Office of Clinical Pharmacology

Clinical Pharmacology Review

NDA/BLA Number	NDA 218879
Associated IND	140073
Link to EDR	\\CDSESUB1\evsprod\NDA218879\0003
Submission Date	March 3, 2024
Submission Type	505(b)(2)
Brand Name	Subvenite
Generic Name	Lamotrigine
Dosage form (Strength)	Oral Suspension (10 mg/mL)
Proposed Indication	For Epilepsy and Bipolar disorder
Applicant	OWP Pharmaceuticals, Inc.
OCP Review Team	Dawei Li, Ph.D., Yun Xu, Ph.D.

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Executive Summary

In the current New Drug Application (NDA) 218879 for lamotrigine oral suspension (10 mg/mL), Subvenite, the Applicant (OWP Pharmaceuticals) is seeking approval for epilepsy (adjunctive therapy in patients aged 2 years and older, monotherapy in patients aged 16 years and older) and bipolar disorder. The applicant filed this application under the 505(b)(2) pathway and relied on previous findings from listed drugs (LD) LAMICTAL (lamotrigine) tablet 100 mg (NDA 020241) for efficacy and safety.

The clinical pharmacology program includes 2 Phase 1 studies in healthy adult volunteers: Study LAMO-159-22, a pivotal relative bioavailability study between Subvenite lamotrigine oral suspension and the LD (LAMICTAL lamotrigine tablet) under fasting conditions; Study LAMO-160-22, a food effect study on the PK of Subvenite. The results from study LAMO-159-22 showed that the 90% confidence intervals of the geometric LSMs for Cmax and AUC0-inf were within the standard bioequivalence acceptance range (80 to 125%) under fasting conditions, indicating that Subvenite lamotrigine oral suspension and LAMICTAL lamotrigine tablet met the bioequivalent criteria.

The primary focus of this review is to evaluate the adequacy of scientific bridge between Subvenite lamotrigine oral suspension, and the LD (LAMICTAL lamotrigine tablet) based on the pivotal relative bioavailability study (Study LAMO-159-22).

Recommendation

The Office of Clinical Pharmacology (OCP) team reviewed the information submitted under this NDA and recommends approval of Subvenite lamotrigine oral suspension provided an agreement is reached between the applicant and the Agency regarding the proposed labeling language. This recommendation is based on an adequate PK bridge demonstrated between Subvenite lamotrigine oral suspension and the LD (LAMICTAL lamotrigine tablet), allowing the applicant to rely upon FDA's previous findings of LD for efficacy and safety.

Summary of Key Clinical Pharmacology Findings

Scientific bridge between Subvenite lamotrigine oral suspension and the LD (LAMICTAL lamotrigine tablet)

The applicant conducted an open label, randomized, balanced, single-dose, two-sequence, two-treatment, two-period, two-way crossover study (study LAMO-159-22) in healthy subjects under fasting conditions. The results from study LAMO-159-22 showed that Subvenite lamotrigine oral suspension met the bioequivalent criteria to the reference LAMICTAL lamotrigine tablet with respect to the overall exposure (AUC0-inf and Cmax) under fasting conditions. PK study conducted by the applicant provided an adequate scientific bridge for this application to rely on the relevant labeling information of LD.

Comparative PK study of Subvenite lamotrigine oral suspension under fasting and fed conditions and the LD (LAMICTAL lamotrigine tablet) under fed conditions.

The applicant also conducted an open label, randomized, balanced, single-dose, two-treatment, three treatment condition, three period, six sequence, crossover study (study LAMO-160-22) in healthy subjects. The results from study study LAMO-160-22 showed that Subvenite lamotrigine oral suspension met the bioequivalent criteria to the reference LAMICTAL lamotrigine tablet with respect to the overall exposure (AUC0-inf and Cmax) under fed conditions. The mean PK profiles are similar with comparable Tmax between Subvenite lamotrigine oral suspension and LAMICTAL lamotrigine tablet under fed condition. LAMICTAL lamotrigine tablet label does not have restriction on food when taking the product. Overall, the present of food had no significant effect on the overall exposure of lamotrigine and Subvenite lamotrigine oral suspension can be administered with or without food, which is aligned with the food effect findings of the LD.

Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling concepts to be included in the final package insert. The review team proposed labeling changes are reflected in red fonts, including proposed deletions, shown as ~~strikethrough~~. The labeling recommendations may not negotiate with the applicant in this cycle due to Complete Response (CR) issues from CMC.

12.3 Pharmacokinetics

The pharmacokinetics of lamotrigine have been studied in subjects with epilepsy, healthy young and elderly volunteers, and volunteers with chronic renal failure. (b) (4) A pharmacokinetic study in heathy adult subjects under fasting conditions at 100 mg dose level demonstrated similar bioavailability for lamotrigine oral suspension and oral tablet. (b) (4)

14 CLINICAL STUDIES

The efficacy of SUBVENITE for the treatment of epilepsy and bipolar disorder is based on the established effectiveness of lamotrigine oral tablet. The studies below described the effectiveness of lamotrigine oral tablet for the treatment of epilepsy and bipolar disorder. SUBVENITE (lamotrigine oral suspension) demonstrated similar bioavailability to lamotrigine oral tablet. *[see Clinical Pharmacology (12.3)]*.

Summary of Relative Bioavailability Study

Study LAMO-159-22 (pivotal BE study of Subvenite lamotrigine oral suspension with LAMICTAL lamotrigine tablet under fasting conditions)

Study Design: This was an open label, randomized, balanced, single-dose, two-sequence, two-treatment, two-period, two-way crossover, oral bioequivalence study of Subvenite (lamotrigine) oral suspension 10 mg/mL with LAMICTAL (lamotrigine) tablet 100 mg in healthy adult human subjects under fasting conditions.

Number of Subjects (Planned and Completed): 36 subjects were planned into the study. 34 subjects completed all study activities.

Subject number (b) (6) was voluntarily withdrawn from the study due to personal reason after pre-dose vitals in period-1; subject number (b) (6) was voluntarily withdrawn from the study due to personal reason after 24.00 hr post-dose in period-1.

Treatments:

Administration of Test Product (T) under fasting conditions

In each period, a single oral dose (T) of suspension was slowly administered directly into the corner of the mouth until all the liquid medicine in the syringe is completed. The syringe was rinsed with adequate amount of water (out of 240 mL) until the syringe is free of medication and subjects were allowed to swallow the rinse. The remaining amount of water from 240 mL was administered at room temperature in sitting posture. Subjects were instructed not to spit the suspension but to consume it as a whole.

Administration of Test Product (T) under fasting conditions

A single oral dose (R) of study medication was administered to the subjects in sitting posture with 240 mL water. Subject were instructed not to chew, crush, or break the tablet but to consume it as a whole.

A washout period of 14 days was maintained between each period.

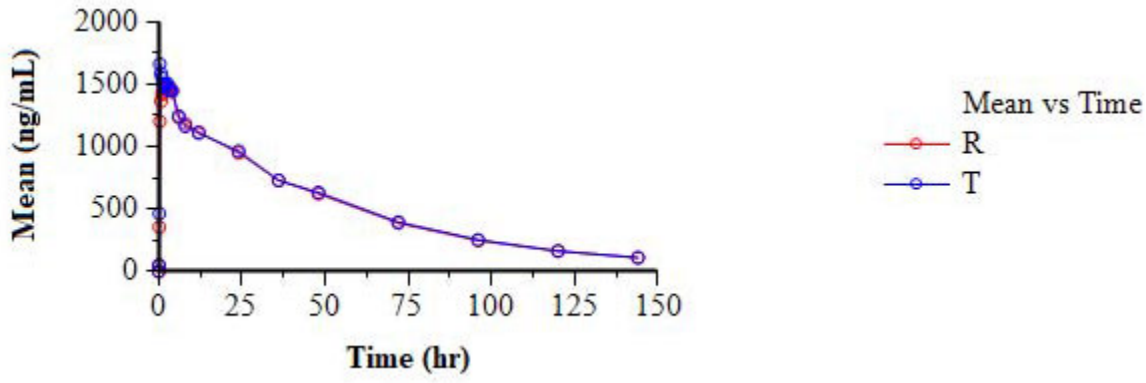
PK Sampling: A total of 24 blood samples (4 mL each) were obtained for PK measurement at the following times relative to each dose: Predose, 0.083, 0.167, 0.33, 0.67, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 6.00, 8.00, 12.00, 24.00, 36.00, 48.00, 72.00, 96.00, 120.00 and 144.00 hrs post-dose.

Bioequivalence Criteria: The 90% CI (Confidence interval) for the geometric least square mean ratios of ln-transformed parameters Cmax, AUC0-t and AUC0-inf of lamotrigine falls within the acceptance range of 80.00 - 125.00%.

Results:

A total of 34 subjects completed the study, and all 34 subjects' concentration data were used in pharmacokinetics and statistical evaluation for lamotrigine. Linear plot of time versus mean plasma concentration for lamotrigine is presented in Figure 1. The descriptive statistics for PK parameters of each treatment are shown in Table 1. The relevant bioequivalence results between Subvenite lamotrigine oral suspension with LAMICTAL lamotrigine tablet under fasting conditions are presented in Table 2. The relevant bioequivalence results indicated that Subvenite lamotrigine oral suspension and LAMICTAL lamotrigine tablet met the bioequivalent criteria for AUC and Cmax in healthy adult human subjects under fasting conditions.

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



Source: Clinical Study Report-Protocol LAMO-159-22, Figure on page 23 of 112.

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: Clinical Study Report-Protocol LAMO-159-22, Table 1 on page 22 of 112.

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: Clinical Study Report-Protocol LAMO-159-22, Table 2 on page 22 of 112.

Reviewer's Comments:

1. The overall design of this pivotal BE study, including the dose selection, route of administration, study population, study sample size, PK sampling schedule, washout period and bioanalytical method validation data are appropriate.

2. The applicant conducted PK analysis and applied statistical testing criteria are acceptable.

3. The reviewer conducted 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 concluding the bioequivalence of the test product to the LD under fasting conditions.

Reviewer's Analysis

Independent NCA analysis was conducted by the reviewer using the raw PK data from study LAMO-159-22. Table 3 summarized the reviewer calculated ratio of the Least Squares Geometric Means for PK parameters and confidence intervals (C.I.) under fasting conditions.

Table 3. Ratio of the Least Squares Geometric Means of PK parameters and 90% Confidence Intervals of Lamotrigine (n=34, Reviewer's Analysis)

Comparison (Test vs Reference)	Parameter	Test Geometric LSM	Reference Geometric LSM	Test/ Reference (%)	90% Confidence Interval
Subvenite lamotrigine oral suspension vs LAMICTAL lamotrigine tablet	Cmax (ng/mL)	1857.08	1731.47	107.26	100.36-114.63
	AUC0-t (hr*ng/mL)	73248.36	72551.76	100.96	98.23-103.76
	AUC0-inf (hr*ng/mL)	79497.91	78666.12	101.06	97.98-104.23

Source: Reviewer's independent analysis

Study LAMO-160-22 (food effect study of Subvenite lamotrigine oral suspension)

Study Design: This was an open label, balanced, randomized, single dose, two treatment, three treatment condition, three period, six sequence, crossover, oral food effect and fed comparative bioavailability and bioequivalence study of lamotrigine oral suspension 10 mg/mL with LAMICTAL (LAMOTRIGINE) tablet100 mg in healthy adult human subjects.

Number of Subjects (Planned and Completed): 36 subjects were planned into the study. 33 subjects completed all study activities.

Subject number (b) (6) was withdrawn from the study due to adverse event (Rash) after 8.00 hr post dose sample in period-I; subject number (b) (6) was withdrawn from the study due to adverse event (Fever) after 24.00 hr post dose sample in period-I; subject number (b) (6) was withdrawn from the study due to adverse event (Vomiting) after 0.67 hr post dose sample in period-II.

Treatments:

Administration of Test product (A) under fasting condition:

After an overnight fasting of at least 10.00 hours, prior to drug administration of investigational product, single oral dose (A) of lamotrigine oral suspension 10 mg/mL was administered.

Administration of Test product (B) under fed condition:

After an overnight fasting of at least 10.00 hours, a high fat and high calorie breakfast was served 30 minutes prior to administration of investigational product, single oral dose (B) lamotrigine oral suspension 10 mg/mL, was administered.

Administration of Reference product (C) under fed condition:

After an overnight fasting of at least 10.00 hours, a high fat high calorie breakfast was served 30 minutes prior to administration of a single oral dose (C) of LAMICTAL® (LAMOTRIGINE) tablet 100 mg.

There was a washout period of 14 days between each single dose administration.

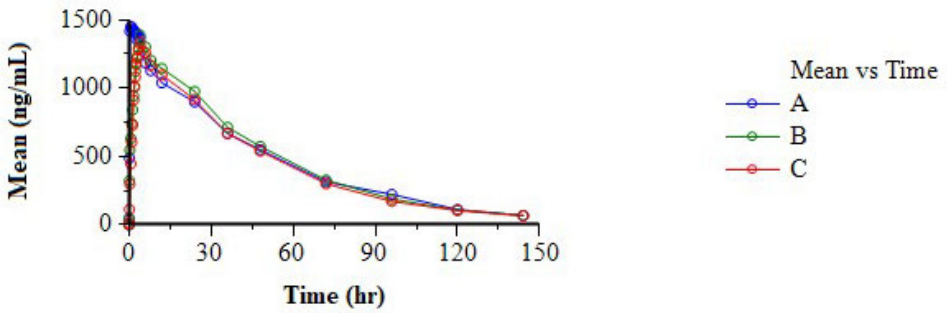
PK Sampling: A total of 24 blood samples (4 mL each) were obtained for PK measurement at the following times relative to each dose: Predose, 0.083, 0.167, 0.33, 0.67, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 6.00, 8.00, 12.00, 24.00, 36.00, 48.00, 72.00, 96.00, 120.00 and 144.00 hrs post-dose.

Bioequivalence Criteria: The 90% CI (Confidence interval) for the geometric least square mean ratios of ln-transformed parameters Cmax, AUC0-t and AUC0-inf of lamotrigine falls within the acceptance range of 80.00 - 125.00%.

Results:

A total of 33 subjects completed the study, and all 33 subjects' concentration data were used in pharmacokinetics and statistical evaluation for lamotrigine. Linear plot of time versus mean plasma concentration for lamotrigine is presented in Figure 2. The descriptive statistics for PK parameters of each treatment are shown in Table 4. The relevant bioequivalence results of Subvenite lamotrigine oral suspension 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)



Source: Clinical Study Report-Protocol LAMO-160-22, Figure on page 25 of 132.

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: Clinical Study Report-Protocol LAMO-160-22, Table 1 on page 23 of 132.

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: Clinical Study Report-Protocol LAMO-160-22, Table 2A on page 23 of 132.

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: Clinical Study Report-Protocol LAMO-160-22, Table 2B on page 24 of 132.

The relative bioavailability results of Subvenite lamotrigine oral suspension under fasting and fed conditions indicated that high fat food slightly decreased the Cmax of lamotrigine and had no impact on the AUCs of lamotrigine. The relevant bioequivalence results of Subvenite lamotrigine oral suspension and LAMICTAL lamotrigine tablet indicated that Subvenite lamotrigine oral suspension and LAMICTAL lamotrigine tablet met the bioequivalent criteria for Cmax and AUC under fed conditions. In addition, the mean PK profiles are similar with comparable Tmax between Subvenite lamotrigine oral suspension and LAMICTAL lamotrigine tablet under fed condition. LAMICTAL lamotrigine tablet label does not have restriction on food when taking the product. Overall, Subvenite lamotrigine oral suspension are not significantly affected by presence or absence of food and the product can be administered with or without food, which is aligned with the food effect findings of the LD.

Reviewer's Comments:

1. *The overall design of this comparative PK study, including the dose selection, route of administration, study population, study sample size, PK sampling schedule, washout period and bioanalytical method validation data are appropriate.*
2. *The applicant conducted PK analysis and applied statistical testing criteria are acceptable.*

3. The reviewer conducted independent analysis and verified the food effect results from study LAMO-160-22.

Reviewer's Analysis

Independent NCA analysis was conducted by the reviewer using the raw PK data from study LAMO-160-22. Table 7 summarized the reviewer calculated ratio of the Least Squares Geometric Means for PK parameters and confidence intervals (C.I.) under fasting and fed conditions of the test product. The applicant's analysis used fed arm as the reference to calculate point estimate and 90% confidence interval. The reviewer's analysis verified their analysis result. If the fasting arm is used as reference, it indicates that high fat food slightly decreased the Cmax (~18%) of lamotrigine and had no impact on the AUCs of lamotrigine.

Table 7. Geometric Means and Confidence Intervals ofTest (Fasting) versus Test (Fed) for Lamotrigine (N = 33, Reviewer's Analysis)

Comparison	Parameter	Test Geometric LSM	Reference Geometric LSM	Test/ Reference (%)	90% Confidence Interval
Subvenite lamotrigine oral suspension (Fasting vs Fed)	Cmax (ng/mL)	1737.08	1419.62	122.36	111.88-133.82
	AUC0-t (hr*ng/mL)	63938.37	64954.04	98.44	93.20-103.97
	AUC0-inf (hr*ng/mL)	66841.92	67683.17	98.76	93.46-104.35

Source: Reviewer's independent analysis

Appendices

Summary of Bioanalytical Method Validation and Performance

A validated liquid chromatographic-tandem mass spectrometric (LC-MS/MS) method was used for determining the lamotrigine concentration in human plasma. The method met the acceptance criteria for bioanalytical methods according to the Bioanalytical Method Validation Guidance for Industry the FDA Guidance for the Industry. Description of method validation parameters for lamotrigine (validation report BMVR321-00) are summarized in table below.

Table 8. Summary of Bioanalytical Method and Validation Characteristics

Analyte	Lamotrigine
Internal standard (IS)	Lamotrigine 13CD3
Lower Limit of Quantitation (LLOQ) (ng/mL)	10.004
Standard curve concentrations (ng/mL)	10.004 – 4001.688
QC Concentrations (ng/mL)	LLOQQC: 10.216 LQC: 27.837 GMQC: 235.909 MQC: 1965.909 HQC: 3092.025
Intraday Accuracy and Precision	Biases: -1.7% to 8.9% CV: 0.4% to 5.1%.
Interday Accuracy and Precision	Biases: -13.0% to 8.9% CV: 0.4% to 13.0% %
Freeze and Thaw Stability	6 cycles
Bench-top stability	23hours 05minutes (25°C±3°C).
Processed Sample stability	Auto Injector Stability for 02days 06hours 09minutes @ 7ºC
Long-Term Stability	85Days 19hours 20minutes @-20°C ± 5°C 85Days 19hours 23minutes @-70°C ± 15°C

Source: Method validation report BMVR321-00

Reviewer's Comments: Method validation and sample analysis are acceptable.

OSIS Consult Request for Biopharmaceutical Inspection

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 concluded that data from the reviewed study (study LAMO-159-22) were reliable. Please refer to OSIS review in

DARRTS dated 08/05/2024 for additional details.

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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