CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212576Orig1s000

PRODUCT QUALITY REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL

Branch 1, Division of New Drug Products 1 (DNDP 1)
Office of New Drug Products (ONDP)
Office of Pharmaceutical Quality (OPQ)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 06, 2020
OND Clinical Division:	Division of Hematology Malignancies 1 (DHM1)
Application Type and Number:	NDA 212576
Product Name:	INQOVI® (decitabine and cedazuridine) Tablets
Product Strength:	35 mg decitabine and 100 mg cedazuridine
Route of Administration:	Oral
Applicant Name:	Astex Pharmaceuticals, Inc.
Final Label Submission Date:	July 02, 2020 (SD 0061 and SD 0062)

1 PURPOSE OF MEMO

The applicant had proposed [redacted] (b) (4) in the original NDA submission. However, on June 30, 2020, the applicant indicated that INQOVI will be launched only in blister packaging configuration in the US. [redacted] (b) (4) Astex updated the USPI Section 16 to reflect this change.

2 EVALUATION OF CHANGES

The applicant deleted all references to [redacted] (b) (4) in the Section 16 HOW SUPPLIED/STORAGE AND HANDLING of the USPI and the patient package insert (SD 0061). The applicant also updated the formatting of the drug substance structures (font size for the atom labels and bond lengths) in Section 11 DESCRIPTION of the USPI for consistency (SD 0062).

[redacted] (b) (4)

3 CONCLUSION AND RECOMMENDATION

The proposed changes to labeling are acceptable. (b) (4) The updated formatting of the atom labels and bond lengths in the drug substance structures in Section 11 of the USPI for consistency is acceptable.

The USPI is acceptable from CMC point of view.

Anamitro Banerjee, PhD
Primary Drug Product Reviewer
Office of New Drug Products

Thomas Oliver, PhD
Secondary Drug Product Reviewer
Office of New Drug Products

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/

ANAMITRO BANERJEE
07/06/2020 08:43:39 AM

THOMAS F OLIVER
07/06/2020 09:23:47 AM

NDA OPQ Review and Evaluation

NDA 212576
Addendum to Review # 01

Drug Name/Dosage Form	INQOVI (ASTX727) Tablet
Strength	35mg decitabine/100 mg cedazuridine
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Indication	INQOVI is a combination of cedazuridine, a cytidine deaminase inhibitor, and decitabine, a nucleoside metabolic inhibitor, indicated for treatment of adult patients with myelodysplastic syndromes (MDS) including previously treated and untreated, de novo and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.
Applicant	Astex Pharmaceuticals, Inc.
US agent, if applicable	N/A

Review Team Comment:

*In the header of Page 1 of the OPQ Review 1, the proposed drug product was listed as "*INQOVI® (cedazuridine and decitabine) Tablet*." The review team determined, and the applicant agreed, that the proposed drug should be "*INQOVI® (decitabine and cedazuridine) Tablet*."*

Sherita D. McLamore *Date: 06/25/2020*

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/

SHERITA D MCLAMORE
06/25/2020 11:30:18 AM

NDA OPQ Review and Evaluation

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

All FDA assessment is indicated in blue colored fonts
OPQ Recommendation: APPROVAL

Drug Substance Retest Period: *Applicant to insert proposed retest period and storage conditions.*

A (b) (4) month retest period is proposed for cedazuridine at the recommended storage temperature of (b) (4) °C, when packaged (b) (4)

FDA Assessment: Drug substance retest period of (b) (4) months may be granted.

Drug Product Expiration Dating Period: *Applicant to insert proposed shelf life and storage conditions*

A 24-month shelf life is proposed for ASTX727 tablets packaged in (b) (4) blisters, at the recommended storage condition of 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) (See USP Controlled Room Temperature).

FDA Assessment: The proposed shelf life of 24-month for the ASTX727 tablets packaged in (b) (4) blisters may be granted when stored at the recommended storage conditions.

NDA 212576
Review # 01

[Applicant will complete this section.]

Drug Name/Dosage Form	INQOVI (ASTX727) Tablet
Strength	100 mg cedazuridine/35mg decitabine
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Indication	INQOVI is a combination of cedazuridine, a cytidine deaminase inhibitor, and decitabine, a nucleoside metabolic inhibitor, indicated for treatment of adult patients with myelodysplastic syndromes (MDS) including previously

	treated and untreated, de novo and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.
Applicant	Astex Pharmaceuticals, Inc.
US agent, if applicable	N/A

[FDA will complete these sections.]

Submit Date(s)	December 11, 2019
Received Date(s)	December 11, 2019
PDUFA Goal Date	August 11, 2020
Division/Office	Office of Pharmacuetical Quality
Review Completion Date	
Established Name	cedazuridine and decitabine
(Proposed) Trade Name	Inqovi
Pharmacologic Class	Decitabine is a nucleoside metabolic inhibitor Cedazuridine is a cytidine deaminase inhibitor
Recommendation on Regulatory Action	

SUBMISSION(S) REVIEWED	*DOCUMENT DATE*	*DISCIPLINE(S) AFFECTED*
SDN-0001	*12/11/2010*	*All*
SDN-0004	*01/08/2020*	*Facilities; Biopharmaceutics*
SDN-0006	*01/23/2020*	*Biopharmaceutics*
SDN-0007	*01/28/2020*	*Biopharmaceutics*
SDN-0009	*01/31/2020*	*Biopharmaceutics*
SDN-0016	*02/24/2020*	*Blister pack representative samples*
SDN-0017	*02/25/2020*	*Drug Substance*
SDN-0019	*03/03/2020*	*Drug product, Process, Biopharmaceutics*
SDN-0024	*03/18/2020*	*Biopharmaceutics*
SDN-0026	*03/23/2020*	*Process*
SDN-0030	*03/31/2020*	*Process*
SDN-0033	*04/07/2020*	*Drug Substance, Drug Product*
SDN-0043	*04/29/2020*	*Biopharmaceutics*
SDN-0046	*05/07/2020*	*Process*

SDN-0047	05/14/2020	Labeling
SDN-0049	05/19/2020	Drug Product
SDN-0050	05/22/2020	Labeling
SDN-0051	06/01/2020	Drug Substance (updated DS specification table to reflect the previously agreed PSD limits)

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Anamitro Banerjee	Ali Al Hakim
Drug Product	Anamitro Banerjee	Thomas Oliver
Process and Facility	Zhaoyang Meng	Rakhi Shah
Microbiology	n/a	
Biopharmaceutics	Gerlie Gieser	Om Anand
Regulatory Business Process Manager	Teshara Bouie	n/a
Application Technical Lead	Sherita McLamore	n/a
ORA Lead	Caryn McNab	n/a
Environmental	Ranaan Bloom	n/a

ORBIS Partner Agency Quality Review Team

Agency	PRIMARY REVIEWER	SECONDARY REVIEWER
Health Canada Drug Substance Drug Product Biopharmaceutics		
HAS Singapore	NA	NA
TGA Australia		
Swissmedic	NA	NA

RELATED/SUPPORTING DOCUMENTS

DMFs:

[Applicant will complete]				*[FDA will complete]*	
DMF #	***Type***	***Holder***	***Item Referenced***	***Status***	***Comments***
(b) (4)	II	(b) (4)	(b) (4)	Adequate	NA
				Adequate	These DMFs are not reviewed per current ONDP policy.

(b) (4)	III	(b) (4)		(b) (4)	

Other Documents: *IND, RLD, or sister applications*

[Applicant will complete this section.]

DOCUMENT	*APPLICATION NUMBER*	*DESCRIPTION*
IND	116145	For ASTX727 Tablets

CONSULTS

[FDA will complete this section.]

None

TABLE OF CONTENTS

Evaluation of the Quality Information

[Applicant to provide link to the data in m3 sections as appropriate]

1. EXECUTIVE SUMMARY

[FDA will complete this section.]

NDA 212576 was submitted as a 505(b)(1) NDA under the Federal Food, Drug and Cosmetic Act for ASTX727 (cedazuridine and decitabine) tablets. ASTX727 an oral fixed dose combination product containing 100 mg of cedazuridine and 35 mg decitabine. Decitabine is a nucleoside metabolic inhibitor and a hypomethylating agent (HMA) that was approved under NDA 21790 in 2006. Cedazuridine is an NME and a novel cytidine deaminase inhibitor.

Cedazuridine

Cedazuridine is a small chiral molecule with four stereocenters. Cedazuridine is produced as a (b) (4), white to off-white (b) (4) solid (b) (4). Cedazuridine is manufactured (b) (4) The applicant provided adequate information in the NDA to justify these as regulatory starting materials. The specifications (b) (4) are reasonable. The applicant adequately described the manufacturing process, controls for critical steps and intermediates, details of the impurity (b) (4) studies and identified CQAs and CPPs.

The applicant provided spectroscopic evidence to support the structure of cedazuridine. The single crystal X-Ray Diffraction data supports the structure as well as stereochemistry of cedazuridine. The applicant also provided NMR data for the specified impurities.

The proposed drug substance specifications for cedazuridine is acceptable. The applicant (b) (4) the acceptance limits for impurities and particle size distribution based on available data per the Agency's request. (b) (4) The applicant provided adequate description of the analytical methods and validation data consistent with ICH Q2. The batch data shows no out of specifications data.

The applicant provided adequate description of the container closure system for the drug substance.

The stability data provided by the applicant shows adequate stability of the drug substance. The proposed retest date of (b) (4) months may be granted.

Decitabine

The decitabine drug substance [redacted] is used for the manufacturing. [redacted] in response to agency IR. The applicant referred to the DMF [redacted] for the manufacture and control of this drug substance and provided a LOA from the DMF holder. The DMF [redacted] was reviewed on May 27, 2020 and found adequate for use in the proposed product.

Drug Product

The drug product, ASTX727, is an immediate release, fixed-dose combination (FDC) product containing two active ingredients, cedazuridine and decitabine. The drug product is presented as a biconvex, oval-shaped, film-coated, red tablet, plain-faced on one side, and debossed with "H35" on the other side. The drug product formulation includes 100 mg of cedazuridine and 35 mg decitabine together with compendial excipients that are commonly used in solid oral dosage forms (lactose monohydrate [redacted] hypromellose [redacted] croscarmellose sodium, colloidal silicon dioxide, and magnesium stearate). The film coating material contains polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide red.

The QTPP for the drug product was established based on the properties of the drug substance, characterization of the drug product and the intended patient population. The proposed drug product specifications are consistent with CQAs, which were identified based on the QTPP include appearance, identification, assay, content uniformity, degradation products, dissolution, microbial limits [redacted]. The applicant provided adequate description of the analytical methods and validation data per ICH Q2. The batch data complies to the proposed specifications.

The drug product is packaged in [redacted] 5-cavity blister pack formed by aluminum foil on foil lidding containing one tablet per cavity. The applicant refers to appropriate CFR and FDA guidances regarding the packaging materials. The proposed container closure is typical for solid oral dosage forms.

The drug product is manufactured by [redacted] at a commercial batch size of [redacted] which corresponds to [redacted] tablets.

[redacted]

(b) (4) All were described in sufficient detail and adequately justified. The applicant demonstrated the suitability of the manufacturing process for the drug product at commercial scale. The description of the manufacturing process includes appropriate in-process controls and operating parameters.

The applicant provided adequate stability data (b) (4) and the available stability data shows consistency over time. Based on the stability data provided, Astex Pharmaceuticals proposed and the FDA accepts the **24 month** expiry (b) (4) of the drug product when stored between 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) (See USP Controlled Room Temperature).

Biopharmaceutics

The biopharmaceutics review focused on (1) the acceptability of the proposed dissolution method and acceptance criterion for the routine QC testing of the proposed drug product at batch release and on stability and (2) bridging of the clinical and commercial formulations.

Dissolution Specification and Method: The proposed dissolution method [USP Apparatus 2 (paddle) rotating at 75 rpm; 900 mL of 50 mM phosphate buffer, pH 6.8, 37°C] was considered adequate for the quality control testing of Decitabine/Cedazuridine Tablets, 35 mg/100 mg. Based on the overall evaluation of the provided data, the Biopharmaceutics reviewers recommended tightening of the dissolution acceptance criteria to "Q = (b) (4)% at 15 min", as well as the use of cumulative dissolution data without (b) (4) for both drug substances

Bridging of the Clinical Formulations: The drug product formulation used in the pivotal clinical study (ASTX727-02) is same as the formulation used in the primary stability batches and the intended to-be-marketed commercial drug product.

The submitted in vitro dissolution and in vivo PK data were considered adequate to bridge the drug products evaluated in clinical studies and stability studies to the final proposed to-be-marketed drug product

Facilities

There were 10 facilities included in this application:

(b) (4)

(b) (4)

All the facilities ((b) (4) are approvable, based on acceptable compliance history and 704(a)(4) review (Drug product manufacturing site: (b) (4)

The applicant's request for a categorical exclusion from environmental assessment for INQOVI® in accordance with 21 CFR 25.31(b) is granted.

The NDA 212576 is recommended for approval from CMC perspective.

2. *APPLICATION BACKGROUND*

[Applicant will complete this section.] Include information such as IND references, BTD/Fastrack/Orphan designations, etc.

Referenced IND 116145

ASTX727 received Orphan-drug Designation for the "treatment of myelodysplastic syndromes, including chronic myelomonocytic leukemia," dated August 21, 2019.

Priority Review is requested at time of this NDA submission on December 11, 2019.

3. *SUMMARY OF CMC SPECIFIC PRESUBMISSION/SUBMISSION REGULATORY ACTIVITY*

The Applicant's Position:

[To the Applicant: Insert text here.] Include CMC meeting dates and any Pre-NDA agreements

End of Phase 2 (EOP2) CMC Meeting:

- EOP2 CMC Meeting Request was submitted to FDA on April 11, 2019
- FDA issued a Meeting Preliminary Comments on May 31, 2019 for a scheduled meeting date on June 13, 2019.
- Astex accepted FDA comments. Thus, the EOP2 meeting did not occur

- FDA agreed that:
  - [redacted] starting materials [redacted] appears to be reasonable.
  - The overall approach of cedazuridine specification attributes appear to be reasonable
  - The approach, in which process impurities [redacted] is not listed in drug product specification, appears to be reasonable.

Pre-NDA CMC Meeting:

- Pre-NDA CMC Meeting Request was submitted to FDA on July 30, 2019.
- FDA issued a Meeting Preliminary Comments on October 3, 2019 for a scheduled meeting date on October 10, 2019.
- After a face-to-face meeting on October 10, 2019, FDA issued a pre-NDA Meeting Minutes on November 5, 2019.
- FDA agreed that:
  - Discussion of potential genotoxic impurities appears reasonable.
  - Attributes to be tested for drug product appear reasonable.
  - The approach that decitabine drug product impurities are reported [redacted] appears reasonable.
  - The approach, which is to provide, at time of submission, [redacted] 12-month data at long term storage stability data of three (3) primary stability batches in blisters, and additional stability update during NDA review, is reasonable.
  - Cedazuridine can be sourced from either [redacted] so long as cedazuridine from [redacted] uses the same manufacturing process, has the same impurities at comparable levels, meet the same specification, and has the same stability profile.

The FDA's Assessment: ***NA***

[FDA will complete this section.]

Consistent with FDA's records.

4. ENVIRONMENTAL ASSESSMENT

The Applicant's Position:

Astex Pharmaceuticals Inc. requests a categorical exclusion for ASTX727 in accordance with 21 CFR 25.31(b). The maximum projected Astex production of cedazuridine and decitabine on the 5th year of manufacturing are (b) (4) kg/year, respectively. Based on these production values, the Expected Introductory Concentration (EIC) for each ingredient is (b) (4) and (b) (4) ppb, respectively. These EIC values are both much lower than the regulatory criteria of 1 ppb. Accordingly, ASTX727 is not expected to pose a significant risk to the environment and qualifies for categorical exclusion.

To the best of Astex Pharmaceuticals Inc.'s knowledge, no extraordinary circumstances, as referenced in 21 CFR 25.21, exist relative to this action.

The FDA's Assessment: ***Acceptable***

[FDA will complete this section.]

The applicant has submitted a claim of categorical exclusion including a statement of no extraordinary circumstances. The categorical exclusion cited at 21 CFR 25.31(b) is appropriate for the estimated amount of drug to be produced for direct use. The claim of categorical exclusion is acceptable.

5. *BIOWAIVER REQUEST/BCS DESIGNATION REQUEST/BRIDGING (if applicable/known)*

The Applicant's Position: Not applicable.

The NDA does not contain a biowaiver request

If applicable, details are provided under section 7e) BIOPHARMACEUTICS

The FDA's Assessment:

[FDA will complete this section.]

Refer to Section 7e) BIOPHARMACEUTICS

6. *DRUG SUBSTANCE*

(b) (4)

73 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

The FDA's Assessment: ***Acceptable***

[FDA will complete this section.]

The batch data provided by the applicant conforms to the proposed specifications. For evaluation of the dissolution data, refer to section 7e below.

e. *BIOPHARMACEUTICS*

[To the Applicant: Insert text here brief summary on the data to support the adequacy of dissolution method (medium, apparatus etc.), discriminating ability of the dissolution method for critical material attributes and process parameters, justification of selection of the acceptance criterion, include multipoint dissolution profile in a graphical format from clinical/PK and primary registration batches, data to support the BCS designation request, information on the purpose and data to support the biowaiver request i.e. compositional proportionality, PK linearity, comparative dissolution profiles with f2 analysis],bridging between the formulations/process/site changes that occurred throughout development and in vitro or in vivo data to support bridging, data to support IVIVC and/or PBPK modeling, if applicable. (approx. 300 words)]

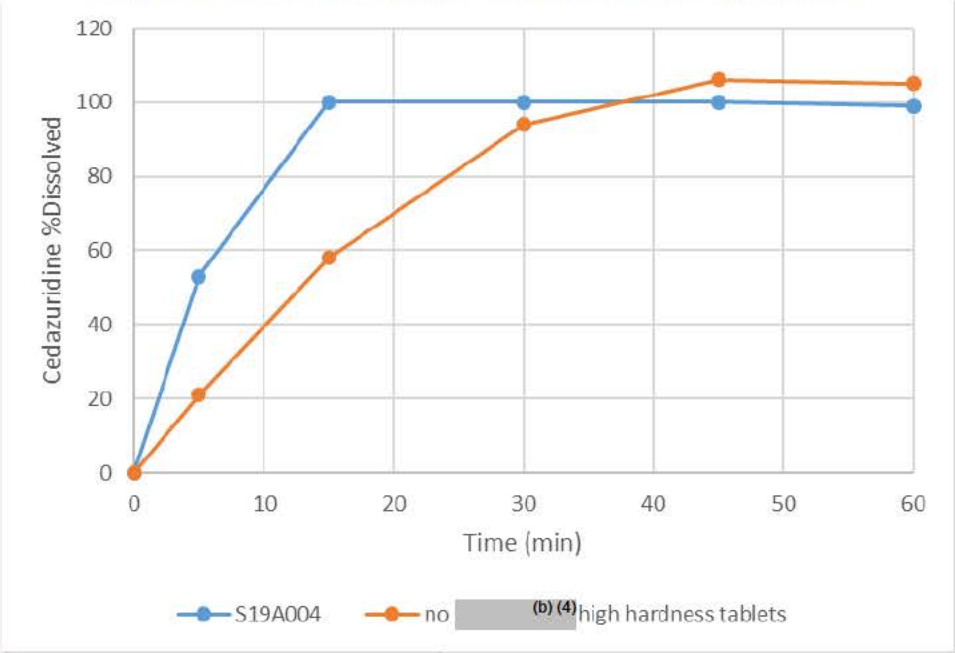
USP Apparatus	Paddle Rotation Speed	Medium Volume	Temperature	Medium	Acceptance Criterion
2 (rotating paddle)	75 rpm	900 mL	37°C	50mM phosphate buffer pH 6.8	Q (b) (4)% at (b) (4) minutes

The dissolution conditions were selected in accordance with ICH Q6A guidance, based on the dissolution results for ASTX727 tablets evaluated with multiple dissolution conditions. (b) (4)

[redacted]

The dissolution method was able to discriminate aberrant tablets without (b) (4) and high hardness from regular tablets. As shown in the below two figures, aberrant tablets made with no (b) (4) and high hardness (b) (4) resulted in slower dissolution compared to regular tablets. As agreed with the FDA during re-NDA meeting on October 10, 2019 (see FDA pre-NDA CMC Meeting Minutes issued Nov. 5, 2019), additional dissolution data assessing discriminating capability will be provided during review.

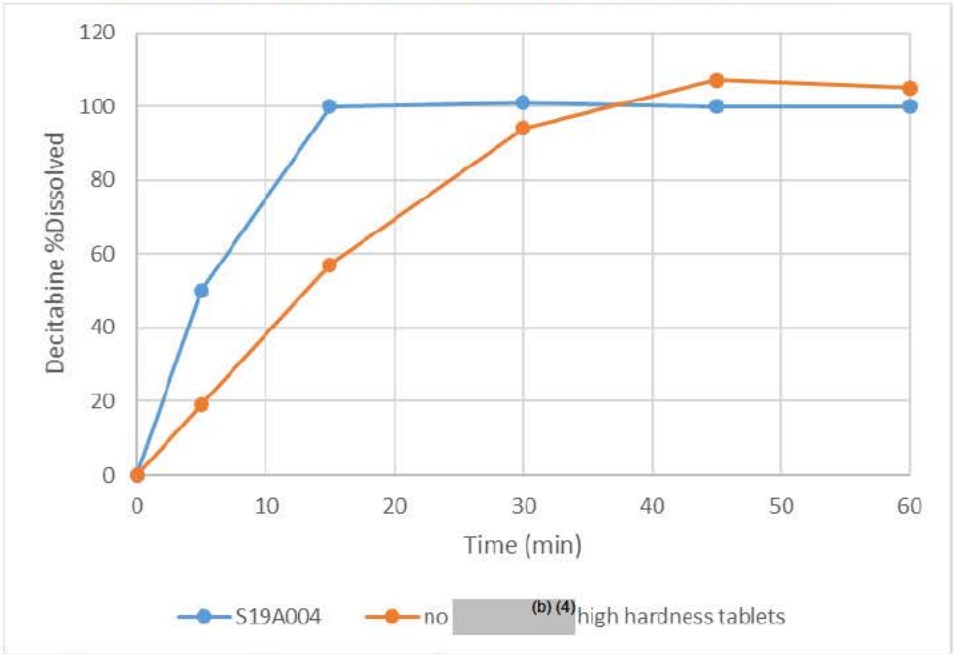
Cedazuridine Dissolution of ASTX727 Aberrant Tablets



50mM phosphate pH6.8 media, 900 mL, 75 rpm, n=6. (b) (4)

.

Decitabine Dissolution of ASTX727 Aberrant Tablets



50mM phosphate pH6.8 media, 900 mL, 75 rpm, n=6. (b) (4)

A summary of the key considerations and attributes for the proposed dissolution method and specification is as following:

1 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Dissolution Profiles of ASTX727 Tablets (Decitabine Mean %Dissolved) of Nine Batches

(b) (4)

The FDA's Assessment:

[FDA will complete this section.]

1. DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

DISSOLUTION METHOD*- Adequate*

Justification for the Chosen Method Parameters

(b) (4)

Discriminating Ability

As shown in the Applicant's figures above, the proposed dissolution method was able to detect the decreased cedazuridine and decitabine ((b) (4) *dissolution*

rates of an intentionally aberrant tablet manufactured with no (b) (4) *AND higher than target* ***tablet hardness*** *level (i.e., however,* (b) (4) *). The additional data submitted by the Applicant on 1/31/2020 demonstrated that the proposed dissolution method is also discriminating for changes in the* (b) (4) *[refer to the final DMDR's Table 11 for the description of the lots used in the study, and specifically Figures 18 and 19 for the cedazuridine dissolution* (b) (4) *and decitabine dissolution (* (b) (4) *profiles of tablet lots manufactured with varying levels and different grades of* (b) (4) *. Refer also to the FDA* ***Reviewer's Figure 1*** *below showing the* (b) (4) *decitabine dissolution profiles of all the intentionally aberrant and the target drug product lots evaluated in the Applicant's study. Both the Reviewer's figure below (with* (b) (4) *decitabine dissolution profiles) and the Applicant's figures in the DMDR show that except for the batch manufactured with the different* (b) (4) *and higher than target level of* (b) (4) *all studied intentionally aberrant and target drug product lots achieve* (b) (4) *% cedazuridine and decitabine release within* (b) (4) *min.*

Note that the target drug product contains (b) (4) *, so based on the dissolution study results, the Applicant was requested by FDA to specify the* (b) (4) *in the drug product composition table, batch formula, manufacturing batch records, and all pertinent NDA documents. With regard to tablet hardness level, this Reviewer considers the proposed mean tablet hardness range of* (b) (4) *kP reasonable based on the mean (range) values reported for the Phase 3 Clinical Lots #S17I007, #S18B006, #S18B007, and #S18B008, i.e.,* (b) (4) *kP.*

Reviewer Figure 1: (b) (4) ***Decitabine Dissolution Profiles of Target vs. Intentionally Aberrant Tablet Lots***

(b) (4)

Using the proposed dissolution method, drug product lots with differences in cedazuridine and decitabine ***API particle size distributions*** *were all very rapidly dissolving* (b) (4) *in the proposed dissolution medium. The FDA* ***Reviewer's Figure 2*** *below shows that lots of the Final (formulation/process) Tablets manufactured with lowest API particle sizes exhibited either*

comparable or numerically slightly higher dissolution rate, i.e., at the earliest sampling time points (e.g., 5 minutes). [Note that Lot 16-0162 in Applicant's Figures 10 and 11 of the DMDR was not included in this Reviewer's figure because this particular (Early) tablet lot was manufactured using formulation and process that were different from those for the Final Tablets lots, which likely explains the counter-intuitive comparative in vitro dissolution results relative to decitabine particle size, as depicted in the Applicant's figures.] The limitations of the proposed dissolution method could be attributed to (at least in part) (b) (4)

Reviewer Figure 2**: Cedazuridine and Decitabine* (b) (4) ***Dissolution Profiles of Final (Clinical) Tablet Lots Manufactured using APIs with Different Particle Sizes

(b) (4)

Analytical Method Validation

HPLC with UV detection (b) (4) is used for the assay of cedazuridine and decitabine (b) (4) respectively, in the dissolution samples. The dissolution samples are passed through (b) (4) prior to HPLC assay. The validation studies included specificity, linearity ((b) (4)), accuracy, precision (repeatability), intermediate precision (reproducibility), range, sample and standard solution stability, and robustness (with respect to HPLC parameters and dissolution medium pH (6.8 (b) (4) . The sample solutions were reported to be stable for 18 hours under refrigerated conditions. Per the Drug Product Reviewer, the analytical method validation for dissolution is adequate.

For QC testing of the proposed drug product, this Reviewer does not recommend the Applicant's approach (b) (4) For further details, refer to the discussion below regarding dissolution of the stability samples.

Sink Conditions

(b) (4)

greater than sink conditions are anticipated to be achieved and maintained during dissolution testing of the tablets in 900 mL of phosphate pH 6.8 buffer at 37 °C.

***DISSOLUTION ACCEPTANCE CRITERIA** – Revised Dissolution Acceptance Criterion Adequate*

The originally proposed dissolution acceptance criterion is "Q = (b) (4) % at (b) (4) min" for both cedazuridine ((b) (4) and decitabine (b) (4) , based on the historical data of nine (9) clinical/stability batches of the early and final tablet formulations (Figures 1 and 2 of 3.2.P.5.6, excerpted by the Applicant above).

*Based on the very rapid dissolution profiles of the two APIs (**Reviewer's Figure 3** for decitabine), as well as the relative capability to reject drug product lots with unacceptable quality attributes (e.g., two intentionally abberant tablet lots manufactured with no (b) (4) and high hardness, and another aberrant lot with changes in the level and grade of the (b) (4); **Reviewer's Figure 1**), the recommended dissolution acceptance criterion is Q = (b) (4)% at 15 min for both cedazuridine and decitabine (b) (4).*

(b) (4)

Based on the dissolution profile data (n=6) provided for the long-term stability samples, the proposed drug product is anticipated to be able to conform to this Reviewer's recommended dissolution acceptance criterion (Q = (b) (4)% at 15 min (b) (4), i.e., by USP Stage 2 testing (n = 6 or 12).

Reviewer Figure 3**: Decitabine (b) (4) **Dissolution Profiles of Clinical Trial Lots over 18 Months of Long-Term Storage

(b) (4)

Dissolution on Stability

(b) (4)

Based on up to 18 months of long-term, 12 months of intermediate, 6 months of accelerated stability data for the three primary registration drug product lots (b) (4) *5-count blister packaged, Lots (S18B006, S18B007 and S18B008), as well as up to 24 months of long-term, 12 months of intermediate, 6 months of accelerated stability data for supportive stability/clinical lots (S17F013, S17I007), and up to 6 months of long-term and accelerated stability data for 1 additional supportive stability (proposed commercial/intended clinical) lot (S18M015) with the proposed commercial* (b) (4) *blister packaging configurations, the proposed expiration dating period for the proposed drug product is 24 months when stored under USP Controlled Room Temperature.* (b) (4)

(b) (4)

(b) (4)

(b) (4)

In SDN-43, the Applicant agreed with the FDA recommended dissolution acceptance criterion for batch release and stability testing, i.e., Q = (b) (4)% (b) (4) at 15 min for cedazuridine and decitabine. The dissolution standard test procedure (3.2.P.5.2), the analytical methods validation report (3.2.P.5.3), and the Finished Product QC Specifications (3.2.P.5.1) were revised accordingly.

The approved vitro dissolution method and dissolution acceptance criterion are shown in the table below.

USP Apparatus	Paddle Rotation Speed	Medium/ Volume/Temperature
2 (rotating paddle)	75 rpm	50mM phosphate buffer pH 6.8/900 mL/ 37°C
Acceptance Criterion		
Cedazuridine		15 minutes: Q = (b) (4)%
Decitabine (b) (4) *):		15 minutes: Q = (b) (4)%

(b) (4)

2. BCS DESIGNATION REQUEST – Not Applicable

There is no BCS-1 or BCS-3 Designation Request for the drug substances/fixed dose

combination drug product.

(b) (4)

[redacted]

3. BIOWAIVER REQUEST – Not Applicable

*A **biowaiver request for non-bio-strengths** is not applicable because there is only one proposed commercial fixed-dose combination tablet strength (100 mg cedazuridine/35 mg decitabine) which was the strength evaluated in pivotal clinical and stability studies. Additionally, the CMC changes introduced to the drug product after initiation of the Phase 3 clinical trial are not considered major and thus, do not require in vivo BA/BE bridging.*

4. BRIDGING THE CLINICAL DRUG PRODUCT TO THE FINAL PROPOSED TO-BE-MARKETED DRUG PRODUCT - Adequate

The drug product used in the Phase 3 clinical trial and the stability studies was manufactured using the final/proposed commercial formulation/dosage form and process [redacted] *facility/site* [redacted] *) at a similar batch scale* [redacted]

For the CMC changes that occurred after the Phase 2b clinical stage, there were adequate in vitro and in vivo data to support comparability of the pre-change and post-change drug products, as discussed in more detail below.

Note that the cedazuridine 100 mg/decitabine 35 mg fixed-dose combination tablets used in the Phase 3 clinical/PK bridging study were manufactured using the cedazuridine drug substance supplied by (b) (4) *Overall, the comparative in vitro cedazuridine (and decitabine) dissolution profile data provided for the tablet lots used in Phase 3 clinical/PK bridging, primary (registration) stability, and supportive stability studies (e.g., as shown in Figures 7 to 9 of the DMDR) supported* ***bridging of the original and the new/alternate cedazuridine drug substance suppliers****,* (b) (4) *and* (b) (4) *respectively. The proposed commercial decitabine drug substance supplier (* (b) (4) *is the same supplier used for the manufacture of the clinical/stability lots.*

Note that both the unmarked ***pre-market image (PMI) tablets and the final commercial image (FCI) debossed tablets*** *were used in the Phase 3 clinical/PK bridging and Food-Effect studies. Additionally, the primary registration stability studies used the FCI tablets, and one unmarked tablet lot was used for supportive stability. Thus, comparative in vitro data are not necessary for bridging the PMI and the FCI tablets. Nevertheless, it is noted that the available in vitro cedazuridine and decitabine dissolution profile data (using the proposed QC dissolution method) do confirm that the addition of debossing and "H35" imprint to the tablet did not alter the cedazuridine and decitabine* (b) (4) *dissolution profiles of the final proposed to-be-marketed drug product.*

(b) (4) ***blister packaging configurations*** *were evaluated in primary stability studies,* (b) (4) *However, the favorable dissolution on stability data (as shown in Reviewer's Figure 4 above) support the Applicant's proposal to market the blister configuration even though it was not used in clinical trials.*

Should ***bridging to the early formulations/dosage forms****, i.e., "Early (fixed dose combination) Tablet, and single API capsules, be needed, PK data are available. Note that the "Early" FDC Tablet used in (supporting) Phase 2 Study ASTX-01-B differs from the Final FDC Tablet used in the (pivotal) Phase 3 Study ASTX-02, i.e., in terms of formulation and drug product manufacturing process/site, and cedazuridine/decitabine API suppliers. However, per the Clinical Pharmacology Reviewer (Dr. Sriram Subramaniam), the "Early" and the "Final" FDC Tablets exhibited comparable drug exposures.*

REVIEWER NOTE: Relative bioavailability data in cancer patients are also available to establish the decitabine ***PK bridge between the final proposed to-be-marketed oral FDC drug product and the Listed Drug product (DACOGEN® IV).*** *Per the proposed labeling (and as confirmed by FDA's Office of Clinical Pharmacology), steady state decitabine AUC exposures were equivalent following daily administrations of oral cedazuridine/decitabine 100 mg/35 mg and DACOGEN® 20 mg/m^2 via IV infusion.*

f. CONTAINER CLOSURE SYSTEM

[To the Applicant: Insert text here (approx. 50 words + any diagrams, references to appropriate CFR and USP chapters, MVTR data etc).]

(b) (4)

(b) (4)

Blister configuration

Primary packaging:

ASTX727 tablets are packaged in a five-cavity blister pack formed by aluminum foil on foil lidding containing one tablet per cavity. The primary packaging complies with 21 CFR Part 175.300.

Secondary packaging:

The carton has child resistance feature in accordance with 16 CFR 1700.14(a)(10).

The FDA's Assessment: ***Acceptable***

[FDA will complete this section.]

(b) (4)

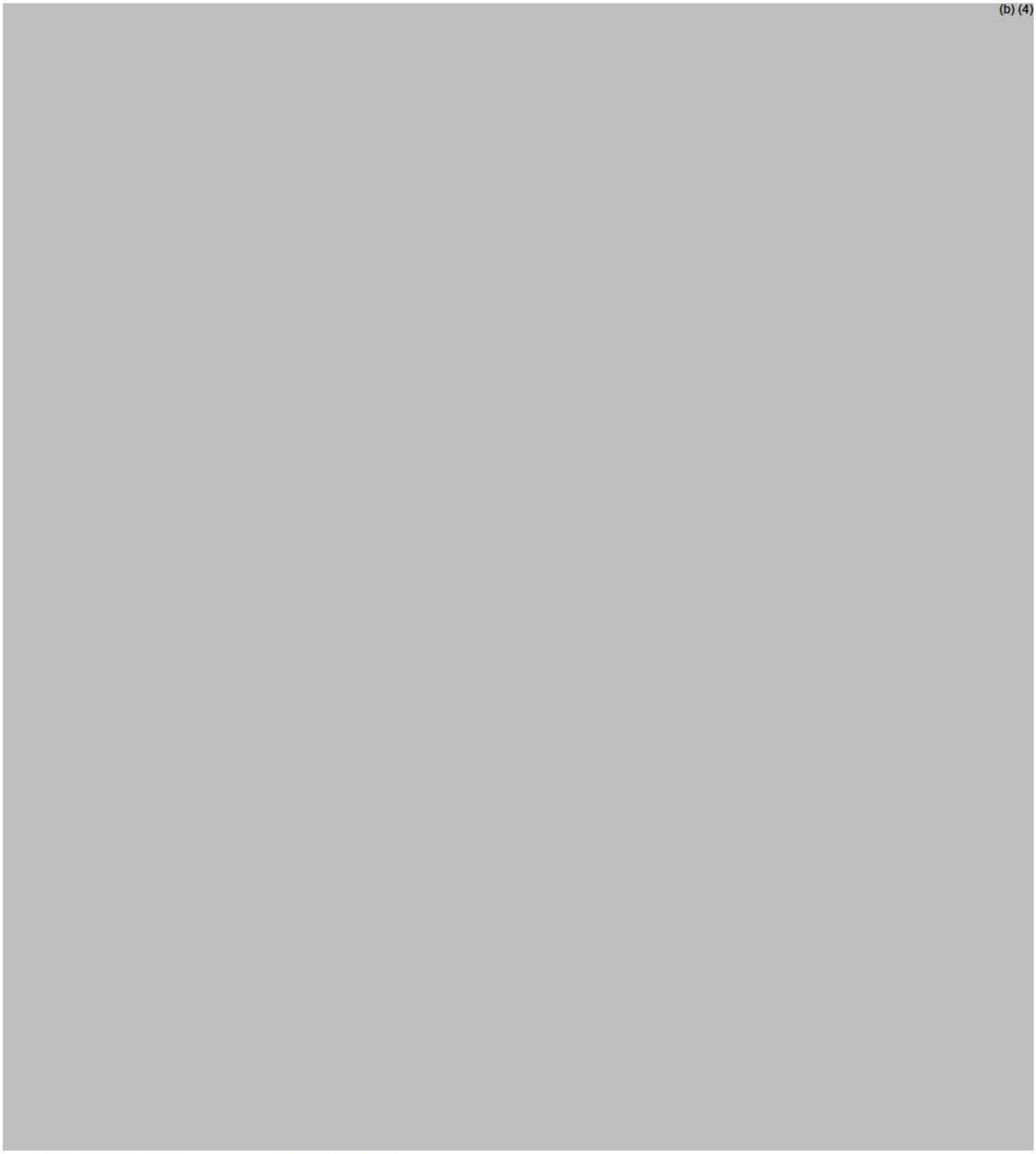
Blister configuration
Each foil contains 5 cavities, with one tablet per cavity. The applicant referred to the DMF (b) (4) (b) (4) *The secondary packaging is child-resistant in accordance with 16 CFR 1700.14(a)(10).* (b) (4) *The proposed packaging material appears appropriate for this dosage form.*

g. STABILITY
[Applicant to fill out]

Performed per ICH Q1A:	Yes *If no, specify*		
Strength(s) and # of Batches	(b) (4) Cedazuridine 100 mg/ decitabine 35 mg (3 batches in blister)		
Bracketing	No **(In)Adequate** If inadequate, explain		
Matrixing	No **(In)Adequate** If inadequate, explain		
Container Closure System	**Commercial:** Yes; If yes, specify. If no, explain (b) (4) Blister packaging: Five-cavity foil on foil blister pack with 1 tablet per cavity.		
Storage Conditions/Storage Times			
Long-term	**25°C ± 2°C/60% RH ± 5% RH**	CCS Orientation	N/A
Min/Max storage time	**12 months**	36 months	
Intermediate	**30°C ± 2°C/65% RH ± 5% RH**	CCS Orientation	N/A
Max storage time	12 months		
Accelerated	**40°C ± 2°C/75% RH ± 5% RH**	CCS Orientation	N/A
Max storage time	**6 months**		

3 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)



The FDA's Assessment: ***Acceptable***

[FDA will complete this section.]

Stability data for 3 batches (primary batches S18B006, S18B007, and S18B008) packaged in (b) (4) *blisters under long term (25°C/60%RH,* (b) (4) *12 months in blisters), intermediate (30°C/65%RH, 12 months), and accelerated conditions (40°C/75%RH, 6 months) and 24 months stability data under long term storage for several supportive batches are*

adequately summarized in the table above. The applicant updated the stability data of the primary registration batches via amendment dated May 19, 2020 to include (b) (4) *18 months of stability data for blisters under long term storage conditions (25°C/60%RH). The updated dissolution on stability data provided was measured per acceptance criteria proposed in the original submission. This is acceptable to the Biopharmaceutics review team as the acceptance criteria for dissolution was finalized after the withdrawal of the samples at the most current long-term stability timepoints, and the applicant proposed to implement the FDA recommended acceptance criteria for the release and stability testing of the process validation batches and the future commercial batches. No out of specification results, or trends are apparent in the data. With this updated data, the applicant has provided* (b) (4) *6 months extrapolation for the blister.*

Photostability study conducted per ICH Q1B shows the tablet to be photostable. (b) (4)

The applicant is proposing a shelf life of 24 months for the ASTX727 tablets packaged in (b) (4) *blisters, at the recommended storage conditions of 20°C to 25°C (68°F to 77°F) with excursions permitted from 15°C to 30°C (59°F to 86°F) (See USP Controlled Room Temperature). The proposed 24 months shelf may be granted as requested by the applicant* (b) (4)

LABELING

[FDA will complete this section.]
*The applicant listed the drug substances in alphabetical order based on the the current FDA policy. Since the product will be dosed based on decitabine, the clinical division is recommending that decitabine be listed first in the USPI and the carton container labels. The OPQ defers to the clinical division on this. The applicant accepted the clinical division's recommendations and reversed the order of the drug substance in the USPI and carton/container labels to "**INQOVI® (decitabine and cedazuridine) tablets, for oral use**" via amendment dated May 14, 2020.*
The quality sections of the Prescribing Information, sections 2 DOSAGE AND ADMINISTRATION, 3 DOSAGE FORMS AND STRENGTH, 11 DESCRIPTION, and 16 HOW SUPPLIED/STORAGE AND HANDLING provided by the applicant appear appropriate. The applicant provided adequate manufacturer information. The final version of this document will be cleared by the clinical division following input from all the review divisions and interactions with the applicant.
*The applicant provided carton and container label appropriate with the proposed dosage form. The labels indicate the proposed brand name (INQOVI), drug substance proprietary name, strength, dosage form, route of administration, storage temperature range, NDC number, space for lot and expiry date, and manufacturer information. The applicant submitted updated carton and container labels to reflect the change in the order of listing of the drug substance (decitabine before cedazuridine) on May 22, 2020. The proposed change in order was recommended by the clinical division. **Refer to the EDR for the current carton container labeling**.*

The Prescribing Information and Carton and Container labels are adequate from a CMC standpoint.

Final Risk Assessments

[FDA will complete this section.]

Initial Risk Identification			*Review Assessment*		
Attribute/ CQA	***Factors that can impact the CQA***	***Risk Ranking***	***Risk Mitigation Approach***	***Final Risk Evaluation***	***Lifecycle Considerations/ Comments***
Assay (API), stability	• *Formulation* • *Container closure* • *Raw materials* • *Process parameters* • *Scale/equipment* • *Site*	*L*	(b) (4)	*L*	*Both the APIs are tested at release and stability*
Physical stability (solid state)	• *Formulation* • *Container closure* • *Raw materials* • *Process parameters* • *Scale/equipment* • *Site*	*L*		*L*	
Content Uniformity	• *Formulation* • *Container closure* • *Process parameters* • *Scale/equipment* • *Site*	*M*		*L*	
Moisture content	• *Formulation* • *Container closure* • *Process parameters* • *Scale/equipment* • *Site*	*L*		*L*	
Microbial Limits	• *Formulation* • *Raw materials* • *Process parameters* • *Scale/equipment* • *Site*	*L*		*L*	
Dissolution	• *Formulation* • *Raw materials* • *Process parameters* • *Scale/equipment* • *Site* • *Packaging*	*L*		*L*	
Facility	(b) (4)				*Post approval inspection for* (b) (4) (b) (4) *will be requested.*

Recommendation Page

[FDA will complete this section.]

Drug Substance: Approval

Primary Reviewer: Anamitro Banerjee *Date: 05/08/2020*
Secondary Reviewer: Ali Al-Hakim *Date: 05/09/2020*

Drug Product: Approval

Primary Reviewer: Anamitro Banerjee *Date: 05/27/2020*
Secondary Reviewer: Thomas Oliver Ph.D. *Date: 05/29/2020*

Process and Facility: Approval

Primary Reviewer: Zhaoyang Meng *Date: 06/16/2020*
Secondary Reviewer: Rakhi Shah *Date: 06/16/2020*

Biopharmaceutics: Approval

Primary Reviewer: Gerlie Gieser, Ph.D. *Date: 05/08/2020*
Secondary Reviewer: Om Anand, Ph.D. *Date: 05/12/2020*

Labeling: Approval

Primary Reviewer: Anamitro Banerjee *Date: 05/22/2020*
Secondary Reviewer: Thomas Oliver *Date: 05/29/2020*

Application Technical Lead: Approval

Sherita D. McLamore *Date: 06/24/2020*

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/

SHERITA D MCLAMORE
06/24/2020 11:22:33 AM

ALI H AL HAKIM
06/24/2020 11:36:16 AM

THOMAS F OLIVER
06/25/2020 07:08:17 AM

RAKHI B SHAH
06/25/2020 07:13:20 AM

GERLIE GIESER
06/25/2020 07:32:11 AM

ZHAOYANG MENG
06/25/2020 07:36:25 AM

OM ANAND
06/25/2020 09:29:41 AM

ANAMITRO BANERJEE
06/25/2020 09:33:21 AM