CLINICAL TRIAL PROTOCOL

COGNITIVE EFFECTS OF ADJUVANT VORTIOXETINE IN EARLY SCHIZOPHRENIA.

PROTOCOL CODE: CAVES

EudraCT Number: 2021-001333-38

VERSION: 1.0 (10 Sep 2021)

1.- INDEX

2. - SYNOPSIS

2.1 Type of request

Single-centre clinical trial with an active principle of a pharmaceutical specialty already marketed in Spain to be used as an adjuvant in the treatment of schizophrenia in the early stages of the disease Vs other pharmaceutical specialties authorized as routine clinical use.

Coordination Centre: UGC Salud Mental- Clinical Trials Unit (UICEC-HUVR).

2.2 Sponsor identification

Fundación Investigación Sevilla (FISEVI).
Hospital Universitario Virgen del Rocío.
Edificio de laboratorios, 6ª planta.
Avda. Manuel Siurot S/N
41013
Sevilla
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2.3 Protocol Title:

Cognitive effects of adyuvant vortioxetine in early schizophrenia

2.4 Protocol Code:

CAVES

EudraCT Number: 2021-001333-38

2.5 Principal Investigator

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2.6 Centre of performace of the study

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2.7 Ethical committee for clinical research

Reference committee: Provincial CEIm of Seville.

2.8 Responsible for monitoring

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2.9 Study intervention:

Each patient will be treated with each of the study arms, due to the cross-over design; so every of the 37 foreseen patients to be included will be acting as autocontrol receiving both, experimental and control arm with a 2-week wash out period between the 2 phases of the study.

Experimental treatment: Vortioxetine.

Dose: Vortioxetine will be started at 10 mg / day for 2 weeks, followed by 20 mg / day for the remainder of the study. The vortioxetine dose may be reduced to 5 mg or 10 mg for reasons of tolerability at the discretion of the physician.

Control treatment: TAU (Treatment as usual)

As TAU, any medication, routine support or referral to other services, which are deemed medically appropriate, is allowed.

A 2-week washout phase will be required from week 24 to week 26 and at the end of the study (week 50 to week 52).

The two trial periods in which the patient receives the different treatments whose effects are being compared should be separated by a washout phase that is

sufficient to rule out any carry-over effects. In other words, the effect of the first treatment must have completely worn off before the starting of the second period.

The first trial period will last for 24 weeks, then a two-week washout period, and the second trial period will last for 24 weeks, with a two-week washout period at the end of the trial.

The total trial time will last 52 weeks.

2.10 Study products

Financing and supply of study products: H. Lundbeck A/S

Product: vortioxetine

Trademark: *Brintellix®*

Pharmaceutical Form: tablets

Administration way: Oral

Therapeutic Group: Psychoanaleptics; Other antidepressants

Quantitative and qualitative composition of the product: the product is presented in doses of 5, 10 and 20 mg / tablet. Each carton contains 25 blisters with 10 tablets per blister.

According to product data sheet (about protocol, period of treatment is 24 weeks):

- first 2 weeks: 10 mg/day → 14 tablets/patient of 10mg

- next 22 weeks: 20 mg/day → 308 tablets/patient of 10mg

- 322 tablets/patient/10mg + 10% → 355 tablets/patient/10 mg

- as each box of Brintellix contains 250 tablets → 2 box of 10 mg/patient

TOTAL: 2 box of 10mg/ patient x **37** patients → **74 box of 10 mg and 15 box of 5 mg.**

Treatment control: usual antipsychotic treatment (TAU)

As TAU, any medication, routine support or referral to other services, which are deemed medically appropriate, is allowed. The only limitations are to refrain from:

1. Refer patients for Cognitive Behavioural Therapy (CBT) or other brief cognitive therapies unless absolutely necessary.
2. Adding other cognitive enhancers. Antidepressant medication as a routine part of routine treatment is not restricted.

3. ECT (Electroconvulsive Therapy) may not be prescribed for the duration of the trial.

2.11 Clinical trial phase

Phase IIb/III

2.12 Objectives

Principal objective: evaluate the efficacy of vortioxetine against TAU in the treatment of cognitive impairment in newly diagnosed schizophrenia, measured by the change from baseline to week 24 (and from week 26 to week 50 in the 2nd period) in the BACS App Scale scores, using the Composite Z Score defined as the weighted sum of the patient's Individual Z Score (frame time: baseline visit, week 24, week 26 and week 50).

Secondary objective: to evaluate the efficacy of vortioxetine against TAU in the treatment of negative symptoms in newly diagnosed schizophrenia, measured by the change in the severity of negative symptoms (SANS total scores, NSA-4) from baseline. until completion (frame time: baseline visit, week 4, week 12, week 24, week 26, week 30, week 38 and week 50).

- Additionally the following secondary objectives will be evaluated To assess the efficacy of vortioxetine versus TAU in the treatment of cognitive deficits in newly diagnosed schizophrenia, as measured by change in general functioning (GAF total score) (frame time: baseline visit, week 12, week 24, week 26, week 38 and week 50)

Evaluate the safety of vortioxetine in patients with newly diagnosed schizophrenia measured through the communication of any serious adverse event evaluated in relation to the Experimental Treatment (frame time: from consent signature to week 52).

- Evaluate the efficacy and reliability of the BACS App Vs BACS, measured by performing both scales and comparing results. The purpose is to confirm the reliability of the results when performing the BACS App as a faster and more practical model at the beginning and end of each period (Measurement time: baseline visit, week 24, week 26 and week 50) compared to the results

obtained with the BACS scale performed at each trial visit (Measurement time: from consent signature to week 52).

2.13 Study design:

Open-label, randomized, crossover, single-centre clinical trial IIb / III to evaluate the efficacy of vortioxetine compared to standard treatment in recently diagnosed schizophrenia.

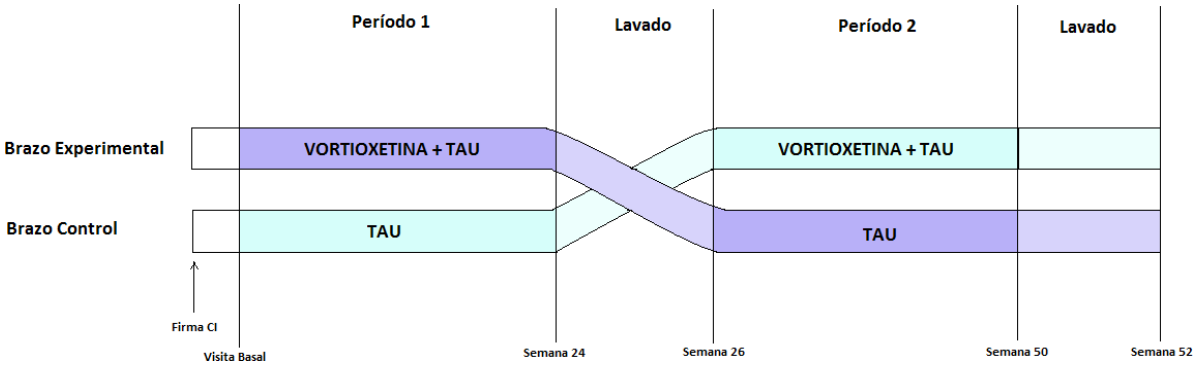

Figure 1

This is a 12-month (52-week), randomized, crossover study comparing vortioxetine as adjunctive treatment in 37 stabilized patients (25 per arm) in early stages of the disease (less than 3 years from first treatment. stable antipsychotic) with a diagnosis of schizophrenia spectrum disorder determined by the structured DSM-5 clinical interview (SCID).
Subjects who drop out of the trial before its completion will not be replaced.

2.14 Study indication

Recently diagnosed schizophrenia.

In the literature there is a great diversity of definitions that describe the period called "early course" of schizophrenia. Given the lack of consensual and standardized definitions, a recent review was made, reaching the conclusion that the definitions that use the duration criterion for the definition of schizophrenia of recent onset, use a range of cut-off points ranging from 1 month up to 10 years, with 1, 2 and 5 years being the most frequent. Based on this review, the 3-year inclusion criterion is adjusted to the current literature in the field of early schizophrenia.

2.15 Primary endpoint

To assess the effectiveness of Vortioxetine vs. TAU measured by the change in Brief Assessment of Cognition in Schizophrenia (BACS App) scores

2.16 Study population and number of planned subjects.

Patients in the early stage of the disease (less than 3 years from the first stable antipsychotic treatment) with a diagnosis of schizophrenia disorder determined by the DSM-5 Structured Clinical Interview (SCID).

50 patients will be recruited from the area covered by the Virgen del Rocío University Hospital (whose population is 800,000 people). Outpatients will be evaluated for inclusion and exclusion criteria.
Patients with a clinical stability of at least 3 months, with stable treatment of antipsychotics and psychotropic medications for at least the last 4 weeks. Patients without depression diagnosis, positive psychotic symptoms (PANSS) or extrapyramidal EPS symptoms (SAS, BARS) will be eligible.

2.17 Duration of treatment

The duration of the treatment will be 24 weeks in the first period with two weeks of washing after the treatment (week 24 to week 26). After this wash, the patient will undergo another 24 weeks (week 26 to week 50) of treatment corresponding to the second period and will end with another 2 weeks of wash (week 50 to 52).

In total, the trial will last 52 weeks, comprising two periods of 24 weeks of treatment each and 2 weeks of washing in each period.

2.18 Schedule and expected completion date

The study is expected to begin, once the permits have been obtained, in a maximum time of 3 months from its acceptance to obtain the approval of the Spanish Regulatory Authority (AEMPS: Agencia Española del Medicamento y Productos sanitarios) and the Ethic Committee (CEIm: Comité Etico de Investigación con medicamentos)

The recruitment period will be 24 months from the activation of the center and the total follow-up of each patient will be 52 weeks spread over 18 visits. The study is expected to finish in December 2025.

- Start of trial (estimate): November 2021
- Recruitment period: 24 months
- End of recruitment (estimate): November 2023
- End of treatment of the last patient (estimate): November 2024
- End of follow-up period: 12 months after the last dose to the last patient
- End of the test. Estimate (estimate): December 2025

3.- GENERAL INFORMATION

3.1 Trial identification

Protocol Study: CAVES
EudraCT Number: 2021-001333-38
Version 1.0 10 Sep 2021

3.2 Type of clinical trial

Open-label, randomized, crossover, single-center clinical trial IIb / III to evaluate the efficacy of vortioxetine compared to standard treatment in recently diagnosed schizophrenia.

3.3 Information relating to the promoter

Fundación Investigación Sevilla (FISEVI).
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3.3.1 Person authorized by the promoter

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3.3.2 Responsible for monitoring

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3.4 Description of the products of study

Experimental treatment

Generic name: Vortioxetine
Therapeutic Group: Psychoanaleptics; Other antidepressants

VORTIOXETINE is a multimodal antidepressant with a long duration of action. It is used in the treatment of cases of major depression. The mechanism of the antidepressant action of vortioxetine appears to be related to the direct modulation of serotonin receptor activity and the inhibition of the serotonin transporter. In vitro studies indicate that vortioxetine is an antagonist of the 5-HT3, 5-HT7 and 5-HT1D receptors, a partial agonist of the 5-HT1B receptor, a 5-HT1A receptor agonist. It which leads to modulation of neurotransmission in various systems, including predominantly serotonin, but probably also norepinephrine, dopamine, histamine, acetylcholine, GABA, and glutamate systems. This multimodal activity is believed to be responsible for the antidepressant and anxiolytic effects, as well as the improvement in cognitive function, learning, and memory observed with vortioxetine in animal studies.

Control treatment

Generic name: antipsychotics used in routine clinical practice.

3.5 Data from the study investigators

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3.6 Laboratories, Medical Department or Related Institutions

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4.- JUSTIFICATION

Comprehensive meta-analysis reviews consistently show marked impairments in a wide range of cognitive domains in schizophrenia, with considerable long-term effects. The effects tend to be somewhat higher especially for tests that assess memory and processing speed. The patients are cognitively outperformed by the controls at the onset of the disease, and the cognitive performance of the patients improves in a similar way to the controls over time (Rodriguez-Sanchez et al, 2013). Although the course of cognitive performance is generally stable, there is a subset of patients who experience cognitive decline over time. Patients whose cognitive performance experiences a decreasing trend show poorer progression in terms of clinical and disability variables.

The degree of baseline impairment in cognitive functions related to the prefrontal cortex are critical determinants of quality of life and functionality in schizophrenia (Treen Calvo et al, 2018 FEP). Therefore, cognition is an important goal of treatment, given the strong association between it and functional outcomes in people with psychotic disorders. Antipsychotics are quite effective in reducing the severity of positive symptoms and preventing relapse, but their impact on negative and cognitive symptoms is limited. In the last two decades, different strategies have been proposed to treat cognitive impairment in schizophrenia with uncertain achievements (Robbins et al, 2019). Cognitive enhancement agents are pharmaceuticals that are suggested to enhance cognitive performance by acting on the relevant neurotransmission systems, typically the glutamatergic and cholinergic systems. Results from individual studies have been mixed, and a recent meta-analysis of 93 studies, comparing cognitive enhancement agents with placebo, reported a small significant effect of cognitive enhancers on general cognition, but no significant effects on cognitive domains. individual. The main limitations are that many of these studies are underpowered to detect effects, that the number of studies investigating these agents is few, and the treatment durations are short (Sinkeviciute et al, 2018; Keefe et al, 2013).

The search for new cognitive treatments may be favored by the recognition of apparently analogous cognitive dysfunctions in different neuropsychiatric phenotypes. Therefore, cognitive impairments in schizophrenia could possibly be treated with a medication similar to that of Major Depressive Disorder (MDD), accepting that recurrent comorbidity in psychiatry can also extend to cognitive dimensions (Robbins, 2019).

The mechanism of action of Vortioxetine combines direct modulation of the 5-HT receptor (antagonist of 5-HT3, 5-HT7 and 5HT1D receptors, 5-HT1B receptor partial

agonist, 5-HT1A receptor agonist) and inhibition of the transporter of serotonin (5-HT): SERT inhibition. This target profile appears to consist of the modulated control of neuronal activity in key areas of the brain involved in Major Depressive Disorder, but also in the improvement of synaptic plasticity and cognitive function.

McIntyre et al (2014) reported cognitive improvement effects after 8 weeks of vortioxetine treatment, on a composite cognitive variable in depression. Importantly, the cognitive-enhancing effect was not associated with its mood-enhancing effects, suggesting the possibility of parallel effects on mood and cognition, through serotonergic actions.

Mahableshwarkar et al (2015) also identified that in adults with MDD who had reported cognitive dysfunction, vortioxetine significantly improved cognitive function, depression, and functionality, regardless of its effects on depressive symptoms.

Vortioxetine is a multimodal antidepressant similar to a SSRI in that it inhibits the serotonide transporter, but with additional actions on the 5-HT3 and 5-HT7 receptors, but it is not yet clear whether these contribute to cognitive enhancement effects and how. . One suggestion has been that its 5-HT3 action may serve to disinhibit GABAergic receptors on interneurons (McIntyre et al, 2014).

Vortioxetine is approved for MDD in adults at a starting dose of 10 mg per day, which can be increased to 20 mg per day. Treatment providers may consider giving 5 mg daily for patients who cannot tolerate higher doses. Vortioxetine can be stopped abruptly, but a decrease to 10 mg per day is recommended for patients taking 15 mg per day or more for a week before complete discontinuation. Vortioxetine is in pregnancy category C. There are no data on its effects on lactation.

The two trial periods in which the patient receives the different treatments whose effects are being compared should be separated by a wash-out phase long enough to rule out any carry-over effects. In other words, the effect of the first treatment must have completely worn off before the start of the second period. With vortioxetine that period is 2 weeks.

5.- HYPOTHESIS AND OBJECTIVES

5.1 Hypothesis

Our hypothesis is that adjuvant vortioxetine treatment could have a beneficial effect on cognitive symptoms and / or cognition in the early stages of patients with schizophrenia.

5.2 Objectives

5.2.1 Principal objective: To investigate the effect of vortioxetine on cognitive functioning and the severity of negative symptoms in the early stages of schizophrenia, measuring the change in the BACS App Scale at the beginning and end of each period.

5.2.2 Secondary objective: To assess the efficacy of vortioxetine versus TAU in treating negative symptoms in newly diagnosed schizophrenia, as measured by change in severity of negative symptoms (SANS total scores, NSA-4) from baseline to completion of the study.

- Additionally, the following secondary objectives will be evaluated. To assess the efficacy of vortioxetine versus TAU in the treatment of cognitive deficits in recently diagnosed schizophrenia, as measured by change in general functioning (GAF total score)
- To assess the safety of vortioxetine in recently diagnosed schizophrenia patients as measured by the reporting of any serious adverse event evaluated in relation to the Experimental Treatment during the 52 weeks of the trial.
- Evaluate the efficacy and reliability of the BACS App Vs BACS, measured by performing both scales and comparing results. The purpose is to confirm the reliability of the results when performing the BACS App as a faster and more practical model at the beginning and end of each period (Measurement time: baseline visit, week 24, week 26 and week 50) compared to the results obtained with the BACS scale performed at each trial visit (Measurement time: from consent signature to week 52).

6.- STUDY DESIGN

6.1 Endpoints

6.1.1 Principal endpoint

The primary endpoint of the response consists of the improvement in cognitive functioning as assessed by the change in the BACS App Scale score: changes from baseline to week 24 (and from week 26 to week 50 in the 2nd period) in the scores of the BACS App Scale, using the Composite Z Score defined as the weighted sum of the patient's Individual Z Score (frame time: baseline visit, week 24, week 26 and week 50).

6.1.2 Secondary endpoint

Secondary endpoints consist of improvement in the severity of negative symptoms as measured by the change in severity of negative symptoms on the SANS and NSA-4 score over the visits of each period (frame time: baseline visit, week 4, week 12, week 24, week 26, week 30, week 38 and week 50).

- Additionally the following secondary objectives will be evaluated. Functional improvement due to the change in general functioning measured by the GAF scale score from the beginning to week 24 of each period (frame time: baseline visit, week 12, week 24, week 26, week 38 and week 50)
- Safety assessment by measuring the frequency, severity, and relationship with study medication of any adverse event described during treatment. The reasons for withdrawal and / or abandonment of the trial will also be evaluated (if applicable): from the signing of the IC until week 52.

6.2 Design

Open-label, randomized, crossover, single-center clinical trial IIb / III to evaluate the efficacy of vortioxetine compared to standard treatment in recently diagnosed schizophrenia.

Experimental treatment: Vortioxetine (20 mg / day) added to current antipsychotic treatment versus usual treatment (TAU).

Control treatment: antipsychotic treatment used in routine clinical practice.

6.3 Randomization procedure

Patients will be recruited within the health area corresponding to the center participating in the trial, the Virgen del Rocío University Hospital in Seville. They will be detected from institutionalized patients who attend the mental health network devices on an outpatient basis.

In those patients with a diagnosis of early evolution Schizophrenia with a stable treatment with antipsychotics for at least 4 weeks, the inclusion and exclusion criteria of the study will be verified, and informed consent will be requested after completing the ACE questionnaire, to measure the degree capacity of understanding of the person who signs. Patients who meet all the inclusion criteria, but have some exclusion, will be considered screening failure, and the reason for exclusion should be collected. Subjects who drop out of the trial before the end of the trial will not be replaced.

Once the informed consent has been signed, randomization will be carried out, which will be centralized online, in a 1: 1 ratio (adjuvant treatment with vortioxetine vs treatment in usual clinical practice).

The randomization system will be available online in the CRDe (Electronic Data Collection Notebook) designed for this purpose. The list of assignments will be generated using specific software and will be included in the CRD.

The randomization list will be guarded by the Clinical Trials Unit (UICEC). Once you have entered that you meet all the inclusion criteria and none of the exclusion criteria, the researcher will obtain the assigned treatment and the patient's code, which will be made up of a numerical code that identifies the center and patient (per example: XX-XXX).

6.4 Blinding procedures

There are no blinding techniques, as it is an open study. Therefore, no procedure for breaking the blind is applicable either.

6.5 Follow-up

The follow-up of the patients will be carried out in the visits defined in this protocol. After signing the informed consent, patients will undergo a screening visit to confirm their eligibility for the study. If all the inclusion and exclusion criteria are correct, patients will undergo an initial evaluation and then will be randomized 1: 1 to 24 weeks of adjuvant treatment with vortioxetine or TAU.

Thereafter, patients will be seen in week 1, 4 and monthly for the next 5 months. At the end of this period, having reached week 24, the patient will undergo a washout

period of two weeks (regardless of the assigned arm) to ensure that in the case of starting the trial in the experimental arm, there will be no effect. carry-over caused by vortioxetine at the start of the second period (week 26)

There are 2 wash weeks that will take place between the two test periods (week 24 to week 26), and a second wash that will take place at the end of the second period (week 50 to week 52) (figure 1).

6.6 Discontinuation of study treatment and withdrawal of subjects from the study

Premature discontinuation of the clinical trial may occur due to a decision of the regulatory authorities, due to a change in the opinion of the Clinical Research Ethics Committees, due to safety and / or drug problems or indications of ineffectiveness.

It will be considered that there is a voluntary abandonment of the trial due to the refusal of the patient or legal guardian of the same to continue with the treatment or in the study, and the subject will be considered as abandonment immediately after communicating his decision to the Investigator. A patient may discontinue the trial at any time if the person, the legal representative, the investigator or the motorization committee determine that it is not in the best interest of the patient to maintain their participation.

Other reasons for discontinuation include:

- Patients with low compliance with the study drug, below 80%
- Patients requiring hospitalization for worsening psychotic disorder and / or behavioural disturbances associated with psychotic disorder.
- Patients in whom, during the study period, there is a high risk of detected suicide, according to the criteria established by Columbia University according to the risk assessment with the C-SSRS scale.
- Female patients who test positive for urine pregnancy at any time during their participation in the study.
- Any serious adverse event that recommends withdrawal at the discretion of the investigator with the agreement of the monitoring committee.
- The patient decides not to continue with the trial.
- Others: The researcher, as well as the sponsor, reserve the right to interrupt the study at any time for reasonable medical and / or administrative reasons.

Patients who drop out after randomization will not be replaced.

Patients who terminate treatment prematurely will complete an early termination interview and a safety visit.

The patient who has completed the protocol is considered to be one who has completed all the visits included in the 52-week follow-up period.

The interruption of the treatment does not imply that the case is excluded from the statistical analysis. These subjects will be part of the study and will be taken into account when analyzing the data.

There may be other circumstances for the abandonment, which in its case the researcher must make sure that the patient has abandoned the study, and will verify the causes of said abandonment.

6.7 Medication accountability

The sponsor will ensure the traceability of the experimental drug by collecting data to allow it to be monitored, and by counting the excess medication at each visit to the trial. The administration of the experimental treatment will be obtained through the Hospital Pharmacy of Clinical Trials of the Virgen del Rocío University Hospital, the trial drug being guarded by the Hospital Pharmacy Service.

The specific control of the prescription carried out exclusively by the referring Psychiatrist will also be carried out.

The pharmaceutical specialties used in the study do not require special storage or handling conditions, under normal conditions of humidity and temperature.

6.8 End of trial

The day of the final visit of the last patient included in the study will be considered the end of the trial.

7.- SELECTION OF SUBJECTS

Patients between 18 and 50 years old diagnosed with recently diagnosed Schizophrenia.

7.1 Inclusion criteria

1. Recent SCID (Structured Clinical Interview for DSM-IV: F20) diagnosis of schizophrenia spectrum disorders (diagnosis of the disease must have been a maximum of 3 years before signing the consent).

2. Outpatient regimen; patients hospitalized will not be included.

3. Age between 18 and 50 years.

4. Stable doses of antipsychotic medication for at least 4 weeks (all second generation antipsychotics, excluding clozapine).

5. No antidepressant treatment for at least 8 weeks prior to randomization.

6. PANSS: negative score> 14 with at least two of the items at a level ≥ 4 (moderate)

7. PANSS: positive score ≤ 14 with no more than one of the items at a level ≥ 4 (moderate).

8. Total HAMD-17 score ≤ 12

9. Simpson Angus score of any item <2

10. BARS of any item ≤ 1

11. Competent and willing to sign the informed consent

12. In case the patient is a potentially fertile woman, she must agree not to become pregnant during the study, as well as the use of adequate and highly effective contraceptives.

7.2 Exclusion criteria

1. Patients taking any antidepressant and its use cannot be discontinued at least 8 weeks prior to randomization.
2. Structural brain disease (based on previous medical records).
3. Cognitive disability by history and estimated IQ <70 (ID DSM-5 diagnosis).
4. Any serious chronic medical condition that may interfere with the patient's ability to comply with study procedures or that interferes with cognition.
5. Organic mental disorders or mental disorders due to a general medical condition. Any neurological or neurodegenerative disorder.
6. Any current diagnosis of substance abuse or dependence.
7. Serious risk of suicide.
8. Patients with diseases of the thyroid gland.
9. Intolerance or ineffectiveness of vortioxetine in the past. Patients who have had unsuccessful vortioxetine treatment will also be excluded.
10. Pregnant or lactating woman.

7.3 Withdrawal criteria

In accordance with the Declaration of Helsinki (Annex III), patients have the right to withdraw from the study at any time and for any reason, being able to express it personally or through their representative.

7.3.1 Due to efficacy criteria

Trial withdrawal Criteria

- Patients with a level of compliance with the study drug lower than 80%
- Patients in whom at some point during the study period a high risk of suicide is detected, according to the criteria established by Columbia University according to the evaluation of said risk using the C-SSRS scale
- Female patients who have a positive urine pregnancy test throughout their participation in the study
- Patients who have a seizure during their participation in the study.
- Patients who, during the period with Vortioxetine, require treatment with another antidepressant different from the study medication.
- Patients who require some treatment contraindicated with the use of Vortioxetine during the study.

7.3.2 Due to safety criteria

- Any adverse event described in the technical data sheet of the product that at the discretion of the clinician forces the withdrawal of the study
- When, for any reason, the treatment is no longer safe for the patient
- Any other reason that could endanger the life of the patient or have serious consequences for the same

7.3.3 For breach or violation of the rules contained in the protocol

When the patient no longer complies with the rules of the trial, they may be withdrawn at the discretion of the responsible investigator or due to loss of follow-up.

7.3.4 Follow-up of prematurely withdrawn patients

If a patient is withdrawn from the trial prematurely, the investigator will provide the main reason for the suspension and, as indicated by the GCP guidelines, the procedures will be followed according to the usual treatment protocols for their pathology at the discretion of the responsible clinician.

8.- TREATMENT OF SUBJECTS

Experimental Group

The experimental group will be based on including Vortioxetine as an adjunct drug to the usual antipsychotic treatment that the subject is taking.

The route of administration of vortioxetine is oral in a single daily dose.

It will start with 10 mg / day for the first 2 weeks, followed by 20 mg / day for the remainder of the study. The vortioxetine dose may be reduced to 5 mg or 10 mg for reasons of tolerability at the discretion of the physician.

Control group

In the case of being included in the control group, patients will be treated according to usual clinical practice that includes the use of antipsychotics according to the indications in their technical data sheet.

The most convenient habitual antipsychotic treatment will be chosen according to the criteria of the prescribing physician.

8.1 Treatment duration and adjustments

- The duration of treatment in each arm will be 24 weeks
- To avoid carry-over effects of the medication, a 2-week washout phase will be needed from week 24 to week 26, and another 2-week washout phase at the end of the study (week 50 to 52)
- The trial will last 52 weeks in total

8.2 Concomitant medication

Any concomitant medication must be reflected in the CRD (product, dose, route, day of administration, reason for treatment, etc.) throughout the study follow-up period.

8.2.1 Allowed medications

- Oral contraceptives and other hormonal methods; Oral contraceptives must have been started 30 days before the inclusion of the patient.
- Benzodiazepines.

8.2.2 Prohibited medications

The following medications will be prohibited for the duration of the study:

- Antidepressant medications
- Clozapine
- Drugs that are contraindicated with the use of vortioxetine or that have a potential interaction with vortioxetine.
- Inducers or inhibitors of cytochrome P450 (CYP) 1A2 (medications, over-the-counter agents, or dietary supplements) from 30 days prior to randomization and during follow-up.
- Anticholinergics

8.2. 3 Methods of fertility control

Women of childbearing potential must have documentation of a negative pregnancy test prior to administration of study medication.

Women are not considered of childbearing age if they have had a total hysterectomy and / or bilateral tubal ligation or hysteroscopic sterilization (documentation for surgeries must be provided prior to inclusion) or are in a postmenopausal state (i.e. women who have stopped menstruating for ≥24 months with no alternative causes) or women with premature ovarian failure.

All women of childbearing potential and men who may father children must agree to abstain from sexual intercourse or use highly effective contraception during the study and for at least 30 days after completing study drug dosing.
A highly effective contraceptive method is defined as one that results in a low failure rate (i.e. <1% per year) when used consistently and correctly.

These methods include:

- Combined hormonal contraception (containing estrogens and progestogens) associated with inhibition of ovulation
  - oral
  - intravaginal
  - transdermal
- Progestin-only hormonal contraception associated with inhibition of ovulation
  - oral
  - injectable

  - implantable: Intrauterine Device (IUD)

- Intrauterine hormone releasing system (IUS)

- Bilateral tubal occlusion

- Vasectomized couple, provided that this partner is the only sexual partner of the woman participating in the trial of childbearing age and that the vasectomized couple has received a medical evaluation of surgical success.

- Sexual abstinence is considered a highly effective method only if it is defined as abstaining from heterosexual intercourse for the entire risk period associated with the study treatments. The reliability of sexual abstinence should be assessed in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

NOTE: Contraceptive methods that are not considered highly effective:

- Progestin-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action

- Male or female condom with or without spermicide

- Cap, diaphragm or sponge with spermicide

8.3 Rescue medication

The use of rescue medication is not planned. If a patient is withdrawn due to lack of efficacy or some similar condition, they will be treated according to the clinical guidelines and the usual clinical practice for these cases.

9.- SCHEDULED VISITS AND EVALUATIONS

Procedures PERIOD 1	**Visit 1 (-30 days) Screening**	**Visit 2 (Day1) Baseline**	**Visit 3 (Day 8±3) Week 1**	**Visit 4 (Day 29±3) Week 4**	**Visit 5 (Day 57±3) Week 8**	**Visit 6 (Day 85±3) Week 12**	**Visit 7 (Day 113±3) Week 16**	**Visit 8 (Day 141±3) Week 20**	**Visit 9 (Day 169±3) Week 24[1]**
Informed Consent / ACE	X								
Inclusion/Exclusion Criteria	X	X							
Randomization		X							
Pregnancy Test	X	X							
Medical History	X	X	X	X	X	X	X	X	X
HAMD-17[2]	X								
BARS[3]	X								
PANSS[4]	X								X
SAS[5]	X	X	X	X	X	X	X	X	X
SANS[6]		X		X		X			X
BACS[7]		X				X			X
BACS App[8]		X							X
NSA-4[9]		X		X		X			X
GAF[10]		X				X			X
Vitals Signs: weigth, Height, Blood Pressure, Pulse Rate, abdominal perimeter		X		X		X			X

Hematology/Chemistry[13]		X							X
Dispense Treatment [11]		X	X	X	X	X	X	X	
Compliance [12]			X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X	X	X

1. Between week 24 and week 26 the first wash period takes place. The washing time between one period and another will be 2 weeks
2. HAMD-17: Hamilton Rating Scale for Depression
3. BARS: Behaviorally Anchored Rating Scale
4. PANSS: Positive and Negative Syndrome Scale
5. SAS: Sedation-Agitation Scale
6. SANS: Scale for Assessment of Negative Symptoms
7. BACS: Brief Assessment of Cognition in Schizophrenia
8. BACS App: Brief Assessment of Cognition in Schizophrenia App. Versión de la Escala BACS en aplicación para Tablets: facilitará la realización de pruebas repetidas y reducirá efectos de la práctica. Existen diferentes versiones de la prueba.
9. NSA-4: Negative Symptom Assessment (4-Item)
10. GAF: Global Functionality Assessment Scale
11. Vortioxetine dosage according to Summary of Product Characteristics (section 6.5 of protocol)
12. Patient must bring test medication at each visit for counting. Empty boxes will stay in the center
13. Complete blood count including leukocyte, neutrophil, hemoglobin, and platelet counts. Blood chemistry that includes the determination of sodium, potassium, creatinine, urea, lipid profile, glycemia.

Procedures PERIOD 2	**Visit10 (Day 183±3) Week 26**	**Visit11 (Day 190±3) Week 27**	**Visit12 (Day 211±3) Week 30**	**Visit13 (Day 239±3) Week 34**	**Visit14 (Day 267±3) Week 38**	**Visit15 (Day 295±3) Week 42**	**Visit16 (Day 323±3) Week 46**	**Visit17 (Day 351±3) Week 50[1]**	**Visit18 (Day 379±3) Week 52**
Pregnancy Test	X								X
Medical History	X	X	X	X	X	X	X	X	X
HAMD-17	X								
BARS	X								
PANSS	X							X	X
SAS	X	X	X	X	X	X	X	X	
SANS	X		X		X			X	
BACS	X				X			X	X
BACS App	X							X	
NSA-4	X		X		X			X	
GAF	X				X			X	X
Vitals Signs: weigth, Height, Blood Pressure, Pulse Rate, abdominal perimeter	X		X		X			X	X
Hematology/Chemistry	X							X	X
Dispense Treatment	X	X	X	X	X	X	X		
Compliance		X	X	X	X	X	X	X	
Concomitant Medication	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X

1. Between week 50 and week 52 the second wash period takes place. The visit corresponding to week 52 corresponds to the FINAL VISIT OF THE TRIAL.

9.1 Procedures per visit

The follow-up of the patients in the present study consists of 9 scheduled visits in each period (18 in total). Depending on which arm the patient falls on, the trial treatment will begin in one period or another. That is, if after the randomization of the patient, he falls into the Experimental Arm, the treatment will begin on Visit 2 (Day 1) and will end in week 24, corresponding to period 2 as the TAU treatment period. If, on the other hand, the patient falls into Control Arm, the study will begin with a first TAU period (continues with the treatment according to clinical criteria) and it will be in period 2 when the trial treatment begins (in week 26 of the study).

In this protocol the visits are arranged in chronological order, specifying the week to which each one corresponds.

The following sections detail the procedures that must be carried out at each visit.

9.1.1 Visit 1: Screening (-30 days)

During the screening or selection visit (visit 1), certain actions must be carried out as a step prior to inclusion, as well as data collection prior to inclusion. The procedures that will be carried out during this visit are detailed below:

- Signature of the informed consent
- Capacity Assessment (ACE)
- Assessment of the inclusion / exclusion criteria
- In the case of women of childbearing age, a urine or blood pregnancy test will be requested (the most feasible)
- Demographic data: age, sex, race, educational level, marital status, illiteracy
- Clinical history / anamnesis with collection of: developmental data, onset of behavioural or psychotic disorders, previous treatments, family history of schizophrenia, history of epilepsy, history of prison and history of consumption habits (alcohol, tobacco and drugs)
- Diagnosis of schizophrenia
- HAMD-17
- BARS, PANSS, SAS.
- Review of concomitant medication

9.1.2 Visit 2: Randomization (Treatment Day 1 / Baseline Visit)

- Review of inclusion and exclusion criteria
- Physical examination: weight, blood pressure, heart rate, respiratory rate, temperature and abdominal perimeter
- Blood extraction (hemogram and biochemistry)
- Clinical, cognitive and functional evaluation: SAS, SANS, BACS, BACS App, NSA-4 and GAF
- Review of concomitant medication
- Medication administration (day 1 of treatment)

9.1.3 Visit 3 (Week 1: day 8 ± 3 days)

- Clinical, cognitive and functional evaluation: SAS
- Dosing and dispensing treatment
- Adherence to treatment
- Review of concomitant medication
- Review of adverse events

9.1.4 Visit 4 (Week 4: day 29 ± 3 days)

- Physical examination: weight, blood pressure, heart rate, respiratory rate, temperature and abdominal perimeter
- Clinical, cognitive and functional assessment: SAS, SANS and NSA-4
- Dosage and dispensing treatment
- Adherence to treatment
- Concomitant medication review
- Review of adverse events

9.1.5 Visit 5 (Week 8: day 57 ± 3 days)

- Clinical, cognitive and functional evaluation: SAS
- Dosing and dispensing treatment
- Adherence to treatment
- Review of concomitant medication
- Review of adverse events

9.1.6 Visit 6 (Week 12: 85 ± 3 days)

- Physical examination: weight, blood pressure, heart rate, respiratory rate, temperature and abdominal perimeter
- Clinical, cognitive and functional evaluation: SAS, SANS, BACS, GAF and NSA-4
- Dosing and dispensing treatment
- Adherence to treatment
- Review of concomitant medication
- Review of adverse events

9.1.7 Visit 7 (Week 16: day 113 ± 3 days)

- Clinical, cognitive and functional evaluation: SAS
- Dosing and dispensing treatment
- Adherence to treatment
- Review of concomitant medication
- Review of adverse events

9.1.8 Visit 8 (Week 20: day 141 ± 3 days)

- Clinical, cognitive and functional evaluation: SAS
- Dosing and dispensing treatment
- Adherence to treatment
- Review of concomitant medication
- Review of adverse events

9.1.9 Visit 9: End of Treatment Visit (Week 24: day 169 ± 3 days)

- Physical examination: weight, blood pressure, heart rate, respiratory rate, temperature and abdominal perimeter
- Clinical, cognitive and functional evaluation: SAS, SANS, BACS, PANSS, GAF and NSA-4
- Dosing and dispensing treatment
- Adherence to treatment
- Review of concomitant medication
- Review of adverse events

9.1.10 Visit 10 (Week 26: day 183 ± 3 days)

- In the case of women of childbearing age, a urine or blood pregnancy test will be requested (the most feasible)
- Physical examination: weight, blood pressure, heart rate, respiratory rate, temperature and abdominal perimeter
- Blood extraction (hemogram and biochemistry)
- HAMD-17
- Clinical, cognitive and functional evaluation: BARS, PANSS, SAS, SANS, BACS, BACS App, NSA-4 and GAF
- Medication administration (day 1 of treatment)
- Review of concomitant medication
- Review of adverse events

9.1.11 Visit 11 (Week 27: day 190 ± 3 days)

- Clinical, cognitive and functional evaluation: SAS
- Dosing and dispensing treatment
- Adherence to treatment
- Review of concomitant medication
- Review of adverse events

9.1.12 Visit 12 (Week 30: day 211 ± 3 days)

- Physical examination: weight, blood pressure, heart rate, respiratory rate, temperature and abdominal perimeter
- Clinical, cognitive and functional assessment: SAS, SANS and NSA-4
- Dosage and dispensing treatment
- Adherence to treatment
- Concomitant medication review
- Review of adverse events

9.1.13 Visit 13 (Week 34: day 239 ± 3 days)

- Clinical, cognitive and functional evaluation: SAS
- Dosing and dispensing treatment
- Adherence to treatment
- Review of concomitant medication
- Review of adverse events

9.1.14 Visit 14 (Week 38: day 267 ± 3 days)

- Physical examination: weight, blood pressure, heart rate, respiratory rate, temperature and abdominal perimeter
- Clinical, cognitive and functional evaluation: SAS, SANS, BACS, GAF and NSA-4
- Dosing and dispensing treatment
- Adherence to treatment
- Review of concomitant medication
- Review of adverse events

9.1.15 Visit 15 (Week 42: day 295 ± 3 days)

- Clinical, cognitive and functional evaluation: SAS
- Dosing and dispensing treatment
- Adherence to treatment
- Review of concomitant medication
- Review of adverse events

9.1.16 Visit 16 (Week 46: day 323 ± 3 days)

- Clinical, cognitive and functional evaluation: SAS
- Dosing and dispensing treatment
- Adherence to treatment
- Review of concomitant medication
- Review of adverse events

9.1.17 Visit 17: End of Treatment Visit (Week 50: day 351 ± 3 days)

- Physical examination: weight, blood pressure, heart rate, respiratory rate, temperature and abdominal girth
- Blood extraction (hemogram and biochemistry)
- Clinical, cognitive and functional evaluation: SAS, SANS, PANSS, BACS, BACS App, NSA-4 and GAF
- Adherence to treatment
- Review of concomitant medication
- Review of adverse events
- Beginning of the washing period (two weeks)

9.1.18 Visit 18: End of Study Visit (Week 52: day 379 ± 3 days)

- In the case of women of childbearing age, a urine or blood pregnancy test will be requested (the most feasible)
- Physical examination: weight, blood pressure, heart rate, respiratory rate, temperature and abdominal girth
- Blood extraction (hemogram and biochemistry)
- Clinical, cognitive and functional evaluation: BACS, PANSS and GAF
- Review of concomitant medication
- Review of adverse events

9.1.19 Unscheduled Visit

If a patient presents changes in their marked clinical status or there is a suspicion of an adverse event, an assessment (less than 24 hours) should be made of the need for an unscheduled visit.

To do this, the patient must have a telephone number to contact the research team in case of need due to recurrence of symptoms and an adverse event.

In the unscheduled visit the following procedures will be carried out:

- In the case of women of childbearing age, a urine or blood pregnancy test will be requested (the most feasible)
- Physical examination: weight, blood pressure, heart rate, respiratory rate, temperature and abdominal girth
- Blood extraction (hemogram and biochemistry)
- HAMD-17

- Clinical, cognitive and functional assessment: BARS, PANSS, SAS, SANS, BACS, BACS App, NSA-4 and GAF
- Adherence to treatment
- Concomitant medication review
- Review of adverse events

10.- EFFECTIVENESS ASSESSMENT

10.1 Primary efficacy endpoint

The primary efficacy endpoint is the change in the BACS total score throughout the trial.

The BACS scale (Brief Assessment of Cognition in Schizophrenia) was designed (Keefe et al. (2004), Spanish version Segarra et al., (2011)) to assess different aspects of cognition that tend to appear impaired in patients with schizophrenia.

The domains evaluated are:

- Verbal memory, evaluated through the word list test.
- Working memory, evaluated through the digit sequence test.
- Motor speed, assessed through the token motor test.
- Verbal fluency, assessed through the word generation test.
- Attention, evaluated through the symbol code test.
- Executive functions, assessment through the Tower of London test.

Two versions of the instrument were created in order to repeat the test avoiding the recall effect.

For correction, an overall score and scores are obtained for each of the tests included. The possible scores for each of the tests are:

- Word list test: 0-75 points.
- Digit sequence test: correct answers 0-28 points; longest sequence remembered 0-8 points.
- Token motor test_ 0-100 points.

- Symbol code test: 0-110 points.
- Tower of London: 0-22 points

Administration time: 30-60 minutes.

Psychometric properties of the BACS scale:

The results showed that all tests are capable of discriminating between patients with schizophrenia and healthy subjects. In the Spanish version, the concurrent validity was similar to that reported in other languages.

Other variables of clinical improvement in terms of severity of negative symptoms are measured with the total score of SANS and NSA-4 and improvement in general functioning evaluated with changes in GAF.

10.2 Lab tests

Blood tests are contemplated at the initial visit and thereafter as specified in the visit schedule. Said analyzes will be carried out locally in each center, in accordance with the standards of routine clinical practice. The following tests will be carried out:

- Complete blood count including white blood cell, neutrophil, hemoglobin, and platelet counts. Blood chemistry that includes the determination of sodium, potassium, creatinine, urea, lipid profile glycemia.

11.- SAFETY ASSESSMENT

11.1 Security Assessments

The following clinical evaluations will be performed to assess the safety profile of the trial treatment.

11.1.1 Physical examination: vital signs

A physical examination and constants will be taken according to the visit schedule (section 9)

11.1.2 Laboratory tests

An analytical extraction with hemogram and biochemistry will be performed that includes lipid and glycemic profile at Visit 2 (Baseline). After visit 2, patients should have another hematological and biochemical control at Visit 9, 10, 17 and 18 (Week 24, 26, 50 and 52).

11.2 Definitions

Adverse Event (AE)

An adverse event is any unwanted medical reaction experienced by the patient at any time during the course of the study, whether or not it is considered to be related to the study treatment. This definition includes the appearance of a new disease and the exacerbation of pre-existing disorders other than the indication under study.

Adverse Reaction (AR)

An AR is any harmful and unintended reaction to an investigational drug, regardless of the dose administered.

Serious Adverse Event (SAE) and Serious Adverse Reaction (SAR)

AEs or ARs are considered serious that, at any dose, can cause death, threaten the life of the subject, require hospitalization of the patient or prolong an existing hospitalization, cause permanent or significant disability or disability, or give rise to an anomaly or malformation congenital. Suspicions of AE or AR that are medically important, even if they do not meet the above criteria, are also considered serious, including important medical events that require intervention to prevent one of the consequences described above from occurring. Likewise, all suspicions of transmission of an infectious agent through a drug will be reported as serious.

The concept "threatening the life of the subject" in the definition refers to the fact that, in the opinion of the researcher, the patient at the time of AE or AR is at real risk of death; It does not refer to the hypothetical AE / AR could have caused death if it had been more intense.

The concept "require hospitalization" will exclude both planned hospitalizations for scheduled treatments and those that have been planned or anticipated prior to commencing the study in relation to a pre-existing medical situation.

Unexpected Adverse Reaction

Any AR whose nature, intensity or consequences do not correspond to the referenced security information.

Serious and Unexpected Adverse Reaction

SAR (previously defined), the nature, severity or consequences of which do not correspond to the reference security information.

Causality Criteria

- Related AE: The temporal relationship of AE with the study medication indicates a possible causal relationship and cannot be explained by factors such as the patient's clinical status, therapeutic interventions.
- Unrelated AE: The temporal relationship of AE with study medication indicates an unlikely causal relationship, or other factors (medication or concomitant conditions), other therapeutic interventions provide a satisfactory explanation for AE

For expedited notification purposes, the following categories will be considered **related:** highly probable, probable and not clearly attributable; and as **unrelated**, the improbable, excluded and impossible to assess category.

11.3 Reference safety information

In this study the reference safety information (RSI) will be the Summary of Product Characteristics (SPC) ANNEX IV

11.4 Information of Adverse Events

The investigator will monitor and systematically collect the AEs related to study medication (ARs) starting from the signing of the Informed Consent Form until the final follow-up visit of each subject.
Also, the investigator will assess and record, in detail, the AR, including the start and dates, the description of the event, severity, course, outcome, and the measures taken (treatments, additional complementary examinations, etc).

The AR will be recorded in the medical history and recorded in the Case Report Form.
The subjects who present an AR will be subjected to relevant follow-up until duration of the same.

11.5 Notification and collection of serious adverse events

The principal investigator or a collaborator must report to the Pharmacovigilance (PhV) department PhV -UICEC-HUVR, all serious adverse events (as defined below), which are related to the treatment and unexpected (SUSAR), within 24 hours (one business day), as of its knowledge (Annex II). Serious adverse events that occur should be reported at any time from the patient's inclusion in the study (defined as the time the subject signs the informed consent) and up to 30 days after the subject concludes or leaves the study. A subject is considered complete either after the conclusion of the last visit or contact (telephone contact with the investigator or a collaborator), as indicated in the protocol evaluation schedule, or after the last dose study medication, whichever occurs later. Withdrawal is defined as the date a subject and / or the investigator determine that the subject can no longer meet the study requirements at any subsequent visits and evaluations.

The investigator will complete and sign the SAEs notification form (Annex II) that will be sent by fax or email to:

Unidad de Investigación Clínica y Ensayos Clínicos
Hospital Universitario Virgen del Rocío
Dpto. Farmacovigilancia
Email: **uicec.hvr.sspa@juntadeandalucia.es**

Avda. Manuel Siurot S/N
41013. Sevilla
Tel.: 955 01 30 72
Fax: 955 09 53 38

PhV staff will review the form received and, if applicable, will request additional information from the investigator. The researcher will provide information to the promoter or whoever assumes the tasks delegated by the promoter (PhV-UICEC-HUVR Unit) whenever requested and, in any case, when his initial assessment regarding severity or causality changes. To communicate the follow-up information, the notification procedure described previously will be followed.

The PhV-UICEC-HUVR staff will keep a detailed record of all the SUSARs, pregnancies, medications errors, etc. that are communicated to them by the researchers.
Each SUSAR, pregnancy or medication error communicated to the Promoter's PharmacoVigilance team will be reported to the LundBeck laboratory within 24 hours of being aware of it., to the email: safetyluspain@lundbeck.com

In the event that a medication error occurs or the investigational medication is used outside of the protocol provided during the study, the investigator will notify the PhV-UICEC-HUVR within 24 hours of being aware of it. The circuit for notification and the form will be the same as for SAEs.

Those AEs that meet the severity criteria described in the definitions section described for this purpose will be considered serious. Clinically significant events that are not life threatening or fatal or require hospitalization may be considered serious adverse drug experiences when, based on sound medical judgment, they may endanger the subject or require medical or surgical intervention to prevent one of the results listed in this definition. Examples of such medical events are allergic bronchospasm requiring intensive treatment, at home or in an emergency unit, blood dyscrasias or seizures that do not lead to hospitalization, or the development of a dependence or substance abuse.

Reporting of laboratory test abnormalities (grade 3 or 4) is also required, unless otherwise noted in this section of the protocol.

11.6 SUSARs expedited notification

The PhV-UICEC-HUVR department is responsible for notifying the AEMPS and the CCAA where the test is carried out, all the SUSAR that are collected in the study, following the procedure indicated in the current legislation.

The maximum period of notification of an individual case of suspicion of SUSAR will be 15 calendar days from the moment in which the promoter has become aware of it. When the suspicion of SUSAR has caused the death of the patient, or endangered his life, the promoter will send the information within a period of 7 calendar days from the moment in which he becomes aware of it. It will complete this information, if possible, in the following 8 days.

This information should include an evaluation of the significance and implication of the findings, including relevant prior experience with the same or similar medications.

Likewise, the competent body of each of the Autonomous Communities where the test is carried out must be notified of the suspicions of SUSAR that have occurred in the health centers of their Community. In both cases, the SUSAR notification form will be used for this.

11.7 Expedited notification of other relevant safety information

The PhV-UICEC-HUVR department will notify as soon as possible and no later than 15 days after it becomes aware of any information that could modify the benefit / risk ratio of the investigational drug (for example: increase in the percentage of the appearance of the expected AGRs, the AGRs that occur after the completion of a clinical trial, new events related to the conduct of the trial or the development of the investigational drug, any recommendation of the data monitoring committee relevant to the safety of the subjects, etc.).

11.8 Notification to researchers

The sponsor will present the researchers with safety information that could impact the safety of the patients included in the study as soon as possible.

In addition, the investigator will be informed throughout the study about any safety aspect, including protocol modifications due to safety reasons.

11.9 Medication errors

Medication errors are unintentional errors in prescribing, dispensing, administering or monitoring a medication while it is under the control of a healthcare professional or the patient and that may cause harm to the patient.

Misuse refers to a situation in which the medical product is used intentionally in an inappropriate way, not in accordance with the protocol.

Study medication errors and use outside the scope of the protocol will be recorded in the data collection log (CRF), regardless of whether they are associated with an AE / SAE or not. The misuse or abuse will be collected and reported in the security database within 24 hours of the investigator's knowledge of it.

11. 10 Pregnancy

Subjects will be instructed to notify the investigator of the pregnancy if it occurs, and the subject will immediately exit the study.

In the event of any pregnancy occurring during the development of the study, the researcher will notify the promoter or whoever assumes the tasks delegated by the promoter within 24 hours of their knowledge. Likewise, the pregnancy will be monitored to document its outcome and the newborn's health status. If the outcome of the pregnancy meets the criteria for SAE or if the newborn presents a serious event, the procedures described for the notification of SAE will be followed.

The notification will be made using the specific SAE notification form which will be sent by fax or email to the same contact that will receive the notifications from SAE. The PhV-UICEC-HUVR department will notify within 24 hours of their knowledge to the LundBeck laboratory.

11.11 Periodic Safety Report

During the course of the study, the sponsor will prepare periodic safety reports annually following the recommendations outlined in the ICH E2F guidelines, and they must be submitted to the regulatory authorities and the CRECs involved following the timetable established in the legislation.

12.- STATISTICS

12.1 Sample size calculation

As it is a crossover design, each individual acts as their own control, that is, an initial treatment is assigned and after a while it is changed. Therefore, the correct thing to do would be to calculate the sample under the premise of related or paired samples, for this case it would be the dependent samples T test.
The sample size can be calculated in two ways, in the first one, the difference in the means to be detected of the primary variable (BACS), the standard deviations of the treatment change, and the correlation coefficient must be established; while the second is to consider the difference in the means to be detected for the primary variable (BACS) and the standard difference of the differences.

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a bilateral contrast, 37 subjects are required to detect a difference equal to or greater than 0.5 units. A standard deviation of 1 is assumed. A loss to follow-up rate of 15% has been estimated.

That is, based on the previous parameters, and using a confidence level of 95% and power of 80%, 37 subjects are needed.

12.2 Statistic analysis

Descriptive analysis:

Initially, the normal distribution characteristics of all the trial variables will be evaluated, especially that of the main variable BACS.

Comparative analysis between cases vs controls:

A comparison of means will be made by means of T test of dependent samples of the main variable BACS between both arms in the first period. Subsequently, the same analysis will be carried out in the second period, comparing T test of dependent samples means with a 95% confidence margin. If necessary, the Mann-Whitney Test would be applied.

In addition, a study will be carried out where the same sample is compared in period 1 and 2 and a repeated measures analysis will be carried out. That is, the change in the variables of the same patient will be evaluated when he has the experimental drug compared to when he is with his usual treatment. In the same way, it will be done with the mean of the sample of each arm and period.

12.3 Definitions of the study analysis populations

- Intent-to-treat (ITT) population: all randomized patients
- Modified intention-to-treat population (ITTm): randomized patients who have received at least one dose of treatment after randomization
- Population per protocol (PP): all patients who have completed the protocol evaluations while maintaining the established randomization group
- Clinically evaluable population (CE): clinically evaluable population (randomized population that received at least 80% of the scheduled treatment or in a lower percentage if the interruption was due to an adverse effect. In addition, these patients had the result of one or more variables available at the end of treatment, at the healing visit or at the last follow-up visit and did not show significant deviations from the protocol that could affect the efficacy evaluation, including good documentary control)

13.- ETHICAL ASPECTS

The trial will be carried out in accordance with the principles that emanate from the Declaration of Helsinki, and according to current legal regulations (Royal Decree 1090/2015), and will not start until the approval of the reference CEIC, the conformity of the Directors of the Institutions, and the authorization of the Spanish Agency for Medicines and Health Products.

The trial will be developed in compliance with the Standards of Good Clinical Practice (*Note for guidance on Good Clinical Practice, CPMP / ICH / 135/95*), as well as international guidelines on ethical issues such as the Declaration of Helsinki, the Union and the Charter of Fundamental Rights of the European Union (2000), the Universal Declaration on Bioethics and Human Rights (2005), the Universal Declaration of Human Rights of the United Nations, 1948, and the Convention of the Council of Europe on the Protection of Human Rights that ensure the protection of the rights, safety and well-being of the subjects participating in the study and ensure the integrity and credibility of the data obtained in a clinical trial.

The investigator must meet all the requirements of the protocol. If a situation arises in which a temporary deviation from the protocol is required, the investigator or other physician responsible for the patient should contact the monitor as soon as possible in order to comment on the situation and agree on an appropriate course of action. The investigator will document the deviation from protocol and the circumstances that required it.

Human biological samples for research would be stored in the HUVR biobank and would be governed by Law 14/2007 on Biomedical Research, provided that the prior informed consent of the patient or their legal representatives is given.

13.1 Informed consent

The patient must give their consent before being admitted to the clinical study.

The consent will be adapted to an easy-to-read version by expert validators in cognitive accessibility and full inclusion. The physician must explain the nature, purposes and possible consequences of the clinical trial, in a way that is understandable to the patient. The information provided by the doctor must also be recorded. In obtaining and documenting it, the researchers will comply with the relevant legislation (article 4 of Royal Decree 1090/2015), the rules of good clinical practice and the ethical principles that have their origin in the Declaration of Helsinki.

The subject to participate in the clinical trial, or his legal representative, can revoke his consent at any time, without pressure of cause and without thereby deriving any responsibility or damage to the participating subject.

The subject of the study will give their consent, signing the corresponding model. The investigator will receive an adequate number of informed consent templates through the sponsor. To this end, each model must bear the signature of the researcher and the patient.

The investigator will not initiate any investigation for the trial until the consent of the patient has been obtained.

Since the patient's biological samples will be stored and distributed by the biobank, information and an informed consent document are also included to donate biological samples to the biobank for biomedical research. The biobank document for the consent to obtain, store or conserve and use biological samples of human origin for the purposes of biomedical research will contain the information required in Legal Decree 1716/2011. All samples will be pseudonymised.

The pseudonymization of biological samples and the confidentiality of the data will specify the information and identity data of the subject. This information may only be reviewed by authorized personnel during evaluation and quality control visits or in the event of a serious adverse event.

13.2 Data Protection

The treatment, communication and transfer of personal data of all participating subjects will comply with the provisions of Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27, 2016 regarding the protection of individuals with regard to the processing of personal data and the free circulation of these data and Organic Law 3/2018, of December 5, Protection of Personal Data and guarantee of digital rights. In accordance with the provisions of the aforementioned legislation, the patient may exercise the rights of access, modification, opposition and cancellation of data, for which he must contact his study doctor.

The anonymity of the subjects participating in the study will be maintained at all times. Thus, the data collected for the study will be identified by a code and only the researcher and collaborators will be able to relate said data to the patient and to their medical history. Therefore, the identity of the patient will not be revealed to anyone except for exceptions: personnel authorized by the promoter, when required, to verify the data and procedures of the study, but always maintaining their confidentiality in accordance with current legislation; in case of medical emergency

or legal requirement (health authorities: Spanish Agency for Medicines and Health Products and Local Committee for Clinical Trials).

The data from this study will only be used for the specific purposes of this study.

13.3 Responsibilities of study participants

The participating subject must follow the instructions of the researchers and communicate any eventuality to them. The subject will be duly informed of the prohibitions or restrictions that must be observed during the performance of the trial. Failure to comply with these recommendations will lead to abandonment of the study.

All the subjects participating in the study have the right to leave the study at any time, withdrawing their consent, without having to justify this decision and without detriment to their clinical follow-up. If this occurs, the investigator will try to have the subject perform all the necessary evaluations to ensure that no adverse events occur and to ensure appropriate follow-up in the event that any type of problem has occurred.

13.4 Responsibilities of the trial investigators

The principal investigator will review and approve the trial protocol, will delegate the CEIm authorization request to UICEC-HUVR, as well as the agreement of the Director of the Institution and the signature of the investigator's commitment form.

The collaborating researchers will have the mission of evaluating the eligibility of the patient, informing patients and their representatives, requesting written consent, evaluating the efficacy and safety of the treatment, completing and signing the Data Collection Notebooks (CRD) and the realization of the follow-up of adverse events.

Investigators are responsible for complying with the requirements of the protocol.

UICEC-HUVR will act as a Clinical Research Organization (CRO) in order to ensure compliance with all applicable requirements for the studies. He will act as a supervisor of the activities of the monitor. The monitor will ensure that the data included in the CRD correspond to those in the Clinical History, that the patients have been adequately informed and included in the treatment group that has been randomly assigned to them, and the study is carried out under the protocol version approved.

13.5 Monitoring and auditing

The study will be monitored through local visits, telephone calls and periodic inspection of the CRDs frequently enough to verify the following:

- Rate of inclusion of patients, compliance with the rules of the protocol procedures, completeness and accuracy of the data entered in the notebooks, verification against the original documents and appearance of adverse events.

- The monitoring visits will be made by the studio monitors. It is understood that these monitors will be able to access the medical records of the patients after the investigator requests it. The researcher will dedicate sufficient time to these visits and will facilitate access to all the documentation to authorized persons.

- The study may be audited by an independent body. Likewise, members of the CEIC will be able to follow up on it.

13.6 Premature termination or suspension of the study

If the trial is prematurely terminated or suspended, the sponsor must promptly inform the investigator and regulatory authorities of the termination or suspension and the reason for it. The sponsor or researcher must promptly inform the CEIC and provide the reason for the termination or suspension, as specified by the relevant regulatory requirements.

13.7 Study documentation

The documentation related to the study (protocol, CRD, informed consent, authorizations, etc.) will be filed in a safe place and easily accessible by the research team. All the information contained in clinical, histological, biochemical reports, observations or other activities is necessary for the reconstruction and evaluation of the study.

14.- FINANCING AND INSURANCE

14.1 Financing

The promoter has a donation made by the MAH (Marketing Authorization Holder) to carry out this study, ensuring compliance with the applicable quality standards.

A document of independence of the intellectual property of the data has been signed by the promoter. All study data belongs to the sponsor, but the sponsor agrees that MAH may use it for training activities, registration of any intellectual property, etc.

14.2 Insurance

The promoter undertakes to contract a Civil Liability Insurance policy within the period provided for in Art. 9.3 of Royal Decree 1090/2015 in order to cover the damages that a subject may suffer as a result of their participation in the trial. . This policy will also cover the responsibilities that the promoter, the main investigator and their collaborators may incur, including the contracted clinical investigators, and the hospital or center where the clinical trial is carried out, by virtue of the provisions of Art. 61 of Royal Legislative Decree 1/2015, of July 24, which approves the revised text of the Law of guarantees and rational use of medicines and health products, and in the terms and risks defined in Art. 9 and Art. 10 of Royal Decree 1090/2015, of December 4, which regulates clinical trials with drugs, the Ethics Committees for Drug Research and the Spanish Registry of Clinical Studies.

15.- PUBLICATION POLICY

The researchers will publish the study results in internationally indexed documents and open access journals. Both MAH and sponsor-investigator are interested in publication of results of the study. Publication interest and manuscript are agreed to be sent to MAH one month before the submission to a journal.
The results dissemination plan will also include national presentations and international scientific conferences and meetings and development of clinical guidelines for the treatment of these patients.

Participation in informational social events organized by associations of users and relatives of patients for dissemination and education on this subject.

These will comply with the provisions of Royal Decree 1090/2015 of December 4, which regulates Clinical Trials with medicines, the Ethics Committee for Research with medicines and the Spanish Registry of Clinical Studies, article 42, which collects the following text:

"1. The sponsor is obliged to publish the results, both positive and negative, of authorized clinical trials, preferably in scientific journals before being disclosed to the non-health public, regardless of the obligations to publish the report of the results in the Spanish Registry. of clinical studies (REec) and the provisions in this regard in Regulation (EU) No. 536/2014 of the European Parliament and of the Council, of April 16, 2014.

2. When studies and research works on drugs are made public, aimed at the scientific community, the funds obtained by the author, by or for their realization, and the source of funding will be stated.

3. The anonymity of the subjects participating in the trial will be maintained at all times.

4. Treatments of as yet undetermined efficacy will not be released prematurely or sensationally, nor will it be exaggerated. Intermediate results that could compromise the reliability of the final test results will not be publicized.

5. The advertising of medicines for human use in research is strictly prohibited, as established in the revised text of the Law on guarantees and rational use of medicines and health products, in Royal Decree 1416/1994, of June 25 , which regulates the advertising of medicines for human use, in Royal Decree 1907/1996, of August 2, on advertising and commercial promotion of products, activities or services with purported health purposes, and in Law 34 / 1988, of November 11, General Advertising.

6. In all cases, to make public the general results of the investigations once concluded, the guidelines of the European Commission and, where appropriate, the instructions of the Spanish Agency for Medicines and Health Products will be followed.

7. When a sub-study of a clinical trial ends later than the rest of the trial, it will be necessary for the summary of its results to be published in the year following its completion, without this implying a delay in the presentation of the results of the rest of the trial."

ANNEX I. BIBLIOGRAPHY

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ANNEX II. SAE NOTIFICATION FORM

(Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla)
(2021-001333-38 / CAVES)
Formulario Evento Adverso Grave
FAX: 955 09 53 38
E-Mail: uicec.hvr.sspa@juntadeandalucia.es

Tipo de informe:	Inicial ☐	De Seguimiento ☐

1. Datos del centro del estudio	
Número de centro:	País:
Nombre del investigador principal:	Nombre del Notificador:
Fecha:	Firma del investigador:

2. Datos del paciente				
Número de Paciente *(número de selección y/o asignación al azar)*	Año de Nacimiento	Sexo	Altura (cm)	Peso (kg)
	AAAA	M ☐ V ☐		

3. Evento Adverso Grave/ Evento Adverso de especial interés *(para reportar eventos adicionales copiar esta página)*	
Término del Evento *(Agrupar los síntomas como un único diagnóstico, para ser consistente con el CRD)*	Fecha de inicio (DD / MM / AAAA)
Descripción del evento *(evolución del EA, incluidos los signos/síntomas relacionados, los hallazgos relevantes, las contramedidas, los factores de confusión y la causa probable del EAG)*	
¿Evento Adverso de especial interés? Sí ☐ No ☐	

NOMBRE DEL ESTUDIO/NÚMERO DE ENSAYO	NÚMERO DE CENTRO	NÚMERO DE PACIENTE

4. Gravedad del EAG	5. Criterio de gravedad	6. Evolución del evento (en el momento del informe)
☐ Muerte ☐ Riesgo inmediato para la vida ☐ Hospitalización/ prolongación Hospitalización ☐ Discapacidad/ Incapacidad funcional ☐ Anomalías congénitas ☐ Medicamente significativa	☐ Leve ☐ Moderado ☐ Severo	☐ Recuperado fecha:_____ ☐ Recuperándose ☐ Recuperado con secuelas fecha:_____ ☐ No recuperado ☐ Muerte fecha:_____ ☐ Se desconoce

7. Fase del estudio en el momento del evento	
☐ Cribado	☐ Tratamiento
☐ Lavado	☐ Seguimiento
☐ Otra, por favor especificar:	

8. Información del producto				
Producto del estudio	Dosis / unidades	Frecuencia	Fecha primera administración (DD / MM / AAAA)	Fecha última administración (DD / MM / AAAA)

9. Evaluación de la causalidad	10. Acción tomada con el producto como resultado del evento	11. Retirada / Reexposición del producto
☐ Muy probable ☐ Probable ☐ No claramente atribuible ☐ Improbable ☐ Excluida ☐ Imposible de evaluar	☐ Mantenimiento de dosis ☐ Reducción de dosis ☐ Discontinuado temporalmente ☐ Discontinuado permanentemente ☐ No aplicable ☐ Se desconoce	**Retirada:** ¿El evento desapareció tras dejar de utilizar el producto? ☐ Sí ☐ No ☐ N/A ☐ Se desconoce **Reexposición:** ¿Reaparición del evento tras la reintroducción del producto? ☐ Sí ☐ No ☐ N/A ☐ Se desconoce

12. Desenmascaramiento
¿Se rompió el código de desenmascaramiento? ☐ No ☐ Sí En caso afirmativo, proporcione la fecha:_____

NOMBRE DEL ESTUDIO/NÚMERO DE ENSAYO	NÚMERO DE CENTRO	NÚMERO DE PACIENTE

13. Medicación Concomitante Sí ☐ No ☐ Producto sospechoso: 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐
UTILIZADA EN EL MOMENTO DEL EAG *Excluir aquellos productos utilizados como tratamiento del evento*

	Nombre comercial/ Principio activo	Dosis	Frecuencia	Ruta	Indicación	Fecha de inicio DD / MM / AAAA	Fecha de fin DD / MM / AAAA
1.							
2.							
3.							
4.							
5.							

Medicación concomitante sospechosa: *Si el EAG está causado por uno de los productos mencionados arriba, por favor marque la casilla correspondiente en el encabezado del apartado.*

14. Información médica relevante *(Ej. alergias, disfunción renal/hepática)* Sí ☐ No ☐

	Condición / Enfermedad	Fecha de inicio DD / MM / AAAA	Fecha de fin DD / MM / AAAA
1.			
2.			
3.			
4.			

15. Hospitalización *(completar, si procede)*

☐ Nueva hospitalización
☐ Prolongación de la hospitalización

Fecha de admisión:

_____

Fecha de alta:

_____

16. Muerte *(completar, si procede)*

Fecha: _____

Causa(s) principal de muerte:

_____

_____

Autopsia: ☐ Sí ☐ No
(en caso afirmativo, por favor adjuntar el informe)

17. Información adicional *(Continúe en una página adicional si es necesario)*

SEND IMMEDIATELY (24 hours after knowledge) BY FAX TO THE PHARMACOVIGILANCE TEAM OF THE RESEARCH AND CLINICAL TRIALS UNIT OF THE VIRGEN DEL ROCÍO UNIVERSITY HOSPITAL (UICEC-HUVR).

(FAX: 955 09 53 38)

Email: uicec.hvr.sspa@juntadeandalucia.es

ANEXO III. HELSINKI DECLARATION

THE WORLD MEDICAL ASSOCIATION, INC.

DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53th WMA General Assembly, Washington, United States, October 2002
(Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo, Japan, October 2004
(Note of Clarification on Paragraph 30 added) WMA General Assembly, Seoul, Korea, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current DoH/Oct2008 2 interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.

12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources

of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.

14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.

15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor DoH/Oct2008 3 ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.

18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.

20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.

21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.

23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.

24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent

to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that DoH/Oct2008 4 the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.

26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.

27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized

representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication. DoH/Oct2008 5

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances: • The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or • Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.

35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

ANNEX IV. Summary of PRODUCT CHARACTERISTICS

ANNEX V. SCALES

1. HAMD-17 *(Hamilton Rating Scale for Depression)*
2. BARS *(Behaviorally Anchored Rating Scale)*
3. PANSS *(Positive and Negative Syndrome Scale)*
4. SAS *(Sedation-Agitation Scale)*
5. SANS *(Scale for Assessment of Negative Symptoms)*
6. BACS *(Brief Assessment of Cognition in Schizophrenia)*
7. BACS App *(Brief Assessment of Cognition in Schizophrenia App).* Versión de la Escala BACS en aplicación para Tablets: facilitará la realización de pruebas repetidas y reducirá efectos de la práctica. Existen diferentes versiones de la prueba.
8. NSA-4 *(Negative Symptom Assessment (4-Item))*
9. GAF *(Global Functionality Assessment Scale)*