

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

217677Orig1s000

PRODUCT QUALITY REVIEW(S)

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

This Executive Summary includes a revision to the shelf life recommendation on the basis of stability data that was submitted after the OPQ IQA was finalized and filed to Panorama & DARRTs.

SDN 0045 was submitted June 2, 2023. SpringWorks Therapeutics, Inc. has updated 3.2.P.8.1 and 3.2.P.8.3 to include 18-month stability data for the process performance qualification (PPQ) batches and 36-month stability data for the primary (registration) drug product batches at the long-term storage conditions of 25°C/60%RH. There are no new trends noted in the updated stability data. Using principles of ICH Q1E, and extrapolated shelf life can be granted.

The application is recommended for approval with a 48 month shelf life for (b) (4) 180-count configurations when stored “at 20°C-25°C (68CF-77°F). Excursions permitted between 15°C-30°C (59°F-86°F). See USP Controlled Room Temperature.”

The rest of this Executive Summary including statements regarding the control of particle size distribution (PSD) remain intact and are retained in this version of the Executive Summary:

The application originally proposed no control for particle size distribution (PSD) in the drug substance specifications. The 10 commercial drug substance batches manufactured to date have a very tight D_{90} of (b) (4) mm. The developmental batches and pivotal batches had a D_{90} range of (b) (4) mm.

The dissolution method is not discriminating to PSD. However, even though this is a BCS Class II product, the product dissolves under physiological pH very quickly (>90% by 10 minutes). The specification for the dissolution method is $Q = (b) (4) \%$ at 15 minutes.

The CMC team discussed the controls on drug substance PSD during the CMC Midcycle Meeting held on 3/20/23, as well as via email communications dated 3/20/23, 5/14/23, and 5/15/23. The drug substance manufacturing process appears to be under control. There is not an apparent product quality risk the review team could use to compel PSD monitoring in the specifications. The team agreed that any potential future risk may be controlled by providing comments under the post-approval lifecycle considerations.

During lifecycle management, if the applicant makes manufacturing process, scale, or site changes the applicant should provide data to compare PSD pre- and post-change. A comparability protocol was deemed to be too rigid of a requirement for this low risk.

The application includes a comparability protocol [REDACTED] (b) (4) [REDACTED] via a CBE-30. This protocol can be approved with the NDA.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Ogsiveo (nirogacestat) tablets is a gamma secretase inhibitor indicated for the treatment of adults with desmoid tumors. Desmoid tumors are also referred to as aggressive fibromatosis. They are rare, locally aggressive, slow growing soft tissue tumors that can cause severe pain, functional impairment, nerve damage, and bowel obstruction or perforation by infiltrating or exerting mass effects on vital structures. There is currently no approved therapy for desmoid tumors or standard of care for patients with advanced progressing tumors. The 50 mg tablets will be administered orally at 150 mg twice daily until disease progression or unacceptable toxicity.

The drug product is composed of compendial excipients, manufactured from conventional manufacturing processes, stored in standard presentations for solid oral dosage forms, and stored at controlled room temperature. No product quality issues related to identity, assay, purity, or quality were identified during review.

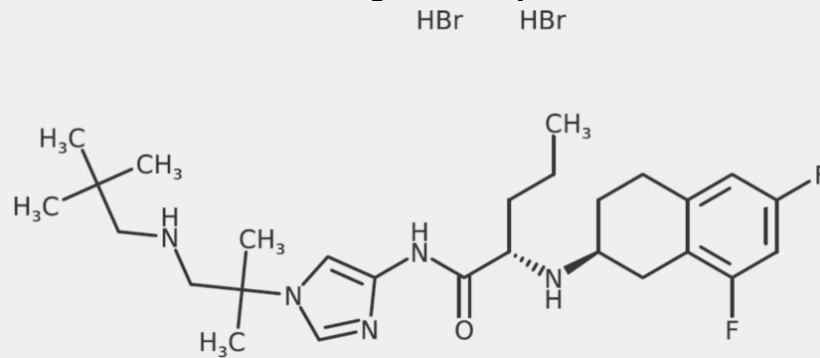
Proposed Indication(s) including Intended Patient Population	Treatment of adults with desmoid tumors
Duration of Treatment	Treat until disease progression or unacceptable toxicity
Maximum Daily Dose	150 mg PO BID
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

Nirogacestat hydrobromide is the USAN name for the drug substance (DS). Nirogacestat hydrobromide is a white to off-white powder and a crystalline substance. Nirogacestat hydrobromide drug substance is a salt containing two hydrogen bromide molecules.

Molecular structure of nirogacestat hydrobromide:



USAN: Nirogacestat hydrobromide

IUPAC: (S)-2-(((S)-6,8-Difluoro-1,2,3,4-tetrahydronaphthalen-2-yl)amino)-N-(1-(2-methyl-1-(neopentylamino)propan-2-yl)-1H-imidazol-4-yl)pentanamide dihydrobromide

The manufacturing process for nirogacestat hydrobromide described in this NDA produces (b) (4) form referred to as (b) (4) is the (b) (4) stable solid-state form of the DS.

Crystallization experiments identified approximately ten materials beside (b) (4) including (b) (4) material. However, (b) (4) experiments with the other materials produced only (b) (4)

Nirogacestat hydrobromide is optically active. It contains two chiral centers. The DS is the S,S enantiomer. The R,R enantiomer and the diastereomers (R,S and S,R) are controlled in the release specification for nirogacestat hydrobromide DS at the level of Not More Than (b) (4) % w/w.

Nirogacestat hydrobromide is manufactured (b) (4)

Nirogacestat hydrobromide drug substance is controlled using a specification that contains tests for Identification using IR spectroscopy and HPLC retention time, solid state form using XRPD, Assay by HPLC with UV detection, and impurities using three different analytical procedures. One of these three procedures uses HPLC with UV detection for identification, assay and determination of six specified impurities, a second one uses HPLC with UV detection for determination of two specified impurities which co-elute using the other procedure, and a third uses HPLC with UV detection for chiral impurities (the enantiomer

and diastereomers). The specification also includes tests for Elemental Impurities, Residual Solvents, Residual (b) (4), (b) (4), and Water.

Nirogacestat hydrobromide drug substance is packaged in (b) (4)

The retest period for nirogacestat hydrobromide drug substance is (b) (4) months when stored in the indicated packaging between (b) (4). The retest period is supported by stability data with storage through (b) (4) months at the ICH Controlled Room Temperature storage condition (CRT) (25°C/65%RH) and (b) (4) months storage at the ICH Accelerated condition (ACC) (40°C/75%RH), generated from samples of three batches of DS produced at about ½ commercial scale, and data through (b) (4) months storage at CRT and (b) (4) months at ACC generated from five (5) batches of DS produced at commercial scale. Nirogacestat hydrobromide DS does not exhibit degradation after exposure to light degradation conditions described in ICH Q1B. It is concluded that nirogacestat hydrobromide drug substance is not light sensitive under the recommended storage conditions.

Drug Product: Adequate

The Applicant submitted this 505(b)(1) NDA 217677 for Ogsiveo® (nirogacestat) Tablets, 50 mg indicated for treatment of adult patients with desmoid tumors. Nirogacestat is a gamma secretase inhibitor. The proposed Ogsiveo® (nirogacestat) film-coated, debossed, Immediate-Release 50 mg Tablets, are prepared from (b) (4) (as free base), which corresponds to (b) (4) as the dihydrobromide salt. The film-coated tablets intended for oral administration. Each tablet contains 50 mg nirogacestat as 66.525 mg nirogacestat dihydrobromide. They are debossed with “50” on one face and plain on the other face. The tablets are comprised of the active ingredient and compendial excipients. The pivotal clinical trial formulation and commercial presentation have the same tablet core.

The tablets are controlled by specifications for appearance, identity (HPLC and IR), assay, individual/total impurities, dissolution, content uniformity, total aerobic microbial count, total combined yeast/mold count, and *E. coli*. There are no specified impurities as none of the drug substance process impurities are also drug product degradation products.

The Ogsiveo® (nirogacestat) tablets are available in (b) (4) 180-count configurations in HDPE bottles with induction seals and CR closures. All

container materials comply with the requisite 21 CFR 177.1520 and 21 CFR 178.3297 and testing monographs USP <661.1> and <671>. 24 months of long-term stability data at 25°C/60%RH and 6 months of accelerated stability data at 40°C/75%RH is available for three registration batches in the 180-count configuration. (b) (4)

(b) (4) . A

36-month shelf life is granted the commercial product (b) (4)

No special storage conditions are required. The tablets are labeled for storage "at 20°C-25°C (68CF-77°F). Excursions permitted between 15°C-30°C (59°F-86°F). See USP Controlled Room Temperature."

Labeling: Adequate

Minor edits were requested during labeling negotiation including alphabetizing the excipients in the formulation and including the appearance, solubility and pKa information for the drug substance in Section 11 of the label. Section 16 was edited to include a statement that the closure is a child-resistant configuration. The container labels include salt equivalence statements.

Manufacturing: Adequate

Nirogacestat tablets 50 mg are immediate release film coated tablets intended for oral administration. The API load is (b) (4) % (w/w).

Process: The manufacturing process is (b) (4)

(b) (4) The intended commercial manufacturing batch size is identical to exhibit batches. The manufacturing equipment proposed for commercial batches are of same size and operating principle as of the exhibit batches. All clinical studies were conducted using drug product manufactured at the commercial manufacturing site (b) (4) No changes in manufacturing process and formulation are identified from clinical to registration and proposed commercial batches.

Nirogacestat tablets are manufactured (b) (4)

(b) (4) Refer to the Executive Summary regarding internal CMC discussions regarding the control of the drug substance particle size distribution on the manufacturing and control of the drug product.

The applicant submitted a comparability protocol describing their intent on a planned post-approval change to include (b) (4)

(b) (4) nirogacestat 50 mg tablets (3.2.R). Per Agency's recommendation, the sponsor agreed to submit a CBE 30 to obtain Agency's approval for (b) (4).

The manufacturing process is Adequate to support the commercial manufacturing of Nirogacestat tablets, 50 mg.

Facilities: All manufacturing facilities including testing and packaging sites proposed for the commercial manufacturing of Nirogacestat tablets 50 mg are found acceptable based on GMP compliance and firm's prior experience in performing the proposed responsibilities. No preapproval inspection was recommended for any facility. The primary drug product manufacturing site is (b) (4). The drug substance manufacturing site is (b) (4). The OMIR is recommended to Approve.

Biopharmaceutics: Adequate

This Biopharmaceutics Review focused on evaluating the in vitro dissolution method and acceptance criterion as a quality control (QC) test, and the bridging between the clinical and the proposed to-be-marketed drug product. The Applicant developed an in-house dissolution method and submitted a Dissolution Method Development Report investigating the selection of each parameter. Based on the dissolution data and information submitted, the following dissolution method and acceptance criterion are found acceptable for the Quality Control (QC) test of Ogsiveo® (Nirogacestat) Tablets, 50 mg, at batch release and on stability:

Approved Dissolution Method and Acceptance Criterion for Ogsiveo® (Nirogacestat) Tablets, 50 mg				
Apparatus	Speed	Volume/Temp	Medium	Acceptance Criterion
USP II (Paddle)	75 rpm	500 mL/ 37 °C	pH 1.2 (HCl buffer)	Q = (b) (4) % at 15 min

The Applicant used uncoated tablets for the blinded phase of Pivotal Study NIR-DT-301 and film-coated tablets for the open-label extension phase of the same study. There were no changes to the formulation (except non-functional coating), manufacturing process, or manufacturing site between the clinical batches (e.g., uncoated tablet; batch# 9111) versus the registration /proposed commercial batches (e.g., film-coated tablet; batch# 1140X); comparative in vitro dissolution profile/data were needed using multi-pH media (e.g., pH 1.2 [proposed QC], pH 4.5 and pH 6.8) to bridge the uncoated clinical tablets with the proposed commercial film coated product. The Applicant's dissolution data showed a comparatively similar dissolution profile across all pH conditions. The clinical batches (e.g., uncoated tablet; batch# 9111) and registration/proposed commercial batch (e.g., film-coated tablet; batch# 1140X) are deemed adequately bridged.

Microbiology (if applicable): N/A

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, stability	(b) (4)	Low	(b) (4)	Low	
Physical Stability		Low		Low	
Content Uniformity	(b) (4)	Low		Low	
Microbial Limits		Low		Low	
Dissolution	The drug substance has pH- dependent solubility, that decreased with increase in pH	Medium		Low	

¹ The Applicant indicates that they were initially pursuing “Q= (b) (4) min” during the developmental/ IND phase

Content Uniformity, dissolution	(b) (4)	Low		(b) (4) Low	
Content Uniformity, dissolution, Assay	(b) (4)	Medium		Low	
Content Uniformity, dissolution, Assay	(b) (4)	Medium		Low	

			(b) (4)		
Dissolution	Coating	Low		Low	

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: Olen Stephens 6/5/2023

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/

OLEN M STEPHENS

06/05/2023 01:18:45 PM

CMC recommendation remains for Approval. A 48-month shelf life is recommended

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The application is recommended for approval with a 36 month shelf life for (b) (4) 180-count configurations when stored “at 20°C-25°C (68CF-77°F). Excursions permitted between 15°C-30°C (59°F-86°F). See USP Controlled Room Temperature.”

The application originally proposed no control for particle size distribution (PSD) in the drug substance specifications. The 10 commercial drug substance batches manufactured to date have a very tight D₉₀ of (b) (4) mm. The developmental batches and pivotal batches had a D₉₀ range of (b) (4) mm.

The dissolution method is not discriminating to PSD. However, even though this is a BCS Class II product, the product dissolves under physiological pH very quickly (>90% by 10 minutes). The specification for the dissolution method is Q = (b) (4) % at 15 minutes.

The CMC team discussed the controls on drug substance PSD during the CMC Midcycle Meeting held on 3/20/23, as well as via email communications dated 3/20/23, 5/14/23, and 5/15/23. The drug substance manufacturing process appears to be under control. There is not an apparent product quality risk the review team could use to compel PSD monitoring in the specifications. The team agreed that any potential future risk may be controlled by providing comments under the post-approval lifecycle considerations.

During lifecycle management, if the applicant makes manufacturing process, scale, or site changes the applicant should provide data to compare PSD pre- and post-change. A comparability protocol was deemed to be too rigid of a requirement for this low risk.

The application includes a comparability protocol (b) (4) via a CBE-30. This protocol can be approved with the NDA.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Ogsiveo (nirogacestat) tablets is a gamma secretase inhibitor indicated for the treatment of adults with desmoid tumors. Desmoid tumors are also referred to as aggressive fibromatosis. They are rare, locally aggressive, slow growing soft tissue tumors that can cause severe pain, functional

impairment, nerve damage, and bowel obstruction or perforation by infiltrating or exerting mass effects on vital structures. There is currently no approved therapy for desmoid tumors or standard of care for patients with advanced progressing tumors. The 50 mg tablets will be administered orally at 150 mg twice daily until disease progression or unacceptable toxicity.

The drug product is composed of compendial excipients, manufactured from conventional manufacturing processes, stored in standard presentations for solid oral dosage forms, and stored at controlled room temperature. No product quality issues related to identity, assay, purity, or quality were identified during review.

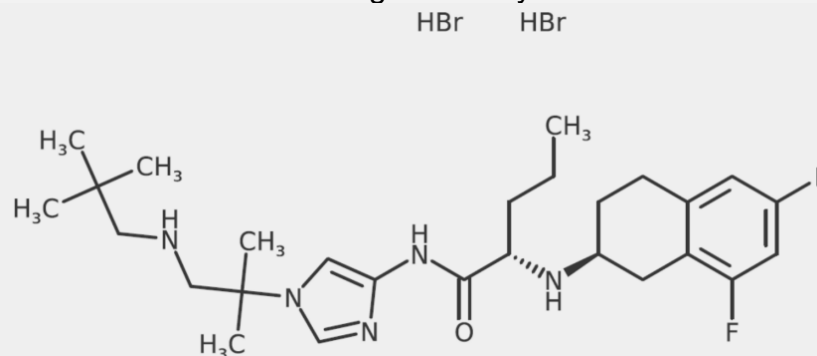
Proposed Indication(s) including Intended Patient Population	Treatment of adults with desmoid tumors
Duration of Treatment	Treat until disease progression or unacceptable toxicity
Maximum Daily Dose	150 mg PO BID
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

Nirogacestat hydrobromide is the USAN name for the drug substance (DS). Nirogacestat hydrobromide is a white to off-white powder and a crystalline substance. Nirogacestat hydrobromide drug substance is a salt containing two hydrogen bromide molecules.

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The manufacturing process for nirogacestat hydrobromide described in this NDA produces (b) (4) form referred to as (b) (4) is the (b) (4) stable solid-state form of the DS. Crystallization experiments identified approximately ten materials beside (b) (4) including (b) (4) material. However, (b) (4) experiments with the other materials produced only (b) (4)

Nirogacestat hydrobromide is optically active. It contains two chiral centers. The DS is the S,S enantiomer. The R,R enantiomer and the diastereomers (R,S and S,R) are controlled in the release specification for nirogacestat hydrobromide DS at the level of Not More Than (b) (4) % w/w.

Nirogacestat hydrobromide is manufactured using (b) (4)

Nirogacestat hydrobromide drug substance is controlled using a specification that contains tests for Identification using IR spectroscopy and HPLC retention time, solid state form using XRPD, Assay by HPLC with UV detection, and impurities using three different analytical procedures. One of these three procedures uses HPLC with UV detection for identification, assay and determination of six specified impurities, a second one uses HPLC with UV detection for determination of two specified impurities which co-elute using the other procedure, and a third uses HPLC with UV detection for chiral impurities (the enantiomer and diastereomers). The specification also includes tests for Elemental Impurities, Residual Solvents, Residual (b) (4), (b) (4), and Water.

Nirogacestat hydrobromide drug substance is packaged in (b) (4)

The retest period for nirogacestat hydrobromide drug substance is (b) (4) months when stored in the indicated packaging between (b) (4). The retest period is supported by stability data with storage through (b) (4) months at the ICH Controlled Room Temperature storage condition (CRT)

(25°C/65%RH) and (b) (4) months storage at the ICH Accelerated condition (ACC) (40°C/75%RH), generated from samples of three batches of DS produced at about ½ commercial scale, and data through (b) (4) months storage at CRT and (b) (4) months at ACC generated from five (5) batches of DS produced at commercial scale. Nirogacestat hydrobromide DS does not exhibit degradation after exposure to light degradation conditions described in ICH Q1B. It is concluded that nirogacestat hydrobromide drug substance is not light sensitive under the recommended storage conditions.

Drug Product: Adequate

The Applicant submitted this 505(b)(1) NDA 217677 for Ogsiveo® (nirogacestat) Tablets, 50 mg indicated for treatment of adult patients with desmoid tumors. Nirogacestat is a gamma secretase inhibitor. The proposed Ogsiveo® (nirogacestat) film-coated, debossed, Immediate-Release 50 mg Tablets, are prepared from (b) (4) (as free base), which corresponds to (b) (4) as the dihydrobromide salt. The film-coated tablets intended for oral administration. Each tablet contains 50 mg nirogacestat as 66.525 mg nirogacestat dihydrobromide. They are debossed with “50” on one face and plain on the other face. The tablets are comprised of the active ingredient and compendial excipients. The pivotal clinical trial formulation and commercial presentation have the same tablet core.

The tablets are controlled by specifications for appearance, identity (HPLC and IR), assay, individual/total impurities, dissolution, content uniformity, total aerobic microbial count, total combined yeast/mold count, and *E. coli*. There are no specified impurities as none of the drug substance process impurities are also drug product degradation products.

The Ogsiveo® (nirogacestat) tablets are available in (b) (4) 180-count configurations in HDPE bottles with induction seals and CR closures. All container materials comply with the requisite 21 CFR 177.1520 and 21 CFR 178.3297 and testing monographs USP <661.1> and <671>. 24 months of long-term stability data at 25°C/60%RH and 6 months of accelerated stability data at 40°C/75%RH is available for three registration batches in the 180-count configuration. (b) (4)

(b) (4) A
36-month shelf life is granted the commercial product (b) (4). No special storage conditions are required. The tablets are labeled for storage “at 20°C-25°C (68CF-77°F). Excursions permitted between 15°C-30°C (59°F-86°F). See USP Controlled Room Temperature.”

Labeling: Adequate

Minor edits were requested during labeling negotiation including alphabetizing the excipients in the formulation and including the appearance, solubility and pKa information for the drug substance in Section 11 of the label. Section 16 was edited to include a statement that the closure is a child-resistant configuration. The container labels include salt equivalence statements.

Manufacturing: Adequate

Nirogacestat tablets 50 mg are immediate release film coated tablets intended for oral administration. The API load is (b) (4) % (w/w).

Process: The manufacturing process is (b) (4)

The intended commercial manufacturing batch size is identical to exhibit batches. The manufacturing equipment proposed for commercial batches are of same size and operating principle as of the exhibit batches. All clinical studies were conducted using drug product manufactured at the commercial manufacturing site (b) (4). No changes in manufacturing process and formulation are identified from clinical to registration and proposed commercial batches.

Nirogacestat tablets are manufactured by (b) (4)

Refer to the Executive Summary regarding internal CMC discussions regarding the control of the drug substance particle size distribution on the manufacturing and control of the drug product.

The applicant submitted a comparability protocol describing their intent on a planned post-approval change to (b) (4)

(b) (4) nirogacestat 50 mg tablets (3.2.R). Per Agency's recommendation, the sponsor agreed to submit a CBE 30 to obtain Agency's approval (b) (4).

The manufacturing process is Adequate to support the commercial manufacturing of Nirogacestat tablets, 50 mg.

Facilities: All manufacturing facilities including testing and packaging sites proposed for the commercial manufacturing of Nirogacestat tablets 50 mg are found acceptable based on GMP compliance and firm's prior experience in performing the proposed responsibilities. No preapproval inspection was recommended for any facility. The primary drug product manufacturing site is (b) (4). The drug substance manufacturing site is (b) (4). The OMIR is recommended to Approve.

Biopharmaceutics: Adequate

This Biopharmaceutics Review focused on evaluating the in vitro dissolution method and acceptance criterion as a quality control (QC) test, and the bridging between the clinical and the proposed to-be-marketed drug product. The Applicant developed an in-house dissolution method and submitted a Dissolution Method Development Report investigating the selection of each parameter. Based on the dissolution data and information submitted, the following dissolution method and acceptance criterion are found acceptable for the Quality Control (QC) test of Ogsiveo® (Nirogacestat) Tablets, 50 mg, at batch release and on stability:

Approved Dissolution Method and Acceptance Criterion for Ogsiveo® (Nirogacestat) Tablets, 50 mg				
Apparatus	Speed	Volume/Temp	Medium	Acceptance Criterion
USP II (Paddle)	75 rpm	500 mL/ 37 °C	pH 1.2 (HCl buffer)	Q = ^{(b) (4)} % at 15 min

The Applicant used uncoated tablets for the blinded phase of Pivotal Study NIR-DT-301 and film-coated tablets for the open-label extension phase of the same study. There were no changes to the formulation (except non-functional coating), manufacturing process, or manufacturing site between the clinical batches (e.g., uncoated tablet; batch# 9111) versus the registration /proposed commercial batches (e.g., film-coated tablet; batch# 1140X); comparative in vitro dissolution profile/data were needed using multi-pH media (e.g., pH 1.2 [proposed QC], pH 4.5 and pH 6.8) to bridge the uncoated clinical tablets with the proposed commercial film coated product. The Applicant’s dissolution data showed a comparatively similar dissolution profile across all pH conditions. The clinical batches (e.g., uncoated tablet; batch# 9111) and registration/proposed commercial batch (e.g., film-coated tablet; batch# 1140X) are deemed adequately bridged.

Microbiology (if applicable): N/A

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, stability	(b) (4)	Low	(b) (4)	Low	
Physical Stability		Low		Low	
Content Uniformity	(b) (4)	Low		Low	
Microbial Limits		Low		Low	
Dissolution	The drug substance has pH-dependent solubility, that decreased with increase in pH	Medium		Low	
Content Uniformity, dissolution	(b) (4)	Low		Low	

¹ The Applicant indicates that they were initially pursuing "Q=(b) (4) min" during the developmental/ IND phase

			(b) (4)		
Content Uniformity, dissolution, Assay	(b) (4)	Medium		Low	
Content Uniformity, dissolution, Assay	(b) (4)	Medium		Low	

			(b) (4)		
Dissolution	(b) (4)	Low		Low	

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: Olen Stephens 5/23/2023

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate pending labeling negotiations, which occur after the completion of the initial labeling review.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s) ¹	Adequate	OGSIVEO™ (nirogacestat) tablets
Route(s) of administration	Adequate	For oral use
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	Tablets: 50 mg
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	Adequate	Established in section 3 and section 11.

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

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	Adequate	Swallow whole and do not break or chew the tablets.
For parenteral products: include statement: <i>"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"</i>	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	

For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement <i>“DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.x”</i> with x numerical citation to <i>“OSHA Hazardous Drugs”</i>.	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Tablets
Strength(s) in metric system	Adequate	50 mg
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	Adequate	50 mg nirogacestat (b) (4)
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	Round, orange, film-coated, and debossed with “50” on one face.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 11 (DESCRIPTION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	OGSIVEO (nirogacestat) tablets
Dosage form(s) and route(s) of administration	Adequate	Oral tablets
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP . For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	Adequate	Each tablet contains 50 mg nirogacestat as 66.525 mg nirogacestat hydrobromide
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	The applicant was instructed to reorganize the inactive ingredients in alphabetical order and this has been resolved
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	Inhibitor of gamma secretase.
Chemical name, structural formula, molecular weight	Adequate	Provided
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Adequate	The applicant was asked to include this information during labeling negotiation and the applicant included appearance, solubility, and pKa information

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	Adequate	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	Tablets
Strength(s) in metric system	Adequate	50 mg
Available units (e.g., bottles of 100 tablets)	Adequate	(b) (4) 180-tablets per bottle
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	Orange, film-coated, debossed with a "50" on one face
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.x" with x numerical citation to "OSHA Hazardous Drugs."	N/A	

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	Store at 20°C-25°C (68CF-77°F). Excursions permitted between 15°C-30°C (59°F-86°F). See USP Controlled Room Temperature.
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: <i>"Not made with natural rubber latex. Avoid statements such as "latex-free."</i>	N/A	
Include information about child-resistant packaging	Adequate	The applicant was instructed to add the statement that the closure is a child-resistant configuration.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	Manufactured for SpringWorks Therapeutics Inc. (b) (4) 

2.0 PATIENT LABELING

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

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

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels



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

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ³ , (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	50 mg
Route(s) of administration	Adequate	Oral administration is implied by the tablet formulation
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP .	Adequate	Equivalence statement provided on side panel
Net contents (e.g., tablet count, volume of liquid)	Adequate	Provided
“Rx only” displayed on the principal display	Adequate	Present
NDC	Adequate	Provided
Lot number and expiration date	Adequate	Space indicated
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Provided
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a “Not for direct infusion” statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	Applicant instructed to add bar code to product label.

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

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

Assessment of Carton and Container Labeling: Adequate

All changes made to the current label were communicated in the 74-day filing letter and are consistent with the OPQ labeling template

ITEMS FOR ADDITIONAL ASSESSMENT

The product labels include Country of Origin statements. This claim is being confirmed as I believe the Country of Origin is based on the drug substance manufacturing site and not the drug product manufacturer or labeling site.

Overall Assessment and Recommendation:

Primary Labeling Assessor Name and Date: Olen Stephens 3/21/2023

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



Olen
Stephens

Digitally signed by Olen Stephens
Date: 5/15/2023 05:50:49PM
GUID: 508da71e00029e680c3cf42984dfa0ee



Xing
Wang

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Date: 5/16/2023 09:11:01AM
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CHAPTER VI: BIOPHARMACEUTICS

NDA Number	NDA 217677-ORIG-1; 505(b)(1)
Submission History ¹	NDA 217677—Original Submission 2/10/2023 (SDN-9): Response to the CMC IR regarding the proposed Comparability Protocol 4/19/2023 (SDN-31): Response to the Biopharmaceutics IR regarding supportive comparative dissolution data between the coated vs uncoated tablets used in the pivotal study
Drug Product Name/ Strength	Ogsiveo® (Nirogacestat) Tablets, 50 mg
Route of Administration	Oral
Applicant Name	SpringWorks Therapeutics Inc.
Therapeutic Classification/ OND Division	DO3
Proposed Indication	Treatment of adult patients with desmoid tumors (DT), (b) (4)
Primary Reviewer	Min Kang, PharmD, MS
Secondary Reviewer	Anitha Govada, PhD
Assessment Recommendation	Adequate

EXECUTIVE SUMMARY:

The Applicant submitted this 505(b)(1) NDA 217677 for Ogsiveo® (Nirogacestat) Tablets, 50 mg indicated for treatment of adult patients with desmoid tumors. The proposed Ogsiveo® (Nirogacestat) film-coated, debossed, Immediate-Release 50 mg Tablets, are prepared from (b) (4) (as free base), which corresponds to (b) (4) as the dihydrobromide salt.

Assessment Summary:

This Biopharmaceutics Review focuses on evaluating (1) the in vitro dissolution method and acceptance criterion as a quality control (QC) test, and (2) the bridging between the clinical and the proposed to-be-marketed drug product.

¹ IND 1382107—Summary of Submission History by Dates: <\\CDSESUB1\EVSPROD\nda217677\0005\m1\us\1-6-3-correspondence-regarding-meetings-final-2022-12-22.pdf>

- In Vitro Dissolution Method and Acceptance Criterion:**

The Applicant developed an in-house dissolution method and submitted a Dissolution Method Development Report investigating the selection of each parameters. Based on the dissolution data and information submitted, the following dissolution method and acceptance criterion are found acceptable for the Quality Control (QC) test of Ogsiveo® (Nirogacestat) Tablets, 50 mg, at batch release and on stability:

Approved Dissolution Method and Acceptance Criterion for Ogsiveo® (Nirogacestat) Tablets, 50 mg				
Apparatus	Speed	Volume/ Temp	Medium	Acceptance Criterion
USP II (Paddle)	75 rpm	500 mL/ 37 °C	pH 1.2 (HCl buffer)	Q = (b) (4) % at 15 min

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment	Comments
Dissolution	Medium	The drug substance has pH-dependent solubility, that decreased with increase in pH	Low	(1) Adequately controlled PSD ² (2) Tightened dissolution acceptance criterion from “Q= (b) (4) % in (b) (4) min ³ ” to “Q= (b) (4) % in 15 min”

- Product Bridging:**

The Applicant has used uncoated tablets for the blinded phase of Pivotal Study NIR-DT-301 and film-coated tablets for the open-label extension phase of the same study. Although, there were no changes to the formulation (except non-functional coating), manufacturing process, nor manufacturing site between the clinical batches (e.g., uncoated tablet; batch# 9111) versus the registration /proposed commercial batches (e.g., film-coated tablet; batch# 1140X), the comparative in vitro dissolution profile/data were needed using multi-pH media (e.g., pH 1.2 [proposed QC], pH 4.5 and pH 6.8) in order to bridge the uncoated clinical tablets with the proposed commercial film coated product. The Applicant’s provided dissolution data showed a comparatively similar dissolution profile across all pH conditions tested, therefore, the clinical batches (e.g., uncoated tablet; batch# 9111) and the registration /proposed commercial batch (e.g., film-coated tablet; batch# 1140X) are deemed adequately bridged.

² See Appendix II

³ The Applicant indicates that they were initially pursuing “Q= (b) (4) min” during the developmental/ IND phase

List of Submissions Being Assessed:

IND/NDA	eCTD sequence #	Date of response	Document
NDA	0001	12/27/2022	Original NDA submission
NDA	0009	02/10/2023	Quality/Response ⁴ to the CMC IR regarding the proposed Comparability Protocol
NDA	0031	04/19/2023	Quality/Response ⁵ to the Biopharmaceutics IR regarding supportive comparative dissolution data between the coated vs uncoated tablets used in the pivotal study

Concise Description of Outstanding Issues (list bullet points with key information and update as needed):

None.

Overall Biopharmaceutics Recommendation:

From the Biopharmaceutics perspective, NDA 217677-ORIG-1 for Ogsiveo® (Nirogacestat) Tablets, 50 mg, is **Adequate** and recommended for Approval.

⁴ M.1.11.1 (SDN-9): <\\CDSESUB1\EVSPROD\nda217677\0009\m1\us\response-to-fda-ir-27-jan-2023.pdf>

⁵ M.1.11.1 (SDN-31): <\\CDSESUB1\EVSPROD\nda217677\0031\m1\us\response-to-fda-ir-final-2023-04-18.pdf>

BIOPHARMACEUTICS ASSESSMENT

B.1 BCS DESIGNATION

Assessment: N/A.

Solubility: The Applicant has submitted the solubility of Nirogacestate hydrobromide (drug substance) as shown in Table 1 below.

Table 1: Solubility (mg/mL) of Nirogacestat at 37°C at various pH

pH	Solubility (mg/mL)
1.2	25.86
4.5	11.55
5.0	12.16
5.5	2.43
6.0	0.31
6.8	0.02

Reviewer's comments:

A BCS designation is not requested by the Applicant, nor required by the FDA. Based on the submitted solubility data, this Reviewer considers nirogacestate hydrobromide as a drug substance with its pH-dependent solubility with higher solubility at lower pH condition such as between 1.2 to 6.0 and with lower solubility at and above pH 6.8. The drug product is an immediate release (IR) tablet dosage from designed to release drug at gastric pH condition. Therefore, the risk of drug release and bioavailability from this IR product at pH 1.2 is considered low. The risk is further mitigated by tight acceptance criterion for dissolution.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERION

Assessment: Adequate

Table 2: The Applicant's proposed dissolution method and the acceptance criterion for Nirogacestat Tablets, 50 mg.

Apparatus	Speed	Volume/ Temp	Medium	Acceptance Criterion
USP II (Paddle)	75 rpm	500 mL/ 37 °C	pH 1.2 (HCl buffer)	Q= ^(b) ₍₄₎ % at 15 min

(b) (4)

B. 2.3. Evaluation of discriminating ability: The Applicant investigated the dissolution method's discriminating ability against the following Critical Bioavailability Attributes [CBAs]: (i) Critical Material Attributes [CMAs] such as varying Particle Size, (ii) Critical Formulation Attributes [CFAs] such as varying amounts of the excipients [e.g., (b) (4)], and (iii) Critical Processing Parameters [CPPs] such as varying level of (b) (4) process and (b) (4) times; see **Table 4** below.

Figure 4: Dissolution profile of Nirogacestat 50 mg Tablets containing varying PSD

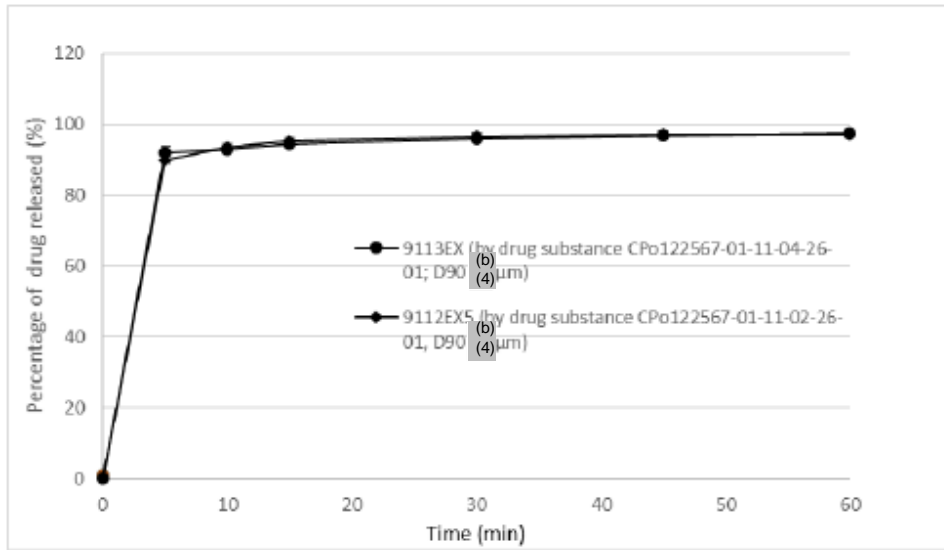


Figure 5: Dissolution profile of Nirogacestat 50 mg Tablets of varying Tablet Hardness

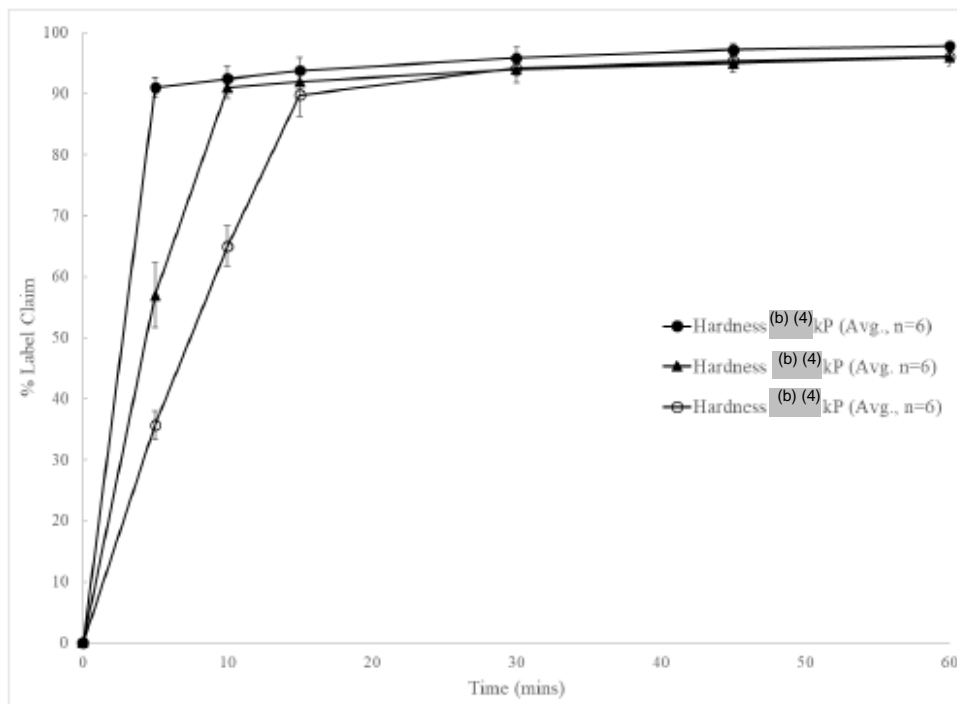


Figure 6: Dissolution profile of Nirogacestat 50 mg Tablets with varying (b) (4)

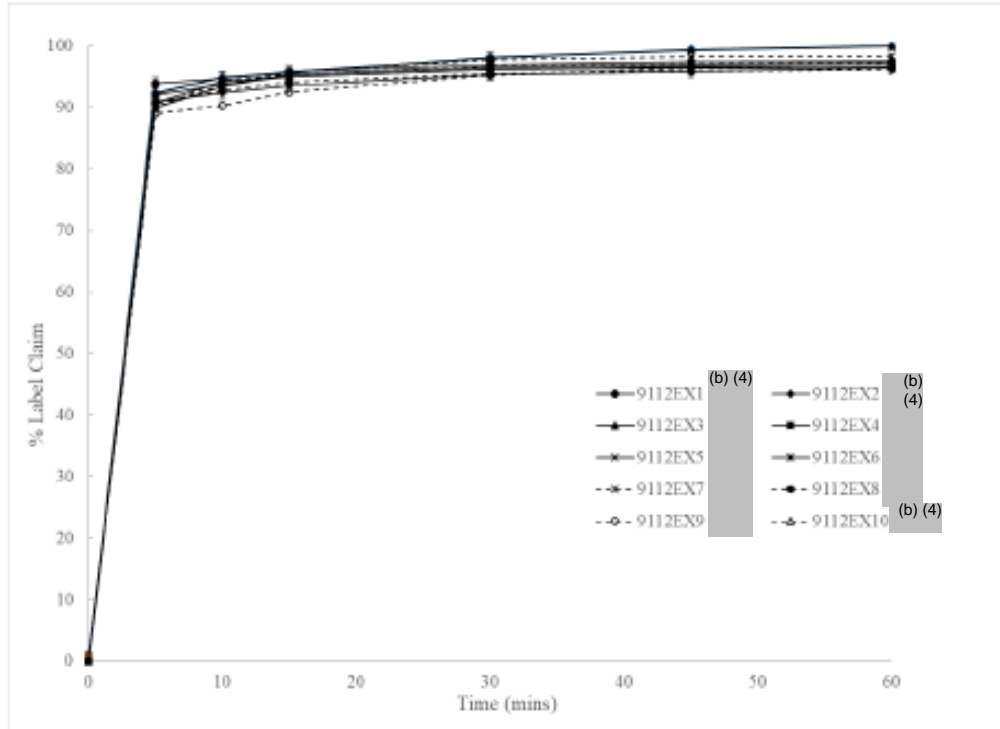


Figure 7: Dissolution profile of Nirogacestat 50 mg Tablets with varying Times (b) (4)

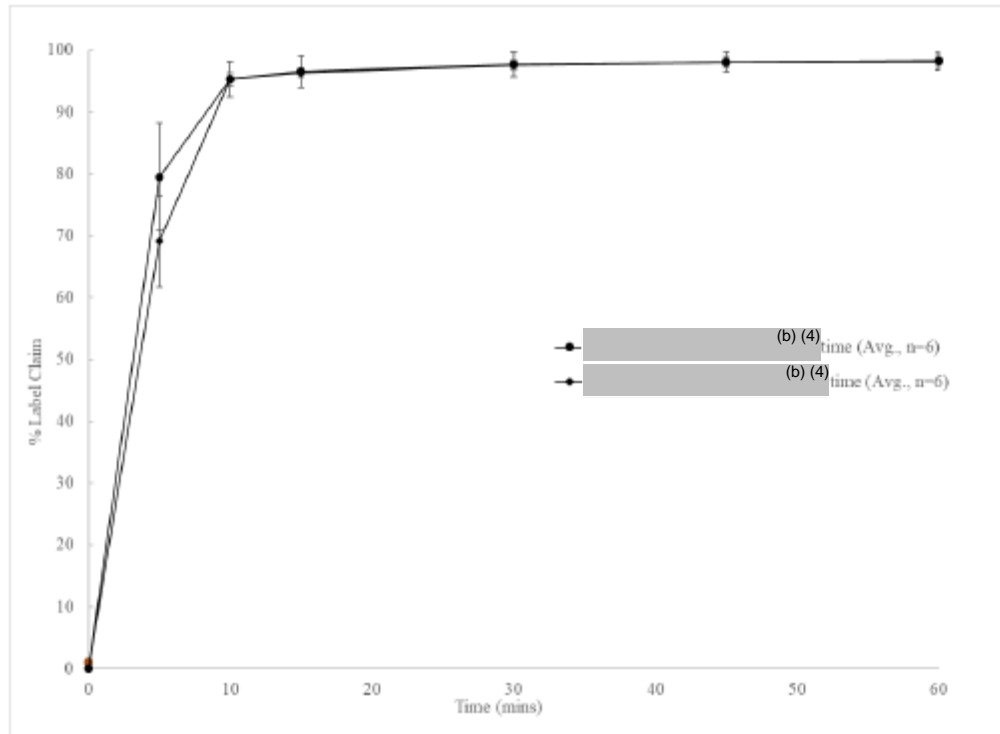


Figure 8: Dissolution profile of Nirogacestat 50 mg Tablets with Multi-factor formulation/processing variations (described in Table 4)

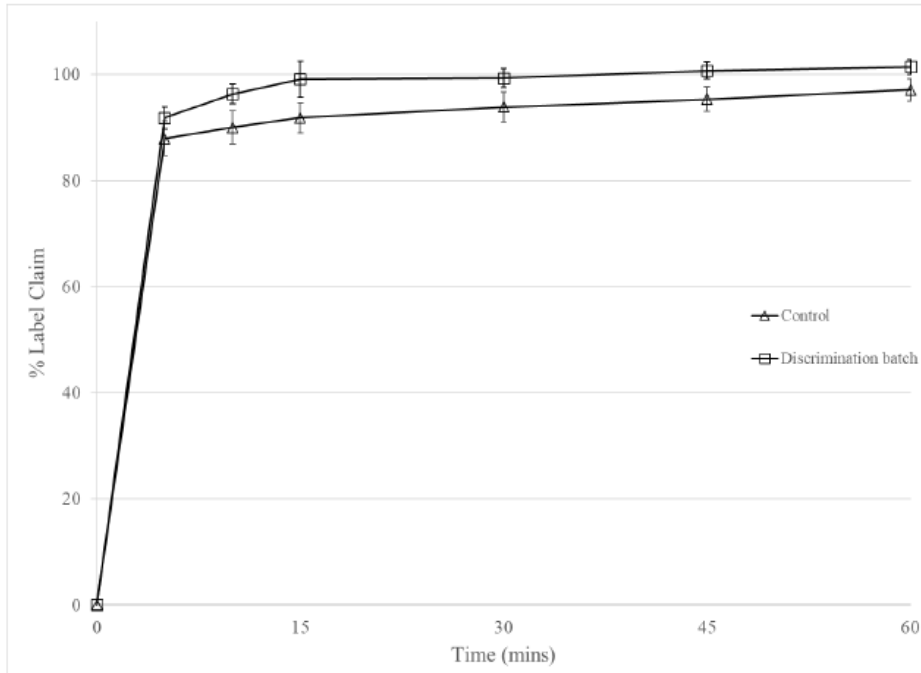


Table 4: Multi-factor formulation/processing variations

	(b) (4)
Batch 1 (Control)	
Batch 2 (Variation)	

Reviewer's comments:

As discussed above, this reviewer notes that the Applicant had several communications with FDA during the IND development phase of their QC dissolution method to find the dissolution method most suitable for their proposed drug product. The proposed drug substance is of low solubility at pH above 6.8 with pH-dependent solubility profile exhibiting higher solubility at lower pH values and vice versa. Dissolution medium (b) (4)

given that the proposed dosage form is of an immediate-release with t_{max} of about 1 hour (0.5-1.5 hr), using a more physiologically-relevant pH (i.e., 0.1 N HCl which is the closest to an acidic stomach pH [pH 1-2] where the drug product would dissolve) as the dissolution medium was deemed more

appropriate for the proposed drug product. The Applicant has investigated paddle speeds (b) (4)

(b) (4) 75 rpm was selected because of the minimal coning/variability shown at this speed.

Given the low solubility of the drug substance and in an effort to mitigate the risk, it was important that the Applicant's proposed dissolution method is capable of showing discriminating ability. However, of the following identified Critical Bioavailability Attributes [CBAs] [e.g., (i) Critical Material Attributes [CMAs] such as varying Particle Size, (ii) Critical Formulation Attributes [CFAs] such as varying amounts of the excipients [e.g., (b) (4)], and (iii) Critical Processing Parameters [CPPs] such as varying level of (b) (4) process and (b) (4) times], the Applicant was not able to demonstrate the discriminating ability due to rapid drug release in less than 15 minutes. Because the dissolution method cannot discriminate the batches produced with different particle size, control of consistent particle size at the drug substance specification level was critical to ensure the drug release from the product and the Applicant was asked to justify their DS particle size control strategy during the IND phase.

Based on the totality of the submitted data/information available in the NDA submission, after having discussed this with the CMC team several times (see Appendix II), it was concluded that the proposed drug substance manufacturing process appears to be under tight control consequently mitigating the risk as it relates to the PSD. Refer to the Drug Product, Drug Substance, and OPMA Reviews for more information. Overall, this reviewer deems that the Applicant's proposed dissolution method [USP Apparatus II (Paddle) in 500 mL of 0.1 N HCl (pH 1.2) at 75 rpm] is acceptable for Quality Control at batch release and on stability with a tightened dissolution acceptance criterion (see Section B.2.4. below).

B.2.4. Dissolution Data and Acceptance Criterion:

Table 5: Registration Batches

Batch Number	Date of Manufacture	Site of Manufacture	Batch Size	Use of Batch	Drug Substance Manufacturer	Drug Substance Input Batch
1140X	Sept-2021	(b) (4)	(b) (4) g	PPQ/Intended Commercial	(b) (4)	CPo122567-03-11-03-28-01
1141X	Oct-2021		g	PPQ/Intended Commercial		CPo122567-03-11-04-28-01
1142X	Oct-2021		g	PPQ/Intended Commercial		CPo122567-03-11-05-28-01
9116X	Mar-2020		g	Registration/Clinical		CPo122567-01-11-02-26-01
9117X1	Mar-2020		g	Registration/Clinical		CPo122567-01-11-03-26-01
9118X	Mar-2020		g	Registration/Clinical		CPo122567-01-11-04-26-01

Table 6: Dissolution Profile

Batch Number:		1140X	1141X	1142X	9116X	9117X1	9118X
Usage:		PPQ/Intended Commercial			Registration Stability/CTM		
Dissolution Time (min)	Acceptance Criteria	%Label claim, n = 12					
10	(b) (4)	(b) (4)					
		Mean: 96	Mean: 95	Mean: 96	Mean: 93	Mean: 96	Mean: 92
15		(b) (4)					
		Mean: 97	Mean: 96	Mean: 97	Mean: 95	Mean: 97	Mean: 94
30		(b) (4)					
		Mean: 98	Mean: 97	Mean: 98	Mean: 97	Mean: 99	Mean: 97
45		(b) (4)					
		Mean: 99	Mean: 98	Mean: 98	Mean: 98	Mean: 99	Mean: 98
60		(b) (4)					
		Mean: 99	Mean: 99	Mean: 99	Mean: 98	Mean: 100	Mean: 98

Reviewer’s Comments:

The Applicant has proposed a dissolution acceptance criterion of “Q= (b) (4)% in 15 minutes”. Based on the submitted dissolution data of the pivotal/clinical and registration batches (see **Table 6**), the Applicant’s proposed acceptance criterion is deemed adequate to mitigate risk from biopharmaceutics perspective.

B.3. PRODUCT BRIDGING

Assessment: Adequate

It was noted that the Applicant has used uncoated tablets for the blinded phase of Pivotal Study NIR-DT-301 and film-coated tablets for the open-label extension phase of the same study. Although, there were no changes to the formulation, manufacturing process, nor manufacturing site between the clinical batches (e.g., uncoated tablet; batch# 9111) versus the registration /proposed commercial batches (e.g., film-coated tablet; batch# 1140X), the comparative in vitro dissolution profile/data were needed using multi-pH media (e.g., pH 1.2 [proposed QC], pH 4.5 and pH 6.8) in order to bridge the two. Therefore, an Information Request #2 was sent out to the Applicant on 3/28/23 (see Appendix) requesting additional data, and in response dated 4/19/23, the Applicant has provided with the requested data which showed a comparatively similar dissolution across all pH (e.g., very rapid dissolution [$\geq 85\%$ dissolution in 15 minutes] in pH 1.2 and pH 4.5 media as well as a comparatively similar dissolution in pH 6.8 with f_2 value of about 75). Therefore, from biopharmaceutics perspective, the clinical batches (e.g., uncoated tablet; batch# 9111) and the registration /proposed commercial batch (e.g., film-coated tablet; batch# 1140X) are deemed adequately bridged.

Table 7: Nirogacestat 50 mg Tablet Batches Evaluated

Batch	Type	Date of Manufacture	Age of Batch at Time of Testing	Storage Condition
9111	Uncoated tablets	May-2019	• pH 1.2: 40 months • pH 4.5: 47 months • pH 6.8: 47 months	Ambient conditions
1140X	Film-coated tablets	Sept-2021	• pH 1.2: 0 months • pH 4.5: 17 months • pH 6.8: 17 months	Ambient conditions

Table 8: Mean dissolution profiles for Nirogacestat 50 mg Batch# 9111 (uncoated) versus Batch# 1140X (Film-coated Tablet) at varying pH, N=12 (%RSD)

Time (min)	pH 1.2 HCl Buffer Mean (%RSD)		pH 4.5 Acetate Buffer Mean (%RSD)		pH 6.8 Phosphate Buffer Mean (%RSD)	
	Uncoated	Film-coated	Uncoated	Film-coated	Uncoated	Film-coated
10	99 (3)	96 (4)	87 (2)	91 (6)	13 (8)	13 (7)
15	100 (1)	97 (3)	87 (1)	92 (6)	14 (6)	13 (7)
30	100 (1)	98 (3)	88 (1)	93 (5)	15 (6)	13 (7)
45	100 (1)	99 (2)	90 (2)	94 (5)	17 (4)	13 (7)
60	100 (1)	99 (2)	90 (1)	95 (5)	17 (5)	12 (7)

B.4. BIOWAIVER REQUEST

Assessment: Not Applicable

The NDA does not contain a biowaiver request. Only one dosage strength (50 mg) is being sought for approval and thus a biowaiver request is not applicable to the application.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

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/s/

OLEN M STEPHENS

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CMC recommends approval with 36-month shelf life at CRT.