CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213312Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 213312 Assessment 1

Drug Product Name	Fyarro [Sirolimus protein-bound particles for injectable suspension (albumin-bound)]
Dosage Form	Injection, suspension
Strength	100 mg of sirolimus in a (b) (4) vial
Route of Administration	IV
Rx/OTC Dispensed	Rx
Applicant	AADI BIOSCIENCE INC
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original NDA	05/28/2021	All CMC
Quality Amendment	08/10/2021	DP
Quality Amendment	08/19/2021	Microbiology
Quality Amendment	09/01/2021	DP, OPMA
Quality Amendment	09/08/2021	OPMA
Labeling	09/10/2021	DP
Quality Amendment	09/13/2021	OPMA
Quality Amendment	09/15/2021	OPMA
Quality Amendment	09/16/2021	DP
Quality Amendment	09/22/2021	OPMA
Quality Amendment	10/07/2021	DP
Quality Amendment	10/29/2021	DP

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Soumya Mitra	Paresma Patel
Drug Product	Hailin Wang	Anamitro Banerjee
Manufacturing	Quamrul Majumder	Rakhi Shah
Microbiology	Shannon Heine	Erika Pfeiler
Biopharmaceutics	Mei Ou	Banu Zolnik
Regulatory Business Process Manager	Rabiya Haider	
Application Technical Lead	Xing Wang	
Environmental	Hailin Wang	Anamitro Banerjee

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EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The applicant of NDA 213312 provided sufficient information to assure the identity, strength, purity, quality, and bioavailability of the proposed drug product. The labels and labeling include adequate quality information as required. All associated manufacturing, testing, packaging facilities were deemed acceptable.

OPQ recommends **APPROVAL of NDA 213312** for sirolimus protein-bound particles for injectable suspension (albumin-bound). OPQ grants a 24-month expiration dating period for the drug product, stored at 2 to 8°C in the proposed container closure system. Protect from light.

The drug product review team determined that the following **post-marketing commitment** is necessary. The applicant has agreed with the Post-Marketing Commitment for Quality and the associated timelines (SN 0036, 11/01/2021).

PMC:
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 (e.g. Abraxane®) 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

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

An injectable IV formulation of sirolimus was desired to achieve higher dose delivery as compared to the poorly bioavailable oral formulation of the reference listed drug. FYARRO is a white to off-white lyophilized

powder of 100 mg of sirolimus and approximately 850 mg of human albumin in a single-dose (b) (4) glass vial. Each vial of the drug product will be reconstituted using 20 mL of 0.9% sodium chloride injection, USP, to get a 5 mg sirolimus/mL solution before being administered by IV infusion over 30 minutes without further dilution. RLDs are Rapamune (sirolimus) Tablets (NDA 21110) and Rapamune Oral Solution (NDA 21083).

Drug substance sirolimus (rapamycin), a macrocyclic lactone produce by *Streptomyces hygroscopicus*, is an antineoplastic and a selective immunosuppressant agent, an mTOR inhibitor. Sirolimus drug substance is white to off-white powder, insoluble in water. (b) (4) . DMF (b) (4) is referenced for sirolimus drug substance, LOA provided. A retest period of (b) (4) is found acceptable.

The excipient, human albumin (HSA), is an approved product added to the formulation (b) (4) sirolimus. LOA to (b) (4) is provided. (b) (4) . Extensive physical characterizations of the product, e.g., the amorphous state of sirolimus, (b) (4) , supports the intended design outcome of the sirolimus IV formulation.

The drug product manufacturing steps include (b) (4) (b) (4)

The drug product specification includes tests to ensure identify, strength, purity, and quality/performance of the product. Particle size distribution and albumin content and species are considered critical quality attributes specific/unique to the proposed drug product. Two complimentary methods (b) (4) are used to control the particle size distribution. Human albumin to sirolimus ratio is added in the DP specification (b) (4) and the labeled ratio of 8.5 :1 is met. Additional data/justification is needed to support the upper limit of the albumin dimer + oligomer content which will be followed up by PMC.

Long-term stability data and accelerated stability data support the proposed shelf-life of 24 months, when the product is stored at 2-8˚C in the proposed commercial package.

Proposed Indication(s) including Intended Patient Population	FYARRO is an mTOR inhibitor indicated for the treatment of advanced (metastatic or locally advanced) malignant perivascular epithelioid cell tumor (PEComa).
Duration of Treatment	Until disease progression or unacceptable toxicity
Maximum Daily Dose	(b) (4) mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance is Sirolimus, which is a fermentation product. (b) (4) (b) (4) (b) (4). The Applicant has cross-referenced DMF# (b) (4) for all information pertaining to Sirolimus (Rapamycin). The DMF holder (b) (4) has provided satisfactory risk assessment studies for this fermentation product, which was used by the Applicant (Aadi BioSciences, Inc.) to complete risk assessment of the drug product.
The latest DMF amendments (SDN 46, 47 and 48) were reviewed by this reviewer and was assessed to be Adequate in support of this NDA (Refer to DMF Review#5 in Panorama, by Dr. Soumya Mitra and Dr. Paresma Patel, dated 07/22/2021). The structure of the API was unequivocally established by spectroscopic studies. The drug substance specification for Sirolimus (Rapamycin) were in-line with ICH guidances, with acceptable justification for limits of related substances. The Applicant has provided manufacturing schemes of APIs with satisfactory controls in their manufacturing process.

Risk assessments were provided for elemental impurities, related substances, (b) (4) impurity, and residual solvents, which were deemed to be acceptable. Analytical methods and method validation provided by the cross-referenced DMF (b) (4) were satisfactory. Batch analysis data are provided and well within the pre-set acceptance criteria, consistent and comparable. The container closure system was suitable for intended use. The stability data has been cross-referenced to the corresponding DMF# (b) (4) from the drug substance manufacturer. The Applicant sets a retest period of (b) (4) for Sirolimus, which is acceptable based on the stability data under long-term conditions and accelerated stability conditions provided in the cross referenced DMF.

Drug Product: Adequate

The strength of the product is based on entire sirolimus molecule (a macrolide) as active ingredient. The excipient, human albumin (HSA), is a CBER approved product added to the formulation (b) (4) (b) (4). LOA (b) (4) (b) (4) is provided. (b) (4)

The collected data from extensive physical characterizations of the nanoparticles, e.g. the amorphous state of API, (b) (4) supports the intended design outcome of the sirolimus IV formulation prepared using the albumin-bound nanoparticles platform adopted from Abraxane.

Results from original in-use compatibility studies performed with (b) (4) and the repeated study (b) (4) support the stability of ABI-009 when reconstituted in the original vial and stored for 6 hours at 2 to 8 °C protected from light, followed by storage in polyolefin or PVC IV bags for 9 hours at 2 to 8 °C, then storage for 4 hours at controlled room temperature under ambient light conditions as described in the PI. No concern with leachables from the CCS and administration set.
The drug product specification includes tests to ensure identify, strength, purity and quality/performance of the product. The known impurity, seco-rapamycin A, (b) (4) is (b) (4) (b) (4) formed by ring opening of sirolimus. The control strategy for this impurity implemented during manufacturing and at final product testing is adequate. Particle size distribution and albumin content and species are considered critical quality attributes specific/unique to the proposed drug product formulation/ dosage. Two complimentary methods (b) (4) (b) (4) are used to control the particle size distribution. Human albumin to sirolimus ratio is added in the DP specification (b) (4) and the labeled ratio of 8.5 :1 is met. However, additional data/justification is needed to support the upper limit of the albumin dimer + oligomer content which will be followed up as PMR/PMC.

When stored in (b) (4) glass vials closed with (b) (4) rubber and (b) (4) seal, ABI-009 exhibit good physicochemical stability. Satisfactory results from available of long-term stability data up to 48 months (at 5 ± 3°C) and 6 months of accelerated stability data at 25 ± 2 °C/60 ± 5%RH for the five primary stability batches (b) (4) supports the proposed shelf-life of 24 months.

The applicant has submitted a claim of categorical exclusion including a statement of no extraordinary circumstances. The applicant provided the correct categorical exclusion: 21 CFR 25.31(b) in SD 17 on 09/01/2021 as requested in the quality IR on 08/04/2021. The EIC calculation is below 1ppm for sirolimus. The claim of categorical exclusion is acceptable.

Labeling: Adequate

All CMC comments/edits have been conveyed to OND and the applicant.

Manufacturing: Adequate

(b) (4)

Lyophilized vials when reconstituted with 20 mL of Sodium Chloride Injection, USP, 0.9% yields a suspension for intravenous infusion containing 5 mg sirolimus/mL.

Submitted Clinical/stability and proposed theoretical commercial batch size batch sizes are same (b) (4).

DP manufacturer is an experienced lyophilized products CMO and has been recently inspected five times for lyophilized products, therefore, PAI is not recommended/conducted for this application. The site is recommended for "approve", based on acceptable SVL profile, history, and DFR.

DFR recommendation for DS facility is also approve.

Applicant withdrew the OAI testing site and transferred microbiology test to the DP mfg site. All testing sites are also acceptable.

Biopharmaceutics: Adequate

The Division of Biopharmaceutics review focuses on: (i) the need of an in vitro drug release method as a quality control (QC) test for the final drug product, (ii) bridging.

In Vitro Drug Release Method:

Based on the overall data submitted, the Division of Biopharmaceutics decided that in vitro drug release test is not considered a meaningful quality control (QC) test for the proposed drug product for the following reasons:

In vitro drug release of sirolimus from the sirolimus albumin-bound nanoparticles suspension is determined by the sirolimus solubility limit only, (b) (4)
In vitro drug release of sirolimus is not governed by any formulation or manufacturing process attributes.

Therefore, the Division of Biopharmaceutics agreed that the in vitro drug release method is not a meaningful QC test for the proposed drug product. Note that the in vitro drug release method is not one of the proposed drug product specifications in this NDA (e.g., M.3.2.P.5.1).

In Vitro Formulation Bridging:
There are no composition or meaningful manufacturing process changes of the proposed drug product during the pharmaceutical development. Therefore, no additional bridging studies are needed.

Microbiology: Adequate

The applicant has met regulatory expectations regarding the test method, acceptance criteria, and verification of the suitability of use of: the sterility test that will be used for in process testing; the container closure integrity test that will be used for release testing; the bacterial endotoxins test;

The applicant has met regulatory expectations for validating (b) (4) (b) (4) the subject drug product. (b) (4).

The following program were reviewed under DMF (b) (4) and are deemed adequate: environmental monitoring program (b) (4); the validation/requalification studies (b) (4) for vials used during the commercial manufacture of the subject drug product; the validation/requalification studies (b) (4) used during the commercial manufacture of the subject drug product; the validation/requalification studies (b) (4) to be used during the commercial manufacture of the subject drug product; the recent (b) (4) summary data provided (b) (4) to be used during the commercial manufacture of the subject drug product.

The validation of the (b) (4) stoppers in DMF (b) (4) was reviewed for sterility assurance and

found adequate in Microbiology Review of DMF (b) (4) (b) (4) M17R01.docx), dated 20 May 2021. Therefore, the applicant has met regulatory expectations for stopper (b) (4).

C. Risk Assessment

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Sterility	100			(b) (4)
Endotoxin Pyrogen	32			
Assay (API), stability	36			
Uniformity of Dose (Fill Volume/deliverable volume)	36			
Appearance (Color/turbidity)	9			
Particulate matter	45			
Leachable extractables	24			
pH- (b) (4)	12			

D. List of Deficiencies for Complete Response N/A

Application Technical Lead Name and Date:

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U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III	(b) (4)	(b) (4)	Adequate	10/19/2021	Per MAPP 5015.5 (Rev. 1).
	III			Adequate		
	III			Adequate		
	V			Adequate	08/24/2021	Refer to microbiology review
	II			Adequate	08/27/2021	Refer to drug substance review

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
BLA	(b) (4)	Human Albumin
IND	(b) (4)	Drug Development

2. CONSULTS N/A

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CHAPTER IV: LABELING

NDA 213312

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION (as in SD31 on 10/20/21)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	**Recommended revision conveyed to OND** OPPQ/PQL team (email on 09/26/2021) recommends the following established name and product title: FYARRO (sirolimus protein-bound particles for injectable suspension)(albumin-bound), for intravenous use
Route(s) of administration	Adequate	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	**Recommended revision conveyed to OND** From (b) (4) to "powder", deleted (b) (4)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Adequate	**Recommended revision conveyed to OND** From "(b) (4) to "single-dose"

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Adequate	**Recommended revisions conveyed to OND**
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	Refer to DP review for supporting in-use stability data
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	Adequate	**Recommended revision conveyed to OND**
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling	N/A	

requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).		
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs".	Adequate	**Recommended addition conveyed to OND**

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	**Recommended revision conveyed to OND** From [redacted] (b) (4) to "powder", delete [redacted] (b) (4)
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Adequate	**Recommended revision conveyed to OND** From [redacted] (b) (4) to "single-dose"

Section 11 (DESCRIPTION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	**Recommended revision conveyed to OND** Established name revised to be consistent with product title
Dosage form(s) and route(s) of administration	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Adequate	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	Adequate	
Pharmacological/Therapeutic class	Adequate	**Recommended revision conveyed to OND**
Chemical name, structural formula, molecular weight	Adequate	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Adequate	DS solubility properties is consistent with information provided in section 3.2.S.1.

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	Adequate	**Recommended deletion conveyed to OND** Delete [redacted] (b) (4) as it is not necessary for the prescriber or the patient.
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

APPEARS THIS WAY IN ORIGINAL

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	**Recommended addition/revisions conveyed to OND** Added "for injectable suspension", and revised [redacted] (b) (4) to "protein-bound particles for injectable suspension) (albumin-bound)".
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	**Recommended addition conveyed to OND** Added "white to yellow, sterile lyophilized powder"
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Adequate	**Recommended revision conveyed to OND** From [redacted] (b) (4) to "single-dose"

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	Adequate	Protect from light statement is provided

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	Proposed storage condition is supported by primary batch stability data.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2]	Adequate	**Recommended revisions conveyed to OND**
Special preparation instructions (if applicable)	Adequate	
Storage and handling information (if applicable)	Adequate	
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	Adequate	
Alphabetical listing of inactive ingredients (if applicable)	Adequate	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	

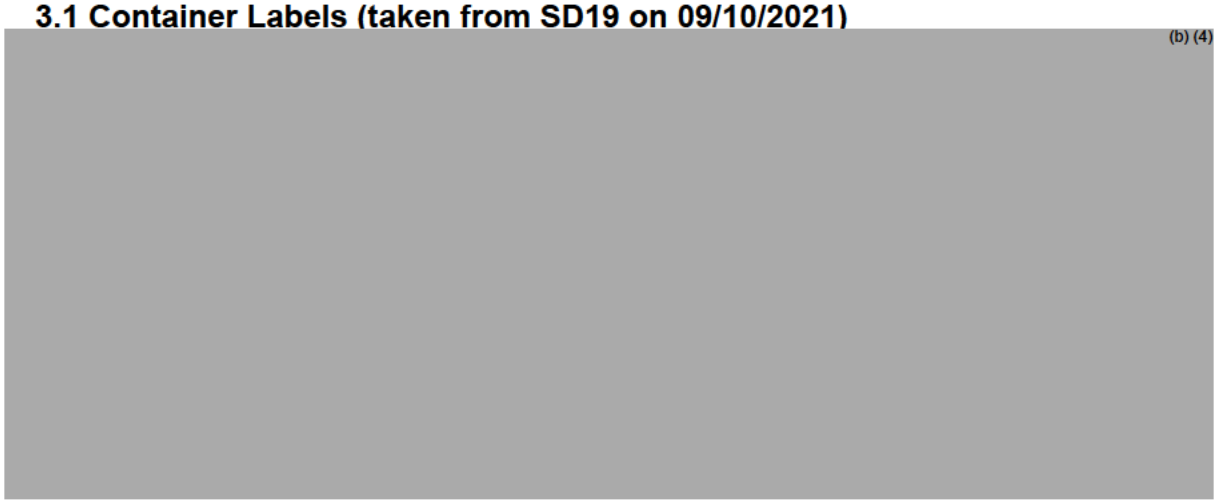
[2] Established name = [Drug] [Route of Administration] [Dosage Form]

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels (taken from SD19 on 09/10/2021)

(b) (4)



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Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[3], (font size and prominence (21 CFR 201.10(g)(2))	Adequate	The font of the established name does not appear to be at least half as large as the letters comprising the proprietary name. The propriety name and established name do not appear to have same prominence. **Recommended revision conveyed to OND:** Increase the font size of the established name to be at least half as large as the letters comprising the proprietary name so that they have to same prominence. Revise the established name to be consistent with the PI.
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents ((21 CFR 201.51(a) e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	

[3] Established name = [Drug] [Route of Administration] [Dosage Form]

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	Adequate	**Recommended revision conveyed to OND:** From (b) (4) to "single dose"
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Adequate	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

Item	**Items in Proposed Labeling** (choose "Adequate", "Inadequate", or "N/A")	**Assessor's Comments about Carton Labeling** (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: *{Adequate}*

The following comments has been conveyed to OND:

Regarding Container and Carton Labels:

1. Revise the established name to be consistent with the recommended product title for the PI.

2. Increase the font size of the established name to be at least half as large as the letters comprising the proprietary name so that they have to same prominence.

3. The package term should be changed from (b) (4) to "single-dose"

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation: Adequate

Primary Labeling Assessor Name and Date: 10/21/2021

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Anamitro Banerjee 10/25/2021

Sheena Hailin Wang

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Anamitro Banerjee

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CHAPTER VI: BIOPHARMACEUTICS

NDA: 213312-ORIG-1 [505(b)(2)]
Drug Product Name/Strength: FYARRO™ (Sirolimus albumin-bound nanoparticles for injectable suspension), 100 mg per vial
Route of Administration: Intravenous injection
Proposed Indication: Advanced (metastatic or locally advnaced) Malignant Perivascular Epithelioid Cell Tumor (PEComa)
Applicant Name: Aadi Bioscience, Inc.
Submission Date: 05/28/2021
Primary Reviewer: Mei Ou, Ph.D.
Secondary Reviewer: Banu Zolnik, Ph.D.

EXECUTIVE SUMMARY

The proposed drug product, FYARRO™ (ABI-009, Sirolimus albumin-bound nanoparticles for injectable suspension), 100 mg per vial, is indicated for the treatment of patients with advanced (metastatic or locally advanced) malignant perivascular epithelioid cell carcinoma (PEComa). The active ingredient is sirolimus. The proposed drug product is a sterile lyophilized powder of albumin-bound sirolimus nanoparticles with a mean particle size of less than (b) (4) nm. The drug product is supplied as a white to off-white lyophilized powder of 100 mg of sirolimus and approximately 850 mg of human albumin in a single-dose (b) (4) glass vial. Each vial of the drug product will be reconstituted using 20 mL of 0.9% sodium chloride injection, USP, to get a 5 mg sirolimus/mL solution before being administered by IV infusion over 30 minutes without further dilution. The recommended dose is 100 mg/m^2 administered as an IV infusion over 30 minutes on days 1 and 8 of a 21-day cycle.

This 505(b)(2) application relies on FDA's previous findings of safety and efficacy, non-clinical data and literature data of the listed drug (LD) products, RAPAMUNE® (sirolimus tablets, NDA 021110) and RAPAMUNE® (sirolimus oral solution, NDA 021083). The Applicant conducted nonclinical studies and four oncology clinical studies, [Study PEC-001 (a Phase 2 safety and efficacy study), Study CA401 (a Phase 1 dose-finding study), Study GBM-007 (a Phase 2 safety and efficacy study), Study COLO-007 (a Phase 1/2 safety and efficacy study), and one non-oncology clinical study, Study PAH-001 (a Phase 1 safety and efficacy study)] to support approval of this application.

The final module of this rolling submission was submitted on 05/28/2021. The Division of Biopharmaceutics review focuses on: (i) the need of an in vitro drug release method as a quality control (QC) test for the final drug product, (ii) bridging.

In Vitro Drug Release Method:
Based on the overall data submitted, the Division of Biopharmaceutics decided that in vitro drug release test is not considered a meaningful quality control (QC) test for the proposed drug product for the following reasons:

1) In vitro drug release of sirolimus from the sirolimus albumin-bound nanoparticles suspension is determined by the sirolimus solubility limit (b) (4) .
2) In vitro drug release of sirolimus is not governed by any formulation or manufacturing process attributes.

Therefore, the Division of Biopharmaceutics agreed that the in vitro drug release method is not a meaningful QC test for the proposed drug product. Note that the in vitro drug release method is not one of the proposed drug product specifications in this NDA (e.g., M.3.2.P.5.1).

In Vitro Formulation Bridging:
There are no composition or meaningful manufacturing process changes of the proposed drug product during the pharmaceutical development. Therefore, no additional bridging studies are needed.

RECOMMENDATION

From the Biopharmaceutics perspective, NDA 213312-ORIG-1 for the proposed drug product, FYARRO™ (ABI-009, Sirolimus albumin-bound nanoparticles for injectable suspension), 100 mg per vial, is recommended for **APPROVAL.**

BIOPHARMACEUTICS REVIEW

1. In Vitro Drug Release Method

In the IND 125669, Type B, pre-NDA meeting, held on 02/25/2020, the Applicant proposed that an in vitro drug release test is not necessary for the proposed drug product. In the meeting minutes, FDA recommended the Applicant to include all the supporting data in the NDA and stated that their justification will be reviewed in the NDA[1].

(1) The Composition of the Proposed Drug Product

The composition of the proposed drug product is presented in Table 1 below. Active ingredient, Sirolimus, is a potent mTOR (mammalian Target of Rapamycin) inhibitor, which is insoluble in water (solubility 2.6 µg/mL). Human albumin is the single excipient in the finished product. Sirolimus binds to human albumin by noncovalent bonds with high affinity.

Table 1: The composition of ABI-009
(from Table 1 in M.3.2.P.2)

Component	Reference	Function	mg/vial
Sirolimus	In-House	Active Pharmaceutical Ingredient	100
Human Albumin	Ph. Eur./USP	(b) (4)	(b) (4)

(2) Sirolimus/Human Albumin/Nanoparticle Composition Study

Per the Applicant, the drug product has the following properties in solution: sirolimus-albumin nanoparticle, (b) (4)

[1] IND 125669 meeting minutes dated 03/24/2020: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8054ea99&_afrRedirect=919473786653770

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(b) (4)

Therefore, all these efforts as mentioned above have not been successfully develop an in vitro drug release method (b) (4) which would provide a profile of release and discriminate between batches of variations in manufacturing or storage conditions impacted the drug release rate.

(b) (4)

(b) (4) The release data generated on clinical batches, (b) (4) experimental batches and stability batches demonstrated that an in vitro release test will not provide data to discriminate between batches with variations in manufacturing process parameters, age or when stored under different conditions. Therefore, the Applicant proposed that an in vitro drug release method is unnecessary.

Based on the overall data submitted, the Division of Biopharmaceutics decided that in vitro drug release test is not considered a meaningful quality control (QC) test for the proposed drug product for the following reasons:

1) In vitro drug release of sirolimus (b) (4)
(b) (4)

2) In vitro drug release of sirolimus is not governed by any formulation or manufacturing process attributes.

Therefore, the Division of Biopharmaceutics agreed that the in vitro drug release method is not a meaningful QC test for the proposed drug product. Note that the in vitro drug release method is not one of the proposed drug product specifications in current submission (e.g., M.3.2.P.5.1).

2. Formulation Bridging

There are no composition or meaningful manufacturing process changes of the proposed drug product during the pharmaceutical development. Therefore, no additional bridging studies are needed.

Banu Zolnik

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Mei Ou

Digitally signed by Mei Ou
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CHAPTER VII: MICROBIOLOGY

IQA ANDA Assessment Guide Reference

Product Information	
NDA Number	213312
Assessment Cycle Number	1
Drug Product Name / Strength	Sirolimus albumin-bound nanoparticles for injectable suspension (Fyarro), (b) (4) mg/vial
Route of Administration	Intravenous (IV)
Applicant Name	Aadi Bioscience, Inc.
Manufacturing Site	(b) (4)
Method of Sterilization	(b) (4)

Assessment Recommendation: *Adequate*

Theme:

☒ N/A	☐ Depyrogenation Validation Data
☐ Product Sterility Assurance	☐ Product Release and/or Stability Specifications
☐ Media Fill Data	☐ Validation for Product Release and/or Stability Test Method
☐ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: *view justification statements found at:*

N/A

Assessment Summary:

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
Seq 0015 (15)	19 August 2021
Seq 0008 (8)	28 May 2021
Seq 0006 (6)	24 February 2021

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The subject drug is a sterile, white to yellow lyophilized cake containing 100 mg of sirolimus formulated as albumin-bound nanoparticles in a (b) (4) vial for reconstitution. The drug product is packaged in a (b) (4) glass vial with a (b) (4) stopper and (b) (4) seal. The drug product is indicated for the treatment of Advanced Malignant Perivascular Epithelioid Cell Tumor. The submission was granted Priority review and Breakthrough Therapy designation on 12 December 2018 with Fast Track granted 24 October 2018. Deficiencies were conveyed to the applicant in a product quality microbiology Information Request, dated 2 August 2021.

The submission is recommended for approval from the standpoint of product quality microbiology.

Concise Description of Outstanding Issues: N/A

Supporting Documents:

- Type V DMF (b) (4) for sterility assurance and process validation details for (b) (4) manufacturing facility (b) (4)
- Microbiology Review of DMF (b) (4) ((b) (4) *mic1.doc*), dated 16 April 2014, for building and facilities, commercial production (b) (4) process parameters, and the environmental monitoring program for (b) (4) manufacturing facility.
- Microbiology Review of DMF (b) (4) ((b) (4) *mic2.doc*), dated 20 January 2015, for locations of critical equipment and the environmental monitoring program for (b) (4) manufacturing facility.
- Microbiology Review of DMF (b) (4) ((b) (4) *M08R02.docx*), dated 13 June 2018 for (b) (4) manufacturing facility.
- Microbiology Review of DMF (b) (4) ((b) (4) *M36R01.docx*), dated 18 August 2021 for manufacturing equipment, validation/requalification of the (b) (4) product (b) (4), validation/requalification (b) (4), validation/requalification of the (b) (4) (b) (4) manufacturing facility.

- (b) (4) "Albumin (Human) (b) (4)

Select Number of Approved Comparability Protocols: 0

S DRUG SUBSTANCE

The drug substance is not provided sterile. Therefore, a product quality microbiology review of the drug substance was not performed [redacted].

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product**

(See Section 3.2.P.1 (Seq 0008), *Description of Drug Product*)

The subject drug product is a sterile, white to yellow lyophilized cake in a [redacted] vial for reconstitution. The drug product is packaged in a [redacted] glass vial [redacted] stopper and [redacted] seal. Once reconstituted, each vial contains a suspension of nanoparticles containing 5 mg/mL of sirolimus bound to albumin for intravenous infusion.

- **Drug product composition**

Sirolimus albumin-bound nanoparticles for injectable suspension

Ingredient	Theoretical quantity per unit	Function
Sirolimus	100 mg	Active Pharmaceutical Ingredient
Albumin (Human)	[redacted]	Excipient [redacted]
[redacted]		

- **Description of container closure system**

(See Section 3.2.P.1 (Seq 0008), *Description of Drug Product* and Section 3.2.P.7 (Seq 0008), pg. 3 of *3.2.P.7 Container Closure System*)

Component	Description	Manufacturer
Vial	[redacted] Glass Vial	[redacted]
Stopper	[redacted] Rubber Stopper, [redacted]	

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Seal	(b) (4)

Assessment: *Adequate*
The applicant provided an adequate description of the drug product composition and the container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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(b) (4)

[redacted]

R REGIONAL INFORMATION

Executed Batch Records
(See Section 3.2.R, *3.2.R Regional Information and ABI-009 Batch Records*)

Executed lot #(s):
C345-001
C346-003
C348-003
C348-006
C349-001

The batch records confirm that validated (b) (4) procedures and (b) (4) (b) (4) processes were used for the manufacture of the exhibit batches.

Assessment: *Adequate*
The executed batch records provide adequate support for (b) (4) manufacturing of the drug product.

Comparability Protocols
N/A

2. ASSESSMENT OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Prescribing Information
Post-dilution/constitution hold time
(Section 1.14.1.3 (Seq 0008), pg. 1 of *Draft Labeling Text (MS Word) - Clean*)

Storage temperature: Store the vials in the original cartons at 2° to 8°C [USP Refrigerated Temperature] (36° to 46°F). Retain in the original package to protect from light
Maximum storage time: Unopened vials of FYARRO are stable until the date indicated on the package when stored between 2ºC to 8ºC (36ºF to 46ºF) in the original package. Neither freezing nor thawing adversely affects the stability of the product. Reconstituted FYARRO in the vial should be used immediately but may be refrigerated at 2ºC to 8ºC (36ºF to 46ºF) for a maximum of 6 hours if necessary. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from light. Discard any unused portion. The suspension for infusion when prepared as recommended in an infusion bag should be used immediately but may be refrigerated at 2°C to 8°C (36°F to 46°F) and protected from light for a maximum of 9 hours.
The total combined refrigerated storage time of reconstituted FYARRO in the vial and in the infusion bag is 15 hours. This may be followed by storage in the infusion bag at ambient temperature (approximately 25°C) and lighting conditions for a maximum of 4 hours. Discard any unused portion.
Route of administration: IV
Container: sterile lyophilized cake containing 100 mg of sirolimus formulated as albumin-bound nanoparticles in a (b) (4) vial for reconstitution

Reconstituted/Further Diluted Drug Product
Each vial is reconstituted by injecting 20 mL of 0.9% Sodium Chloride Injection, USP aseptically.

Assessment: *Adequate*
The proposed maximum combined holding period of 15 hours at refrigeration for the reconstituted subject drug product poses minimum risk to patient safety and is acceptable from a product quality microbiology standpoint. The applicant

has met regulatory expectations regarding product quality microbiology information provided in the package insert.

APPENDICES

A.2 ADVENTITIOUS AGENTS SAFETY EVALUATION

The subject drug product contains Albumin (Human), (b) (4). An LOA (Section 1.4.2 (Seq 0006), *LoA* (b) (4)*)* was included to reference (b) (4) (b) (4) Chemistry, manufacturing, and controls information, including adventitious agents safety evaluation for the Albumin (Human), (b) (4) used as an excipient in the subject drug product are referenced. Additionally, a viral inactivation statement was provided (b) (4) confirming that conditions used in the manufacturing process assure viral inactivation.

Assessment: *Adequate*
The Albumin (Human), (b) (4) used as an excipient in the subject drug product is an approved biological product. It is listed in the Purple Book Database of Licensed Biological Products, indicating that the BLA is in good standing. Therefore, no additional review is necessary.

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MICROBIOLOGY LIST OF DEFICIENCIES

None.

Primary Microbiology Assessor Name and Date: Shannon Heine, PhD, 24 August 2021
Secondary Assessor Name and Date: Erika Pfeiler, PhD, 24 August 2021
"I concur."

Shannon Heine

Digitally signed by Shannon Heine
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Erika Pfeiler

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