The effect of gamma light therapy on ADHD-symptoms in adults:

a randomized, double-blind, controlled trial

Attention deficit/hyperactivity deficit disorder (ADHD) is a prevalent neurodevelopmental disorder in childhood that usually lasts into adulthood.[1–3]. Worldwide, approximately 2%–5% of adults experience attention-deficit/hyperactivity disorder (ADHD) symptoms such as inattention, hyperactivity, and impulsivity (*1*,*2*). While research focus has mainly focused on the treatment of childhood ADHD, there has been a significant increase in the number of adults diagnosed with ADHD in the last decade. Between 2015 and 2021, the number of adults in Denmark receiving ADHD medication increased by approximately 40%, rising from around 18,000 to over 26,000 individuals (Sundhedsstyrelsen, 2022).

While this development is positive in terms of identifying and helping more individuals, significant challenges in treating ADHD in adults remain. There is a significant gap in research regarding treatment options for ADHD in adults. Pharmacotherapy is the first-line treatment, typically with stimulant medications such as methylphenidate and amphetamines, or non-stimulant medications like atomoxetine. These medications have well-documented short-term effects, including reducing core symptoms such as inattention, impulsivity, and hyperactivity, however medical treatment has significant shortcomings such as high drop-out rates, limited long term effects and undesirable side-effects such as weight loss and poor sleep. A prospective cohort study of adults diagnosed with ADHD found that 90% of participants initially received medical treatment, but half discontinued it within six years (Fredriksen et al., 2014). While medication often reduces ADHD symptoms, it does not necessarily improve quality of life, work performance, or social relationships. A meta-analysis found that while ADHD medication has strong short-term effects on core symptoms, it does not necessarily lead to significant improvements in everyday functioning and overall well-being (Cortese et al., 2018). Additionally, many adults with ADHD experience side effects such as sleep disturbances, appetite loss, increased anxiety, and elevated blood pressure. These adverse effects often lead to treatment discontinuation. Stimulant medication misuse is common, which can be concerning, particularly for patients with a history of substance abuse (Faraone et al., 2021).

Without effective treatment, ADHD can have severe consequences both for individuals and society. Untreated ADHD in adulthood is associated with increased risk of unemployment, lower income, and frequent job changes, often due to difficulties with time management, inattention, and impulsivity (Barkley et al., 2008). Untreated ADHD also increases the risk of depression, anxiety disorders, and low self-esteem, particularly if individuals experience repeated failures in personal and professional settings (Kessler et al., 2006). There is evidence showing that individuals with untreated ADHD have a higher likelihood of developing substance and alcohol use disorders, as they often seek ways to self-medicate their symptoms (Wilens et al., 2011).

Given the many challenges associated with medical treatment and the severe consequences of untreated ADHD, it is crucial to explore alternative and complementary treatment methods for adult ADHD. The increasing number of individuals with a diagnosis of ADHD in adulthood in Denmark necessitates a broader approach to treatment options. Future research should focus on developing integrated treatment strategies

that combine medication with psychosocial interventions to optimize the quality of life for adults with ADHD.

Emerging research indicates that mindfulness meditation and physical exercise may offer beneficial effects for adults with Attention-Deficit/Hyperactivity Disorder (ADHD). Mindfulness meditation has been associated with improvements in attention and reductions in hyperactivity and impulsivity. A study by Zylowska et al. (2008) found that adults with ADHD who participated in an 8-week mindfulness training program exhibited significant reductions in ADHD symptoms and anxiety. The active mechanism is thought to involve enhanced self-regulation and increased activation in brain regions responsible for attention and executive function. Similarly, regular physical exercise, particularly aerobic activities, has been shown to improve attention, executive functioning, and behavioral symptoms in individuals with ADHD. A review by Den Heijer et al. (2017) concluded that exercise leads to increased availability of dopamine and norepinephrine in the brain, neurotransmitters that are typically deficient in ADHD, thereby enhancing cognitive functions and reducing symptom severity. These findings suggest that integrating mindfulness practices and regular physical activity may serve as effective complementary strategies in managing adult ADHD symptoms. There is growing interest in lifestyle-based interventions such as physical exercise, mindfulness-based therapies, and neurofeedback. These methods may help regulate attention and impulse control in ways that complement or replace medication (Young et al., 2020).

The active mechanisms underlying these interventions likely involve the modulation of neural pathways (frontal and pre-frontal cortical pathways) associated with attention and self-regulation. By engaging in mindfulness practices and regular physical activity, individuals with ADHD may experience neuroplastic changes that support improved cognitive control and emotional regulation. Unfortunately, meditation and physical activity can be difficult to implement for adults with ADHD as it requires a level of self-discipline. Modulating neural pathways is not a novel phenomenon in ADHD treatment, as multiple pharmacological interventions for ADHD also influence the brain's oscillatory activity (Mizuno et al., 2022; Wang et al., 2016; Zammit & Muscat, 2019). Modulation of neural pathways can be done in a variety of ways, and research has now shown that brain rhythms can be entrained through non-invasive neurostimulation methods known as Non-Invasive Brain Stimulation (NIBS), drawing upon sensory modalities such as auditory, tactile, or visually evoked stimulus. A repetitive visual stimulus can produce so-called Steady State Visually Evoked Responses (SSVEP), whereby oscillations in the brain synchronize to a visual stimulus, such as a rhythmic flicker. This process is referred to as entrainment, and allows us to introduce treatment directly at the level of brain rhythms.

Oscillatory activity within the lower gamma frequency range (brain rhythms in the frequency range 30-50 Hz) is increasingly recognized as a contributing factor in several psychiatric and neuropsychiatric disorders, including ADHD (Chen et al., 2014; Fitzgerald et al., 2018; Liu et al., 2012; McNally et al., 2016; Pizzagalli et al., 2006; Wang et al., 2017, Cheung et al., 2017), prompting substantial interest in exploring the therapeutic potential of boosting gamma-band activity. This interest is rooted in the vital role these oscillations play in cognitive processes such as attention, perception, and memory encoding – all higher order cognitive domains relevant for the clinical manifestations of ADHD.

Gamma entrainment is particularly promising given their interaction with parvalbumin-positive (PV+) interneurons. These PV+ interneurons not only initiate gamma oscillations but also sustain and respond to them by exerting inhibitory control over excitatory pyramidal neurons. This targeted inhibition refines action potential timing and synchronizes neuronal ensembles, thereby promoting effective neural communication necessary for attention and higher order cognitive processes (Uhlhaas & Singer, 2014; Tiemann et al., 2012; Wilson et al., 2013). These findings are further supported by Wang (2010), whose influential study revealed that an imbalance between excitatory and inhibitory signaling results in mis-timed action potentials and desynchronized neuronal ensembles, thereby disrupting attentional selection and information processing. Wilson et al. (2013) further demonstrate that deficits in gamma oscillations may undermine the effective coordination among brain regions that regulate timing and attention.

Similarly, a correlation has been found between reduced resting state gamma activity and severity of neuropsychological deficits in ADHD patients (Tombor, 2018). This relationship is further supported by another study by Tombor (2021) which investigated gamma band dynamics in response to pharmacological intervention and found increased gamma activity in response to stimulant medications. These accounts suggest that the therapeutic potential of enhancing gamma oscillations might bridge the gap between neurophysiological functioning and clinical symptoms. The promise of this avenue has been demonstrated successfully, as gamma entrainment through various modalities has repeatedly been shown to boost performance on cognitive measures (Lee et al., 2023; Dockstader et al., 2014; Roß & Lopez, 2020). For example, a study which used auditory binaural beats at a 40 Hz frequency found a significant enhancement in performance on attention tasks (Melnichuk et al. 2025). Moreover, working memory is considered an important function for sustaining attention by temporarily holding and manipulating information required for goal directed behavior. Thompson et al. (2021) demonstrated that entraining gamma frequencies through transcranial altermatic current stimulation (tACS) enhanced performance on working memory tasks. Utilizing a similar paradigm in patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD) patients, another study found enhanced overall cognitive functioning, including domains such as memory, working memory, and executive functioning (Manippa et al., 2023). Consequently, the promising results of these investigations pave the way for novel neuromodulatory treatments that translate into meaningful improvements in everyday functioning for individuals with ADHD.

It has been demonstrated that gamma entrainment can be achieved with a 40 Hz stroboscopic flicker light (Hermann, 2001), but that such setups are often uncomfortable for most users. This discomfort makes daily treatment applications—particularly at lower clinical symptom thresholds—impractical. This study will test the clinical efficacy of a novel non-invasive brain stimulation (NIBS) device that can entrain gamma activity and produce SSVEP comparable to those of true stroboscopic flicker, but without the associated flashing discomfort. The device utilizes the combination of three led diodes at specific color combinations blinking off-beat of each other to create what is perceived by the eye as a continuous light, while EEG measures show 40 Hz SSVEP gamma response. A feasibility trial with Alzheimer's disease patients found good adherence to a one-hour daily stimulation paradigm introduced as a daily treatment accommodated to various lifestyles.

In conclusion, modulating gamma activity in individuals with ADHD is a promising avenue of investigation for this patient population, given that alterations in gamma activity overlap with the key cognitive domains

disrupted in the disorder. Therefore, we aim to explore the potential of this novel, non-invasive therapy introduced at the level of brain rhythms through an at-home daily intervention paradigm that can easily fit into most lifestyles.

40 Hz gamma stimulation with light can be acutely observed in an EEG spectrum. An EEG power analysis can be used to monitor increased attention and cognitive processing. Typically, we associate specific EEG power bands with particular mental states:
Delta (0.5–4 Hz): Deep sleep, unconscious states, not relevant for attention monitoring.
Theta (4–8 Hz): Associated with drowsiness, daydreaming, or distractibility. Increased theta activity can indicate reduced attention.
Alpha (8–12 Hz): Reflects relaxation and idling. A decrease in alpha power, especially in frontal regions, is linked to increased attentional focus.
Beta (12–30 Hz): Associated with active thinking, focus, and problem-solving. Increased beta activity suggests heightened attention.
Gamma (30–100 Hz): Related to high-level cognitive processing and concentration.
In this study we will be looking specifically at the short and long term effects of Evy Light™ on frequency bands > 12 Hz, as an objective measure for improvement in attention.

2.1. Objective

To test the effect of the EVY™ light on function and ADHD symptoms in adults with ADHD compared to placebo (non-flickering light).
The primary objective of the study will be to assess efficacy of EVY Light light on ADHD symptoms and function.
Secondary objectives will include measures of sleep quality and neuropsychiatric endpoints.
Biomarkers will consist of EEG biomarkers for treatment effect;

- First, we will record 5 min eyes open, 5 minutes eyes closed and 5 min eyes open with EVY™ Light stimulation. This is done to determine if the lamp allocated to the individual elicits an immediate response in the individual patient. This will be done at each patient visit (T1, T2 and T3).
- Secondly, we will collect in-ear EEG data during daily lamp use and after lamp use in order to establish if attention (beta-power) is improved over time. We will look at both immediate treatment effect and sustained effect after lamp use.

2.2. Hypothesis:

Null Hypothesis (H_0): 1 hour of daily visual gamma sensory stimulation delivered via Invisible Spectral Flicker will have no effect on the clinical presentation of ADHD symptoms in patients diagnosed with ADHD.

Alternative Hypothesis (H_1): 1 hour of daily visual gamma sensory stimulation delivered via Invisible Spectral Flicker will result in measurable improvements in the clinical presentation of ADHD symptoms as reflected in the ADHD Investigator Symptom Rating Scale (AISRS) in patients diagnosed with ADHD, compared to a control group receiving sham treatment.

Alternative Hypothesis (H_1'): Daily visual gamma sensory stimulation delivered via Invisible Spectral Flicker during execution of executive tasks will result in measurable improvements in the clinical presentation of

Attention as measured using qEEG paradigm establishing Theta/Alpha and Theta/Beta ratio in patients diagnosed with ADHD, compared to a control group receiving sham treatment.

2.3. Study purpose

The purpose of the clinical study is to evaluate the device's indications for use in the home use environment. The study's data will demonstrate that:

1. Confirm through successful completion of this study that the device functions as intended in the home use environment; and can be operated by user or caregiver.
2. Confirm through successful completion of this study that the light delivered from the device is safe and well tolerated 12
3. Confirm that the device demonstrates a clinically significant improvement in the primary, co-primary and secondary endpoints and biomarkers.

2.4. Study design:

Randomized, Double-blind, Sham-controlled, Pivotal Study of 40 Hz Sensory Stimulation in adult patients with ADHD

2.4.1. Inclusion criteria:

- Age above 18 years; a clinical diagnosis of ADHD
- Individuals with a minimum score of >=28-30 on ACDS (Adult ADHD Clinical Diagnostic Scale).
- Stable medication for a minimum of 4 weeks before intervention

2.4.2. Exclusion criteria

- Participants with a history of substance abuse or medications known to impair cognitive function. Suicidal ideation corresponding to 2 or more on the Hamilton Depression Rating Scale (HDRS-17) .
- Self-reported photosensitive related migraine or photosensitivity
- History of photo-induced migraine
- Planned medication change within study period
- Any significant systemic illness of unstable medical condition, which could lead to difficulty complying with the protocol

2.4.3. Intervention:

Evy Light™: Is a lamp that delivers a 40 Hz light flicker stimulus without visible flickering, able to produce Steady State Visually Evoked Potentials (SSVEPs) comparable to that of a true stroboscopic flicker. Unlike the traditional stroboscopic flicker devices, this device alternates between specific LED color combinations, creating a rhythmic light where the pulsations are nearly invisible to the eye while still stimulating gamma activity. This approach minimizes discomfort, making it more suitable for daily use in cognitive and neurophysiological interventions. The lamp is portable and can be used flexibly.

The proposed intervention is at least 1 hour daily for 12 weeks. From ongoing studies in Alzheimer's disease we know that a minimum treatment paradigm of 1 hour daily is beneficial, additional in-house real-world evidence (RWE) suggest that Adult ADHD patients may benefit from extended use. A variability in daily use

will allow for the establishment of a dose-response relationship. There will be a 1 month follow up after treatment..

2.4.4. Control condition:
The control group condition will receive a continuous light matched in color and temperature to background ambient light.

2.4.5. Randomization

In this randomized, controlled trial participants are randomized 1:1 to the intervention group or control group in a web-based randomization system. The allocation sequence is computer-generated with a varying block size kept unknown to the investigators and set up by an independent statistician, who is not involved in the trial.

Informed consent

Recruitment and information letters are handed out to all adult participants. Information folders are also visible in the waiting rooms of the clinics. Individuals who show interest in the trial will be offered an individual information meeting regarding trial details by a psychologist associated with the trial. After the meeting individuals can decide if they wish to participate. Signature of the written consent is required for the participation in the trial and will be collected by research staff. The trial will not intrude in any way with the individual's general assessment and treatment procedure.

Procedures

All Adult participants are asked to sign the ICF.

2.5. Trial sites

Participants are included at the following sites: Adult Psychiatric Department Aaabenraa, Tønder, Haderslev og Sønderborg and general practitioner physicians offices. Will we be able to recruit from RHP and private practices in Copenhagen also?

2.6. Blinding
Both participants and staff will be blind to the participants group allocation. We will employ blinding in all other possible areas e.g. as outcome assessments and data analysis.

2.7. Data collection
All data is collected by research assistants, who are either a clinical nurse or psychologists or equivalent.

2.7.1 Data Storage

The storage and processing of personal data produced in the CLARA Study will be conducted according to the General Data Protection Regulation (EU Regulation 2016/679) and the Danish Data Protection Act. Furthermore, the clinical investigation conforms to the principles of the Declaration of Helsinki and is authorized by the Danish Data Protection Agency (Datatilsynet) and the relevant Regional Videnskabsetisk Komité (VMK) in Region Syddanmark.

Identifiable data such as full name, address, and civil registration number (CPR-nummer) will only be shared with key personnel (e.g., principal investigator and study coordinators) and only for essential purposes, such as data collection from electronic patient journals or participant verification. Include here a statement if data is to be shared between both parts

All data is stored securely at the investigational site (Region Syddanmark) in the REDCap system, which will contain sensitive data such as name and CPR-nummer.

2.8. Time points

Assessments are collected at three time points:

T0: Screening visit, consent form - before intervention**.**

T1: Baseline measures: Device delivery, AISRS, TOVA, Baseline EEG recording

T2: Within 2 weeks of the completion of the intervention: AISRS, TOVA, EEG, Psychometrics

T3: 1 month after the completion of the intervention: AISRS, TOVA, Psychometrics

2.9. Outcome measures:

	Endpoints	Description
Primary	Adult ADHD Investigator Symptom Rating Scale (AISRS) Time Points of Measurement: Baseline (T1), Stable treatment(T2), and One-month post-treatment follow-up(T3). Primary Endpoint: The mean difference in AISRS score change from baseline to post-treatment between treatment and placebo groups.	The AISRS is a clinician-administered scale designed to assess the severity of ADHD symptoms in adults. Conducted by a trained healthcare professional, it evaluates 18 DSM-IV ADHD symptoms (inattention and hyperactivity-impulsivity) based on patient reports and clinical observation over the past week. The total score ranges from 0 to 54 (each of 18 symptoms scored 0–3): [0–10] = Minimal or no ADHD symptoms [11–20] = Mild ADHD [21–30] = Moderate ADHD [31–54] = Severe ADHD A 5-point reduction in the total score is considered a minimum clinically important difference (MID), reflecting a meaningful decrease in ADHD symptom severity.

Co-primary	2-part Exploratory EEG biomarker of acute effect of light on attention	First part (25 minutes) A brief, visually-driven evoked-potential (EP) test using a 64-channel EEG cap. The protocol generates composite EEG features via Vistim Labs' machine learning algorithms to produce estimates of brain health markers, feeding AI regression models for neurodegeneration assessment. Second part (35 minutes) Same montage is carried over to assess acute biomarkers for induction of attention. The power spectrum for each epoch is calculated; beta-power connectivity and Theta/alpha (beta) ratio are used as measures of attention. Conducted at T1, T2, and T3. Resting state (eyes-open/eyes-closed, counterbalanced): 5 min EC + 5 min EO (alternating 30 s EC, 30 s EO). 5 min 40 Hz stimulation Sustained attention task (10 min): a simple, well-tolerated visual attention paradigm (e.g., continuous performance or oddball-style target detection) to elicit attention-related ERPs (e.g., P3) and trial-by-trial spectral dynamics. Relaxed breathing (10 min): paced, relaxed nasal breathing with breath-focus instructions to probe frontal midline theta and aperiodic/1-f slope during low-arousal attention. These tasks expand the feature space beyond the evoked-potential block while maintaining total time per participant at ~60 minutes.

Secondary	Test of Variables of Attention (TOVA) Time Points of Measurement: Baseline, post-treatment, and one-month post-treatment follow-up. Endpoint: The mean difference in TOVA change from baseline to post-treatment between treatment and placebo groups.	The Test of Variables of Attention (TOVA) is a computerized continuous performance test designed to assess attentional and inhibition deficits in ADHD by measuring response time, variability, and errors across both visual and auditory stimuli. Administered by trained personnel, it evaluates sustained attention, impulsivity, and sensory processing over a 21.6-minute session (10.8 minutes per subscale). The Attention Comparison Score (ACS) is a z-score-like metric, typically ranging from -10 to +2: [>-1.80] = within normative range (no ADHD impairment) [≤ -1.80] = indicative of ADHD Lower scores reflect greater impairment. A 2.5-point improvement in ACS is considered a minimum clinically important difference (MID), moving scores toward the normative range.
	Adult ADHD Quality of Life Scale (AAQoL) Time Points of Measurement: Baseline, post-treatment, and one-month post-treatment follow-up.	The AAQoL is a patient-reported questionnaire designed to assess quality of life in adults with ADHD. It contains 29 items across four domains (life productivity, psychological health, life outlook, and relationships), evaluating the impact of ADHD symptoms on daily functioning over the past two weeks. The total score ranges from 0 to 100 (higher scores indicate better quality of life): [0–30] = severe impairment [31–50] = moderate impairment [51–70] = mild impairment [71–100] = minimal to no impairment A 7–10-point improvement in the total score is considered a minimum clinically important difference (MID), reflecting meaningful improvement in quality of life.

	Clinical Global Impression-Severity (CGI-S) Time Points of Measurement: Baseline, post-treatment, and one-month post-treatment follow-up.	The CGI-S is a clinician-rated scale designed to assess the severity of ADHD symptoms in adults based on a comprehensive evaluation of the patient's clinical presentation. Administered by a trained healthcare professional, it reflects the clinician's judgment of symptom severity at a given time point, considering the past week. The score ranges from 1 to 7: [1] = Normal, not at all ill [2] = Borderline ill [3] = Mildly ill [4] = Moderately ill [5] = Markedly ill [6] = Severely ill [7] = Among the most extremely ill A 1-point reduction in the CGI-S score is considered a minimum clinically important difference (MID), indicating a meaningful decrease in ADHD symptom severity.
	Clinical Global Impression-Improvement (CGI-I) Time Points of Measurement: Post-treatment and one-month post-treatment follow-up (not assessed at baseline).	The CGI-I is a clinician-rated scale designed to assess improvement in ADHD symptoms in adults relative to baseline, based on a comprehensive clinical evaluation. Administered by a trained healthcare professional, it reflects the clinician's judgment of treatment-related change in symptom severity over the past week. The score ranges from 1 to 7: [1] = Very much improved [2] = Much improved [3] = Minimally improved [4] = No change [5] = Minimally worse [6] = Much worse [7] = Very much worse A CGI-I score of 2 or lower (much or very much improved) is considered a minimum clinically important difference (MID), indicating meaningful clinical improvement in ADHD symptoms.

	Adult ADHD Self-Report Scale Time Points of Measurement: Baseline, post-treatment, and one-month post-treatment follow-up.	The ASRS is a self-reported questionnaire designed to assess the severity of ADHD symptoms in adults over the past six months (or since the last assessment for follow-up time points). Completed by the patient, it consists of 18 items based on DSM criteria for ADHD, with Part A (6 items) focusing on the most predictive symptoms of inattention and hyperactivity/impulsivity, and Part B (12 items) providing additional context. The response options for each item are on a 5-point Likert scale: [0] = Never [1] = Rarely [2] = Sometimes [3] = Often [4] = Very Often Items are scored by assigning 1 point if the response is in the shaded (symptomatic) range (≥2 for items 1–3 and 7–8 in Part A; ≥3 for items 4–6 in Part A; similar thresholds apply to Part B). The total score ranges from 0 to 18, with Part A scores from 0 to 6. A Part A score of 4 or higher is considered a positive screen for ADHD, indicating likely clinically significant symptoms. A reduction of at least 30% in the total ASRS score (or a standardized effect size improvement) is often considered a minimum clinically important difference (MID), indicating a meaningful decrease in self-reported ADHD symptom severity.

	Adult ADHD Clinical Diagnostic Scale (ACDS) Time Points of Measurement: Baseline, post-treatment, and one-month post-treatment follow-up.	The ACDS is a clinician-administered, semi-structured interview designed to assess the severity of ADHD symptoms in adults. Conducted by a trained healthcare professional, it evaluates 18 DSM-IV ADHD symptoms (inattention and hyperactivity-impulsivity) over the past six months, adapted for current severity. The total score ranges from 0 to 54 (each of 18 symptoms scored 0–3): [0–10] = Minimal or no ADHD symptoms [11–20] = Mild ADHD [21–30] = Moderate ADHD [31–54] = Severe ADHD A 5–7-point reduction in the total score is considered a minimum clinically important difference (MID), reflecting a meaningful decrease in ADHD symptom severity.
Sleep	Pittsburgh Sleep Quality Index (PSQI) Time Points of Measurement: Baseline, post-treatment, and one-month post-treatment follow-up. Primary Endpoint: The mean difference in PSQI score change from baseline to post-treatment between treatment and placebo groups.	The PSQI is a patient-reported questionnaire designed to assess sleep quality and disturbances in adults. It consists of 19 items across seven components (e.g., sleep duration, sleep latency, sleep disturbances) evaluating sleep patterns over the past month. The global score ranges from 0 to 21 (each component scored 0–3, summed): [0–4] = Good sleep quality [5–10] = Poor sleep quality [11–21] = Severe sleep disturbance A 3-point reduction in the global score is considered a minimum clinically important difference (MID), reflecting a meaningful improvement in sleep quality.
Safety	The UKU Side Effects Scale Adverse Event (AE) Report Form The safety endpoint is the presence or absence of any adverse events during the treatment period.	All device-related adverse events will be reported and analyzed throughout the treatment and follow-up periods.

3.0. Statistical plan and data analysis:

Sample size power analysis
Primary outcome: 5-point reduction difference in AISRS between active and placebo group
Significance Level (alpha) = 0.05
Power (1−beta) = 0.90 (90%)
Statistical Test: Two-sample t-test
Effect Size Estimation:
Baseline AISRS Mean = 32 (moderate symptom severity)
Expected Reduction in Treatment Group = 8 points
Placebo Group Reduction = 3 points
Standard Deviation (SD) of AISRS = 8 (based on AISRS validation studies)
Effect Size (d) = (8 - 3) / 8 = 0.625 (medium to large effect size)
Sample Size Calculation:
Using the formula for two-sample t-test:
n per group = 2 * ((z_alpha/2 + z_beta)^2 * SD^2) / (difference in means)^2
n per group = 2 * ((1.96 + 1.28)^2 * 8^2) / (8 - 3)^2
n per group = 34
Accounting for 10% dropout:
Adjusted n per group = 34 / (1 - 0.10) = 38 (rounded up)
Total sample size: 76 (38 per group)

This sample size provides 90% power to detect a 5-point difference in AISRS score reduction between the treatment and placebo groups, with a medium to large effect size (d = 0.625) at a significance level of 0.05. The calculation accounts for an expected 3-point reduction in the control group and an 8-point reduction in the treatment group, maintaining the 5-point difference between groups. The sample size has been increased to 38 per group (76 total) to account for an anticipated 10% dropout rate, ensuring sufficient statistical power even with potential participant attrition.

Analytical model
Under the null hypothesis (H0) of no effect the within-subject changes from Baseline would be distributed around zero change (dx); some subjects would have positive changes, others negative changes. If the data analysis results in the rejection of the null hypothesis in favor of the alternative hypothesis (H1), the deltas

would be collectively shifted away from zero, indicating that the treatment had an effect on the AISRS (increase or decrease). The statistical methodology to determine whether the shift is significant, is Wilcoxon Signed Rank (WSR) test. Similarly, WSR would be employed to evaluate the exploratory endpoints. More details will be presented in the Statistical Analysis Protocol (SAP).

Monitoring of patient compliance issues
Patient compliance and device use is monitored through an internal memory card recording lamp activity.

Monitoring of side effects
In accordance with Good Clinical Practice (GCP) guidelines, side effects will be systematically monitored using the UKU Side Effect Rating Scale and comprehensive adverse event (AE) reporting. Previous trials have reported minimal adverse effects, primarily mild headaches and nausea. All potential adverse events will be documented during patient visits or via patient-reported calls to ensure thorough safety monitoring throughout the study.

Ethics approval and consent to participate
This trial will be submitted to the Regional Scientific Ethical Committees for Southern Denmark for approval. The act concerning the processing of personal data is respected. The protocol adheres to the latest version of the Declaration of Helsinki. Participation in the trial is contingent upon obtaining written informed consent from each individual. Prior to signing, all participants will attend a personal information meeting to ensure they fully understand the study's purpose, procedures, and potential risks.

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