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RESEARCH**

APPLICATION NUMBER:

218879Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	September 16, 2025
From	Philip H. Sheridan, MD Emily Freilich, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	NDA 218879 Class 2 Resubmission
Applicant	OWP Pharmaceuticals, Inc.
Date of Submission	March 17, 2025
PDUFA Goal Date	September 17, 2025
Proprietary Name	Subvenite
Established or Proper Name	Lamotrigine Oral Suspension
Dosage Form(s)	Oral Suspension 10 mg/ml
Applicant Proposed Indication/Population	Epilepsy: Subvenite is indicated as adjunctive therapy for the following seizure types in patients aged 2 years and older: • partial-onset seizures. • primary generalized tonic-clonic (PGTC) seizures. • generalized seizures of Lennox-Gastaut syndrome. Subvenite is indicated for conversion to monotherapy in adults (aged 16 years and older) with partial-onset seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single antiepileptic drug (AED). Bipolar Disorder: Subvenite is indicated for the maintenance treatment of bipolar I disorder to delay the time to occurrence of

	mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy.
Applicant Proposed Dosing Regimen	Dosing is the same as for the listed drug, Lamictal. The numerous dosing tables in the Lamictal prescribing information are based on concomitant medications, indication, and patient age and are proposed for the Subvenite prescribing information.
Recommendation on Regulatory Action	Approval

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Subvenite (lamotrigine oral suspension, 10 mg/ml) is a new formulation of an already approved drug (lamotrigine). Subvenite is proposed for the same indications as the listed drug (LD), Lamictal (lamotrigine) tablets, NDA 020241:

1. as adjunctive therapy for the following seizure types in patients aged 2 years and older:
 - partial-onset seizures.
 - primary generalized tonic-clonic (PGTC) seizures.
 - generalized seizures of Lennox-Gastaut syndrome.
2. for conversion to monotherapy in adults (aged 16 years and older) with partial-onset seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single antiepileptic drug (AED).
3. for the maintenance treatment of bipolar I disorder to delay the time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy.

This submission is a Class 2 NDA resubmission of this 505(b)(2) application using Lamictal (lamotrigine) tablets, approved under NDA 020241, as the LD. The determination of benefit and risk for this new formulation of lamotrigine depends on the previous findings of effectiveness and safety for the LD and on a demonstration of adequate bridging with bioavailability and bioequivalence studies from Subvenite to the LD.

Lamotrigine is currently marketed as immediate release tablets, extended-release tablets, orally disintegrating tablets, and tablets for suspension.

Lamotrigine has a well characterized safety profile. The primary risk associated with lamotrigine use is that of severe allergic reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and multiorgan hypersensitivity reactions (drug reaction with eosinophilia and systemic symptoms, DRESS). Additional risks include hemophagocytic lymphohistiocytosis, cardiac rhythm and conduction abnormalities, blood dyscrasias, aseptic meningitis, suicidal behavior and ideation, and medication errors. Common adverse reactions with lamotrigine use include dizziness, headache, diplopia, ataxia, nausea, vomiting, abdominal pain, blurred vision, and somnolence. Despite these risks and adverse reactions, lamotrigine has proven to be an effective medication for the treatment of epilepsy and bipolar disorder.

Subvenite has been shown to have comparative bioavailability to the LD, Lamictal, in a pivotal comparative bioavailability study and a food effect study in healthy adult volunteers. No new or unexpected adverse events were discovered in the course of the development program of Subvenite in healthy adult volunteers.

When this NDA was previously submitted on March 4, 2024, the Office of Product Quality (OPQ) review team found that the Applicant had failed to adequately characterize the identity, strength, and purity of the proposed drug product); therefore, the NDA received a Complete Response on January 3, 2025. In this current Class 2 resubmission, the Applicant has successfully addressed the previous OPQ-identified deficiencies in the NDA.

A more detailed benefit risk assessment is presented in the Cross-Discipline Team Leader (CDTL) summary review, dated January 3, 2025, of the original NDA submission.

2. Background

This 505(b)(2) Class 2 NDA resubmission for Subvenite (lamotrigine) relies on the Agency's findings of safety and effectiveness for the LD, Lamictal 100 mg tablet (NDA 020241), which was approved in 1994.

In the original NDA submission of March 4, 2024, the Applicant provided evidence from two Phase 1 clinical pharmacology studies that Subvenite has similar bioavailability to that of the LD. However, due to Product Quality deficiencies, this application received a Complete Response letter on January 3, 2025.

Key Regulatory History since January 2025

Significant interactions between FDA and the Applicant include the following:

March 17, 2025 Class 2 Resubmission of NSA 218879

August 12, 2025 Pediatric Research Committee (PeRC) concurred with the Division's plan to issue two PREA PMRs to address the use of Subvenite in pediatric patients 1 month to less than 2 years of age for the epilepsy indications

August 15, 2025 Agreement with Applicant on Postmarketing Requirements and milestone dates

September 15, 2025 Agreement with Applicant on prescribing information and medication guide.

3. **Product Quality**

The technical lead for the Office of Product Quality (OPQ) review team was Dr. Martha Heimann, and the reviewers were Dr. Grace Chiou, Dr. Martha Heimann, and Dr. Julia Pinto (drug product/labeling); Dr. Khalid Khan and Dr. Tianhong Tim Zhou (manufacturing); Dr. Swapna Parnu and Dr. Ta-Chen Wu (biopharmaceutics); and Erica Keafer (regulatory business process manager).

During the previous review of the original NDA submission, the OPQ review team had determined that the proposed drug substance, microbiology, and labeling were adequate. However, the OPQ review team had found that the Applicant had not provided adequate information on the proposed drug product to ensure its identity, strength, and purity. The outstanding deficiencies of the original application were related to inadequate information to support acceptable quality control of the drug product. The reviewers noted in their review of the original NDA that “extensive deficiencies related to the proposed dissolution method, validation of analytical methods used for release and stability testing, lack of in-use stability data, and control of container closure leachables were communicated as information requests (IRs) early in the review cycle. The Applicant adequately addressed some of the IRs; however, the responses to the remaining IRs are either incomplete (i.e., ‘reports to be submitted at a later time’) or inadequate.”

In addition, during the review of the original NDA submission, the OPQ team was advised by the Office of Regulatory Affairs that the manufacturing inspection made a (b) (4) recommendation for one of the drug substance manufacturing facilities (b) (4).

Therefore, although the other discipline reviews recommended approval, the OPQ review team recommended a Complete Response to the original NDA submission due to these deficiencies as summarized in the Complete Response letter of January 3, 2025.

After review of the current NDA resubmission, the OPQ reviewers now state, “The applicant has provided adequate information to ensure the identity, strength, quality, and purity and performance for this drug/device combination product. The overall manufacturing

inspection recommendation is approved for all facilities associated with this application. The proposed labeling is acceptable from a product quality perspective . . .The applicant has withdrawn both (b) (4) sites. All remaining facilities are acceptable.” (Executive Summary, OPQ NDA 218879 Integrated Quality Assessment, August 19, 2025, pages 2-3)

The OPQ review team therefore recommends Approval of NDA 218879 Subvenite.

4. Nonclinical Pharmacology/Toxicology

No nonclinical data were submitted in this application, and no nonclinical issues arose during review of this application. Therefore, a nonclinical pharmacology/toxicology review was not conducted.

5. Clinical Pharmacology

No new clinical pharmacology data were submitted in this application, and no new clinical pharmacology issues arose during review of this application. Therefore, a new review by the Office of Clinical Pharmacology (OCP) was not conducted.

The OCP review team review of the original NDA application, dated December 18, 2024, was written by Dr. Dawei Li (primary reviewer) and Dr. Yun Xu (secondary reviewer). The two key clinical pharmacology studies were noted to be a pivotal bioavailability and bioequivalence (BA/BE) study under fasting conditions (Study LAMO-159-22) and a food effect study (Study LAMO-160-22). Based on these studies, the OCP review team concluded that the Applicant had provided adequate evidence that Subvenite has similar bioavailability to the LD, Lamictal, which constitutes an adequate scientific bridge. Therefore, the OCP review team recommended approval of this application.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

No efficacy data were submitted since the application relies on the previous finding of effectiveness for the LD and on the determination of the comparative bioavailability of Subvenite to the LD.

8. Safety

No new safety data were submitted in this application, and no new safety issues arose during review of this application. Therefore, no new safety review by the clinical safety reviewer, Dr. Amy Kao, was conducted.

Dr. Kevan VanLandingham, previous clinical safety reviewer, wrote the clinical safety review (dated January 2, 2025) of the original NDA submission. He concluded that no substantial new safety signal has been identified for Subvenite compared to the LD relied upon for a safety determination.

9. Advisory Committee Meeting

There was no advisory committee for this 505(b)(2) application.

10. Pediatrics

The Applicant had not submitted an Agreed initial Pediatric Study Plan (iPSP) prior to the original submission of this NDA. Therefore, the Division presented a plan to the Pediatric Research Committee (PeRC) that, if the NDA were to be approved, a postmarketing requirement (PMR) (rather than the iPSP) would address the PREA requirement to study this formulation for the treatment of partial onset seizures in pediatric patients 1 month to less than 2 years of age. The Division of Psychiatry had determined that no further studies are required for the pediatric indication of bipolar disorder because of an earlier negative study in pediatric patients 10 to 17 years of age. The PeRC agreed with this plan on November 19, 2024.

The planned PMRs were communicated to the Applicant in the 8-week Postmarketing Requirement Communication letter dated November 7, 2024. After the Class 2 resubmission of the NDA, the PeRC again reviewed the proposed PMRs on August 12, 2025, and concurred with the Division's plan. See Section 13 of this CDTL Summary Review for the PMRs as stated in the approval letter.

11. Other Relevant Regulatory Issues

Dr. VanLandingham determined that there were no investigators with disclosable financial interests/arrangements in the two clinical pharmacology studies submitted with the original NDA application.

The Division of Medication Error Prevention and Analysis 2 (DMEPA2) review (based on its evaluation of the proposed Prescribing Information, medication guide, and container label and carton labeling) provided specific recommendations to include in negotiations with the Applicant.

The Division of Medical Policy Programs (DMPP) review of the proposed Medication Guide provided specific recommendations to include in the labeling negotiations with the Applicant.

12. Labeling

Refer to the final negotiated product label. Labeling negotiations with the Applicant have been completed, and the Applicant has accepted all recommended changes.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

There is no need for a Risk Evaluation and Management Strategy (REMS) for this drug product because the LD used to establish safety for Subvenite in the context of this 505(b)(2) submission does not have a REMS, and the additional data submitted for Subvenite in the original NDA submission did not identify any new safety signals.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

See Section 10 (Pediatrics) of this CDTL summary review for the history of the required PMR studies.

The required PMR studies, as stated in the NDA approval letter, are as follows:

- | | |
|--------|--|
| 4884-1 | Conduct a study to evaluate the pharmacokinetics, safety, and tolerability of an age-appropriate formulation of lamotrigine oral suspension (Subvenite) to determine a dosing regimen for partial-onset seizures in pediatric patients 1 month to less than 2 years of age. The study should identify the drug exposure that is similar to the exposure that is effective in patients 2 years and older with partial-onset seizures. |
| | Draft Protocol Submission: 03/2026 |
| | Final Protocol Submission: 07/2026 |
| | Study Completion: 07/2028 |
| | Final Report Submission: 01/2029 |
| 4884-2 | Conduct a long-term open-label safety study of lamotrigine oral suspension (Subvenite) in pediatric patients 1 month to 2 years of age. |
| | Draft Protocol Submission: 03/2026 |
| | Final Protocol Submission: 01/2029 |
| | Study Completion: 01/2031 |
| | Final Report Submission: 07/2031 |

There are no planned postmarketing commitments for this NDA.

14. Recommended Comments to the Applicant

See the Approval letter.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PHILIP H SHERIDAN
09/16/2025 09:09:08 AM

EMILY R FREILICH
09/16/2025 09:26:26 AM
On behalf of DN2

Cross-Discipline Team Leader Review

Date	January 3, 2025
From	Philip H. Sheridan, MD Paul R. Lee, MD, PhD, MA
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	NDA 218879
Applicant	OWP Pharmaceuticals, Inc.
Date of Submission	March 4, 2024
PDUFA Goal Date	January 4, 2025
Proprietary Name	Subvenite
Established or Proper Name	Lamotrigine Oral Suspension
Dosage Form(s)	Oral Suspension 10 mg/ml
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	mood episodes (depression, mania, hypomania, mixed episodes) in patients treated for acute mood episodes with standard therapy.
Applicant Proposed Dosing Regimen	Dosing is the same as for the listed drug, Lamictal. The numerous dosing tables in the Lamictal prescribing information are based on concomitant medications, indication, and patient age and are proposed for the Subvenite prescribing information.
Recommendation on Regulatory Action	Complete Response

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

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This submission is a 505(b)(2) application using Lamictal (lamotrigine) tablets, approved under NDA 020241, as the LD. The determination of benefit and risk for this new formulation of lamotrigine depends on the previous findings of effectiveness and safety for the LD and on a demonstration of adequate bridging with bioavailability and bioequivalence studies from Subvenite to the LD.

Lamotrigine is currently marketed as immediate release tablets, extended-release tablets, orally disintegrating tablets, and tablets for suspension.

Lamotrigine has a well characterized safety profile. The primary risk associated with lamotrigine use is that of severe allergic reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and multiorgan hypersensitivity reactions (drug reaction with eosinophilia and systemic symptoms, DRESS). Additional risks include hemophagocytic lymphohistiocytosis, cardiac rhythm and conduction abnormalities, blood dyscrasias, aseptic meningitis, suicidal behavior and ideation, and medication errors. Common adverse reactions with lamotrigine use include dizziness, headache, diplopia, ataxia, nausea, vomiting, abdominal pain, blurred vision, and somnolence. Despite these risks and adverse reactions, lamotrigine has proven to be an effective medication for the treatment of epilepsy and bipolar disorder.

Subvenite has been shown to have comparative bioavailability to the LD, Lamictal, in a pivotal comparative bioavailability study and a food effect study in healthy adult volunteers. No new or unexpected adverse events were discovered in the course of the development program of Subvenite in healthy adult volunteers.

However, because the Office of Product Quality (OPQ) review team found that the Applicant failed to characterize adequately the identity, strength, and purity of the proposed drug product (discussed in Section 3 of this review), this NDA will receive a Complete Response.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- Approximately 0.5 to 1% of the US population suffers from epilepsy, a condition of recurrent seizures, most commonly focal seizures, but also generalized seizures. - Approximately 30% of patients continue to have seizures, despite treatment with multiple antiseizure medications (ASMs). - Patients with uncontrolled seizures are at risk of increased morbidity and mortality. - Epilepsy can begin at any time of life, but it is most commonly first diagnosed in children, and people over the age of 65. - Bipolar disorder is characterized by alternating episodes of depression and either mania (Bipolar I) or hypomania (Bipolar II). - The prevalence of bipolar disorder I and II in the US is estimated to be approximately 4%. - Bipolar disorder is most often identified in young adults, but it can occur in adolescents. It is rare but can be diagnosed in children. - The presence of severe manic episodes, potential psychotic features, and a propensity for cycling between manic and depressive episodes contribute to higher functional impairment and a higher risk of hospitalization in patients with bipolar I.	Epilepsy and bipolar disorder are serious diseases with significant morbidity and mortality which are often refractory to therapy, and which may require multiple effective treatments with formulations suitable for children and adults.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• More than 20 ASMs have been approved for the treatment of focal or generalized seizures • The most common types of medications prescribed for bipolar disorder include mood stabilizers and atypical antipsychotics. Mood stabilizers such as lithium, lamotrigine, and valproate can help prevent mood episodes or reduce their severity. Lithium also can decrease the risk of suicide. • Lamotrigine is currently marketed as immediate release tablets, extended-release tablets, tablets for oral suspension and fast melt tablets. • Currently, there is no marketed premixed oral suspension or solution formulation of lamotrigine.	Lamotrigine is approved and commonly used for the treatment of epilepsy and bipolar disorder. There is a need for a premixed oral solution or suspension of lamotrigine for individuals who have difficulty administering or receiving the currently marketed formulations of lamotrigine.
Benefit	• Lamotrigine has been previously demonstrated to improve seizure control in multiple seizure types and to delay the time to occurrence of manic episodes when used as a maintenance therapy of bipolar disorder. • Subvenite (lamotrigine oral suspension) has been shown to have comparative bioavailability to the LD, Lamictal, in a pivotal comparative bioavailability study and a food effect study in healthy adult volunteers. • This new oral suspension formulation (Subvenite) will facilitate lamotrigine use in very young patients, in patients who have difficulty swallowing the currently marketed oral formulations of lamotrigine, and in patients requiring administration of lamotrigine by gastric or gastrojejunal tube.	Subvenite will provide another option to patients who have difficulty receiving the currently marketed formulations of lamotrigine including children, elderly patients, and patents requiring a gastric or gastrojejunal tube.
Risk and Risk Management	• The serious risks for lamotrigine include: ○ Allergic reactions, including Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) , and drug reaction with eosinophilia and systemic symptoms (DRESS) ○ Drug-drug interactions affecting lamotrigine metabolism and effects of lamotrigine on other drugs (e.g. estradiol) ○ Potential cardiac rhythm and conduction abnormalities • These adverse events have been adequately managed by the extensive	The adverse effects and drug-drug interactions of Subvenite are the same as those of the LD Lamictal and can be managed by the proposed extensive labeling instructions and Medication Guide which align with that of the LD. Due to the deficiencies in product quality, a Complete Response action will be taken for

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	instructions in current approved labeling and the Medication Guide of the LD, Lamictal. • No new or unexpected adverse events were identified in the development program of this new formulation of lamotrigine.	this application, therefore, labeling recommendations will not be made, and postmarketing requirements (PMRs) will not be issued during this review cycle.

2. Background

This 505(b)(2) application for Subvenite (lamotrigine) relies on the Agency's findings of safety and effectiveness for the LD, Lamictal 100 mg tablet (NDA 020241), which was approved in 1994.

The Applicant has provided evidence from two Phase 1 clinical pharmacology studies that Subvenite has similar bioavailability to that of the LD.

Regulatory History

NDA 218879 relies on the Agency's previous finding of safety and effectiveness for the LD, Lamictal 100 mg tablet (NDA 020241).

Significant interactions between FDA and the Applicant include the following:

August 16, 2018	Type B pre-IND meeting Written Responses stated that the 505(b)(2) regulatory pathway appears appropriate.
February 13, 2019	Sponsor opened IND 140073.
April 4, 2019	IND 140073 was placed on Full Clinical Hold, as the Sponsor had not provided adequate CMC information to support the safety of the proposed study.
May 15, 2019	Complete response to hold submitted.
June 3, 2019	Remove Full Clinical Hold letter issued.
September 21, 2021	iPSP submitted.
November 29, 2021	Proprietary name found conditionally acceptable.
December 20, 2021	iPSP Written Response sent to Sponsor. (See Section 10 [Pediatrics] of this summary review)

March 17, 2022 Revised iPSP submitted (iPSP-Other).

September 29, 2022 Email correspondence to Sponsor regarding revised iPSP

December 4, 2023 Type B Pre-NDA Written Responses issued regarding product quality.

March 4, 2024 NDA 218879 submitted by Applicant.

See the clinical review for additional regulatory interactions.

3. Product Quality

The technical lead for the Office of Product Quality (OPQ) review team was Dr. Martha Heimann, and the reviewers were Dr. Sophie Rubashkin and Dr. Katherine Duncan (drug substance), Dr. Grace Chiou and Dr. Julia Pinto (drug product/labeling), Dr. Khalid Khan and Dr. Tianhong Tim Zhou (manufacturing), Dr. Swapna Parnu and Dr. Ta-Chen Wu (biopharmaceutics), Dr. George Arhin and Bethanie Lee (microbiology), and Erica Keafer (regulatory business process manager).

The OPQ review team determined that the proposed drug substance, microbiology, and labeling were adequate.

However, the OPQ review team found that the Applicant had not provided adequate information on the proposed drug product to ensure its identity, strength, and purity. The outstanding deficiencies are related to inadequate information to support acceptable quality control of the drug product. The reviewers note that “extensive deficiencies related to the proposed dissolution method, validation of analytical methods used for release and stability testing, lack of in-use stability data, and control of container closure leachables were communicated as information requests (IRs) early in the review cycle. The Applicant adequately addressed some of the IRs; however, the responses to the remaining IRs are either incomplete (i.e., ‘reports to be submitted at a later time’) or inadequate.”

In addition, the OPQ team was advised by the Office of Regulatory Affairs that the manufacturing inspection made a “Withhold” recommendation for one of the drug substance manufacturing facilities (b) (4).

See the complete response letter for the OPQ team’s detailed comments to the Applicant regarding these deficiencies and the actions required to address them.

The OPQ review team recommends a Complete Response for NDA 218879 Subvenite.

4. Nonclinical Pharmacology/Toxicology

No nonclinical data were submitted in this application, and no nonclinical issues arose during review of this application. Therefore, a nonclinical pharmacology/toxicology review was not conducted.

5. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) review was written by Dr. Dawei Li (primary reviewer) and Dr. Yun Xu (secondary reviewer).

The two key clinical pharmacology studies were a pivotal bioavailability and bioequivalence (BA/BE) study under fasting conditions (Study LAMO-159-22) and a food effect study (Study LAMO-160-22).

Study LAMO-159-22: Pivotal Comparative Bioavailability and Bioequivalence Study

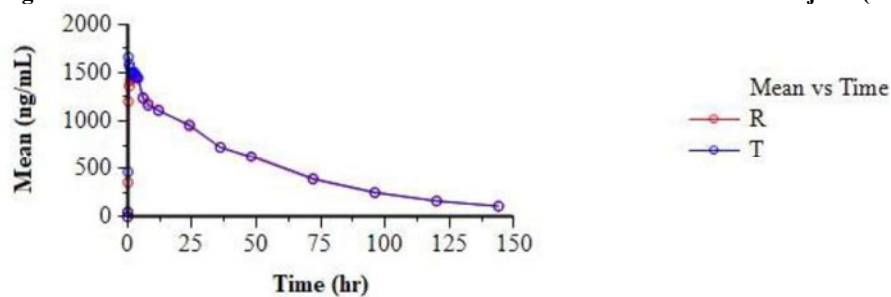
Study LAMO-159-22 was an open-label, randomized, balanced, single-dose, two-sequence, two-treatment, two-period, two-way crossover BA/BE study of Subvenite 10 mg/mL and the LD Lamictal tablet 100 mg in healthy adult volunteers under fasting conditions.

Dr. Li states that the overall design of Study LAMO-159-22 (including the dose selection, route of administration, study population, study sample size, PK sampling schedule, washout period and bioanalytical method validation data) was appropriate.

Thirty-six subjects were enrolled into the study, and 34 subjects completed all study activities. The two subjects who withdrew are discussed in Section 8 of this summary review.

All 34 subjects' concentration data were used in pharmacokinetics and statistical evaluation for lamotrigine. A linear plot of time versus mean plasma concentration for lamotrigine is presented in Figure 1 ("R" denoting the LD and "T" denoting Subvenite). The descriptive statistics for the PK parameters of each treatment are shown in Table 1. The relevant bioequivalence results between Subvenite and the LD under fasting conditions are presented in Table 2.

Figure 1. Linear Plot of Time versus Mean Plasma Concentration for all Subjects (n=34)



R (reference): Lamictal (LD); T (test): Subvenite

Source: Applicant's Clinical Study Report-Protocol LAMO-159-22, page 23

Table 1. Descriptive statistics for PK parameters for Lamotrigine (Fasting, n=34)

Summary of Pharmacokinetic Results: Lamotrigine				
Parameters	Test (T)		Reference (R)	
	Mean $\pm$ SD	CV (%)	Mean $\pm$ SD	CV (%)
t_{max} (hr)	0.330 (0.330 – 12.000)	191.9	1.000 (0.330 – 3.500)	81.6
C_{max} (ng/mL)	1894.749 $\pm$ 404.971	21.4	1777.679 $\pm$ 444.521	25.0
AUC_{0-t} (hr $\cdot$ ng/mL)	74891.438 $\pm$ 16118.343	21.5	73962.589 $\pm$ 14731.795	19.9
AUC_{0-inf} (hr $\cdot$ ng/mL)	82081.018 $\pm$ 21635.447	26.4	80847.083 $\pm$ 19356.613	23.9
K_{el} (1/hr)	0.019 $\pm$ 0.005	24.1	0.019 $\pm$ 0.004	22.8
$t_{1/2}$ (hr)	38.783 $\pm$ 10.831	27.9	38.706 $\pm$ 8.515	22.0

Source: Applicant's Clinical Study Report-Protocol LAMO-159-22, Table 1, page 22

Table 2. Ratio of the Least Squares Geometric Means of PK parameters and 90% Confidence Intervals of Lamotrigine (Fasting, n=34)

Parameters	Geometric Mean		% Ratio	90% CI		Power	ISCV %
	Test	Reference		Lower	Upper		
Ln (C _{max}) (ng/mL)	1856.5930	1733.1991	107.12	100.07	114.67	99.93	16.6
Ln (AUC _{0-t}) (hr*ng/mL)	73266.7508	72609.0111	100.91	98.06	103.83	>99.99	6.9
Ln (AUC _{0-inf}) (hr*ng/mL)	79522.2104	78732.3721	101.00	97.82	104.30	>99.99	7.8

Source: Applicant's Clinical Study Report-Protocol LAMO-159-22, Table 2, page 22

Dr. Li conducted an independent analysis and verified that the C_{max}, AUC_{0-t}, and AUC_{0-inf} results were within the acceptable limits of 80.00% to 125.00% for establishing the bioequivalence of Subvenite to the LD under fasting conditions.

Study LAMO-160-22: Food Effect Study

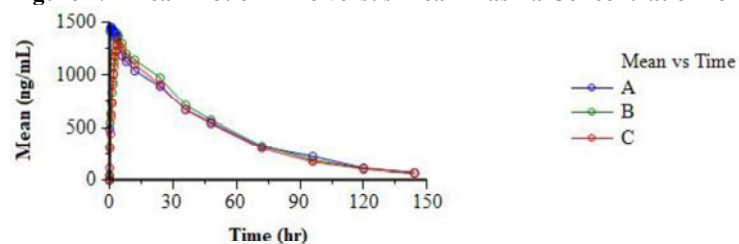
Study LAMO-160-22 was an open-label, randomized, balanced, single-dose, two-treatment, three treatment condition, three-period, six-sequence, crossover oral food effect and fed BE/BA study of Subvenite and the LD in healthy adult volunteers.

Dr. Li states that the overall design of this food effect study (including the dose selection, route of administration, study population, study sample size, PK sampling schedule, washout period and bioanalytical method validation data) was appropriate.

Thirty-six subjects were enrolled into the study, and 33 subjects completed all study activities. The three subjects who withdrew are discussed in Section 8 of this summary review.

All 33 subjects' concentration data were used in the pharmacokinetics and statistical evaluation for lamotrigine. A linear plot of time versus mean plasma concentration for lamotrigine is presented in Figure 2 ("A" denoting Subvenite under fasting conditions, "B" denoting Subvenite under fed conditions, and "C" denoting the reference/LD under fed conditions). The descriptive statistics for the PK parameters of each treatment are shown in Table 4. The relevant bioequivalence results of Subvenite under fasting and fed conditions are presented in Table 5.

Figure 2. Linear Plot of Time versus Mean Plasma Concentration for all Subjects (n=33)



A: Subvenite under fasting conditions; B: Subvenite under fed conditions; C: Lamictal (LD) under fed conditions

Source: Applicant's Clinical Study Report-Protocol LAMO-160-22, page 2

Table 4. Descriptive Statistics for PK parameters for Lamotrigine (N = 33)

	Arithmetic Mean $\pm$ SD (N = 33)		
	Test (Fasting) product	Test (Fed) product	Reference (Fed) product
$^{\#}T_{max}$ (hr)	1.000 (0.330 – 4.000)	4.000 (0.330 – 8.000)	4.000 (1.000 – 24.000)
C_{max} (ng/mL)	1775.642 $\pm$ 412.163	1429.437 $\pm$ 184.713	1410.312 $\pm$ 264.829
AUC_{0-4} (hr*ng/mL)	66017.007 $\pm$ 13331.890	67269.055 $\pm$ 14616.335	62909.725 $\pm$ 13986.965
$AUC_{0-\infty}$ (hr*ng/mL)	69471.526 $\pm$ 15454.130	70623.083 $\pm$ 17102.889	66861.901 $\pm$ 16670.303
K_{el} (1/hr)	0.024 $\pm$ 0.011	0.023 $\pm$ 0.004	0.023 $\pm$ 0.005
$t_{1/2}$ (hr)	31.618 $\pm$ 7.403	30.925 $\pm$ 5.139	31.701 $\pm$ 7.481

Note: $^{\#}$ For T_{max} median (min – max).

Source: Applicant's Clinical Study Report-Protocol LAMO-160-22, Table 1, page 23

Table 5. Geometric Means and Confidence Intervals of Test (Fasting) versus Test (Fed) for Lamotrigine (N = 33)

Parameters	Geometric Mean		% Ratio	90% CI		Power	ISCV %
	Test	Reference		Lower	Upper		
Ln (C _{max}) (ng/mL)	1730.4904	1419.0990	121.94	111.81	132.99	98.64	21.0
Ln (AUC _{0-t}) (hr*ng/mL)	64746.8285	65832.9591	98.35	92.81	104.22	>99.99	13.9
Ln (AUC _{0-inf}) (hr*ng/mL)	67863.3328	68764.2653	98.69	93.03	104.69	99.99	14.2

Source: Applicant's Clinical Study Report-Protocol LAMO-160-22, Table 2A, page 23

Table 6. Geometric Means and Confidence Intervals of Test (Fed) versus Reference (Fed) for Lamotrigine (N = 33)

Parameters	Geometric Mean		% Ratio	90% CI		Power	ISCV %
	Test	Reference		Lower	Upper		
Ln (C _{max}) (ng/mL)	1427.2503	1396.0317	102.24	96.69	108.10	>99.99	13.3
Ln (AUC _{0-t}) (hr*ng/mL)	65994.5244	61333.0320	107.60	102.25	113.23	>99.99	12.2
Ln (AUC _{0-inf}) (hr*ng/mL)	68963.0683	64845.2172	106.35	100.83	112.17	>99.99	12.7

Source: Applicant's Clinical Study Report-Protocol LAMO-160-22, Table 2B, page 24

Dr. Li conducted an independent analysis and verified the food effect results from Study LAMO-160-22.

Dr. Li noted that the relative bioavailability results of Subvenite under fasting and fed conditions indicated that high fat food slightly decreased the C_{max} of lamotrigine but had no impact on the AUCs of lamotrigine.

Dr. Li concluded that the pharmacokinetics of Subvenite are not significantly affected by the presence or absence of food, and that the product can be administered with or without food, which is aligned with the food effect findings of the LD.

The OCP review team recommends approval of this application.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

No efficacy data were submitted since the application relies on the previous finding of effectiveness for the LD and on the determination of the comparative bioavailability of Subvenite to the LD. As discussed in Section 5 of this review, the OCP review team concluded that the Applicant provided adequate evidence that Subvenite has similar bioavailability to the LD, which constitutes an adequate scientific bridge.

8. Safety

Dr. Kevan VanLandingham conducted the clinical safety review of this application.

This application primarily relies on the previous findings of safety for the LD, Lamictal 100 mg tablets, to establish the safety of Subvenite for the proposed indications.

The Applicant provided additional safety data from exposures of healthy volunteers to one or two doses of Subvenite during the two Phase 1 clinical pharmacology studies discussed in Section 5 of this review:

1. Study LAMO-159-22: Pivotal Comparative Bioavailability and Bioequivalence Study
2. Study LAMO-160-22: Food Effect Study

Dr. VanLandingham independently verified the Applicant's presentation of the safety results of these two studies by examining the study adverse event and clinical datasets and by reproducing the safety result summaries presented by the Applicant.

Overall Exposure

In Study LAMO-159-22, 36 subjects were enrolled, and 35 subjects received at least one dose of either the reference treatment (Lamictal, 100 mg tablet) or test treatment (Subvenite, 100 mg). A total of 34 subjects completed the study.

In Study LAMO-160-22, 36 subjects were enrolled in the study and all 36 received at least 1 dose of study drug. A total of 33 subjects completed the study.

Adequacy of the safety database

The submitted safety database provides limited safety data for 1 or 2 doses of Subvenite administered to healthy adult volunteers in Studies LAMO-159-22 and LAMO-160-22.

Based on the overall subject exposure to Subvenite in these two studies, Dr. VanLandingham concludes that the safety database is adequate to provide additional information about the safety of Subvenite for the proposed indication, in the presence of an adequate scientific bridge to the LD. However, the primary assessment of safety remains dependent upon the data from placebo-controlled trials of the LD, Lamictal.

Relevant characteristics of the safety population from Study LAM-159-22 and Study LAM-160-22

Limited demographic information was collected for each subject, including sex, age, weight, and body mass index. Other demographic information, including race, was not collected in these two studies. Demographic characteristics of subjects in Studies LAM-159-22 and LAM-160-22 are presented in Tables 7 and 8, respectively.

Table 7. Demographic characteristics, subjects of Study LAMO-159-22

Demographic characteristic	Total N= 35 (n %)
Sex	
Male	33 (91.7)
Female	3 (8.3)
Age (years)	
Mean	33.8
Median	35.5
Min, max	22, 43
Weight (kg)	
Mean	63.5
Median	63.6
Min, Max	51.0, 83.8
Body Mass Index	
Mean	23.0
Median	24.2
Min, Max	18.7, 24.8

Source: Clinical review, page 29

Table 8. Demographic characteristics, subjects of Study LAMO-160-22

Demographic characteristic	Total N= 36 (n %)
Sex	
Male	32 (88.9)
Female	4 (11.1)
Age (years)	
Mean	32.3
Median	32.0
Min, max	22, 43
Weight (kg)	
Mean	63.7
Median	63.1
Min, Max	51.8, 75.9
Body Mass Index	
Mean	23.2
Median	24.1
Min, Max	18.9, 24.9

Source: Adapted from the clinical review

Safety Results

Deaths

There were no deaths were reported during the two clinical pharmacology studies conducted using Subvenite.

Serious Adverse Events

Dr. VanLandingham verified that the safety summaries of the two studies corresponded to the datasets submitted by the Applicant and concluded that no serious adverse events had occurred.

Dropouts and/or Discontinuations Due to Adverse Events

In Study LAMO-159-22, there were 2 subjects who dropped out of the study due to personal reasons. Subject (b) (6) withdrew from the study during pre-dose vital signs assessment before any dosing, and Subject (b) (6) withdrew from the study 24 hours after dosing in period I (Lamictal 100 mg tablet).

In Study LAMO-160-22, there were 3 subjects who dropped out of the study due to adverse events (AEs):

- Subject (b) (6) experienced a rash 8 hours post dose sample in period I (Lamictal tablet, 100 mg, fasting), cohort II. The rash was considered to be of moderate intensity and did not involve mucosal surfaces. The subject received a 100 mg injection of hydrocortisone and a 22.75 mg injection of pheniramine. The rash resolved after 2 hours, and the subject was withdrawn from the study. Rash is an established risk of lamotrigine treatment and is described prominently within a boxed warning in approved labeling for the LD, Lamictal.
- Subject (b) (6) experienced nausea and vomiting, which occurred 0.67 hours post-dose in period II (Subvenite 100 mg), cohort I; Subject (b) (6) was treated with ondansetron 4 mg IV for the nausea and vomiting of mild intensity, with resolution of the nausea and vomiting after approximately 45 minutes. Subject (b) (6) subsequently exited the study. Nausea is listed as a common adverse reaction with the LD, Lamictal, in current approved labeling.
- Subject (b) (6) experienced an adverse event of fever of mild intensity, 24 hours post dose in period I (Lamictal tablet, 100 mg, fasting), cohort II. Subject (b) (6) was treated with two doses of oral acetaminophen (625 mg each), with resolution of the fever after 9.25 hours. Subject (b) (6) subsequently exited the study. This episode of fever appears unrelated to study treatment.

Treatment Emergent Adverse Events

In Study LAMO-159-22, no adverse events were reported.

In Study LAMO-160-22, a total of 3 adverse events were reported, as described above under “Dropouts and/or Discontinuations Due to Adverse Events.”

Dr. VanLandingham independently examined the individual subject line listings in the study datasets to verify this paucity of adverse events reported in the two studies.

Laboratory Findings

Clinical laboratory assessments during both studies included complete blood counts (hemoglobin, hematocrit, white blood cell count with differential, and platelets), serum clinical chemistry (sodium, potassium, creatinine, urea, glucose, beta HCG [for women only], ALT, AST, alkaline phosphatase, bilirubin, cholesterol, albumin, and total protein), urine toxicology screen (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, ethanol, and morphine), urinalysis with microscopy, and HLA 1A and 1B antigen PCR typing.

Dr. VanLandingham verified that, in both Study LAMO-159-22 and Study LAMO-160-22, all pre- and post-dose laboratory assessments were within normal limits.

Vital Signs

Dr. VanLandingham reviewed the reported vital signs and concluded that they were within acceptable limits throughout the two studies.

Electrocardiograms (ECGs)

Dr. VanLandingham reviewed the ECG data from the two studies and concluded that no clinically relevant changes were observed in the reported data.

Overall Safety Conclusion

Dr. VanLandingham concluded that no substantial new safety signal has been identified for Subvenite compared to the LD relied upon for a safety determination.

9. Advisory Committee Meeting

There was no advisory committee for this 505(b)(2) application.

10. Pediatrics

The Applicant had not submitted an Agreed initial Pediatric Study Plan (iPSP) prior to submission of this NDA. The clinical review team attempted to negotiate an Agreed iPSP with the Applicant during the NDA review, but was unsuccessful. Therefore, the Division presented a plan to the Pediatric Research Committee (PeRC) that, if the NDA were to be approved, a postmarketing requirement (PMR) (rather than the iPSP) would address the PREA requirement to study this formulation for the treatment of partial onset seizures in pediatric patients 1 month to less than 2 years of age. The PeRC agreed with this plan on November 19, 2024. This planned PMR was communicated to the Applicant in the 8-week Postmarketing Requirement Communication letter dated November 7, 2024. However, when it was determined that this NDA submission would receive a Complete Response, issuance of this PMR was deferred to a future NDA submission.

11. Other Relevant Regulatory Issues

Dr. VanLandingham determined that there were no investigators with disclosable financial interests/arrangements in the two clinical pharmacology studies submitted with this application.

The Office of Prescription Drug Promotion (OPDP) and Division of Medical Policy Programs (DMPP), given the pending Complete Response action, deferred comment on the proposed Prescribing Information and the proposed carton and container labeling until the next review cycle.

The Division of Medication Error Prevention and Analysis 2 (DMEPA2) review (based on its evaluation of the proposed Prescribing Information and carton/container labeling) provided specific recommendations to include in future negotiations with the Applicant.

The Office of Study Integrity and Surveillance (OSIS) was consulted for clinical and analytical site inspections for the pivotal relative bioavailability Study LAMO-159-22. OSIS determined that data from this study were reliable. The OSIS review dated August 5, 2024, provided additional details.

12. Labeling

When it was determined that this submission would receive a Complete Response, product labeling negotiations were deferred.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

There is no need for a Risk Evaluation and Management Strategy (REMS) for this drug product because the LD used to establish safety for Subvenite in the context of this 505(b)(2) submission does not have a REMS, and the additional data submitted for Subvenite did not identify any new safety signals.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

As discussed in Section 10 of this summary review (Pediatrics), a planned PMR to satisfy the PREA requirement to study pediatric patients 1 month to less than 2 years of age for the indication of partial onset seizures has been deferred until the next review cycle because a Complete Response action will be taken for this application.

There were no planned postmarketing commitments for this NDA.

14. Recommended Comments to the Applicant

See the Complete Response letter.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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01/03/2025 08:03:43 AM

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