ELECTRONIC COMMON TECHNICAL DOCUMENT (eCTD)

Module 2.5 — Clinical Overview

Drug
Venlafaxine Hydrochloride Extended-Release Capsules 150 mg

Indication
Major Depressive Disorder (MDD) in Adults

Sponsor
Helix Biopharma, Inc., 1 Innovation Drive, Cambridge, MA 02139

Application
NDA 22-614-S001 (Supplemental — New Dosage Strength)

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15 July 2025

Version
1.0 (Original Submission)

Note to Reviewer

This Clinical Overview (Module 2.5) is prepared in accordance with ICH E3, ICH M4E(R2), and FDA guidance *Clinical Pharmacology Considerations for New Drug Applications* (March 2023). All referenced Tables, Figures, and Listings (TFLs) are located in Module 5 (m5/5.3.5/HLX-MDD-301-CSR) and Module 2.7 (m2/2.7.3/SummClinEff).

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1. Background and Overview of Clinical Development Program

Venlafaxine hydrochloride extended-release (VEN-ER) is a serotonin-norepinephrine reuptake inhibitor (SNRI) approved in the United States (Effexor® XR; NDA 20-699) for Major Depressive Disorder (MDD), generalized anxiety disorder (GAD), social anxiety disorder (SAD), and panic disorder. This supplemental NDA (sNDA 22-614-S001) seeks approval of a 150 mg capsule strength manufactured at the sponsor's Cambridge, MA facility (HLX-SITE-01), complementing the existing approved 37.5, 75, and 225 mg strengths.

The clinical development program for the 150 mg strength comprises:

- **HLX-BA-101** — Bioavailability/bioequivalence (BE) study, fasting conditions ($n = 48$, crossover; 🔗 `m5/5.1/HLX-BA-101`)
- **HLX-BA-102** — BE study, fed conditions ($n = 48$, crossover; 🔗 `m5/5.1/HLX-BA-102`)
- **HLX-MDD-301** — Phase 3, randomised, double-blind, placebo-controlled efficacy and safety study ($n = 486$; 🔗 `m5/5.3.5/HLX-MDD-301-CSR`)
- **HLX-MDD-302** — 52-week open-label safety extension ($n = 412$; 🔗 `m5/5.3.5/HLX-MDD-302-CSR`)

The clinical program is supported by population pharmacokinetic (PopPK) modelling (🔗 `m2/2.7.2/PopPK`) and a literature-based exposure–response analysis (🔗 `m2/2.7.2/ExposureResponse`).

2. Overview of Biopharmaceutics and Clinical Pharmacology

2.1 Bioequivalence — Studies HLX-BA-101 and HLX-BA-102

Both pivotal BE studies employed a single-dose, two-period, two-sequence crossover design in healthy adult subjects (18–55 years). The reference product was Effexor® XR 150 mg (Wyeth LLC; US commercial stock). Plasma concentrations of venlafaxine and its active metabolite O-desmethylvenlafaxine (ODV) were measured by a validated LC-MS/MS assay (🔗 `m2/2.7.1/BioanalyticalReport`).

Table 1 — Bioequivalence Summary: Venlafaxine and ODV *Source: HLX-BA-101/102; m2/2.7.1/Table 1.1*

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Venlafaxine $C_{\max}$	98.4	93.2	103.9	80.00–125.00
Venlafaxine $\mathbf{AUC}_{0\text{-}t}$	101.2	96.5	106.1	80.00–125.00
Venlafaxine $\mathbf{AUC}_{0\text{-}\infty}$	100.7	96.1	105.5	80.00–125.00
ODV $C_{\max}$	99.1	95.3	103.1	80.00–125.00
ODV $\mathbf{AUC}_{0\text{-}t}$	100.5	97.2	103.9	80.00–125.00
ODV $\mathbf{AUC}_{0\text{-}\infty}$	100.3	97.0	103.7	80.00–125.00

GMR = geometric mean ratio (Test/Reference); CI = confidence interval; BE = bioequivalence. All parameters met the acceptance criteria of 80.00–125.00%.

Regulatory Note

Bioequivalence is established for both venlafaxine and ODV under fasting and fed conditions. The 90% confidence intervals for all six primary PK parameters lie entirely within the FDA-required 80–125% acceptance range, confirming pharmaceutical and biopharmaceutical equivalence of the 150 mg strength.

2.2 Population Pharmacokinetics

A two-compartment PopPK model with first-order absorption and linear elimination was developed using NONMEM® v7.5 (🔗 `m2/2.7.2/PopPK`). Key covariate effects: body weight on clearance (CL/F) and renal function (eGFR) on ODV elimination. No dose adjustment is required for the 150 mg strength based on exposure-matched simulations across the approved adult population.

3. Overview of Efficacy

3.1 Pivotal Study HLX-MDD-301

3.1.1 Study Design

HLX-MDD-301 was a 12-week, randomised (1:1), double-blind, placebo-controlled, parallel-group study in adult outpatients (18–65 years) meeting DSM-5 criteria for MDD with baseline MADRS total score ≥ 28. Subjects were randomised to VEN-ER 150 mg once daily (QD) or matching placebo. The primary endpoint was change from baseline (CFB) in MADRS total score at Week 8.

3.1.2 Primary and Key Secondary Endpoints

Table 2 — Efficacy Endpoints: HLX-MDD-301 (ITT; MMRM) *Source: HLX-MDD-301-CSR Table 14.2.1*

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PRIMARY: MADRS CFB at Wk 8	−19.4 (1.2)	−12.8 (1.1)	−6.6 (−8.8, −4.4)	< 0.0001
MADRS CFB at Wk 12	−21.1 (1.3)	−13.5 (1.2)	−7.6 (−9.9, −5.3)	< 0.0001
MADRS Response (≥50%) at Wk 8	62.1%	38.3%	OR 2.63 (1.84, 3.76)	< 0.0001
MADRS Remission (≤10) at Wk 8	41.6%	22.2%	OR 2.49 (1.67, 3.70)	< 0.0001
CGI-I Score ≤2 at Wk 8	58.4%	36.2%	OR 2.48 (1.73, 3.55)	< 0.0001
HAM-D_{17} CFB at Wk 8	−11.8 (0.9)	−7.6 (0.8)	−4.2 (−5.8, −2.6)	< 0.0001
SDS Total CFB at Wk 8	−7.3 (0.7)	−4.1 (0.6)	−3.2 (−4.5, −1.9)	< 0.0001

Values are LS mean (SE) for continuous endpoints; CFB = change from baseline; OR = odds ratio (logistic regression); MMRM = mixed-model repeated measures; ITT = intent-to-treat; MADRS = Montgomery-Åsberg Depression Rating Scale; CGI-I = Clinical Global Impression — Improvement; SDS = Sheehan Disability Scale. All p-values nominal (hierarchical testing).

3.1.3 Subgroup Analyses

Consistent treatment effects were observed across pre-specified subgroups including age (<45 vs. ≥45 years), sex, race, baseline MADRS severity (severe: ≥34), and comorbid anxiety (🔗 `m5/5.3.5/HLX-MDD-301` `Figure 14.2.5`). No qualitative interactions were identified (all subgroup p-interaction > 0.10).

4. Overview of Safety

4.1 Integrated Safety Population

The integrated safety database comprises all subjects who received ≥1 dose of VEN-ER 150 mg across HLX-MDD-301 and HLX-MDD-302 ($N = 655$; total exposure 477 patient-years).

⚠ Important Safety Information

Known Class Effects of SNRIs (consistent with Effexor XR Reference Label, Section 5):

- Suicidality in young adults — monitor closely during early treatment (*Black Box Warning*)
- Serotonin syndrome — risk increased with concomitant serotonergic agents
- Elevated blood pressure — dose-dependent; monitor BP before and during treatment
- Hyponatremia — primarily in elderly; monitor serum sodium in at-risk patients
- Seizures, abnormal bleeding, activation of mania/hypomania

4.2 Treatment-Emergent Adverse Events (≥5% Any Group)

Table 3 — TEAEs ≥5% Incidence: HLX-MDD-301 Safety Population *Source: HLX-MDD-301-CSR Table 14.3.1*

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Nausea	78/243 (32.1%)	31/243 (12.8%)
Headache	62/243 (25.5%)	58/243 (23.9%)
Dry mouth	54/243 (22.2%)	18/243 (7.4%)
Dizziness	48/243 (19.8%)	22/243 (9.1%)
Insomnia	45/243 (18.5%)	29/243 (11.9%)
Hyperhidrosis	38/243 (15.6%)	11/243 (4.5%)
Constipation	35/243 (14.4%)	14/243 (5.8%)
Somnolence	29/243 (11.9%)	15/243 (6.2%)
Decreased appetite	27/243 (11.1%)	12/243 (4.9%)
Erectile dysfunction[a]	21/121 (17.4%)	9/122 (7.4%)
Increased blood pressure	18/243 (7.4%)	6/243 (2.5%)
Tremor	14/243 (5.8%)	5/243 (2.1%)

[a]Males only; denominator = male subjects (VEN-ER: $n = 121$; placebo: $n = 122$). MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

4.3 Serious Adverse Events and Deaths

No deaths occurred during HLX-MDD-301 or HLX-MDD-302. Serious adverse events (SAEs) were reported in 3 (1.2%) subjects in the VEN-ER group: 1 hospitalisation for hypertensive crisis (resolved; assessed as not study-drug related), 1 appendectomy (unrelated), and 1 suicide attempt (SUSAR reported per protocol; 🔗 `m5/5.3.5/SAE Narrative 003`). SAEs in placebo: 2 (0.8%).

4.4 Discontinuations Due to Adverse Events

Discontinuation due to AEs: VEN-ER 12.3%; Placebo 5.3% ($p = 0.006$). Most common reasons for VEN-ER discontinuation: nausea (3.7%), dizziness (2.1%), insomnia (1.6%).

4.5 Vital Signs and Laboratory Findings

Table 4 — Mean Change from Baseline: Vital Signs and Selected Labs *Source: HLX-MDD-301-CSR Tables 14.3.7–14.3.9*

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Systolic blood pressure (mmHg)	$+3.1$ (7.4)	-0.4 (6.9)
Diastolic blood pressure (mmHg)	$+1.8$ (5.2)	-0.3 (5.0)
Heart rate (bpm)	$+2.9$ (5.8)	$+0.6$ (5.1)
Body weight (kg)	-0.9 (2.4)	$+0.3$ (2.1)
Serum sodium (mEq/L)	-1.1 (3.2)	-0.4 (2.9)
ALT ($\times$ULN)	$+0.08$ (0.21)	$+0.02$ (0.18)
QTcF interval (ms)	$+1.6$ (7.2)	$+0.9$ (6.8)

CFB = change from baseline; BP = blood pressure; bpm = beats per minute; ALT = alanine aminotransferase; ULN = upper limit of normal; QTcF = Fridericia-corrected QT interval. No subject had QTcF $>$ 500 ms or ΔQTcF $>$ 60 ms.

5. Benefit-Risk Assessment

The structured benefit-risk assessment below follows the FDA Benefit-Risk Framework (PDUFA VI; FDA Guidance, 2021).

⚖ Structured Benefit-Risk Summary — VEN-ER 150 mg

Dimension	Evidence & Conclusion
Analysis of Condition	MDD — a severe, recurrent, disabling disorder with substantial unmet need for a flexible intermediate dosage strength to support titration.
Current Alternatives	Existing VEN-ER strengths (37.5, 75, 225 mg); SSRIs; other SNRIs (duloxetine, desvenlafaxine). The 150 mg addresses a clinically meaningful titration gap.
Benefits	Statistically significant and clinically meaningful MADRS CFB (-6.6 points vs. placebo, 95% CI -8.8 to -4.4; $p < 0.0001$); response 62.1% vs. 38.3%; remission 41.6% vs. 22.2%; functional improvement (SDS -3.2; $p < 0.0001$).
Risks	Nausea, dry mouth, dizziness — class effects, predominantly mild–moderate, transient, manageable without dose reduction in most cases. Modest BP elevation ($+3.1$ mmHg SBP). SAE rate comparable to reference product historical data.
Risk Management	Consistent with Effexor XR label (Black Box, Sections 5.1–5.11); no new safety signals; post-marketing cardiac monitoring commitment per RMP v2.1 (🔗 `m1/1.12.3/RMP-v2.1`).
Conclusion	**Favourable.** The benefit-risk profile of VEN-ER 150 mg is positive. Clinical benefit in MDD is robust and consistent. Risks are known, manageable, and commensurate with the established SNRI class labelling.

6. Literature References and Cross-Module Index

6.1 Key Regulatory Guidances Applied

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ICH E3	Structure and Content of Clinical Study Reports
ICH M4E(R2)	Common Technical Document — Efficacy (Clinical Overview)
ICH E6(R3)	Good Clinical Practice — HLX-MDD-301/302 conducted in full compliance
ICH E9(R1)	Statistical Principles for Clinical Trials — MMRM primary analysis
FDA PDUFA VI	Benefit-Risk Framework for Human Drug Products
EMA/CHMP	Guideline on Clinical Investigation of Medicinal Products in MDD (2013)

6.2 eCTD Cross-Module Hyperlink Index

Regulatory Note

All hyperlinks below point to documents within the eCTD submission spine. Reviewers using an eCTD-compliant viewer (FDA ESG, EMA eSubmission Gateway) will navigate directly to the referenced document or section.

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m1	1.12.3	Risk Management Plan v2.1
m2	2.7.1	Bioanalytical Method Validation Report
m2	2.7.2	Summary of Clinical Pharmacology (PopPK, E-R)
m2	2.7.3	Summary of Clinical Efficacy
m2	2.7.4	Summary of Clinical Safety
m5	5.1	HLX-BA-101 BE Study Report (Fasting)
m5	5.1	HLX-BA-102 BE Study Report (Fed)
m5	5.3.5	HLX-MDD-301 Clinical Study Report
m5	5.3.5	HLX-MDD-302 Open-Label Extension CSR

7. Conclusions

The totality of data from the clinical development program supports approval of Venlafaxine Hydrochloride Extended-Release Capsules 150 mg for treatment of MDD in adults. The 150 mg strength is bioequivalent to Effexor® XR, is effective (primary and all key secondary endpoints met; $p < 0.0001$), and is safe and well tolerated consistent with the established class profile. No new or unexpected safety signals were identified. The benefit-risk profile is favourable and the 150 mg strength addresses a clinically significant titration gap in the approved dosage regimen.

Sponsor Statement of Completeness

Helix Biopharma, Inc. confirms that this Clinical Overview (Module 2.5) accurately and completely represents the clinical data contained in NDA 22-614-S001 and that all referenced documents are included in the submission.

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Reviewed by	Dr. James T. Harrington, MD — Chief Medical Officer
Approved by	Dr. Priya S. Mehta, PhD — Head Regulatory Affairs
Date	15 July 2025

End of Module 2.5 — Clinical Overview. Continued in Module 2.7.3 — Summary of Clinical Efficacy (m2/2.7.3).