# Cross-Discipline Team Leader Review

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| **Date** | January 3, 2025 |
| **From** | Philip H. Sheridan, MD<br>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 |
| **Applicant Proposed Indication/Population** | **Epilepsy:**<br>Subvenite is indicated as adjunctive therapy for the following seizure types in patients aged 2 years and older:<br>• partial-onset seizures.<br>• primary generalized tonic-clonic (PGTC) seizures.<br>• generalized seizures of Lennox-Gastaut syndrome.<br><br>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).<br><br>**Bipolar Disorder:**<br>Subvenite is indicated for the maintenance treatment of bipolar I disorder to delay the time to occurrence of |

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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**

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 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.<br>• Approximately 30% of patients continue to have seizures, despite treatment with multiple antiseizure medications (ASMs).<br>• Patients with uncontrolled seizures are at risk of increased morbidity and mortality.<br>• Epilepsy can begin at any time of life, but it is most commonly first diagnosed in children, and people over the age of 65.<br>• Bipolar disorder is characterized by alternating episodes of depression and either mania (Bipolar I) or hypomania (Bipolar II).<br>• The prevalence of bipolar disorder I and II in the US is estimated to be approximately 4%.<br>• Bipolar disorder is most often identified in young adults, but it can occur in adolescents. It is rare but can be diagnosed in children.<br>• 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<br>• 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.<br>• Lamotrigine is currently marketed as immediate release tablets, extended-release tablets, tablets for oral suspension and fast melt tablets.<br>• 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.<br><br>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.<br>• 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.<br>• 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:<br>○ Allergic reactions, including Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) , and drug reaction with eosinophilia and systemic symptoms (DRESS)<br>○ Drug-drug interactions affecting lamotrigine metabolism and effects of lamotrigine on other drugs (e.g. estradiol)<br>○ Potential cardiac rhythm and conduction abnormalities<br>• 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.<br><br>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.<br>• 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:

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| 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) |

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| 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**

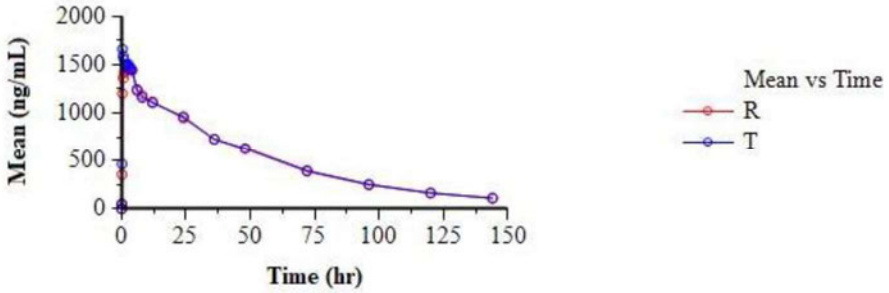
Study LAMO-159-22 was an open-label, randomized, balanced, single-dose, two-sequence, two-treatment, two-period, two-way crossover BA/BE study of Subvenite 10 mg/mL and the LD Lamictal tablet 100 mg in healthy adult volunteers under fasting conditions.

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 ± SD | CV (%) | Mean ± 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 ± 404.971 | 21.4 | 1777.679 ± 444.521 | 25.0 |
| $AUC_{0-t}$ (hr*ng/mL) | 74891.438 ± 16118.343 | 21.5 | 73962.589 ± 14731.795 | 19.9 |
| $AUC_{0-inf}$(hr*ng/mL) | 82081.018 ± 21635.447 | 26.4 | 80847.083 ± 19356.613 | 23.9 |
| $K_{el}$(1/hr) | 0.019 ± 0.005 | 24.1 | 0.019 ± 0.004 | 22.8 |
| $t_{½}$(hr) | 38.783 ± 10.831 | 27.9 | 38.706 ± 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 | T/R | 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 Cmax, AUC0-t, and AUC0-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**

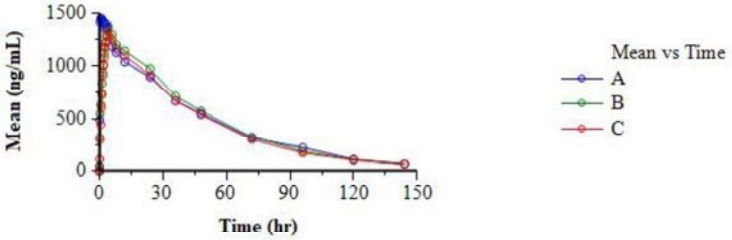
Study LAMO-160-22 was an open-label, randomized, balanced, single-dose, two-treatment, three treatment condition, three-period, six-sequence, crossover oral food effect and fed BE/BA study of Subvenite and the LD in healthy adult volunteers.

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 ± 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 ± 412.163 | 1429.437 ± 184.713 | 1410.312 ± 264.829 |
| **$AUC_{0-t}$ (hr*ng/mL)** | 66017.007 ± 13331.890 | 67269.055 ± 14616.335 | 62909.725 ± 13986.965 |
| **$AUC_{0-inf}$(hr*ng/mL)** | 69471.526 ± 15454.130 | 70623.083 ± 17102.889 | 66861.901 ± 16670.303 |
| **$K_{el}$(1/hr)** | 0.024 ± 0.011 | 0.023 ± 0.004 | 0.023 ± 0.005 |
| **$t_{½}$(hr)** | 31.618 ± 7.403 | 30.925 ± 5.139 | 31.701 ± 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 Cmax 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.

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/s/

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01/03/2025 08:03:43 AM

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01/03/2025 10:08:54 AM