Phase III, randomized, multicenter, open-label clinical trial to evaluate the efficacy and safety of the Aurora® digital medical device with conventional drug treatment, compared to conventional drug treatment alone, in adult patients with moderate to severe generalized anxiety disorder.

STUDY INNOVA 2024-01

COFEPRIS Mexico Authorization number registered:

253300410C1001/2025

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SUMMARY STUDY INNOVA 2024-01

Title of the study	**Phase III, randomized, multicenter, open-label clinical trial to evaluate the efficacy and safety of the Aurora® digital medical device with conventional drug treatment, compared to conventional drug treatment alone, in adult patients with moderate to severe generalized anxiety disorder.**
Methodology	**Phase III clinical trial, controlled (with active comparator), randomized, open-label, longitudinal, analytical, experimental, prospective, multicenter.**
Duration	**8 months**
Objective	**Primary** **To evaluate the superiority of cognitive behavioral therapy using the Aurora® digital medical device + conventional drug treatment, compared to conventional drug treatment alone, in reducing anxiety symptoms, as assessed by the change in the GAD-7 scale at 12 weeks of treatment, relative to baseline.** **Secondary** **- Evaluate the effect of Aurora® + conventional drug treatment, compared to conventional drug treatment alone, on the reduction of anxiety symptoms, assessed using the GAD-7 scale at 4, 8, and 12 weeks of treatment, compared to baseline.** - **Evaluate the effect of Aurora® + conventional drug treatment versus conventional drug treatment on the reduction of symptoms of concern, according to the PSWQ, at 4, 8, and 12 weeks of treatment, compared to baseline.** - **Evaluate the effect of Aurora® + conventional drug treatment versus conventional drug treatment on depressive symptoms, according to the PHQ-9 scale, at 4, 8, and 12 weeks of treatment, compared to baseline.** - **Determine the frequency of psychiatric emergency events at 12 weeks of treatment in both treatment groups.** - **Determine the frequency and characteristics of adverse events and incidents during the subjects' participation in the study.**

	- **Determine the percentage of patients who required a switch from SSRIs to SNRIs during the study in both treatment groups.** - **Determine the percentage of patients who required a dose increase, both those treated with SSRIs and those treated with SNRIs.**
Selection criteria	**Inclusion Criteria:** 1. **Men and women aged ≥18 and ≤65 years.** 2. **Diagnosis of generalized anxiety disorder (GAD) based on DSM-5-TR criteria.** 3. **Score ≥10 on the GAD-7 (Generalized Anxiety Disorder Scale) instrument** 4. **That they agree to participate in the study by signing the informed consent form.** **Exclusion Criteria:** **1. Concomitant alcohol use disorder or recreational drug use disorder. Consumption of energy drinks.** **2. Excessive caffeine consumption (more than 150 mg per day).** **Patients with hypersensitivity to escitalopram (Selective®) or duloxetine (Arquera®) and/or any component of the formulation.** **3. Having received psychiatric drug treatment within the 6 months prior to inclusion in this protocol, including but not limited to prescription drugs such as SSRIs, SNRIs, benzodiazepines, herbal medicines, or unauthorized substances such as cannabis, microdoses of LSD, CBD, ayahuasca, or any other recreational psychotropic substance.** - **Having received psychotherapy or having been part of support groups, meditation, mindfulness, or equivalent groups will not be grounds for exclusion, provided that this has not been accompanied by medication aimed at modifying any psychiatric disorder.** **4. Any clinical or sociodemographic condition that prevents the use of the Aurora® digital medical device as established in this protocol; for example, severe visual impairment, complete lack of knowledge about the use of personal electronic devices such as cell phones or tablets, among others.** **5. Presence of other psychiatric comorbidities, with the exception of depressive disorders not induced by substances or medications.**

	6. Patients who, at the time of the selection assessment, present any psychiatric emergency (psychosis, catatonia, manic episode, risk of self-harm or harm to others, etc.). **7. Diagnosis or suspicion of bipolar disorder.** **8. History of seizures, even while undergoing anti-seizure treatment.** **9. Identification of prolonged QT interval length on the initial assessment electrocardiogram.** **10. Previous diagnosis of chronic liver failure, Child-Pugh class B or C.** **11. Previous diagnosis of chronic kidney disease stage KDIGO 3 or higher.** **12. Diagnosis of NYHA functional class III/IV heart failure.** **13. Diagnosis of pheochromocytoma.** **14. Diagnosis of acute or chronic degenerative diseases that are not included in control targets, or that, in the investigator's opinion, represent an additional risk to the patient.** **15. Patients requiring concomitant treatment with medications contraindicated with the use of escitalopram (Selective®) or duloxetine (Arquera®), such as the following: monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants, class I antiarrhythmics or sodium channel blockers, acetylsalicylic acid, cimetidine, beta-adrenergic blockers, buspirone, digoxin, carbamazepine, lithium, sumatriptan, theophylline, warfarin, vortioxetine, bupropion, mirtazapine, agomelatine, and phentermine.** **16. Any other clinical condition that, in the investigator's opinion, contraindicates the use of conventional treatment.** **17. Pregnant or breastfeeding women.** **18. Any alteration in laboratory tests that, in the opinion of the Investigator, is considered clinically relevant and represents a risk to the patient.** **19. Patients who have received or are scheduled to receive any investigational product from another clinical study within 90 days prior to the selection process.** **20. Patients who, in the investigator's opinion, are unable to comply with the protocol activities or whose inclusion poses a risk to their health.** **21. Patients who are receiving cognitive behavioral therapy prior to or at the time of study entry.** **Elimination Criteria:**

	1. **Serious adverse events during the study.** 2. **Adverse events that pose a serious threat to public health.** 3. **Presence of a psychiatric emergency (psychosis, catatonia, manic episode, risk of self-harm or harm to others, etc.) during the study.** 4. **Presence of other conditions that, in the opinion of the Investigator, may put the patient at risk.** 5. **Voluntary withdrawal of the study subject.** 6. **Low adherence to treatment (less than 80%).**
Sample size	**The sample size calculation was based on the methodological design established as a clinical superiority trial; that is, to determine whether Aurora® Digital Therapy for 12 weeks plus conventional drug treatment is superior to conventional drug treatment alone. To this end, the following superiority hypothesis is considered: H0: $\mu A - \mu B \leq \delta$ vs. H1: $\mu A - \mu B > \delta$.** **The calculation used the formula recommended by Flight L et al (2015), taking as a reference the calculation values published in the study by Richards D et al (2020), which determined the efficacy of cognitive behavioral therapy using a digital medical device compared to placebo using the GAD-7 scale, reporting a detectable mean difference (δ) of 2.59 points and a standard deviation (σ) of 5.31 points. Considering a value of $\alpha = 0.05$, a value of $\beta = 0.20$, and a proportion $k = 1$, a sample of 134 patients was determined to be adequate, with 67 patients per treatment arm.** **However, after considering an approximate loss rate of 20% of the sample (26.8 patients), it was deemed appropriate to add 28 more patients to recruit a total of 162 patients, 81 patients per treatment arm.** **The calculation was performed with the support of the Epidat statistical program: Program for epidemiological data analysis Version 4.2 (2016) endorsed by the Pan American Health Organization.**
Intervention	**Test arm:** **Escitalopram (Selective®) 10 mg Tablet (days 1 to 28, 1 tablet/day; at the discretion of the principal investigator based on tolerance and therapeutic response, increase in dose to 2 tablets per day, from day 29 to the end of the study) or Duloxetine (Arquera®) 30 mg 1 capsule/day (with the possibility of increasing to 60 mg per day at the discretion of the principal investigator based on tolerance and therapeutic response) from day 29 to the end of the study + Aurora® digital medical device.** **Comparator arm:**

	Escitalopram (Selective®) 10 mg Tablet (days 1 to 28, 1 tablet/day; at the discretion of the principal investigator based on tolerance and therapeutic response, increase the dose to 2 tablets per day, from day 29 to the end of the study) or Duloxetine (Arquera®) 30 mg 1 capsule/day (with the possibility of increasing to 60 mg per day at the discretion of the principal investigator based on tolerance and therapeutic response) from day 29 to the end of the study. **Switching to Duloxetine (Arquera®) in cases of intolerance or lack of response to escitalopram (Selective®) will not be considered a rescue medication and will be considered part of the standard treatment for GAD, as indicated in the literature and clinical practice guidelines. based on current evidence, it is estimated that switching to another first-line option may be necessary in 40 to 50% of patients with GAD after the initial therapeutic trial.**
Outcome variables	***Primary Superiority Variable:*** **Change in GAD-7 scale score at week 12 compared to baseline, value used to determine the primary efficacy variable and evaluate the superiority of treatment A over treatment B.** ***Other variables of interest for secondary objectives:*** • **GAD-7 scale score at baseline, week 4, week 8, and week 12.** • **PSWQ score at baseline, week 4, week 8, and week 12.** • **PHQ-9 scale score at baseline, week 4, week 8, and week 12.** • **Percentage of patients switching from SSRIs to SNRIs.** • **Percentage of treatment adherence at visits 3 to 5.** • **Presence of psychiatric urgency.** • **Adverse events.** • **Concomitant medications.** ***Sociodemographic variables and other variables:*** **Age, sex, weight, body mass index, vital signs, body mass index, history of smoking.**

Statistical methods	**The analysis of the primary efficacy variable (change in GAD-7 score) will be performed using a covariance analysis model (ANCOVA) on the per-protocol population.** ***Dependent variable:*** **Change from baseline = GAD-7 post-treatment − GAD-7 baseline** **Predictors: Treatment (categorical variable [A vs. B]), GAD-7 baseline (continuous covariate [adjusted to reduce standard error]), research center (fixed effect [to control for heterogeneity between sites]).** **Taking the above into account, and given that the minimum clinically significant change on the GAD-7 scale is 3 points, as established by Kroenke et al. (2019), the following hypotheses aimed at testing superiority of efficacy will be considered for this protocol:** • **H0: μA – μB ≤ 3 (Treatment A is not clinically superior to B at 12 weeks).** • **H1: μA − μB > 3 (Treatment A is clinically superior to B at 12 weeks).** ***Inference and Success Criteria:*** – **Effect estimate: The adjusted difference β1 (A vs. B) and its standard error will be calculated using least squares.** – **Superiority test: One-tailed t-statistic, p-value (Ho will be rejected if p < 0.025 [one-tailed α level]).** – **Confidence interval: One-tailed 97.5% CI for β1:** $$\left[\hat{\beta}_1 - t_\alpha \cdot \mathrm{SE}(\hat{\beta}_1), +\infty\right)$$ – **Clinical superiority will be declared only if p-value < 0.025 and lower limit (LL) of the 97.5% CI > 3.**

	For descriptive statistics, measures of central tendency will be used for numerical variables with parametric distribution, such as mean and standard deviation, and measures of position will be used for numerical variables with nonparametric distribution, such as median and interquartile range. Rates and proportions will be used for categorical variables. Inferential statistics will be determined with a 95% confidence interval, and $p<0.05$ will be considered significant for all tests. Based on the parametric distribution of the variables, differences between numerical variables will be determined using Student's t-test or Mann-Whitney's U test. Where appropriate, the numerical correlation of variables will be evaluated using Spearman's test if the distribution is non-parametric, and Pearson's test if it is parametric. The association between categorical variables will be evaluated using the χ^2 test, and if necessary, the association of numerical variables with categorical variables will be evaluated using logistic regression.
Keywords	**Generalized anxiety disorder, digital therapy, cognitive behavioral therapy, pharmacological treatment.**