EXPEDIENTE GC16_01_SER_4

PLIEGO DE PRESCRIPCIONES TÉCNICAS PARA LA CONTRATACIÓN DEL SERVICIO DE COORDINACIÓN, MONITORIZACIÓN, SEGUIMIENTO Y ANÁLISIS DE UN ESTUDIO EN FASE II, MULTICÉNTRICO, PARA EVALUAR LA SEGURIDAD Y LA RESPUESTA CLÍNICA A UN FÁRMACO EN PACIENTES CON DETERIORO COGNITIVO LEVE O ESTADIOS INICIALES DE LA DEMENCIA DE TIPO ALZHEIMER

En este documento se detallan las especificaciones técnicas mínimas de obligado cumplimiento que deberán incluir sine die los presupuestos presentados, incluyendo la relación detallada de todos los servicios ofertados así como la metodología en la aplicación de los mismos.

1.- OBJETO: DESCRIPCIÓN DEL SERVICIO

El presente pliego tiene por objeto la regulación de las condiciones técnicas que han de regir la contratación del servicio de coordinación, monitorización, seguimiento y análisis de un estudio en fase II, multicéntrico, para evaluar la seguridad y la respuesta clínica a un fármaco en pacientes con deterioro cognitivo leve o estadios iniciales de la demencia de tipo Alzheimer. Dicho servicio deberá ser prestado por una Organización de Investigación Clínica o Clinical Research Organitation (CRO)
El servicio descrito se desarrollará en el marco de ejecución del Proyecto de investigación "A 26 week multicenter double-blind, placebo-controlled, randomized, parallel-group study to evaluate the safety and tolerability of three oral doses of Sativex® in patients with mild cognitive impairment or early Alzheimer dementia".

Se especifican las siguientes **actividades a realizar** en el marco de la presente contratación:

1. Coordinar a los distintos agentes implicados (Investigadores, Promotor, diferentes Servicios de los Centros donde se ejecuten el estudio, Comités de Ética, personal de apoyo, etc.).
2. Asegurar que el estudio se realiza de acuerdo a la normativa vigente, a los Procedimientos Normalizados de Trabajo (PNTs) establecidos por el promotor y a las normas de Buena Práctica Clínica.
3. Monitorización y cierre del estudio (incluye la preparación y envío del material y documentación necesaria al centro para la adecuada realización de estas visitas).
4. Gestión del Archivo del estudio.
5. Verificar que los investigadores participantes en el estudio siguen el protocolo y las modificaciones aprobadas del mismo.
6. Revisar las tareas realizadas por los data managers del estudio asegurando el cumplimiento de las normas de Buena Práctica Clínica.
7. Elaboración trimestral de un informe sobre la marcha del estudio.
8. Elaboración de informes anuales de seguimiento del estudio y apoyo a la elaboración de los informes anuales de seguridad del mismo.
9. Realizar las comunicaciones al promotor de cualquier desviación del protocolo, consentimiento informado mal obtenido, notificación de AAG/RAGIs, o cualquier aspecto relevante que suceda en el estudio.
10. Responsabilizarse de las tramitaciones a efectuar en el estudio con las Autoridades Sanitarias Competentes (Comités Autonómico y locales de Ensayos Clínicos, Agencia Española de Medicamentos y Productos Sanitarios).

11. Realizar la doble entrada de datos en la base de datos, tras la recogida de los CRDs en los centros.
12. Depurar las bases de datos hasta la total resolución de las queries generadas.
13. Otras actividades, no especificadas entre las anteriores, pero directamente relacionadas con el objeto de este contrato.

Aunque el listado contempla de manera exhaustiva todas las actividades a realizar en el marco del estudio referido en las actuales circunstancias, hay que tener en cuenta que los estudios clínicos son proyectos vivos que pueden sufrir alteraciones en su desarrollo (marcadas entre otros aspectos por cambios en el marco legal o disposiciones de obligado cumplimiento por parte de entidades reguladoras o supervisoras) que no pueden ser previsibles en este momento. Por tanto no cabe descartar que, por circunstancias sobrevenidas, deban plantearse actividades adicionales, que en todo caso se llevarían a cabo por acuerdo entre ambas partes.

Detalle específico del estudio objeto del contrato:

Periodo regulatorio: 6 meses.
Duración del estudio: 21 meses (12 meses reclutamiento, 6 meses seguimiento y 3 meses para cierre de la base de datos y centros).
Número de pacientes totales: 60 pacientes.
Número de centros investigadores: 6-10 centros en España.
Plazo de ejecución: la duración del contrato estará supeditada a la fecha de finalización efectiva del estudio, que puede no coincidir con la fecha de finalización prevista del mismo, por protocolo. La duración del servicio será de 28 meses.

Detalle de las tareas a Realizar:

1. **Preparación del Estudio:**
   - 1.1 Documentación.
     - Elaboración del protocolo del estudio.
     - Elaboración de HIP/CI.
     - Elaboración del CRD.
   - 1.2 Archivo del Estudio.
     - Preparación del archivo del investigador.
     - Preparación del archivo central del estudio.

2. **Aprobación por las autoridades sanitarias:**
   - Trámites para la preparación y obtención de la documentación esencial de los centros.
   - Trámites para la presentación al CEIM.
   - Obtención documentación específica del resto de centros.
   - Preparación y envío de la documentación a AEMPS para evaluación.
   - Solicitud del Eudra CT y preparación del Anexo 1ª.
   - Alta y actualización del estudio en www.clinicaltrials.gov.
   - Alta y actualización del estudio en el Registro Nacional de EECC de la AEMPS (REC).
   - Tramitación y gestión de los contratos con los centros.
   - Solicitud y obtención de las conformidades de las Direcciones de los Centros.

3. **Tareas de monitorización:**

Elaboración del plan de monitorización.
Realización de visitas de inicio.

Realización de visitas de monitorización trimestrales (incluyendo desplazamientos).
Realización de visitas de cierre.
Site management:

- Contacto con los investigadores para resolución de cuestiones durante el reclutamiento y tratamiento de los pacientes.
- Newsletters.
- Gestión de queries.
- Mantenimiento del archivo.
- Gestión de SAEs.
- Asistencia a TC mensuales.
- Gestión de medicación y muestras.

4. Gestión del Estudio:

Coordinación del estudio por el responsable de proyecto.
Asistencia a reuniones, coordinación, informes periódicos, newsletters.
Seguimiento y recogida de cuestionarios de pacientes.

5. Programación de e-Clinical:

Módulo Base:

- Programación del CRD en formato electrónico
- Programación del sistema de alertas

Servicio de asistencia técnica líneas 900.
Módulo de bloqueo de pacientes Web.
Diseño e impresión del manual de usuario y tarjetas de claves de acceso.

6. Farmacovigilancia:

Elaboración del plan de gestión de Farmacovigilancia.
Evaluar los SAES, determinar su causalidad y generar el CIOMS.
Evaluar los FU de SAES y determinar causalidad con fármacos en estudio.
Emisión de queries de FV.
Comunicación de SUSARs a autoridades y CEIM.
Elaboración de informes anuales DSUR.
Gestión de la BBDD y coordinación (Elaboración SDEA, Revisión protocolo, etc.).
Mantenimiento del archivo de FCV.

7. Biometría:

Diseño de la base de datos para análisis estadístico.
Elaboración del plan de queries.
Programación del plan de queries.
Plan de análisis estadístico.
Validación y depuración de datos.
Informe estadístico final.

8. Fin del Estudio:

Elaboración y envío del informe a autoridades sanitarias, CEIM e investigadores.
Entrega del archivo al promotor.

2.- CONDICIONES ESPECÍFICAS PARA LA PRESTACIÓN DEL SERVICIO

Especialización de la CRO y experiencia demostrable en estudios clínicos con productos sanitarios y específicamente en el área de neurología:

- Experiencia previa mínima de 10 años, en la gestión de ensayos clínicos en CRO o en la industria farmacéutica.
- Más de 3 ensayos/estudios con 100 pacientes o más.
- Más de 3 ensayos/estudios con 10 centros o más.
- Volumen de la compañía superior a 50 profesionales.
- Disponibilidad interna de los departamentos de redacción, operaciones, estadística e IT.
- Desarrollo de CRDs electrónicos con más de 10 años de experiencia en uso y manejo.

Requisitos técnicos mínimos de las personas designadas por el adjudicatario para llevar a cabo el servicio:

- Licenciatura en ciencias de la salud (Farmacia, Medicina, etc.).
- Formación en metodología de ensayos clínicos.
- Conocimientos de la normativa ética y legal que regula los ensayos clínicos.
- Formación en normas de Buena Práctica Clínica.
- Experiencia previa mínima de 3 años, en la gestión de ensayos clínicos en CRO o en la industria farmacéutica.
- Aporte de documentos que avalen la titulación y experiencia especificada en el CV presentado.
- Formación acreditada en investigación clínica.

La empresa adjudicataria responderá de los daños causados a terceras personas, continente y contenido, cuando estos hayan sido originados por las personas que tengan a su cargo en el desempeño de sus funciones.

CIBERNED podrá exigir la inmediata sustitución de las personas que por cuenta del adjudicatario presenten los servicios objeto del presente contrato, cuando estos tuvieran comportamientos incorrectos o se aprecie que no realizan el servicio correctamente, previo requerimiento justificado al contratista. Asimismo el personal, que preste el servicio, no podrá ser sustituido por el contratista sin el consentimiento expreso de CIBERNED.
Los servicios contratados estarán siempre cubiertos. El contratista preverá en todo caso la sustitución del personal por imposibilidad de asistencia del trabajador o profesional que habitualmente realice el servicio. El contratista, independientemente de su personalidad jurídica, deberá garantizar el seguimiento de la actividad en todo momento, de tal manera que tenga previsto en su equipo un sustituto. El incumplimiento de esta cláusula, así como la relativa al derecho de sustitución del personal por requerimiento de CIBERNED, será causa específica de resolución.
La empresa adjudicataria cumplirá las obligaciones empresariales que establece la ley de prevención de riesgos laborales, así como la normativa y reglamentación que le sea de aplicación en su caso.

3 ANEXO I: SINOPSIS DEL PROTOCOLO

ANEXO I
DRAFT Protocol SYNOPSIS

Study **Sat CIEN-02**

DRAFT Protocol SYNOPSIS

STUDY IDENTIFIERS

Title of Study: **A 26 week multicenter double-blind, placebo-controlled, randomized, parallel-group study to evaluate the safety and tolerability of three oral doses of Sativex ® in patients with mild cognitive impairment of Alzheimer type or early Alzheimer dementia.**

Clinical Study Code: **Sat CIEN-02**

Type of Study: Phase II study for safety, biomarkers and clinical response

Study sites: Multicentric, 6 - 10 sites in Spain

RATIONALE

Sativex® reduces the toxicity of Aβ peptide in experimental models and improves cognition and reduces neuroinflammation in transgenic animal models of AD at early stages of the disease. Therefore, Sativex® may be a therapeutic alternative for the treatment of Alzheimer's disease at early stages. The doses of Sativex® expected to be efficacious (1, 2 or 3 sprays per day corresponding to 2.5/5/7.5 mg of 1:1 Δ^9-tetrahidrocannabinol and 2.7/5.4/7.1 mg of cannabidiol) may result in a safe, well-tolerated treatment with a virtual absence of the side effects commonly associated with its psychotropic properties.

STUDY OBJECTIVES

Primary objectives:

- To evaluate the safety and tolerability of three doses of Sativex ®
- To evaluate the efficacy of three doses of Sativex ® to reduce inflammatory markers of AD in CSF.
- To evaluate the efficacy of three doses of Sativex ® to reduce brain atrophy progression

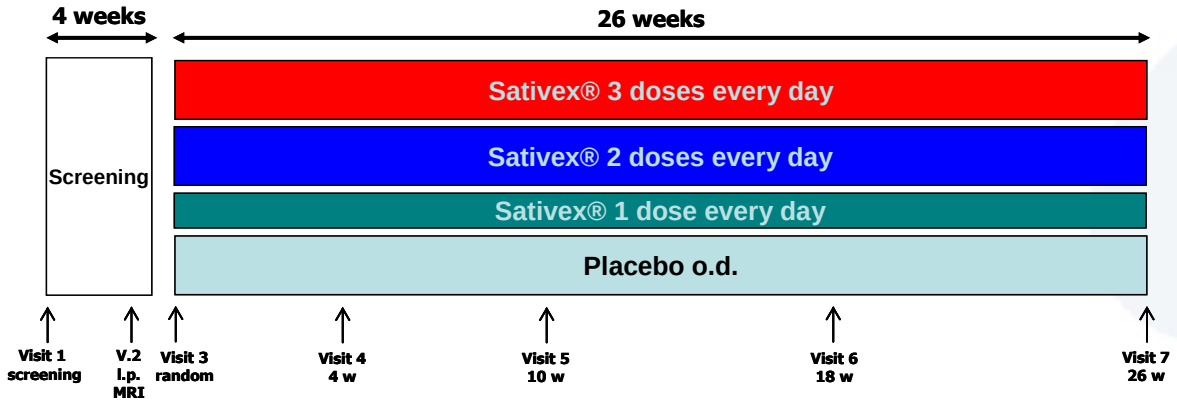
Secondary Objectives:

- To find out a clinical and biological dose effect of Sativex ® and identify the best dose to be tested in a future phase III trial.
- To evaluate the effect of Sativex ® on cognition, behavior, mood, function and quality of life

Exploratory Objectives *:

- To evaluate the effect of Sativex ® on:
  - several c.s.f. parameters related to the physiopathology of the disease (τ, phospho-τ, Aβ)

SCHEME OF THE STUDY DESIGN



STUDY DESIGN AND METHODS

Study Design:

The study will be randomized, double-blind, placebo-controlled, parallel-group, multi-center, and conducted in compliance with the Declaration of Helsinki and ICH Good Clinical Practice Guidelines.

The study will evaluate the safety, tolerability, neurobiological and clinical effect of 1 , 2 or 3 administrations of Sativex® versus a matching placebo in patients with mild cognitive impairment MCI or early dementia of Alzheimer type. The study will consist of a screening period and a 26 week double-blind treatment period. Individuals will attend 7 visits: visit 1 for screening, visit 2 for lumbar puncture and brain MRI, visit 3 for baseline within 4 weeks after screening, 3 additional follow up visits at 4, 10 and 18 weeks, and a final visit at 26 weeks.

Screening/Baseline period: The participants will be recruited and assessed in the screening visit 1 after signature of informed consent. At visit 1 and 3, demographic and basic clinical data, physical examination, vital signs and ECG will be recorded. Diagnosis and inclusion-exclusion criteria will be checked; baseline cognitive, functional and behavioral state will be established and blood will be drawn by venous puncture.

A lumbar puncture to collect CSF must be performed at visit 2 within a time window of 0-15 days before baseline visit and before any intake of study medication, in the morning, with the participant in resting state and overnight fasted.

A standardized brain MRI assessment must be performed within 1-15 days before the baseline visit.

Double-blind treatment period: Participants who satisfy the eligibility criteria will be included in the study at visit 3 and randomly assigned to Sativex® (1, 2 or 3 sprays every day corresponding to 2.5/5/7.5 mg of 1:1 Δ^9-tetrahidrocannabinol and 2.7/5.4/7.1 mg of cannabidiol) or placebo in a double-blind condition for a period of 26 weeks. The treatment will start 1-7 days after the baseline visit. Physical examination will be performed at visits 2 and 7, cognitive and behavioral assessment at visits 3, 5 and 7 and ECG at visits 3 and 7. Vital signs, adverse events (AEs) concomitant medication and treatment compliance will be recorded at each visit to the clinic (visits 2 to 7) and blood and urine samples will be also taken for safety analysis.

At the end of the double-blind treatment period (visit 7 + allowed window of 1-7 days before the last drug administration) a lumbar puncture will be performed, at the same daytime (±1 hour) and in the same resting and fasting state as the baseline lumbar puncture. Samples of blood and CSF will be obtained for biomarker monitoring.

A second standardized brain MRI assessment must be performed within 1-15 days around the last drug administration and will be centrally read to corroborate its quality.

The participants should be seen by the same clinician, study nurse and rater, who will be trained to ensure the consistency of the assessments across study sites.

Participants will be informed that benzodiazepines or opioid containing analgesics must be avoided for two days before cognitive assessments at the clinic.

Safety procedures:

Any clinically relevant exploratory finding or analytical abnormality should be monitored by study staff. All participants will be informed about the safe administration of the medication, its side effects and safety measures for its prevention.

A participant will be withdrawn from the study if he/she withdraws consent or:

- shows lack of adequate compliance with medication or clinic appointments
- presents: - a Suspected Unexpected Serious Adverse Reaction (SUSAR)
  - suicidal ideation
  - a treatment related serious adverse event (SAE)
  - an intolerable treatment related AE, as determined by the investigator such as grade 3 neurological, cardiovascular, gastrointestinal or respiratory symptoms or local reactions *
  - an intercurrent illness, condition or complication interfering with his(er) participation.

Participants who discontinue their medication because of any AE should contact the study staff and will be given appropriate clinical follow-up.

The random code will not be opened until database lock unless necessary for safety reasons.

* according to the criteria of the Modified NCI Toxicity Grades for AEs and Laboratory Test Abnormalities

Safety measures:

- Since the safety profile of the study medication is rather known, at least in a younger population, unexpected serious adverse reactions are not anticipated. Notwithstanding, patients will be recruited at a slow rate of around 6 per month in order to detect any relevant safety issue and have enough time to take the appropriate measures if necessary.

- The AEs, SAEs and SUSARs will be described and recorded at every visit for every participant, as well as their severity, duration and eventual relationship with the medication of the trial.

- Physical and neurological exam, vital signs and body weight will be recorded at visit 1, 3, 6 and 8.

- A 12-lead ECG will be recorded after 5 minutes in the supine position at visits 3, 5 and 7.

- The following Safety laboratory tests of blood and urine will be performed at visits 1, 3, 4, 5, 6 and 7 and at any other time decided by the investigator:
  - ***Hematology*** (erythrocytes, hemoglobin, haematocrit , MCH, MCV, leucocytes, neutrophils, eosinophils, basophils, lymphocytes, monocytes and thrombocytes)
  - ***Clinical chemistry*** (total bilirubin, ALT, AST, LDH, alkaline phosphatase, gamma-GT, creatinine, BUN, uric acid, CK, sodium, potassium, phosphate, calcium, albumin, total cholesterol, triglycerides, glucose and prothrombin time)
  - ***Urine laboratory*** (Ph, glucose, albumin, ketones, red and white blood cells).

The trial will be prematurely terminated if:

- the incidence or severity of AEs indicated that the investigational medications or trial activities constitute a potential health hazard.
- new scientific data on the investigational product did not justify the continuation of the clinical study.

Trial will be terminated at a specific site if serious and/or persistent non-adherence to the protocol, Good Clinical Practice or applicable regulatory requirements by an Investigator/institution are detected.

Efficacy measures:

Primary efficacy measures:

- The levels of several cytokines involved in the neuroinflammatory process of AD (IL-1β, IL-6, IL-8, IL-10, IL-12, IL-17, IL-23 and TNF-α) will be analyzed in CSF samples before and after treatment using Invitrogen™ multiplex assay kits.

- The rate of brain atrophy progression in MRI is a reliable, sensitive and objective surrogate of disease progression. It will be assessed by fully automated, observer-independent volumetric methods.

Secondary efficacy measures: the participants will be assessed with the following tests and questionnaires at several visits (see the Study Schedule at the end of the document):

Cognitive assessment:

- Mini Mental Status Examination
- Alzheimer's Disease Assessment Scale cognitive (ADAS-cog)
- Symbol Digit Modalities
- Word fluency test
- Word learning test

Behavioral and functional assessments: will be examined at randomization (visit 2) and visits 3, 5 and 7:

- Neuropsychiatric Inventory (NPI)
- Geriatric depression scale (GDS)
- Alzheimer's Disease Cooperative Study Group – Activities of Daily Living (ADCS-ADL)
- EuroQol questionnaire (EQ-5D)

Exploratory efficacy measures:

- c.s.f. parameters related to the physiopathology of the disease: τ, □□phospho-τ□, Aβ

Study population:

Male and female ≤ 85 years old patients with diagnosis of MCI of Alzheimer type or early Alzheimer's dementia.

Randomization:

Patients will be randomized according to 1:1:1:1 schedule (15 to each dose group of Sativex® and 15 to placebo group) stratified by diagnosis of MCI or dementia.

Patient sample size:

A total number of 60 patients will be randomized in the study, 15 patients in each treatment group and 15 in placebo group. Drop-out patients after randomization can be replaced. Thirteen patients are expected to be available for final analysis in every group (13% drop-out rate).

Study medication:

Code name:	Sativex ® or placebo
Drug product:	27 mg/ml of Δ-9-tetrahydrocannabinol (THC) and 25 mg/ml of cannabidiol (CBD)
Placebo:	vehicle
Vehicle:	ethanol, propylene glycol and peppermint oil.
Administration:	1 spray every 8 hours by mouth
Distribution:	by a central specialized agency
Drug supply:	in the pharmacy of the sites at every visit

Medication will be supplied in three containers of different color and label for the breakfast, lunch and dinner administration time. None, one, two or three of them will contain placebo in accordance to the assigned group.

Concomitant medication:

Patients may take previously prescribed anticholinesterasic agents or memantine if they were stable and well tolerated for at least 6 months.

Selective serotonin reuptake inhibitors (SSRIs) and benzodiazepines are permitted if dose and regimen are stable and well tolerated for at least 3 months prior to baseline.

Pharmacological treatment of any other chronic condition must be stable for at least 1 month prior to screening.

No regular intake of other medications acting on central nervous system or anti-inflammatory agents will be allowed (see inclusion-exclusion criteria).

Duration of the study:

- Screening:	1 – 4 weeks	visit 1
- Pre-randomization:		visit 2
- Baseline:		visit 3
- Double-blind treatment:	26 weeks	visits 4 - 7

Total: 27 - 30 weeks.

Inclusion Criteria:

1. Men and women (without childbearing potential) aged ≤ 85 years
2. Diagnosis of probable Alzheimer's disease or mild cognitive impairment due to Alzheimer's disease according to the diagnostic guidelines of the National Institute on Aging-Alzheimer's Association workgroups.
3. Prodromal or early stage of Alzheimer's disease according to GDS scores 2-4 and MMSE >20.
4. A baseline MRI study corroborating the clinical diagnosis (diffuse brain atrophy predominating in midtemporal and frontal regions) and excluding other potential causes of dementia, especially cerebrovascular lesions.
5. A baseline lumbar puncture with low levels of Aβ (total or $A\beta_{42}$) and high levels of tau (total or phosphorilated) in CSF and acceptance of another lumbar puncture at the end of the treatment period.
6. Modified Hachinsky ischemic score equal or below 4.
7. Education for more than 8 years.
8. Female patients must be either surgically sterilized, at least 1 year postmenopausal or using adequate birth control.
9. Caregiver available, if not living in the same household, controlling patient at least 4 times a week.
10. Patients living at home or old people's home without continuous nursing care.
11. General health status acceptable for a participation in a 6 month clinical trial.
12. Treatment with anticholinesterasic agents or memantine will be allowed but it must be stable and well tolerated for at least 6 months.
13. SSRIs as antidepressants and benzodiazepines as anxiolytics or sleep inductors are permitted after maintenance of dose for three months prior to baseline evaluations.
14. Stable pharmacological treatment of any other chronic condition for at least one month prior to screening.
15. No regular intake of medications acting on central nervous system or anti-inflammatory agents.
16. Signed informed consent by caregiver and patient (if mentally competent) prior to the initiation of any study specific procedure.

Exclusion Criteria:

1. Failure to perform screening or baseline examinations.
2. Hospitalisation or change of concomitant medication 1 month prior to screening or during screening period.
3. Clinical, laboratory or neuroimaging findings consistent with:
    - other primary degenerative dementia, (dementia with Lewy bodies, frontotemporal dementia, Huntington's disease, Jacob-Creutzfeld Disease, Down's syndrome, …)
    - other neurodegenerative condition (Parkinson's disease, amyotrophic lateral sclerosis, …)
    - cerebrovascular disease (major infarct, one strategic or multiple lacunar infarcts, extensive white matter lesions)
    - other central nervous system diseases (severe head trauma, tumours, subdural haematoma or other space occupying processes, …)
    - other infectious, metabolic or systemic diseases affecting central nervous system (syphilis, hypothyroidism, vitamin B12 or folate deficiency, serum electrolytes out of normal range, juvenile onset diabetes mellitus …)
4. A current DSM-IV diagnosis of major depression, schizophrenia or bipolar disorder.
5. Clinically significant, advanced or unstable disease that may interfere with primary or secondary variable evaluations, may bias the assessment of the clinical or mental status of the patient or put the patient at special risk, such as:
    - epileptic seizures within the last 3 years
    - hepatic or respiratory insufficiency
    - renal insufficiency (serum creatinine >2mg/dl)
    - heart disease (myocardial infarction, unstable angina, heart failure, cardiomyopathy within 6 months before screening)
    - bradycardia (heart beat <50/min.) or tachycardia (heart beat >95/min.)
    - hypertension or hypotension requiring treatment with more than 2 drugs
    - AV block (type II / Mobitz II and type III), congenital long QT syndrome, sinus node dysfunction or prolonged QTcB-interval (males >450 and females >470 msec)
    - uncontrolled diabetes
    - malignant tumors within the last 5 years
    - metastases
6. Disability that may prevent the subject from completing all study requirements (e.g., blindness, deafness, severe language difficulty, …)
7. Women who are fertile and of child bearing potential.
8. Chronic drug intake of:
    - antidepressants (other than SSRIs), neuroleptics or major sedatives
    - antiepileptic drugs prescribed to control seizures
    - anticholinergics
    - nootropics
    - centrally active anti-hypertensive drugs (clonidine, α-methyl dopa, guanidine, guanfacine, …)
    - opioid containing analgesics
    - anti-inflammatory, cortico-steroids or immunosuppressants
9. Suspected or known drug or alcohol abuse.
10. Suspected or known allergy or intolerance to cannabis or any components of the study treatment.
11. Enrollment in another investigational study or intake of investigational drug within the previous 3 months.
12. Any condition which in the opinion of the investigator makes the patient unsuitable for inclusion in the study.

Clinical assessments (see Study Schedule in page 10)

Screening (visit 1)**:**

Informed consent.
Demographic data and medical history.
Modified Hachinski Ischemic Score.
Physical exam: general examination, vital signs, weight, height, head circumference, body mass index (BMI).
Concomitant Medication.
ECG: A 12-lead ECG will be recorded after 5 minutes in supine posture.
Cognitive screening: Mini Mental State Examination and Word fluency test.
Inclusion / Exclusion criteria.
Safety Laboratory tests: blood and urine samples for ***Hematolog, Clinical chemistry*** and ***Urine laboratory***.
Diagnostic laboratory tests: TSH, free T4, folate, vitamin B12, and RPR test for syphilis.

Pre-randomization assessments (visit 2; time window of 0-15 days before baseline visit)**:**

Brain MRI: a standardized MRI study will be performed during the screening period and centrally read to exclude other lesions and to assess the overall and mid temporal atrophy of the patients.
Lumbar puncture: performed before any intake of study medication, in the morning, with the participant in resting state and overnight fasted. The following samples will be taken:

- 3 cerebrospinal fluid aliquots for: determination of cytokines, τ, phospho-τ and Aβ.

Baseline assessments (visit 3)**:**

Concomitant Medication.
Adverse events.
Physical exam: vital signs and standardized neurological examination.
ECG: A 12-lead ECG will be recorded after 5 minutes in supine posture.
Inclusion / Exclusion criteria.
Safety Laboratory tests: blood and urine samples for ***Hematolog, Clinical chemistry*** and ***Urine laboratory***.
Cognitive assessments:

- Mini Mental Status Examination
- Alzheimer's Disease Assessment Scale cognitive (ADAS-cog)
- Symbol Digit Modalities
- Word fluency test
- Word learning test

Behavioral and functional assessments:

- Neuropsychiatric Inventory (NPI)
- Geriatric depression scale (GDS)
- Alzheimer's Disease Cooperative Study Group – Activities of Daily Living (ADCS-ADL)
- EuroQol questionnaire (EQ-5D)

Follow up assessments (visits 4, 5 and 6)**:**

Vital signs
Concomitant Medication.
Adverse events.
ECG: A 12-lead ECG will be recorded after 5 minutes in supine posture at visit 5.
Safety Laboratory assessments: blood and urine samples for ***Hematolog, Clinical chemistry***, ***Urine laboratory***.
Cognitive assessments: at visits 5 and 6
Behavioral and functional assessments: at visits 5 and 6

Final Assessments (visit 7)**:**

Physical exam: general examination, vital signs, weight, body mass index (BMI).
ECG: A 12-lead ECG will be recorded after 5 minutes in supine posture.
Concomitant Medication.
Adverse events.
Safety Laboratory assessments: blood and urine samples for ***Hematolog, Clinical chemistry***, ***Urine laboratory***.
Cognitive assessments: at visits 5 and 6
Behavioral and functional assessments: at visits 5 and 6
Brain MRI: a standardized MRI study will be performed during the screening period and centrally read to exclude other lesions and to assess the overall and mid temporal atrophy of the patients.
Lumbar puncture: performed before any intake of study medication, in the morning, with the participant in resting state and overnight fasted. The following samples will be taken:
- 3 cerebrospinal fluid aliquots for: determination of cytokines, τ, phospho-τ and Aβ.

Statistical Methods:

Sample Size:

A total of 60 patients will be recruited and randomized in the study, with 15 patients into every active and placebo groups. The sample size may be increased with the same number of additional patients as those who drop-out before visit 7. Thirteen patients in the three active treatment groups and in the placebo group (assuming a maximum 13% drop-out rate) are expected to be available for the main analyses at 26 week.

Since this is an exploratory trial to assess safety, tolerability and efficacy trends, no sample size calculation has been performed.

All quantitative parameters will be described per treatment group and time point using standard descriptive statistics. Qualitative parameters will be described using frequency and percentage of response.

Primary safety analyses

The AEs will be summarized by dose, severity and relation to trial medication. Descriptive statistics will be displayed for all AEs and Chi square for trend analyses will be performed on those with frequency > 2 within the same cohort.. Additionally, they will be analyzed using a logistic regression model, overall and by most frequently occurring preferred terms and presented according to odds ratios, together with 95% confidence intervals for the contrasts of interest: overall active group versus placebo group.

Primary efficacy analyses

- The changes from baseline in the CSF levels of cytokines and TNF-α will be compared between the two active treatment groups and placebo using ANCOVA model. The model will include factors for treatment and center and the interaction between treatment and center as well as the baseline levels as a covariate.
- The rates [(baseline volume – final volume) / baseline volume x 100%] of whole brain, grey matter, lateral and third ventricles and regional (hippocampal, mesial and lateral temporal areas) brain atrophy will be assessed and compared across the treatment groups using an ANCOVA model with treatment and center and the interaction between treatment and center as factors, and baseline volume as a covariate.

Secondary efficacy analyses

The changes from baseline in every cognitive, behavioral and functional scale will be compared between the three active treatment groups and placebo using ANCOVA model. The model will include factors for treatment and center and the interaction between treatment and center as well as the baseline levels as a covariate.

Exploratory analyses of biomarkers

The changes from baseline in the different biomarkers will be compared between the three active treatment groups and placebo using an ANCOVA model with treatment and center as factors, baseline levels as a covariate and baseline*Treatment interaction term.

Exploratory analyses of biomarkers

The changes from baseline in the different biomarkers will be compared between the three active treatment groups and placebo using an ANCOVA model with treatment and center as factors, baseline levels as a covariate and baseline*Treatment interaction term.

Post hoc analyses

Other post hoc analyses of treatment interaction with several variables such as age, gender, education, head circumference, brain atrophy at baseline, vascular burden and other biological markers, and their effect on cognitive, behavioral and functional response will be performed.

A responder analysis for ADAS-cog, ADAS-cog and EQ-5D will be performed using a binary logistic regression model and considering as positive responders those participants having at the end of the trial the same or better score than at baseline.

No adjustment of significance level and/or sample size due to multiple comparisons will be performed in this study.

Steering and Safety Committee:

A Steering and Safety Committee will monitor and control the trial. It will be constituted by the promoter of the trial, one Spanish delegate of the Alzheimer's Association and one independent clinician with experience in clinical trials for Alzheimer's disease.

This Committee will be established before the inclusion of any patient. A Charter will be drafted stating the composition, responsibilities, communications, data, meetings and documents of the Committee.

Quality control

A quality audit of the most recruiter site and the Trial Master File will be performed at the end of the trial.

Proposed Timing:

Final updated design and contract signed:	July 2016
Submission to Regulatory Agency / Ethical C.:	September 2016
Trial authorization (Spanish Drug Agency)	December 2016
First patient first visit:	January 2017
Last patient first visit	December 2017
Last patient last visit:	July 2018
Preliminary results (double-blind period):	October 2018
Final Report	December 2018

STUDY SCHEDULE

	Screen	Pre-random	Random	Double blind treatment			Final
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Study activities	**week -4**		**week 0**	**week 4**	**week 10**	**week 18**	**week 26**
Informed Consent	X						
Demographic and Medical data	X						
Modified Hachinski Ischemic score	X						
Physical Examination	X		X				X
Vital signs	X	X	X	X	X	X	X
ECG	X		X			X	X
Cognitive screening[1]	X		X				X
Diagnostic laboratory: blood & urine	X						
Inclusion-exclusion criteria	X		X				
Safety laboratory: blood & urine	X			X	X	X	X
Standardized MRI		X					X
Lumbar puncture		X					X
CSF for cytokines and biomarkers		X				X	X
Cognitive battery [2]			X	X		X	X
Behaviour and functional assessments [3]			X			X	X
Concomitant medication	X		X	X	X	X	X
Adverse Events		X	X	X	X	X	X
Drug supply			X	X	X	X	X

1. M.M.S.E. and Word Fluency test 2. Alzheimer's Disease Assessment Scale cognitive (ADAS-cog), Symbol Digit Modalities, Word fluency test, Word learning test. 3. Neuropsychiatric Inventory, Geriatric depression scale, Alzheimer's Disease Cooperative Study Group – Activities of Daily Living (ADCS-ADL), EuroQol questionnaire