001559418, cn=Diana L. Bradford S Date: 2021.11.16 05:03:35 -05'00'			
Statistical Reviewer	Ting-Yu (Jeff) Chen	OB/DV	Section 8	<u>X</u> Authored Approved
	Signature: Ting-yu Chen -S Digitally signed by Ting-yu Chen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ting-yu Chen -S, 0.9.2342.19200300.100.1.1=2002894402 Date: 2021.11.15 16:31:50 -05'00'			
Statistical Team Leader	Mallorie Fiero	OB/DV	Section 8	<u>X</u> Authored <u>X</u> Approved
	Signature: Mallorie H. Fiero -S Digitally signed by Mallorie H. Fiero S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002084959, cn=Mallorie H. Fiero S Date: 2021.11.15 16:28:41 -05'00'			
Division Director (OB)	Shenghui Tang	OB/DV	Section 8	Authored <u>X</u> Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Shenghui Tang S, 0.9.2342.19200300.100.1.1=1300224175 Date: 2021.11.17 08:26:18 -05'00'			
Safety Analyst	Peter Schotland	OOD	Section 8	<u>X</u> Authored Approved
	Signature: Peter A. Schotland -S Digitally signed by Peter A. Schotland S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001366044, cn=Peter A. Schotland S Date: 2021.11.16 08:33:04 -05'00'			

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/

SHARON K SICKAFUSE
11/22/2021 03:19:06 PM

MARTHA B DONOGHUE
11/22/2021 03:22:54 PM