CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216203Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	216203
Applicant Name	Lexicon Pharmaceuticals, Inc.
Drug Product Name	(b) (4) (sotagliflozin)
Dosage Form.	Tablet
Proposed Strength(s)	200 mg and 400 mg
Route of Administration	Oral
Maximum Daily Dose	400 mg
Rx/OTC Dispensed	Rx
Proposed Indication	Indicated to: • Reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with heart failure, including those with acute or worsening heart failure. • Reduce the risk of cardiovascular death, hospitalization for heart failure, urgent heart failure visit, nonfatal myocardial infarction, and nonfatal stroke in adults with type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors, including a history of heart failure.
Drug Product Description	Each 200 mg tablet is an oval, blue film-coated tablet imprinted in black ink with “LX200” on one side. Each 400 mg tablet is an oval, yellow film-coated tablet debossed with 2457 on one side.

Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F)		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Joseph Leginus OPQ/ONDP/DNDAPI/NDB3	Sithamalli Chandramouli OPQ/ONDP/DNDAPI/NDB3
	Drug Product/ Labeling	Ali Mohamadi OPQ/ONDP/DNDPIII/NDPB5	Theodore Carver OPQ/ONDP/DNDPIII/NDPB5
	Manufacturing	Alexander Gontcharov OPQ/OPMA/DPMAIII/PMB7	Feiyan Jin OPQ/OPMA/DPMAIII/PMB7
	Biopharmaceutics	Zhuojun Zhao OPQ/ONDP/DB/BB3	Haritha Mandula OPQ/ONDP/DB/BB3
	Microbiology	N/A	
	Other (specify):	N/A	
	RBPM	Grafton Adams OPQ/OPRO/DRBPMI/RBPMB2	
	ATL	Theodore Carver OPQ/ONDP/DNDPIII/NDPB5	
Consults	None.		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: An expiry dating period of 24 months is granted when the drug is stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

b. Additional Comments for Action: None.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1.) Background: Lexicon Pharmaceuticals, the Applicant, has submitted this 505(b)(1) new drug application (NDA) seeking marketing approval of sotagliflozin tablets. The Applicant previously withdrew this NDA on February 28, 2022; there were no filing issues from the OPQ perspective at that time. Sotagliflozin is a new molecular entity proposed as a sodium-glucose cotransporter 2 (SGLT2) inhibitor and is indicated (1) to reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with type 2 diabetes mellitus (b) (4) (b) (4) worsening heart failure regardless of left ventricular ejection fraction; or (2) to reduce the risk of cardiovascular death, hospitalization for heart failure, urgent heart failure visit, nonfatal myocardial infarction, and nonfatal stroke in adults with type 2 diabetes mellitus and chronic kidney disease with other cardiovascular risk factors, including a history of heart failure (b) (4) (b) (4). This application includes the results of pivotal Phase 3 clinical studies to support approval for the proposed indications.

2.) Drug Substance:
Sotagliflozin drug substance has a molecular formula of $C_{21}H_{25}ClO_5S$ and a molecular weight of 424.9 g/mol. It is a small, neutral (non-salt) compound isolated as a white to off-white solid and is not hygroscopic or light sensitive. The drug substance is manufactured in a (b) (4) (b) (4) The molecule has 5 asymmetric centers and is (b) (4) (b) (4) (b) (4) The structure of sotagliflozin has been adequately established using a combination of IR, MS, NMR (1H and 13C), UV, and Elemental Analysis characterization methods. X-ray (single crystal) supports the assignment of the absolute configurations at the five stereogenic centers of sotagliflozin. Risk assessments provided for elemental impurities, potential genotoxic impurities, and potential (b) (4) support a low risk for presence of these impurities in the drug substance. The specification includes adequate tests to support the potency, purity, and quality of the drug substance. In response to an information request recommend that the Applicant (b) (4) the Particle Size Distribution (PSD) from NMT (b) (4) µm for D90, based on PSD D90 values (approximately (b) (4) µm to (b) (4) µm) for relevant clinical drug substance batches, the Applicant revised the drug

substance PSD D90 value to NMT (b) (4) µm. Stability results support a retest period of (b) (4) months for sotagliflozin when stored at (b) (4) (b) (4) (b) (4).

3.) *Drug Product:* The drug product is immediate release, film-coated tablets provided in two strengths, 200 mg and 400 mg. All excipients are compendial (USP/NF), including components of the printing ink. The drug product specification includes adequate tests to ensure the potency, purity, and quality of the drug product. All potential drug product degradants are controlled at the ICH Q3B-recommended limit of 0.2% and there are no specified related substances. Data provided by the Applicant support a low risk for the presence of potential elemental impurities and (b) (4) in the drug product. During the review, the Applicant provided data to support resolution of a tablet (b) (4) (b) (4) Based on these data, the 200 mg tablet will have an ink code imprint, whereas the 400 mg tablets will be debossed. For the 200 mg tablet strength, the Applicant provided up to 67 months long-term stability data for three primary stability batches and 18 months stability data for three validation batches, stored at 25ºC/60%RH; for the 400 mg tablet strength, the Applicant provided 12 months of stability data for 3 primary stability batches stored at 30ºC/75% RH, in addition to 6 months accelerated stability data and other supporting stability data. Based on the available data, the drug product review concluded that a shelf life of 24 months when the drug product is stored at 20ºC to 25ºC is granted.

4.) *Manufacturing:* The immediate release coated tablets of 200- and 400-mg strength are manufactured using a (b) (4) The manufacturing process was deemed adequate after the Applicant provided satisfactory responses to information requests regarding the manufacturing equipment and process parameters and revised the in-process tests to provide improved controls, including tests for (b) (4) Microbiological quality and controls were assessed during review of the manufacturing process. With respect to (b) (4) observed during manufacturing of the primary stability batches, the Applicant provided satisfactory

responses with respect to CAPAs, process optimization, and in-process testing.

Facilities: All manufacturing facilities have been found acceptable to perform their intended functions for commercial manufacture under this NDA. See Table 2, page 2 of the Manufacturing Integrated Assessment for the basis for the approval status for each facility.

1.) *Biopharmaceutics:* The Biopharmaceutics review was focused on the evaluation and acceptability of the proposed quality control dissolution methods and acceptance criteria as well as the in vitro bridging study for the 200 mg and 400 mg tablets. The two dissolution methods developed for the tablets were found to be acceptable with the proposed conditions after review of the supporting information. The Applicant did not request an official BCS designation, but an in vitro study of intestinal permeability showed high permeability, and the Applicant stated that the sotagliflozin drug substance has low solubility and high permeability. The review concluded that adequate in vitro data were provided to support bridging of the 200 mg and 400 mg formulations.

2.) Quality Labeling: The quality labeling review concluded that the labeling will be adequate when the Applicant implements recommended revisions, which will be assessed during final labeling discussions.

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

Recommendation by Subdiscipline:

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

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

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: None.

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: This review is based on the amendment in sequence 0027

The CMC team added PI recommendations in the SP file.

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	Tradename (sotagliflozin) tablet, for oral use Adequate contingent on DMEPA accepting the tradename.
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: 200 mg and 400 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	N/A	

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

active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).		

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)	N/A	
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	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	N/A	

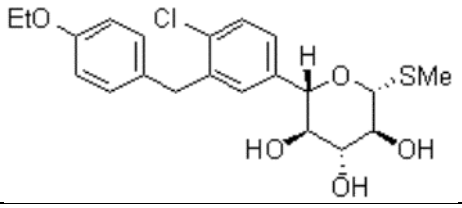
requirement may be applicable to another section of the PI (e.g., Section 11).		
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures"* with x numerical citation to "OSHA Hazardous Drugs".	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	Tablet
Strength(s) in metric system	Adequate	200 mg and 400 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).	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	Adequate per the revisions below: **TRADENAME 400 mg tablets are available as oval, yellow film-coated tablets debossed with 2457 on one side.**
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	TRADENAME tablets for oral administration, Sotagliflozin. Adequate contingent on DMEPA accepting the tradename
Dosage form(s) and route(s) of administration	Adequate	Tablet, for oral use
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	Adequate per revisions below: **The core of the tablet contains colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and talc.** **The film coating for the 200 mg tablet contains: indigo carmine aluminum lake, polyethylene glycol , polyvinyl alcohol (partly hydrolyzed), talc, and titanium dioxide.** **The film coating for the 400 mg tablet contains: hypromellose, lactose monohydrate, titanium dioxide, triacetin, and yellow iron oxide.** **The black printing ink contains ammonium hydroxide, black iron oxide, isopropyl alcohol, N-butyl alcohol, propylene glycol, and shellac.**

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	(b) (4)
Chemical name, structural formula, molecular weight	Adequate	The chemical name of sotagliflozin is (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triol. Its molecular formula is C21H25ClO5S and the molecular weight is 424.94. The structural formula is: 
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	N/A	Sotagliflozin is a white to off-white solid. It is practically insoluble in water.

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”)	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 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	200 mg and 400 mg
Available units (e.g., bottles of 100 tablets)	Adequate	• Bottles of 30 tablets • Bottles of 90 tablets
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	Adequate per revision below: **TRADENAME 400 mg tablets are available as oval, yellow film-coated tablets debossed with 2457 on one side**.
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	Adequate per revision below: **Revision: store at 20°C to 25°C; (68°F to 77°F) excursions permitted between 15°C and 30°C (59°F and 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: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling

1.2.6 Manufacturing Information After Section 17

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: Lexicon Pharmaceuticals, Inc. (The Woodlands, TX 77381)

2.0 PATIENT LABELING

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	TRADENAME (HOW-to-SAY-TRADE-NAME) (sotagliflozin)
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	N/A	
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	sotagliflozin
Alphabetical listing of inactive ingredients (if applicable)	Adequate	Adequate per revision below: **The core of the tablet contains colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and talc.** **The film coating for the 200 mg tablet contains: indigo carmine aluminum lake, polyethylene glycol , polyvinyl alcohol (partly hydrolyzed), talc, and titanium dioxide.** **The film coating for the 400 mg tablet contains: hypromellose, lactose monohydrate, titanium dioxide, triacetin, and yellow iron oxide.** **The black printing ink contains ammonium hydroxide, black iron oxide, isopropyl alcohol, N-butyl alcohol, propylene glycol, and shellac.**

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

Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Adequate	Manufactured for: Lexicon Pharmaceuticals, Inc. The Woodlands, TX, 77381.

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

(b) (4)

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

Item	Items in Proposed Labeling	Assessor's Comments about Carton Labeling
Established name[3], (font size and prominence)	Adequate	Trade name is acceptable contingent upon DMEPA confirmation. Adequate per revisions below: (b) (4) **1. For all carton and container labeling, remove the statement (b) (4) from the strength statement in the side panel ("Each tablet contains… (b) (4) (b) (4)) and keep this statement on the principal display panel only.** **2. For carton and container labels for the physician samples, we recommend that you include the route of administration on the principal display panel to match the current commercial carton/container label.**
Strength(s) in metric system	Adequate	200 mg and 400 mg

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

Route(s) of administration	Adequate	Adequate per revision below **1. For all carton and container labeling, remove the statement (b) (4) from the strength statement in the side panel ("Each tablet contains… (b) (4) (b) (4) and keep this statement on the principal display panel only.** **2. For carton and container labels for the physician samples, we recommend that you include the route of administration on the principal display panel to match the current commercial carton/container label.**
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Choose an item.	Bottle: 30 and 90 tablets Blister: Carton contains one blister of 7 tablets (b) (4)
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	200 mg: (b) (4) 400 mg: (b) (4)
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Store at 20°C to 25°C; (68°F to 77°F) excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

For injectable drug products for parenteral 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	

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.	Adequate	(b) (4) [redacted]
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*

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Adequate contingent upon accepting recommendations stated in this review. Note that, at the time of filing this review, the labeling review is in progress.

Primary Labeling Assessor Name and Date:

Ali Mohamadi, Ph.D., 1/11/2022

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

Ali Mohamadi

Digitally signed by Ali Mohamadi
Date: 1/13/2023 12:59:29PM
GUID: 508da6ea0002750ec7c6cb7cfc37f10e

Theodore Carver

Digitally signed by Theodore Carver
Date: 1/13/2023 01:00:38PM
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CHAPTER VI: BIOPHARMACEUTICS

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

Product Information	
NDA Number	216203
Assessment Cycle Number	001
Drug Product Name/ Strength	Sotagliflozin Tablets, 200 and 400 mg
Route of Administration	Oral
Applicant Name	Lexicon Pharmaceuticals, Inc
Therapeutic Classification/ OND Division	Division of Cardiology and Nephrology (DCN)
Proposed Indication	• Reduce the risk of cardiovascular death, hospitalization for heart failure (HF), and urgent heart failure visit in adults with heart failure, including those with acute or worsening heart failure • Reduce the risk of cardiovascular death, hospitalization for heart failure, urgent heart failure visit, nonfatal myocardial infarction, and nonfatal stroke in adults with type 2 diabetes mellitus (T2DM), chronic kidney disease, and other cardiovascular risk factors, including a history of heart failure.

Assessment Recommendation: **Adequate**

Assessment Summary:

Lexicon Pharmaceuticals, Inc submitted a 505(b) (1) application for the proposed Sotagliflozin Tablets, 200 and 400 mg for HF and T2DM indications. The proposed Sotagliflozin Tablets, 200 mg was previously submitted under NDA 210934 for Type 1 diabetes mellitus (T1DM) indication.

The Biopharmaceutics review is focused on the evaluation and acceptability of the proposed quality control dissolution methods and acceptance criteria as well as the formulation bridging in vitro study.

Dissolution method and Acceptance Criterion:

Based on the provided information, the proposed dissolution methods and dissolution acceptance criteria are found acceptable:

Dissolution Methods and Acceptance Criteria		
Strength	200 mg	400 mg
Medium	Purified water with 0.2% sodium lauryl sulfate	Purified water with 0.28% sodium lauryl sulfate

Apparatus	USP II (Paddle)	
Volume	900 mL	
Rotation Speed	75 RPM	
Temperature	37°C	
%Drug release	Q= (b) (4) % at 45 minutes	Q= (b) (4) % at 30 minutes

Bridging Formulations:
The Applicant also provided adequate in vitro dissolution data to bridge the formulations, DS substance sources and drug product manufacturers for the proposed Sotagliflozin Tablets, 200 and 400 mg.

List Submissions Being Assessed:

Document Assessed	Date Received
Original Submission (0001)	**12/30/2021**
Resubmission (0021)	**5/27/2022**

Highlight Key Issues from Last Cycle and Their Resolution: None

Concise Description of Outstanding Issues: None

B.1 BCS DESIGNATION

Solubility:
The Applicant provided equilibrium solubilities of the drug substance at 37°C as a function of pH in Table 1 and stated that no effect of pH is observed as drug substance, Sotagliflozin, is a non-ionizable molecule.

Table 1: Equilibrium Solubility of Sotagliflozin at 37°C as a Function of pH

Solvent pH (buffer)	Concentration after 24h[a] [mg/mL]
pH 1.2 (HCl + KCl)	0.039[b]
pH 4.5 (acetate buffer)	0.041[b]
pH 6.8 (phosphate buffer)	0.043[b]

[a] Performed by HPLC in triplicate on batch 201305230201.
[b] (b) (4)

Permeability:
The Applicant provided in vitro study of intestinal permeability in NDA 210934[1] and showed high permeability.

Assessment: *{Adequate}*
The Applicant did not request an official BCS designation. Based on the provided information, the Applicant reported the drug substance, Sotagliflozin, to be a low soluble and high permeable substance according to regulatory criteria.

[1] \\CDSESUB1\EVSPROD\nda210934\0001\m2\27-clin-sum\summary-clin-pharm.pdf

B.2 FORMULATION

The proposed commercial dosage forms of Sotagliflozin tablets are 200 mg and 400 mg strength immediate release film-coated tablets. The 200 and 400 mg tablets are dose weight proportional and differ only in the color of the film coating and imprint (Table 2 & Table 3).

The proposed commercial Sotagliflozin tablet, 200 mg is a blue film-coated, oval shaped tablet, imprinted in black ink with "LX200" code on one side, and neutral on the other side, (b) (4)

Table 2: Composition of Sotagliflozin 200 mg Film-Coated Table

Components	Unit quantity (mg/tablet)	Percentage (w/w)	Function	Reference to standards[a]
Sotagliflozin	200.000	(b) (4)	Active substance	In-house monograph
(b) (4)			(b) (4)	Ph. Eur.-NF
Microcrystalline cellulose (b) (4)				Ph. Eur.-NF
Croscarmellose sodium				Ph. Eur.-NF
(b) (4)				Ph. Eur.-NF
Talc				Ph. Eur.-USP
Magnesium stearate[c]				Ph. Eur.-NF
Core tablet mass	(b) (4)	100.00		
Film-coating				
(b) (4)			(b) (4)	In-house monograph
				Ph. Eur.-USP
Black ink[f]				In-house monograph
Film-coated tablet mass	384.533			

a When reference is made to a Pharmacopoeia, this means that the current edition of this Pharmacopoeia is applied.

b Also referred to as Colloidal silicon dioxide NF common standard.

c (b) (4)

d (b) (4) polyvinyl alcohol partly hydrolyzed (Ph. Eur.-USP), (b) (4) titanium dioxide (b) (4) (Ph. Eur.-USP), (b) (4) talc (Ph. Eur.-USP) and (b) (4) indigo carmine aluminum lake (b) (4) -

e (b) (4)

f shellac (b) (4) (Ph. Eur.-USP/NF), (b) (4) isopropyl alcohol (Ph. Eur.-USP), 23.409% (b) (4) black iron oxide (b) (4) (NF), (b) (4) N-butyl alcohol (NF), (b) (4) propylene glycol (Ph. Eur.-USP), (b) (4) ammonium hydroxide at (b) (4) (Ph. Eur.-NF).

[2] https://panorama.fda.gov/task/view?ID=5b168ffd001a16f6cb298a65430b7c5c

The proposed commercial Sotagliflozin tablet, 400 mg is a yellow film-coated, oval shaped tablet, [redacted] on one side, and neutral on the other side.

Table 3: Composition of Sotagliflozin 400 mg Film-Coated Table

Components	Unit quantity (mg/tablet)	Percentage (w/w)	Function	Reference to standards[a]
Sotagliflozin	400.000	[redacted]	Active substance	In-house monograph
[redacted]	[redacted]	[redacted]	[redacted]	Ph. Eur.-NF
Microcrystalline cellulose [redacted]	[redacted]	[redacted]	[redacted]	Ph. Eur.-NF
Croscarmellose sodium	[redacted]	[redacted]	[redacted]	Ph. Eur.-NF
[redacted]	[redacted]	[redacted]	[redacted]	Ph. Eur.-NF
Talc	[redacted]	[redacted]	[redacted]	Ph. Eur.-USP
Magnesium stearate[c]	[redacted]	[redacted]	[redacted]	Ph. Eur.-NF
Core tablet mass	[redacted]	**100.00**		
Film-coating				
[redacted]	[redacted]	[redacted]	[redacted]	In-house monograph
[redacted]	[redacted]	[redacted]	[redacted]	Ph. Eur.-USP
[redacted]	[redacted]	[redacted]	[redacted]	In-house monograph
Film-coated tablet mass	**769.066**			

a When reference is made to a Pharmacopoeia, this means that the current edition of this Pharmacopoeia is applied.

b Also referred to as Colloidal silicon dioxide NF common standard.

c [redacted]

d [redacted] lactose monohydrate (Ph. Eur.-NF), [redacted] hypromellose [redacted] (Ph. Eur.-USP), [redacted] titanium dioxide [redacted] (Ph. Eur.-USP), [redacted] triacetin (Ph. Eur.-USP), [redacted] yellow iron oxide [redacted] (NF).

e [redacted]

f [redacted]

B.3 DISSOLUTION METHOD

The Applicant proposed the following dissolution methods for the proposed Sotagliflozin tablets, 200 and 400 mg.

Dissolution Methods		
Strength	200 mg	400 mg
Medium	Purified water with 0.2% sodium lauryl sulfate	Purified water with 0.28% sodium lauryl sulfate
Apparatus	USP II (Paddle)	
Volume	900 mL	
Rotation Speed	75 RPM	
Temperature	37°C	

The Applicant's proposed dissolution method for Sotagliflozin tablets, 200 mg is the same as the one proposed in NDA 210934[3], which was reviewed and found adequate[4]. Therefore, this review is focused on the evaluation and acceptability of the proposed quality control dissolution method for Sotagliflozin tablets, 400 mg. The Applicant provided data to support the choice of dissolution method in the Pharmaceutical Development (Module 3.2.P.2.2).

Dissolution Medium

(b) (4)

(b) (4)

[3] \\CDSESUB1\EVSPROD\nda216203\0001\m3\32-body-data\32p-drug-prod\sotagliflozin-tablet-200-mg-(b) (4)\32p2-pharm-dev\pharmaceutical-development-200mg.pdf

[4] https://panorama.fda.gov/task/view?ID=5b168ffd001a179e83a94e20f9f2618b

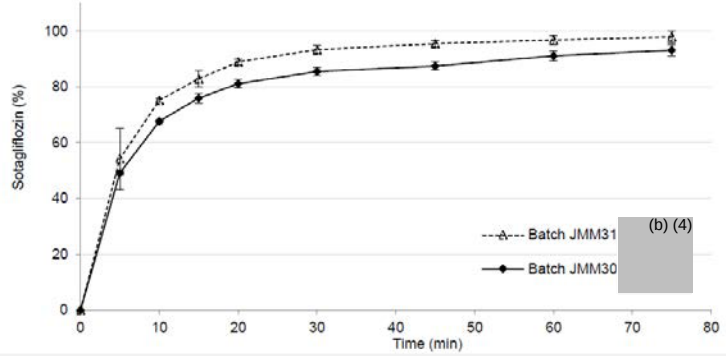
Discriminating Power Assessment

The Applicant studied the discriminatory power of the selected medium (purified water with 0.28% SLS) with regards to the [redacted] and [redacted] content, which are the same parameters demonstrated for the 200 mg tablets.

[redacted]

As it was demonstrated for the 200 mg tablets that there was no significant difference in dissolution when [redacted] The Applicant therefore selected the [redacted] for the 400 mg tablets (Figure 1).

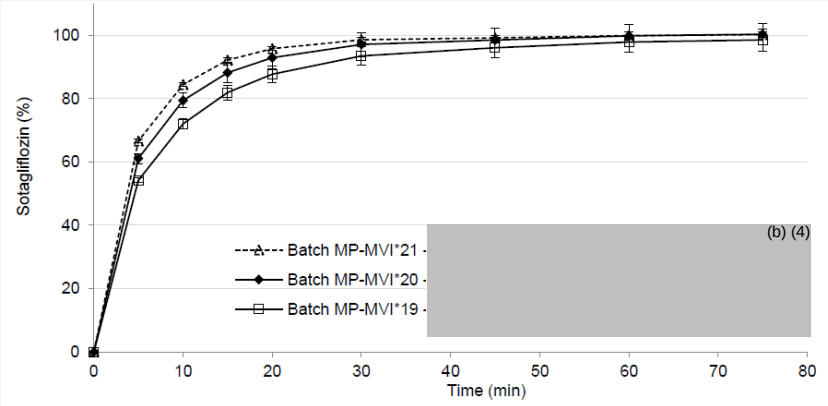
Figure 1 Dissolution Profiles of Sotagliflozin 400 mg Tablet - Discriminatory Power of the Method with Regards to Variation of [redacted] (Paddle Apparatus, 0.28% Sodium Lauryl Sulfate Medium, 75 r/min, n = 6)



[redacted] Content

The Applicant studied the effect of variation of formulation composition, changing the [redacted]

Figure 2 Dissolution Profiles of Sotagliflozin 400 mg Tablet - Discriminatory Power of the Method with Regards to [redacted] (Paddle Apparatus, 0.28% Sodium Lauryl Sulfate Medium, 75 r/min, n = 3)



Assessment: ***{Adequate}***

Although a single dissolution method is preferred for drug product across all strengths, the Applicant's proposed dissolution methods are found acceptable for the QC of the proposed Sotagliflozin Tablets for the following reasons:

- The Applicant's proposed dissolution method for the proposed Sotagliflozin Tablet, 200 mg is agreed upon under NDA 210934 for T1DM indication. Therefore, the method remains adequate for the 200 mg strength.

- For low solubility drug substance, the Applicant adequately demonstrated and justified the suitability of the proposed dissolution medium with increased SLS concentration from 0.2% to 0.28% for the proposed Sotagliflozin Tablet, 400 mg. The proposed dissolution method for Sotagliflozin Tablet, 400 mg showed similar discriminating ability towards quantitative variation of formulation composition of (b) (4) as the dissolution method for Sotagliflozin Tablet, 200 mg. Thus, the different amount of surfactant is deemed appropriate to attain sink conditions for the proposed Sotagliflozin Tablets.

- The proposed Sotagliflozin Tablets, 200 and 400 mg, were used in the BE study BEQ14993 and thus no waiver is required. Therefore, different dissolution method for each strength is applicable for the proposed Sotagliflozin Tablets.

B.4 DISSOLUTION METHOD ACCEPTANCE CRITERION

Sotagliflozin Tablet, 200 mg

Under NDA 210934, the dissolution acceptance criteria were agreed upon (b) (4) 45 minutes Q= (b) (4) %)[4]. In the current submission, the Applicant manufactured additional batches for the HF/T2DM indication and provided additional dissolution data (Appendix I).

Based on the overall dissolution data including primary stability batches (TXWK, TXWM and VSHH) as well as clinical batches (YVSX (BE study BEQ14993), ZHTF (Phase 3 EFC14835, EFC14875, EFC15156, EFC15166, PDY15079), ZBFD (Phase 1 & 3 EFC14833, EFC14837, EFC14838, EFC14867, EFC15166, PKM15402), ZSGK (Phase 3 EFC14875), ZSGM (Phase 3 EFC14875), and CBDNB (Phase 3 EFC14875), the Applicant proposes using the originally proposed single time point of dissolution acceptance criterion Q= (b) (4) % at 45 minutes.

The Applicant also provided dissolution profiles under stability conditions[5]. The dissolution data for the studies do not suggest any trend indicating loss, which will be further reviewed by DP reviewer.

[5] \\CDSESUB1\EVSPROD\nda216203\0001\m3\32-body-data\32p-drug-prod\sotagliflozin-tablet-200-mg-(b) (4) 32p8-stab\stability-data-intro-200mg.pdf

Sotagliflozin Tablet, 400 mg

During the course of the development, the Applicant generated the dissolution profiles at the time points of 10, 15, 20, 25, 30, 45 minutes and "infinity" to acquire information and to develop data along with the proposed acceptance criterion. The data on the primary stability batches (8A401 (used in BE study BEQ14993), 8A402 and 8A403) and CDZGY (development batch used for stability) are presented in Table 5.

Table 5: Release Dissolution Data of Sotagliflozin 400 mg Film-Coated Tablet (0.28% SLS Dissolution Media)

Test		Batch identity			
		8A401	8A402	8A403	CDZGY**
Dissolution profile (development data)	Time (min)				
	10	66	71	70	62
	15	76	81	81	73
	20	82	89	87	81
	30	89	93	94	89
	45	93	96	97	95
	75*	98	98	99	98
		Dissolution at 30 minutes (sotagliflozin dissolved in %)			
		Mean: 89	Mean: 93	Mean: 94	Mean: 89
		(b) (4)			
		RSD: 2.7% (n=12)	RSD: 2.9% (n=12)	RSD: 2.5% (n=12)	RSD: 3.9% (n=6)

*"infinity" spin applied to check dissolution completeness during development phases

** The dissolution data for 30 minutes are from release testing. The dissolution data for 10, 15, 20, 45 and 75 minutes are from testing of in-process sample SPL-200793-W, in order to have a complete dissolution profile. Dissolution data at release did not include the complete dissolution profile.

The Applicant also provided dissolution profiles under stability conditions[6]. The dissolution data for the studies do not suggest any trend indicating loss, which will be further reviewed by DP reviewer.

Based on the above data, the Applicant proposed acceptance limit Q=(b) (4)% in 30 minutes of the labeled content for both release and shelf life of Sotagliflozin Tablets, 400 mg.

Assessment: ***{Adequate}***

Based on the dissolution data in the current submission, the proposed dissolution acceptance criteria are found acceptable.

Acceptance Criteria	
200 mg	*400 mg*
Q=(b) (4)% at 45 minutes	*Q=(b) (4)% at 30 minutes*

[6] \\CDSESUB1\EVSPROD\nda216203\0001\m3\32-body-data\32p-drug-prod\sotagliflozin-tablet-400-mg-(b) (4)32p8-stab\stability-data-intro-400mg.pdf

B.5 B.6 BRIDGING OF FORMULATIONS

Early formulations used in clinical trials for Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM) include: Oral solution formulations of 10 mg/mL, A capsule formulation of 50 mg strength and Tablets of 50, 75 and 150 mg strength (Table 6).

Table 6: History of Clinical and Commercial Formulation Development

Year	Dosage Form and Strength	Developed For	Site
2008	10 mg/mL oral solutions	Phase 1 clinical studies + one Phase 2 clinical study	(b) (4)
2009	50 mg hard gelatin capsule	Phase 1 clinical study	
2010 - 2011	50 mg ((b) (4)% drug load) and 150 mg ((b) (4)% drug load) clear film-coated white tablets	Phase 1 clinical studies LX4211.102[a]	
2011	75 mg ((b) (4)% drug load) and 200 mg ((b) (4)% drug load) clear film-coated white tablets	Phase 2 clinical studies	
2012 - 2018	200 mg clear film-coated white tablets ((b) (4)% drug load)	Phase 3 clinical studies (T1DM, then T2DM)[b]	
2015	200 mg imprinted blue film-coated tablet ((b) (4)% drug load)	Primary stability batches **Proposed commercial formulation** BDR14994[a]	
2015	400 mg film-coated tablets ((b) (4)% drug load)	Stability batches (imprinted blue film-coated tablet) BDR14994[a]	
2017	400 mg blue film-coated tablets ((b) (4)% drug load)	BDR14994[a]	Sanofi
2018	200 mg imprinted blue film-coated *tablet* ((b) (4)% drug load)	Validation and stability batches	(b) (4)
2018	200 mg imprinted blue film-coated *tablet* ((b) (4)% drug load)	Evaluation of alternate DS and DP manufacturers Batch data used to support in process hold times **Proposed commercial formulation**	Sanofi
2018	400 mg yellow film-coated engraved tablet ((b) (4)% drug load)	Primary stability batches BEQ14993[a]	Sanofi
2020	400 mg yellow film-coated engraved tablet ((b) (4)% drug load)	(b) (4) kg technical feasibility batch	(b) (4)
Anticipated 2022	400 mg (b) (4) yellow film-coated tablet ((b) (4)% drug load)	**Proposed commercial formulation** Validation and stability batches	

Source: 3.2.P.2.2 Pharmaceutical Development, Introduction - 200 mg, 400 mg
DS = drug substance; DP = drug product; HF = heart failure; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus
a Bioavailability/bioequivalence study
b Studies were initially performed for T1DM or T2DM, but support the HF indication.

The clinical tablet of 200 mg strength was used in various Phase 1 and Phase 2 studies, and in all Phase 3 clinical studies for the heart failure indication. The proposed commercial clinical tablets of 200 mg and 400 mg strengths were used in BE study BEQ14993.

The comparative dissolution data of Sotagliflozin 200 mg film-coated tablets used for Phase 3 clinical studies and stability batches tested (representative of the commercial formulation) were assessed under NDA 210934 and found adequate[4].

In the current submission, three primary stability batches of Sotagliflozin 400 mg were manufactured at Sanofi Ambarès at pilot scale of (b) (4) kg with drug substance from (b) (4) and Sanofi Chimie.

Table 7: History of Sotagliflozin 400 mg Batches of Yellow Engraved Film-Coated Tablets Manufactured at Pilot Scale at Sanofi Ambarès with the Commercial Manufacturing Process

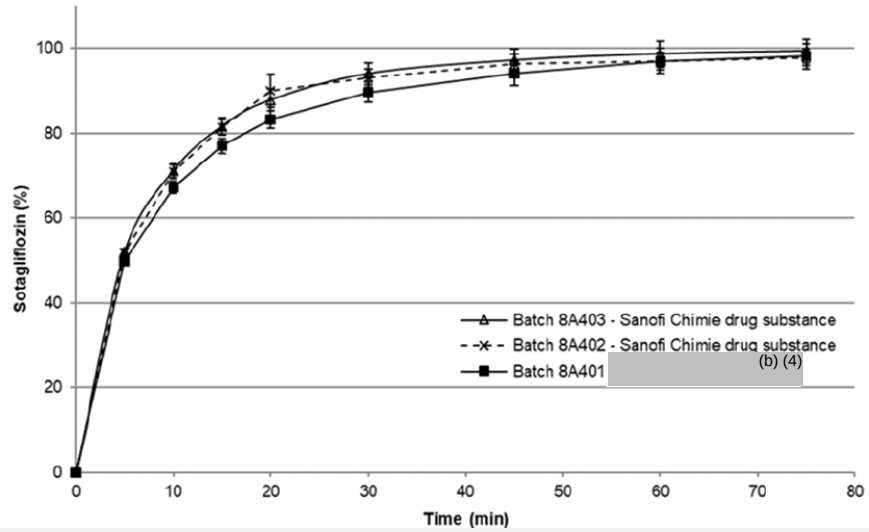
DP batch number	DS batch number	DS source	Manufact. date	Manufact. site	Batch size (tablets)	Use
8A401	20170904317	(b) (4)	18-Jun-2018	SWI[a]	(b) (4)	Primary stability BEQ14993
8A402	JS03001	Sanofi Chimie	19-Jun-2018	SWI		Primary stability
8A403	JS03003	Sanofi Chimie	20-Jun-2018	SWI		Primary stability

a Sanofi Winthrop Industrie, Ambarès et Lagrave France.

*8A401 was used in BE study BEQ14993.

The Applicant provided dissolution profile for those bathes using the proposed dissolution method for the 400 mg strength (i.e., 0.28% SLS), which showed comparable release of Sotagliflozin (Figure 3).

Figure 3. Dissolution Profile of Sotagliflozin 400 mg Batches Used in Primary Stability, Including the Batch (8A401) Used in BEQ 14993 Study (Paddle Apparatus, 0.28% Sodium Lauryl Sulfate, 75 r/min, n = 6)



The Applicant states that the to-be-marketed formulation of the 400 mg will have a change from (b) (4) (Table 1Table 3 & Table 10) and (b) (4) will be used. Based on OPQ drug product and process reviewers' assessment, those changes are considered minor (as level 1 per SUPAC IR). The Applicant manufactured feasibility/registration batch CDZGX/CDZGY, at (b) (4) (commercial drug product manufacturing site) as representative of the proposed commercial process and provided comparative dissolution data (Table 8). The *f*2 value between 8A401 and CDZGY is 76.8, suggesting similar profiles.

Table 8: Release Dissolution Data of Sotagliflozin 400 mg Film-Coated Tablet (0.28% SLS Dissolution Media)

Test	Batch	8A401	8A402	8A403	CDZGY
	Use	BEQ14993 Primary Stability	Primary Stability	Primary Stability	Technical Feasibility, Stability
Dissolution profile (development data)	Time (min)				
	10	66	71	70	62
	15	76	81	81	73
	20	82	89	87	80
	30	89	93	94	88
	45	93	96	97	94
	75*	98	98	99	98
		Dissolution at 30 minutes (sotagliflozin dissolved in %)			
		Mean: 89	Mean: 93	Mean: 94	Mean: 89
		(b) (4)			
		RSD: 2.7% (n=12)	RSD: 2.9% (n=12)	RSD: 2.5% (n=12)	RSD: 3.5% (n=6)

Assessment: *{Adequate}*

The Applicant's bridging results for the formulations, DS substance source and drug product manufacturers are found acceptable.

B.6 BIOWAIVER REQUEST

Assessment: N/A

A biowaiver is not submitted nor required for this NDA.

Primary Biopharmaceutics Assessor's Name and Date: Zhuojun Zhao, Ph.D., 1/9/2023

Secondary Assessor Name and Date: Haritha Mandula, Ph.D., 1/12/2023

Appendix I: Dissolution Data of Sotagliflozin Tablets, 200 mg

Table 9: Release Dissolution Data for Representative Batches of Sotagliflozin 200 mg Film-Coated Tablet

Test	Batch	NSFX	WTXD	TXWK	TXWM	VSHH	YKBY	ZBBG
	Use	Stability / Phase 1, 2 & 3	Phase 1 & 3	Primary Stability	Primary Stability / Phase 1	Primary Stability	Manufacturing parameter justification (full scale)	Manufacturing process pre-qualification
Dissolution profile (development data)	Time (min)	Mean (sotagliflozin dissolved in %)						
	10	67	60	61	62	63	58	49[b]
	15	78	72	73	74	73	71	60[b]
	20	85	79	81	81	82	78	67[b]
	30	93	88	90	90	90	86	77[b]
	45	98	95	96	96	97	93	85[b]
	Infinity*	100	99	101	99	100	98	95[b]
Dissolution profile (development data)		Dissolution at 15 minutes (sotagliflozin dissolved in %)						
		Mean: 78	Mean: 72	Mean: 73	Mean: 74	Mean: 73	Mean: 71	Mean: 60[b]
		(b) (4)						
		RSD: 1.6% (n=6)	RSD: 2.2% (n=6)	RSD: 3.7% (n=12)[a]	RSD: 1.8% (n=12)[a]	RSD: 5.4% (n=12)[a]	RSD: NA% (n=6)	RSD: NA% (n=6)
		Dissolution at 30 minutes (sotagliflozin dissolved in %)						
		Mean: 93	Mean: 88	Mean: 90	Mean: 90	Mean: 90	Mean: 86	Mean: 77[b]
		(b) (4)						
		RSD: 1.9% (n=6)	RSD:2.4 % (n=6)	RSD: 2.2% (n=12)[a]	RSD: 1.3% (n=12)[a]	RSD: 3.2% (n=12)[a]	RSD: NA% (n=N6)	RSD: NA% (n=6)
Dissolution data		Dissolution at 45 minutes (sotagliflozin dissolved in %)						
		Mean: 98	Mean: 95	Mean: 96	Mean: 96	Mean: 97	Mean: 93	Mean: 89
		(b) (4)						
		RSD: 2.0% (n=6)	RSD: 2.5% (n=6)	RSD: 1.8% (n=12)[a]	RSD: 1.2% (n=12)[a]	RSD: 2.3% (n=12)[a]	RSD: 1.3% (n=6)	RSD: 0.9% (n=6)

* "infinity" spin applied for at least 15 or 30 min to check dissolution completeness during development phases

a The three primary batches used for ICH stability studies were tested on 12 tablets for dissolution by default

b Dissolution profile generated on the corresponding non printed tablet batch (YTBF) sampled at the middle of the manufacture. At 45 minutes results were: Mean: 85% (Min: (b) (4) Max (b) (4) RSD: 2.6% (n=12)

Test	Batch	WTXF	WTXG	XHSX	YGKG	YGKH	ZBFD	ZHTF
	Use	Phase 3	Phase 3	Phase 3	Phase 3	Phase 3	Phase 3	Phase 3
Dissolution profile (development data)	Time (min)	Mean (sotagliflozin dissolved in %)						
	10	62	59	56	61	57	52	52
	15	74	70	67	69	69	63	62
	20	81	78	74	76	75	70	69
	30	90	87	82	84	84	80	78
	45	96	93	89	91	91	87	84
	Infinity*	100	98	97	97	98	98	94
Dissolution profile (development data)		Dissolution at 15 minutes (sotagliflozin dissolved in %)						
		Mean: 74	Mean: 70	Mean: 67	Mean: 69	Mean: 69	Mean: 63	Mean: 62
		(b) (4)						
		RSD: 1.8% (n=6)	RSD: 3.0% (n=6)	RSD: 2.4% (n=6)	RSD: 2.5% (n=6)	RSD: 1.6% (n=6)	RSD: 2.8% (n=6)	RSD: 5.1% (n=6)
		Dissolution at 30 minutes (sotagliflozin dissolved in %)						
		Mean: 90	Mean: 87	Mean: 82	Mean: 84	Mean: 84	Mean: 80	Mean: 78
		(b) (4)						
		RSD: 1.5% (n=6)	RSD: 2.5% (n=6)	RSD: 2.9% (n=6)	RSD: 2.5% (n=6)	RSD: 1.4% (n=6)	RSD: 1.8% (n=6)	RSD: 3.8% (n=6)
Dissolution data		Dissolution at 45 minutes (sotagliflozin dissolved in %)						
		Mean: 96	Mean: 93	Mean: 89	Mean: 91	Mean: 91	Mean: 87	Mean: 84
		(b) (4)						
		RSD: 1.4% (n=6)	RSD: 2.5% (n=6)	RSD: 2.7% (n=6)	RSD: 2.3% (n=6)	RSD: 1.4% (n=6)	RSD: 1.3% (n=6)	RSD: 2.9% (n=6)

* "infinity" spin applied for at least 15 or 30 min to check dissolution completeness during development phases

Test	Batch	ZHTG	ZFDN	ZFDP	ZSFZ	ZSGC	ZSGF	ZSGG
	Use	Phase 3	Phase 3	Phase 3	Phase 3	Phase 3	Phase 3	Phase 3
Dissolution profile (development data)	Time (min)	Mean (sotagliflozin dissolved in %)						
	10	55	54	56	64	62	56	58
	15	65	67	68	71	72	69	69
	20	72	74	76	78	78	78	72
	30	80	84	84	87	87	85	86
	45	88	91	91	93	93	92	93
	Infinity*	94	96	96	97	97	97	97
Dissolution profile (development data)		Dissolution at 15 minutes (sotagliflozin dissolved in %)						
		Mean: 65	Mean: 67	Mean: 68	Mean: 71	Mean: 72	Mean: 69	Mean: 69
		(b) (4)						
		RSD: 4.0% (n=6)	RSD: 2.8% (n=6)	RSD: 3.4% (n=6)	RSD: 2.6% (n=6)	RSD: 4.0% (n=6)	RSD: 4.0% (n=6)	RSD: 4.9% (n=6)
		Dissolution at 30 minutes (sotagliflozin dissolved in %)						
		Mean: 80	Mean: 84	Mean: 84	Mean: 87	Mean: 87	Mean: 85	Mean: 86
		(b) (4)						
		RSD: 3.4% (n=6)	RSD: 2.6% (n=6)	RSD: 1.5% (n=6)	RSD:1.9 % (n=6)	RSD: 2.3% (n=6)	RSD: 3.0% (n=6)	RSD: 3.2% (n=6)
Dissolution data		Dissolution at 45 minutes (sotagliflozin dissolved in %)						
		Mean: 88	Mean: 91	Mean: 91	Mean: 93	Mean: 93	Mean: 92	Mean: 93
		(b) (4)						
		RSD: 2.9% (n=6)	RSD: 2.1% (n=6)	RSD: 1.3% (n=6)	RSD: 1.9% (n=6)	RSD: 1.8% (n=6)	RSD:2.4 % (n=6)	RSD: 3.0% (n=6)

*" infinity "spin applied for at least 15 or 30 min to check dissolution completeness during development phases

Test	Batch	ZSGH	ZSGK	ZSGM	YVSW/ CBHHP	YVSY/ CBHHS	YVSX/ CBHHT	CBCYF
	Use	Phase 3	Phase 3	Phase 3	Stability / Validation	Phase 1/ Stability / Validation	Stability / Validation	Phase 3
Dissolution profile (development data)	Time (min)	Mean (sotagliflozin dissolved in %)						
	10	53	49	53	NA	NA	NA	53
	15	67	58	65	64	65	65	64
	20	73	65	73	NA	NA	NA	71
	30	82	85	83	82	83	82	80
	45	90	91	90	89	90	89	87
	Infinity*	97	98	95	NA	NA	NA	96
Dissolution profile (development data)		Dissolution at 15 minutes (sotagliflozin dissolved in %)						
		Mean: 67	Mean: 58	Mean: 65	Mean: 64	Mean: 65	Mean: 65	Mean: 64
		(b) (4)						
		RSD: 3.6% (n=6)	RSD: 10.6% (n=6)	RSD: 4.9% (n=6)	RSD: 2.7% (n=12)[a]	RSD: 2.1% (n=12)[a]	RSD: 6.8% (n=12)[a]	RSD:3.3 % (n=6)
		Dissolution at 30 minutes (sotagliflozin dissolved in %)						
		Mean: 82	Mean: 85	Mean: 83	Mean: 82	Mean: 83	Mean: 82	Mean: 80
		(b) (4)						
		RSD: 3.0% (n=6)	RSD: 2.3% (n=6)	RSD: 3.7% (n=6)	RSD: 2.3% (n=12)	RSD: 1.8% (n=12)[a]	RSD: 6.0% (n=12)[a]	RSD: 3.5% (n=6)
Dissolution data		Dissolution at 45 minutes (sotagliflozin dissolved in %)						
		Mean: 90	Mean: 91	Mean: 90	Mean: 89	Mean: 90	Mean: 89	Mean: 87
		(b) (4)						
		RSD: 2.4% (n=6)	RSD: 1.9% (n=6)	RSD: 3.3% (n=3.3)	RSD: 2.2% (n=12)[a]	RSD: 1.7% (n=12)[a]	RSD: 4.5% (n=12)[a]	RSD: 2.8% (n=6)

* "infinity" spin applied for at least 15 or 30 min to check dissolution completeness during development phases
a The three validation batches used for ICH stability studies were tested on 12 tablets for dissolution by default
NA = not applicable

Test	Batch	CBDMZ	CBDNB	CBDNC	CBDND	CBDNF
	Use	Phase 2 & 3	Phase 3	Phase 3	Phase 3	Phase 3
Dissolution profile (development data)	**Time (min)**	**Mean**	**(sotagliflozin dissolved in %)**			
	10	53	53	56	55	55
	15	66	65	69	66	74
	20	73	72	74	74	74
	30	82	81	83	83	84
	45	89	88	90	90	91
	Infinity*	97	96	97	96	98
Dissolution profile (development data)		Dissolution at 15 minutes (sotagliflozin dissolved in %)				
		Mean: 66	Mean: 65	Mean: 69	Mean: 66	Mean: 74
		(b) (4)				
		RSD: 5.2% (n=6)	RSD: 5.7% (n=6)	RSD: 1.8% (n=6)	RSD: 2.0% (n=6)	RSD: 4.4% (n=6)
		Dissolution at 30 minutes (sotagliflozin dissolved in %)				
		Mean: 82	Mean: 81	Mean: 83	Mean: 83	Mean: 84
		(b) (4)				
		RSD: 3.6% (n=6)	RSD: 2.9% (n=6)	RSD: 0.9% (n=6)	RSD: 2.2% (n=6)	RSD: 3.8% (n=6)
Dissolution data		Dissolution at 45 minutes (sotagliflozin dissolved in %)				
		Mean: 89	Mean: 88	Mean: 90	Mean: 90	Mean: 91
		(b) (4)				
		RSD: 3.0% (n=6)	RSD: 2.7% (n=6)	RSD:1.0 % (n=6)	RSD: 2.1% (n=6)	RSD: 4.1% (n=6)

* "infinity" spin applied for at least 15 or 30 min to check dissolution completeness during development phases

Appendix II: Initial Commercial Formulation (BE Batch 8A401)

Table 10: Composition of Sotagliflozin 400 mg Yellow Engraved Film-Coated Tablet

Components	Unit quantity	
	% (w/w)	mg/unit
(b) (4)		
Sotagliflozin	(b) (4)	400.00
		(b) (4)

Zhuojun Zhao

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Date: 1/12/2023 11:38:59PM
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Haritha Mandula

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