

Protocol Full Title prospective observational trial:

S60932 Multimodal retinal imaging in the detection and follow-up of Alzheimer's disease

Protocol Acronym/short title:

RetAD

Version and date of protocol:

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1. Study Synopsis

Title of clinical trial	Multimodal retinal imaging in the detection and follow-up of Alzheimer's disease
Protocol Short Title/Acronym	RetAD
Sponsor name	UZLeuven
Principal Investigator	Prof. Dr. Ingeborg Stalmans
Medical condition or disease under investigation	Alzheimer's disease
Purpose of clinical trial	To evaluate the use of non-invasive, multimodal retinal imaging for the early detection of Alzheimer's disease and for the evaluation of disease progression
Primary objective	To identify retinal biomarkers for Alzheimer's disease by means of non-invasive, multimodal retinal imaging
Secondary objective(s)	<ul style="list-style-type: none">- To evaluate the diagnostic performance of selected ocular biomarkers for Alzheimer's disease- To deliver a proof-of-concept for the use of retinal biomarkers to quantitatively measure cerebral Aβ load

	<ul style="list-style-type: none">- To deliver a proof-of-concept for the use of retinal biomarkers to follow Alzheimer's disease progression
Trial Design	Observational, cross-sectional and prospective cohort
Endpoints	<ul style="list-style-type: none">- Technical capability to detect Alzheimer's disease by means of non-invasive retinal imaging- Technical capability to follow up Alzheimer's disease progression by means of non-invasive retinal imaging<ul style="list-style-type: none">- If acceptable technical capability demonstrated: determination of diagnostic accuracy of multimodal retinal imaging in Alzheimer's disease (sensitivity and specificity)
Sample Size	90 individuals (35 amyloid-negative, 55 amyloid-positive)
Summary of eligibility criteria	<ul style="list-style-type: none">• Age between 50 and 85• In stable medical condition and willing and able to perform study procedures.• Fluent in written and verbal Dutch.• Capable of giving informed consent.
Maximum duration of treatment of a subject	/
Version and date of final protocol	v 1.2 27/10/2017
Version and date of protocol amendments	

2. Background, rationale and novelty

Alzheimer's disease (AD) is the most common neurodegenerative disorder and the leading cause of dementia worldwide.¹ A growing number of people are surviving into their 80s-90s and the number of AD patients projected to nearly triple in the next three decades, affecting 80-90 million people worldwide by 2040.^{1,2} As such, AD will become the third cause of death for older people, just behind cardiovascular disease and cancer. In contrast to the latter, AD cannot be prevented, slowed or cured. AD represents an enormous socio-economic burden and has become a trillion dollar disease.³ Despite decades of intensive research, diagnosis and treatment remain challenging for AD. A string of recent failures in clinical trials for AD drugs has pointed out that our understanding of the disease is still far from complete. More in detail, three major reasons underlying this treatment gap have been identified:

- i. **The lack of techniques for patient screening and early diagnosis.**
- ii. **The incomplete understanding of the complex interplay of pathological processes that underlie AD.**
- iii. **The many hurdles between drug discovery and approval.**

With this study, we propose a novel way to address these needs, by using the retina as a model organ to study the central nervous system (CNS). Many of the hallmark cerebral pathophysiological processes of AD have also been observed in the retina. Unlike the rest of the CNS, the retina can be visualized directly, with an imaging resolution up to 100x higher than PET and MR scans. Using these high-resolution imaging tools such as Optical Coherence Tomography (OCT), studies have demonstrated microvascular changes and neuro-retinal thinning in AD patients. Pilot data show that retinal A β can be visualized non-invasively solely based on the intrinsic hyperspectral signature of aggregated amyloid deposits.⁴ Non-invasive retinal imaging (e.g., fundus photography, OCT, hyperspectral imaging (HSI)) – which are all available at affordable cost –, could therefore represent novel means for identifying patients at risk, for longitudinal follow-up of disease progression in AD patients, and for research in a quest for more effective treatments.

3. Trial objectives and design

The ambition of this study is to contribute to AD diagnosis and clinical research via noninvasive multimodal imaging of the retinal manifestation of AD. It aims to respond to four problems that are currently being faced within the AD research field, by delivering a proof-of-concept for the use of multimodal imaging of retinal biomarkers for diagnosis and disease staging of AD, thereby tackling:

1. the lack of an affordable, multimodal retinal imaging platform for clinical research and practice;
2. the difficulties in recruiting A β -positive presymptomatic patients for phase III clinical trials;
3. the need for non-invasive markers to monitor disease progression from a presymptomatic stage of the disease onwards;
4. the lack of integrative prognostic software for disease identification.

The main contribution will consist of the examination of the validity of retinal biomarkers as a diagnostic measure for A β -positivity, and the determination of their ability to quantitatively measure change in A β load. At the end of the project, we aim to deliver a research setup of a hyperspectral camera for retinal imaging, standardized image acquisition protocols for retinal imaging of AD biomarkers using different technologies (including hyperspectral imaging) and a data science approach for AD diagnosis. Proof-of-concept for the predictive value of multimodal imaging of selected retinal biomarkers in diagnosing and classifying AD patients will be delivered.

This may be in the future useful for screening, early diagnosis and follow-up of AD. This is of major importance because AD has a long preclinical and prodromal phase, and by the time symptoms suggestive of a clinical diagnosis appear, neurodegeneration may have led to damage too extensive to repair.

The primary objective of the human clinical diagnostic trial is to validate the retinal biomarkers against A β load measured with ^{18}F -flutemetamol PET as standard-of-truth. The cross-sectional data collection is mainly aimed at exploring retinal biomarkers as a diagnostic measure for A β -positivity, while gathering the longitudinal information is mainly aimed at determining their ability to quantitatively measure change in A β load. The discriminative value of retinal imaging will be assessed (phase 1) and

subsequently evaluated (phase 2). All patients will be followed longitudinally over the course of 24 months.

This is an open-label longitudinal biomarker study without investigational medicinal product in subjects in different stages of the AD spectrum.

The data that we will collect consist of amyloid imaging, MRI, blood, genetic, general health and cognitive data, as well as visual acuity, ocular biomicroscopy and funduscopy, fundus photographs, hyperspectral retinal images, Optical Coherence Tomography (OCT) retinal images and OCT angiography (OCT-A) retinal images. Subjects will be followed longitudinally. In the current study we will primarily investigate the potential of non-invasive, multimodal retinal imaging for the early detection of Alzheimer's disease and for the evaluation of disease progression. This will be done in comparison with amyloid imaging and neuropsychological evaluations.

We will build a **longitudinal database** of ocular, systemic, neuro-psychiatric, MRI and PET imaging parameters of A β -positive and A β -negative patients with different stages of cognitive impairment. This database will be used to provide proof-of-concept that retinal biomarkers provide an early, accurate and non-invasive tool for AD detection and follow-up. All data will be collected in a database for statistical analysis.

3.1 Preparation, organization and management of phase 1 study

The primary objective of this exploratory phase 1 study is to evaluate which ophthalmological measures optimally differentiate between A β -positive, clinically probable AD patients and A β -negative, cognitive-intact healthy controls, matched for age, education, gender and apoE status.

Methodology

Study cohorts:

1. Fifteen clinically probable AD patients, according to the National Institute of Aging (NIA)-Alzheimer's Association (AA) diagnostic criteria,⁵ with an MMSE of 12 or higher, and with a positive CSF biomarker analysis or a positive amyloid-PET scan in the past or a positive amyloid-PET scan at inclusion, will be included in this group. Patients will be recruited via the memory clinic UZ

Leuven, which is headed by Prof. dr. Rik Vandenberghe (total number of dementia patients due to AD currently in follow-up = 486).

2. Fifteen A β -negative cognitive-intact healthy controls will be recruited from a longitudinal cohort of 180 cognitively healthy older adults who are followed at the Laboratory for Cognitive Neurology of Prof. dr. Rik Vandenberghe (UZ Leuven) (mean age = 68.4 \pm 6.4, range 55-80 years).^{6,7} These community-dwelling participants were first recruited between 2010 and 2015 for multimodal brain imaging (A β PET and volumetric MRI) combined with neuropsychological assessment. One of the key inclusion criteria was neuropsychological test scores within the published norms at baseline. This cohort has been well characterized at baseline by means of detailed evaluation of lifestyle factors (lifelong cognitive and physical activity), quantitative parameters (weight, height, blood pressure under standardized conditions), cognitive reserve score (Cognitive Reserve Questionnaire), and neuropsychological performance. Participants are longitudinally followed with neuropsychological assessments at two-yearly intervals. The ready availability of this deeply phenotyped cohort is a strength of this project.

A β -negative cognitive-intact controls will be matched to the AD patients for age, gender, education and apoE status. The A β -negative status and the cognitive-intact status will be verified by a repeat A β PET scan and a neuropsychological assessment at inclusion in the current study.

Study procedures:

After signing the informed consent, patients will be asked to fill in a questionnaire. All eligible participants will then undergo detailed ophthalmological examination, an MRI scan, ¹⁸F-flutemetamol PET scan, blood sampling (apoE genotyping and fasting laboratory tests – Table 1), as well as a detailed neuropsychological assessment.

Hematology	Chemistry	Genotyping
Hematocrit	Gamma GT	apoE polymorphism
Hemoglobin	Alkaline phosphatase	
Platelet count	Alanine aminotransferase (ALT)	
WBC (total and differential)	Aspartate aminotransferase (AST)	

Sedimentation rate	Bicarbonate	
	Calcium	
	Chloride	
	Potassium	
	Sodium	
	Creatinin	
	Urea	
	Low-density Lipoprotein	
	C-reactive protein	
	Glycemia	
	HbA1c	

Table 1: Laboratory tests

- Ophthalmological examination will include visual acuity measurement, biomicroscopy and funduscopy, followed by the acquisition of hyperspectral, (angio-) OCT, and fundus photography using predetermined protocols.
- PET images will be acquired on a TruePoint Siemens PET scanner using static acquisition during an acquisition window of 30 minutes, starting 90 minutes post-injection. A low-dose computed tomography scan will be performed for attenuation correction, prior to the PET scan. The summed ¹⁸F-flutemetamol PET image (sumPET) will be co-registered to the subjects' T1-weighted MRI image. Segmentation parameters from the subjects T1-weighted MRI will be used to normalize the co-registered sumPET. A Standardized Uptake Value Ratio (SUVR) image will be created by dividing the normalized sumPET image by the uptake in the cerebellar grey matter reference region. SUVR values will then be calculated in a composite volume of interest (VOI) (SUVRcomp), consisting of frontal, parietal, anterior cingulate, posterior cingulate and lateral temporal VOIs, masked by the subject-specific gray matter map.⁶
- MRI will be performed on a 3T Achieva dstream Philips MRI scanner with a 32-channel head coil. The MRI sequence will consist of an MPRAGE volumetric MRI, and a FLAIR and Gradient Echo sequence.

- The Neuropsychological test battery will consist of the Auditory Verbal Learning Test (AVLT), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), Raven's Progressive Matrices (RPM), Mini Mental State Examination (MMSE), Neuropsychiatric Inventory (NPI), and Cornell Scale for Depression in Dementia (CSDD).

Statistical analysis:

The primary statistical analysis will be based on a Receiver Operating Characteristic analysis of the different ophthalmological measures, to determine which have the best diagnostic accuracy (area under the curve) compared to the binary A β PET classification as standard-of-truth. In the cross-sectional studies, the standard-of-truth will consist of the binary distinction between A β -positive cases and A β -negative cases, based on A β PET. This distinction will rely on a semi-quantitative analysis and a cut-off based on independent data.⁷ The phase 1 study is considered exploratory and the diagnostic accuracy of a wide range of ophthalmological parameters will be assessed. The three ophthalmological parameters with the best diagnostic accuracy will be selected as primary outcome measures for further validation in the phase 2 study in an independent cohort.

3.2 Preparation, organization and management of phase 2 study

The primary objective of this study is to evaluate the diagnostic accuracy of three ophthalmological measures, selected based on the phase 1 study, for discriminating between A β -negative and A β -positive healthy cognitive-intact older adults and for discriminating between A β -negative cognitive-intact older adults and A β -positive MCI patients.

Methodology

Study cohorts:

1. Patients with amnestic MCI due to AD (A β -positive MCI), according to the NIA-AA diagnostic criteria, an MMSE 24 or higher, and with a positive CSF biomarker analysis or a positive amyloid-PET scan in the past or a positive amyloid-PET scan at inclusion, recruited via the memory clinic UZ Leuven (total number of amnestic MCI patients currently in follow-up = 64).
2. A β -positive cognitive-intact older adults. These will be recruited from the longitudinal cohort of older adults followed at the Laboratory for Cognitive Neurology described above. At inclusion

(between 2010-2015) 30 out of 180 participants were A β -positive. A positive CSF biomarker analysis or a positive amyloid-PET scan in the past or a positive amyloid-PET scan at inclusion is a prerequisite for inclusion in this group.

3. A β -negative cognitive-intact older adults, recruited from the same longitudinal cohort.

Study procedures:

cfr. Phase 1 study

Statistical analysis:

The primary analysis will be based on a contingency table, in which cognitively intact subjects will be classified according to one ophthalmological parameter and compared to the classification based on the A β PET. This will be done for the three parameters that have been selected based on the phase 1 data. The same will be done for the classification of the cognitively intact A β -negative cases versus the A β -positive MCI cases.

3.3 Preparation, organization and management of longitudinal follow-up

All participants of the phase 1 and phase 2 study (n = 90) will be invited to participate in the longitudinal component.

Methodology

Study procedures:

Subjects will undergo 6-monthly ophthalmological evaluations. After 24 months, all baseline examinations will be repeated. For longitudinal studies, the optimal reference region has been shown to be subcortical white matter rather than cerebellum or pons.⁸ The calculated SUVRcomp values at follow-up (t24) will be subtracted from the SUVRcomp values at baseline (t0).

Statistical analysis:

The primary analyses will consist of a regression analysis between the change in the three selected ophthalmological parameters and the change in A β load. The second primary objective will be the correlation between the change in these three parameters and the change in the total learning and

the delayed recall of the AVLT. Secondary objectives will consist of a regression analysis between the change in the ophthalmological parameters and the change in the RBANS score, a regression analysis between the change in these parameters and the volumetric changes on the MRI, and a regression analysis between the change in the ophthalmological parameters and the changes in A β load analyzed in a voxelwise manner. In a further secondary analysis, the participants will be divided into A β accumulators and non-accumulators, based on the A β PET, and the ophthalmological parameters will be compared between these two groups.

This project is financed by external funding (FWO SBO project, decision will be communicated in December 2017).

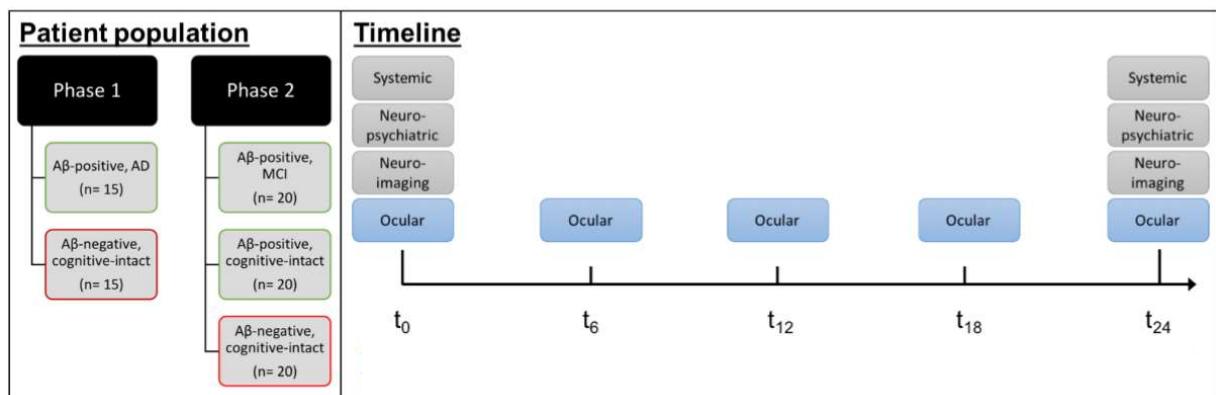


Figure 1: study timeline

Devices that will be used:

- MRI: 3T Achieva dstream Philips MRI scanner with a 32-channel head coil, Philips, Netherlands
- PET-CT: TruePoint Siemens PET scanner, Siemens, Germany
- OCT: Spectralis, Heidelberg Engineering, Germany
- Fundus picture: Topcon DRC 50-DX fundus camera, Topcon Corporation, Japan
- Hyperspectral retinal imaging:

XIMEA SNM4x4 hyperspectral snapshot camera, Ximea, Germany

SNAPSCAN VNIR hyperspectral snapscan camera, Imec, Belgium

4. Selection and withdrawal of subjects

4.1 Inclusion criteria

Between \geq 50 and \leq 85 years of age.

In the opinion of the investigator, the patient is in stable medical condition and willing and able to perform study procedures.

Patient is fluent in written and verbal Dutch.

Patient is capable of giving informed consent.

4.2 Exclusion criteria

Patient has a history or current evidence of a neurological disorder, which, in the opinion of the primary investigator, may contribute to the subject's cognitive impairment.

Patient has a history of large-vessel stroke or evidence of a large-vessel infarction or other focal lesions on baseline MRI scan, which may contribute to the cause of the memory impairment in the opinion of the investigator. Vascular white matter lesions or other signs of microangiopathy will not be considered an exclusion.

Patient has a history of malignancy \leq 5 years prior to signing informed consent, except for patients who have undergone potentially curative therapy with no evidence of recurrence for 1 year, and who are deemed at low risk for recurrence by her/his treating physician.

Patient is currently participating or has participated in a study with an investigational compound within 30 days of signing informed consent.

Subject has any magnetizable metal prostheses, implants or foreign objects that could pose a hazard during MRI scans.

Patient has a known history of ocular diseases other than the exception of cataract and/or wearing glasses/contact lenses.

4.3 Expected duration of trial

First-patient first-visit is planned for January 2018, last-patient first-visit is planned for December 2018.

Final data expected to be collected December 2020.

5. Trial procedures

5.1 MRI and ^{18}F -flutemetamol PET-CT scans

Cfr. Paragraph 3.

5.2 Sample collection and handling

Venous blood samples will be collected at start, and after 2 years in glass EDTA-containing (4), serum-separating (2) and RNA Paxgene blood collection (1) tubes, and frozen according to specific instructions. Blood and serum samples will be stored in double at KU Leuven.

5.3 Genetic analysis

Samples for genotyping of the apoE polymorphism will be analyzed according to standard procedures by the Center for Human Genetics, UZ Leuven.

5.4 Fasting laboratory test analysis

Samples will be analyzed by the Department of Laboratory Medicine of UZ Leuven.

5.5 Ocular exams

Cfr. Paragraph 3.

5.6 Summary of visits/procedures

Procedure		Timing
<i>Venous blood sampling</i>	Hematology: Hematocrit, Hemoglobin, Platelet count, WBC (total and differential), Sedimentation rate	t0, t24
	Chemistry: Gamma GT, Alkaline phosphatase, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Bicarbonate, Calcium, Chloride, Potassium, Sodium, Creatinin, Urea, Low-density Lipoprotein, C-reactive protein, Glycemia, HbA1c	t0, t24
	Genotyping: apoE polymorphism	t0
<i>Brain MRI</i>	MPRAGE volumetric MRI, en FLAIR and Gradient Echo sequence	t0, t24
¹⁸ F-Flutemetamol PET CT		t0, t24
<i>Neuropsychiatric testing</i>	Auditory Verbal Learning Test (AVLT) Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Raven's Progressive Matrices (RPM) Mini Mental State Examination (MMSE) Neuropsychiatric Inventory (NPI) Cornell Scale for Depression in Dementia (CSDD)	t0, t24
<i>Ocular examination</i>	Visual acuity, biomicroscopy, funduscopy Fundus pictures, including hyperspectral imaging OCT + angio-OCT	t0, t6, t12, t18, t24

Table 2: Summary of visits/procedures

5.7 Supervision and responsibilities

The study will be performed under the supervision of Profs. Ingeborg Stalmans and Rik Vandenberghe, UZ Leuven. The local study nurses will coordinate the logistics and take the blood samples. Ocular exams and retinal imaging will be performed by MD PhD students skilled with the procedures. The participating investigators will perform their part of the study fully in accordance with the terms of the Protocol, the applicable national laws (amongst others: the Belgian Law of May 7, 2004 relating to experiments on human persons; the Belgian Law of August 22, 2002 on Patient Rights; the Belgian Law of December 8,

1992 (as amended) regarding the Protection of Privacy in relation to the Processing of Personal Data.) and apply and adhere to regulations and rules as, amongst others, the Declaration of Helsinki (2008) and ICH GCP Guidelines.

5.7.1 Insurance

In accordance with the Belgian Law relating to experiments on human persons dated May 7, 2004, UZ/KULeuven shall assume, even without fault, the responsibility of any damages incurred by a Study Patient from the UZ/KU Leuven site and linked directly or indirectly to the participation to the Study, and shall provide compensation therefore through their insurance.

5.7.2 Informed consent

The Participating Site acknowledges that the Study can and will be conducted only on the basis of prior informed consent by the Subjects, or their legal representatives, to participate in the Study. The Participating Site shall obtain a signed informed consent form (ICF) for all patients prior to their enrollment and participation in the Study in compliance with all applicable laws, regulations and the approval of the (local) Ethics Committee, if required. The Participating Site shall retain such ICFs in accordance with the requirements of all applicable regulatory agencies and laws.

6. Assessment of efficacy

/

7. Assessment of safety

The radiation exposure for the volunteers is for the ¹⁸F-flutemetamol scan (150 MBq target dose) maximally 5 mSv.

No permanent adverse effects have been described after any of the planned ocular examinations. Only light from the visible spectrum is used. A temporary decreased vision due to the flashlight (generally less than 1 minute) is expected after the fundus picture.

8. Statistics

8.1 Sample size

Phase 1: based on previous trials on OCT measurements in AD and age-matched cognitive-intact controls,⁹ a sample size of 8 patients would be sufficient to discriminate both groups using a two-tailed t-test with alpha 0.05, a power of 0.90 and an estimated effect size of 2.73 µm (RFNL change). For this proof-of-concept study, we aim to recruit 15 patients per group.

Phase 2: based a previous trial,¹⁰ comparing OCT measurements in Aβ-positive versus Aβ-negative cognitive-intact subjects, the target sample size is at least 13 patients per group (alpha = 0.05, power = 0.90, estimated effect size of 1.33). We aim to include 20 patients in each group.

Longitudinal: all participants of the phase 1 and phase 2 study (n = 90) will be invited to participate in the longitudinal component.

8.2 Analysis

Cfr. Paragraph 3.

9. Quality assurance

To assure maximal quality and reproducibility, the trial protocol will be followed rigorously.

10. Direct access to source data and documents

Only data gathered in the context of the trial will be used.

11. Ethics and regulatory approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (2008), the principles of Good Clinical Practice and in accordance with all applicable regulatory

requirements. This protocol and related documents will be submitted for review to Ethics Committee of the University Hospitals Leuven.

The Study will be conducted only on the basis of prior informed consent by the Subjects to participate in the Study. We shall obtain a signed informed consent form (ICF) for all patients prior to their enrollment and participation in the Study in compliance with all applicable laws, regulations and the approval of the (local) Ethics Committee, if required. We shall retain such ICFs in accordance with the requirements of all applicable regulatory agencies and laws.

12. Data Handling

We shall treat all information and data as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the performance of the Study. The collection, processing and disclosure of personal data, will comply with applicable personal data protection and the processing of personal data (Directive 95/46/EC and Belgian law of December 8, 1992 on the Protection of the Privacy in relation to the Processing of Personal Data). We will protect the data from disclosure outside the research according to the terms of the research protocol and the informed consent document. The subject's name or other identifiers will be stored separately from their research data and replaced with a unique code to create a new identity for the subject.

13. Data Management

All data will be analyzed and stored in a coded fashion, with a unique anonymous identifier for every subject. In the future, these data could be used in the context of this project, and for related projects regarding cognitive functions, Alzheimer's disease and related conditions.

14. Translational research

From every included patient, a blood sample will be collected and stored for genotyping and biochemical analysis.

15. Publication Policy

Any publication will be submitted to all co-authors at least thirty (30) days prior to submission or disclosure.

16. Financial Aspects

This project is financed by external funding (FWO SBO project, decision will be communicated in December 2017).

All medical expenses (medication and visits) arising from participation in the study will not be charged to the volunteer. Volunteers do not receive a financial compensation for their participation. Transportation costs and parking fees in the context of this study will be reimbursed accordingly, as well as the cost of a meal, with a maximum of 50 Euros per visit.

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