ISRCTN43889760 https://doi.org/10.1186/ISRCTN43889760

A study examining the effect of Cimzia on inflammation in the brain

Submission date	Recruitment status	[X] Prospectively registered
13/08/2014	Stopped	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
01/10/2014	Stopped	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
24/03/2016	Mental and Behavioural Disorders	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims

Alzheimers disease (AD) is the most common type of dementia. Its a condition that results in a loss of mental ability due to the gradual death of brain cells. Brain inflammation may play a role in the development and progression of AD and poor memory in general. The TNF (tumour necrosis factor) alpha protein controls the bodys inflammatory response; it is increased in AD and is linked with progression of the disease. Cimzia is a medicine that is used to treat inflammatory diseases, such as rheumatoid arthritis by reducing the inflammatory response. Here, we want to find out if Cimzia reduces brain inflammation.

Who can participate?

Adults aged between 50-90 that have a mild cognitive impairment due to AD. They must also have a study partner anyone who spends more than 8 hours a month in their company.

What does the study involve?

Participants are randomly allocated into one of two groups. Those in group 1 are given Cimzia for up to a year. Those in group 2 are given a placebo for the same time period. The drug is given as an injection once every two weeks; participants and their study partners receive training on how to administer it. Each participants general health and memory is checked over a series of 7 sessions over the course of the study. Tests include blood and memory tests, a chest X-ray, MRI scan of the brain and PET scan. A PET scan is also referred to as a brain scan. Here, we give each participant a radioactive tracer. This is an extremely small dose of a drug that is radioactively tagged so that its movements around the body can be seen. The tracer is injected and the brain then looked at by the PET scan.

What are the possible benefits and risks of participating?

Like all medicines, Cimzia can cause side effects, although not everybody gets them. They include skin rashes, fever, allergic reactions, and reduced production of blood cells. There have been reports of cancers which may be related to taking Cimzia. These include cancers of the blood and lymphatic system (including lymphoma, which is a tumour of the lymph nodes, and leukaemia), solid organ tumours and non-melanoma skin cancers. Cimzia may decrease the participants ability to fight infection. Each participant is monitored carefully during the study for possible side effects.

Where is the study run from?
The Memory and Assessment Research Centre (MARC) at Moorgreen Hospital (Southampton)

When is the study starting and how long is it expected to run for?
November 2014 to November 2017

Who is funding the study?
1. European Union FP7 (Grant agreement no: 278850)
2. Union Chimique Belge (UCB) pharmaceuticals (Belgium)

Who is the main contact?
Professor Clive Holmes
c.holmes@soton.ac.uk

Contact information

Type(s)
Scientific

Contact name
Prof Clive Holmes

Contact details
Memory Assessment & Research Centre
Tom Rudd Unit
Moorgreen
Botley Rd
West End
United Kingdom
Southampton
United Kingdom
SO30 3JB
+44 (0)23 80 475216
c.holmes@soton.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2014-003101-14

Protocol serial number
INMiND-01

Study information

Scientific Title
A double-blind, placebo-controlled study of the effect of a TNFα antibody, certolizumab pergol (Cimzia), on microglial activation in amyloid PET positive patients with mild cognitive impairment due to AD-Intermediate likelihood (INMiND-01)

Acronym
INMiND

Study objectives
In MCI (mild cognitive impairment) due to AD (alzheimers disease), systemic inflammation and elevated systemic levels of TNF-alpha cause partially activated, or primed, microglial cells, to become fully activated, which can be modulated by the administration of a peripheral TNF-alpha antibody, certolizumab pergol (Cimzia).

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee South Central - Hampshire A, 13/02/2015, ref: 15/SC/0015

Primary study design
Interventional

Study design
Double-blind randomised placebo-controlled study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
MCI (Mild Cognitive Impairment) due to AD (Alzheimer's disease)

Interventions
Following the screening period, subjects will receive certolizumab pegol (Cimzia) or placebo. Subjects will have a 50% chance of receiving Cimzia and a 50% chance of receiving placebo.

1. Subjects receiving Cimzia will receive a loading dose of 400mg of certolizumab pegol at base-line, week 2 and week 4. The loading dose will be given as two subcutaneous injections of 200mg each.

2. Subjects receiving placebo will receive an imitation loading dose of placebo at base-line, week 2 and week 4, given as two subcutaneous injections of the placebo.

The subjects will attend for a safety visit at week 4, after receiving the third of the loading doses of Cimzia or placebo. Thereafter, the subjects receiving Cimzia will receive a two weekly maintenance dose of 200mg of certolizumab pegol, given as a two weekly subcutaneous injection of 200mg of certolizumab pegol from week 6 to week 52 inclusive, and the subjects receiving placebo will receive an imitation two weekly subcutaneous injection of the placebo from week 6 to week 52, inclusive.

Subjects who receive the final dose of the study medication at week 52 will be asked to attend a follow up visit at week 54, for a full safety check. Subjects with unresolved Adverse Reactions or unresolved Serious Adverse Events will be followed up until the problems have resolved, by means of unscheduled clinic visits and/or telephone consultations, as clinically indicated.

Intervention Type

Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
certolizumab pergol

Primary outcome(s)
To ascertain the change in microglial activation on PK 111 95 PET scans from baseline to the final imaging visit in the treatment group compared to the placebo group.

Key secondary outcome(s)
1. To ascertain the change in the primary cognitive outcome measure, the Montreal Cognitive Assessment, (MOCA), from baseline to final treatment visit in the treatment group compared to the placebo group.

Exploratory objectives/ Outcome measures
1. To ascertain the change in the first of the exploratory cognitive outcome measures, the Repeatable Battery for the Assessment of Neuro-psychological Status, (RBANS), from baseline to final treatment visit in the treatment group compared to the placebo group
2. To ascertain the change in the second of the exploratory cognitive outcome measures, the Free and Cued Recall Selective Reminding Test with Immediate Recall (FCSRT-IR), from baseline to final treatment visit in the treatment group compared to the placebo group.
3. To ascertain the change in the Cornell Scale score from base-line to final treatment visit in the treatment group compared to the placebo group.
4. To ascertain the change in the behavioural assessment the Apathy Inventory from baseline to final treatment visit in the treatment group compared to the placebo group.
5. To ascertain the change in the behavioural assessment the Apathy Clinicians Diagnostic Criteria from baseline to final treatment visit in the treatment group compared to the placebo group.
6. To ascertain the change in the levels of plasma markers of neuro-inflammation (pro and anti-inflammatory cytokines: IL-1; IL-6, TNF-alpha, IFN-gamma, IL-4, IL-10, IL-12, IL-13; CRP, and TGF-beta) through the study, in the treatment group compared with the placebo group.
7. To study the relationship between the changes in the levels of plasma markers of neuro-inflammation (IL-1; IL-6, TNF-alpha, IFN-gamma, IL-4, IL-10, IL-12, IL-13; CRP, TGF-beta) and changes of microglial activation on PK1195 PET scan, and clinical outcomes, in the treatment group compared with the placebo group.

Completion date
01/11/2017

Reason abandoned (if study stopped)
Lack of funding/sponsorship

Eligibility

Key inclusion criteria
Subjects will have to meet all of the following criteria at screening to enter the study:
1. All subjects must have the capacity to make an informed decision as to whether they would like to take part in this specific clinical research trial.

2. A subject can be male or female and they must be between 50 to 90 years old, inclusive.
3. A subject must have received a minimum of 7 years of formal education.
4. A subject must be able to hear, read, write and perform study neuro-psychological tests in English.
5. A subject must have adequate visual and auditory acuity to allow neuro-psychological testing, based on the research clinicians judgement.
6. A subject must fulfil the NIA-AA criteria for the diagnosis of Mild Cognitive Impairment due to AD at the screening visit (Albert et al, 2011.) A subject must have a MOCA score of 19 to 25 inclusive at screening, at the discretion of the Principal Investigator.
7. A subject must have a study partner who spends at least 8 hours a month with the subject. The study partner may be a close friend or a neighbour and not necessarily a close relative, spouse, son or daughter, and should be present at all visits. Every effort should be made to ensure that the study partner will be the same throughout the study. If it becomes necessary for the study partner to change, the new study partner must satisfy the requirements of this criterion and the change of study partner must be clearly documented.
8. A subject must have been on a stable medication regime for more than 3 months.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Senior

Sex
All

Key exclusion criteria
Subjects meeting any of the following criteria during screening or baseline will be excluded from the study:
General criteria
1. Inability or refusal to provide informed consent from subject or study partner.
2. Absence of study partner.
3. Unlikely to cooperate in the study, not able to attend scheduled examinations and visits, or not able to follow study instructions.
4. Participation in another study with administration of any investigational drug in the previous 3 months or already enrolled in another study.
Medical and therapeutic criteria
1. Any contraindications to the use of certolizumab pergol as per the Summary of Product Characteristics: 1. Hyper-sensitivity to the active substance or to the excipients in the injection (sodium acetate, sodium chloride, water), 2. Active tuberculosis or other severe infections such as sepsis or opportunistic infections, 3. Moderate to severe heart failure (NYHA classes III/ IV).
2. Parkinsons disease, Dementia with Lewy Bodies or clinically significant Parkinsonian symptoms.
3. Vascular disorder (modified Hachinski Ischaemic Scale score > 4).
4. Recent Transient Ischaemic Attack (TIA) within the last 3 months.
5. Signs of major cerebrovascular disease on MRI or CT scan prior to entry into study, (i.e. evidence of an established cortical or basal ganglia infarct).
6. Signs of major cerebrovascular disease on the MRI performed at the screening imaging visit

prior to the amyloid and microglial PET scans.
7. Any other previous or ongoing chronic or recurrent disease of the central nervous system, including demyelinating disease or psychiatric diseases, that may have an impact on cognitive performance, left to the research clinicians judgement.
8. Any of the following laboratory abnormalities at the screening visit:
8.1. Clinically significant Vitamin B12 levels less than the lower limit of normal.
8.2. Clinically significant folate levels less than the lower limit of normal.
8.3. Clinically significant thyroid-stimulating hormone (TSH) levels greater than the upper limit of normal and a clinically significant free thyroxine (FT4) level lower than the lower limit of normal. (Subjects who are successfully treated for folate, vitamin B12 or thyroxine deficiencies may be re-screened after 3 months)
9. Subjects with a previous or present history of severe medical conditions, or medical conditions which are poorly controlled, such as hypertension or diabetes, left to the research clinicians judgement.
10. History of alcohol or drug dependence or abuse within the last 2 years. Current alcohol >35 units per week for men, or >28 units per week for women, or drug abuse, at the discretion of the research clinician.
11. Surgical intervention planned during the study period.
12. Treatment with immunosuppressive drugs including any systemic corticosteroid drugs (Topical and nasal corticosteroids and inhaled corticosteroids for asthma are permitted.)
13. Treatment with benzodiazepines within a period of three days prior to PK11195 imaging.
14. Vaccination or immunization with any live vaccine (e.g.: polio, rubella, yellow fever) or the pneumococcal vaccine within the past 30 days.
15. Pregnancy or breast feeding (women of child bearing age must have a negative HCG urine test at the start of the study and at each study visit)..
16. Severe hepatic, renal or cardiac disease.
17. Previous use of a TNFα agent.
18. Known skin photosensitivity.
19. Infection in past 4 weeks or active infection.
20. Heart failure: New York Heart Association (NYHA) Grade 3-4.
21. History of blood disorders or current WCC ≤ 3.5 x 109/l; platelet count ≤ 100x109/l; Hb ≤ 10g /dl.
22. Active or latent tuberculosis.
23. Rheumatoid arthritis; psoriasis; psoriatic arthritis or ankylosing spondylitis.
24. Septic arthritis in past 12 months.
25. Sepsis of prosthesis in past 12 months.
26. Chronic leg ulcers.
27. Indwelling urinary catheter.
28. Pulmonary fibrosis.
29. History of neoplasms / malignancies in past 3 years.
30. Pre-malignant conditions including Barretts oesophagus; cervical dysplasia; large bowel polyps.
31. Other clinically significant abnormality on physical, neurological, ECG or laboratory examination that could compromise the study evaluations or be detrimental to the patient during the course of the study.
32. Use of experimental medications for AD, or any other investigational medication or device, within 60 days. Patients who have been involved in a monoclonal antibody study are excluded unless it is known that they were receiving placebo in that trial.

Imaging exclusion criteria.

33. Subjects with significant cortical or basal ganglia infarct or other significant pathology found on MRI brain scan.
34. Subject with a negative Amyloid PET scan.

Date of first enrolment
01/11/2014

Date of final enrolment
01/11/2017

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Memory Assessment & Research Centre
Southampton
United Kingdom
SO30 3JB

Sponsor information

Organisation
University of Southampton (UK)

ROR
https://ror.org/01ryk1543

Funder(s)

Funder type
Government

Funder Name
European Union FP7 (Grant agreement no: 278850)

Funder Name
Union Chimique Belge (UCB) pharmaceuticals (Belgium)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No