Safety and efficacy of plasma transfusion from exercise-trained donors in patients with early Alzheimer’s disease: protocol for the ExPlas study

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ABSTRACT
Introduction Given that exercise training reduces the risk of developing Alzheimer’s disease (AD), induces changes in the blood composition and has widespread systemic benefits, it is reasonable to hypothesise that exercised plasma (ExPlas) may have rejuvenative properties. The main objective is to test safety and tolerability of transfusing ExPlas from young, healthy, fit adults to patients with mild cognitive impairment (MCI) or early AD. The study is a pilot for a future efficacy study. The key secondary objectives are examining the effect of plasma transfusions on cognitive function, fitness level, vascular risk profile, assessment of cerebral blood flow and hippocampal volume, quality of life, functional connectivity assessed by resting state functional MRI and biomarkers in blood and cerebrospinal fluid.

Methods and analysis ExPlas is double-blinded, randomised controlled clinical single-centre trial. Patients up to 75 years of age with diagnosis early symptomatic phase AD will be recruited from two Norwegian hospitals. ExPlas is plasma drawn by plasmapheresis once a month for 4 months, from a total of 30 fit male donors (aged 18–40, BMI≤27 kg/m2 and maximal oxygen uptake>55 mL/kg/min). All units will be virus inactivated by the Intercept method in accordance with procedures at St. Olavs University Hospital. Comparison with isotonic saline allows differentiation from a non-blood product.

Ethics and dissemination Written informed consent will be obtained from all participants and participation is voluntary. All participants have a next of kin who will follow them throughout the study to represent the patient’s interest. The study is approved by the Regional Committee for Medical and Health Research Ethics (REK 2018/702) and the Norwegian Medicines Agency (EudraCT No. 2018-00148-24). The study will be published in an open access journal and results will be presented at numerous national and international meetings as well as on social media platforms.

Trial registration number EudraCT No. 2018-000148-24. ClinicalTrials.gov, NCT05068830

BACKGROUND
The forecast of about 2 billion people being above the age of 60 by the year 20501 implies an expected increased prevalence of...
Alzheimer’s disease (AD) from today’s 36 million to 108 million within the next three decades. New estimates from Norway show a higher prevalence of dementia and mild cognitive impairment (MCI) in both younger adults and in the elderly compared to previous calculations. Recent American data show that deaths from AD increased by 145% during the last two decades; while for comparison, deaths from heart disease decreased by 7.3%. During the COVID-19 pandemic, deaths from AD or other dementias have additionally increased by 16% from that expected based on previous years. As of 2021, there is no proven cure for AD and the WHO has stated that AD is a global crisis that requires a global solution. Without intervention, the expected rise in AD adds a major burden to public health and healthcare costs globally.

It is hypothesised that around 40–50% of dementia cases worldwide are caused by modifiable risk factors, and that many factors associated with higher risk of cardiovascular disease, such as obesity, hyperlipidaemia, hypertension, smoking, diabetes and physical inactivity are also associated with increased risk of AD. These factors have in common that they can be substantially modified through physical activity that secures above average age-specific and sex-specific levels of cardiorespiratory fitness (CRF) measured as peak or maximal oxygen uptake (PeakVO2 / VO2max). In line with this, we demonstrated in a prospective cohort study of 30 695 adults that participants who increased or sustained high PeakVO2 over time (10 years apart) had 40–50% reduced risk of incident dementia, 30–40% reduced risk of dementia-related mortality, approximately 2.0 years delayed dementia onset and 2–3 years of life gained when compared with persistently unfit individuals. Thus, at present exercise training leading to a high age-relative PeakVO2 may be the most promising preventive ‘AD-medicine’. Although it is well established that exercise positively influences brain neurogenesis, plasticity, and cognition, it is not well understood how these effects are mediated. The beneficial effects of exercise on the brain have traditionally been thought not to be mediated through systemic changes. However, a number of studies in both rodents and humans demonstrates direct effects on the brain of exercised blood: donor mice into sedentary, aged mice conferred beneficial effects of exercise on hippocampal neurogenesis and cognition. Given that exercise training reduces the risk of AD development, induces changes in the blood composition and has widespread systemic benefits, it is reasonable to hypothesise that exercised plasma may have rejuvenative properties similar to, or stronger than young blood. In this study, we aim to test the safety profile of transfusing exercised plasma from young, healthy adults in AD patients and perform a pilot test for potential therapeutic effects.

ENDPOINTS
The purpose of this study is to explore the safety of transfusion of plasma from exercise-trained donors (ExPlas) compared with Octaplasma, a commercially available virus inactivated plasma product pooled from approximately 1000 donors, and Sodium Chloride 0.9% (saline) in patients in the early symptomatic phase of AD and provide pilot data regarding efficacy. An additional aim is to provide advancements to the field by exploring therapeutic effects on AD of blood-borne factors.

Primary endpoint of ExPlas
Proportion of patients with adverse events after 1 year as a measure of safety and tolerability, and number of subjects who comply with the research protocol as a measure of feasibility.

Secondary endpoints of ExPlas after 1, 2 and 5 years
- Change in performance in the CERAD (The Consortium to Establish a Registry for Alzheimer’s Disease) 10 word Test
- Change in the Mini-Mental State Examination (MMSE) score
- Change in performance in Trail-Making test A and B
- Change in scores in other cognitive tests: the Clock Drawing Test, Controlled Oral Word Association Test (COWAT)-FAS, Visual Object and Space Perception (VOSP) Silhouettes
- Change in Clinical Dementia Rating Scale Global score and Sum of Boxes, and The Lawton Instrumental Activities of Daily Living Scale (IADL)
- Change in performance in the 6 minute walk-test
- Change in / reduced hippocampal atrophy and preservation of functional connectivity assessed by resting state functional MRI
- Change in score of quality-of-Life SF-36 Questionnaire
- Change in biomarkers in blood and cerebrospinal fluid (CSF)
- Change in cardiac dimensions, volumes and functional indices
Hypothesis, primary outcome
(I) ExPlas transfusions to patients in early symptomatic phase of AD is safe.

Hypotheses secondary outcome
(II) ExPlas transfusions to patients in early symptomatic phase of AD ameliorates the biomarker-profile in blood and CSF, structural MRI and functional MRI, cognitive function, functional capacity, fitness and quality of life.

METHODS
Design
The study is a double-blinded, randomised controlled clinical phase II trial recruiting from two Norwegian hospitals to a single study site at St. Olav's University Hospital in Trondheim, Norway. The first patient was enrolled and randomised on September 15th, 2021. The anticipated recruitment period is 36 months and the estimated date of last patient enrolled is September 1st, 2024. The treatment duration is 1 year, and the follow-up period is 61 months, including screening. There are three study arms with patient ratio 1:1:1 (ExPlas, Octa-plasma, saline), stratified by APOE genotype. Electronic randomisation, provided by the Unit for Applied Clinical Research at Norwegian University of Science and Technology (NTNU), ensures that allocation of patients to a treatment group is random. Electronic randomisation is conducted by the blinded ExPlas study nurse. The results of the randomisation are not visible to any member of the study team. An automated message on each patient allocation is sent directly to the study nurses who undertake transfusions. The flow chart of the ExPlas study is given in figure 1.

Figure 1 Flow chart of the ExPlas study. Infusion solution, Sodium Chloride 0.9% (Saline); fMRI, functional MRI; US, ultrasound of the heart.
oxygen uptake, as described in detail elsewhere, using the Zepp mobile Application downloaded from Apple Store or Google Play.

**Donor inclusion criteria**
- Healthy male donors
- Age 18–40 years
- BMI ≤27 kg/m²
- Maximal oxygen uptake ($V_{O2 \text{MAX}}$) ≤55 mL/kg/min
- Already an approved donor at the St. Olav’s University Hospital Blood Bank

**Donor exclusion criteria**
- Injury or other incident preventing regular exercise during the last month
- Previous recipient of blood transfusion
- $V_{O2 \text{MAX}}$ ≤55 mL/kg/min

Several aspects regarding donors were considered in the planning of the study. Particularly age and required fitness level have been up for thorough discussions. Our idea is that we believe, although not ever studied, that ‘exercised plasma’ may confer additional benefit to the brain compared with young plasma only. Thus, the point of departure was that we wanted the donors to have a fitness level (maximal oxygen uptake) that is regarded as ‘fit’, and not be ‘classified’ as old. We regard 40 years of age to be a relatively young age, and we, therefore, chose to require donors to be below the age of 40 and have a maximal oxygen uptake above 55 mL/kg/min, which is above the average for a 20-year-old man in Norway.

**Settings and participants - patients**
Patients are recruited from the Department of Neurology or Geriatrics out-patient clinics at St. Olav’s University Hospital, and from the Department of Geriatric psychiatry, Levanger Hospital, both Norway. The diagnostic work-up of the patient will decide if the patient is eligible for inclusion. Eligible patients who sign informed consent to join the study go through a further screening and are evaluated regarding the defined inclusion and exclusion criteria.

**Patient inclusion criteria**
- Signed informed consent
- Age up to 75 years
- Diagnosis AD in early phase according to the IWG-2 criteria
- Decreased Aβ42 together with increased t-tau or p-tau in CSF
- Increased tracer retention on amyloid Positron Emission Tomography (PET)
- MMSE Score ≥20
- Ability to communicate in Norwegian or another Scandinavian language

**Patient exclusion criteria**
Patients will be excluded from the study if they meet any of the following criteria:
- Pregnancy or unwilling to use adequate birth control for the duration of and 6 months beyond study participation Defined according to Clinical Trial Facilitation Group document ‘Recommendations related to contraception and pregnancy testing in clinical trials’
- Positive for Hepatitis B, Hepatitis C or HIV at screening
- Lack of competency to provide informed consent at inclusion
- Any other condition judged to interfere with the safety of the patient or the intent and conduct of the study

**Related to medical history**
- Stroke
- Anaphylaxis
- Prior adverse reaction to any human blood product
- Any history of a blood coagulation disorder or hypercoagulability
- Congestive heart failure, defined as any previous heart failure hospitalisation, or current symptomatic heart failure in New York heart association class ≥II with reduced, mid-range or preserved ejection fraction.
- Coagulation defect or hypercoagulopathy
- Uncontrolled hypertension
- Renal failure
- Prior intolerance to intravenous fluids
- Recent history of uncontrolled atrial fibrillation
- Bone marrow transplant
- IgA deficiency
- Severe protein S deficiency
- Thrombocytopenia (platelets <40 x 10⁹ /L)
- Contraindication for Octaplasma

**Related to medications or other treatments**
- Any concurrent use of anticoagulant therapy, clopidogrel or acetylsaliclyc acid/dipyridamole in combination
- Initiation or change in the dosage of a acetylcholine esterase inhibitor (AChEI) or memantine during the trial (weeks 0–52). Participants will be urged to start on AChEI when diagnosis is communicated, and must be on a stable dose for at least 1 month prior to screening
- Concurrent participation in another treatment trial for AD. If there was prior participation, the last dose of the investigational agent must have been given at least 6 months prior to screening, except if the patient received placebo medication
- Prior or concurrent participation in amyloid antibody trials, except if the patient received placebo medication
Treatment with any human blood product, including intravenous immunoglobulin, during the 6 months prior to screening or during the trial

Concurrent daily treatment with benzodiazepines, typical or atypical antipsychotics, long-acting opioids or other medications that are judged to interfere with cognition. Intermittent treatment with short-acting benzodiazepines or atypical antipsychotics may be permitted, provided that no dose is administered within 72 hours prior to cognitive assessment.

Cognitive test battery

All tests will be undertaken at baseline, weeks 24, 52 and 104 after inclusion, and performance at all time points will be evaluated against baseline values.

- **Mini-Mental State Examination Score (MMSE-NR-3)** will be used as a screening tool for cognitive function. The test consists of standardised questions within five areas: orientation for time and place, short-term memory, attention, short-term recall and language. The test may help to evaluate degree of cognitive impairment. The maximum score is 30.

- **Trail-Making test A and B (TMT-NR3)** will be used to measure visual attention, processing speed and executive function.

- **Clock Drawing Test** is a cognitive screening tool and will be used as a supplement for examining visuospatial function and executive function.

- **The Controlled Oral Word Association Test (COWAT)-FAS** will be used to measure verbal fluency and executive function.

- **Visual Object and Space Perception Battery (VOSP)** Visuospatial abilities will be evaluated with the silhouettes test from the VOSP. The test also assesses semantic memory and name retrieval.

- **Clinical Dementia Rating Scale (CDR)** is a clinical scale for the staging of dementia. The participant is rated from 0 to 3 on six cognitive and behavioural categories: memory, orientation, judgement and problem solving, community affairs, home and hobbies and personal care. The Global score is calculated according to an established algorithm, where memory is considered the primary category and all others are secondary categories. A global score of 0 equals no dementia, 0.5 questionable dementia, 1 mild dementia, 2 moderate dementia and 3 severe dementia. The Sum of Boxes score is a continuous measure of dementia severity and ranges from 0 to 18. The CDR Sum of Boxes is found to be adequate for use in prodromal AD and continued use is warranted and recommended in clinical trials because it is continuous and provides a greater variation in values. Both the CDR-Global score and Sum of Boxes will be calculated.

- **The Lawton Instrumental Activities of Daily Living Scale (IADL)**. This IADL scale evaluates eight items, related to complex everyday activities, and each can be scored 0 that equals ‘dependent’ and one that reflect ‘completely independent’. Change from 0 to 1 in any of the eight items is considered a ‘clinically relevant change’.

- **Unified Parkinson’s Disease Rating Scale (UPDRS)** The motor examination part of UPDRS will be used to detect development of parkinsonian motor signs, such as tremor, rigidity, bradykinesia and postural-gait abnormalities.

- **The 6-minute walk test** Fitness level will be measured using the 6-minute walk-test which is a good alternative to direct measurement of VO2max. The 6-minute walk test is considered safer for the current patient group than a treadmill test.
Quality of life will be evaluated by the questionnaire SF-36, which contains questions about physical and mental health, pain, vitality and general health perceptions.59 60

Structural MRI and functional MRI
For increased sensitivity, we will use multiparametric MRI at 7T MRI to assess brain structure and function to uncover both neurodegenerative and cerebrovascular changes from baseline to 1, 2 and 5 years. The 7T protocol consists of the following scans: whole brain 3D MP2RAGE, gradient echo SWI/quantitative susceptibility mapping and FLAIR, high resolution T2-weighted spin echo sequence of the medial temporal lobe, multishell DTI, asl FLAIR and rs-fMRI. The primary outcomes are hippocampal and entorhinal cortex structure ((subfield)-volume/thickness, diffusion characteristics, T2*-mapping) and function (blood flow, connectivity and BOLD signal). Other quantitative measures include brain morphometry (e.g., parenchymal fraction, at-risk AD pattern volume loss), and diffusion metrics in white and grey matter. Cerebrovascular pathology (perfusion, white matter hyperintensities, perivascular spaces (quantitative from multishell DTI), microhaemorrhages, microinfarction and hyperintensities, perivascular spaces (quantitative from multishell DTI), microhaemorrhages, microinfarction and macroinfarction) will be evaluated. For participants where 7T is contraindicated, but not 3T, a similar examination will take place using 3T.

A secondary aim is to identify any effect of treatment on MRI markers of both neurodegenerative and cerebrovascular disease. MRI at 7T allows for a stronger signal and better anatomical localisation in less time, but with the stronger magnetic field, there are also more contraindications.

Quality of life
Quality of life will be evaluated by the questionnaire SF-36, which contains questions about physical and mental health, pain, vitality and general health perceptions.59 60

Echocardiography
All patients will undergo echocardiography examination at screening and four times during the first year, and potentially at the 2 and 5 years follow-up. Screening echo is performed to ensure safety of transfusions for patients included in the study. Patients with reduced cardiac function will be excluded due to risk of developing heart failure triggered by fluid overload. Screening echocardiography serve as baseline for included patients. Following echocardiography will be performed at week 5 (1 week after the first 4-week transfusion treatment period), week 20 (before the second treatment period), week 48 (before the third treatment period), week 52 (1 week after the final 4-week transfusion treatment period) and assumedly at 2 and 3 years follow-up. The echocardiography examination will be a complete examination of cardiac structure and function, including ultrahigh frame-rate recordings at each time point.

Biomarkers in blood and spinal fluid
Although no single ideal biomarker yet exists for AD, there are substances currently considered to be ‘core’ biomarkers for AD. According to a landmark paper published in 2017 from the joint proceedings of the International Working Group (IWG) and the American Alzheimer’s Association, the most important early indicators of incipient AD are changes in two key proteins: reduced amyloid-beta 1-42 (Aβ42) and increased total tau protein and hyperphosphorylated tau measured biochemically in CSF, or increased deposition of amyloid plaque and neurofibrillary tangles of tau protein in the brain as shown by PET.61 62 Since PET is very expensive, we plan to analyse these substances in CSF. Collected CSF and blood will be analysed for established AD risk markers (including APOE genotyping in blood and Amyloid Beta 1–42, Amyloid Beta 1–40, phosphor tau and total tau in CSF). Individuals apparently without clinical symptoms of cognitive decline but with pathological levels of both these biomarkers are considered to have ‘preclinical AD’. If only one of the biomarkers is found to have a pathological level, the individual is considered to be ‘at risk of AD’ (the difference being that the individual is only at risk of AD, whereas preclinical AD is considered to be an early manifestation of the disease itself). In order to better understand the potential link between the cardiovascular system and the brain, the collected blood will also be analysed with respect to cardiovascular profile (Albumin, Ferritin, Sodium, Potassium, Creatinine, Glucose, ALT, GGT, Cholesterol, Triglycerides, HDL, Hs-CRP, NT-proBNP, Troponin, Leukocyte, Trombo-cyte, Hemoglobin and HbA1c). Some of the biological material will be stored for future analysis in the search for new biomarkers. For instance, the study team has previously identified potential ‘fitness-microRNAs’ that could distinguish high-fitness and low-fitness individuals.63 In the ExPlas study, we aim (as a start) to detect microRNAs that show a significant change in expression concomitant with ExPlas treatment and examine changes in level in relation to speed of AD progression. Unbiased screenings of microRNAs will be performed at the NTNU Genomics Core Facility and analysed together with the NTNU Bioinformatics Core Facility. Identification of other circulating factors will be performed by gel-free shotgun proteomics analysis. Proteomic RNA analyses will be performed at the NTNU Proteomics and Modomics Experimental Core Facility and analysed together with the NTNU Bioinformatics Core Facility.

Blood sampling procedures
All blood samples will be taken by trained biomedical engineers or nurses. Serum and plasma samples are collected by venous puncture using sterile disposable equipment in serum-gel, EDTA plasma and lithium heparine tubes. The tubes are centrifuged and stored on ice while shipped for further handling and analysis. Those not analysed right away will be be stored at −80°C (in the established Trønderbrain biobank, contact: Geir Brathen, geir.brathen@ntnu.no). Blood tests will be taken on seven occasions in addition to screening and after 2 years as well as offered 5 years after baseline (figure 1).

Spinal puncture procedures
Lumbar puncture will be performed by a neurologist. A thin needle is inserted into the spinal canal in the lowerback, while the patient is lying down on the side. The procedure is performed using sterile technique (the area is cleaned with chlorhexidine and air dried before inserting the needle). The sample is collected directly into polypropylene
tubes (used for dementia markers), and stored on ice until shipped to further handling. The samples are to be stored at −80°C (Trønderbrain biobank, Geir Bråthen) until analysis. The sample will be analysed for risk genes and AD-related biomarkers. Some portion of the sample will be stored for future analysis. Spinal puncture will be performed at baseline, week 24, week 52, after 2 years and offered 5 years after baseline (figure 1). All sample collection, handling and analysis will be performed in accordance with hospital/laboratory standard procedures.

Sample size and statistics

We do not expect that ExPlas will cause more adverse effects than Octaplasma, but have made the following considerations about power calculations related to safety. The most common reaction to transfusion of Octaplasma is allergy and occurs in up to 1% of the elderly. If we consider that ExPlas would cause a dramatic increase in allergic reactions, of for example, 35% versus 1% after Octaplasma treatment, 19 participants will be needed in each group to show significant differences (with alpha 0.05 and power of 0.8). There are substantial uncertainties in the assumptions for this power calculation. However, considering that another study found that transfusing plasma from young donors to patients (n=18) with MCI or early AD was safe with no adverse events,39 we find it likely that 20 patients in each group will be enough to test safety in ExPlas.

The magnitude of a possible treatment effect of ExPlas is currently not established. The following information has been established: (i) a difference of 2 points on the MMSE score primarily between those receiving ExPlas versus Octaplasma will be clinically relevant after 1 and 2 years; (ii) based on several clinical studies in this population, we expect an average MMSE-NR-3 of about 24 in our population, (iii) based on previous studies, we expect a SD of MMSE-NR-3 score of approximately 3. These assumptions suggest that 17 participants are needed in each group (with alpha 0.05, and power 0.8) to demonstrate a clinically relevant effect of ExPlas. Given potential dropouts, it is reasonable to include 20 in each group. The plan is therefore to include 60 patients in the study.

For the primary endpoints, counts will be reported and compared using recommended methods for analysis of contingency tables.57 Secondary and other endpoints will be analysed using mixed models with the outcome variable as the dependent variable, treatment group, time and their interaction as categorical covariates, and patient as random effect. In these analyses, we will adjust for the baseline value of the outcome variable, as recommended.64 65

Ethics

The study will be performed according to the Declaration of Helsinki. Written informed consent will be obtained from all participants by the treating neurologist, and participation is voluntary. Patients will be insured according to Norwegian regulations for patients involved in medical research (npe.no). The patients’ abilities to keep track of the objectives of the project and assess its relevance will progressively deteriorate during the project period. In view of this, all participants are required to include a next of kin who will follow them throughout the study and represent the patient’s interest. The burden from participation, number of tests and time points of conducting tests during the study have been planned in dialogue with the user board consisting of three next of kin of current and previous AD-patients. The study is approved by the Regional Committee for Medical and Health Research Ethics (REK 2018/702) and the Norwegian Medicines Agency (Statens Legemiddelverk, EudraCT No. 2018-000148-24).

Organisation

The steering committee of ExPlas has developed the study protocol and is responsible for overall study management, data collection, analyses, publications and the final data set.

A safety committee consisting of two clinicians (one neurologist and one specialist in transfusion medicine) has been appointed to ensure the safety of study participants. In case of adverse events, the safety committee will evaluate whether treatments can continue or must be stopped. A study nurse will observe the patients during and for 1 hour after infusion and a physician will evaluate the patients in case of adverse effects. Neither the safety committee nor the attending physician responsible for each infusion are involved in other parts of the study and they are not be blinded for the treatment given.

Study monitors

The primary goal of the study monitors is to ensure that the site follows the standardised operation procedures described for the trial, and to report and manage any deviations that may occur from the investigational plan. The ExPlas study has been appointed two study monitors by the Unit for Applied Clinical research at NTNU, one who has the overall overview of the study, and is blinded to the treatment randomisation, and one who is unblinded. A study monitoring plan has been developed and includes regular visits by the Clinical Study Monitors, who will check the following:

- Informed consent process
- Reporting of adverse events and all other safety data
- Adherence to protocol
- Maintenance of required regulatory documents
- Study supply accountability
- Facilities and equipments (treatment storage and manufacturing at the Blood Bank)
- Data completion on the CRFs including source data verification

The monitor will review the relevant CRFs for accuracy and completeness and will ask the site staff to adjust any discrepancies as required. Sponsor’s representatives (eg, monitors, auditors) and/or competent authorities will be allowed access to source data for SDV in which case a review of those parts of the hospital records relevant to the study will be required.
Data management

The Clinical Data Management System (CDMS) used for the electronic case report forms (eCRF) in this study is The Unit for Applied Clinical Research at NTNU. The setup of the study specific eCRF in the CDMS will be performed by The Unit for Applied Clinical Research at NTNU. The eCRF system will be FDA Code of Federal Regulations 21 Part 11 compliant. The designated investigator staff will enter the data required by the protocol into the eCRF. The Investigator is responsible for ensuring that data entered into the eCRF is complete, accurate and that entry is performed in a timely manner. The signature of the investigator will attest the accuracy of the data on each eCRF. If any assessments are omitted, the reason for such omissions will be noted on the eCRFs. Corrections, with the reason for the corrections will also be recorded. After database lock, the investigator will receive a digital copy of the subject data for archiving at the institutional site.

The medical records of each patient will clearly describe at least:
- Date when Informed Consent was obtained from the patient and a statement that the patient received a copy of the signed and dated Informed Consent
- Results of all assessments confirming a patient’s eligibility for the study
- Diseases (past and current; both the disease studied and others, as relevant)
- Surgical history, as relevant
- Treatments withdrawn/withheld due to participation in the study
- Results of assessments performed during the study
- Treatments given, changes in treatments during the study and the time points for the changes
- Visits to the clinic/telephone contacts during the study, including those for study purposes only
- Non-Serious Adverse Events and Serious Adverse Events (if any) including causality assessments
- Date of, and reason for, discontinuation from study treatment
- Date of, and reason for, withdrawal from study
- Date of death and cause of death, if available
- Additional information according to local regulations and practice
- That the patient is participating in the study, by including the enrollment number and the study code or other study identification

Data management will be performed by the Unit for Applied Clinical Research at NTNU (Berit Bjelkåsen). The Data management procedures will be performed in accordance with the department's Standard Operating Procedures and ICH (The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) guidelines. The data management process will be described in the study-specific data handling plan and the study-specific data handling report after database closure. Data entered into the eCRF will be validated as defined in the data validation plan. Validation includes, but is not limited to, validity checks (eg, range checks), consistency checks and customised checks (logical checks between variables to ensure that study data are accurately reported) for eCRF data and external data (eg, laboratory data). A majority of edit checks will be triggered during data entry and will therefore facilitate efficient ‘point of entry’ data cleaning. Data management personnel will perform both manual eCRF review and review of additional electronic edit checks to ensure that the data are complete, consistent and reasonable. The electronic edit checks will run continually throughout the course of the study and the issues will be reviewed manually online to determine what action needs to be taken. Manual queries may be added to the system by clinical data management or study monitor. Clinical data managers and study monitors are able to remotely and proactively monitor the patient eCRFs to improve data quality. All updates to queried data will be made by authorised study centre personnel only and all modifications to the database will be recorded in an audit trail. Once the queries have been resolved, eCRFs will be signed by electronic signature. Any changes to signed eCRFs will be approved and resigned by the Investigator. Once the full set of eCRFs have been completed and locked, the Sponsor will authorise database lock and all electronic data will be sent to the designated statistician for analysis. Subsequent changes to the database will then be made only by written agreement. The data will be stored in a dedicated and secured area at NTNU. Data will be stored in a deidentified manner, where each study participant is recognisable by his/her unique trial subject number. The data will be stored until 15 years after database lock.

Patients and public involvement

To ensure a high study quality and relevance, a user board consisting of three next kin of present and past AD patients has been established. As we conduct research on a patient group that is considered vulnerable, this board is particularly important. We have met the user group on several occasions while working on the study protocol (first meeting in February 2017) and have received input on several matters, such as how to ensure a tolerable load of participation for the individual patient/relatives. The study team will continue to consult the user board twice annually throughout the study period, on implementation, results and future developments. They are encouraged to give their opinions regarding the project as a whole and particularly on the patients’ well-being. The study group has already made changes and adjustments in the planned protocols based on feedback from the user board. The study has a user representative who participates in meetings and presentations of the study to the general public. On initiative from the ExPlas user board, we are currently making three information videos about ‘AD and participation in research studies’, for AD patients and their families, where patients and their next of kin tell their story to help new patients and their next of kin in the coming process. These videos will also be used in
the recruitment phase of the study to inform and motivate to take part in ExPlas.

Dissemination

Direct communication with users and patient organisations: ExPlas study group regularly present at various meetings of patient organisations (such as the National Association for Public Health) and for senior citizens’ societies. We plan to intensify participation in such meetings to inform about current knowledge about prevention and treatment of AD, particularly via the established user board. Communication via Internet: one of the most important media for spreading the news and awareness will be the Internet. The results and information (including videos) about the studies will be presented on CERG’s webpage (ntnu.edu/cerg), one of the most visited sites at Scandinavian universities; and ExPlas’s own Norwegian webpage (ntnu.no/cerg/explas). Scientific and non-scientific communication: general communication activities include publication in open access peer-reviewed journals, non-scientific journals and at national and international meetings, to reach the general public, patients, scientists and policy makers. Importantly, our group is closely linked and active partners in the Norwegian Research School in Neuroscience, Physical Activity and Health (master programme) and medical education where we actively will present our research to the next generation of healthcare personnel and scientists. We also have a journalist at CERG (Anders Revdal), available for ExPlas, who will be responsible for communication.

DISCUSSION

To the best of our knowledge, ExPlas will be the first study with the aim of studying safety and efficacy of transfusion of plasma from well-endurance trained donors to patients in the early symptomatic phase of AD. Even if prevention probably will be the most effective way to reduce the number of patients with AD worldwide, a cure for this devastating disease which impacts the lives of patients, their families and the society as a whole is much needed. There is also a need to understand the mechanisms behind the beneficial effects of physical exercise on the brain, and so trying to exploit this effect in treatment of early phase AD is a logical move.

On June 7th, 2021, the US Food and Drug Administration approved aducanumab (marketed as Aduhelm) for use in treatment of AD due to its ability to reduce amyloid plaques in the brain, under an accelerated approval pathway. Confirmation of the clinical benefit is still required for it to be confirmed for continued approval. Independent of the usefulness of aducanumab in AD therapies, other interventions capable of delaying the clinical onset of AD dementia should be studied continuously. The findings from preclinical AD models, and a small clinical trial clearly indicate that there is communication between the systemic environment and the hippocampus. Systemic factors are capable of inducing changes, and even yield therapeutic effects, in the brain without hindrance by the blood-brain barrier; potentially an effective strategy to reverse neurodegeneration in the AD-brain. There are myriads of factors and processes that are set in motion during and after exercise training, and much of this is reflected in the composition of the blood. Thus, it is not likely that it is a single factor orchestrating the beneficial effects of exercise, but rather an interplay between several molecular factors that need to be discovered and understood to allow for development of first-generation exercise-mimicking drugs. This is a promising idea as a large population of patients are simply unable to exercise, such as patients in the intensive care unit, the critically ill, patients recovering from accidents, the morbidly obese and paralysed patients. For these patients, innovative exercise-mimicking therapies could be of benefit.

However, development of exercise-mimicking therapies is a very complex and time-consuming undertaking, that should not delay the testing of a potential benefit of exercise-trained plasma, with most of its natural components, on safety and therapeutic effect in patients with AD. In the context of lack of disease-modifying treatments, ExPlas is innovative and potentially groundbreaking if it is found to be safe with few side effects and with similar promising results as seen in preclinical AD models.

Another key question is at what stage of AD interventions such as ExPlas treatment can be expected to have an effect. Today we know that AD-related changes in the brain are present 10–30 years before clinical symptoms. The optimal time window for treatment is probably as early as possible during this period, to decelerate or stop the progressive loss of neurons before functions are lost. As in all diseases, prevention will always be the optimal path. Depending on the outcomes in the ExPlas study, a natural next step may be treatment with ExPlas of patients in the preclinical phase of the disease.

A small clinical trial found that plasma from young donors (young blood) transfused to patients with mild to moderate AD dementia (MMSE score ranging from 12 to 24) was safe with no adverse events and possibly beneficial with improvement in functional activity. In this study, 9 patients were randomised to a cross-over cohort, receiving four once-weekly infusions of either 250 mL of plasma from male donors (aged 18–30 years) or 250 mL of saline, followed by a 6-week washout and crossover to four once-weekly infusions of the alternate treatment. In addition, 9 patients were included in an open-label design in which patients received four once-weekly infusions of only young plasma. Considering the low number of patients, short follow-up period and promising findings in the study by Sha et al., there is reason to believe that transfusion of exercise-trained plasma also is safe. With increased treatment periods and extended follow-up, we believe that the ExPlas study is well designed also to evaluate the potential therapeutic effect of exercise-trained plasma. The relatively large number of patients will also likely enable us to assess whether endpoints become differentially affected by APOE4 status. As the ExPlas study is the first of its kind, it is not straightforward to undertake power calculations, and the results of our study may be useful for planning an appropriately sample sized study in the future.
We expect the ExPlas study to give new knowledge about whether transfusion of plasma from exercise-trained donors is safe and indications on whether it has therapeudic effects. ExPlas will also contribute to pioneering the discovery of molecular targets to potentially treat AD and lay the foundation for first-generation exercise-mimicking drugs, by capturing the molecular signature of high-fitnes and molecular mechanisms provided by exercise.

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REFERENCES
1 World Health Organization. Aging and life course, 2015. Available: http://www.who.int/ageing/en/
2 Alzheimer’s Disease Facts and Figures [Report], 2018[updated 2018. 5.8]. Available from:. Available: http://www.alz.org.
3 Andrieu S, Coley N, Lovestone S, et al. Prevention of sporadic Alzheimer’s disease: lessons learned from clinical trials and future directions. Lancet Neurol 2015;14:926–44.
4 d’H. Demensplan, 2025.
5 Giøra L, Strand BH, Bergh S, et al. Current and future prevalence estimates of mild cognitive impairment, dementia, and its subtypes in a population-based sample of people 70 years and older in Norway: the HUNT study. J Alzheimers Dis 2021;79:1213–26.
6 Kvello-Alme M, Bråthen G, White LR, et al. The prevalence and subtypes of young onset dementia in central Norway: a population-based study. J Alzheimers Dis 2019;69:479–87.
7 Association As. Alzheimer’s Disease Facts and Figures. 2021, 2021.
8 Potter PE. Investigational medications for treatment of patients with Alzheimer disease. J Am Osteopathic Assoc 2010;110:S27–36.
9 Mullan K, Williams M. Alzheimer’s therapeutics: continued clinical failures question the validity of the amyloid hypothesis—but what lies beyond? Biochem Pharmacol 2013;85:289–305.
10 Cummings JL, Morstorf T, Zhong K. Alzheimer’s disease drug-development pipeline: few candidates, frequent failures. Alzheimers Res Ther 2014;6:37.
11 Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet 2020;396:413–46.
12 Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer’s disease prevalence. Lancet Neurol 2011;10:819–28.
13 Colcombe SJ, Erickson KI, Raz N, et al. Aerobic fitness reduces brain tissue loss in aging humans. J Gerontol A Biol Sci Med Sci 2003;58:176–80.
14 de Brujin RFAG, Ikram MA. Cardiovascular risk factors and future risk of Alzheimer’s disease. BMC Med 2014;12:130.
15 Levine DA, Langa KM. Vascular cognitive impairment: disease mechanisms and therapeutic implications. Neurotherapeutics 2011;8:361–73.
16 Rovio S, Kääriäinen H, Heikka E-L, et al. Leisure-Time physical activity at midlife and the risk of dementia and Alzheimer’s disease. Lancet Neurol 2005;4:705–11.
Tari AR, et al. BMJ Open 2022;12:e056964. doi:10.1136/bmjopen-2021-056964

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17 Qiou C, Xu W, Fratigioni L. Vascular and psychosocial factors in Alzheimer’s disease: epidemiological evidence toward intervention. J Alzheimers Dis 2010;20:689–97.
18 Qiou C. Preventing Alzheimer’s disease by targeting vascular risk factors: hope and gap. J Alzheimers Dis 2012;32:721–31.
19 Exalto LG, Quesenberry CP, Barnes D, et al. Midlife risk score for the prediction of dementia four decades later. Alzheimers Dement 2014;10:562–70.
20 Tolppanen A-M, Solomon A, Soininen H, et al. Midlife vascular risk factors and Alzheimer’s disease: evidence from epidemiological studies. J Alzheimers Dis 2012;32:531–40.
21 Norton S, Matthews FE, Barnes DE, et al. Potential for primary prevention of Alzheimer’s disease: an analysis of population-based data. Lancet Neurol 2014;13:789–94.
22 Kaminsky LA, Abu-Rustum S, Beckie TM, et al. The importance of cardiorespiratory fitness in the United States: the need for a national registry: a policy statement from the American heart association. Circulation 2013;127:652–62.
23 Larson EB, Wang L, Bowen JD, et al. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Ann Intern Med 2006;144:73–81.
24 Tari AR, Nauman J, Zisko N, et al. Temporal changes in cardiorespiratory fitness and risk of dementia incidence and mortality; a prospective cohort study. Lancet Public Health 2019;4:e656–74.
25 Hoffmann K, Frederiksen KS, Sobol NA, et al. Preserving cognition, quality of life, physical health and functional ability in Alzheimer’s disease: the effect of physical exercise (ADEX trial): rationale and design. Neuroepidemiology 2013;41:199–207.
26 Lautenschlager NT, Cox KL, Flicker L, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. JAMA 2008;300:1027–37.
27 van Praag H, Shubert T, Zhao C, et al. Exercise enhances learning and hippocampal neurogenesis in aged mice. J Neurosci 2005;25:9680–5.
28 van Praag H, Christie BR, Sejnowski TJ, et al. Running enhances neurogenesis, learning, and long-term potentiation in mice. Proc Natl Acad Sci U S A 1999;96:13427–31.
29 Maass A, Abu-Rustum S, Beckie TM, et al. Vascular hippocampal plasticity after aerobic exercise in older adults. Mol Psychiatry 2015;20:585–93.
30 Bouchard J, Villeda SA. Aging and brain rejuvenation as systemic events. J Neurochem 2015;132:5–19.
31 Pereira AC, Huddleston DE, Brickman AM, et al. An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. Proc Natl Acad Sci U S A 2007;104:5638–43.
32 Fabel K, Fabel K, Tam B, et al. VEGF is necessary for exercise-induced hippocampal neurogenesis. Eur J Neurosci 2003;18:2803–12.
33 Castellano JM, Mosher KI, Abbey RJ, et al. Human umbilical cord plasma proteins revitalize hippocampal function in aged mice. Nature 2017;544:488–92.
34 Tari AR, Norevik CS, Scrimgeour NR, et al. Are the neuroprotective effects of exercise training systemically mediated? Prog Cardiovasc Dis 2019;62:94–101.
35 Villeda SA, Plambeck KE, Middeldorp J, et al. Young blood reverses age-related impairments in cognitive function and synaptic plasticity in mice. Nat Med 2014;20:659–63.
36 Katsimpari L, Litterman NK, Schein PA, et al. Vascular and neurogenic rejuvenation of the aging mouse brain by young systemic factors. Science 2014;344:630–4.
37 Xia E, Xu F, Hu C, et al. Young blood rescues the cognition of Alzheimer’s model mice by restoring the hippocampal cholinergic circuit. Neuroscience 2019;417:57–69.
38 Zhao Y, Qian R, Zhang J, et al. Young blood plasma reduces Alzheimer’s disease-like brain pathologies and ameliorates cognitive impairment in 3x-Tg-AD mice. Alzheimers Res Ther 2020;12:70.
39 Sha SJ, Deutsch GK, Tian L. Safety, tolerability, and feasibility of young plasma infusion in the plasma for Alzheimer symptom amelioration study; a randomized clinical trial. JAMA Neurol 2018.
40 Horowitz AM, Fan X, Bieri G, et al. Blood factors transfer beneficial effects of exercise on neurogenesis and cognition to the aged brain. Science 2020;369:167–73.
41 Aspenske ST, Nilsen TL, Skaug E-A, et al. Peak oxygen uptake and cardiovascular risk factors in 4631 healthy women and men. Med Sci Sports Exerc 2011;43:1465–73.
42 Nauman J, Nee BM, Zisko N, et al. Personal activity intelligence (PAI): a new standard in activity tracking for obtaining a healthy cardiorespiratory fitness level and low cardiovascular risk. Prog Cardiovasc Dis 2019;62:179–85.
43 Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer’s disease: the IWG-2 criteria. Lancet Neurol 2014;13:614–29.
44 Morris JC, Heyman A, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer’s Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer’s disease. Neurology 1989;39:1159–65.
45 Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.
46 McDougall F, Edgar C, Mertes M, et al. Psychometric Properties of the Clinical Dementia Rating - Sum of Boxes and Other Cognitive and Functional Outcomes: A Prospective Study. J Prev Alzheimers Dis 2021;8:151–60.
47 Reitan RM. Validity of the TRAIL making test as an indication of organic brain damage. Perceptual and motor skills 1958;8:271–6.
48 Espenes J, Hessen E, Ellansen ET, et al. Demographically adjusted TRAIL making test norms in a Scandinavian sample from 41 to 84 years. Clin Neuropsychol 2020;34:110–26.
49 Brodaty H, Moore CM. The clock drawing test for dementia of the Alzheimer’s type: a comparison of three scoring methods in a memory disorders clinic. Int J Geriatr Psychiatry 1997;12:519–27.
50 Nutter-Upham KE, Saykin AJ, Rabin LA, et al. Verbal fluency performance in amnestic MCI and older adults with cognitive complaints. Arch Clin Neuropsychol 2008;23:229–41.
51 Patterson C, report WA. Alzheimer’s Disease International. 2018, 2018.
52 Elizabeth K, Warrington MJ. Visual object and space perception battery (VOSP), 1991.
53 Linetti T. Disorders of visual and spatial perception in the early stage of Alzheimers disease. 1996.
54 Hughes CP, Berg L, Danzinger WL, et al. A new clinical scale for the staging of dementia. Br J Psychiatry 1982;140:566–72.
55 O’Bryant SE, Humphreys JD, Smith GE, et al. Detecting dementia with the Mini-Mental State examination in highly educated individuals. Arch Neurol 2008;65:982–7.
56 Lahvis MP, Brody EM. The use of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969;9:179–86.
57 Fagerland M, Lydersen S, Laake P. Statistical analysis of contingency tables. Chapman and Hall/CRC 2017.
58 Reid JS, Ecclemtch JL, Nof L, et al. Test-retest reliability and minimal detectable change scores for the timed “up & go” test, the six-minute walk test, and gait speed in people with Alzheimer disease. Phys Ther 2009;89:569–79.
59 Geschke K, Fellgiebel A, Laux N, et al. Quality of life in dementia: impact of core measures and test of the minimal level of evidence for the SF-36. Am J Geriatr Psychiatry 2013;21:644–54.
60 Ware JE, Sherbourne CD. The mos 36-item short-form health survey (SF-36). I. conceptual framework and item selection. Med Care 1992;30:473–83.
61 Dubois B, Hampel H, Feldman HH, et al. Preclinical Alzheimer’s disease: definition, natural history, and diagnostic criteria. Alzheimers Dement 2016;12:292–333.
62 Bateman RJ, Xiong C, Benzinger TLS, et al. Clinical and biomarker changes in dominantly inherited Alzheimer’s disease. N Engl J Med 2012;367:795–804.
63 Bye A, Rosja H, Aspenset ST, et al. Circulating microRNAs and aerobic fitness—the HUNT-Study. PLoS One 2013;8:e57496.
64 JT, LB, TH, et al. Different ways to estimate treatment effects in randomised controlled trials. Contemp Clin Trials Commun 2018;10:89–5.
65 Coffman CJ, Edelman D, Woolson RF. To condition or not condition? Analysing ‘change’ in longitudinal randomised controlled trials. BMJ Open 2016;6:e013096.
66 Cavazzoni P. FDA’s Decision to Approve New Treatment for Alzheimer’s Disease: fda.gov. 06/07/ 2021 https://www.fda.gov/drugs/news-events-humans-drugs/fdas-decision-approve-new-treatment-alzheimers-disease
67 Sevigny J, Chiao P, Bussière T, et al. The antibody aducanumab reduces Aβ plaques in Alzheimer’s disease. Nature 2016;537:50–6.
68 Villeda SA, Plambeck KE, Middeldorp J, et al. Young blood reverses age-related impairments in cognitive function and synaptic plasticity in mice. Nat Med 2014;20:659-.