

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

216185Orig1s000

PRODUCT QUALITY REVIEW(S)



Title:	NDA Executive Summary		
Document ID:	OPQ-ALL-TEM-0013		
Effective Date:	31 May 2022	Revision:	00
Total Pages:	3		



Template Revision: 03

NDA Executive Summary

1. Application/Product Information

NDA Number	216185		
Applicant Name	Aucta Pharmaceuticals		
Drug Product Name	MOTPOLY (lacosamide)		
Dosage Form	Extended-release capsules		
Proposed Strength(s)	100 mg, 150 mg, and 200 mg		
Route of Administration	Oral		
Maximum Daily Dose	400 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Treatment of partial-onset seizures in pediatric patients weighing greater than 50 kg; patients 17 years of age and older		
Drug Product Description	Capsules: • 100 mg: (b) (4) yellow Opaque cap and White Opaque body with “A” printed in black ink on the cap and “100” printed in black ink on the body, containing white or off-white beads • 150 mg: Brown Opaque cap and White Opaque body with “A” printed in black ink on the cap and “150” printed in black ink on the body, containing white or off-white beads • 200 mg: Blue Opaque cap and White Opaque body with “A” printed in black ink on the cap and “200” printed in black ink on the body, containing white or off-white beads		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	20°C to 25°C, USP controlled room temperature		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Jeffrey Medwid	Gaetan Ladouceur



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Template Revision: 03

	<i>Drug Product/ Labeling</i>	Jizhou Wang	Martha Heimann
	<i>Manufacturing</i>	Vicky He	Shu-Wei Yang
	<i>Biopharmaceutics</i>	Hansong Chen	Ta-Chen Chen
	<i>Microbiology</i>	N/A	N/A
	<i>Other (specify):</i>	N/A	N/A
	<i>RBPM</i>	Erica Keafer	
	<i>ATL</i>	Martha Heimann	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

The following expiration dating periods are granted for MOTPOLY (Iacosamide) extended-release capsules when stored at controlled room temperature, 20°C to 25°C:

60-count bottles (all strengths): 30 months

Blister packs: 24 months

b. Additional Comments for Action

There are no additional comments.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The Office of Product Quality (OPQ) review team recommends APPROVAL of NDA 216185 for MOTPOLY (Iacosamide) extended-release capsules 100 mg, 150 mg, and 200 mg. Based on our evaluation of the available information, the application, as amended, contains sufficient information to support an approval recommendation from the product quality perspective. The Applicant provided adequate information to ensure the identity, strength, purity, and quality of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed



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labeling and labels include adequate information to meet the regulatory requirements.

Lacosamide is a well-characterized, synthetic, small molecule antiepileptic drug originally approved in 2008 and marketed under the tradename VIMPAT. The product proposed in this 505(b)(2) NDA is new dosage form of lacosamide, i.e., extended release-capsules. The product composition, manufacturing process, and controls for the product are typical for the dosage form. During the review, the OPQ team identified a number of minor deficiencies that were adequately addressed by the applicant. The applicant originally proposed (b) (4)

[Redacted]

Refer to the individual discipline reviews for more details.

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:

There are no outstanding issues or lifecycle considerations.

[Redacted] (b) (4)

[Redacted]



Martha
Heimann

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N/A

DRUG PRODUCT LIST OF DEFICIENCIES

N/A

Primary Drug Product Assessor Name and Date: Jizhou Wang, PhD, 03/23/2023

*Secondary Assessor Name and Date (and Secondary Summary, as needed):
Heimann, Martha R, PhD. 03/25/2023*

CHAPTER IV: LABELING

[IQA NDA Assessment Guide Reference](#)

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Proposed in 1.18 for review, Motpoly XR was found conditionally acceptable on May13, 2022	N/A
Established name(s)	lacosamide	Adequate
Route(s) of administration	Oral	Adequate
Summary of the dosage form(s) and strength(s) in metric system.	extended-release capsules	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	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	Adequate

1.2 FULL PRESCRIBING INFORMATION

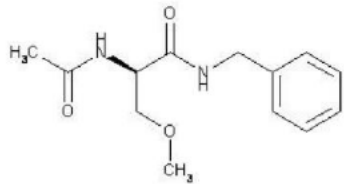
1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	N/A

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	capsules	Adequate
Strength(s) in metric system	(b) (4) 100 mg, 150 mg and 200 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	(b) (4) • 100 mg: (b) (4) yellow Opaque cap and White Opaque body with "A" printed in black ink on the cap and "100" printed in black ink on the body, containing white or off-white beads. • 150 mg: Brown Opaque cap and White Opaque body with "A" printed in black ink on the cap and "150" printed in black ink on the body, containing white or off-white beads • 200 mg: Blue Opaque cap and White Opaque body with "A" printed in black ink on the cap and "200" printed in black ink on the body, containing white or off-white beads.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	lacosamide	Adequate
Dosage form(s) and route(s) of administration	Capsules for oral	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	Adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	ethylcellulose, hypromellose, microcrystalline cellulose, (b) (4) povidone, (b) (4) titanium dioxide, triethyl citrate and dye pigments	Adequate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	Adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Statement of being sterile (if applicable)	N/A	Adequate
Pharmacological/therapeutic class	yes	Adequate
Chemical name, structural formula, molecular weight	 (R)-2-acetamido-N-benzyl-3-Methoxypropionamide The empirical formula C₁₃H₁₈N₂O₃ molecular weight: 250.30	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	N/A	N/A

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	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	N/A

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	capsules	Adequate
Strength(s) in metric system	(b) (4) 100 mg, 150 mg and 200 mg	Adequate
Available units (e.g., bottles of 100 tablets)	Bottles of 60	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Provided color, shape, imprinting and NDC numbers for all dosages.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	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	N/A

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

Item	Information Provided in the NDA	Assessor's Comments

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to “Dispense in original container,” provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	N/A	N/A
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as “Do not eat.”	N/A	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].	Adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “Not made with natural rubber latex. Avoid statements such as “latex-free.”	N/A	N/A
Include information about child-resistant packaging	Provided (the cap is CRC, see P.7)	Adequate

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor’s Comments
Manufacturing Information After Section 17		
Distributed by:	Aucta Pharmaceuticals, Inc. Piscataway, NJ 08854	Adequate

2.0 PATIENT LABELING

N/A

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

Any deficiencies should be listed at the end in the “ITEMS FOR ADDITIONAL ASSESSMENT.”

3.0 CARTON AND CONTAINER LABELING

3.1 & 3.2. Container and Carton Label



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Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	yes	Adequate
Dosage strength	Yes	Adequate
Route of administration	N/A	N/A
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	
Net contents (e.g. tablet count)	Yes	Adequate
"Rx only" displayed on the principal display	Yes	Adequate
NDC number	Yes	Adequate
Lot number and expiration date	Yes	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Yes	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Bar code	Yes	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Yes	Adequate
Medication Guide (if applicable)	Yes	N/A
No text on Ferrule and Cap overseal	N/A	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	N/A
And others, if space is available	Yes	Adequate

Assessment of Carton and Container Labeling: Adequate

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

Overall Assessment and Recommendation:

Primary Labeling Assessor Name and Date:

Secondary Assessor Name and Date (and Secondary Summary)



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Wang

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CHAPTER VI: BIOPHARMACEUTICS

NDA Number	NDA 216185
Assessment Cycle Number	01
Drug Product Name/ Strength	Lacosamide Extended-Release Capsules, 100 mg, 150 mg, and 200 mg
Route of Administration	Oral
Applicant Name	Aucta Pharmaceuticals, Inc
Therapeutic Classification/ OND Division	Anticonvulsant/DN1
LD/RS Number	IMPAT [®] (lacosamide) Tablets (NDA 022253)
Proposed Indication	Treatment of partial-onset seizures in patients 17 years of age and older
Primary Reviewer	Hansong Chen, PharmD, Ph.D.
Secondary Reviewer	Ta-Chen Wu, Ph.D.

Assessment Recommendation: Adequate

Assessment Summary:

The Applicant seeks approval for the proposed Lacosamide Extended-Release Capsules, (b)(4) 100 mg, 150 mg, and 200 mg through the 505(b)(2) regulatory pathway relying on FDA’s safety and efficacy findings of Listed Drug (LD) IMPAT[®] Tablets. The proposed indication is for the treatment of partial-onset seizures in patients 17 years of age and older.

The Biopharmaceutics review focused on the evaluation of the adequacy of the overall information/data pertaining to 1) proposed dissolution method and acceptance criteria, 2) IVIVR/IVIVC models supporting the wider dissolution acceptance criteria, 3) Extended-Release claim, 4) in vitro alcohol dose-dumping study, and 5) biowaiver of lower strengths. Key findings of the Biopharmaceutics assessment are presented below

1) The proposed dissolution method and acceptance criteria

The Applicant’s proposed dissolution method [USP apparatus I (Basket) at 100 rpm; 900 mL of Sodium Phosphate Buffer, pH 6.8 at 37 °C] is considered acceptable. The proposed dissolution method was demonstrated to be discriminatory towards critical formulation variables (b)(4) (b)(4) but not towards changes in critical manufacturing process parameters.

The proposed acceptance criteria have been tightened to “0.5 h: (b)(4) 3 h: (b)(4), 8 h: (b)(4) based on the provided dissolution profile data of pivotal BE batch. The Applicant agreed to the Division’s recommended acceptance criteria during the review cycle.

2) IVIVR/IVIVC models

The establish IVIVR/IVIVC based on three pilot formulations (i.e., T1, T2, and T3) models are acceptable; however, the proposed models failed to support the proposed wider dissolution acceptance range at 3-hour time-point as the dissolution profile of the formulation [REDACTED] (b) (4)

[REDACTED] is out of the IVIVC range established based on T1 and T3 formulations.

3) Extended-Release (ER) claim

The “Extended-Release” claim for the proposed Lacosamide Extended-Release Capsules is supported by the following information/data:

- ER characteristics of the proposed Lacosamide Extended-Release Capsules as demonstrated by comparison of plasma concentration-time profile with the LD, dosing frequency (QD vs. BID), and in vitro drug release/dissolution profile.
- As supportive evidence for drug release as designed, the extended-release characteristics of the proposed drug product were also demonstrated in in vitro test conditions
- The bioavailability profile established for the drug product rules out the occurrence of any dose dumping.
- The proposed drug product's steady-state performance is equivalent to a currently marketed immediate release drug product (i.e., VIMPAT[®]), with smaller PK fluctuation at the steady-state compared to LD.
- The proposed drug product's formulation provides consistent pharmacokinetic performance between individual dosage units, including acceptable variability (%CV <23%) as reported in relative bioavailability/bioequivalence (BA/BE) study.

4) In vitro alcohol dose-dumping potential

The results from the in vitro alcohol dose dumping study show that the presence of alcohol can cause faster release of the drug substance from Lacosamide Extended-Release Capsules, [REDACTED] (b) (4) 200 mg in both 0.1 N HCl and pH 6.8 phosphate buffer [REDACTED] (b) (4). Specifically, the phenomenon of alcohol-induced dose-dumping was observed in the presence of 20% and 40% alcohol at 2 hours, though with faster occurrence with 40% alcohol. With 5% alcohol, the increased drug release resulted in earlier completion dissolution (2-3 hours) vs. control. It is noted that the Applicant did not propose pertinent labeling languages or instruction regarding clinical consequences with consumption of alcohol/alcoholic beverages with the proposed ER drug product, such as potential pharmacodynamic interaction and concerns for adequate disease control as a result of more rapid drug release as observed in in-vitro system. The above findings will be communicated to the Clinical and the Clinical Pharmacology review teams for proper labeling recommendations.

5) Biowaiver of lower strengths

The provided information/data regarding the acceptable BA/BE study results for the highest 200 mg strength, proportionality of the formulation composition for all proposed strengths, the same release mechanism, the same manufacturing process, PK linearity in the proposed range, and similar dissolution profile across the proposed strengths support

the granting of the Applicant's biowaiver request for the proposed lower strengths (i.e., 150 mg and 100 mg). It should be noted that the PK linearity of the proposed lacosamide ER capsules has not been supported by the study data. Given that the physicochemical properties of lacosamide (including pH-independent and high aqueous solubility) and similar drug release/dissolution profiles in multimedia across physiologic pH range, the proposed drug will likely demonstrate linear PK within the same therapeutical range.

(b) (4)

Recommendation:

From a Biopharmaceutics perspective, NDA 216815 for Lacosamide Extended-Release Capsules, 100 mg, 150 mg, and 200 mg is ADEQUATE.

FDA-approved dissolution method and acceptance criteria:

USP Apparatus	Speed (RPMs)	Medium /Temperature	Volume (mL)	Acceptance Criteria
I (Basket)	100	pH 6.8 Sodium Phosphate Buffer / 37 °C ± 0.5°C	900	0.5 h: (b) (4) 3 h: (b) (4) 8 h: (b) (4)

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Sequence 0001 /Original submission	7/7/2022
Sequence 0004 /Response to Biopharmaceutics IR 1	11/7/2022
Sequence 0007 /Response to Biopharmaceutics IR 2	1/17/2023
Sequence 0011 /Response to Biopharmaceutics IR 3	2/17/2023

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

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

B.1 BCS DESIGNATION

The proposed drug is Extended-Release capsules; therefore, Biopharmaceutics Classification System (BCS) designation is not applicable for ER drug products. However, the drug substance itself is a BCS Class I drug. The solubility data in Table 1 show that lacosamide is highly soluble across the physiological pH range, ranging from 26.32 mg/mL to 30.84 mg/mL at 37 °C.

Solubility:

Table 1. Lacosamide aqueous solubility at 37 °C

Media	Solubility
Water	31.01 mg/mL
pH 1.0	30.48 mg/mL
pH 2.0	30.84 mg/mL
pH 4.5	30.18 mg/mL
pH 6.8	28.07 mg/mL
pH 7.5	26.32 mg/mL

Permeability:

The labeling of the LD reports that VIMPAT is completely absorbed after oral administration with negligible first-pass effect with a high absolute bioavailability of approximately 100%, which indicates that lacosamide is highly permeable.

Dissolution:

Refer to Section B.2 below.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: {Adequate}

1. The proposed drug product

Figure 1. Structural representation of (b) (4) beads



The formulation of the proposed Lacosamide Extended-Release Capsules has (b) (4)

(b) (4) as illustrated in Figure 1.

2. Dissolution Method

The Applicant proposed the following dissolution method and acceptance criteria for the proposed drug product:

Table 2. The proposed dissolution method and acceptance criteria

USP Apparatus	Speed (RPMs)	Medium /Temperature	Volume (mL)	Acceptance Criteria
I (Basket)	100	pH 6.8 Sodium Phosphate Buffer / 37 °C ± 0.5°C	900	0.5 h: (b) (4) 3 h: (b) (4) (b) (4) (b) (4)

1) Dissolution method development



(b) (4)

Reviewer’s overall comment on the dissolution method:

The proposed dissolution method demonstrates meaningful discriminatory power towards changes in critical formulation variables (b) (4)

Hence, the proposed dissolution method is considered adequately discriminatory and is acceptable.

3. Dissolution data and dissolution acceptance Criteria

1) Dissolution data

The Applicant provided detailed information and complete dissolution profile data of 1 clinical and 3 registration batches (Tables 9 and 10).

Table 9. List of all clinical and registration batches

Batch number	Strength	Manufacturing Site	Manufacturing date	Use of batch
4530661	200 mg	(b) (4)	07 Dec 2020	BE study 20-VIN-0095 and 21-VIN-0184
4559630	200 mg	(b) (4)	20 Nov 2020	Primary stability
4559631	200 mg	(b) (4)	31 Dec 2020	Primary stability
4569266	150 mg	(b) (4)	07 Dec 2020	Primary stability
4548403	150 mg	(b) (4)	20 Nov 2020	Primary stability
4548404	150 mg	(b) (4)	31 Dec 2020	Primary stability
4543880	100 mg	(b) (4)	07 Dec 2020	Primary stability
4548401	100 mg	(b) (4)	20 Nov 2020	Primary stability
4548402	100 mg	(b) (4)	31 Dec 2020	Primary stability

Table 10. Mean dissolution profile data of pivotal clinical and registration batches (n=12)

Batch number/time(h)	0.5	1	2	3	4	5	6	8	10	12
200 mg Batch 4559661	10.0	14.7	28.6	45.8	64.3	81.2	93.0	102.8	104.7	105.0
200 mg Batch 4559630	10.9	16.8	33.7	53.4	72.2	86.2	94.3	99.2	99.8	99.8
200 mg Batch 4559631	10.0	14.6	27.9	44.0	60.9	76.0	87.1	96.8	99.0	99.6
150 mg Batch 4569266	9.6	14.1	27.6	44.4	62.4	79.0	90.5	99.7	101.5	101.8
150 mg Batch 4548403	10.9	16.7	33.4	52.9	71.8	85.9	94.0	98.8	99.7	99.8
150 mg Batch 4548404	9.8	14.4	27.2	43.2	60.0	75.2	86.6	96.7	99.5	99.9
100 mg Batch 4543880	10.0	14.7	28.7	45.8	63.9	80.7	92.6	101.6	103.6	104.2
100 mg Batch 4548401	11.4	17.5	34.5	54.3	73.3	87.5	95.7	100.9	101.8	101.9
100 mg Batch 4548402	10.1	14.5	27.6	43.4	60.1	75.4	87.1	97.8	100.4	100.8

2) Dissolution acceptance criteria

The Applicant proposed the following dissolution acceptance criteria:

0.5 h: (b) (4)
3 h: (b) (4)
(b) (4)

Reviewer's assessment:

The Applicant initially proposed (b) (4) as the acceptance criterion of 3-hour time point. Later, the newly revised the dissolution criterion at 3 hours as (b) (4) which has (b) (4) range. The Applicant utilized the established IVIVC model to justify the proposed range; however, the justification is not acceptable (see Section B.3 for details).

Based on the dissolution data of the pivotal BE batch and simulation results using the Division of Biopharmaceutics Automation too to simulate the passing rate at different stages 1, this Reviewer recommended the following dissolution acceptance criteria for the proposed ER product (see **Appendix**):

0.5 h: (b) (4)
3 h: (b) (4)
8 h: (b) (4)

Based on the dissolution data of the pivotal BE and other exhibit batches, the simulation results show that the passing rates based on the pivotal BE batch are 100% and 100% at Stage 1 and Stage 2, respectively.

The simulation results also show that the passing rates of the batches that have high dissolution rate at 3 hours (i.e., 200 mg: Batch 4559630; 150 mg: Batch 4548403; 100 mg: Batch 4548401; (b) (4) are 100% and 100% at Stage 1 and Stage 2, respectively.

The actual profile dissolution data show that all exhibit batches can meet the above recommended dissolution acceptance criteria at Stage 1 except (b) (4) 100 mg Batch 4548401, which can meet them at Stage 2.

Table 11. Simulation results based on the dissolution data of Pivotal BE Batch 4530661

Pass Level 1 (%)	Pass Level 2 (%)	Pass Level 3 (%)	No. of simulations
100.00	100.00	100.00	100

Table 12. Simulation results based on the dissolution data of 200 mg Batch 4559630

Pass Level 1 (%)	Pass Level 2 (%)	Pass Level 3 (%)	No. of simulations
100.00	100.00	100.00	100

Table 13. Simulation results based on the dissolution data of 100 mg Batch 4548401

Pass Level 1 (%)	Pass Level 2 (%)	Pass Level 3 (%)	No. of simulations
100.00	100.00	100.00	100

In the response to Biopharmaceutics IR (dated 2/17/2023), the Applicant accepted the above recommended dissolution acceptance criteria.

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

1. In vitro-in vivo relationship (IVIVR)

During the drug development, the Applicant manufactured three pilot formulations with different drug release rates (i.e., T1, T2, and T3; see Table 14) and conducted a pilot crossover relative bioavailability study (20-VIN-0088) under fasted conditions against the approved IR formulation (VIMPAT® (Lacosamide) 200mg film coated tablet of UCB, Inc. Smyrna, GA 30080).

Study 20-VIN-0088:

An open label, balanced, randomized, four-treatment, four-sequence, four-period, oral comparative bioavailability study of Lacosamide 200mg extended-release capsule of Aucta Pharmaceuticals, Inc., USA and VIMPAT® (Lacosamide) 200mg film coated tablet of UCB, Inc. Smyrna, GA 30080 in healthy, adult, human subjects at a dose of 400 mg under fasting conditions.

The proposed dissolution method was used for dissolution testing on pilot formulations.

(b) (4)

(b) (4)

In vivo study results show that median Tmax of T1, T2, and T3 is 8h, 13h, and 18h, respectively, and Cmax is 8071.268 ± 1332.7817 , 7225.770 ± 1073.5309 , and 6559.542 ± 1115.2112 (ng/mL), respectively (Figure 14). As AUC values of the three pilot batches are comparable to VIMPAT® regardless of release rates, investigation is focused more on the relationship of Cmax and release rates of the pilot batches (Table 15).

When percent of dissolution at 3-hour timepoint was taken and plotted against Cmax ratio of T1, T2, and T3 vs. reference drug, a reasonably good relationship between the fractions of in vitro release and Cmax was established with an R² value of 0.98 (Figure 15).

Table 14. Pilot formulation composition



Figure 13. Dissolution profiles of pilot formulations

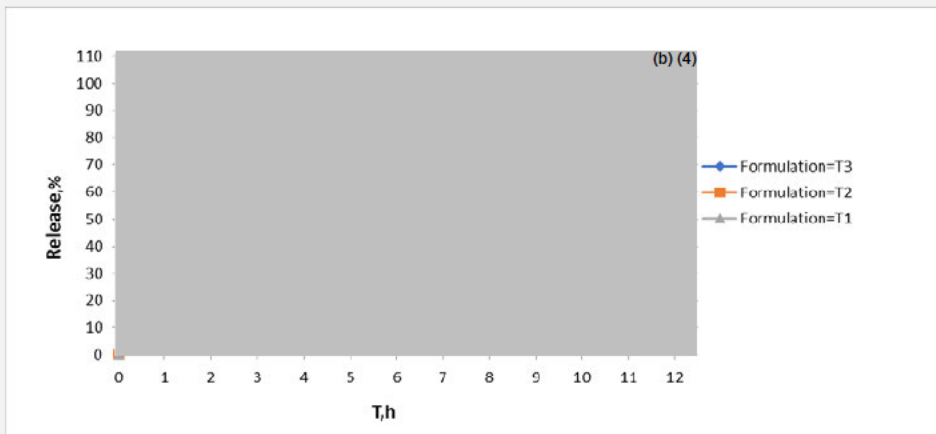


Figure 14. Plasma drug concentration of the Pilot and Reference formulations

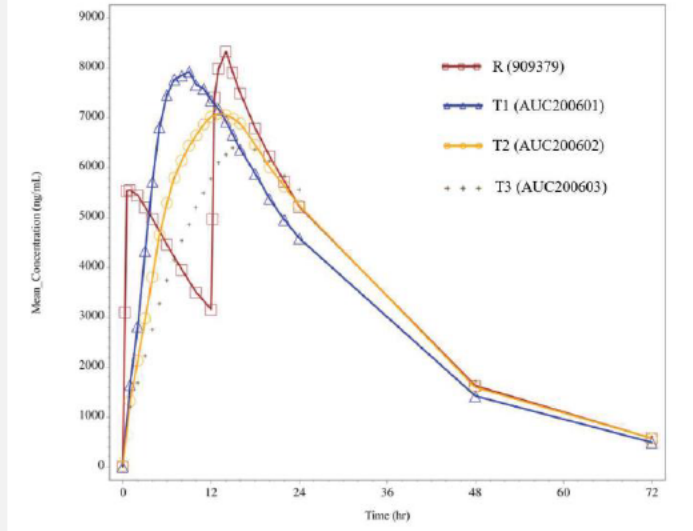
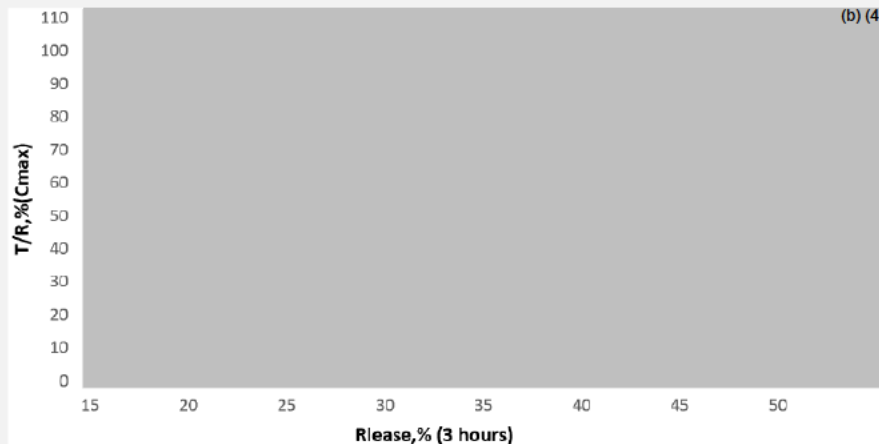


Table 15. Relationship between the fractions of in vitro release and Cmax

%Release at 3 hours	T/R % (Cmax)
(b) (4)	(b) (4)
(b) (4)	(b) (4)
(b) (4)	(b) (4)

Figure 15. Relationship between the fractions of in vitro release and Cmax



The Applicant used the established IVIVR to propose (b) (4) acceptance range for the 3-hour timepoint. Based on the IVIVR, the Applicant predicted the Cmax of XR capsules will be in the range of (b) (4) (unit) with approximately (b) (4) of variability (Table 16).

Table 16. The IVIVR predicted Cmax based on the proposed 3-hour time point range

Limit of 3 hours release (%)	T/R, % (Cmax)
(b) (4)	(b) (4)

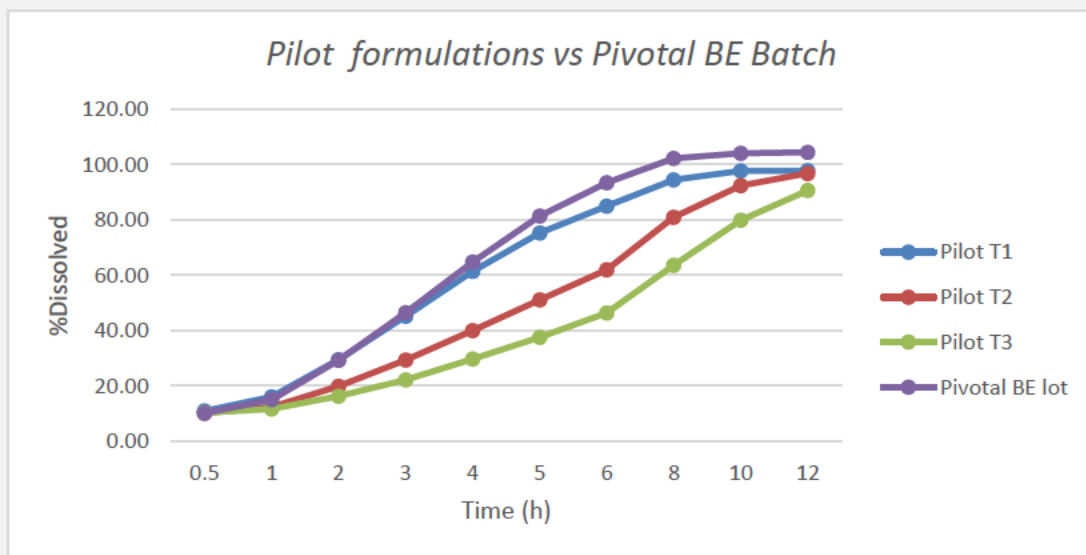
Reviewer's assessment:

The dissolution criterion at 3 hours was proposed as (b) (4), which has (b) (4) range. The Applicant claimed that the proposed 3-hour timepoint criterion is supported by the established IVIVR. However, a linear correlation between in vitro drug release at 3 hours and C_{max} based on the three pilot formulations, ranging 22.19 to 45.20 (unit) at 3 hours (Table 17 and Figure 16). The upper limit of the proposed criterion at 3 hours is beyond the established IVIVR range, hence the proposed wider (b) (4) range is not supported by the IVIVR results. Consequently, an IR was communicated to request the Applicant to clarify how the IVIVR supports the proposed wider dissolution acceptance criteria (see Appendix).

Table 17. Mean dissolution data of pilot and BE batches

Batch/time (h)	0.5	1	2	3	4	5	6	8	10	12
Pilot T1	10.94	16.08	29.49	45.2	61.43	75.34	85.02	94.51	97.67	97.81
Pilot T2	10.20	12.4	19.92	29.37	40.04	51.11	62.04	80.94	92.42	96.85
Pilot T3	10.3	11.72	16.25	22.19	29.77	37.63	46.33	63.58	79.88	90.61
Pivotal BE lot	10.16	15.01	29.26	46.44	64.78	81.46	93.41	102.26	104.06	104.44

Figure 16. Mean dissolution profiles of pilot and BE batches



2. In vitro-in vivo Correlation (IVIVC)

In the response to the above Biopharm IR, the Applicant revised the dissolution acceptance criterion at 3 hours from the previously proposed (b) (4) to (b) (4). The Applicant reported that the criterion of (b) (4) is supported by an established IVIVC model using three pilot formulations (i.e., T1, T2, and T3) and PK data., as described below.

1) In Vitro dissolution modeling

The dissolution data of three pilot formulations shown in Table 17 were generated using the proposed dissolution method. Double Weibull model showed the best fit of the dissolution data and was selected in developing the IVIVC model. Figures 17-19 show good match between fitted and observed values.

Figure 17. Observed and model-fitted in vitro dissolution data (T1) using the Double Weibull equation

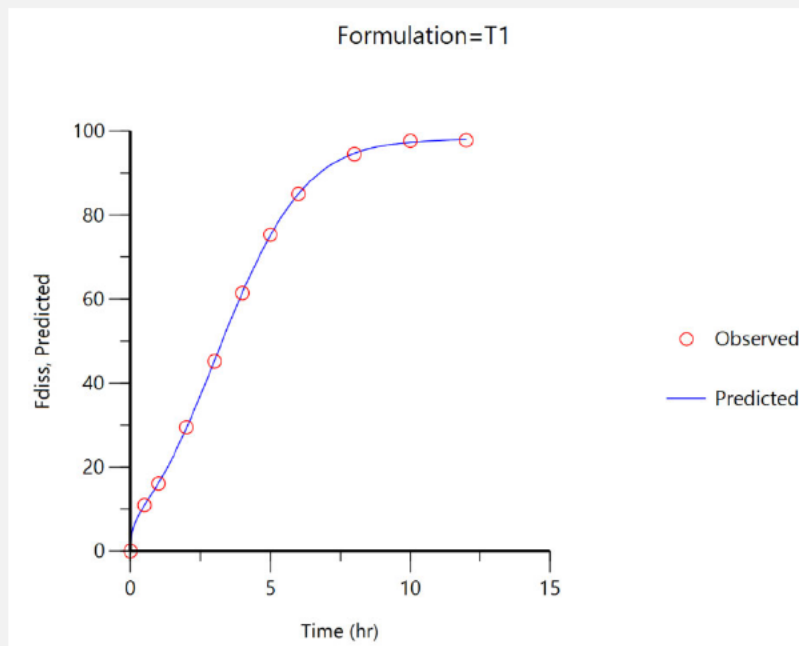


Figure 18. Observed and model-fitted in vitro dissolution data (T2) using the Double Weibull equation

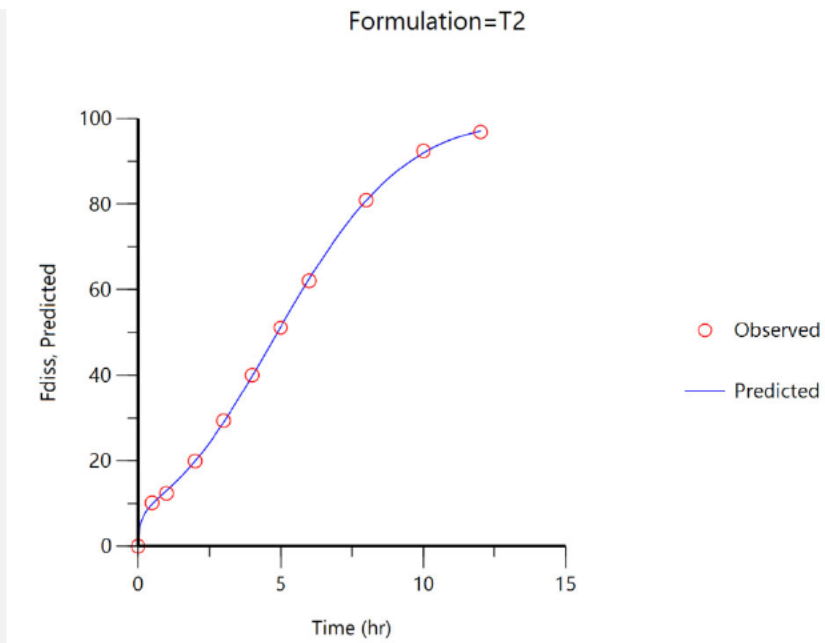


Figure 19. Observed and model-fitted in vitro dissolution data (T3) using the Double Weibull equation

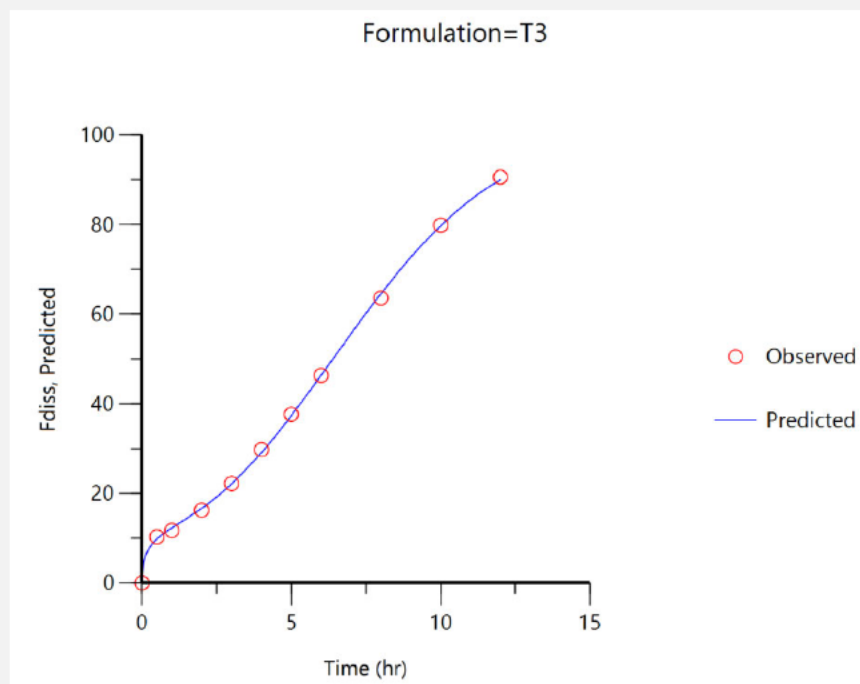


Table 18. Summary of Double Weibull parameters for pilot formulations

	f_1	F_z	MDT1	b1	MDT2	b2	R^2	
T1								(b) (4)
T2								
T3								

2) Deconvolution of in vivo PK data

The data of VIMPAT® (Lacosamide) 200mg film coated tablets in Study 20-VIN-0088 are used to generate the unit impulse response (UIR) to perform deconvolution. VIMPAT was administered twice a day (BID) in the study. To achieve a better numerical deconvolution, it is ideal to have single-dose PK data to generate UIR for each subject. The Applicant

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Figure 20. Observed PK Profiles for twice-a-day dosing and simulated PK profile for once-a-day dosing (semi-log scale)



The computation of the individual plasma concentration for once-a-day dosing is demonstrated in Figure 20. The individual plasma concentration-time data obtained from the PK study (b) (4) was used to generate the unit impulse response (UIR) for each subject.

Figure 21. Mean in vivo absorption profiles for lacosamide extended-release capsules



After the deconvolution, the mean in vivo absorption profiles for three pilot formulations, T1, T2, and T3, are obtained as shown in Figure 21.

Reviewer's comment:

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3) Establishment of IVIVC

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4) Validation of the IVIVC model

The predicted PK profiles of three pilot formulations were convoluted using the established IVIVC correlation and UIR and compared with the observed PK data from the clinical study (20-VIN-0088). The prediction error (%PE) was calculated using the following equations:

$$\%PE_{C_{max}} = \left| \frac{C_{max}(obs) - C_{max}(pred)}{C_{max}(obs)} \right| \times 100\%$$

$$\%PE_{AUC} = \left| \frac{AUC_{inf}(obs) - AUC_{inf}(pred)}{AUC_{inf}(obs)} \right| \times 100\%$$

Table 21. IVIVC model validation results (T1, T2, and T3 as internal validation)

	Simple linear model				User defined model			
	Parameter	Predicted	Observed	%PE	Parameter	Predicted	Observed	%PE
T1 Internal	AUCINF_obs	227032.41	234949.06	-3.37	AUCINF_obs	228306.37	234949.06	-2.83
T1 Internal	Cmax	8248.23	7824.53	5.41	Cmax	8020.76	7824.53	2.51
T2 Internal	AUCINF_obs	226261.67	238651.81	-5.19	AUCINF_obs	227913.21	238651.81	-4.50
T2 Internal	Cmax	7494.14	7016.57	6.81	Cmax	7170.70	7016.57	2.20
T3 Internal	AUCINF_obs	210339.10	234701.06	-10.38	AUCINF_obs	214549.67	234701.06	-8.59
T3 Internal	Cmax	6940.72	6322.03	9.79	Cmax	6542.70	6322.03	3.49
Avg Internal	AUCINF_obs	221074.99	236093.75	6.31	AUCINF_obs	223497.05	236093.75	5.30
Avg Internal	Cmax	7542.16	7027.70	7.34	Cmax	7219.57	7027.70	2.73

As shown in Table 21, the prediction errors for both AUC and Cmax are within the acceptable ranges (i.e., individual PE <15% and average PE <10%).

Reviewers' comment:

This Reviewer could verify and reproduce the IVIVC model which is found acceptable.

5) Application of IVIVC model

a. Prediction of BE batch used in pivotal BE study

The Applicant used the established user defined IVIVC to predict the plasma concentration profile of the single dose of the pivotal BE batch and utilized nonparametric analysis in WinNonlin to calculate the PK profiles at a steady state as shown in Figure 23.

Figure 23. Comparison between the mean plasma concentration at steady state



Table 22. Summary PK parameter comparison at steady state

Steady State	Predicted (mean)	Observed (mean)	%difference
C _{max} (ng/ml)	(b) (4)		
C _{min} (ng/ml)	(b) (4)		
AUC _{0-τ} (hr* ng/ml)	(b) (4)		

Based on the data shown in Table 22, the Applicant claimed that that the IVIVC model can successfully predict the plasma concentration profile of BE batch at the steady state and further demonstrate the robustness of the model.

Reviewer’s comment:

The dissolution profile of the pivotal BE batch is out of the ranges of the IVIVC model that was established based on three pilot formulations. This Reviewer disagrees with the Applicant’s approach to predict the PK profile of the pivotal BE batch by extrapolating the IVIVC model.

b. Setting dissolution specification for lacosamide extended-release capsules

To set dissolution acceptance criteria for the proposed lacosamide extended-release capsules, the Applicant used four different release profiles obtained by changing levels of (b) (4). These profiles were fitted with Double Weibull model and their PK profiles were predicted using the IVIVC model. The dissolution profile

obtained from the formulation (b) (4) is set as the upper limit of the dissolution acceptance criterion at 3 hours and one with (b) (4) as the lower limit. The predicted results shown in Table 23 indicate that the ratio difference for Cmax and AUCinf is less than or equal to (b) (4) when comparing the upper limit (b) (4) release at 3 hours) with the lower limit (b) (4) release at 3 hours). The Applicant's statistical analysis showed that four different formulations (b) (4) were predicted to be bioequivalent to the BE batch.

Table 23. Comparison of Cmax and AUCinf valued for formulations at the upper and lower limits of dissolution acceptance criteria

	% release at 3 hour	Cmax (ng/ml)		AUCinf_obs (ng/ml·hr)		
			Ratio (Cmax)		Ratio (AUC)	
BE batch	(b) (4)					(b) (4)
(b) (4)						

The Applicant concluded that the formulations with the upper limit (b) (4) and the lower limit (b) (4) can be used to set the dissolution limit specification, which is proposed to be (b) (4) at a 3-hour time point.

Reviewer's assessment:

As shown in Table 24 and Figure 24 below, the dissolution profile of the formulation with (b) (4) (the upper limit of the proposed specification for 3 h time point) is out of the IVIVC range established on pilot formulations T1 and T3. Therefore, the prediction PK profile of this formulation based on the IVIVC model is not meaningful. Consequently, the proposed upper limit of the dissolution criterion at 3 h time-point is not acceptable.

Table 24. Mean dissolution data of upper limit, lower limit, BE batch, and pilot formulation

(b) (4)					

Figure 24. Mean dissolution profiles of upper limit, lower limit, BE batch, and pilot formulations

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

Assessment: {Adequate}

The Applicant conducted an in vitro alcohol dose dumping study on the lowest and highest strengths of Lacosamide Extended-Release Capsules, (b) (4) 200 mg, with 12 dosage units (n=12/batch) at multiple time-points up to 12 hours to obtain complete dissolution profiles in dissolution media 0.1N HCl and pH 6.8 phosphate buffer containing 0, 5, 20, and 40 percent of alcohol.

Table 25. Mean dissolution data of Batch 4559661 (200 mg) in 0.1 N HCl with alcohol

Batch number/time(h)	0.5	1	2	3	4	5	6	8	10	12
Batch 4559661 in 0.1 N HCl with 0% alcohol	10	14	29	47	67	84	95	103	105	104
Batch 4559661 in 0.1 N HCl with 5% alcohol	10	18	40	66	88	100	104	105	105	105
Batch 4559661 in 0.1 N HCl with 20% alcohol	18	48	99	106	107	108	108	108	108	108
Batch 4559661 in 0.1 N HCl with 40% alcohol	48	99	110	112	112	112	111	112	112	113

Table 26. Mean dissolution data of Batch 4559661(200 mg) in pH 6.8 Phosphate Buffer with alcohol

Batch number/time(h)	0.5	1	2	3	4	5	6	8	10	12
Batch 4559661 in pH 6.8 phosphate buffer with 0% alcohol	0	15	30	48	66	82	94	104	104	104
Batch 4559661 in pH 6.8 phosphate buffer with 5% alcohol	11	19	42	68	90	102	106	108	107	108

Batch 4559661 in pH 6.8 phosphate buffer with 20% alcohol	17	52	102	107	107	108	108	108	107	107
Batch 4559661 in pH 6.8 phosphate buffer with 40% alcohol	76	111	113	113	113	113	113	113	113	113

(b) (4)

Figure 25. Mean dissolution profiles of Batch 4559661(200 mg) in 0.1 N HCl with alcohol

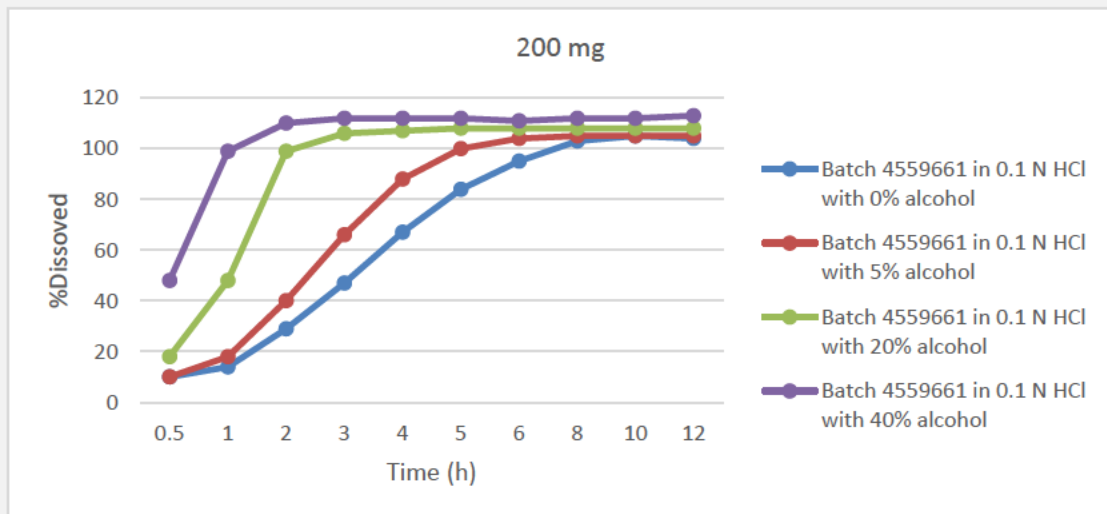
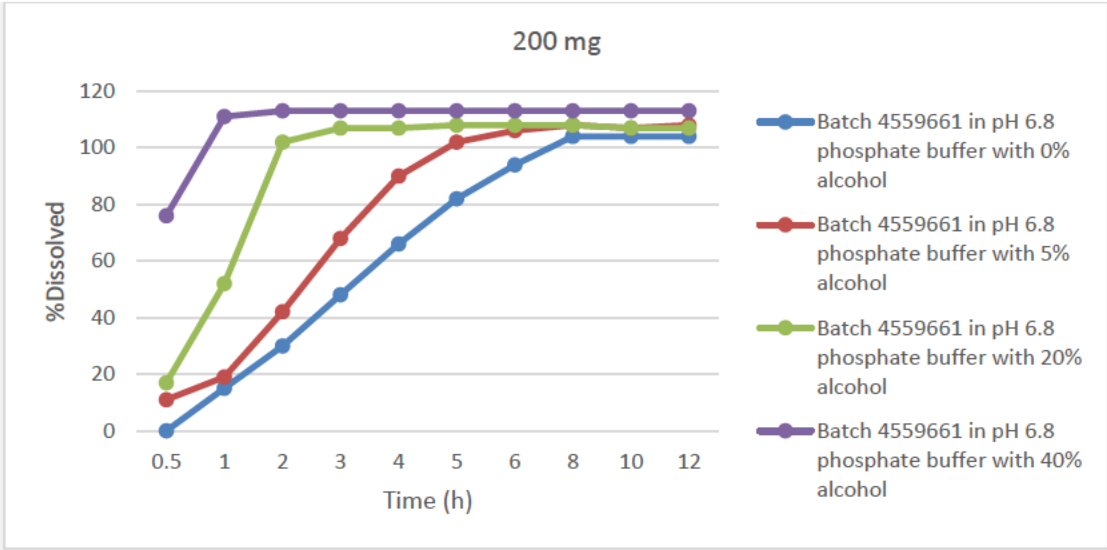


Figure 26. Mean dissolution profiles of Batch 4559661(200 mg) in pH 6.8 Phosphate Buffer with alcohol



(b) (4)

Reviewer's assessment:

The data in Tables 25-28 and Figures 25-28 show that the presence of alcohol can cause faster release of the drug substance from Lacosamide Extended-Release Capsules, (b) (4) 200 mg in both 0.1 N HCl and pH 6.8 phosphate buffer, supported by the calculated similarity factors ($f_2s < 50$). The phenomenon of alcohol-induced dose-dumping was observed in the presence of 20% and 40% alcohol at 2 hours, though with faster occurrence with 40% alcohol. With 5% alcohol, the increased drug release resulted in earlier completion dissolution (2-3 hours) vs. control. It is noted that the Applicant did not propose pertinent labeling languages or instruction regarding clinical consequences with consumption of alcohol/alcoholic beverages with the proposed ER drug product, such as potential pharmacodynamic interaction and concerns for adequate disease control as a result of more rapid drug release as observed in in-vitro system. The above findings will be communicated to the Clinical and the Clinical Pharmacology review teams for proper labeling recommendations.

B.11 EXTENDED-RELEASE DOSAGE FORMS –Extended-Release Claim Assessment: {Adequate}

The provided information supports the “Extended-Release” claim for the proposed lacosamide extended-release capsules, per requirement described in the 21 CFR 320.25(f):

- (i) The drug product meets the extended-release claims made for it.*
- (ii) The bioavailability profile established for the drug product rules out the occurrence of any dose-dumping.*
- (iii) The drug product's steady-state performance is equivalent to a currently marketed non-extended release or extended-release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full new drug application.*
- (iv) The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units.*

1. ER characteristics of the proposed Lacosamide extended-release capsules

Lacosamide extended-release capsules are designed for once-daily (QD) dosing to reduce the frequency of administration and thereby improve patient compliance. In contrast, the listed drug VIMPAT® (Lacosamide) 200 mg film coated tablets is taken twice daily (BID). The clinical PK study (20-VIN-0088) showed that the mean Tmax was prolonged for lacosamide extended-release capsules compared with that of VIMPAT.

As supportive evidence for drug release as designed, the extended-release characteristics of the proposed drug product were also demonstrated in in vitro test conditions (see B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA).

2. The bioavailability profile established for the drug product rules out the occurrence of any dose-dumping

No significant portion of the drug is quickly released in vivo, resulting in a potentially high concentration of the drug being introduced into the systemic circulation. The occurrence of dose dumping is ruled out.

3. The proposed drug product's steady-state performance is equivalent to a currently marketed immediate release drug product (i.e., VIMPAT®)

The results of Study 20-VIN-0095 shows that 400 mg lacosamide extended-release capsules (administered once daily) is bioequivalent to VIMPAT® IR 200 mg tablets (administered twice daily) at a steady state in terms of Cmax, Cmin, and AUC0 to τ.

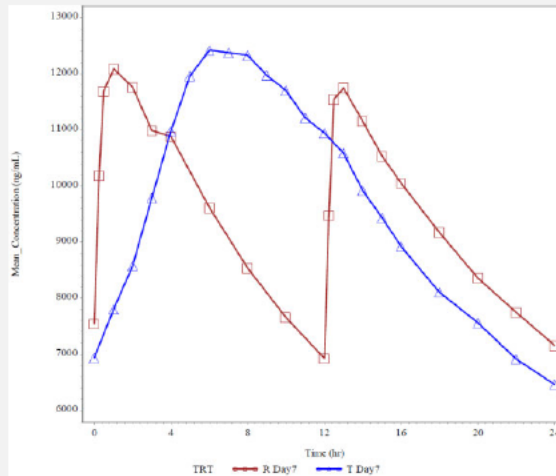
4. The proposed drug product's formulation provides consistent pharmacokinetic performance between individual dosage units

The PK data of Study 20-VIN-0088 and Study 21-VIN-0184 show that the variability (mean %CV across studies) of Cmax and AUCinf is less than 23% for the proposed drug product, as shown in Table 29. Additionally, lacosamide extended-release capsules performance at steady-state is comparable (e.g., degree of fluctuation is lower, mean fluctuation percentage 68.109 for the proposed drug vs 71.568 for VIMPAT) (Figure 29).

Table 29. Variability of single dose lacosamide in PK studies

STUDY	FORMULATION	DOSE (MG)	FOOD CONDITION	N	CV% (C _{MAX})	CV% (AUC _{INF})
20-VIN-0088	T1	400	Fasted	23	16.51	22.77
20-VIN-0088	T2	400	Fasted	24	14.86	21.42
20-VIN-0088	T3	400	Fasted	23	17.00	22.67
21-VIN-0184	Test	200	Fasted	18	11.55	18.15
21-VIN-0184	Test	200	Fed	17	10.54	15.68

Figure 29. Linear plots of mean plasma concentrations versus time at steady state



B. 13 BIOWAIVER REQUEST

Assessment: *Adequate*

The Applicant requested a biowaiver for lower strengths: 150 mg, 100 mg, (b) (4) by providing the following supporting information and data:

1. Pivotal BE study between the proposed 200 mg and LD-VIMPAT® (Lacosamide) 200 mg

Study title:

An open label, balanced, randomized, multiple-dose, two-treatment, two-sequence, two-period, oral comparative bioavailability study of Lacosamide 200 mg extended-release capsule of Aucta Pharmaceuticals, Inc., USA and VIMPAT® (Lacosamide) 200 mg film coated tablet of UCB, Inc. Smyrna, GA 30080 in healthy, adult, human subjects at a dose of 400 mg under fasting condition.

Table 30. Bioequivalence Analysis of the proposed ER lacosamide capsules 200 mg vs VIMPAT® (Lacosamide) 200 mg film coated tablet (Reference) under Fasting Conditions (Study 20-VIN-0095; N=27)

Parameter	Test	N	RLD	N	Ratio	90% C.I.
AUC _{0-τ,ss}	226248.907	27	221131.272	27	102.31	100.63% - 104.03%
C _{min,ss}	6215.101	27	6660.061	27	93.32	90.66% - 96.05%
C _{max,ss}	12584.623	27	13040.136	27	96.51	92.27% - 100.94%

The Applicant reported that the proposed ER lacosamide capsules 200 mg is bioequivalent to VIMPAT® (Lacosamide) 200 mg film coated tablet at steady state under fasting

conditions. The study results are accepted by Office of Clinical Pharmacology review team.

2. Formulation of the proposed drug

All strengths are compositionally proportional regarding active and inactive components, as shown in Table 31.

Table 31. Qualitative and Quantitative Composition of the proposed drug product

Ingredient	(b) (4)
Lacosamide	(b) (4)
(b) (4)	(b) (4)
Povidone	(b) (4)
(b) (4)	(b) (4)
Ethyl cellulose	(b) (4)
Triethyl citrate	(b) (4)
Hypromellose	(b) (4)
(b) (4)	(b) (4)

3. Comparative dissolution assessment between the biobatch and lower strengths

Figure 30. Mean dissolution profile comparison between the biobatch and 150 mg strength

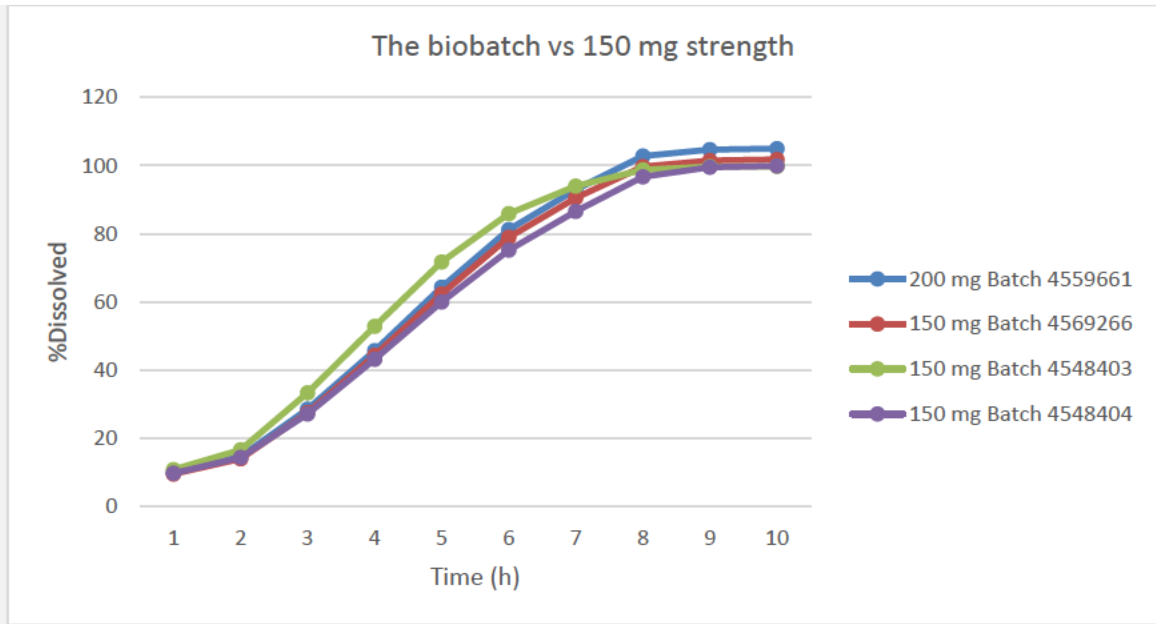
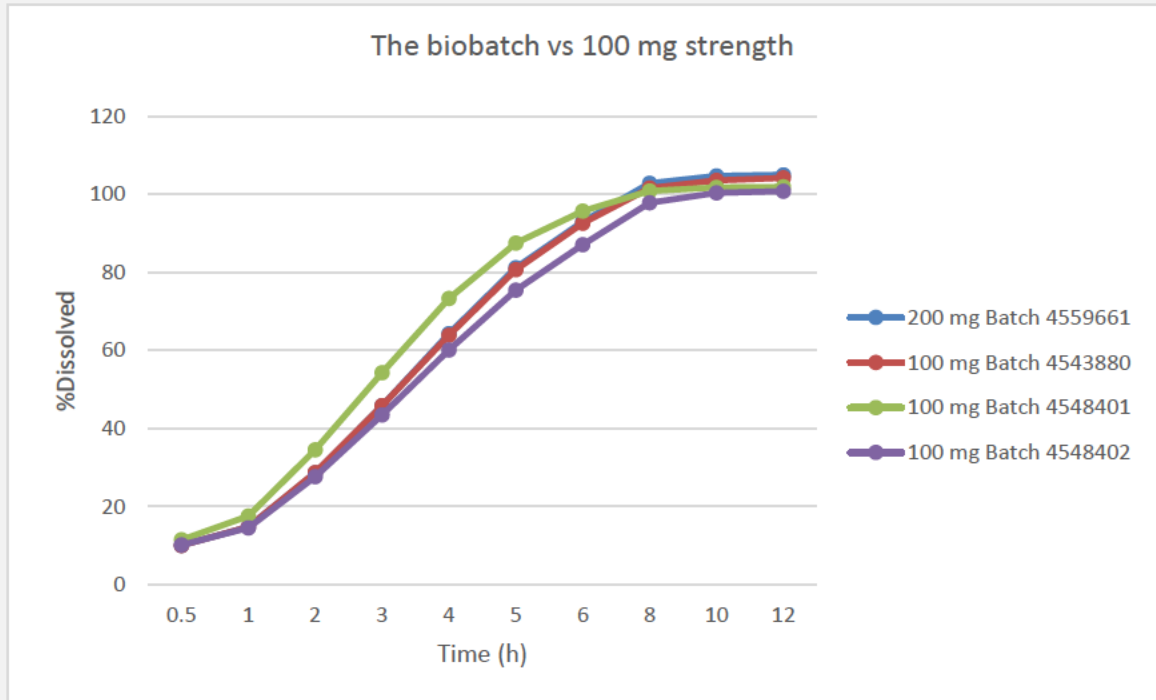


Figure 31. Mean dissolution profile comparison between the biobatch and 100 mg strength



(b) (4)

Table 32. Dissolution Similarity Factors f_2 between the biobatch (Batch 4530661) and lower strengths

Comparison	F2
The biobatch 4530661 vs 150 mg Batch 4569266	85.44
The biobatch 4530661 vs 150 mg Batch 4548403	65.75
The biobatch 4530661 vs 150 mg Batch 4548404	68.67
The biobatch 4530661 vs 100 mg Batch 4543880	99.06
The biobatch 4530661 vs 100 mg Batch 4548401	61.05
The biobatch 4530661 vs 100 mg Batch 4548402	69.73

(b) (4)

Both figurative illustration and calculated similarity factors (Table 32) show that the lower strengths not studied clinically have similar drug release/dissolution profiles to the biobatch/biostrength (200 mg).

4. PK linearity across the therapeutical range

In the response to Biopharmaceutics Information Request (IR 1 dated 11/7/2022; see Appendix), the Applicant stated that lacosamide is a BCS class 1 drug, which has high solubility and high permeability. Lacosamide immediate-release formulation demonstrates complete absorption after oral administration with negligible first-pass metabolism and a bioavailability of approximately 100%. As stated in the LD VIMPAT® original NDA review (N22-253), both C_{max} and AUC increase proportionally, with the doses ranging from 100 mg to 800 mg after a single dose and multiple doses of VIMPAT®. Based on the outcome of the clinical study and drug properties of lacosamide, the Applicant concluded

that Lacosamide XR at 400 mg total doses is expected to achieve complete absorption after oral administration and show linear pharmacokinetics for any doses up to 400 mg.

In addition, the Applicant has initiated a dose proportionality/linearity study of lacosamide XR capsules ranging from 100 mg to 400 mg to provide definitive supporting evidence. The results of the abovementioned study are expected to be submitted in the week of March 15, 2023.

Reviewer's comment

The labeling of VIMPAT shows that the PK of lacosamide from the IR formulation is linear from 100 mg to 800 mg. Considering the physicochemical properties of lacosamide (including pH-independent and high aqueous solubility) and similar drug release/dissolution profiles in multimedia across physiologic pH range, this Reviewer agrees with the Applicant that the proposed lacosamide ER capsules will likely demonstrate linear PK within the same therapeutic range.

(b) (4)

(b) (4)

This Reviewer determines that biowaiver can be granted for lower strengths (i.e., 100 mg, and 150 mg) for the following reasons: (1) there is acceptable PK data for the proposed highest 200 mg strength, (2) the highest strength and lower strengths have the same dosage form; (3) The formulation of lower strengths is proportionally similar in composition to the highest strength; (4) All strength have the same manufacturing process; (5) The highest strength and lower strengths have comparable dissolution profiles; and (6) There is evidence of PK linearity over the proposed dose range.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None.

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