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Intravenous immunoglobulins for the treatment of mild to moderate Alzheimer's disease: a phase II, randomised, double-blind, placebo-controlled dose-finding trial

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Contributors:

Prof. Richard Dodel and Prof. Frank Jessen wrote the draft of the manuscript, which was reviewed by Prof. Martin Farlow and Dr. Stefan Wietek.

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Conflicts of interest:

Stefan Haag was an employee of Octapharma AG and has no other conflict of interests to report. Stefan Wietek is employed as Clinical Project Manager at Octapharma PPG (Vienna, Austria) and has no other conflict of interests to report.

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Abstract

Background—Three small trials have suggested effects of intravenous immunoglobulins (IVIG) on biomarkers and symptoms of mild-to-moderate Alzheimer's disease (AD). We explored the safety, the effective dose, and the infusion interval for *Octagam*® 10% in this patients' group.

Methods—The study was a 24-week multicentre, double-blind, placebo-controlled phase II trial with 8 treatment arms at 7 sites in the USA and 5 sites in Germany. Participants aged 50–85 years were randomised (using a computer-generated randomisation sequence) to either 4 weekly infusions (n=22) (0.2 g/0.5 g/0.8 g/kg body weight), 2 weekly infusions (0.1g/0.25 g/0.4 g/kg) (n=21) or to placebo (n=7, 4-weekly, n=8, 2 weekly). The primary endpoint was the mean area under the curve (AUC) of plasma A β _{1–40} after the last infusion for one infusion interval. We considered the AUC of plasma A β _{1–40} being more representative of the potential effect of IVIG than a single time point measurement. Secondary outcomes included changes in (a) the concentrations of A β _{1–40}, A β _{1–42}, anti-A β autoantibodies in CSF/plasma and tau/ptau₁₈₁ in CSF, (b) cognitive and functional scales, and (c) brain imaging (MRI/FDG-PET). Patients' safety was assessed by recording of adverse events, clinical examinations, MRI investigations, electrocardiography and laboratory tests. The infusions were performed by site personnel who were otherwise not involved in any other assessments; therefore, the patients, caregivers, and investigators were blinded to the treatment allocations. The study medication was blinded by using intransparent overpouches and infusion lines. The trial is registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT00812565) and controlled-trials.com (ISRCTN64846759).

Findings—Fifty-six patients were randomized. AUC of plasma A β _{1–40}, was not significantly different from the placebo for five of the six IVIG arms (median with range: –18.00 [–1347.0; 1068.5] for 0.2 g/kg; 364.25 [–5834.5; 1953.5] for 0.5 g/kg and –351.75 [–1084.0; 936.5] for 0.8 g/kg every 4 weeks compared to –116.25 [–1379.0; 5266.0] for the placebo; –13.75 [–1729.0; 307.0] for 0.1 g/kg, –32.50 [–1102.5; 451.5] for 0.25 g/kg and 47.00 [–341.0; 72.5] for 0.4 g/kg compared to 159.50 [51.5; 303.0] for the placebo; p=0.02 for comparison of the latter two groups). Adverse events were reported in 59.5% and 64.3% of the patients in the IVIG and placebo groups, respectively. No unexpected serious adverse events occurred.

Interpretation—IVIG had a very acceptable safety profile in the patients. The trial did not confirm results from previous studies. Longer trials with greater power are required to assess potential cognitive and functional effects of IVIG in AD.

Introduction

Alzheimer's disease (AD) is the most common form of dementia in the elderly and available symptomatic treatment options have limited efficacy¹.

We and others have reported evidence that intravenous immunoglobulins (IVIG) may have beneficial effects on pathogenic processes in AD (as evaluated by biomarkers) and that IVIG may improve the symptoms in AD patients^{2–5}. IVIG is a fractionated blood product used to

treat a variety of medical conditions⁶. The rationale for using IVIG in AD is based on the existence of naturally occurring antibodies directed against A β (nAbs-A β); these antibodies may interfere with A β metabolism and appear to be reduced in AD patients^{3, 7}. Three small clinical trials using IVIG in mild-to-moderate AD patients have been published. In the initial uncontrolled trial five patients received 1.2 g/kg IVIG every four weeks for six months. The A β _{1–40} level decreased in the CSF and increased in the blood compared to baseline². There was no cognitive deterioration in these subjects. These results were independently reproduced in an uncontrolled trial with eight patients (0.4 g/kg–2 g/kg for six months)⁵. Finally, a 6-months, placebo-controlled (saline) multiple dose (0.2g/kg and 0.4g/kg/bi weekly or 0.4g/kg and 0.8g/kg/monthly) study in 24 AD patients was completed. The data have not yet been published in detail⁸.

The most effective dose and the best treatment interval to maximise IVIG treatment effects while minimising safety risks are not yet known, although preliminary data support a 2-week infusion schedule over a 4-week schedule⁵. Here, we report the results of a phase II exploratory dose-finding study in mild-to-moderate AD patients.

Methods

Study design

We performed a double-blind, randomised, placebo-controlled, parallel group (with balanced randomisation), multi-centre trial at twelve sites (five and seven sites in Germany and the USA, respectively) to assess efficacy and safety of different IVIG dosages (*Octagam*[®] 10%) in out-patients with mild-to-moderate AD.

Participants

The inclusion criteria were probable AD according to the NINCDS-ADRDA criteria⁹, MMSE score between 16–26 (inclusive)¹⁰, age between 50–85 years (inclusive) at baseline, a Modified Hachinski-Rosen Score <5 and a MRI-scan consistent with AD. Patients were required to be on stable doses of approved AD medication for at least three months before screening.

Exclusion criteria were any suspected cause of dementia other than AD, history or present diagnosis of another significant disease of the central nervous system, a score of >7 in the geriatric depression scale, present significant psychiatric disorder, insulin-dependent diabetes mellitus, uncontrolled hypertension, severe liver or kidney disease, history of thromboembolic events or history of hypersensitivity to blood or plasma derived products or IVIG use in the previous six months.

The study was approved by each study site's ethics committee/IRBs and by the regulatory authorities. Each patient provided written informed consent before study participation. An independent data-monitoring committee assessed treatment safety throughout the trial. The trial is registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT00812565) and controlled-trials.com (ISRCTN64846759).

Randomisation and masking procedures

Patients were randomly allocated to receive one of three dosage levels of *Octagam*[®] 10% (0.2g/kg–0.5g/kg–0.8g/kg bodyweight) or placebo (0.9% isotonic sodium chloride) every four weeks, or half of that dosage (0.1g/kg–0.25g/kg–0.4g/kg) every two weeks.

For allocation of the participants, a computer-generated randomization list was created by the CRO using SAS 9.1.3 (SAS Institute Inc., Cary, USA) allocating patients via an IWRS with a block size of 8. Ethylene vinyl acetate bags containing the study medication were blinded by using intransparent overpouches. It was dispensed by the unblinded local pharmacy, which was responsible for study drug preparation. Infusion was performed by a physician who was blinded to the patient's group assignment and not involved in any assessments.

Procedures

All Octagam[®] 10% glass bottles and placebo for the calculated individual dose according to the body weight of the patient were pooled aseptically by the hospital pharmacist in three separate EVA bags of 0.5 L volume and were administered intravenously after the ratings at the respective visits. If a patient was randomised to receive placebo (0.9% w/v isotonic sodium chloride solution), the same volume and infusion rate as in the IVIG arms was applied.

Outcomes—Previous studies suggested that peripherally administered antibodies against A β induce an A β shift from the CSF to the blood, thereby reducing the cerebral A β burden (“peripheral sink hypothesis”)¹¹. In agreement, earlier IVIG studies revealed an increase of plasma A β and a decrease of CSF A β ^{2, 5}. Thus, we selected plasma A β_{1-40} as marker of primary interest. We chose the mean area under the curve (AUC)¹² of the A β_{1-40} plasma change from the trough level value, prior to the last infusion at week 20 (4-week intervals) or 22 (2-week intervals) to the end of an infusion interval (i.e. 4 weeks, 2 weeks) as the primary outcome measure. Because of the dynamics of the IVIG effect over time, the AUC was considered more appropriate than a single time point measure. The primary endpoint measures of the three different IVIG dosage arms in each of the two treatment interval groups were compared with their corresponding placebo arms.

Blood sampling was performed prior to last infusion and on days 1 (+1), 4 ($\pm$ 1), 7 ($\pm$ 1) and 14 ($\pm$ 2) after the week 22 infusion (2-week interval) or additionally on days 21 ($\pm$ 2) and 28 ($\pm$ 2) after the week 20 infusion (4-week interval).

The secondary outcome measures were the plasma AUC of A β_{1-42} , and anti-A β autoantibodies, plasma A β_{1-40} , A β_{1-42} , anti-A β autoantibodies single time point measurements at week 24, and change in CSF A β_{1-40} , A β_{1-42} , anti-A β autoantibodies tau and p-tau₁₈₁ concentration 24 $\pm$ 8 hours following the last infusion compared with baseline.

Secondary outcomes included the Alzheimer's disease Assessment Scale-Cognitive Part (ADAS-cog), the Clinical Dementia Rating Scale – Sum of Boxes (CDR-SOB), the Alzheimer's Disease Cooperative Study–Activities of Daily Living Scale (ADCS-ADL), and

Mini-Mental-State-Examination (MMSE) at baseline and at week 12 or 24. The raters (physicians, neuropsychologists) were blinded with regard to study medication.

Secondary brain imaging outcomes were changes in whole brain and hippocampal volume from baseline to week 12 and week 24 and changes in glucose metabolism between baseline and week 24. No changes of trial outcomes were implemented after the trial commenced.

Lumbar puncture, CSF and plasma analyses—CSF sampling and analyses are detailed in the supplementary material.

MR-Imaging—For safety and volumetric analyses, MRIs were performed at screening and after 12 and 24 weeks using 1.5T MR scanners. The sequences and procedures are outlined in the supplementary material.

FDG-PET—Fifty-five patients underwent baseline FDG-PET scans. In one centre, a PET-scanner was not available; thus 3 patients were not examined. The details of the FDG-PET are outlined in the supplementary material.

Statistical analysis

As this trial was an exploratory phase II study, no confirmatory hypothesis testing was planned. The sample size was determined empirically. It was estimated that 48 patients with a complete AUC for plasma $A\beta_{1-40}$ would be appropriate. Accounting for a possible drop-out rate of 14% a total of 56 patients were planned to be randomized.

The AUC was calculated by using the linear trapezoidal rule (i.e., by summing the trapezoid areas formed by the time intervals $t_n - t_{n-1}$ and the change in the baseline plasma concentrations as heights). The AUC was calculated for plasma $A\beta_{1-40}$, $A\beta_{1-42}$, and the nAbs- $A\beta$. The concentrations were determined at five different time points for the patients, who were treated at 2-week intervals (prior to last infusion, days 1/4/7/14) and at seven different time points for those treated at 4-week intervals (prior to last infusion, days 1/4/7/14/21/28). Areas below the abscissa reduced the overall AUC.

The differences in AUC between each IVIG dose and the corresponding placebo was assessed by calculating the Hodges-Lehmann estimate of the difference in two medians and the corresponding non-parametric 95% confidence interval. Further, the p -value for a Wilcoxon-rank-sum-test was provided.

For the cognitive and functional scales, plasma biomarkers, and MRI outcomes, the differences between week 24 and baseline were calculated. In case of CSF the difference between the time frame of 24 ± 8 hours after last infusion and baseline were calculated. T-tests were used to assess treatment effects for change in plasma and CSF biomarkers, and MRI measures. The difference in change of cognitive and functional scales was assessed with Wilcoxon-rank-sum-tests, by calculating Hodges-Lehmann estimates, and by the corresponding 95% confidence interval. The results of the individual treatment arms against placebo are reported here. The analyses on the pooled IVIG and placebo groups are detailed in the supplementary material. A correction for multiple comparisons was not applied.

For safety data, continuous variables were analysed using standard summary statistics and qualitatively using frequency tables. The statistical analysis was performed using the software package SAS 9.2 (SAS Institute, Cary, USA).

FDG-PET was analysed with paired *t*-tests of normalised scans in the IVIG and the placebo groups comparing baseline with follow-up data at week 24). The different IVIG doses and placebo arms were combined within dosing intervals to increase power. A significance threshold of $p < 0.001$, uncorrected for multiple comparisons was applied due to small sample sizes. In an additional analysis, all IVIG arms were combined ($n = 36$), and a more conservative significance level of $p < 0.05$, whole brain corrected (false discovery rate, FDR) was applied. Contrasts were calculated for metabolism increases and reductions. Age and gender were used as covariates.

Role of the funding source

The study sponsor and co-investigators (RD, FJ, MF) were jointly responsible for the study design/planning. Data management was outsourced to a CRO (ClinResearch, now Aptiv Solutions, Cologne, Germany). The CRO had responsibility for data monitoring and analysis according to the Statistical Analysis Plan developed by the sponsor as well as for writing the study report. After the database lock and study unblinding, all of the investigators had full access to the study data and shared the final responsibility for data analysis. The manuscript for the publication was written and reviewed by the authors. The decision to submit the manuscript for publication was jointly made by the PI (RD) and the sponsor.

Results

Study group

Eighty-nine patients were screened and 58 were randomly assigned to the treatment scheme (Figure 1, period of inclusion: 02 Feb 2009–30 Mar 2010; last patients' visit on 21 Sep 2010). Forty-nine patients (84%) completed the study. Table 1 and 2 list baseline characteristics of the groups.

Primary endpoint

The effect of treatment on the primary outcome measure is shown in Tables 3 to 4. There was a significant difference in the AUC of plasma $A\beta_{1-40}$ in the 0.4g/kg every two weeks group compared to placebo ($p = 0.02$, decrease). There were no significant differences between the other IVIG groups and the respective placebo groups or in the pooled groups.

Secondary endpoints

Plasma biomarkers—There was a significant change in the plasma AUC of $A\beta_{1-42}$ in the 2-week interval middle and high-dosage groups compared to the placebo group ($p = 0.01$; $p = 0.02$, decrease, Table 4). No differences in AUC were found in the 4-week interval groups. In the pooled groups of all six IVIG arms vs. the pooled placebo arms, there was a difference in the AUC of $A\beta_{1-42}$ ($p = 0.01$; decrease; Table 5-SM). There were no significant differences between each dosage group compared to the corresponding placebo group, but

there was a significant change in concentrations of plasma A β _{1–42} in the pooled IVIG groups vs. the pooled placebo groups $p=0.01$; decrease, Table 5-SM).

As expected, there was a dose-dependent increase of nAbs-A β in plasma from baseline in the 4-week interval groups at week 24 (Tables 5). In the 2-week interval placebo group two patients had tenfold higher nAbs-A β values than the others, which prevented significance of the numerical difference compared with the IVIG groups (Table 6).

CSF biomarkers—At 24 $\pm$ 8 hours after last infusion at either week 20 or week 22, changes from baseline in A β _{1–40}, A β _{1–42}, tau and p-tau₁₈₁ concentrations were neither significant for any individual treatment arm (Table 5,6), nor for the IVIG-pooled group compared to the pooled placebo group (Table 6-SM).

Cognitive and functional outcomes—There were no changes in cognitive and functional scales in any of the individual treatment arms. In the combined analysis of all the IVIG arms, there was a significant difference in CDR-SOB in favour of the placebo (Table 6-SM; improvement of the placebo group). There were no significant differences between the individual treatment arms or the combined IVIG treatment group and placebo with respect to changes in ADAS-cog, MMSE, or ACDS-ADL at 24 weeks (Tables 5, 6, 6-SM). There was also no effect on the respective scales at week 12 (data not shown).

MRI—Neither the mean left and right hippocampal atrophy rates nor whole brain volume atrophy rates differed between either individual treatment arm or between the combined IVIG group and placebo over the course of the study (Tables 5, 6, 6-SM) There was also no effect on the atrophy rates between baseline and week 12 (data not shown).

FDG-PET—Voxel-wise analyses in the combined placebo arm revealed a decrease in glucose metabolism in the bilateral hippocampal/temporomesial brain regions within the 24 week follow-up period (Figure 2). Stereotactic coordinates including brain area, peak z-scores and cluster sizes are presented in Figure 2b. Within these clusters, a decrease of –4.3% in FDG uptake was calculated. In the same clusters, glucose metabolism was altered in patients receiving low-dose by +0.4%, medium-dose by –0.9%, and high-dose IVIG by –1.8%, respectively (Figure 2c). Across all subjects in the IVIG arms, glucose metabolism was significantly less reduced than in the placebo group (–0.7%, $p<0.01$). Furthermore, increases in metabolism were observed in the low and high dose group in cortical regions (Figures 2d–g). In the medium dose group, there was no increase, which reached the significance threshold of $p<0.001$, uncorrected. Across all IVIG groups, there was an increase in metabolism in parietal and frontal regions also after statistical correction for whole brain analysis ($p<0.05$, FDR-corr, Figures 2h–j). No increases were observed in the placebo group.

Adverse events

The safety analysis was based on 56 patients, of whom 42 patients were in the IVIG-group and 14 in the placebo group (Table 7). The number of individuals with one or more adverse events in the placebo group ($n=9$; 64.3%) and treatment group ($n=25$; 59.5%) did not differ ($p=0.75$). Similarly, the groups did not differ in the number of serious adverse events with a

total of ten SAEs in eight patients (placebo group: n=4, 28.6%; IVIG: n=4, 9.5%). In the IVIG-group, one patient suffered an ischemic stroke that affected ACM territory. Otherwise, most adverse events in the IVIG-group were either mild or moderate in severity. No deaths were observed during the study period.

Microbleeds—At screening, the MRIs of nine patients (1 in the placebo and 8 in the IVIG arms) showed microbleeds. The rate of incident microbleeds in subjects with microbleeds at baseline was 37.5% (in 3 patients of those 8 receiving IVIG). One microbleed was observed at week 12 and two at week 24. The incidence of microbleeds in subjects without microbleeds at baseline was 7.1% (3 patients out of 42 receiving IVIG). One case was observed at week 12. This subject showed 14 new microbleeds and was therefore taken out of the study. The other two patients were observed at week 24. No dosing effects were observed. There were no incident microbleeds in the placebo group. There were no clinical symptoms associated with microbleeds. We did not observe any changes in white matter (amyloid-related imaging abnormalities (ARIA-E) – such as vasogenic oedema or sulcal effusions).

Discussion

This study is currently the largest completed trial evaluating IVIG in AD patients. Our data suggested a very acceptable safety profile for IVIG in patients with mild-to-moderate AD, which is consistent with previous studies^{2, 5}. We recorded no cases of aseptic meningitis, meningoencephalitis, or amyloid-related imaging abnormalities (vasogenic oedema and sulcal effusions, ARIA-E)¹³. We observed incident microbleeds on MRI in 37.5% and 7.1% of subjects either with or without baseline microbleeds on MRI at baseline (overall incidence 10.7%). Development of microbleeds was slightly higher than expected in AD¹⁴. One subject developed 14 microbleeds. In all cases, the microbleeds were asymptomatic. Incident microhaemorrhages and hemosiderin deposits (ARIA-H) have been reported in other immunisation trials in AD. The pooled data on Bapineuzumab revealed an overall incidence of 16%¹⁵. The clinically observed side-effects and systemic reactions were comparable to the known adverse events of IVIG-treatment. There was no difference between the IVIG and placebo groups in the rate of serious adverse events. No unexpected serious adverse events occurred. One 68-year old female patient in the high-dose IVIG-group with a medical history of Hashimoto's thyroiditis and depression experienced a stroke during the trial. The risk for ischemic stroke is known to increase with IVIG-treatment.

We did not observe an effect of IVIG on the primary endpoint, except for the 0.4g/kg dose every two weeks resulting in a decreased AUC of plasma A β ₁₋₄₀. We defined AUC of plasma A β ₁₋₄₀ as primary endpoint based on the finding of increased plasma A β ₁₋₄₀ and reduced CSF A β ₁₋₄₀ from previous IVIG studies^{2, 5}, which were interpreted as an indicator of the *peripheral sink hypothesis*. The secondary analyses of single time point changes of A β ₁₋₄₀ and of CSF A β ₁₋₄₀ also did not reveal any treatment effects. Thus, our analyses do not confirm the results from previous studies employing 1.2 g/kg or 0.4 and 0.8 g/kg IVIG monthly.

Similarly to the decrease in the AUC of $A\beta_{1-40}$, we observed a decrease of the secondary endpoint AUC of plasma $A\beta_{1-42}$ in the 2-week interval middle- and high-dosage arm and in the pooled analysis. The single point measure of plasma $A\beta_{1-42}$ also revealed a significant decrease at week 24 in the pooled analyses, representing an opposite effect compared to the increase of $A\beta_{1-40}$ in plasma that has been reported previously. This difference may be related to differences in study designs, such as inter-centre, pre-analytical variation¹⁶, different exposure to IVIG or other factors. In addition, the studied sample sizes are still limited. Currently, we cannot explain the differences between our study and the results of previous studies. The available knowledge on the $A\beta$ exchange is still rather limited. Further studies with larger samples and longer exposure to IVIG will be needed before any decisive conclusions can be made regarding effects of IVIG on levels of $A\beta_{1-40}$, $A\beta_{1-42}$, total-tau, and p-tau₁₈₁ in CSF/blood. Based on the data of this study, 0.25g/kg and 0.4g/kg administered at 2-week intervals may have the most pronounced effects on $A\beta$.

More importantly, our study showed a significant dose-dependent attenuation of decreased glucose metabolism in the temporal/hippocampal brain regions within 24 weeks of treatment. These brain regions are known to be affected in AD patients. Over time, progressive hypometabolism has been well documented in a number of brain regions, including the temporal lobe, the precuneus and cuneus, and the parietal, frontal, and occipital cortices¹⁷. Furthermore, IVIG-treated patients displayed significantly increased glucose metabolism in parietal and frontal brain regions at follow-up, even when applying a conservative threshold, whereas placebo-treated patients did not show any increase. However, it needs to be stressed that this increased metabolism is not localized in regions which are typically affected in FDG-PET studies in AD. Thus, the biological meaning of this finding is unclear. Our data suggest that IVIG may reduce the speed of metabolic decline in the MTL in AD, with low doses being more beneficial than high doses. Although these results are promising, they should be interpreted with caution given the limited number of patients in this study.

On the functional and neuropsychological scales, we found effects in favour of the placebo, reaching significance in the case of the CDR-SOB. The decline on the applied functional and cognitive instruments across all the IVIG groups was similar to the decline, which was observed in the natural course of AD and in placebo groups in mild to moderate AD trials¹⁸⁻²¹. The placebo group in this study showed less decline and even improvement on the CDR-SOB, which may have occurred by chance in this particular group. We conclude that there is most likely no symptomatic effect of IVIG. To detect the effects on slope of decline, longer studies are required.

There are limitations of the study, despite its careful study design and execution. The small size in each treatment group with large variations and heterogeneity in disease trajectories limits the likelihood to achieve clinically significant data favouring one dosage over another. Extrapolation of our findings to other patients' groups is limited by the small sample size in each group (especially in the placebo groups) and by the inclusion/exclusion criteria applied. In addition, patients were exposed to IVIG only for 6 months, which prevents detection of a disease-modifying effect. Finally, as in other studies with anti-amyloid agents, our study population might have been too advanced in course of AD to detect an effect. Application at

an earlier disease stage might be more beneficial, particularly with regard to the clinical outcomes. Although different dosages and intervals have been used in this and previous small trials and are used in an ongoing large trial (ranging from 0.1 to 0.4 g/kg bi-weekly or 0.2 to 1.2 g/kg 4-weekly) it is currently not yet possible to conclude whether higher or more frequent dosages may be needed for achieving substantial effects. Lastly, it cannot be ruled out that IVIG treatment might be not effective in AD patients.”

In conclusion, this phase II trial showed favourable safety and tolerability results and the absence of severe autoimmune reactions. Longer studies with larger study populations are required to assess potential effects on the slope of cognitive and functional decline in patients with Alzheimer’s disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in context

Systematic review

Studies were identified by searches of Medline (2000–2012) and the Cochrane Central Register of controlled trials (trials published up to 2012) with the search terms “Alzheimer’s disease” and “immunotherapy”, “immunoglobulins”. Searches were restricted to human studies. All types of trial design were included. We identified two systematic reviews evaluating immunotherapeutic approaches in clinical development for AD that evaluate trials with active and passive immunisation targeting A β . There are currently 6 active and 8 passive immunotherapeutic trials that target A β in different stages of development. These trials include ACC-001, CAD-106, ACI-24, UB-311, V950 and Affitopes AD-01/AD-02 investigating active immunotherapy and Bapineuzumab, GSK933776A, Solanezumab, Ponezumab, Gantenerumab, MABT-5102A, BAN-2401 and immunoglobulins as passive immunotherapeutic approaches. Most recently, two large clinical trials, Bapineuzumab and Solanezumab which target the N-terminal and mid-terminal sequence of A β , respectively, were found to be negative, with Solanezumab seemingly having a small effect in the mild AD patients’ group. Complete results from these trials are not yet available. With regard to using immunoglobulins to treat AD, two small pilot trials have been published showing an effect on the drain of A β from the CSF to the periphery. A large phase III study with immunoglobulins in mild-to moderate AD patients lasting 18 months is currently underway in the USA and a second one planned to start in 2013.

Interpretation

Passive immunisation targeting A β is a potentially therapeutic approach: however, several issues must be addressed such as the disease stage at which immunotherapy should be initiated, the role of biomarkers and whether they translate into the clinical course. Further clinical trials of sufficient length and power to assess cognitive and functional outcomes are needed to establish the efficacy of passive immunisation and immunoglobulins for patients with AD.

Figure 1.
Study flowchart

Figure 2.

Results of the FDG-PET A) The SPM(T) T-maps are illustrated as surface rendering projection showing significant differences follow-up versus baseline of the placebo-treated group, indicating significant decrease of glucose metabolism in green areas (paired *t*-test, $p < 0.001$, uncorr.; $n = 8$). B) Cluster specifications. C) Changes in CMRglc in these clusters for the different treatment arms as well as placebo (error bars are SEM); ** indicate $p < 0.01$ versus placebo. D) SPM(T) T-maps showing significant differences follow-up versus baseline of low-dose treated patients § (paired *t*-test, $p < 0.001$, uncorr.; $n = 12$). E) Cluster

specifications ¥. F) SPM(T) T-maps showing significant differences at follow-up versus baseline of high-dose treated patients, increases in red, decreases in green areas (paired *t*-test, $p < 0.001$, uncorr.; $n = 10$). G) Cluster specifications ¥. H) SPM(T) T-maps showing significant differences follow-up versus baseline of all IVIG-treated patients § (paired *t*-test, $p < 0.05$, FDR-corr.; $n = 36$) J) Cluster specifications ¥.

§ Significant increase of glucose metabolism in red areas. Cluster sizes of > 50 voxels are displayed.

¥ Bold markings delineate a cluster, subsequent non-bold markings identify further peaks within the same cluster.

Table 1

Baseline characteristics of the patients (Full Analysis Set = Intent-to-treat population; n=55).

	IVIG (n=41)	Placebo (n=14)
Demographics		
Age (years; mean $\pm$ SD)	69.4 $\pm$ 7.3	72.0 $\pm$ 10.2
Women n (%)	15 (36.6)	9 (64.3)
White n (%)	40 (97.6)	12 (85.7)
Weight (kg $\pm$ SD)	77.6 $\pm$ 14.1	71.8 $\pm$ 17.7
Duration of symptoms of AD (months; mean $\pm$ SD)	29.6 $\pm$ 27.3	23.6 $\pm$ 21.9
APOE ϵ 4 carrier n (%)	30 (73.2)	10 (71.4)
Use of AChEI or memantine n (%)	36 (87.8)	11 (78.6)
Clinical measures		
Modified Hachinski score (mean $\pm$ SD)	0.6 $\pm$ 0.6	1.0 $\pm$ 0.4
GDS (mean $\pm$ SD)	1.6 $\pm$ 1.5	1.7 $\pm$ 2.0
MMSE score (mean $\pm$ SD)	21.3 $\pm$ 2.8	21.9 $\pm$ 2.4
ADAS-cog (mean $\pm$ SD)	20.5 $\pm$ 8.5	19.5 $\pm$ 10.5
Clinical dementia rating - sum of boxes (mean $\pm$ SD)	4.7 $\pm$ 2.0	5.0 $\pm$ 3.1
ADCS-ADL (mean $\pm$ SD)	65.1 $\pm$ 9.2	63.3 $\pm$ 11.1
Laboratory measures		
A β ₁₋₄₀ : CSF (pg/mL)	8366.8 $\pm$ 2428.3	9237.0 $\pm$ 2799.7
Plasma (pg/mL)	180.6 $\pm$ 43.9	174.4 $\pm$ 57.1
A β ₁₋₄₂ : CSF (pg/mL)	300.6 $\pm$ 122.9	363.9 $\pm$ 138.0
Plasma (pg/mL)	42.3 $\pm$ 11.8	38.1 $\pm$ 9.2
Tau [pg/ml]	711.9 $\pm$ 432.2	600.4 $\pm$ 257.7
Tau181 [pg/ml]	105.7 $\pm$ 53.0	93.7 $\pm$ 28.3
nAbs-A β : CSF[RTU]	3.6 $\pm$ 6.7	5.8 $\pm$ 9.9
Plasma [RTU]	646.6 $\pm$ 1342.2	794.1 $\pm$ 1062.1
Microbleeds n (%)	8 (19.5)	1 (7.1)
Normalized whole brain volume	1288.9 $\pm$ 73.3	1275.9 $\pm$ 120.3
Hippocampal volume left [mm ³]	2650.5 $\pm$ 478.3	2608.2 $\pm$ 491.0
Hippocampal volume right [mm ³]	2829.6 $\pm$ 491.8	2665.6 $\pm$ 434.3

Data are number (%) or mean (SD); MMSE: Mini-Mental State Examination; APOE ϵ 4: Apolipoprotein E ϵ 4; AChEI: Acetylcholinesterase Inhibitor; ADAS-cog: Alzheimer's Disease Assessment Scale-cognitive subscale. GDS: Geriatric Depression Scale; ADCS-ADL: Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory.

Table 2

Baseline characteristics of the patients stratified by 4-week and 2-week dosing interval (Intent-to-treat population; n=55)

	4-week interval		2-week interval	
	0.2 (n=6)	0.5 (n=8)	0.1 (n=6)	0.4 (n=7)
Demographics				
Age (years)	74.8 ± 5.5	65.9 ± 10.2	71.4 ± 11.8	72.9 ± 5.0
Women (n)	2	3	5	3
White (n)	5	8	6	7
Weight (kg)	72.9 ± 15.9	74.8 ± 13.5	65.6 ± 17.9	77.1 ± 17.6
Duration of AD (months)	17.7 ± 16.3	17.9 ± 18.3	21.3 ± 16.4	44.9 ± 15.4
APOE ε4 carrier	4	3	4	5
Use of AChEI or memantine	5	8	5	5
Clinical measures				
Modified Hachinski score	0.3 ± 0.5	0.6 ± 0.9	1.0 ± 0.6	0.1 ± 0.4
GDS	1.3 ± 0.8	1.9 ± 1.8	2.4 ± 2.6	1.7 ± 2.1
MMSE score	19.3 ± 3.4	20.9 ± 2.7	22.1 ± 3.1	21.6 ± 1.7
ADAS-cog	27.2 ± 9.7	21.0 ± 9.7	21.2 ± 14.7	17.6 ± 6.5
CDR - sum of boxes	6.6 ± 3.3	5.1 ± 1.7	5.3 ± 3.7	4.3 ± 1.1
ADCS-ADL	60.5 ± 11.2	65.9 ± 8.3	64.4 ± 12.5	67.1 ± 6.8
Laboratory measures				
Aβ ₁₋₄₀ : CSF (pg/mL)	8499.2 ± 2030.6	8654.6 ± 2357.5	9783.0 ± 2634.0	8534.8 ± 3030.3
Plasma (pg/mL)	169.2 ± 62.7	150.9 ± 17.9	194.7 ± 56.5	189.5 ± 40.6
Aβ ₁₋₄₂ : CSF (pg/mL)	333.8 ± 156.9	279.8 ± 47.5	358.3 ± 161.1	286.0 ± 101.0
Plasma (pg/mL)	42.7 ± 9.4	36.6 ± 16.0	42.0 ± 8.5	39.8 ± 8.7
Total tau (pg/mL)	861.3 ± 848.6	803.6 ± 239.9	714.9 ± 283.0	577.2 ± 174.4
P-tau ₁₈₁ (pg/mL)	113.8 ± 84.9	116.5 ± 27.8	105.9 ± 29.4	84.8 ± 16.6
nAbs-Aβ: CSF [RTU]	7.4 ± 11.9	2.2 ± 2.6	4.7 ± 9.2	2.9 ± 3.1
Plasma [RTU]	431.3 ± 161.3	493.1 ± 252.7	502.1 ± 480.5	562.7 ± 625.1
Whole brain volume	1268.2 ± 43.8	1319.4 ± 98.1	1286.3 ± 78.7	1237.1 ± 49.0

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	IVIG (n=21)		Placebo (n=7)		IVIG (n=20)		Placebo (n=7)	
	4-week interval				2-week interval			
	0.2 (n=6)	0.5 (n=8)	0.8 (n=7)		0.1 (n=6)	0.25 (n=7)	0.4 (n=7)	
Hippocampal volume left	2530.3 ± 387.6	2747.6 ± 444.4	2568.4 ± 579.9	2529.9±353.7	2611.0 ± 450.1	2818.3 ± 660.9	2590.4 ± 392.7	2686.6 ± 618.7
Hippocampal volume right	2693.8 ± 333.9	2842.1 ± 557.7	2761.9 ± 547.8	2679.1±428.4	2754.5 ± 609.5	2923.6 ± 590.3	2969.9 ± 368.2	2652.1 ± 474.2

Data are number (%) or mean (SD); MMSE: mini-mental state examination; APOE ε4: apolipoprotein E ε4; AChEI: acetylcholinesterase Inhibitor; ADAS-cog: Alzheimer's disease assessment scale-cognitive subscale. GDS: Geriatric depression scale; ADCS-ADL: Alzheimer's Disease Cooperative Study - Activities of Daily Living Inventory

Table 3

AUC of the A β plasma change from the trough level in the **4-week** dosing interval (Intent-to-treat population; n=55).

	Placebo (n=7)				IVIG (n=21)				Placebo vs. 0.8 IVIG			
	0.2 (n=6)	0.5 (n=8)	0.8 (n=7)		0.2 (n=6)	0.5 (n=8)	0.8 (n=7)		Placebo vs. 0.2 IVIG	Placebo vs. 0.5 IVIG	Placebo vs. 0.8 IVIG	
Aβ₁₋₄₀	-18.00 [-1347.0; 1068.5] (n=6)	-364.25 [-5834.5; 1953.5] (n=8)	-351.75 [-1084.0; 936.5] (n=7)	-116.25 [-1379.0; 5266.0] (n=6)	-32.50 [-1358.0; 4197.5] p=0.8102	195.25 [-1005.5; 5302.0] p=0.7469	235.50 [-984.5; 4329.5] p=0.5752					
Aβ₁₋₄₂	-41.75 [-244.40; 336.55] (n=6)	-119.25 [-1220.60; 375.00] (n=8)	-107.50 [-173.50; 231.00] (n=6)	-20.50 [-183.70; 489.00] (n=6)	30.25 [-234.55; 346.40] p=0.5752	114.75 [-64.50; 622.00] p=0.2200	87.00 [-95.70; 275.50] p=0.2298					
nAbs-Aβ	932.50 [-2991.5; 3577.0] (n=6)	5770.00 [2892.5; 14426.0] (n=8)	8658.75 [5532.5; 11517.5] (n=6)	636.00 [-1207.5; 1075.5] (n=6)	-915.50 [-2844.5; 1784.0] p=0.5752	-5339.50 [-7203.5; -3814.5] p=0.0024	-8398.25 [-10785.0; -5343.5] p=0.0051					

Data are median [minimum, maximum] (patients analysed) for treatment groups; differences are assessed by Hodges-Lehmann estimates of the difference in two medians and the corresponding non-parametric 95% confidence interval (exact) as well as by Wilcoxon Rank Sum test (normal approximation, two-sided, $\alpha=0.05$).

Table 4

AUC of the A β plasma change from the trough level in the **2-week** dosing interval (Intent-to-treat population; n=55).

	Placebo (n=7)				Placebo vs. 0.1 IVIG				Placebo vs. 0.25 IVIG				Placebo vs. 0.4 IVIG			
	0.1 (n=6)		0.25 (n=7)		0.4 (n=7)		0.4 (n=7)		0.4 (n=7)		0.4 (n=7)		0.4 (n=7)		0.4 (n=7)	
Aβ₁₋₄₀	-13.75 [-1729.0; 307.0] (n=6)	-32.50 [-1102.5; 451.5] (n=7)	-32.50 [-1102.5; 451.5] (n=7)	-32.50 [-1102.5; 451.5] (n=7)	-32.50 [-1102.5; 451.5] (n=7)	-32.50 [-1102.5; 451.5] (n=7)	-32.50 [-1102.5; 451.5] (n=7)	-32.50 [-1102.5; 451.5] (n=7)	-32.50 [-1102.5; 451.5] (n=7)	-32.50 [-1102.5; 451.5] (n=7)	-32.50 [-1102.5; 451.5] (n=7)	-32.50 [-1102.5; 451.5] (n=7)	-32.50 [-1102.5; 451.5] (n=7)	-32.50 [-1102.5; 451.5] (n=7)	-32.50 [-1102.5; 451.5] (n=7)	-32.50 [-1102.5; 451.5] (n=7)
Aβ₁₋₄₂	3.00 [-109.50; 74.50] (n=6)	-33.50 [-190.55; -16.50] (n=7)	-33.50 [-190.55; -16.50] (n=7)	-33.50 [-190.55; -16.50] (n=7)	-33.50 [-190.55; -16.50] (n=7)	-33.50 [-190.55; -16.50] (n=7)	-33.50 [-190.55; -16.50] (n=7)	-33.50 [-190.55; -16.50] (n=7)	-33.50 [-190.55; -16.50] (n=7)	-33.50 [-190.55; -16.50] (n=7)	-33.50 [-190.55; -16.50] (n=7)	-33.50 [-190.55; -16.50] (n=7)	-33.50 [-190.55; -16.50] (n=7)	-33.50 [-190.55; -16.50] (n=7)	-33.50 [-190.55; -16.50] (n=7)	-33.50 [-190.55; -16.50] (n=7)
nAbs-Aβ	299.25 [-105.0; 987.0] (n=6)	1256.00 [1059.0; 5160.0] (n=7)	1256.00 [1059.0; 5160.0] (n=7)	1256.00 [1059.0; 5160.0] (n=7)	1256.00 [1059.0; 5160.0] (n=7)	1256.00 [1059.0; 5160.0] (n=7)	1256.00 [1059.0; 5160.0] (n=7)	1256.00 [1059.0; 5160.0] (n=7)	1256.00 [1059.0; 5160.0] (n=7)	1256.00 [1059.0; 5160.0] (n=7)	1256.00 [1059.0; 5160.0] (n=7)	1256.00 [1059.0; 5160.0] (n=7)	1256.00 [1059.0; 5160.0] (n=7)	1256.00 [1059.0; 5160.0] (n=7)	1256.00 [1059.0; 5160.0] (n=7)	1256.00 [1059.0; 5160.0] (n=7)

Data are median [minimum, maximum] (patients analysed) for treatment groups; differences are assessed by Hodges-Lehmann estimates of the difference in two medians and the corresponding non-parametric 95% confidence interval (exact) as well as by Wilcoxon Rank Sum test (normal approximation, two-sided, $\alpha=0.05$).

Table 5

Mean changes from baseline at week 24 in the 4-week dosing interval (Intent-to-treat population; n=55).

	IVIG (n=21)				Placebo (n=7)		
	0.2 (n=6)	0.5 (n=8)	0.8 (n=7)				
Aβ₁₋₄₀							
CSF* [pg/mL]	561.7 ± 1195.5 (n=6)	403.9 ± 588.1 (n=8)	642.2 ± 1171.3 (n=6)	42.0 ± 874.0 (n=6)	-519.7 [-1866.7; 827.4] p=0.4102	-361.9 [-1210.4; 486.6] p=0.3711 -600.2 [-1929.5; 729.2] p=0.3382	
Plasma [pg/mL]	-20.3 ± 29.2 (n=6)	15.7 ± 29.7 (n=7)	-30.5 ± 42.3 (n=6)	-6.0 ± 23.8 (n=6)	14.3 [-19.9; 48.6] p=0.3729	-21.7 [-55.0; 11.6] p=0.1788 24.5 [-19.7; 68.7] p=0.2446	
Aβ₁₋₄₂							
CSF* [pg/mL]	18.8 ± 40.3 (n=6)	10.5 ± 40.9 (n=8)	24.7 ± 43.2 (n=6)	-5.2 ± 36.3 (n=6)	-24.0 [-73.3; 25.3] p=0.3037	-15.7 [-61.6; 30.3] p=0.4718 -29.8 [-81.1; 21.4] p=0.2239	
Plasma [pg/mL]	-3.5 ± 5.8 (n=6)	-0.1 ± 4.4 (n=8)	-7.0 ± 6.2 (n=6)	-2.0 ± 4.8 (n=6)	1.5 [-5.3; 8.3] p=0.6349	-1.9 [-7.2; 3.5] p=0.4606 5.0 [-2.2; 12.2] p=0.1509	
nAbs-Aβ							
CSF* [RTF]	0.4 ± 1.4 (n=6)	1.1 ± 1.5 (n=8)	0.7 ± 2.3 (n=6)	0.1 ± 0.3 (n=6)	-0.3 [-1.6; 1.1] p=0.6881	-1.0 [-2.3; 0.4] p=0.1083 -0.6 [-2.7; 1.5] p=0.5596	
Plasma [RTF]	96.7 ± 133.7 (n=6)	256.6 ± 214.1 (n=8)	501.3 ± 514.6 (n=6)	-56.3 ± 58.3 (n=6)	153.0 [-285.6; -20.4] p=0.0279	-313.0 [-510.4; -115.6] p=0.0039 -557.7 [-1028.8; -86.6] p=0.0450	
Total tau* [pg/mL]	-141.8 ± 419.5 (n=6)	1.3 ± 86.7 (n=8)	131.3 ± 301.0 (n=6)	-33.2 ± 69.7 (n=6)	108.7 [-278.2; 495.5] p=0.5575	-34.4 [-128.6; 59.8] p=0.4416 -164.5 [-445.6; 116.6] p=0.2438	
P-Tau181* [pg/mL]	3.3 ± 21.2 (n=6)	-2.5 ± 8.6 (n=8)	10.2 ± 19.3 (n=6)	-1.3 ± 10.1 (n=6)	-4.7 [-26.0; 16.7] p=0.6370	1.2 [-9.7; 12.0] p=0.8192 -11.5 [-31.3; 8.3] p=0.2243	
ADAS-cog	5.33 [-4.7; 8.7] (n=6)	1.84 [-8.0; 24.0] (n=8)	-1.50 [-4.3; 18.3] (n=6)	0.33 [-3.3; 5.0] (n=5)	-3.84 [-9.34; 4.00] p=0.2353	-0.34 [7.00; 5.67] p=0.8835 0.84 [-13.33; 7.33] p=0.6466	
MMSE	-3.0 [-8; 2] (n=6)	-1.5 [-4; 1] (n=8)	-1.5 [-7; 2] (n=6)	-1.5 [-11; 4] (n=6)	2.0 [-6.0; 7.0] p=0.5725	0.5 [-5.0; 5.0] p=0.8453 0.0 [-6.0; 5.0] p=1.0000	
CDR-SOB	0.50 [-1.0; 3.0] (n=6)	0.00 [-1.0; 5.0] (n=8)	0.25 [-1.5; 3.0] (n=6)	-0.50 [-6.0; 0.0] (n=5)	-1.50 [-6.50; 0.00] p=0.0641	-0.50 [-6.00; 0.00] p=0.1879 -1.25 [-5.50; 0.50] p=0.1961	
ADCS-ADL	-3.0 [-31; 11] (n=6)	0.0 [-15; 11] (n=8)	-1.5 [-5; 3] (n=6)	-3.0 [-8; 7] (n=5)	-1.0 [-13.0; -25.0] p=0.9273	-4.5 [-14.0; 7.0] p=0.3387 -1.5 [-8.0; 6.0] p=0.7144	

	IVIG (n=21)			Placebo (n=7)			Placebo vs. 0.2 IVIG p=0.6196	Placebo vs. 0.5 IVIG p=0.7094	Placebo vs. 0.8 IVIG p=0.2851
	0.2 (n=6)	0.5 (n=8)	0.8 (n=7)	0.2 (n=6)	0.5 (n=8)	0.8 (n=7)			
Whole brain volume	-1.4 ± 1.8 (n=6)	-1.1 ± 1.0 (n=8)	-1.6 ± 1.1 (n=6)	-0.9 ± 0.8 (n=4)	-137.0 ± 114.8 (n=5)	-137.0 ± 114.8 (n=5)	0.5 [-1.7; 2.7] p=0.6196	0.2 [-1.1; 1.5] p=0.7094	0.7 [-0.7; 2.2] p=0.2851
Hippocampal volume left	-191.2 ± 111.7 (n=6)	-188.4 ± 228.2 (n=8)	-153.5 ± 91.2 (n=6)				54.2 [-100.8; 209.1] p=0.4494	51.4 [-193.0; 295.7] p=0.6526	16.5 [-123.7; 156.7] p=0.7961
Hippocampal volume right	-140.8 ± 60.3 (n=6)	-193.1 ± 137.7 (n=8)	-230.5 ± 165.8 (n=6)	-132.4 ± 122.1 (n=5)			8.4 [-118.9; 135.8] p=0.8842	60.7 [-105.2; 226.6] p=0.4375	98.1 [-104.6; 300.8] p=0.3021

Data are mean ± SD (patients analysed) for CSR and plasma biomarkers as well as MRI results and median [minimum, maximum] (patients analysed) for cognitive and functional scales.

Differences between treatment groups were assessed by using t-test (two-sided, $\alpha=0.05$) for CSF and plasma biomarkers as well as MRI results (displayed as difference between groups [95% confidence interval], p-value) and by calculating Hodges-Lehmann estimates and the corresponding non-parametric 95% confidence interval as well as by using Wilcoxon Rank Sum test (normal approximation, two-sided, $\alpha=0.05$) for the cognitive and functional scales (displayed as Hodges-Lehmann estimate [95% confidence interval] p-value).

* At visit 7 (last infusion at week 20 + 1 day)

Table 6

Mean changes from baseline at week 24 in 2-week dosing interval (Intent-to-treat population; n=55).

	IVIG (n=20)				Placebo (n=7)			
	0.1 (n=6)	0.25 (n=7)	0.4 (n=7)					
Aβ₁₋₄₀								
CSF * [pg/mL]	266.7 ± 996.0 (n=6)	10.6 ± 1104.0 (n=7)	-147.0 ± 1067.9 (n=5)	939.4 ± 1670.8 (n=5)	672.7 [-1160.8; 2506.3] p=0.4280	928.8 [844.7; 2702.3] p=0.2703	1086.4 [-958.5; 3131.3] p=0.2554	
Plasma [pg/mL]	5.5 ± 64.5 (n=6)	-0.3 ± 22.1 (n=6)	-6.5 ± 61.4 (n=6)	27.1 ± 40.2 (n=7)	21.6 [-42.8; 86.1] p=0.4755	27.5 [-13.2; 68.1] p=0.1650	33.6 [-28.7; 96.0] p=0.2602	
Aβ₁₋₄₂								
CSF * [pg/mL]	-8.7 ± 38.2 (n=6)	9.7 ± 54.7 (n=7)	4.0 ± 40.3 (n=5)	32.42 ± 67.0 (n=5)	41.1 [-31.5; 113.7] p=0.2327	22.7 [-55.9; 100.9] p=0.5325	28.4 [-52.2; 109.0] p=0.4403	
Plasma [pg/mL]	-2.3 ± 7.8 (n=6)	-4.5 ± 6.3 (n=6)	-2.7 ± 7.6 (n=6)	4.1 ± 3.8 (n=7)	6.5 [-0.8; 13.8] p=0.0759	8.6 [2.4; 14.8] p=0.0107	6.8 [-0.3; 13.9] p=0.0592	
nAbs-Aβ								
CSF * [RTF]	0.2 ± 1.8 (n=6)	1.9 ± 1.9 (n=7)	-0.8 ± 1.6 (n=5)	0.4 ± 3.7 (n=5)	0.2 [-3.7; 4.0] p=0.9271	-1.5 [-5.1; 2.2] p=0.3861	1.2 [-3.0; 5.4] p=0.5378	
Plasma [RTF]	74.3 ± 35.0 (n=6)	163.9 ± 136.6 (n=7)	310.2 ± 193.0 (n=6)	109.7 ± 284.8 (n=7)	35.4 [-223.8; 294.6] p=0.7553	-54.1 [-314.3; 206.0] p=0.6583	-200.5 [-503.3; 102.4] p=0.1732	
Total tau * [pg/mL]	209.3 ± 416.0 (n=6)	-3.4 ± 35.6 (n=7)	-7.8 ± 51.3 (n=5)	17.4 ± 38.6 (n=5)	-191.9 [-618.1; 234.3] p=0.3110	20.8 [-27.2; 68.9] p=0.3571	25.2 [-41.0; 91.4] p=0.4056	
P-Tau181 * [pg/mL]	-3.2 ± 14.7 (n=6)	0.4 ± 3.6 (n=7)	2.6 ± 5.0 (n=5)	0.6 ± 7.5 (n=5)	3.8 [-12.7; 20.2] p=0.6172	0.2 [-7.0; 7.4] p=0.9586	-2.0 [-11.3; 7.3] p=0.6328	
ADAS-cog	2.50 [-3.7; 6.0] (n=6)	-1.33 [-7.3; 4.0] (n=7)	4.50 [-4.0; 8.3] (n=6)	-0.33 [-5.3; 5.0] (n=7)	-3.00 [-7.00; 1.67] p=0.1979	2.00 [-4.00; 7.00] p=0.6540	-4.34 [-10.66; 2.33] p=0.1004	
MMSE	-2.0 [-10; 2] (n=6)	0.0 [-3; 4] (n=7)	-1.5 [-4; 1] (n=6)	-1.0 [-5; 1] (n=7)	1.0 [-4.0; 7.0] p=0.6643	-1.0 [-5.0; 2.0] p=0.4392	1.0 [-2.0; 4.0] p=0.6656	
CDR-SOB	0.00 [-1.0; 5.0] (n=6)	0.50 [-2.0; 2.0] (n=7)	0.75 [-1.5; 4.0] (n=6)	0.00 [-2.5; 1.5] (n=7)	-1.25 [-3.50; 0.50] p=0.4236	-0.50 [-2.50; 1.00] p=0.4356	-2.50 [-3.50; 0.00] p=0.0953	
ADCS-ADL	-0.5 [-11; 4] (n=6)	-3.0 [-17; 3] (n=7)	-4.0 [-25; 2] (n=6)	2.0 [-6; 10] (n=7)	3.0 [-3.0; 10.0] p=0.3153	5.0 [-1.0; 13.0] p=0.0839	6.5 [0.0; 18.0] p=0.0734	

	IVIIG (n=20)				Placebo (n=7)				
	0.1 (n=6)	0.25 (n=7)	0.4 (n=7)						
Whole brain volume	-2.0 ± 0.8 (n=5)	-1.5 ± 0.7 (n=6)	-1.4 ± 1.7 (n=5)	-1.4 ± 1.0 (n=4)	0.6 [-0.8; 2.0] p=0.3620	0.1 [-1.1; 1.3] p=0.8766	-0.0 [-2.3; 2.2] p=0.9899		
Hippocampal volume left	-166.2 ± 64.0 (n=6)	-183.5 ± 117.4 (n=6)	-131.4 ± 98.0 (n=5)	-216.5 ± 133.2 (n=4)	-50.3 [-193.2; 92.6] p=0.4401	-33.0 [-216.9; 150.9] p=0.6899	-85.1 [-266.6; 96.4] p=0.3042		
Hippocampal volume right	-106.2 ± 112.7 (n=6)	-182.2 ± 179.0 (n=6)	-153.6 ± 226.0 (n=5)	-198.3 ± 30.5 (n=4)	-92.1 [-227.6; 43.4] p=0.1557	-16.1 [-228.6; 194.4] p=0.8373	-44.7 [-317.4; 228.1] p=0.6838		

Data are mean ± SD (patients analysed) for CSF and plasma biomarkers as well as MRI results and median [minimum, maximum] (patients analysed) for cognitive and functional scales.

Differences between treatment groups were assessed by using t-test (two-sided, $\alpha=0.05$) for CSF and plasma biomarkers as well as MRI results (displayed as difference between groups [95% confidence interval, p-value) and by calculating Hodges-Lehmann estimates and the corresponding non-parametric 95% confidence interval as well as by using Wilcoxon Rank Sum test (normal approximation, two-sided, $\alpha=0.05$) for the cognitive and functional scales (displayed as Hodges-Lehmann estimate [95% confidence interval] p-value).

* At visit 13 (last infusion at week 22 + 1 day) for 2-week interval and visit 7 (week 20 + 1 day) for 4-week interval

Table 7

Individuals in each group experiencing an adverse event

Symptom	IVIG (n=42)	Placebo (n=14)
Patients with at least one SAE [%]	4 [9.5]	4 [28.6]
Knee replacement surgery		1 [7.1]
Gastric antral vascular ectasia		1 [7.1]
Post surgery delirium and lumbar laminectomy	1 [2.4]	
Stroke/middle cerebral artery infarct	1 [2.4]	
Nausea and vomiting	1 [2.4]	
Acute aggression		1 [7.1]
Possible seizure		1 [7.1]
Progressively severe Alzheimer's disease	1 [2.4]	
Patients with at least one AE [%]	25 [59.5]	9 [64.3]
Microbleeds	6 [14.3]	
Dizziness		1 [7.1]
Headache	1 [2.4]	
Paraesthesia		1 [7.1]
Chills	1 [2.4]	
Influenza-like illness	1 [2.4]	
Hypoesthesia	1 [2.4]	
Tremor	1 [2.4]	
CSF white blood cell count increased		1 [7.1]
Muscle spasms	1 [2.4]	
Atrial fibrillation		1 [7.1]
Procedural hypertension	1 [2.4]	
Agitation		1 [7.1]
Actinickeratosis	1 [2.4]	
Hyperkeratosis	1 [2.4]	
Pruritus	1 [2.4]	
Headache	2 [4.8]	1 [7.1]
Hypoesthesia	1 [2.4]	
Blood pressure fluctuation	1 [2.4]	
Hypotension	1 [2.4]	1 [7.1]
AST increased	1 [2.4]	
LDH increased	1 [2.4]	
Hearing impaired	1 [2.4]	
Dyspepsia	1 [2.4]	
Post lumbar punctures syndrome	1 [2.4]	
Haematuria	1 [2.4]	
Infusion site extravasation	1 [2.4]	

Symptom	IVIG (n=42)	Placebo (n=14)
Fatigue	1 [2.4]	
Pyrexia	1 [2.4]	
Falls	1 [2.4]	