# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 215192Orig1s000

# PRODUCT QUALITY REVIEW(S)

# NDA Executive Summary

## 1. Application/Product Information

| | | | |
|---|---|---|---|
| **NDA Number.** | 215192 | | |
| **Applicant Name** | Akebia Therapeutics | | |
| **Drug Product Name** | VAFSEO (vadadustat) | | |
| **Dosage Form.** | Tablet | | |
| **Proposed Strength(s)** | 150 mg, 300 mg, 450 mg | | |
| **Route of Administration** | Oral | | |
| **Maximum Daily Dose** | 600 mg | | |
| **Rx/OTC Dispensed** | Rx | | |
| **Proposed Indication** | Treatment of anemia due to chronic kidney disease | | |
| **Drug Product Description** | Film-coated immediate release tablets | | |
| **Co-packaged product information** | N/A | | |
| **Device information:** | N/A | | |
| **Storage Temperature/ Conditions** | 20 °C to 25°C | | |
| **Review Team** | **Discipline** | **Primary** | **Secondary** |
| | *Drug Substance* | N/A | |
| | *Drug Product/ Labeling* | Dan Berger | Theodore Carver |
| | *Manufacturing* | Liya Tang | Feiyan Jin |
| | *Biopharmaceutics* | N/A | |
| | *Microbiology* | N/A | |

| | | | |
|---|---|---|---|
| | *Other (specify):* | N/A | |
| | *RBPM* | Mikee Aguirre | |
| | *ATL* | Theodore Carver | |
| **Consults** | N/A | | |

**2. Final Overall Recommendation - Approval**

**3. Action Letter Information**

**a. Expiration Dating:**

A shelf life of 36 months is granted for the drug product when stored at 20°C to 25°C.

**b. Additional Comments for Action**
None

**4. Basis for Recommendation:**

**a. Summary of Rationale for Recommendation:**
Akebia Therapeutics has submitted NDA 215192 for the marketing approval of Vadadustat Immediate Release (IR) Tablets under the 505(b)(1) regulatory pathway. Vadadustat is a hypoxia-inducible factor prolyl hydroxylase inhibitor that increases cellular levels of hypoxia-inducible factor, thereby stimulating endogenous erythropoietin (EPO) production, increasing iron mobilization, Hb, and red blood cell production.

This application was previously recommended for approval by the Office of Pharmaceutical Quality (refer to Integrated Quality Review of NDA 215192 dated January 18th, 2022). To confirm that the drug product labeling and facilities remain adequate, drug product and manufacturing teams were assigned to review this resubmission. No new information was submitted for any OPQ discipline, and all labeling comments that were previously identified by the drug product reviewer have been addressed., Therefore, no new CMC reviews were required for this resubmission and the CMC information remains adequate. OPQ recommends approval of NDA 215192.

**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** | **-** | **Adequate** |

**Environmental Assessment:** Categorical Exclusion - Adequate
**QPA for EA(s):** No

## 5. Life-Cycle Considerations

**Established Conditions per ICH Q12: No**
**Comments**:

**Comparability Protocols (PACMP): No**
**Comments:**

**Additional Lifecycle Comments:**

**None**

Theodore Carver

Digitally signed by Theodore Carver
Date: 3/04/2024 09:31:29AM
GUID: 5d963967007fd4bc3c9fab2a6c3eaded

Theodore Carver

Digitally signed by Theodore Carver
Date: 3/04/2024 09:35:14AM
GUID: 5d963967007fd4bc3c9fab2a6c3eaded

---

**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/

---

THEODORE E CARVER
03/04/2024 09:48:35 AM

U.S. FOOD & DRUG ADMINISTRATION

# RECOMMENDATION

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

# NDA 215192
# Assessment #01

| | |
|---|---|
| **Drug Product Name** | VAFSEO (vadadustat) |
| **Dosage Form** | Tablets |
| **Strength** | 150 mg, 300 mg, 450 mg |
| **Route of Administration** | Oral |
| **Rx/OTC Dispensed** | Rx |
| **Applicant** | Akebia Therapeutics |
| **US agent, if applicable** | N/A |

| Submission(s) Assessed | Document Date | Discipline(s) Affected |
|---|---|---|
| Original CMC submission | 03/29/2021 | All |
| Amendment | 06/28/2021 | Drug Product, Manufacturing |
| Amendment | 07/30/2021 | Drug Product |
| Amendment | 08/16/2021 | Drug Substance, Drug Product |
| Amendment | 08/23/2021 | Biopharm |
| Amendment | 09/09/2021 | Drug Product |
| Amendment | 09/15/2021 | Manufacturing |
| Amendment | 11/03/2021 | Drug Product |
| Amendment | 12/10/2021 | Manufacturing |
| Amendment | 12/22/2021 | Manufacturing |

**QUALITY ASSESSMENT TEAM**

| Discipline | Primary Assessment | Secondary Assessment |
|---|---|---|
| **Drug Substance** | Ben Zhang | Zhengfu Wang |
| **Drug Product** | Dan Berger | Mohan Sapru |
| **Manufacturing** | Liya Tang | Feiyan Jin |
| **Microbiology** | NA | NA |
| **Biopharmaceutics** | Nadia Ahmed | Poonam Delvadia |
| **Regulatory Business Process Manager** | Grafton Adams | |
| **Application Technical Lead** | Dan Berger | |
| **Laboratory (OTR)** | NA | NA |
| **Environmental** | NA | NA |

# EXECUTIVE SUMMARY

## I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

OPQ recommends approval of NDA 215192 for marketing of VAFSEO (vadadustat) tablets at 150 mg, 300 mg, and 450 mg strengths. The applicant provided adequate information to ensure the identity, strength, purity, and quality of the proposed product. All facilities are in good standing.

## II. SUMMARY OF QUALITY ASSESSMENTS

### A. Product Overview

Akebia Therapeutics has submitted NDA 215192 for the marketing approval of Vadadustat Immediate Release (IR) Tablets under the 505(b)(1) regulatory pathway. Vadadustat is a hypoxia-inducible factor prolyl hydroxylase inhibitor that increases cellular levels of hypoxia-inducible factor, thereby stimulating endogenous erythropoietin (EPO) production, increasing iron mobilization, Hb, and red blood cell production. The Applicant seeks an approval of Vafseo (vadadustat) tablets for the treatment of anemia due to chronic kidney disease (CKD) in adult patients who are on dialysis or not. The proposed maximum dose is 600 mg once daily for all patients. Although there are existing treatments for anemia of CKD, the Applicant contends that the current standard of care (typically injectables) has significant limitations such as increased risk of cardiovascular events, and that alternative treatments may be useful to treat renal anemia. Safety and effectiveness of Vafseo tablets have not been established in pediatric patients.

The proposed drug product is a film-coated, immediate release tablet at 150 mg, 300 mg, and 450 mg strengths which are derived from a (b) (4) (b) (4). OPQ provided advice on the adequacy of the NME drug substance and drug product submission at a Type C meeting on June 17, 2020. The different tablet strengths are differentiated by color, size, shape (round or oval) and debossing. Tablets used for phase 3 clinical studies were (b) (4) while the commercial formulation differs by (b) (4) The formulation differences between the phase 3 tablets and proposed commercial tablets were assessed and determined to be adequately bridged during review. Additionally, comparative dissolution studies were performed to bridge drug product manufactured with API from clinical and commercial suppliers, as well as drug product manufactured at geographically separate commercial sites (b) (4) and (b) (4) All manufacturing sites have been adequately bridged. Although a potential risk for the presence of (b) (4) impurities in the drug product was initially

determined, confirmatory testing on 14 batches of drug product at all 3 strengths verified the absence of any [redacted] Following a Pre-Approval Inspection (PAI) of the [redacted] manufacturing site, it was established that all manufacturing sites are considered to be adequate. The stability data submitted provides adequate support for the proposed expiry dating period of 36 months at 25°C and 30°C, based on extension of shelf-life as per ICH Q1E. Based on the review of NDA 215192, Vafseo (vadadustat) tablets are determined to be of acceptable quality, with minimal risks to patients identified from a CMC perspective when used as directed.

| | |
|---|---|
| **Proposed Indication(s) including Intended Patient Population** | [redacted] |
| **Duration of Treatment** | |
| **Maximum Daily Dose** | |
| **Alternative Methods of Administration** | Oral tablets. |

## B. Quality Assessment Overview

**Drug Substance:** Adequate

Vadadustat is a synthetic small molecule with no chirality and no counterion. The [redacted] vadadustat, which is referred to as [redacted] has been chosen for the development and commercial production of the drug substance and drug product. The manufacturing process of the drug substance has been sufficiently described and the regulatory starting materials are adequately justified as per ICH Q11. The drug substance structure is characterized with various analytical methods, and the ICH M7 risk assessment on the impurities in the drug substance has been found adequate. In response to an Information Request, the Applicant provided purge factor calculations to confirm that levels of [redacted] are sufficiently controlled so that [redacted] formation in the drug product presents minimal risks. The specification of the drug substance is supported by release and stability data.

The stability data support a (b) (4)-month re-test period under long-term storage conditions (b) (4) Polymorphism and particle sizes of the drug substance are routinely tested in the release specification.

**Drug Product: Adequate**

Vadadustat tablets are available at three strengths – 150 mg, 300 mg, and 450 mg, to be dosed at up to 600 mg once daily orally. All excipients are compendial, present in safe quantities and BSE/TSE free. The commercial formulation includes debossment, color, size and shape differences that adequately distinguish the tablet strengths. The specifications are adequate to ensure drug product quality and all drug product batches meet specified acceptance criteria. The key analytical method is the HPLC method used to assess identification, assay, and degradants. No degradation products were detected at release or on stability under tested conditions. In an initial risk assessment, the drug product was considered potentially at risk for containing (b) (4) impurities. However, testing of 14 batches of drug product at all 3 strengths verified the absence of any (b) (4), thereby confirming that these potential impurities present minimal risks to patient safety. Adequacy of the (b) (4) testing methods and validation was confirmed following consultation with the Office of Testing and Research (OTR). Drug product packaging consists of three sizes of induction sealed HDPE bottles (60 count) enclosed with (b) (4) closures, (b) (4) The primary packaging and bulk packaging components that contact the drug product are suitable for pharmaceutical or food contact per 21 CFR regulations. Registration drug product batches manufactured at (b) (4) and (b) (4) meet all acceptance criteria per long-term and accelerated stability studies, with no significant changes or increases in degradants. Vadadustat tablets meet specifications after exposure to intense UV and visible light per prescribed Q1B ICH conditions, as well as 24 months of storage at 25°C/60%RH, 30°C/75%RH (for batches manufactured by (b) (4)) and 6 months at 40°C/75%RH. The overall stability data submitted provides adequate support for a shelf-life of 36 months at 25°C and 30°C, based on extension of shelf-life as per ICH Q1E. In summary, vadadustat tablets are of acceptable quality, with minimal risks to patients identified.

**Labeling: Adequate**

All labeling deficiencies have been addressed. The Prescribing Information, Medication Guide and labels comply with all regulatory requirements from a CMC perspective.

**Manufacturing: Adequate**

The proposed drug product is an immediate release tablet with a (b) (4) (b) (4) coating, presented in three strengths (150 mg, 300 mg, 450 mg) with the same drug loading of (b) (4)%. All three dosage strengths are

made from a [redacted]. The major unit operations for manufacturing are [redacted] Two facilities are proposed as the manufacturing sites for the drug product. Three registration batches for each dosage strength were made from both manufacturing sites at [redacted] kg scale. Commercial batch sizes are proposed based on the manufacturing equipment capabilities at each site, [redacted] kg at [redacted] and [redacted] kg at [redacted]. Three validation batches at commercial scale ([redacted] kg) were manufactured at [redacted] for 150 mg and 300 mg strengths. Each of these batches were made by [redacted]

One of the drug product manufacturers, [redacted] is recommended for approval based on the recent on-site PAI inspection. Other manufacturing facilities are approved based on the compliance history and district recommendation.

**Biopharmaceutics: Adequate**

Akebia Therapeutics has submitted NDA 215192 for the marketing approval of Vadadustat Immediate Release (IR) Tablets (450 mg, 300 mg, and 150 mg strengths) under the 505(b)(1) regulatory pathway. Vadadustat is a hypoxia-inducible factor prolyl hydroxylase inhibitor indicated for the treatment of anemia associated with chronic kidney disease (CKD) in adults on dialysis and not on dialysis. Vadadustat increases cellular levels of hypoxia-inducible factor thereby stimulating endogenous erythropoietin (EPO) production, increasing iron mobilization, Hb, and red blood cell production.

The Applicant has conducted 4 pivotal global phase 3 clinical trials [in non-dialysis dependent CKD patients (NDD-CKD; CI-0014, CI-0015) and dialysis dependent CKD patients (DD-CKD; CI-0016, CI-0017] to support the proposed indication. The recommended starting dose is 300 mg once daily with or without food, with dose adjustment in increments of 150 mg within the range of 150 mg to 600 mg to achieve or maintain hemoglobin levels (10 to 11 g/dL).

Vadadustat is claimed to be a low solubility and highly permeable compound which can be classified as a BCS Class II drug substance. The Applicant has evaluated various dissolution method parameters to determine the optimal dissolution method. Additionally, they have demonstrated the discriminating ability of the proposed dissolution

method towards the critical process parameters: (b) (4) time and (b) (4) amount. All commercial batches consistently demonstrate complete release (> (b) (4) %) at 30 minutes. Additionally, the proposed acceptance criteria would be able to reject aberrant batches. The proposed dissolution methods (USP II, 50 RPM, 900 mL of potassium phosphate buffer pH 6.8, at 37ºC) and acceptance criterion (Q= (b) (4) % in 30 minutes) for all strengths are acceptable.

Akebia has studied 6 formulations throughout development (Formulations A through F). The Applicant has adequately bridged the Formulation B through C with comparative in vitro dissolution studies. However, the remainder of the formulations studied during development (Formulations A through B and C through F) were bridged via in vivo relative BA/BE studies.

The Applicant conducted comparative dissolution studies to bridge the proposed API suppliers, demonstrating similarity (> (b) (4) % release in 15 minutes) between products manufactured using API from pre-change and post-change API suppliers. Additionally, the API supplier used for the Phase 3 clinical batches (b) (4) has been adequately bridged to the proposed commercial API suppliers (b) (4)

Akebia also conducted comparative dissolution studies to bridge the proposed drug product manufacturing sites, demonstrating similarity (> (b) (4) % release in 15 minutes) for products manufactured at pre-change and postchange drug product manufacturing sites. The drug product manufacturing sites proposed for commercial production (b) (4) have been adequately bridged.

The Applicant requested a waiver of the in vivo bioavailability and bioequivalence studies for the proposed intermediate 300 mg strength. The supportive information/data included a comparative BE study using the 150 mg and 450 mg strengths, pharmacokinetic linearity in the range of 80 to 1200 mg, (b) (4) across strengths, and comparative dissolution in multi-pH media. It was confirmed with the clinical pharmacology reviewer that the in vivo BE study and PK linearity data are adequate. Based on the assessment of the information/data, biowaiver for 300 mg strength is granted.

**Microbiology:** Choose an item.

NA

### C. Risk Assessment

| From Initial Risk Identification | | | Assessment | | |
|---|---|---|---|---|---|
| **Attribute/ CQA** | **Factors that can impact the CQA** | **Initial Risk Ranking** | **Risk Mitigation Approach** | **Final Risk Evaluation** | **Lifecycle Considerations/ Comments** |
| Assay | Drug product formulation, stability | Low | - | Acceptable | - |
| Physical Stability | Container closure, process parameters | Medium | (b) (4) | Acceptable | - |
| Content Uniformity | Process parameters, drug load | Low | - | Acceptable | - |
| Microbial Content | Formulation, container closure | Low | - | Acceptable | - |
| Dissolution | Drug substance solubility, polymorphism | Medium | (b) (4) | Acceptable | - |
| Particle Size | Manufacturing process | Medium | | Acceptable | - |

### D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

None

2. Drug Substance Deficiencies

None

3. Drug Product Deficiencies

None

4. Labeling Deficiencies

None

5. Manufacturing Deficiencies

None

6. Biopharmaceutics Deficiencies

None

7. Microbiology Deficiencies

None

8. Other Deficiencies (Specify discipline, such as Environmental)

None

*Application Technical Lead Name and Date:*

Dan Berger January 18, 2022

# QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

## 1. RELATED/SUPPORTING DOCUMENTS

### A. DMFs:

| DMF # | Type | Holder | Item Referenced | Status | Date Assessment Completed | Comments |
|---|---|---|---|---|---|---|
| (b) (4) | III | (b) (4) | | Active | N/A | Sufficient information in NDA |
| | III | | | Active | N/A | |
| | III | | | Active | N/A | |
| | III | | | Active | N/A | |

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

| Document | Application Number | Description |
|---|---|---|
| IND | 102465 | Tablets for treatment of anemia associated with chronic kidney disease and chronic kidney failure. |

## 2. CONSULTS

The Office of Testing and Research (OTR) was consulted to confirm the adequacy of the (b) (4) impurity testing methods and validation. These were confirmed to be acceptable (via email on August 27, 2021), but with an additional requirement for the Applicant to perform intermediate precision experiments. Intermediate precision experiments were subsequently submitted and found acceptable during review of the drug product, thereby completing the requirements for compliance with ICH Q2.

Dan Berger

Digitally signed by Dan Berger
Date: 1/18/2022 10:01:35AM
GUID: 56e6e1b5001a2fedae663c62a5ce7513

Mohan Sapru

Digitally signed by Mohan Sapru
Date: 1/18/2022 10:16:40AM
GUID: 504f821600000ec6d20b59d2b68eb3d2

66 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

# CHAPTER IV: LABELING

## 1.0 PRESCRIBING INFORMATION

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

Section 11 has been edited to alphabetize excipients and to add chemical properties of the API. Section 16 has been edited to add corrected language for USP storage conditions. With these edits, the prescribing information meet 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 | Vafseo | Adequate |
| Established name(s) | Vadadustat | 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. | 150 mg, 300 mg, and 450 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 | 150 mg, 300 mg, and 450 mg | Adequate |
| If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance | NA | NA |
| A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting | round/white, oval/ yellow, oval/pink tablet debossed with "150", "300", or "450" on one side and "VDT" on the other 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) | Vafseo, vadadustat | Adequate |
| Dosage form(s) and route(s) of administration | 150 mg, 300 mg, and 450 mg, oral administration | Adequate |
| If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance. | NA | NA |
| List names of all inactive ingredients. Use USP/NF names. Avoid Brand names. | Colloidal silicon dioxide, hydroxypropyl methyl-cellulose, magnesium stearate, microcrystalline cellulose & sodium starch glycolate. Coating: PEG, polyvinyl alcohol, talc, ferrosoferric oxide, red & yellow iron oxide, titanium dioxide. | Adequate, with edits to alphabetize the inactive ingredients, remove (b) (4) |
| For parenteral injectable dosage forms, include 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 | HIF-prolyl hydroxylase inhibitor | Adequate |
| Chemical name, structural formula, molecular weight | Chemical name*, $C_{14}H_{11}ClN_2O_4$, 306.70. | Adequate |
| If radioactive, statement of important nuclear characteristics. | NA | NA |
| Other important chemical or physical properties (such as pKa or pH) | White to off-white solid practically insoluble in water. | Adequate, with edits made. |

*2-[[5-(3-chlorophenyl)-3-hydroxypyridine-2-carbonyl]amino]acetic acid.

**Section 11 (DESCRIPTION) Continued**

| Item | Information Provided in the NDA | Assessor's 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 |

### 1.2.4 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 | 150 mg, 300 mg, and 450 mg | Adequate |
| Available units (e.g., bottles of 100 tablets) | Bottles of 60 tablets | Adequate, with DMEPA recommended edits. |
| Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number | Shape, size, imprinting, NDC 59922-641-60, 59922-642-60, 59922-643-60. | Adequate, with DMEPA recommended edits |
| 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 and shape differ from the dosage form and desiccant has a warning such as "Do not eat." | NA | NA |
| 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 permitted between 15°C to 30°C (59°F to 86°F) | Adequate, with DMEPA recommended edits |
| 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 | Not present | NA |

### 1.2.5 Other Sections of Labeling

No other sections of the labeling contain product quality information.

### *1.2.6* 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 | Manufactured for: Akebia Therapeutics®, Inc. Cambridge, MA 02142 | Adequate. |

## 2.0 PATIENT LABELING

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

The medication guide is acceptable, following edits made to alphabetize excipients.

## 3.0 CARTON AND CONTAINER LABELING

### 3.1 Container Label

(b) (4)

### 3.2 Carton Labeling

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

| Item | Information Provided in the NDA | Assessor's Comments about Blister, Carton and Bottle Labeling |
|---|---|---|
| Proprietary name, established name, and dosage form (font size and prominence | Vafseo, vadadustat | Adequate |
| Dosage strength | 150 mg, 300 mg, and 450 mg | Adequate |
| Route of administration | Oral | Adequate |
| If the active ingredient is a salt, include the equivalency statement per FDA Guidance | NA | NA |
| Net contents (e.g., tablet count) | Bottles of 60 tablets, blisters of 10 tablets (physician samples) | Adequate |
| "Rx only" displayed on the principal display | Present | Adequate |
| NDC number | 59922-641-60, 59922-642-60, 59922-643-60, (b) (4) (b) (4) | Adequate |
| Lot number and expiration date | Present | Adequate |
| Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD. | Store at room temperature 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 |

| Item | Information Provided in the NDA | Assessor's Comments about Carton Labeling |
|---|---|---|
| Name of manufacturer/distributor | Manufactured for Akebia Therapeutics, Inc. Cambridge, MA 02142 | Adequate |
| Medication Guide (if applicable) | Storage conditions and inactive ingredients. | Adequate, with edits made to inactive ingredients list. |
| No text on Ferrule and Cap overseal | NA | NA |
| 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. | NA | NA |
| And others, if space is available | NA | NA |

**Assessment of Carton and Container Labeling: *Adequate***
The labels are acceptable and comply with all regulatory requirements from a CMC perspective.

## ITEMS FOR ADDITIONAL ASSESSMENT

**None**

***Overall Assessment and Recommendation:***

All labeling deficiencies have been addressed. The Prescribing Information and labels comply with all regulatory requirements from a CMC perspective.

*Primary Labeling Assessor Name and Date:*

Dan Berger January 10, 2022

*Secondary Assessor Name and Date (and Secondary Summary, as needed):*

Mohan Sapru January 10, 2022

Dan Berger

Digitally signed by Dan Berger
Date: 1/10/2022 01:39:49PM
GUID: 56e6e1b5001a2fedae663c62a5ce7513

Mohan Sapru

Digitally signed by Mohan Sapru
Date: 1/10/2022 03:01:22PM
GUID: 504f821600000ec6d20b59d2b68eb3d2

73 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

# CHAPTER VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

| | |
|---|---|
| **Product Information** | Vadadustat Tablets |
| **NDA Number** | 215192 |
| **Assessment Cycle Number** | 1 |
| **Drug Product Name/ Strength** | Vadadustat Tablets/150 mg, 300 mg, and 450 mg |
| **Route of Administration** | Oral |
| **Applicant Name** | Akebia Therapeutics |
| **Therapeutic Classification/ OND Division** | CDER/OCHEN/DNH |
| **RLD/RS Number** | New Molecular Entity |
| **Proposed Indication** | Treatment of anemia associated with chronic kidney disease in adults on dialysis and not on dialysis. |

***Assessment Recommendation:*** **Adequate**

***Assessment Summary:*** The Applicant, Akebia Therapeutics, under the 505(b)(1) regulatory pathway, has submitted NDA 215192 for the marketing approval of Vadadustat Immediate Release (IR) Tablets. Vadadustat is a hypoxia-inducible factor prolyl hydroxylase inhibitor indicated for the treatment of anemia associated with chronic kidney disease (CKD) in adults on dialysis and not on dialysis. Vadadustat increases cellular levels of hypoxia-inducible factor thereby stimulating endogenous erythropoietin (EPO) production, increasing iron mobilization, Hb, and red blood cell production.

The Applicant conducted 4 pivotal global phase 3 clinical trials [in non-dialysis dependent CKD patients (NDD-CKD; CI-0014, CI-0015) and dialysis dependent CKD patients (DD-CKD; CI-0016, CI-0017] to support the proposed indication. The Applicant has proposed three strengths: 450 mg, 300 mg, and 150 mg. The recommended starting dose is 300 mg once daily with or without food. The proposed dose adjustment is in increments of 150 mg within the range of 150 mg to 600 mg to achieve or maintain hemoglobin levels (10 to 11 g/dL).

The Applicant has claimed that Vadadustat is a low solubility and highly permeable compound which can be classified as a BCS Class II drug substance. The Applicant has evaluated various dissolution method parameters to determine the optimal dissolution method. Additionally, they have demonstrated the discriminating ability of the proposed dissolution method towards the critical process parameters: (b) (4) time and (b) (4) amount. All commercial batches consistently demonstrate complete release (> (b) (4) %) at 30 minutes. Additionally, the proposed acceptance criteria would be able to reject aberrant batches. The

Applicant's proposed dissolution method (USP II, 50 RPM, 900 mL of potassium phosphate buffer pH 6.8, at 37°C) and acceptance criterion (Q= (b) (4) % in 30 minutes) for all strengths are acceptable.

The Applicant has studied 6 formulations throughout development (Formulations A through F). The Applicant has adequately bridged the Formulation B through C with comparative in vitro dissolution studies. However, the remainder of the formulations studied during development (Formulations A through B and C through F) were bridged via in vivo relative BA/BE studies.

The Applicant conducted comparative dissolution studies to bridge the proposed API suppliers, demonstrating similarity (> (b) (4) % release in 15 minutes) between products manufactured using API from pre-change and post-change API suppliers. The Applicant has adequately bridged the API supplier used for the Phase 3 clinical batches ( (b) (4) ) to the proposed commercial API suppliers (b) (4) ).

The Applicant also conducted comparative dissolution studies to bridge the proposed drug product manufacturing sites, demonstrating similarity (> (b) (4) % release in 15 minutes) for products manufactured at pre-change and post-change drug product manufacturing sites. The Applicant has adequately bridged the drug product manufacturing sites proposed for commercial production (b) (4) ).

The Applicant requested a waiver of the in vivo bioavailability and bioequivalence studies for the proposed intermediate 300 mg strength. The supportive information/data included a comparative BE study using the 150 mg and 450 mg strengths, pharmacokinetic linearity in the range of 80 to 1200 mg, (b) (4) (b) (4) across strengths, and comparative dissolution in multi-pH media. It was confirmed with the clinical pharmacology reviewer that the in vivo BE study and PK linearity data are adequate. Based on the assessment of the information/data, biowaiver for 300 mg strength is granted.

**Table 1: CQAs and Rankings**

| CQAs | Initial Risk Ranking | Comments | Updated Risk Ranking after Assessment Cycle # | Comments |
|---|---|---|---|---|
| Particle Size Distribution | Medium | For a BCS Class II drug substance dissolution is a (b) (4) (b) (4) | Low | (b) (4) |

**List Submissions Assessed:**

**Table 2: Documents Assessed in this Review**

| Document(s) Assessed | Date Received |
|---|---|
| NDA-215192-ORIG-1 (Seq 0001) | 03/29/21 |
| NDA-215192-ORIG-1 (Seq 0017) | 08/23/21 |

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

**Concise Description of Outstanding Issues (List bullet points with key information and update as needed):** N/A

## B.1 BCS DESIGNATION

**Assessment:** The Applicant has claimed that Vadadustat is a low solubility and highly permeable compound which can be classified as a BCS Class II drug substance.

**Solubility:** Vadadustat is soluble at neutral/basic conditions but has low solubility in acidic conditions. It is noted that the highest strength of the product is not soluble in less than 250 mL at any condition between pH 1.2 and pH 5.5. At pH 6.8 and above, the solubility of Vadadustat increases.

**Permeability:** Based on Caco-2 cell culture study, Vadadustat demonstrates high permeability.

## B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

**Assessment:** ***{Adequate}***

During the course of drug product development, the Applicant studied 4 different dissolution methods, as shown in Table 3. The proposed dissolution method and acceptance criterion are shown in Table 4.

**Table 4: Proposed Dissolution Method and Acceptance Criterion for Finished Drug Product Batch Release and Stability Testing (150 mg, 300 mg, and 450 mg)**

| USP Apparatus | Speed | Medium | Volume/ Temperature | Proposed Acceptance Criterion |
|---|---|---|---|---|
| II (Paddles) | 50 RPM | Potassium Phosphate Buffer pH 6.8 | 90 mL/37°C | Q (b) (4) % in 30 minutes |

The Applicant has noted that the drug substance, Vadadustat, has higher solubility at neutral and basic conditions and low solubility at acidic pH.

(b) (4)

(b) (4) It is noted that though the proposed dissolution method is not discriminating towards changes in some process parameters or API and formulation attributes, the method is acceptable since these attributes are controlled which mitigates the Biopharmaceutics risk. The proposed dissolution method is therefore acceptable.

All pivotal phase 3 clinical batches, pivotal in vivo BE study batches, and commercial batches (at both proposed manufacturing sites) consistently demonstrate complete release (> (b) (4) %) at 30 minutes. It is noted that the proposed acceptance criterion of NLT (b) (4) % (Q) in 30 min would be able to reject aberrant batches that represented changes in (b) (4) time and (b) (4) amount. Therefore, the Applicant's proposed acceptance criterion, "NLT (b) (4) % (Q) in 30 minutes" is acceptable.



3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

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

**Assessment:** There are no in vivo data from the drug development program that can be applied to demonstrate the clinical relevancy of the proposed dissolution method and acceptance criterion.

## B.12 BRIDGING OF FORMULATIONS

**Assessment:** ***{Adequate}***

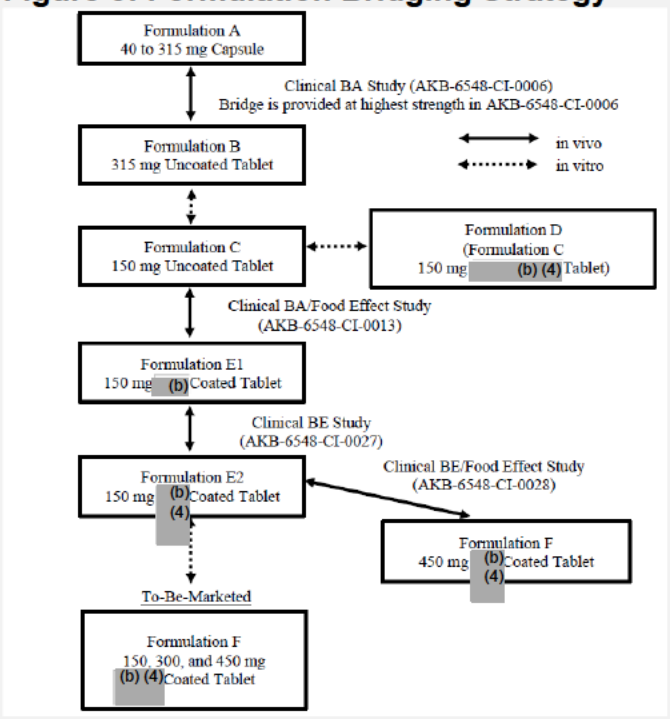
Bridging of Formulations Used in Development:

The Applicant has studied 6 Formulations (A through F) throughout the development (Table 5 and Figure 3).

**Table 5: Formulations and Dosage Forms**

| Formulation | Dosage Form |
|---|---|
| Formulation A | (b) (4) |
| Formulation B | |
| Formulation C | |
| Formulation D | |
| Formulation E1 and E2 | |
| Formulation F (intended commercial formulation) | Debossed film-coated tablet, 150, 300, and 450 mg |

**Figure 3: Formulation Bridging Strategy**




(b) (4)

[redacted]


The Applicant has adequately bridged the Formulation B through C with comparative in vitro dissolution studies. However, the remainder of the formulations studied during development (Formulations A through B and C through F) were bridged via in vivo relative BA/BE studies, the assessment of which is under the Clinical Pharmacology Reviewer's purview.

Bridging of Drug Substance Manufacturers:

Per the Comparability Report, the Applicant has provided comparative dissolution between the two drug substance manufacturers (b) (4) However, it is noted that (b) (4) and (b) (4) are the two drug substance sources proposed for commercial manufacturing. Additionally, it is noted that the provided comparative dissolution results between the two API manufacturers are averages of registration batches rather than individual dissolution profiles of each batch. Therefore, the Applicant was asked to provide the individual dissolution profiles of one batch from each API supplier for comparison via an Information Request dated 08/09/21. The Applicant sufficiently responded to the IR.[1] The Applicant has adequately bridged the drug

[1] \\CDSESUB1\evsprod\nda215192\0017\m1\us\111-info-amend\qual-info-amend-12-20210809.pdf

product batches manufactured with API from (b) (4) to drug product batches manufactured with API from (b) (4) (Commercial API Supplier). Both of these drug product batches manufactured with API from (b) (4) and (b) (4) were used in pivotal phase 3 clinical studies (CI-0014, CI-0015, CI-0016, CI-0017). Both batches compared were manufactured at the same facility (b) (4) and both batches exhibit > (b) (4)% release in 15 minutes. Additionally, the Applicant has bridged drug product batches manufactured using API from (b) (4) API Supplier and the (b) (4) (Alternate Commercial API Supplier). These drug product batches were manufactured at different facilities (b) (4) but dissolution profiles exhibit > (b) (4)% release in 15 minutes. Therefore, the Applicant has adequately bridged both proposed commercial API suppliers (b) (4) to the API supplier for the phase 3 batches (b) (4)

Bridging of Drug Product Manufacturers:

The pivotal phase 3 clinical batches were manufactured at both (b) (4) It is noted that formulation E2 (Lot YZFT, 150 mg) and formulation F (Lot ZKFB, 450mg) studied in the pivotal BE study (CI-0028)were manufactured at (b) (4) (b) (4) The Applicant is proposing two manufacturing sites (b) (4) (b) (4) for commercial production.

The Applicant had originally provided comparative dissolution studies to bridge the two drug product manufacturing sites using the average of 4 registration batches at (b) (4) (pivotal phase 3 clinical batch manufacturing site and proposed commercial manufacturing site) and the average of 3 registration batches at (b) (4) (alternate proposed commercial manufacturing site). Averaging dissolution profiles of registration batches for comparison does not allow for dissolution profile comparisons between all registration batches. Additionally, it was noted that the Applicant had not provided complete dissolution profiles to support the bridging between the manufacturing sites which was requested via IR. In response to the IR[1], the Applicant provided complete dissolution profile data between these sites (b) (4) for comparison. The dissolution profiles between these two sites both exhibit > (b) (4)% release in 15 minutes indicating dissolution similarity. Thus, the Applicant has adequately bridged both drug product manufacturing sites proposed for commercial manufacturing.

## B. 13 BIOWAIVER REQUEST

**Assessment: *{Adequate}***

The Applicant is requesting a waiver of the in vivo bioavailability and bioequivalence studies for the 300 mg tablet. For the biowaiver request, the Applicant is relying on the in vivo BE study (CI-0028, 3X150 mg vs 1X450 mg), PK

linearity (80 mg-1200 mg), (b) (4) across strengths, and comparative multi-media dissolution.

In clinical study (AKB-6548-CI-0028), Vadadustat 150 mg (Formulation E1, (b) (4) (b) (4)) and 450 mg tablets (Formulation F, (b) (4) (b) (4) were demonstrated to be bioequivalent to each other. Per the discussion with the Clinical Pharmacology Reviewer, it was confirmed that the in vivo BE study is adequate.

The Applicant noted that Vadadustat demonstrates linear pharmacokinetics (PK) profiles in the range of 80 mg to 1200 mg, which was also confirmed by the clinical pharmacology reviewer.

The proposed 300 mg tablet is bracketed by the highest and lowest proposed strengths (450 mg and 150 mg), and the formulations are all manufactured via a (b) (4) (b) (4) Formulations for each strength are shown in Table 6.

**Table 6: 150 mg, 300 mg, and 450 mg Formulations**

| Component | Function | Quality Standard | 150 mg | | 300 mg | | 450 mg | |
|---|---|---|---|---|---|---|---|---|
| | | | Mass (mg) | % | Mass (mg) | % | Mass (mg) | % |
| | | | | | | | | (b) (4) |
| Vadadustat Drug Substance | Active Ingredient | | | | | | | |
| Microcrystalline Cellulose | (b) ( | | | | | | | |
| Sodium Starch Glycolate | | | | | | | | |
| Hydroxypropyl Methylcellulose | | | | | | | | |
| (b) (4) | | | | | | | | |
| Colloidal Silicon Dioxide | | | | | | | | |
| Magnesium Stearate | | | | | | | | |
| **Total Weight of Core Tablets** | | | | | | | | |
| **Film-coating Components** | | | | | | | | |
| (b) (4) | Tablet Coating for 150 mg | | | | | | | (b) (4) |
| | Tablet Coating for 300 mg | | | | | | | |
| | Tablet Coating for 450 mg | | | | | | | |
| **Total Weight of Coated Tablets** | | | | | | | | |

The Applicant noted that since the 150 mg strength and the 450 mg strength bracket the 300 mg tablets, comparative dissolution was conducted only between the 150 mg and 300 mg tablets. However, the Applicant has provided two times the dose of 150 mg in single dissolution vessel for comparison rather than comparison of one dose of 150 mg vs 300 mg. It is also noted that no comparisons were originally made to the 450 mg strengths. Therefore, the Applicant was requested to provide rationale on why 2 units of the 150 mg strength were used to support the biowaiver and provide comparative dissolution profile data of the

150 mg vs 300 mg strengths and 300 mg vs 450 mg strengths using single units via IR. The Applicant responded that the dissolution comparisons of 2 units of 150 mg vs 1 unit of 300 mg strength was performed to provide comparisons at the same dose levels (Tables 7a and 7b).

As requested, the Applicant conducted comparative dissolution studies of single unit dosage across multiple pH levels (Tables 8a-8c). Comparisons at pH 1.2 and 4.5 did not demonstrate complete release for any strength, however, performance across strengths was similar. At pH 6.8, all but one lot of 300 mg (ZYXG) demonstrate ≥ (b) (4)% dissolution in 15 minutes and dissolution performance of these batches is therefore considered to be similar to that of 150 mg BE batch (YZFT; CI-0028) that also showed > (b) (4)% in 15 min. One 300 mg batch, ZYXG, had (b) (4)% dissolution in 15 minutes, which was compared to the 150 mg batch that had (b) (4)% dissolution in 15 minutes, indicating dissolution dissimilarity; however, this is not a concern as the dissolution profile of the batch ZYXG is similar to the 450 mg batch ZKFB (*f*2 = 56.94) that was also evaluated in the in vivo BE study (Table 9). At pH 6.8, when the 300 mg batches were compared to the 450 mg BE batch (ZKFB; CI-0028) via f2 test, the results indicated dissolution similarity (Table 9) except the batch ZXHF. However, this dissolution dissimilarity can be attributed to differences in dissolution at 5 min only since the dissolution performance at all other time points is comparable. Overall, from a Biopharmaceutics perspective, dissolution profile similarity is demonstrated for the 300 mg batches when compared to the in vivo BE study batches of the 150 mg and 450 mg strengths.

**Table 7a: Comparative Dissolution Using Proposed QC Method- (1x300 mg vs 2x150 mg)**

Mean Data

| Batch names \ Time | 5 | 10 | 15 | 20 | 30 | 45 | 60 |
|---|---|---|---|---|---|---|---|
| Phase 3 Batch 150 mg YZFT (CI-0028) (BE Batch)_ (b) (4) 2x | 44 | 87 | 96 | 99 | 101 | 101 | 102 |
| Primary Stability Batch 300 mg ZYXF (b) (4) | 36 | 81 | 89 | 93 | 97 | 100 | 102 |

**Table 7b: Comparative Dissolution Using Proposed QC Method- (1x450 mg vs 3x150 mg)**

Mean Data

| Batch names \ Time | 5 | 10 | 15 | 20 |
|---|---|---|---|---|
| Primary Stability Batch 450 mg ZKFB (BE Batch)_ (b) (4) | 30 | 73 | 82 | 86 |
| Phase 3 Batch 150 mg YZFT (CI-0028) (BE Batch)_ (b) (4) EFERENCE_3x | 51 | 89 | 97 | 98 |

**Table 8a: Comparative Dissolution Using Proposed QC Method Conditions - pH 6.8 (1x150mg, 1x300mg, 1x450mg)**

pH 6.8 Mean Data

| Batch names \ Time | 5 | 10 | 15 | 20 | 30 | 45 | 60 |
|---|---|---|---|---|---|---|---|
| Phase 3 Batch 150 mg YZFT (CI-0028) (BE Batch) (b) (4) | 46 | 87 | 99 | 101 | 102 | 103 | 103 |
| Primary Stability Batch 300 mg ZYXF (b) (4) | 36 | 81 | 89 | 93 | 97 | 100 | 102 |
| Primary Stability Batch 300 mg ZXHK | 53 | 77 | 85 | 89 | 96 | 99 | 100 |
| Primary Stability Batch 300 mg ZYXG | 16 | 72 | 78 | 87 | 96 | 101 | 102 |
| Primary Stability Batch 300 mg FP257203-C19004 (b) (4) | 36 | 85 | 95 | 98 | 100 | 102 | 102 |
| Primary Stability Batch 450 mg ZKFB (BE Batch) | 30 | 73 | 81 | 86 | 94 | 98 | 99 |

**Table 8b: Comparative Dissolution Using Proposed QC Method Conditions - pH 4.5 (1x150mg, 1x300mg, 1x450mg)**

pH 4.5 Mean Data

| Batch names \ Time | 5 | 10 | 15 | 20 | 30 | 45 | 60 |
|---|---|---|---|---|---|---|---|
| Phase 3 Batch 150 mg YZFT (CI-0028) (BE Batch) (b) (4) | 13 | 29 | 37 | 41 | 46 | 51 | 53 |
| Primary Stability Batch 300 mg ZYXF (b) (4) | 12 | 22 | 26 | 27 | 28 | 29 | 30 |
| Primary Stability Batch 450 mg ZKFB (BE Batch) (b) (4) | 9 | 16 | 18 | 19 | 20 | 20 | 20 |

**Table 8c: Comparative Dissolution Using Proposed QC Method Conditions - pH 1.2 (1x150mg, 1x300mg, 1x450mg)**

pH 1.2 Mean Data

| Batch names \ Time | 5 | 10 | 15 | 20 | 30 | 45 | 60 | 75 |
|---|---|---|---|---|---|---|---|---|
| Phase 3 Batch 150 mg YZFT (CI-0028) (BE Batch) (b) (4) | 5 | 11 | 13 | 15 | 16 | 17 | 18 | 19 |
| Primary Stability Batch 300 mg ZYXF (b) (4) | 7 | 8 | 9 | 9 | 10 | 10 | 10 | 10 |
| Primary Stability Batch 450 mg ZKFB (BE Batch) (b) (4) | 4 | 6 | 6 | 7 | 7 | 7 | 7 | 7 |

**Table 9. Dissolution Profile Similarity Results Comparing 300 mg test batches and 450 mg Reference In Vivo BE batch**

| Reference Batch (450mg) | Test Batch (300mg) | Time Points Used | *f2* |
|---|---|---|---|
| ZKFB | ZYXF | 5, 10, and 15 | 56.36 |
| | ZXHK | 5, 10, 15, and 20 | 46.08 |
| | ZYXG | 5, 10, 15, and 20 | 56.94 |

Based on the overall information and data on the in vivo BE study (150 mg vs 450 mg), PK linearity (80 mg to 1200 mg), compositional proportionality, and comparative in vitro dissolution, the biowaiver request for the 300 mg strength is granted.

***Primary Biopharmaceutics Assessor's Name and Date:***

*Nadia Ahmed, PharmD*

*10/20/21*

***Secondary Assessor Name and Date:***

*Poonam Delvadia, PhD*

*10/21/2021*



2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Nadia Ahmed

Digitally signed by Nadia Ahmed
Date: 10/21/2021 03:05:58PM
GUID: 5e0e0b9100939fa4af29f1127f130ee2

Poonam Delvadia

Digitally signed by Poonam Delvadia
Date: 10/21/2021 03:15:51PM
GUID: 5388edae000671a12787e2fcf4cde1bb

---

**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/

---

DAN M BERGER
01/18/2022 10:37:32 AM

MOHAN K SAPRU
01/18/2022 10:41:18 AM