Development of novel clinical endpoints for interventional clinical trials with a regulatory and patient access intention in patients with intermediate age-related macular degeneration (AMD) - MACUSTAR

Published: 14-08-2018
Last updated: 05-10-2024

2.1 Primary objectives2.1.1 Cross-sectional part• Technical evaluation of the functional and structural outcome measures to support a biomarker qualification by regulatory authorities and payers. 2.1.2 Longitudinal part • Assessment of prognostic...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Retina, choroid and vitreous haemorrhages and vascular disorders
Study type	Observational invasive

Summary

ID

NL-OMON44313

Source
ToetsingOnline

Brief title
MACUSTAR

Condition

- Retina, choroid and vitreous haemorrhages and vascular disorders

Synonym
age-related Macula degeneration, retina aging

Research involving

Human

Sponsors and support

Primary sponsor: University Hospital Bonn, UKB
Source(s) of monetary or material Support: De studie wordt georganiseerd door het MACUSTAR-consortium met financiering van de Gemeenschappelijke Onderneming Innovative Medicines 2;die wordt ondersteund door het Horizon 2020 Onderzoeks- en Innovatieprogramma van de Europese Unie en de Europese Federatie van Farmaceutische Industrie en Verenigingen (EFPIA).

Intervention

Keyword: intermediate AMD, novel clinical endpoint

Outcome measures

Primary outcome

The MACUSTAR clinical study will generate a large volume of data in relation to

functional, structural and patient reported outcome measures (PROMs).

3.1.1 Functional outcomes

• Mean change from baseline in best corrected visual acuity (BCVA) using an

Early Treatment Diabetic Retinopathy Study (ETDRS) chart (standard parameter,

tested for comparison) (reference variable)

• Mean change from baseline in scotopic and mesopic microperimetry sensitivity

• Mean change from baseline in LLVA

• Mean change from baseline in vanishing optotypes VA

• Mean change in low luminance deficit (LLD = BCVA-LLVA)

• Mean change in absolute threshold

• Proportion of subjects with progression in dark adaptation deficit beyond

coefficient of repeatability (as determined in the re-test assessment in the

cross-sectional part)

• Mean change from baseline in the rod intercept time of the dark adaptation test

3.1.2 Structural outcomes

• Mean change from baseline in the cube root of drusen volume by SD-OCT

• Proportion of subjects with reduction in drusen volume (different cut offs at >=15, 30, 50%; to baseline of cube root drusen volume estimated by SD-OCT without progression to GA and/or nAMD)

• Mean change from baseline of retinal thickness (total, inner retina, outer nuclear layer, photoreceptor layer and Retinal Pigment Epithelium (RPE) layer) by SD-OCT

• Focal pigmentary changes captured by colour fundus photography (CFP)

• Presence of refractile deposits

• Presence of intraretinal cystoid spaces

• Presence of localized RPE hypertransmission

• Presence of localized disruption of ellipsoid zone

• Presence of localized subsidence of the outer plexiform layer and the inner nuclear layer

• Presence of hyporeflective wedge-shaped bands

• Changes in localized fundus autofluorescence signal alterations

• Presence of reticular drusen/subretinal drusenoid deposits and associated local changes as determined by multimodal imaging

• Proportion of subjects with study eye that progressed to GA and/or nAMD

• Presence of quiescent choroidal neovascularization (CNV) as assessed by OCT angiography (OCT-A) (at equipped sites)

• OCT-A findings (at equipped sites)

• Proportion of conversions to late AMD detected with fluorescein angiography (FA) that could be detected with OCT-A (at equipped sites)

3.1.3 Patient reported outcomes

• Mean change from baseline in patient-reported low luminance visual functioning, as measured by the VILL questionnaire, including the domains of:

o Reading & accessing information

o Orientation & mobility (incl. driving)

o Safety

o Socio-emotional well-being

• Change in utility index from baseline as measure by the PROM utility index

• Mean change from baseline in patient-reported health status and utility using the EQ-5D-5L (https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/)

3.1.3 Door de patiënt gerapporteerde uitkomsten

• Gemiddelde verandering ten opzichte van de uitgangswaarde bij door de patiënt gerapporteerd visueel functioneren met lage luminantie, zoals gemeten met de VILL-vragenlijst, inclusief de domeinen van:

o Lezen en toegang tot informatie

o Oriëntatie en mobiliteit (incl. rijden)

o Veiligheid

o Sociaal emotioneel welbevinden

• Verandering in de gebruiksindex van de basislijn als maatstaf door de

PROM-hulpprogramma-index

• Gemiddelde verandering ten opzichte van baseline in door de patiënt

gerapporteerde gezondheidsstatus en het nut met behulp van de EQ-5D-5L

(https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/)

Secondary outcome

not applicable

Study description

Background summary

Age-related macular degeneration (AMD) affects almost 30% of the older population and progresses slowly from early AMD to intermediate AMD (iAMD) and ultimately late-stage AMD with severe and frequently irreversible visual loss over a decade.1 Population aging will lead to a considerable increase in AMD prevalence. Today, late stage AMD is the leading cause of blindness among the elderly in industrialized countries and affects more than 2.5 million patients in the European Union (EU)2, 3 resulting in direct annual costs of over 2 billion Euros.4
In order to reduce the significant burden of late AMD, novel interventions that stop or delay progression from iAMD to late AMD will need to be developed.5 In order to do this, clinical endpoints validated and accepted by regulatory agencies, health technology assessment (HTA) bodies, and payers are needed since currently these do not exist for iAMD clinical trials (CTs). In fact, at the moment, effective treatment options are only available for neovascular AMD (nAMD), and even then, it still remains a vision threatening disease as justified by the risk of sub-retinal hemorrhages or atrophy and long-term fibrosis development.
Regarding atrophic late AMD (geographic atrophy, GA), a limited number of agents are in ongoing phase III CTs with no confirmatory proof of efficacy so far. Given that GA is an advanced stage of AMD with irreversible loss of photoreceptors and severe loss of vision in cases of foveal involvement, a recovery of visual function is not expected when the patients reach this stage of the disease. Therefore, currently there is no therapeutic intervention to delay or stop the progression to late stage AMD. Consequently, from a public

health perspective, two main objectives exist: 1) find a solution for the often clinically relevant and generally progressive visual impairment of patients with iAMD in low-luminance and low-contrast situations, and 2) identify the iAMD patients who are at risk of progression to late stage AMD in order to treat them prior to any irreversible vision damage and potentially legal blindness.

Although there is good evidence that indicates patients with iAMD experience impairment of visual function, it is unknown to what extend these impact the patients* life nor can it be reliably measured and quantified. It is also unknown whether there are specific risk factors in the population of iAMD patients which identify those with more rapid progression to late stages of the disease.
Therefore, the successful development of iAMD interventions requires validated functional, morphological and patient-reported endpoints to be used in CTs, which must be clinically meaningful and accepted by regulatory agencies. In addition, functional decline in iAMD, as well as specific risk factors for iAMD progression to late AMD need to be better characterized to inform and improve conduct of future iAMD CTs.

Considering this context, MACUSTAR clinical study will focus on iAMD in order to generate data on the visual impairment in iAMD and its impact on patients* lives, as well as data on functional, structural and patient-reported outcomes (PROs) with progression from iAMD to late AMD. These data will lead to validated clinical endpoints for future iAMD CTs.
To achieve this, several different but complementary functional tests, multimodal retinal imaging and tools to evaluate different relevant aspects of patient-reported functioning will be employed in the study. This multi-modal approach aims to develop clinical endpoints that either alone or in combination, serve as surrogate outcomes for progression from iAMD to late stage AMD. Furthermore, PROs will be tested in iAMD patients, and combining these to the functional testing performed under low luminance, will ensure that functional endpoints are patient-relevant and that also data on the tests* minimally important differences will be available. Utility values will be developed for the PROs, which will inform future innovative cost-effectiveness models and will be essential for future health technology assessments.

In the MACUSTAR clinical study, structural changes over time in iAMD patients and structural differences between the AMD stages will also be assessed using advanced imaging technologies. Furthermore, structural data from AMD patients and from subjects with no AMD or aging-changes only will be compared. This will allow the characterization of the disease evolution, the establishment of structural-functional correlations and the identification of points-of-no return in the disease progression. Then, structural biomarkers can be identified and validated as clinical endpoints for future clinical trials assessing iAMD progression.

Finally, the functional, structural and PROs data will be combined with the genetic and demographic data collected in the study, thus providing a wider understanding of iAMD stage, relevant risk factors and better prediction of disease progression.

Study objective

2.1 Primary objectives
2.1.1 Cross-sectional part
• Technical evaluation of the functional and structural outcome measures to support a biomarker qualification by regulatory authorities and payers.
2.1.2 Longitudinal part
• Assessment of prognostic power of changes in retinal sensitivity (as measured by microperimetry) for progression from iAMD to late AMD (nAMD and GA).

2.2 Secondary objectives
2.2.1 Cross-sectional part
• Analyses of correlation between structural and functional outcome measures with the novel Visual Impairment in Low Luminance (VILL) and 5Q-5D-5L PROMs to support patient-relevance of outcome measures.
• To evaluate the ability of outcome measures to differentiate between different AMD stages and no AMD control subjects
• Establish a database with cross-sectional data of controls (no AMD), early, intermediate and late AMD subjects with functional, structural and patient reported outcome assessment data.
2.2.2 Longitudinal part
• Assessment of the association between functional and structural candidate outcome measures with progression from iAMD to late stage AMD. Outcome measures included in these assessments will be:
o Functional outcome measures: Low Luminance Visual Acuity (LLVA), vanishing optotypes visual acuity, contrast sensitivity, absolute threshold, rate of rod mediated dark adaptation, reading performance, and scotopic and mesopic sensitivities by fundus controlled microperimetry.
o Structural outcome measures: based on multi-modal retinal imaging including spectral domain optical coherence tomography (SD-OCT), confocal scanning laser ophthalmoscopy (cSLO), fundus autofluorescence (FAF), on which generalized retinal biomarkers such as change in drusen volume, or change in load of reticular pseudodrusen as well as localized retinal biomarkers such as focal changes in specific SD-OCT bands will be assessed.
• Establish a database with longitudinal data of iAMD subjects with functional, structural and patient PROM outcome assessment data.

Study design

The study consists of two main parts: a cross-sectional part and a longitudinal part.

Cross-sectional part: Four groups of subjects with different stages of AMD (early, intermediate, late and no AMD) will be included.
Longitudinal part: a group of iAMD subjects will be followed-up for a 10-year period.

Study burden and risks

The MACUSTAR clinical study is a low-interventional study, which will not test therapeutic interventions. All devices used are already marketed in the study countries or are market-ready. As almost all assessments and procedures (except for FA and blood collection) are non-invasive, most Adverse Events (AE) may be due to the spontaneous progression of the underlying disease or occurrence of concomitant diseases.
Blood collection will be performed at the baseline visit and for subjects with iAMD participating in the longitudinal study annually thereafter. The normal minor risks associated with blood collection are: hematoma at the injection site; a locally restricted inflammation; and, in very rare cases, a blood clot (thrombosis).
The only invasive assessment planned in the context of the MACUSTAR clinical study is FA. However, this diagnostic assessment will only be performed in a limited number of subjects, in whom the investigator has the clinical suspicion of progression of AMD to late stage and specifically to nAMD. FA is considered to be needed as it is the current gold standard in clinical practice to ascertain diagnosis of nAMD and is required to qualify for most currently available publicly reimbursed treatments for nAMD in EU countries. In a retrospective review of all adverse reactions to intravenous sodium fluorescein injection (n=11 898) in subjects undergoing fluorescein angiography between June 1998 and June 2004, a total of 132 adverse drug reactions (ADR) were recorded, all classified as mild to moderate, with the most common ADRs being nausea and vomiting. No serious ADRs or deaths were reported 7.

Contacts

Public
University Hospital Bonn, UKB

Sigmund Freud Str. 2
Bonn 53127
DE
Scientific
University Hospital Bonn, UKB

Sigmund Freud Str. 2
Bonn 53127

DE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

General Inclusion criteria (applicable to all groups)
1. Male and female subjects.
2. Aged 55 - 85 years at baseline.
3. Able and willing to provide written informed consent and to comply with the study protocol visits and assessments.Intermediate AMD
1. Study eye must have iAMD and,
2. The fellow eye must have iAMD and/or, in addition, extrafoveal GA (no atrophy within the central ETDRS subfield), maximum total GA size is 1.25 mm2. Definition of iAMD: large drusen >125 µm and/or any AMD pigmentary abnormalities, that are definite hyper- or hypopigmentary abnormalities associated with medium or large drusen but not associated with other known disease entities. (See table 4-1 for more specifications). If both eyes are eligible for the study based on inclusion criteria, the eye with better visual acuity (i.e. on BCVA) will be selected as the study eye as this will improve reliability of functional testing and quality of image acquisition and thus improve sensitivity to detect change over time. In cases in which both eyes have the same visual acuity, the study eye will be selected at random by the investigator.
3. ETDRS letter chart BCVA in the study eye not worse than 72 letters (approximately 20/40 Snellen VA equivalent).
4. All general inclusion criteria.Late AMD
1. Subjects with bilateral GA, bilateral nAMD or nAMD in one eye and GA in the other (See table 4-1 for more specifications).
2. BCVA between 20/80 and 20/200 in study eye.
3. All general inclusion criteria.Early AMD
1. Subjects with medium drusen > 63µm and <= 125µm and no AMD pigmentary

abnormalities in both eyes and not signs of intermediate or late AMD. (See table 4-1 for more specifications).
2. All general inclusion criteria. No AMD
1. No signs of early, intermediate or late AMD in both eyes. (See table 4-1 for more specifications).
2. All general inclusion criteria only.ãÞ*Öç*ÍRÚ

Exclusion criteria

General Exclusion criteria (applicable to all groups)
1. Media opacity or eye movement disorder (nystagmus) that interferes with retinal imaging data quality in the opinion of the investigator.
2. Severe ptosis, extraocular motility restriction or head tremor preventing adequate fundus visualization in the opinion of the investigator.
3. Any signs of nAMD or GA according to the criteria descried in table 4-1 (does not apply to the late AMD group).
4. Any concurrent intraocular condition in the study eye (e. g. glaucoma or cataract) that, in the opinion of the investigator would either require surgical intervention during the study to prevent or treat visual loss that might result from that condition or affect interpretation of study results.
5. Severe non-proliferative diabetic retinopathy, or proliferative diabetic retinopathy.
6. Any diabetic macular edema or macular disease
7. Ocular disorders in the study eye (i. e., pre-retinal membrane) at the time of enrolment that may confound interpretation of study results and compromise visual acuity.
8. Diagnosis of uncontrolled glaucoma with intraocular pressure of >30 mmHg (despite current pharmacological or non-pharmacological treatment).
9. Known systemic illness which in the opinion of the investigator will prevent from actively participating in the study.
10. Concomitant treatment for AMD in either eye (concomitant use of vitamins/supplements is not excluded; does not apply to the late AMD group).
11. Any periocular or intravitreal injections (IVT) in either eye (does not apply to the late AMD group).
12. Participation in any other interventional trial.
13. Obvious retinal changes due to causes other than AMD (e.g. evidenced by an existing diagnosis of monogenetic macular dystrophies, Stargardt disease, cone rod dystrophy, or toxic maculopathies).
14. Any history of allergies to fluorescein.Intermediate AMD
1. Any GA in the study eye
2. Any extrafoveal GA larger than 1.25 mm2 (as defined above) in the fellow eye.
3. All general exclusion criteria.Late AMD
1. All general exclusion criteria only.Early AMD
1. Intermediate or late AMD (following Beckman classification) in any eye.
2. All general exclusion criteria.No AMD

1. Early to late AMD (following Beckman classification) in any eye.
2. All general exclusion criteria.
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Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-09-2018
Enrollment:	80
Type:	Actual

Ethics review

Approved WMO Date:	14-08-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-11-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-02-2019
Application type:	Amendment

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Not approved Date:	05-03-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-09-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-10-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-08-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT03349801
CCMO	NL64026.091.17