UZ LEUVEN

Protocol Full Title prospective trial:

Omega 3 and Vitamin D dosage in a population with moderate to high risk of AMD

Protocol Acronym/short title:

OVID-AMD

Version and date of final protocol:

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Sponsor:

Name: UZLeuven
Address: Herestraat 49, 3000 Leuven

Principal Investigator:

Name: Dr. Julie Jacob
Address: Kapucijnenvoer 33, 3000 Leuven
Telephone:016/342874
Fax:016/332367
Email: julie.jacob@uzleuven.be

Sub-investigator:

Name: Prof. Dr. A. Leys & Dr. E. Mangelschots
Address: Meerdegatstraat 78/A, 3570 Alken
Telephone: 011/313859
Fax:
Email: info@oogartsenalken.be

Signatures

Principal Investigator	Date
Print Name:	
Subinvestigator	Date
Print Name:	
Subinvestigator	Date
Print Name:	

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1. Study Synopsis

Title of clinical trial	Omega 3 and Vitamin D dosage in a population with moderate to high risk of AMD
Protocol Short Title/Acronym	OVID-AMD
Sponsor name	UZ Leuven
Principal Investigator	Dr. Julie Jacob
Medical condition or disease under investigation	AMD
Purpose of clinical trial	Blood serum dosage of omega 3 and vitamin D in individuals with moderate and high risk of AMD as determined by STARS scores of ≥10
Primary objective	To detect individuals at high and moderate risk of AMD in the Belgium population and to perform a blood serum dosage of omega 3 and Vitamin D
Secondary objective (s)	Dosage of zinc oxide and cupric oxide
Trial Design	Multi-centric, epidemiological and interventional survey

Endpoints	Blood dosage of omega 3 and Vitamin D, zinc oxide and cupric oxide
Sample Size	Not applicable
Summary of eligibility criteria	- subjects ≥ 55 years - subjects with family history of AMD - age-related maculopathy present - no previous intake of eye nutritional supplements < 4 months prior to enrollment - no current intake of multivitamins especially when containing Vit D
Maximum duration of treatment of a Subject	1 visit
Version and date of final protocol	
Version and date of protocol amendments	

2. Background and rationale

Age-related macular degeneration (AMD) is the leading cause of irreversible vision loss in industrialized countries; its incidence increases with life expectancy. Age-related macular

degeneration is a multifactorial disease, with environmental risk factors such as smoking, dietary habits, or obesity interacting with genetic determinants. According to that, a Simplified Théa AMD Risk-assessment Scale (STARS) was developed to detect individuals at high risk of AMD. The objective of the STARS questionnaire is to help the ophthalmologists to identify AMD risk factors to prevent AMD in clinical practice. It should be used also in general population to detect subjects at high risk for AMD (F066 EVER 2014). Another risk factor is dietary habits, and observational studies suggest that higher dietary intake of lutein-zeaxanthin, ω-3 longchain, polyunsaturated fatty acids (DHA and EPA), or both are associated with a decreased risk of developing advanced AMD. In the retina, DHA increases mitochondrial activity and has anti-oxidative, anti-inflammatory, anti-apoptotic, and antiangiogenic effects. An imbalance in retinal lipids leads to photoreceptor degradation and the accumulation of lipid and lipoprotein debris in the retinal pigment epithelium layer. Because the continuous renewal of retinal membranes requires a constant supply of omega-3 fatty acids by retinal pigment epithelium cells, diets rich in DHA may improve retinal function and may delay the development of exudative AMD[1]. Blood DHA concentrations were shown to be inversely related to other degenerative diseases of the retina, such as retinitis pigmentosa[2]. Cho et al, showed a modest inverse associations between DHA intake and AMD in both men and women suggest a protective role of this fatty acid in the development of the disease. In addition, intake of fish, a major source of DHA, was inversely associated with AMD [2]. Seddon et al confirm the previous observations in 2013 by showing that an increased self- reported dietary intake of ω-3 fatty acids is associated with reduced risk of geography atrophy (GA) and may modify genetic susceptibility for progression to GA[3]. Following micronutrients constitute the currently existing supplement formulae: vitamin C, vitamin E, lutein/zeaxanthin, zink oxide and cupric oxide[4,5]. However the dosages as proposed in the aforementioned studies are not allowed in Europe, therefore there is increasing interest in adding other micronutrients with antioxidant properties and components with biological plausibility effect, such as omega-3, resveratrol, vitamin B and vitamin D.

Association between vitamin D status (as assessed by the serum 25(OH)D) and the risk of early or late AMD have been reported in several cross sectional studies. Two meta-analyses were performed recently. Annweiler et al.[6] concluded that there is evidence that high blood 25(OH)D may be protective against AMD, especially late AMD. On the opposite, Wu et al.[7] concluded that there is no evidence to indicate an inverse association between serum vitamin D levels and any stages and subtype of AMD risk. Thus, the association between vitamin D status and AMD needs additional assessments. However, there are experimental evidences suggesting that vitamin D inhibits the inflammatory reaction[8] and angiogenetic process[9] involved in the development of AMD. It will be interesting to conduct randomized controlled clinical trials to assess the effects of vitamin D supplementation in the development or progression of AMD.

More than 50% of the world's population is at risk for vitamin D deficiency[10] and especially elderly individuals are at risk because of poor dietary vitamin D intake, reduce mobility, decreased exposure to sunlight and decline in renal function.[11]

3. Trial objectives and Design

3.1 Trial objectives

To detect individuals at high and moderate risk of AMD in the Belgium population and to perform a blood serum dosage of omega 3 , Vitamin D, zinc oxide and cupric oxide.

3.2 Trial Design

Multi-centric, epidemiological and interventional survey

3.3 Trial Flowchart

	Screen visit	
Informed consent	X	
STARS questionnaire	X	
Blood omega 3 dosage	X	
Blood Vit D dosage, zinc oxide and cupric oxide	X	
BCVA	X	
OCT	X	
Color fundus photography	X	

4. Selection and withdrawal of subjects

4.1 Inclusion criteria

* Subjects > 55 years

* STARS questionnaire score ≥ 10 (moderate to high risk for AMD)

4.2 Exclusion criteria

- Previous intake of eye nutritional supplements < 4 months prior to enrollment (half-life 25-OH D = 3-4 weeks, half-life of red blood cells: 100-120 days)
- STARS questionnaire score < 10 (low risk for AMD)
- Patient with AMD (stage 3 and 4)

4.3 Expected duration of trial

1 visit

5. Trial Procedures

5.1 By visit

One single study visit

5.2 Laboratory tests

One blood sample for omega 3 , Vitamin D dosage, zinc oxide and cupric oxide

5.3 Other investigations

Visual acuity assessment, OCT scan, Color fundus photography, stars questionnaire.

6. Assessment of efficacy

Not applicable, no treatment will be administered

7. Assessment of Safety

Not applicable, no treatment will be administered

8. Statistics

8.1 Sample size

We anticipate to include 50 subjects to this pilot study. There is no control group and it is an exploratory study, so no power calculation has been done. The study results will provide us trends to build a bigger study.

8.2 Analysis

The study is an exploratory study.
Definition of vitamin D status:

Nmol/L	Ng/mL	Health status	Vitamin D status
< 30	< 12	Associated with vitamin D deficiency, leading to rickets in infants and children and osteomalacia in adults	Deficiency
30-50	12-20	Generally considered inadequate for bone and overall health in healthy individuals	Insufficiency
≥ 50	≥ 20	Generally considered adequate for bone and overall health in healthy individuals	Adequacy
> 125	> 50	Emerging evidence links potential adverse effects to such high levels, particularly > 150 nmol/L (>60 ng/mL)	Toxicity

9. Quality assurance

Give details as to how QA will be maintained, mention SOP's if available

10. Direct access to source data and documents

Dr. J. Jacob, Prof. Dr. A. Leys , Dr. E. Mangelschots and the institutions will permit trial-related monitoring, audits, EC review, and regulatory inspections (where appropriate) by providing direct access to source data and other documents (ie subjects' case sheets, blood test reports, X-ray reports, histology reports etc).

11. Ethics and regulatory approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (current version), the principles of GCP and in accordance with all applicable regulatory requirements. This protocol and related documents will be submitted for review to Ethics Committee of UZ Leuven.

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 subjects 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.

The Investigator and the Participating Site shall treat all information and data relating to the Study disclosed to Participating Site and/or Investigator in this Study 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, such as patient health and medical information is subject to compliance 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)

Data are **anonymous** if no one, not even the researcher, can connect the data to the individual who provided it. No identifying information is collected from the individual.
When data are **coded**, there continues to be a link between the data and the individual who provided it. The research team is obligated to 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 should be stored separately from their research data and replaced with a unique code to create a new identity for the subject. Note that coded data are not anonymous.

12. Data Handling

Electronic patient file

13. Data Management

Electronic patient file

Paper CRF to collect questionnaires

14. Translational research

Blood sample will be taken.

15. Publication Policy

E.g in case of multicentre trial:

It is anticipated that the results of the overall Study shall be published in a multi-centre publication, involving the data of all clinical sites participating in the Study.
Participating Site is not allowed to publish any data or results from the Study prior to the multicentre publication, provided however that Participating Site is allowed to publish the results generated at the Participating Site if the multicentre publication has not occurred after 12 months from Study database lock.
Any publication by Participating Site will be submitted to the Sponsor for review at least thirty (30) days prior to submission or disclosure. Sponsor shall have the right to delay the projected publication for a period of up to three (3) months from the date of first submission to the Sponsor in order to enable the Sponsor to take steps to protect its intellectual property rights and know-how.

Publications will be coordinated by the Investigator of Sponsor. Authorship to publications will be determined in accordance with the requirements published by the International Committee of Medical Journal Editors and in accordance with the requirements of the respective medical journal.

16. Insurance/Indemnity

In accordance with the Belgian Law relating to experiments on human persons dated May 7, 2004, Sponsor shall assume, even without fault, the responsibility of any damages incurred by a Study Patient and linked directly or indirectly to the participation to the Study, and shall provide compensation therefore through its insurance."

17. Financial Aspects

Thea Pharma allows a subsidy of 15000€

18. References

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