

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

216540Orig1s000

PRODUCT QUALITY REVIEW(S)



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	5		



Template Revision: 03

NDA Executive Summary

1. Application/Product Information

NDA Number.	216540		
Applicant Name	BridgeBio Pharma, Inc.		
Drug Product Name	ATTRUBY(acoramidis)		
Dosage Form.	Tablet		
Proposed Strength(s)	356 mg		
Route of Administration	Oral		
Maximum Daily Dose	1424 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Indicated for the treatment of the cardiomyopathy of wild-type or variant transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular (b) (4) and cardiovascular-related hospitalization.		
Drug Product Description	White, film-coated, oval tablets, printed with the BridgeBio company logo followed by “ACOR” in black ink on one side.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	20-25 °C		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Ben Zhang	Zhengfu Wang
	<i>Drug Product/ Labeling</i>	Dan Berger	Theodore Carver



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	<i>Manufacturing</i>	Ke Ren	Feiyan Jin
	<i>Biopharmaceutics</i>	Min Sung Suh	Kevin Wei
	<i>Microbiology</i>	N/A	N/A
	<i>Other (specify):</i>	N/A	
	<i>RBPM</i>	Grafton Adams CDER/OPQ/OPRO/DRBPMI	
	<i>ATL</i>	Theodore Carver CDER/OPQ/OPQAI/DPQAI	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

A shelf life of 30 months is granted for the acoramidis drug product when stored at 25°C.

b. Additional Comments for Action

None.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1) Background

BridgeBio Pharma, Inc. has submitted a 505(b)(1) original New Drug Application (NDA) for acoramidis 356 mg tablets for the treatment of the cardiomyopathy of wild-type or variant transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular (b) (4) and cardiovascular-related hospitalization. Acoramidis is a small molecule inhibitor that acts as a stabilizer of transthyretin tetramers, thereby inhibiting formation of TTR monomers that contribute to amyloidosis. Acoramidis received orphan drug designation for this indication on



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October 2, 2018. The NDA relies on results of a Phase 3 pivotal clinical study evaluating the safety and efficacy of acoramidis in ATTR-CM patients.

2) Drug Substance (acoramidis hydrochloride)

The drug substance is an achiral small molecule (b) (4) and forms a white to tan solid that is hygroscopic. The drug substance review concluded that the regulatory starting materials are appropriate, the manufacturing process is adequately controlled, and the drug substance is adequately characterized. The specifications, batch analyses, and stability data were determined to be adequate and support a re-test period of (b) (4) months. The specification for particle size was revised in response to an information request to include a (b) (4) specification to meet requirements for the tablet drug product. Overall, the drug substance information is adequate to support the NDA.

3) Drug Product (Acoramidis Tablets)

The acoramidis tablets are manufactured as a single strength, 356 mg, equivalent to 400 mg of the acoramidis hydrochloride salt. The tablets are film-coated and imprinted with black ink. The tablet excipients are all USP/NF grade and were determined to be present at acceptable levels based on the maximum daily dose. The Phase 3 drug product is identical to the commercial product except for absence of the ink imprint. In response to an information request, the Applicant added a test for polymorphic form to the drug product specification, and the final specification was determined to be adequate, and all analytical procedures adequately validated. All drug product impurities are controlled according to limits recommended in the ICH Q3B Guideline. The long-term and accelerated stability data were deemed adequate to support a shelf life of 30 months for the drug product when stored at 25°C, based on extension of shelf-life as per ICH Q1E.

4) Manufacturing

Process – The tablet drug product is manufactured using a (b) (4) process (b) (4). In response to information requests, the Applicant provided additional information regarding manufacturing environmental conditions (humidity), commercial manufacturing equipment, in-process controls, yield limits, and (b) (4) testing; revised in-process parameters, (b) (4) and content uniformity testing. The manufacturing process was deemed adequate.



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Facilities – All facilities were deemed approvable based on previous CGMP inspection history. The facilities are adequate.

5) Biopharmaceutics

The biopharmaceutics review was focused on the drug product dissolution method and acceptance criteria and the bridging of formulations used during clinical development. The initially proposed dissolution method and acceptance criteria were inadequate to support drug product quality, but after the Applicant agreed to revise the method to be more discriminating with respect to critical quality attributes such as API particle size and polymorphic form and more stability indicating, the method was determined to be adequate. With respect to bridging clinical formulations, the dissolution profiles of the Phase 3 and commercial tablets, which differ only in the addition of the tablet imprint, were determined to be similar. Overall, the biopharmaceutics team recommended approval.

6) Microbiology

No microbiology review was required as the microbiological aspects of drug product manufacturing and specification were addressed in the manufacturing and drug product reviews. Microbiological testing for the drug product is performed as recommended for solid oral dosage forms and no microbiological concerns or risks were identified.

7) Quality Labeling

After the Applicant made recommended changes to the prescribing information and carton and container labeling, the quality aspects of the drug product labeling were deemed to be acceptable.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	-	Adequate
Drug Product	-	Adequate
Quality Labeling	-	Adequate
Manufacturing	-	Adequate
Biopharmaceutics	-	Adequate
Microbiology	-	N/A

Environmental Assessment: Categorical Exclusion - Adequate

QPA for EA(s): No



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5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comments:

None.

Comparability Protocols (PACMP): No

Comments:

None.

Additional Lifecycle Comments: None.



Theodore
Carver

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate

With edits made to Section 11 for the therapeutic class and a comment to include important chemical or physical properties, the prescribing information meets all regulatory requirements from a CMC perspective.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Attruby	Adequate
Established name(s)	Acoramidis	Adequate
Route(s) of administration	Oral	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	356 mg	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
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.	NA	NA

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
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)	NA	NA

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Tablets	Adequate
Strength(s) in metric system	356 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Hydrochloride salt	Adequate, strength presented as the corresponding free base
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	White, film-coated, oval tablets, printed with (b) (4) on one side.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	NA	NA

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Attruby, acoramidis	Adequate
Dosage form(s) and route(s) of administration	356 mg tablets, oral administration	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	356 mg acoramidis equivalent to 400 mg acoramidis HCl.	Adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and silicon dioxide. Coating/ink: black iron oxide, glyceryl monocaprylocaprate, hypromellose, polyvinyl alcohol, propylene glycol, talc, titanium dioxide, and vinyl alcohol graft copolymer.	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.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Statement of being sterile (if applicable)	NA	NA
Pharmacological/ Therapeutic class	Stabilizer of transthyretin (TTR).	Adequate following edits
Chemical name, structural formula, molecular weight	Name*, C ₁₅ H ₁₈ FN ₂ O ₃ Cl, 328.77	Adequate
If radioactive, statement of important nuclear characteristics.	NA	NA

* 3-[3-(3,5-dimethyl-1H-pyrazol-4-yl)propoxy]-4-fluorobenzoic acid hydrochloride.

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
Other important chemical or physical properties (such as pKa or pH)	Acoramidis HCl is a white to tan solid. The solubility of acoramidis is ≥ 2 micrograms/mL from pH 1.2 to 6.8 in aqueous media.	Adequate following Applicant response to labeling comments.
For oral prescription drug products, include gluten statement if applicable	NA	NA
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	NA	NA

1.2.3 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	tablets	Adequate
Strength(s) in metric system	356 mg	Adequate
Available units (e.g., bottles of 100 tablets)	carton of 112 tablets: 4 blister cards (each containing 28 tablets)	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Shape, color, print, NDC 82228-712-28 carton.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
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.	NA	NA

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

Item	Information Provided in the NDA	Assessor's Comments
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.)	NA	NA
If the product contains a desiccant, ensure the size	NA	NA

and shape differ from the dosage form and desiccant has a warning such as “Do not eat.”		
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20°C to 25°C (68°F to 77°F); excursions to 15°C to 30°C (59°F to 86°F)	Adequate
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.”	NA	NA
Include information about child-resistant packaging	NA	NA

1.2.4 Other Sections of Labeling

No other sections of the labeling contain product quality information.

1.2.5 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor’s Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Distributed by: BridgeBio Pharma, Inc. Palo Alto, CA 94304	Adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): Patient information contains acceptable storage and inactive ingredient information.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

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Item	Information Provided in the NDA	Assessor's Comments about Container and Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	Attruby (acoramidis) tablets	Adequate
Dosage strength	356 mg (b) (4)	Adequate. DMEPA has recommended revising the (b) (4) strength to "356 mg per tablet"
Route of administration	Not required for oral tablets	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	356 mg acoramidis (equivalent to 400 mg acoramidis HCl).	Adequate
Net contents (e.g. tablet count)	112 Tablets. 4 28-Count Blister Cards (28 tablets per blister card).	Adequate
"Rx only" displayed on the principal display	Present in current	Adequate
NDC number	82228-712-28, (b) (4)	Adequate
Lot number and expiration date	Absent in current presentation	Adequate, following recommendation by DMEPA.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 20° C to 25° C (68° F to 77° F), excursions permitted between 15° C to 30° C (59° F to 86° F)	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	NA	NA
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	NA	NA
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Bar code	Present	Adequate



Dan
Berger

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CHAPTER VI: BIOPHARMACEUTICS

For more details about the items in this template, please see [Chapter VI \(Biopharmaceutics\) of the NDA IQA Guide](#)

Product Information	
NDA Number	216540
Assessment Cycle Number	1
Drug Product Name/ Strength	Acoramidis Tablet, 356 mg
Route of Administration	Oral
Applicant Name	Bridgebio Pharma, Inc.
Therapeutic Classification/ OND Division	Division of Cardiology and Nephrology
RLD/RS Number	N/A, 505 (b)(1)
Proposed Indication	Treatment of the cardiomyopathy of wild-type or variant transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular (b) (4) and cardiovascular-related hospitalization

Assessment Recommendation: Adequate

Assessment Summary:

The Applicant, Bridgebio Pharma, Inc., submitted this 505(b)(1) NDA for approval of Acoramidis Tablet, 356 mg. Acoramidis is a second-generation, oral, potent, highly selective, small-molecule transthyretin (TTR) stabilizer, indicated for the “Treatment of the cardiomyopathy of wild-type or variant transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular (b) (4) and cardiovascular-related hospitalization.” Acoramidis was granted Orphan Drug Designation on 10/02/2018. The recommended dose of acoramidis is 712 mg BID daily (2×356 mg tablets). This Biopharmaceutics review was focused on the following aspects:

Quality control (QC) dissolution method and acceptance criterion: In the NDA, the Applicant initially proposed a dissolution method of USP Apparatus 2 (paddles) at (b) (4) rpm in 900 mL of (b) (4) N HCl at 37°C with an acceptance criterion of $Q = \frac{(b) (4)}{(4)}\%$ in 45 minutes for the QC of the proposed drug product at batch release and on stability testing. In the submitted dissolution method development report, the Applicant evaluated the discriminating ability of the originally proposed dissolution towards the changes in API particle size, level of API crystalline content, (b) (4) level and tablet hardness. The originally proposed dissolution method was not found acceptable because there is inadequate data and information to support the use of 1) (b) (4) paddle rotational

speed of (b) (4) rpm: 2) (b) (4) concentration of HCl in the dissolution medium. Therefore, the Applicant was recommended to provide additional dissolution data/information to support an appropriate paddle rotation speed and concentration of HCl in the dissolution medium. Based on the assessment of the additional data and information provided in the IR responses, a (b) (4) paddle rotational speed of 50 rpm and (b) (4) concentration of HCl (0.02N HCl) are found more appropriate for the QC of the proposed drug product due to the better 1) discriminating ability towards the API particle size and level of API crystalline content and 2) stability-indicating ability towards the older batches. Based on the submitted dissolution data from the clinical batches using the recommended dissolution, a two-point dissolution specification was found more appropriate for the QC of the proposed drug product due to the slow-dissolving profile. Therefore, based on the overall provided dissolution data and information, the following dissolution method and acceptance criteria are found acceptable for the QC testing of Acoramidis Tablets, 356 mg, at batch release and on stability/shelf-life:

Apparatus	USP Apparatus 2 (Paddle)
Medium	0.02N HCl
Volume	900 mL
Vessel Temperature	37 ± 0.5 °C
Paddle Speed	50 rpm
Acceptance Criterion	NLT (b) (4)% in 15 minutes; Q= (b) (4)% in 45 minutes

Bridging:

According to the Applicant, immediate-release oral tablet formulations have been used throughout the clinical development. The proposed product was initially formulated as (b) (4) mg film-coated tablets ((b) (4) mg as acoramidis HCl, respectively) for Phase 1 and 2 clinical studies. The tablet formulation was further optimized to a single-strength 356 mg Tablet for Phase 3 clinical studies. The Applicant has conducted a two-way crossover relative bioequivalence (BE) study under fasting conditions (Study AG10-003) to bridge Phase 1/2 tablet formulation to the Phase 3 tablet formulation and the in vivo bridge (BE) study is under the evaluation by the OCP. The formulation composition for Acoramidis Tablets, 356 mg, has been unchanged through the pivotal Phase 3 clinical safety and efficacy studies (Studies AG10-301 and AG10-304). The intended commercial formulation of Acoramidis Tablets, 356 mg, differs from the Phase 3 clinical formulation only by adding a printed logo and code (being applied onto one side of each film-coated tablet in black ink for identification purposes) and similar dissolution profiles between the pivotal clinical and primary stability batches using the QC method were observed, indicating that adding a printed logo and code to the commercial tablets is unlikely to impact the dissolution, in vivo performance or stability of the proposed product. Therefore, from a Biopharmaceutical perspective, no further bridging data/information are needed.

Biowaiver:

The proposed Acoramidis Tablets only contain one strength (356 mg), no biowaiver request is proposed/needed for this NDA.

Overall, from a Biopharmaceutics perspective, NDA 216540 for Acoramidis Tablets, 356 mg, is **adequate** and recommended for **approval**.

List of Submissions Being Assessed:

Document(s) Assessed	Date Received
Orig-1 NDA	11/29/2023
Response to IR#1 ¹	04/05/2024
Response to IR#2 ²	05/20/2024
Response to IR#3 ³	06/03/2024
Response to IR#4 ⁴	08/01/2024

Highlight Key Issues from Last Cycle and Their Resolution: None. This is the first review cycle.

Concise Description of Outstanding Issues (list bullet points with key information and update as needed): None

B.1 BCS DESIGNATION

Assessment: Adequate
Solubility: Low

A HCl salt form of acoramidis has an intrinsic dissolution flux of (b) (4) mg/cm²/min in simulated gastric fluid, while the free form has an intrinsic dissolution flux of (b) (4) mg/cm²/min. The HCl salt of acoramidis (acoramidis HCl) was selected for development due to the superior in vitro dissolution properties of the HCl form. Table 1 shows the solubility of acoramidis HCl in aqueous media at physiologically relevant pH values. Acoramidis is zwitterionic with pKa values of 4.16 and 4.20. Acoramidis has high aqueous solubility at either low pH (as the cation) or high pH (as the anion), but from pH 3.2 to 5.2, where acoramidis exists predominantly as the zwitterion, its solubility is low. Based on the solubility data, the recommended dose (712 mg) is not completely soluble in ≤ 250 mL of aqueous media over the physiological pH range, and thus acoramidis is considered as a low solubility compound per the ICH M9 BCS criteria.

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Table 1. Solubility of acoramidis in various pH media at 25°C

Buffer/Medium	Stir Time (hr)	pH	Solubility (mg/mL)
KCl, HCl	24	1.2	5.63
Citrate	24	3.2	0.12
Citrate	24	4.2	0.01
Phosphate	24	5.2	0.03
Phosphate	24	6.8	1.14
Purified Water	NA	NA	0.53
Simulated Gastric Fluid (SGF)	2	1.2	3.83
Fed State SIF (FeSSIF)	2	5.0	0.3
Fasted State SIF (FaSSIF)	2	6.5	0.4

Permeability: Not determined

The permeability classification for acoramidis in the BCS system has not been established due to efflux observed in permeability assays. In the Caco-2 permeability assay, the permeability results for acoramidis in the A→B direction for concentrations of 1, 10, and 50 µM were $0.04 \pm 0.01 \times 10^{-6}$ cm/s, $0.04 \pm 0.00 \times 10^{-6}$ cm/s, and $0.07 \pm 0.01 \times 10^{-6}$ cm/s, respectively. The efflux ratios were 421, 347, and 181 for concentrations of 1, 10, and 50 µM, respectively.

Because passive transport is required to establish the BCS permeability classification using the Caco-2 assay, there is no data available to definitively assign a BCS permeability classification.

Dissolution: See “B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA”

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: Adequate

➤ **Drug Product Background**

The proposed drug product is an immediate-release tablet that contains 356 mg of acoramidis drug substance (provided as 400 mg of the acoramidis HCl salt) and the following excipients: microcrystalline cellulose (b) (4) croscarmellose sodium (b) (4), silicon dioxide (b) (4) magnesium stearate (b) (4) and film coating (b) (4) acoramidis has been selected for drug development, and the particle size has no significant impact on dissolution because the proposed product shows rapid dissolution ((b) (4) % within 15 minutes) in acidic media (e.g., (b) (4) N HCl).

➤ **Dissolution Method Development**

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Table 12. Proposed and Revised (acceptable) dissolution method and acceptance criterion(a)

	Proposed	Revised(acceptable)
Apparatus	USP Apparatus 2 (Paddle)	USP Apparatus 2 (Paddle)
Medium	(b) (4) HCl	0.02N HCl
Volume	900 mL	900 mL
Temperature	37 ± 0.5 °C	37 ± 0.5 °C
Paddle Speed	(b) (4) rpm	50 rpm
Acceptance Criterion(a)	Q= (b) (4) % in 45 minutes	NLT (b) (4) % in 15 minutes Q= (b) (4) % in 45 minutes

Based on the totality of the provided information and data, the above revised dissolution method and acceptance criteria are deemed acceptable for the QC of the proposed Acoramidis Tablets, 356 mg.

➤ **Dissolution Variability**

Variabilities in the dissolution data meet the recommendations (%CV < 10% at all timepoints).

➤ **Dissolution Acceptance criteria**

See the dissolution method review addressed above.

B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERIA (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Assessment: N/A

During IND stage, the dissolution method of USP apparatus 2 (Paddles) at (b) (4) rpm in 900 mL of (b) (4) mM pH (b) (4) at 37°C was developed for release and stability testing. However, the Applicant was recommended to develop a physiologically relevant in vitro dissolution method using (b) (4) pH media since the median T_{max} of acoramidis in the fasted state showed (b) (4) hour across the dose range up to 712 mg.

Therefore, the Applicant further developed dissolution method conditions using (b) (4) pH media, and the recommended method using 900 mL of 0.02N HCl medium was finalized for release and stability testing.

B.5 MODIFIED RELEASE ORAL DRUG PRODUCTS – In-Vitro Alcohol Dose Dumping

Assessment: N/A

The proposed drug product is an immediate-release tablet formulation.

B.11 EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Assessment: N/A

The proposed drug product is an immediate-release tablet formulation.

B.12 BRIDGING OF FORMULATIONS

Assessment: *Adequate*

According to the Applicant, immediate-release oral tablet formulations have been used throughout the clinical development. The proposed product was initially formulated as (b) (4) mg film-coated tablets ((b) (4) mg as acoramidis HCl, respectively) for Phase 1 and 2 clinical studies. The tablet formulation was further optimized to a single-strength 356 mg Tablet for Phase 3 clinical studies. The Applicant has conducted a two-way crossover relative bioequivalence (BE) study under fasting conditions (Study AG10-003) to bridge Phase 1/2 tablet formulation to the Phase 3 tablet formulation and the in vivo bridge (BE) study is under evaluation by the OCP. The formulation composition for Acoramidis Tablets, 356 mg, has been unchanged through the pivotal Phase 3 clinical safety and efficacy studies (Studies AG10-301 and AG10-304). The intended commercial formulation of Acoramidis Tablets, 356 mg, differs from the Phase 3 clinical formulation only by adding a printed logo and code (being applied onto one side of each film-coated tablet in black ink for identification purposes) and similar dissolution profiles between the pivotal clinical and primary stability batches using the QC method were observed, indicating that adding a printed logo and code to the commercial tablets is unlikely to impact the dissolution, in vivo performance or stability of the proposed product. Therefore, from a Biopharmaceutical perspective, no further bridging data/information are needed.

B. 13 BIOWAIVER REQUEST

Assessment: *N/A*

The Applicant proposes only one strength (356 mg).

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Assessor's Name and Date: Min Sung Suh, Ph.D. 09/09/2024

Secondary Assessor's Name and Date: Kevin Wei, Ph.D. 09/11/2024



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Wei

Digitally signed by Kevin Wei
Date: 9/13/2024 02:56:22PM
GUID: 59e9fc4600508706ab6b474203201f10



Theodore
Carver

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THEODORE E CARVER
09/20/2024 09:00:14 PM