Eudract summary report

2015-002145-63

A double-blind, placebo-controlled study of the effect of a TNF alpha inhibitor, etanercept (Enbrel), on microglial activation in amyloid PET positive patients with Mild Cognitive Impairment due to AD-Intermediate likelihood

Principal investigator : Clive Holmes

Start date: 11/11/15

End date: 01/03/18

Brief lay summary.

This study was the first randomised placebo controlled trial of the anti-TNFα agent Etanercept in patients with Mild Cognitive Impairment (MCI) who had amyloid confirmed to be present in their brains using imaging. These patients were treated for one year with either Etanercept or placebo and changes in the amount of brain inflammation and amyloid were measured using brain imaging. The study shows that at baseline that inflammation is higher in MCI subjects compared with controls. However, we could not see any overall changes in the amount of brain inflammation after one year or any differences in brain inflammation in those subjects taking Etanercept compared with those taking placebo. Likewise, clinically we couldn't see any major changes in measurement of memory function or other thinking tasks in those subjects taking Etanercept compared with placebo or any major changes in measurement of amyloid load in those subjects taking Etanercept compared with placebo. Unfortunately the study start was delayed by 20 months due to two drug companies stopping their support of the study and the main funder of the study (The European Union) would not allow us to extend the study duration. This meant the numbers recruited into the study was smaller than planned (13 randomised c.f. our aimed 46 patients) and this has limited our conclusions.

Scientific aims.

Primary Objective: To ascertain the change in microglial activation on [11C] (R)-PK-111-95 PET scans from base-line to the final imaging visit in the treatment group (Etanercept) compared to the placebo group.

Secondary Objectives

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.

2. To ascertain the change in cortical amyloid load on AMYVID PET scans from base-line to the final imaging visit in the treatment group compared to the placebo group

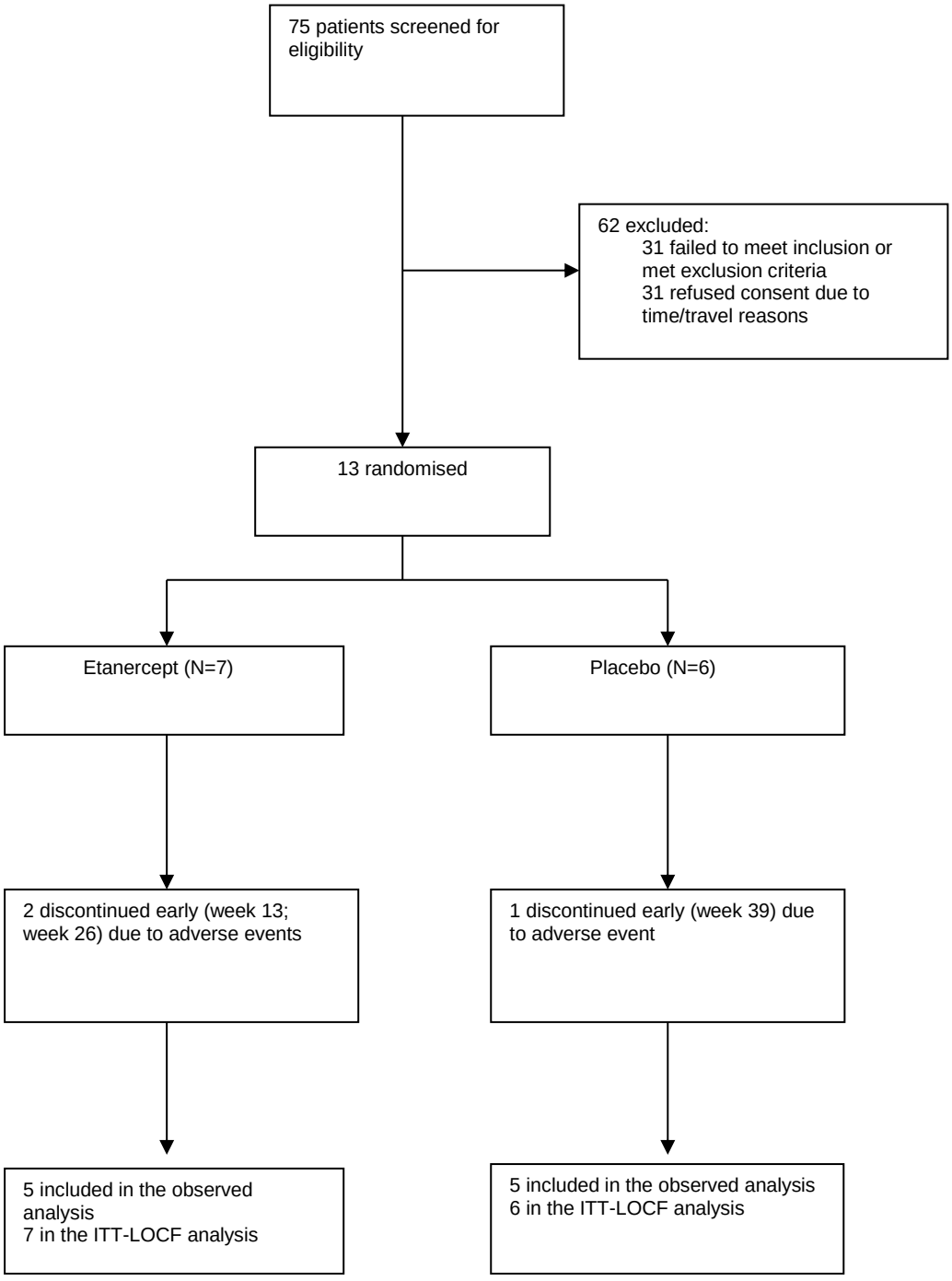
Participant disposition.

Participant disposition is detailed in Figure 1. Between Nov 2015 and Feb 2017, a total of 75 patients with amnestic Mild Cognitive Impairment were screened of whom 31 subjects declined to take part after interview due to the time commitment/overnight stay requirement of the study; 44 subjects consented to the study and underwent full screening. 28 subjects failed screening procedures. Reasons for screen failure included MOCA screen failure (n=5), prior exposure to tuberculosis or latent tuberculosis (n=4), abnormal CXR unspecified (n=1); diagnosed with DLB (n=1); previously undiagnosed malignancy (n=2), psychiatric disease (n=2), skin disease (n=1), cardiac disorder (n=1); low platelet count (n=1); low B12 (n=1); active infection (n=1). Of the subjects who entered the imaging phase of the study 8 (18.2%) were amyloid negative on visual inspection leading to 13 subjects randomised. 3 patients who consented were not able to complete screening due to early termination of study.

The secondary clinical treatment part of the study shows that of the 13 patients randomised 3 patients didn't complete treatment.

1. Two patients in the treatment arm had a diagnosis of squamous cell carcinoma (considered possibly related) and which led to treatment being halted (but they both went on to be scanned at the end of the study).
2. One patient in the placebo arm developed a UTI/back pain (UTI considered possibly related) that meant treatment was halted (she did not go for final scan).

Figure 1. Trial profile by treatment



Randomisation phase. The mean age of the 13 patients entering the study was 74.1 (SD 6.4) years, with the majority (9 (69%)) being men. Randomisation of patients at baseline led to two treatment groups that were similar with respect to demographic details and psychometric test scores (p values in all cases >0.1 except FCSRT p = 0.05) (Table 1).

Table 1. Characteristics of patients entering the randomisation phase.

Characteristics	Etanercept 50mg (n = 7)	Placebo (n = 6)	Mean difference (95% CI) or X^2 p value
Mean age, years (se)	73.4 (2.3)	74.8 (2.9)	1.4 (-6.7 to 9.5) yrs p = 0.7
Men, n (%)	5 (71)	4 (66)	X^2 0.03 p = 0.9
Disease duration, years (se)	3.4 (1.2)	5.3 (1.1)	1.9 (-1.8 to 5.6) yrs p = 0.3
MOCA pts(se)	21.1 (1.6)	24.7 (1.0)	3.5 (-0.6 to 7.6) pts p = 0.09
FCSRT pts (se)	36.4 (4.3)	46.8 (1.0)	10.4 (-0.03 to 20.8) pts p = 0.051
RBANS pts (se)	82.0 (2.9)	88.3 (4.6)	6.3 (-0.5 to 18.0) pts p = 0.3
ADCS-MCI pts (se)	38.9 (2.9)	43.5	4.6 (-3.1 to 12.4) pts p = 0.2

MOCA = the Montreal Cognitive Assessment; FCSRT= Free and Cued Selective Reminding Test with Immediate Recall*; RBANS =* Repeatable Battery for the Assessment of Neuropsychological Status*; ADCS-MCI =* Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory for MCI.

Tolerability and safety. Compliance to medication was high over the twelve month trial period (overall median 94%). There was no significant difference in the median compliance frequency between treatment groups (etanercept 94% [IQR 56 to 96%] vs placebo 94% [IQR 88% to 98%]; MWU p = 0.5). Three (20%) participants (2 on etanercept and 1 on placebo) failed to complete the study following randomisation. Of the 3 non-completers, 1 failed to complete the study to 26 weeks; 1 failed to complete the study to 39 weeks and 1 failed to complete the study to 52 weeks. Of the 2 non-completers in the etanercept group both developed a malignancy and were withdrawn due to safety concerns. The 1 non-completer in the placebo group was withdrawn due to recurrent urinary tract infections.

The overall study completion was 77% [10/13]. There was no statistical difference in the completion rates between those allocated etanercept and those allocated placebo (71% [5/7] from the etanercept group were completers vs 83% [5/6] from the placebo group; Fishers exact p = 0.6).

A total of 105 adverse events occurred during the 52 week randomisation phase of the study.

In summary there were 6 serious adverse events in five participants:

- In the treatment arm two participants had a diagnosis of squamous cell carcinoma both thought to be possibly related to treatment. Both participants completed final imaging at 52 weeks.
- In the placebo arm one participant was admitted to hospital with a urinary tract infection thought to be possibly related to study drug. Treatment was stopped. The same patient also had back pain thought unlikely to be related to the treatment but this symptom prevented final imaging. One participant in the placebo arm had a

transient ischaemic attack thought unlikely to be related to treatment; treatment was continued and patient proceeded to final scanning. One participant had a lower respiratory tract infection thought to be possibly related to study drug. Study drug was withheld briefly and the patient proceeded to final scanning.

All adverse events (non and serious adverse) grouped by system are summarised in Table 2. There were 38 (36%) adverse events in 7 participants in the etanercept group and 67 (64%) in 6 participants in the placebo group.

Table 2. Incidence of Adverse Events by Disease or Event Category

- Adverse Events could be definitely related, probably related, possibly related; unlikely related, or unrelated, to study intervention
- Coded by the Medical Dictionary for Regulatory Activities (MedDRA 20.1) preferred term
- Participants could report multiple events in any category

Disorders	Adverse events ([number events] [number of participants])	
	Etanercept (n= 7)	Placebo (n= 6)
All disorders	38 events	67 events
Blood and lymphatic disorders (Bruising of arm, bruising (2))	0 [0]	3 [1]
Cardiac disorders (Chest tightness, bundle branch block right)	0 [0]	2 [1]
Congenital, familial and genetic disorders	0 [0]	0 [0]
Ear and labyrinth disorders	0 [0]	0 [0]
Endocrine disorders	0 [0]	0 [0]
Eye disorders (retinal tear, vision disorder)	2 [2]	0 [0]
Gastrointestinal disorders (dyspepsia, diarrhoea, constipation)	6 [4]	1 [1]

General disorders and administration site injections (Pain (3), hay fever (2), feeling cold, blister, injection site discomfort, injection site bruising, giddiness, haematoma.	5 [3]	10 [4]
Hepatobiliary disorders (Hypertension)	1 [1]	0 [0]
Immune system disorders	0 [0]	0 [0]
Infections and infestations (cellulitis, skin bacterial infection (2))	2 [2]	1 [1]
Injury, poisoning and procedural complications (falls (5), skin abrasion, corneal abrasion, vitreous detachment, injury, tooth fracture)	4 [3]	6 [4]
Investigations (itching, irregular pulse, irritable mood)	1 [1]	2 [2]
Metabolism and nutrition disorders (mouth ulcer, muscle pain)	0 [0]	2 [1]
Musculoskeletal and connective tissue disorders (neck pain, back pain (4), musculoskeletal stiffness,	1[1]	6 [3]
Neoplasms, benign and malignant (squamous cell carcinoma (2))	2 [2]	0 [0]
Nervous system disorders (insomnia (2), headache (3), migraine, diplopia, numbness localised, dizziness (2), anxiety, transient cerebrovascular event)	5 [4]	7 [5]
Pregnancy, puerperium and perinatal conditions	0 [0]	0 [0]
Psychiatric disorders (Alzheimer's dementia (2), low mood, Raynaud's disease)	2 [2]	2 [2]
Renal and urinary disorders (urinary tract infection (5), nocturia)	1 [1]	5 [3]
Reproductive system and breast disorders	0 [0]	0 [0]
Respiratory, thoracic and mediastinal disorders (Viral upper respiratory tract infection (6), upper respiratory	3 [1]	10 [5]

tract infection (2), lower respiratory tract infection, coughing and associated symptoms (3), shortness of breath)		
Skin and subcutaneous tissue disorders (Herpes simplex (2), rash papular, rash erythematous, acne, dry skin, skin tear)	2 [2]	5 [3]
Social circumstances	0 [0]	0 [0]
Surgical and medical procedures (Eye laser surgery, carpal tunnel syndrome surgery, tooth pain, tooth extraction, toe surgery,	1 [1]	5 [3]
Vascular disorders	0 [0]	0 [0]

Adverse events include definitely, probably, possibly, unlikely and not thought to be related to the study intervention.

Participants could report multiple events in any category.

Adverse drug reactions are coded by the MedDRA preferred term (Medical Dictionary for Regulatory Activities MedDRA 15.0)

Secondary clinical outcomes.

Changes in psychometric scores for observed cases and ITT-LOCF at 52 weeks following randomisation are shown in Table 3. Decreases in psychometric scores from baseline indicate a worsening in all outcomes. None of the clinical outcomes were statistically significant between treatment groups.

Table 3. Changes in psychometric scores at 52 weeks for observed and ITT-LOCF after randomisation compared with baseline.

	Observed cases				ITT-LOCF			
	Etanercept n = 5	Placebo n = 5	Mean difference corrected* (95%) CI	p value	Etanercept n = 7	Placebo n = 6	Mean difference corrected*(95%) CI	p value
MOCA (se)	**0.4 (1.0)**	**-1.0 (1.3)**	**-1.4 (-5.2 to 2.4)** **1.9 (-4.2 to 8.0)***	**0.4** **0.5**	**0.7 (0.9)**	**-0.5 (1.2)**	**-1.2 (-4.4 to 2.0)** **0.2 (-3.8 to 4.2)***	**0.4** **0.9**
FCSRT (se)	-0.4 (2.0)	-0.6 (0.9)	-0.2 (-5.2 to 4.8) -2.5 (11.8 to 6.7)*	0.9 0.5	-0.7 (1.4)	-0.8 (0.7)	-0.1 (-3.9 to 3.6) -2.2 (-7.3 to 3.0)*	0.9 0.4
RBANS (se)	-4.8 (1.3)	-3.8 (3.0)	1.0 (-6.6 to 8.6) 3.1 (-7.8 to 14.1)*	0.8 0.5	-5.6 (1.0)	-5.4 (2.9)	0.2 (-6.1 to 6.60 -0.6 (-8.0 to 6.8)*	0.9 0.8
ADL (se)	2.8 (2.1)	2.4 (1.8)	-0.4 (-6.8 to 6.0) 1.4 (-6.5 to 9.4)*	0.9 0.7	3.3 (2.1)	1.0 (2.0)	-2.3 (-8.7 to 4.1) -0.5 (-8.0 to 7.1)*	0.5 0.9

* corrected for baseline age; gender and baseline psychometric score. MOCA = the Montreal Cognitive Assessment; FCSRT= Free and Cued Selective Reminding Test with Immediate Recall; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; ADCS-MCI = Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory for MCI. ITT-LOCF = intention to treat-last observation carried forward. All p values are two sided.

Imaging outcomes

Methodology.

All imaging procedures were performed at the Wolfson Molecular Imaging Centre (WMIC) at the University of Manchester.

Imaging procedures and analysis were conducted in line with the study protocol and previously established imaging protocols for MRI, Florbetapir F 18 (Amyvid) PET, and [11C] (R)-PK-111-95 PET.

In brief:

a) MRI
Participants underwent a T1-weighted and inversion-recovery structural, volumetric MRI scan for grey-white matter segmentation, intra-individual co-registration with the PET scans and volumetric studies on the 1.5T MRI scanner. Additionally a T2 weighted sequence for assessment of potential confounding pathology was performed.

b) PET
Florbetapir F 18 (Amyvid) PET imaging was performed on a High Resolution Research Scanner in accordance with a slightly modified previously established protocol for this procedure at WMIC [1] and a target dose of 370 MBq.
Emission data over 60 minutes were acquired in list mode. After reconstruction of the image the amyloid scan was visually assessed by a trained reader.

[11C] (R)-PK-111-95 PET imaging was performed using the High Resolution Research Scanner in accordance with a previously approved protocol for this procedure at WMIC (ARSAC 595/3586/24989). Approx. 7 min after the start of the emission scan, 740 MBq [11C] (R)-PK-111-95 were injected as a single bolus within 30 seconds followed by an infusion line flush with 15-20 ml of saline. Emission data over 60 minutes were acquired in list mode.

Reconstruction of images followed previous methods with binding potential values and further quantitative analysis performed using a simplified reference tissue model and supervised cluster analysis as previously described [2] Binding potential maps were further interrogated and baseline (and follow-up scans) compared using a region of interest and Statistical parametric mapping approach.

Imaging results

A total of 19 patients proceeded to first MRI and Florbetapir F 18 (Amyvid) PET imaging after clinical screening. Six patients were found to be amyloid negative while the others were amyloid positive on visual read of the PET scans [3]. Therefore 13 patients proceeded to have a baseline [11C] (R)-PK-111-95 PET scan on the following day.

All 13 patients completed the baseline [11C] (R)-PK-111-95 PET scan without complications. Mean injected activity was 679.31 MBq ±123.82 (SD). One baseline scan was not analysable due to technical problems during the data acquisition of the scan.

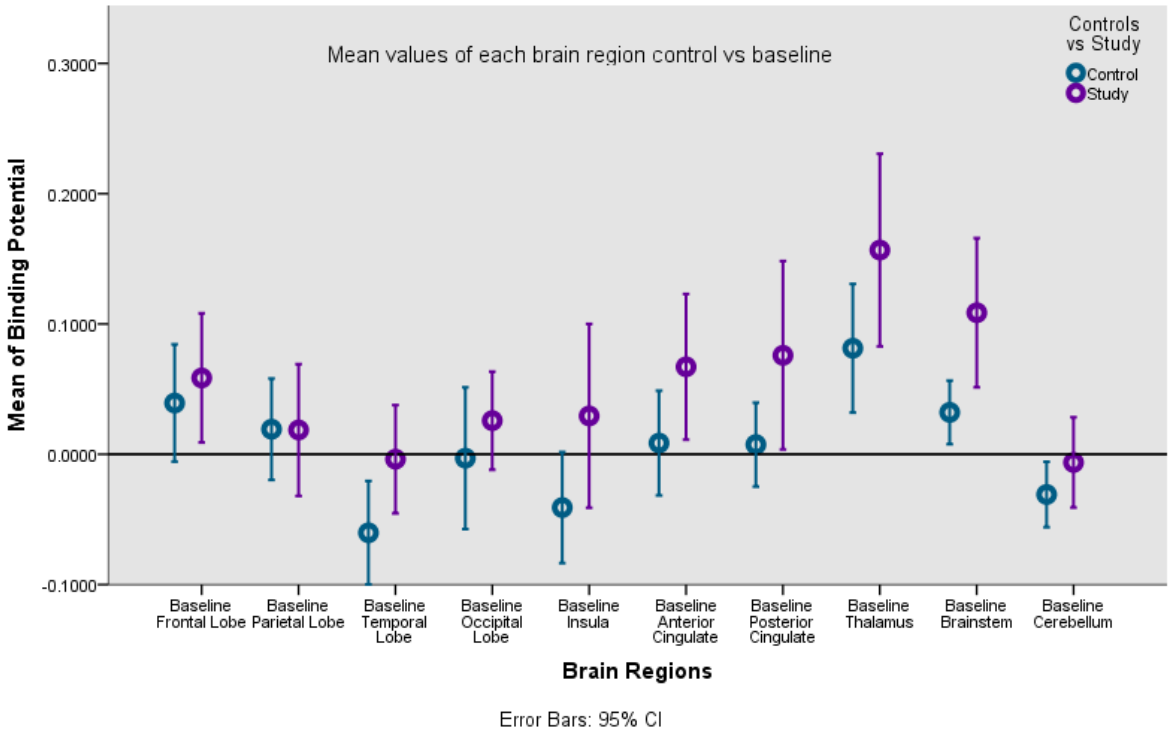


Figure 2

The region of interest analysis of the [11C] (R) PK-11195 binding potential (BP) so far shows (in line with previous work [4]) an almost global increase in MCI patients as compared to age-matched controls with the cingulate gyrus being targeted. The increases are however only borderline significant.

Of the 13 patients randomised 3 patients did not have final image data analysis due to:

- one patient in the placebo arms baseline PK1195 scan was technically faulty.
- one patient in the placebo arm had back pain (sae) that prevented her having the final scan.
- one patient in the active arm had a qualitatively amyloid positive scan at baseline but when quantitatively analysed was later found to be a false positive.

Of these patients 10 had also follow-up Amyvid scanning and 8 follow-up MRI (both these modalities were optional for the patients).

When comparing the regional and global PK11195 for these 10 patients at baseline and follow-up after one year, there were no significant differences (Figure 3)

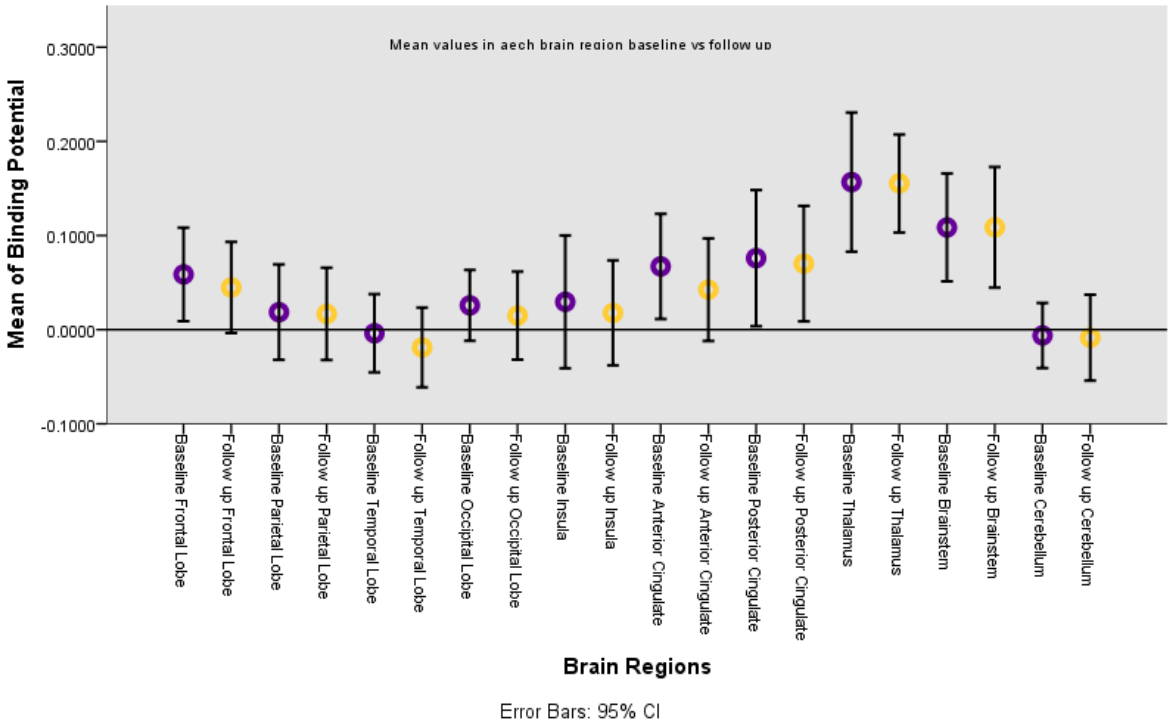
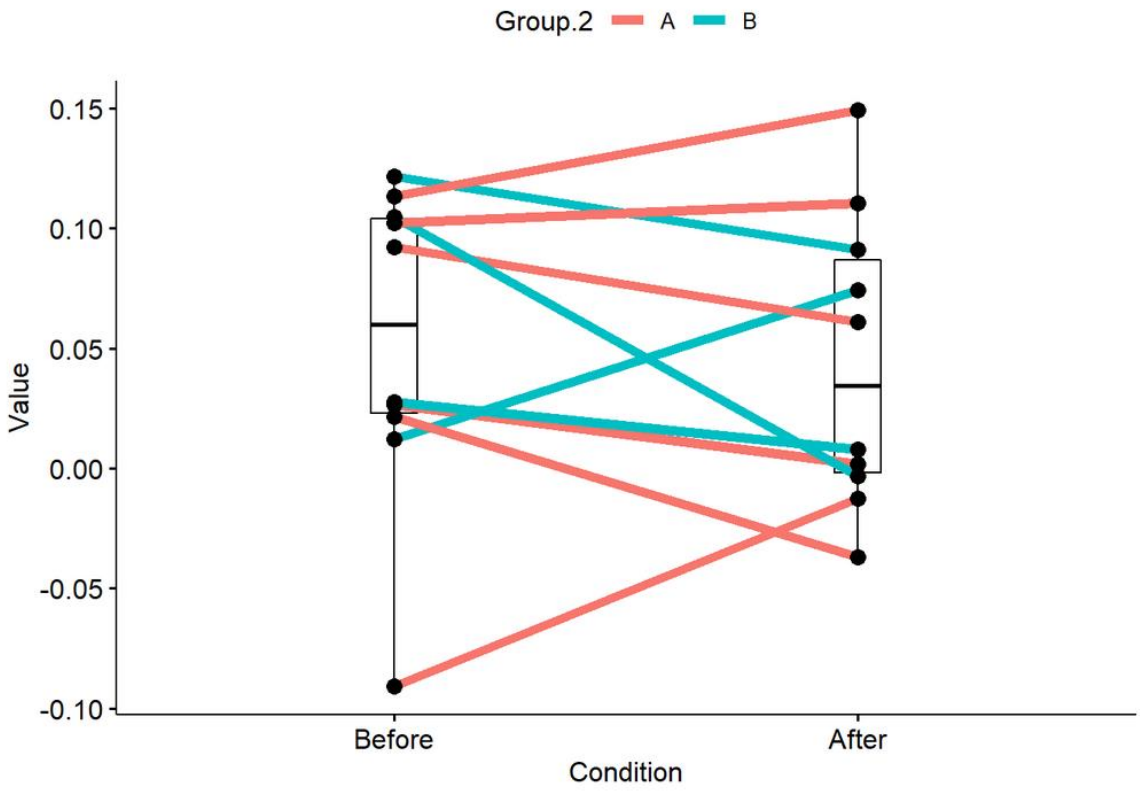


Figure 3: Regional PK11195 binding potential values for all 10 patients included in the final analysis for baseline and follow-up. No significant differences could be detected.

When the groups were split into group A (active drug/ etanercept) and B (placebo) we were also not able to detect a significant difference between baseline and follow-up on the respective group levels for whole brain volume (Figure 4).

Figure 4. demonstrates the changes before and after treatment. Group A received Etanercept, Group B placebo.

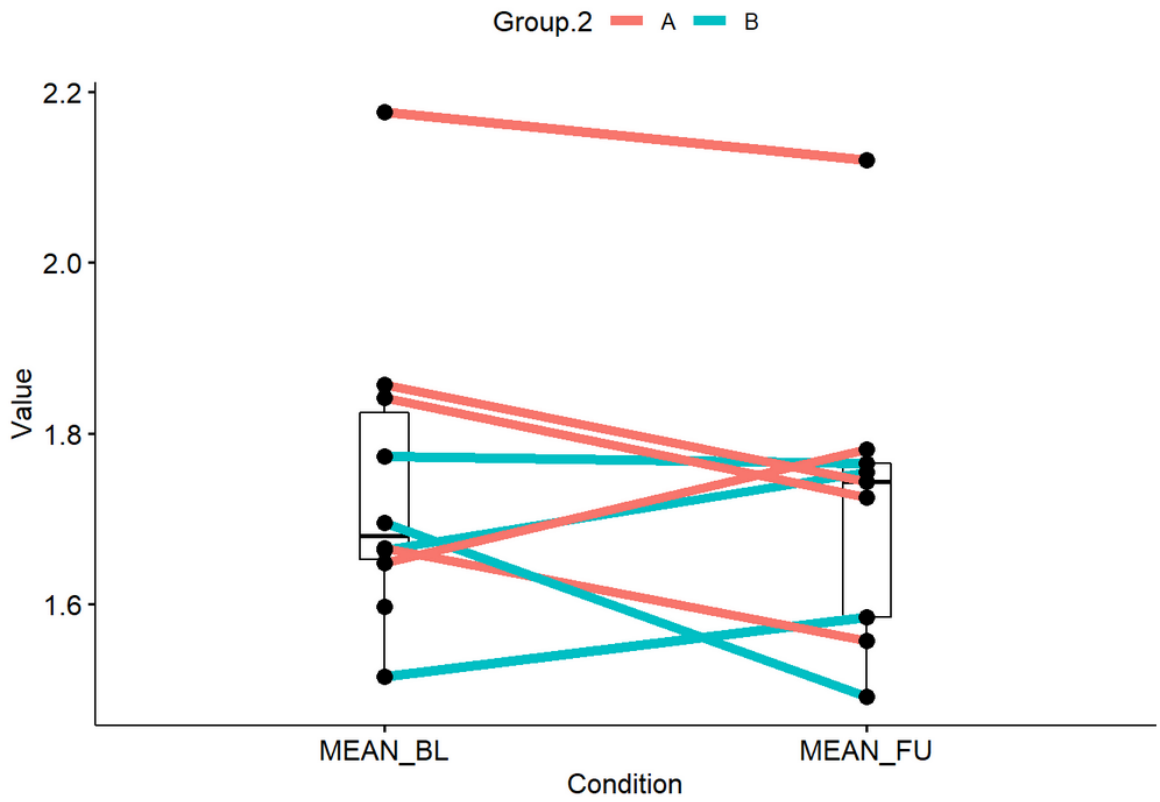


There was a slight increase in the binding potential in the treatment group and a slight decrease in the placebo group but no statistical differences between groups.
(Etanercept + 0.00139 c.f. Placebo – 0.02398: mean difference + 0.02537 (95% CI – 0.07785 to + 0.12860) p = 0.55).

Secondary cortical amyloid load outcome.

Figure 5. demonstrates the changes in global amyloid load before and after treatment. Group A received Etanercept, Group B placebo. There was no significant difference in global average amyloid loads between groups. Both groups showed a slight decrease in amyloid loading but there was no statistical differences between groups. (Etanercept -0.0523 c.f. Placebo – 0.0125: mean difference – 0.0648 (95% CI – 0.2439 to + 0.1643) p = 0.64).

Figure 5. Changes in global amyloid load before and after treatment. Group A received Etanercept, Group B placebo



Serum inflammatory markers

Serum levels for IL-1; IL-2; IL-4 and IL-13 were largely undetectable (>90%). No significant differences were found in serum levels of IFN-γ; IL-10, IL-12, IL-6, IL-8; TNFα; TGF-β or CRP by treatment group allocation at baseline. Following randomisation serum TNFα was higher in the treatment compared with the placebo group at all time points (Week 13 (placebo 2.0 (se 0.2) pg/ml c.f. etanercept 26.9 (se 3.1) pg/ml mean difference 24.9 (18.0 to 31.7) pg/ml, $p < 0.0001$); (Week 26 (placebo 2.1 (se 0.2) pg/ml c.f. etanercept 24.5 (se 1.8) pg/ml mean difference 22.3 (18.1 to 26.6) pg/ml, $p < 0.0001$); (Week 39 (placebo 2.3 (se 0.2) pg/ml c.f. etanercept 21.6 (se 4.0) pg/ml mean difference 19.3 (8.6 to 30.0) pg/ml, $p = 0.004$); (Week 52 (placebo 2.3 (se 0.3) pg/ml c.f. etanercept 27.4 (se 6.9) pg/ml mean difference 25.1 (5.7 to 44.5) pg/ml, $p = 0.04$). There were no significant differences between other serum inflammatory markers between the treatment and placebo groups at weeks 13, 26, 39 or 52 (data not shown).

References

1. Kobylecki, C., et al., *18F-florbetapir PET in patients with frontotemporal dementia and Alzheimer disease.* J Nucl Med, 2015. 56(3): p. 386-91.

2. Su, Z., et al., *[(1)(1)C]-(R)PK11195 tracer kinetics in the brain of glioma patients and a comparison of two referencing approaches.* Eur J Nucl Med Mol Imaging, 2013. **40**(9): p. 1406-19.
3. Joshi, A.D., et al., *Performance characteristics of amyloid PET with florbetapir F 18 in patients with alzheimer's disease and cognitively normal subjects.* J Nucl Med, 2012. **53**(3): p. 378-84.
4. Okello, A., et al., *Microglial activation and amyloid deposition in mild cognitive impairment: A PET study.* Neurology, 2009. **72**(1): p. 56-62.

Challenges encountered

The original timeline of the INMiND project foresaw 18 months to decide on the most appropriate study drug to be used for the WP9 clinical trial and get an agreement with pharma companies on study design, supplies and monitoring and 24 months to get all ethics and regulatory approvals in place. Within the first two project years the decision was made to use an anti-TNF-α agent, based on publications, efficacy profile, and the fact that the pharma company UCB endorsed free supply of the study drug Cimzia (certolizumab pegol) and placebo. GE agreed to supply the imaging ligands [18F]GE-180 and [18F]Flutametamol. Gratis for the study. Ethics and regulatory approvals were thus prepared based on the use of drug Cimzia and the imaging ligands [18F]GE-180 and [18F]Flutametamol. Unfortunately, in October 2013 (month 20) GE withdrew its agreement to supply the imaging ligands for free. After careful re-evaluations, plans were adjusted to employ [11C]PK11195 and [18F]florbetapir (Amyvid; Lilly) instead and start of the study was anticipated for March 2015. However, on 20th February 2015 (month 36) UCB also withdraw their secured agreement to provide the study drug Cimzia for free. After careful re-evaluation, P17 made an application to the Alzheimer's Society UK and the Alzheimer's Drug Discovery Foundation for funding for the TNF-α inhibitor Etanercept (Pfizer). Both foundations agreed to jointly pay for the provision of Etanercept with placebo and randomisation by ACE pharmaceuticals. Following the NIHR clinical trials road map all necessary approvals for both sites were finally in place on 11.11.2015 (a delay of 21 months with respect to the original time line). The first patient was consented on 18.11.2015 and the first study patient randomised in February 2016 in Southampton. The EU were informed and we were told to reassess recruitment rates and if necessary apply for a no cost extension once it was clear that we couldn't increase recruitment rates to make up for the delayed start. In Sept 2016 we formally requested a no-cost extension of 22 months to complete the study. In March 2017 we had still received no answer to our request and so we had to stop further recruitment since there was no funding guaranteed beyond March 2018 and thus beyond the 12 month randomization phase. On Feb 28th 2018 we were formally informed that a no-cost extension of 22 months was not being awarded. At the end of the study 34 subjects (and their study partner) had consented to take part in the study and 13 subjects have been randomized which meant the study was underpowered compared with the original study aim of 46 subjects randomized.

The chief investigator responsible for the neuroimaging data analysis (Alex Gerhard) moved post to Germany in March 2018 which delayed the final data analysis.