REGULATORY WRITING

Clinical Overview of a Novel Investigational Treatment for Treatment-Resistant Depression

HGX-217 Clinical Development
Mock CTD Module 2.5 Clinical Overview

FICTIONAL EDUCATIONAL SCENARIO

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Selected Works | Project 2 | Version 3.0

Executive assessment

This educational case study assesses the fictional development program for HGX-217 as adjunctive treatment to a stable SSRI or SNRI in adults with treatment-resistant depression (TRD). It demonstrates regulatory-style synthesis, interpretation of aggregate data, numerical verification, and clinical discussion.

The assumed Phase III results favor HGX-217 on depressive symptoms at Week 8. Calculated binary outcomes meet the illustrative remission and response testing criteria in Study 301. Study 302 does not meet the remission criterion, so its response result remains descriptive. Increased adverse-event discontinuation and unresolved seizure, interaction, and long-term safety questions support a conditional further-development conclusion rather than an approval recommendation.

Scope and data provenance

HGX-217, its pharmacology, study identifiers, participants, and results are invented. No patients were enrolled and no trials or regulatory submissions occurred. Real references support background and methods only. This document is not clinical evidence, prescribing advice, or an approved label.

The dataset consists of fictional aggregate counts and stipulated continuous-outcome estimates. Percentages, binary risk differences, approximate confidence intervals, nominal p-values, and population reconciliations are reproducibly calculated. No patient-level model, sensitivity analysis, or clinical AI performance evaluation is reported.

Document organization

Section	Content
2.5.1	Development rationale and program
2.5.2-2.5.3	Biopharmaceutics and clinical pharmacology
2.5.4-2.5.5	Efficacy, missing outcomes, and safety
2.5.6-2.5.7	Benefit-risk conclusion, proposed indication, and references
Appendices A-C	Evidence traceability, calculation audit, and study synopses

2.5.1 Product Development Rationale

Disease background and unmet need

Major depressive disorder can disrupt mood, sleep, cognition, and daily functioning. Some patients remain symptomatic after multiple treatments. TRD commonly refers to lack of improvement after at least two antidepressants; the operational definition used in this exercise is described below. Available approaches include psychotherapy, medication treatment, and brain stimulation. [2]

The January 2025 US esketamine label includes TRD treatment as monotherapy or with an oral antidepressant, with supervised administration and monitoring. This dated label supplies therapeutic context only; it is not an exhaustive description of current treatment options or a comparator dataset. [3, sections 1, 2.1, 5.1-5.5]

The development objective is an additional oral adjunctive option for persistent symptoms. Convenience is a product hypothesis.

Product concept

HGX-217 is postulated to be a selective positive allosteric modulator of the AMPA glutamate receptor. Its proposed activity is enhancement of the receptor response to endogenous glutamate. Selectivity, brain penetration, and downstream effects on synaptic plasticity are fictional assumptions. No mechanistic result establishes clinical efficacy or provides a validated surrogate endpoint.

Target population and treatment resistance

The scenario targets outpatients aged 18-65 years with nonpsychotic major depressive disorder and inadequate response to at least two antidepressants during the current episode. Each qualifying course is assumed to have lasted at least 6 weeks at a therapeutic dose. Treatment history and adherence are assumed to be checked using interviews and records; one qualifying failure is confirmed during an 8-week prospective lead-in. Participants continue one stable selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI). The precise lead-in response threshold, adherence criterion, and rescue-treatment rules were not considered for this specific scenario.

Clinical development program

Table 1. Fictional program inventory. Controlled patient studies use adjunctive treatment on a stable SSRI or SNRI. All allocations and exposure counts are scenario assumptions.

Study	Design	Allocation
101-103	Phase I: dose escalation, food effect, formulation bridge	96 healthy adults; 72 active / 24 placebo
201	Phase II: randomized, double-blind, 8 weeks	240 patients; 80 each at 20 mg, 40 mg, or placebo
301	Phase III: randomized, double-blind, 8 weeks	400 patients; 200 active / 200 placebo
302	Phase III: randomized, double-blind, 8 weeks	480 patients; 240 active / 240 placebo
303	Open-label extension; up to 52 additional weeks	360 Phase III completers; all receive 20 mg

Population reconciliation

The controlled patient studies include 1,120 unique patients: 600 initially receive HGX-217 and 520 receive placebo. The extension includes 240 participants previously assigned to HGX-217 and 120 previously assigned to placebo. Only the latter add to the unique active-exposed population. The total is therefore 720 patients, or 792 persons when the 72 active-exposed healthy volunteers are included.

The 360 extension participants are a subset of the 880 Phase III participants. Extension enrollment must not be added to randomized enrollment as if these were new patients. Cumulative exposure of at least 6 and 12 months is assumed for 280 and 180 patients, respectively. Individual exposure dates are not available to verify duration categories or calculate patient-years.

Program interpretation

Study 201 provides an exploratory dose comparison. Studies 301 and 302 provide the assumed short-term efficacy comparisons. Study 303 can describe events occurring during longer exposure, but selection of completers and the lack of a control group prevent a randomized assessment of maintenance benefit or comparative long-term safety.

2.5.2 Overview of Biopharmaceutics

The assumed product is an immediate-release tablet in 10 mg and 20 mg strengths. Phase II uses capsules; Phase III and the extension use tablets. The constructed tablet-to-capsule geometric mean ratios are 1.02 for exposure (AUC; illustrative 90% interval 0.96-1.08) and 0.98 for peak concentration (Cmax; 0.90-1.07). These values suggest similar exposure within the exercise. These illustrative intervals were not estimated from observed pharmacokinetic data and do not constitute a verified formulation bridge, since there's no empiric base to the study.

The assumed high-fat meal effects are AUC +6% and Cmax +9%. Variability, uncertainty intervals, and exposure-response boundaries are not specified in the scenario. Administration without a food restriction remains a development proposal, not a supported final instruction.

2.5.3 Overview of Clinical Pharmacology

The proposed AMPA modulation provides a rationale for antidepressant investigation and focused assessment of excitatory central nervous system effects. Seizures and behavioral activation are potential severe adverse effects, with the measures of their occurrence, severity, and causal relationship extremely importante in a real-life setting.

Exposure and interactions

Assumed pharmacokinetics include a median time to peak concentration of 2 hours, a half-life of 18 hours, approximately dose-proportional exposure at 10-40 mg, and near steady state within about 4 days. This profile is compatible with evaluating once-daily dosing.

CYP3A4 is assumed to be the principal metabolic pathway, with minor renal elimination of unchanged drug.

Inhibition would be expected to increase, and induction to decrease, exposure if that assumption holds. Magnitudes and clinical dose adjustments cannot be determined without interaction data. Concurrent sedating medicines could increase impairment.

Dose selection and evidence gaps

At 40 mg, the assumed Phase II mean improvement exceeds that at 20 mg by 0.4 MADRS points, while adverse-event discontinuation rises from 6/80 (7.5%) to 11/80 (13.8%). This descriptive comparison supports carrying 20 mg forward for the exercise. The Phase III regimen starts at 10 mg daily for 7 days, then 20 mg daily.

Dedicated organ-impairment, clinical interaction, definitive QT, abuse-potential, and withdrawal assessments are absent. Strong CYP3A4 inhibitors and inducers and clinically significant organ impairment are excluded by assumption. Final interaction, impairment, and risk-management instructions cannot be established from this package.

2.5.4 Overview of Efficacy

Design and applicability

Studies 301 and 302 assume 1:1 allocation, matching tablets, and independent symptom raters, with stratification by region and number of prior antidepressant failures. Baseline MADRS is at least 28. The scale ranges from 0 to 60, with higher values indicating greater symptom severity. [3, section 14.1]

The assumed pooled Phase III population has mean age 43 years, 60% women, mean baseline MADRS 34.1, and median three qualifying treatment failures. Enrollment is limited to North America and Europe. Bipolar disorder, psychotic disorders, recent moderate or severe substance use disorder, seizure history, acute suicidal intent requiring urgent intervention, pregnancy, breastfeeding, and age above 65 years are excluded.

Treatment effect and analysis concept

The intended primary contrast is the difference between assigned regimens in mean MADRS change from baseline to Week 8 among randomized participants, including measurements after study-drug discontinuation or rescue treatment. Follow-up after these events is assumed. This treatment-policy question must be distinguished from the method used to address unobserved outcomes. [4, sections A.3-A.5] No longitudinal model or imputation analysis has been executed; the continuous estimates in Table 2 are stipulated inputs.

Endpoint hierarchy

Within each study, the exercise assumes a fixed sequence: Week 8 MADRS change, remission, then response, each tested at two-sided 0.05 only after the preceding test succeeds. Such a sequence requires prospective specification in a real trial. Here it is a constructed rule, not evidence of actual prespecification. [5, Appendix, method 5]

Remission is MADRS at most 10; response is at least 50% reduction from baseline. The supplied binary counts treat missing Week 8 status as failure. The missing-as-failure convention is not guaranteed to be conservative. Death would require a separate estimand strategy; no deaths are assumed in the randomized studies.

Missing outcomes and robustness

Study	Week 8 available active / placebo	Missing active / placebo	Rescue treatment active / placebo
301	176/200 / 182/200	24/200 (12.0%) / 18/200 (9.0%)	10/200 / 14/200
302	207/240 / 217/240	33/240 (13.8%) / 23/240 (9.6%)	16/240 / 20/240

Week 8 availability includes assumed follow-up after discontinuation and is not a treatment-completion count.

No analysis has assessed robustness to alternative missing-data assumptions. A missing-at-random approach requires assumptions about missingness conditional on observed information; these cannot be evaluated from the supplied aggregates. A sensitivity analysis would examine plausible departures while preserving the treatment effect of interest. [4, sections A.5-A.6]

Efficacy results and interpretation

Table 2. Assumed adjusted mean MADRS changes at Week 8 and illustrative nominal 95% confidence intervals for active-minus-placebo contrasts. Values were selected for the scenario, not fitted to participant data. Negative values indicate improvement. Phase II comparisons are exploratory.

Study / arm	N	MADRS change	Difference (95% CI)
201 placebo	80	-10.8	Reference
201 20 mg	80	-15.0	-4.2 (-7.0 to -1.4)
201 40 mg	80	-15.4	-4.6 (-7.4 to -1.8)
301 placebo	200	-11.9	Reference
301 20 mg	200	-15.7	-3.8 (-5.7 to -1.9)
302 placebo	240	-12.8	Reference
302 20 mg	240	-15.4	-2.6 (-4.4 to -0.8)

Both assumed Phase III intervals exclude zero, so the scenario treats the primary endpoint as meeting its criterion. The 2.6-3.8 point contrasts indicate incremental symptom improvement of uncertain patient-level importance. No universal clinical-importance threshold is applied.

Table 3. Binary outcomes calculated from fictional counts. Differences are percentage points (pp); intervals are unadjusted approximate 95% Wald intervals. Appendix B specifies the calculations. All differences are active minus placebo.

Outcome	Active	Placebo	Difference (95% CI), pp	Nominal p
301 remission	70/200 (35.0%)	46/200 (23.0%)	12.0 (3.2, 20.8)	0.0082
301 response	108/200 (54.0%)	80/200 (40.0%)	14.0 (4.3, 23.7)	0.0050
302 remission	72/240 (30.0%)	55/240 (22.9%)	7.1 (-0.8, 15.0)	0.0786
302 response	120/240 (50.0%)	96/240 (40.0%)	10.0 (1.1, 18.9)	0.0277

Study 301 meets the remission and response criteria under the assumed sequence. Study 302 does not meet the remission criterion (p=0.0786); its response result remains descriptive despite nominal p=0.0277. These calculations illustrate testing logic, not real confirmatory evidence. Remission point estimates yield descriptive 8-week NNTs of 9 and 15. The Study 302 interval spans no effect, so its NNT is especially unstable.

Limits of efficacy interpretation

The results do not establish functional recovery, faster onset, sustained remission, relapse prevention, suicide prevention, or comparative superiority. Mean symptom change does not itself demonstrate restoration of daily functioning. Distinctive adverse effects could compromise blinding.

2.5.5 Overview of Safety

Table 4 pools Studies 301 and 302 only: 440 participants per group, all assumed to receive at least one dose. Events are new or worsened after dosing through 7 days after the last dose. Each participant is counted once per row; categories overlap. This window is a scenario convention, not a judgment that delayed events are adequately captured.

Event	HGX-217 N=440	Placebo N=440
Any treatment-emergent adverse event	286 (65.0%)	220 (50.0%)
Severe adverse event	18 (4.1%)	9 (2.0%)
Serious adverse event	5 (1.1%)	3 (0.7%)
Discontinuation due to adverse event	31 (7.0%)	13 (3.0%)
Nausea	88 (20.0%)	44 (10.0%)
Dizziness	66 (15.0%)	26 (5.9%)
Somnolence	53 (12.0%)	22 (5.0%)
Headache	48 (10.9%)	44 (10.0%)
Insomnia	35 (8.0%)	22 (5.0%)
Dissociation	9 (2.0%)	2 (0.5%)
Mania or hypomania	2 (0.5%)	0 (0.0%)
Suicide attempt	1 (0.2%)	1 (0.2%)
Deaths	0 (0.0%)	0 (0.0%)

Nausea, dizziness, and somnolence show the largest common tolerability imbalances.

Adverse-event discontinuation is 7.0% versus 3.0%; the difference calculated from unrounded counts is 4.1 percentage points (approximate 95% CI 1.2-7.0). The descriptive number needed to harm is 25 over the controlled observation period. Interpreting NNH alongside NNT requires consideration of outcome severity, time horizon, and patient preferences.

Serious events comprise one each of suicide attempt, manic episode, syncope, appendicitis, and pneumonia on active treatment, and suicide attempt, appendicitis, and renal colic on placebo. These scenario case labels do not establish causality. Severity describes intensity; seriousness concerns outcomes such as hospitalization. The categories can overlap.

Safety concerns and long-term exposure

Suicidality and activation

New or worsened suicidal ideation is assumed in 18/440 (4.1%) active and 16/440 (3.6%) placebo participants using structured assessment. One suicide attempt occurs in each group. Equal attempt counts do not demonstrate equal risk or a protective effect.

Two active-treated participants experience mania or hypomania, including the hospitalized manic episode in Table 4. The imbalance warrants review of onset, dose relationship, concomitant drugs, prior bipolar features, and outcomes after discontinuation.

Seizure and other signals

No seizures are assumed in controlled studies. One generalized seizure occurs in the extension (1/360; 0.3%) without documented prior seizure history. Temporal association and the proposed mechanism make it a concern requiring investigation. They do not prove causality. Case timing, exposure, alternative causes, and follow-up are unavailable.

ALT above three times the upper limit of normal is assumed in 3/440 (0.7%) active and 1/440 (0.2%) placebo participants, without concurrent bilirubin above twice the upper limit.

Extension

Among 360 extension participants, 246 (68.3%) have an adverse event, 42 (11.7%) discontinue for an adverse event, and 12 (3.3%) have a serious event, including the seizure. No deaths are assumed. Counts concern the extension period and cannot be added to controlled counts to obtain unique affected patients.

2.5.6 Benefits and Risks Conclusions

2.5.6.1 Therapeutic context

The scenario concerns persistent nonpsychotic major depressive disorder despite antidepressant treatment in adults aged 18-65 years. The product objective is incremental symptom relief alongside a stable SSRI or SNRI. The program does not establish treatment positioning relative to other augmentation options or brain stimulation.

2.5.6.2 Benefits and 2.5.6.3 Risks

Dimension	Scenario evidence	Decision implication
Symptoms	Assumed Week 8 contrasts -3.8 and -2.6 MADRS points	Consistent direction; clinical importance and robustness remain uncertain
Remission	12.0 and 7.1 pp absolute gains; only 301 passes hierarchy	No replicated confirmatory remission conclusion
Tolerability	AE discontinuation 31/440 vs 13/440	Incremental benefit must justify added burden
Serious concerns	Activation imbalance and one extension seizure	Focused case review and further characterization needed
Durability	No randomized maintenance comparison	No maintenance or relapse-prevention claim
Applicability	Selected outpatients; several vulnerable groups excluded	Conclusion restricted to the studied scenario

2.5.6.4 Benefit-risk assessment

The assumed symptom findings and calculated binary outcomes provide a rationale for further development of the 20 mg adjunctive regimen. A potentially favorable short-term balance is plausible in adults matching the scenario population, but important uncertainties prevent a firm judgment of clinical acceptability. This qualitative assessment is an educational interpretation of constructed data.

2.5.6.5 Assessment basis

The assessment considers symptom change, remission, treatment discontinuation, serious safety concerns, and remaining uncertainties. It uses no patient-derived preference weights or quantitative benefit-risk model. Appendices A-B document provenance and calculations. The clinical-overview structure is adapted from ICH M4E(R2). [1]

Proposed indication and development priorities

Proposed indication for the fictional exercise

HGX-217 is proposed for adjunctive treatment with a stable SSRI or SNRI in adults aged 18-65 years with nonpsychotic major depressive disorder and inadequate response to at least two antidepressants given at an adequate dose and duration during the current episode.

This wording reflects the constructed study population. It is not an approved indication. The regimen under evaluation is 10 mg orally once daily for 7 days followed by 20 mg daily, with benefit and tolerability assessed through Week 8. Food instructions, interaction management, organ-impairment dosing, and long-term continuation instructions remain unresolved.

Development priorities

Priority	Question to resolve	Evidence needed
Immediate	Could the seizure or activation findings materially alter acceptability?	Case-level assessment, exposure review, alternative causes, targeted investigation
Before final dosing	How do interactions, impairment, and food alter exposure and risk?	Appropriate pharmacology studies and exposureresponse interpretation
Before broad safety claims	What are QT, withdrawal, abuse, and uncommon risks?	Fit-for-purpose assessments and adequate exposure with follow-up
Before maintenance claims	Does benefit persist and prevent relapse?	Randomized maintenance evidence with a defined clinical question
Before comparative claims	How does treatment affect functioning and compare with alternatives?	Functional outcomes and suitable comparative evidence

Limits of the package

No participant-level dataset, complete protocol, statistical analysis plan, nonclinical report, or clinical study report underlies this exercise. Appendix C contains abbreviated scenario synopses. No subgroup effects or sample-size power claims are supported. These limits define the scope of this completed writing sample; they are not evidence that the missing studies have been performed.

2.5.7 Literature References

The following real sources support background and methodology; none contains HGX-217 data. The esketamine label is identified by its January 2025 version and is not represented as a statement of subsequent labeling changes.

[1] International Council for Harmonisation. M4E(R2): The Common Technical Document - Efficacy. Step 4, 15 June 2016.

Module 2.5, especially 2.5.1 and 2.5.6. Source document

[2] National Institute of Mental Health. Depression.

Symptoms, diagnosis, and treatment. Source document

[3] US Food and Drug Administration. SPRAVATO (esketamine) prescribing information. Revised January 2025.

Sections 1, 2.1, 5.1-5.5, and 14.1. Source document

[4] International Council for Harmonisation. E9(R1): Addendum on Estimands and Sensitivity Analysis in Clinical Trials. 20 November 2019.

Sections A.3-A.6. Source document

[5] US Food and Drug Administration. Multiple Endpoints in Clinical Trials: Guidance for Industry. October 2022.

Appendix, method 5, fixed-sequence method. Source document

Abbreviations

Term	Meaning
AE / ALT	Adverse event / alanine aminotransferase
AMPA	alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AUC / Cmax	Area under concentration-time curve / peak concentration
CNS / CYP3A4	Central nervous system / cytochrome P450 3A4
CI / CTD	Confidence interval / Common Technical Document
MADRS / MMRM	Montgomery-Asberg Depression Rating Scale / mixed model for repeated measures
NNT / NNH / pp	Number needed to treat / harm / percentage points

TRD / QT	Treatment-resistant depression / ECG QT interval
SSRI / SNRI	Selective serotonin reuptake inhibitor / serotonin-norepinephrine reuptake inhibitor

Appendix A Evidence and claim traceability

This map distinguishes external evidence, fictional inputs, calculated outputs, and interpretation. The map covers decision-relevant claims; source references do not transform fictional data into clinical evidence.

ID	Claim or input	Basis	Boundary
E01	Clinical-overview organization	Reference 1; Module 2.5	Adapted structure; no compliance certification
E02	Depression and treatment context	Reference 2; treatment sections	Background only; no exhaustive therapy comparison
E03	Esketamine indication and supervision	Reference 3; sections 1, 2.1, 5	Dated label; no comparison with HGX-217
E04	Estimand and missingness distinction	Reference 4; A.3-A.6	Supports reasoning; does not validate model
E05	Fixed-sequence testing	Reference 5; Appendix, method 5	Sequence is assumed here, not truly prespecified
F01	Allocation and exposure counts	Table 1; program reconciliation	Fictional aggregate inputs
F02	Pharmacology and bridging estimates	Sections 2.5.2-2.5.3	Fictional assumptions; no experiments
F03	Continuous efficacy estimates	Table 2	Assumed values; no fitted model
F04	Binary efficacy counts	Table 3	Fictional numerators and denominators
F05	Safety counts and case labels	Table 4; safety narrative	Fictional counts; no case records
C01	Percentages, differences, intervals, p-values	Appendix B formulas applied to F04-F05	Arithmetic on invented data
J01	Conditional benefit-risk conclusion	F01-F05, C01; section 2.5.6	Qualitative interpretation; no approval conclusion

External references support only the claims listed. Compound-specific findings remain fictional. No nonexistent Module 2.7 summary or Module 5 report is cited as supporting evidence. The scope is targeted regulatory-style synthesis, not a systematic evidence review.

Appendix B Reproducible calculation audit

Methods

Check	Difference, pp	95% interval, pp	Nominal p
301 remission	12.0000	3.1845 to 20.8155	0.008180
301 response	14.0000	4.3145 to 23.6855	0.005031
302 remission	7.0833	-0.7835 to 14.9502	0.078568
302 response	10.0000	1.1439 to 18.8561	0.027670
AE discontinuation	4.0909	1.2237 to 6.9581	-

Other checks completed

Enrollment: 240+400+480=1,120. Initially active patients: 160+200+240=600. Unique active patients: 600+120=720. All active persons: 720+72=792. Extension entrants: 240+120=360. All Table 4 percentages and extension percentages were recalculated with the correct denominators.

All Table 2 arm differences match their stated contrasts. The illustrative continuous intervals and the formulation intervals cannot be validated from aggregate counts. Rare-event safety comparisons are not assigned normal-approximation significance claims. An absence of events does not establish an absence of risk.

Appendix C Abbreviated study synopses

These abbreviated synopses consolidate the fictional scenario. They are not protocols or clinical study reports. No unreported power calculation, randomization implementation, or case-level result is implied.

Study 201

Exploratory, randomized, double-blind, 8-week adjunctive comparison in 240 patients, 80 per arm at 20 mg, 40 mg, or placebo. Week 8 assumed MADRS changes are -15.0, -15.4, and -10.8. Active-arm AE discontinuations are 6/80 and 11/80. The small descriptive efficacy increment and larger tolerability burden at 40 mg motivate the 20 mg development choice.

Study 301

Randomized, double-blind, 8-week adjunctive comparison: 200 active and 200 placebo. Active titration is 10 mg for 7 days then 20 mg daily. Primary contrast is assumed at -3.8 MADRS points. Remission is 70/200 versus 46/200; response 108/200 versus 80/200. Under the constructed primary-endpoint success and fixed sequence, both binary endpoints pass. Week 8 observations are available for 176 and 182 participants.

Study 302

Randomized, double-blind, 8-week adjunctive comparison: 240 active and 240 placebo, with the same regimen. Primary contrast is assumed at -2.6 points. Remission is 72/240 versus 55/240; response 120/240 versus 96/240. The

hierarchy stops at remission, leaving response descriptive. Week 8 observations are available for 207 and 217 participants.

Study 303

Open-label extension of up to 52 additional weeks in 360 Phase III completers; 240 continue active treatment and 120 switch from placebo. All receive 20 mg. Adverse events affect 246 participants, AE discontinuations 42, and serious events 12. One seizure is included among serious events.