PHARMA BIOMARKER SERVICES

Population-Scale QEEG Biomarker Analysis for Phase 1 Clinical Trial Support

Client: Newleos | Indication: Generalized Anxiety Disorder (GAD) | Engagement: ~4 Weeks

NORMATIVE DATABASE	GAD POPULATION	BIOMARKERS ANALYZED
100,000+	**859**	**14**
Clinical EEG subjects	Diagnosed patients characterized	Across 4 neurophysiological domains

Executive Summary

Brainify.AI was engaged by Newleos, a pharmaceutical company developing novel anxiolytic compounds, to provide a population-scale QEEG biomarker reference framework for their Phase 1 clinical trial. The engagement addressed a fundamental challenge in early CNS drug development: interpreting brain signal changes from small clinical trials without an external normative reference. Using Brainify.AI's proprietary clinical EEG database of over 100,000 subjects, the team generated comprehensive normative distributions for 14 QEEG biomarkers, characterized the GAD population's neurophysiological profile, and delivered a quantitative framework that transforms raw EEG observations into interpretable, population-referenced proof-of-mechanism evidence.

The Challenge

Client X is running a Phase 1 study with approximately 30 subjects for a novel CNS compound with a distinctive EEG pharmacodynamic signature. The study faced a critical interpretive challenge that is common across early-stage CNS trials:

> *Without a larger sample size or an external reference point, it was impossible to ascertain whether observed session-to-session EEG changes were genuine drug effects or merely natural variations between subjects.*

Specifically, the client needed answers to questions that a small trial alone cannot address:

- Was the drug-induced EEG change large or small relative to natural population variation?
- Did the treatment shift the patient's brain profile toward or away from the normative range?
- Was the observed change larger than what natural biological variation would predict?

- Were enrolled subjects genuinely outside the healthy range at baseline?
- Could individual responders be identified using objective biological thresholds?

The Solution: Brainify.AI's Population Ruler Framework

Brainify.AI deployed its proprietary Population Ruler Framework — a methodology that overlays clinical trial EEG data onto population-scale normative distributions, providing the statistical grounding needed to interpret small-trial results with the confidence of a 100,000+ subject reference group.

What Was Delivered

1. **QEEG Normative Reference:** Robust reference distributions for 14 QEEG biomarkers generated from over 100,000 normative subjects and 859 GAD-diagnosed patients. Biomarkers spanned spectral power (theta and beta-2), hemispheric alpha asymmetry, fronto-temporal and temporal-parietal connectivity, and graph-theoretic network measures.
2. **Statistical Characterization:** Full summary statistics and probability density functions (KDE) for all features and both populations, establishing quantitative drug-change references including z-scores and Cohen's d effect sizes.
3. **GAD Population Separation Analysis:** Standardized mean difference (Cohen's d) computed for all 14 features, identifying which biomarkers best distinguish the GAD brain profile from the broader population and are therefore most likely to capture drug-related signal.
4. **Trial Enrichment Foundation:** Quantitative inputs for a Batch Screening Method (BSM) to prospectively enrich future trials by selecting patients with the most pronounced QEEG abnormalities, reducing required sample sizes and accelerating the path to statistical significance.

Key Findings

The analysis identified clear population-level biomarker patterns that distinguish the GAD brain profile:

Strongest Signal: High-frequency beta (Beta-2, 20–30 Hz) power showed the largest and most consistent GAD vs. normative separation, with large effect sizes ($d = 0.50–0.59$) in central regions and medium effects ($d = 0.33–0.37$) frontally. This is consistent with established neuroscience literature linking elevated beta oscillations to cortical hyperarousal in anxiety.

Nuanced Finding: Theta power, alpha asymmetry, connectivity, and network features showed negligible population-level GAD separation ($d < 0.2$) in this dataset. This likely reflects the heterogeneity of the broad clinical comparator rather than absence of true group differences — a finding that will be tested against healthy controls in the next phase.

Transformation: With vs. Without the Population Ruler

Question	Without Brainify.AI	With Brainify.AI
Was the change large or small?	Unknown — no population reference	Quantified via z-score and Cohen's d
Therapeutic direction?	Unknown — no definition of "normal"	Assessable against normative range
Drug effect or noise?	Unknown — no variability baseline	Testable — p-value from population spread
Subjects abnormal at baseline?	Unknown — no biological reference	Verifiable via baseline z-scores
Identify responders?	No external threshold	Yes — percentile threshold crossings
Proof of mechanism?	Weak — "EEG changed"	Strong — "shifted toward normative profile"

Strategic Value Delivered

Proof of Mechanism: The combination of population distributions and Phase 1 drug effect data creates a quantitative proof-of-mechanism narrative — demonstrating that the compound shifts the GAD brain profile toward the normative range. This represents a significant valuation inflection point for Newleos' fundraising and partnership discussions.

Phase 2 Trial Enrichment: The population characterization provides the quantitative foundation for a Batch Screening Method (BSM), enabling enrichment of future Phase 2 trials by selecting patients with the most pronounced QEEG abnormalities. This reduces required sample sizes and accelerates the path to statistical significance.

Publication Strategy: The combined dataset supports a multi-pronged publication strategy covering the therapeutic mechanism of action, population-level QEEG characterization of GAD, and magnitude of therapeutic effect — building the scientific credibility package expected by regulators and investors.

Competitive Differentiation: Objective neurophysiological evidence of drug effect, anchored against well-characterized population distributions, differentiates Newleos' clinical narrative from competitors relying solely on subjective symptom scales.

Methodology Overview

The analysis leveraged Brainify.AI's proprietary QEEG database. Data from 859 GAD-diagnosed patients (primary diagnosis, EEG within −3 to +12 months of diagnosis, 65% female) and approximately 103,000 normative subjects were processed through the following pipeline: per-subject averaging of multiple EEG recordings to reduce within-subject measurement variability, Gaussian Kernel Density Estimation (KDE) for distribution characterization, and Cohen's d computation for standardized effect size measurement. All recordings used 250 Hz sampling, standard 10–20 montage, average reference, with spectral analysis across 1–30 Hz.

The 14 biomarkers were selected based on peer-reviewed literature implicating each in GAD neurobiology, spanning four domains: spectral power (theta 4–8 Hz and beta-2 20–30 Hz, frontal and central/global), hemispheric asymmetry (frontal and temporal alpha), functional connectivity (fronto-temporal theta coherence, temporal-parietal coherence, midline theta connectivity), and network topology (theta clustering coefficient).

Next Steps

5. **Integration and analysis of Newleos' Phase 1 EEG data** against the normative framework for direct proof-of-mechanism evidence
6. **Comparison with healthy, non-clinical controls** to establish cleaner normative baselines (1,106 healthy controls available in database)
7. **Subgroup analysis by sex and age** to uncover demographic-specific biomarker profiles

8. **Feature stability validation** to support deployment of the Batch Screening Method for Phase 2 trial enrichment

Ready to leverage population-scale EEG data for your clinical trial?

Contact us at **im@brainify.ai** | **www.brainify.ai**