Holistic approaches to patient care in neovascular age-related macular degeneration

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Overview

EURETINA 2020 Virtual
Holistic approaches to patient care in nAMD

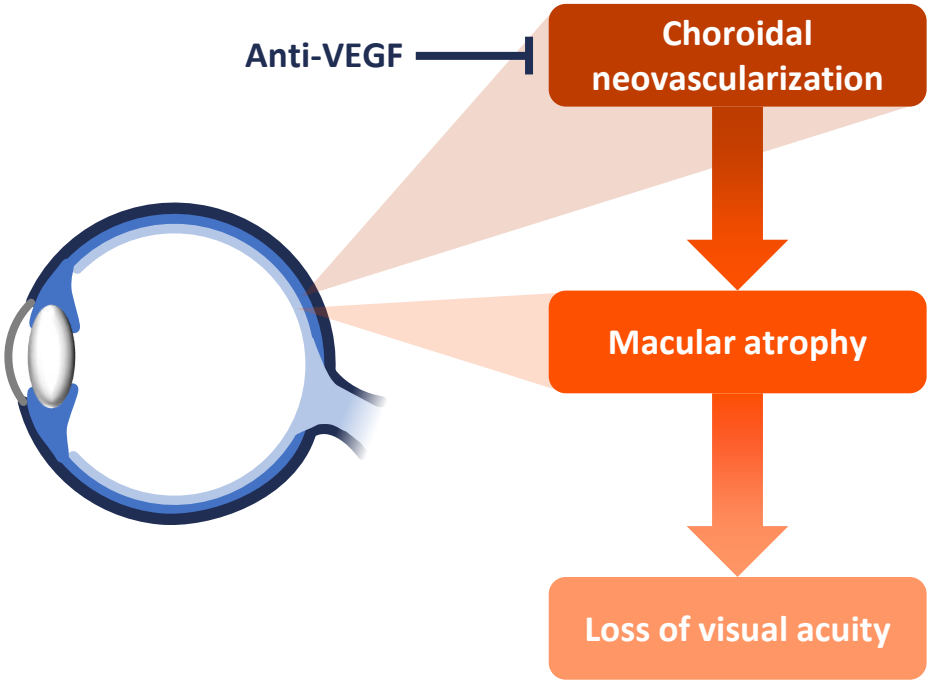
- Part 1: Latest findings on the role of retinal fluid as a marker of disease activity
- Part 2: Latest findings on treatment discontinuation
- Part 3: Latest findings on optimal dosing of anti-VEGF therapy in nAMD

nAMD, neovascular age-related macular oedema; VEGF, vascular endothelial growth factor.

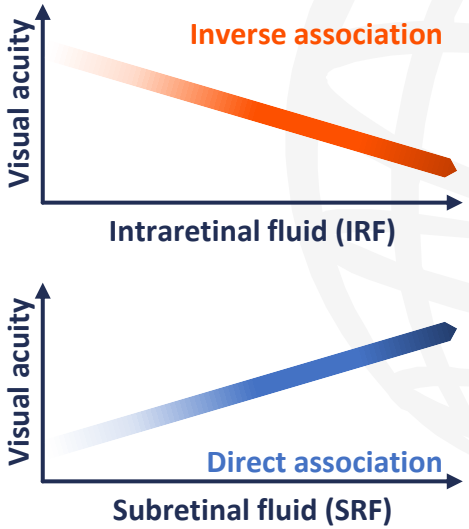
EURETINA 2020 Virtual
Holistic approaches to patient care in nAMD

Retinal fluid as a marker of disease activity in nAMD

Macular fluid and macular atrophy in nAMD[1,2]



CNV activity and the need for retreatment are defined by the presence of macular fluid



CNV, choroidal neovascularization; VEGF, vascular endothelial growth factor.

1. Holekamp NM. *Am J Manag Care*. 2019;25:S172–81; 2. Siedlecki J, et al. *Sci Rep*. 2020;10:8036.

Course of sub-retinal fluid over 10 years

Study design

To investigate the course patterns of SRF over 10 years and their effect on visual acuity outcomes in eyes with nAMD

Five patterns of course of SRF:

i. SRF present throughout (SRF continuous)
ii. SRF only at baseline (Early dry)
iii. SRF absent at baseline but noted during the course of treatment (New SRF)
iv. SRF present at baseline and initial visits, but once dry no recurrence (Late dry)
v. Irregular course of SRF through follow-up (SRF fluctuation).

Visual acuity outcomes were compared among patterns

nAMD, neovascular age-related macular degeneration; PRN, pro re nata/as required; SRF, sub-retinal fluid; T&E, treat and extend.

"Course of sub-retinal fluid over 10 years in patients with neovascular age related macular degeneration and impact on visual acuity" by S. Chandra. EURETINA 2020 Virtual, 2-4 October 2020.

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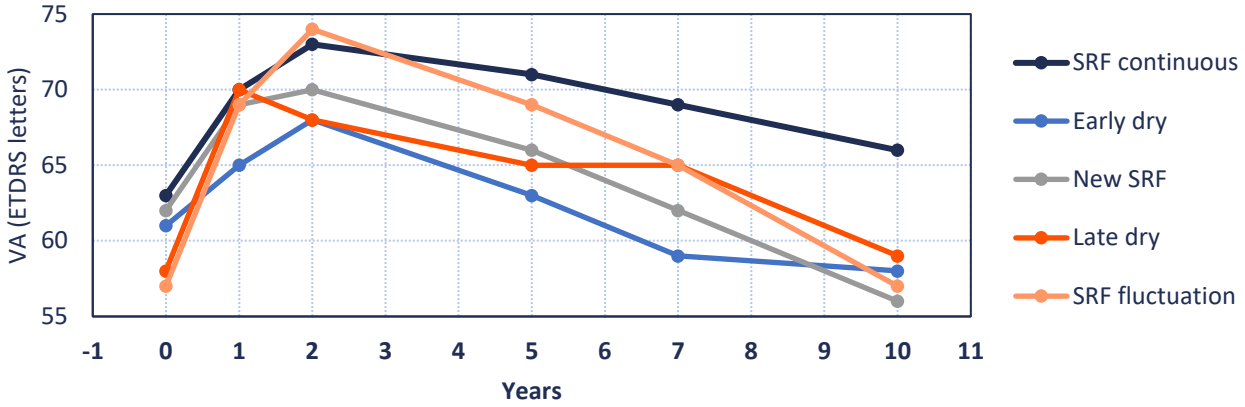
Course of sub-retinal fluid over 10 years

Study outcomes



In all groups, VA improved during the first two years and declined thereafter

Patients in the SRF continuous group showed:

- **the highest mean VA**
- **the slowest decline**
- **the least proportion of patients with atrophy (40%, p=0.01)**

Patients in the early dry and late dry groups had the worst VA at year 2 (67.8 ± 14.0 and 68.1 ± 11.7 letters, respectively)

ETDRS, Early Treatment Diabetic Retinopathy Study; SRF, sub-retinal fluid; VA, visual acuity.

"Course of sub-retinal fluid over 10 years in patients with neovascular age related macular degeneration and impact on visual acuity" by S. Chandra. EURETINA 2020 Virtual, 2-4 October 2020.

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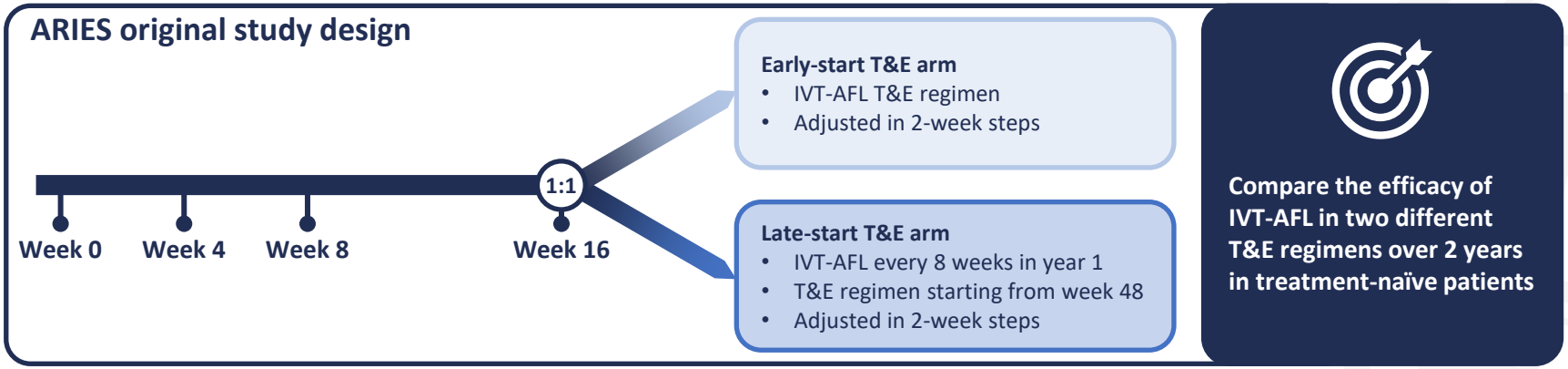
Retinal fluid compartment status: ARIES study

Study design – post-hoc study of ARIES (NCT02581891 – phase IV)



Fluid compartment status (SRF and IRF) was assessed at baseline, week 16 and at every treatment visit

SRF/IRF status and functional outcomes in patients with nAMD treated with IVT-AFL to guide treatment extension decisions

IRF, intra-retinal fluid; IVT-AFL, intravitreal aflibercept; nAMD, neovascular age-related macular atrophy; SRF, sub-retinal fluid; T&E, treat and extend.

"Retinal fluid compartment status and functional outcomes in patients with neovascular age-related macular degeneration treated with intravitreal aflibercept using a treat-and-extend regimen: a post-hoc analysis of the ARIES study" by P. Mitchell. EURETINA 2020 Virtual, 2-4 October 2020.
Clinical trial listed by identifier at: ClinicalTrials.gov (accessed October 2020).

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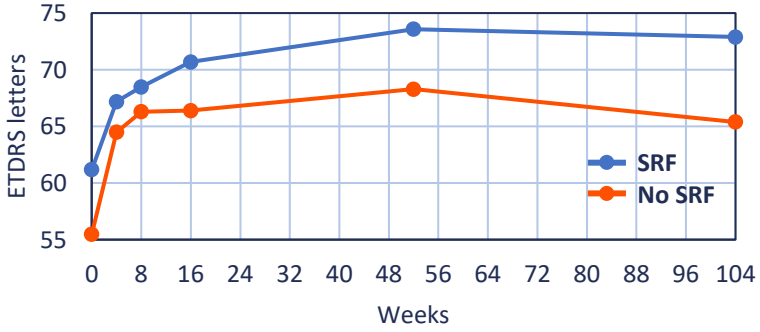
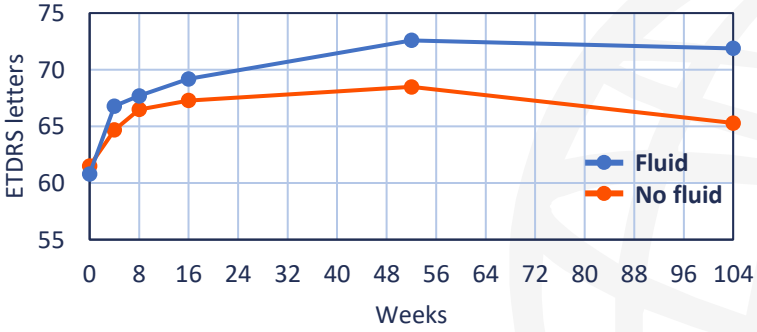
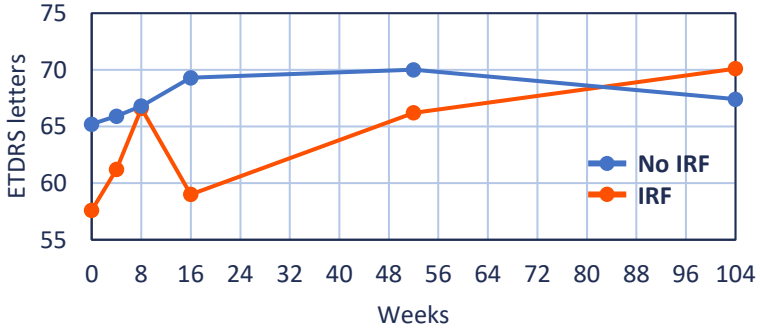
Retinal fluid compartment status: ARIES study

Study outcomes







- **IVT-AFL improved vision in treatment-naïve nAMD eyes regardless of fluid type and early/late T&E regimen**
- **The presence of SRF was consistently associated with better BCVA**
- **Both the presence of IRF and the complete absence of fluid were generally associated with poorer BCVA**

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; IRF, intra-retinal fluid; IVT-AFL, intravitreal aflibercept; nAMD, neovascular age-related macular atrophy; SRF, sub-retinal fluid.

"Retinal fluid compartment status and functional outcomes in patients with neovascular age-related macular degeneration treated with intravitreal aflibercept using a treat-and-extend regimen: a post-hoc analysis of the ARIES study" by P. Mitchell. EURETINA 2020 Virtual, 2-4 October 2020.

Real-world anti-VEGF treatment patterns

Study design – ALTAIR (NCT02305238)

Retrospective cohort study
Medical Data Vision electronic health record

Japan	374 hospitals	Apr 2009 – Dec 2017

Patients aged ≥50 years with nAMD diagnosis with or without evidence of anti-VEGF treatment

To investigate real-world anti-VEGF treatment patterns for patients with nAMD

- **Prevalent nAMD (n=5,933)**
  Diagnosis before Apr 2009
- **Incident nAMD (n=5,377)**
  First diagnosis during Apr 2009 – Dec 2017 and no nAMD diagnosis during the 6 months prior to inclusion
- **Anti-VEGF therapy (n=17,970)**
  Receiving ranibizumab, aflibercept or pegaptanib

nAMD, neovascular age-related macular oedema; VEGF, vascular endothelial growth factor.

"Relationship between retinal fluid and functional outcomes in patients with exudative age-related macular degeneration treated with intravitreal aflibercept using a treat-and-extend regimen: post-hoc analysis of the ALTAIR study" by M. Ohji. EURETINA 2020 Virtual, 2-4 October 2020.
Clinical trial listed by identifier at: ClinicalTrials.gov (accessed October 2020).

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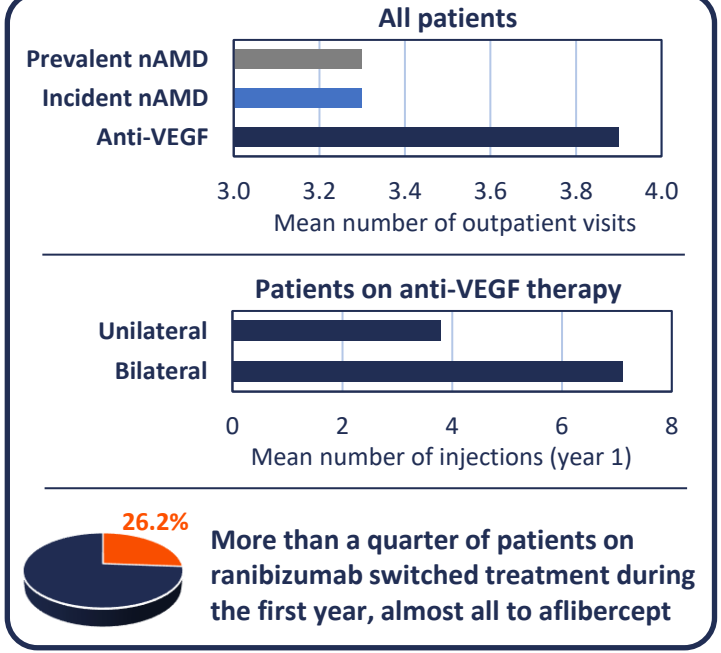
Real-world anti-VEGF treatment patterns

Study outcomes



More than a quarter of patients on ranibizumab switched treatment during the first year, almost all to aflibercept

58.1% Patients who had two or more non-injection visits between injections

43.5% Unilaterally treated patients who received loading doses (≥3 injections during the first 120 days)

Median interval between injections after the loading phase **61 days**

! The mean number of anti-VEGF injections during the first year of treatment was lower than in clinical trials

nAMD, neovascular age-related macular oedema; VEGF, vascular endothelial growth factor.

"Relationship between retinal fluid and functional outcomes in patients with exudative age-related macular degeneration treated with intravitreal aflibercept using a treat-and-extend regimen: post-hoc analysis of the ALTAIR study" by M. Ohji. EURETINA 2020 Virtual, 2-4 October 2020.

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Deep learning-based fluid quantification

Study design

AI-based analysis of real-world OCT images
Vienna Imaging Biomarker Eye Study (VIBES)

Austria

N=38,295 patients

2007–2017

N=585,919 OCT scans

Filtered for at least one anti-VEGF injection for active nAMD

- **Baseline** (60–0 days before first injection) n=1,138
- **1 year** n=656
- **2 years** n=408
- **3 years** n=309
- **4 years** n=221
- **5 years** n=175

OCT scans were automatically analyzed for CRT, IRF and SRF by a validated deep learning algorithm

To quantify IRF and SRF before anti-VEGF treatment initiation and up to 5 years after the first injection

AI, artificial intelligence; CRT, central retinal thickness; IRF, intra-retinal fluid; IVT-AFL, intravitreal aflibercept; nAMD, neovascular age-related macular atrophy; SRF, sub-retinal fluid; OCT, optical coherence tomography.

"Deep learning-based automated fluid quantification in clinical routine OCT images in neovascular AMD" by B. Gerendas. EURETINA 2020 Virtual, 2-4 October 2020.

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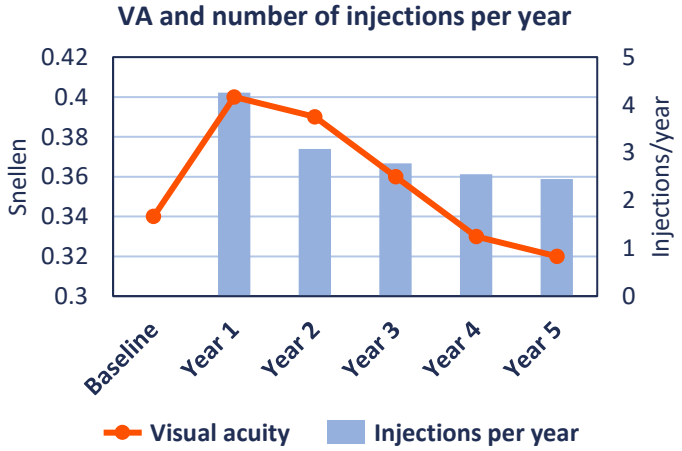
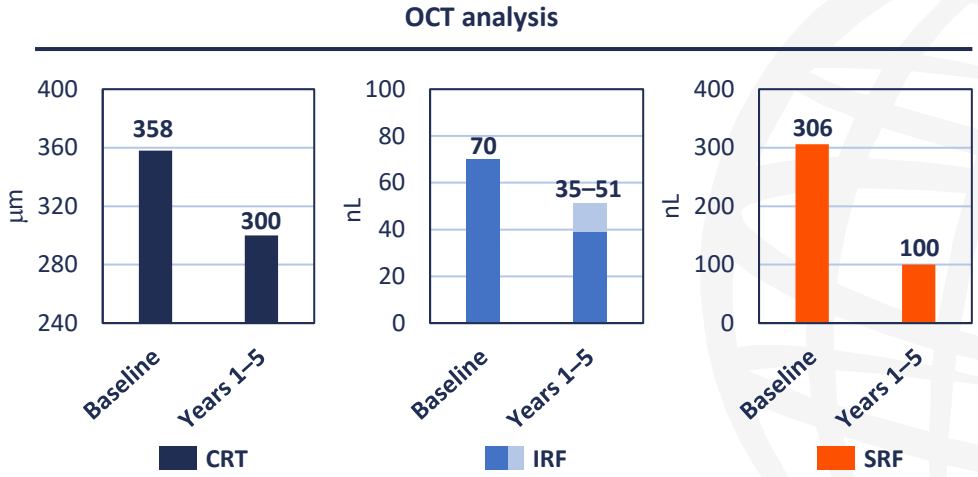
Deep learning-based fluid quantification

Study outcomes





Deep learning-based automated fluid quantification is well-suited to measure treatment response after anti-VEGF treatment and guide the clinical management in nAMD

CRT, central retinal thickness; IRF, intra-retinal fluid; IVT-AFL, intravitreal aflibercept; nAMD, neovascular age-related macular atrophy; SRF, sub-retinal fluid; OCT, optical coherence tomography.

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Holistic approaches to patient care in nAMD

Treatment discontinuation:
Why it occurs and how to reduce it

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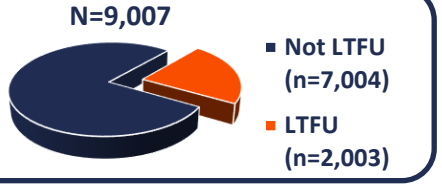
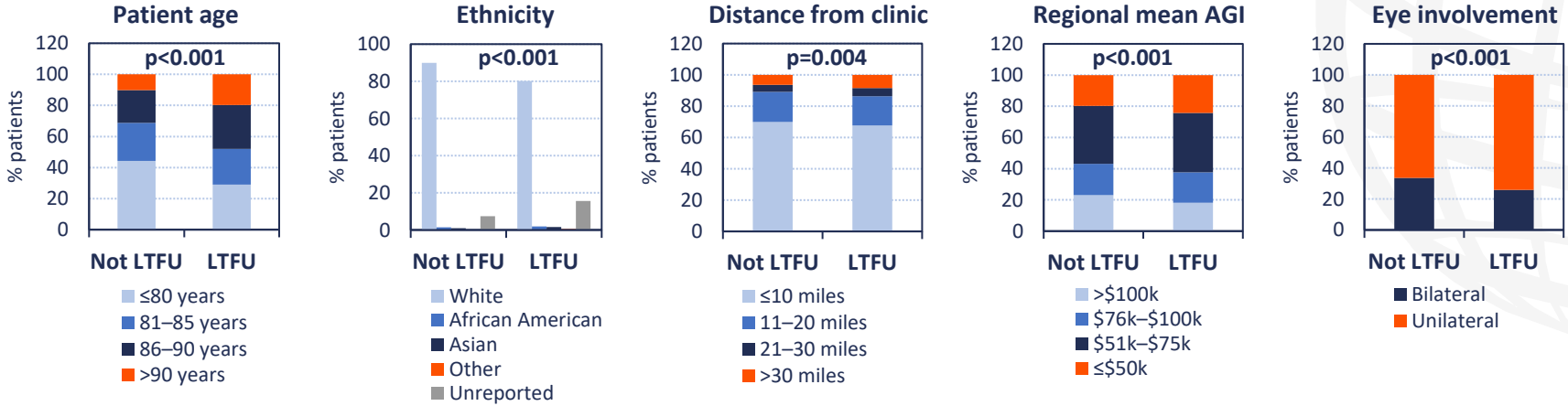
Loss to follow-up in patients with nAMD

Risk factors associated with LTFU – report from a USA cohort[1]

LTFU = no follow-up visit within 12 months after injection





AGI, adjusted gross income; LTFU, loss to follow-up.

1. Obeid A, et al. *JAMA Ophthalmol*. 2018;136:1251–9.

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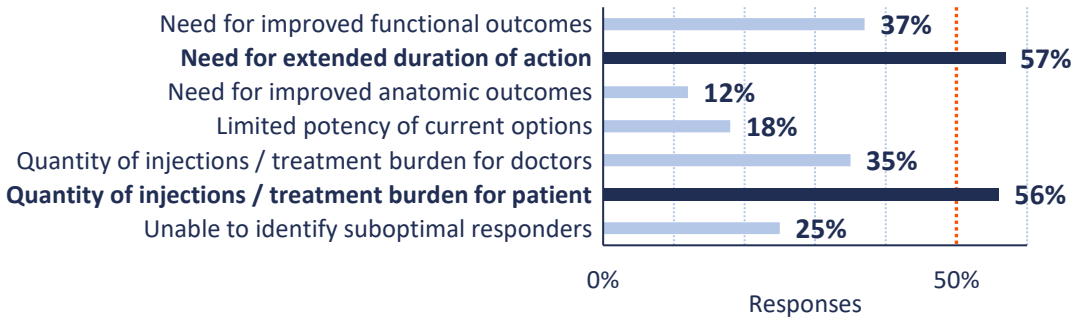
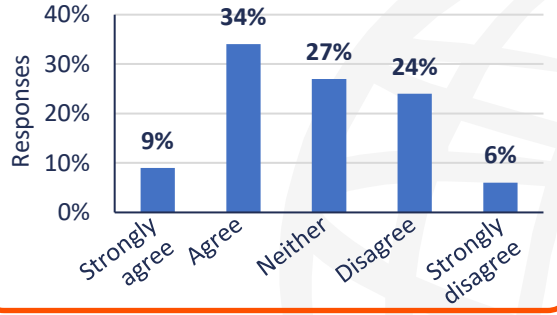
2019 EURETINA Clinical Trends Survey

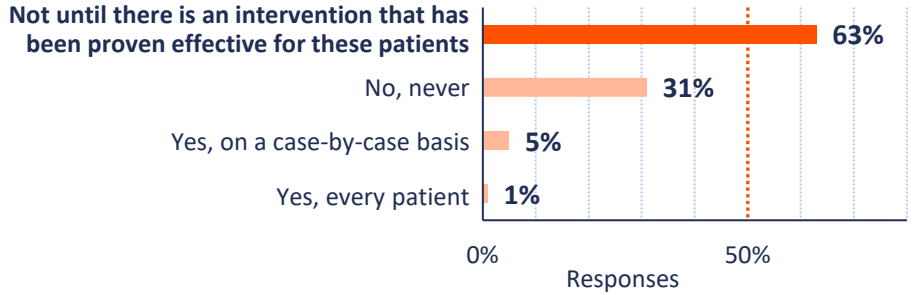
What is the largest unmet need for current anti-VEGF treatment? (select up to 3)



Patients on monthly or PRN schedules are more compliant than those on T&E



Do you perform genetic test on your patients for AMD?



What percentage of your patients who require regular anti-VEGF injections are adherent to their treatment timeframe?

59%

3–6 months

What is your preferred duration of effect for a sustained drug delivery implant when available for you to use?

- **128 questions**
- **1,043 responses from EURETINA delegates**

AMD, age-related macular degeneration; PRN, pro re nata/as required; T&E, treat and extend; VEGF, vascular endothelial growth factor.

"Welcome & Review of EURETINA AMD Clinical Trends Survey Data" by A. Loewenstein. EURETINA 2020 Virtual, 2-4 October 2020.

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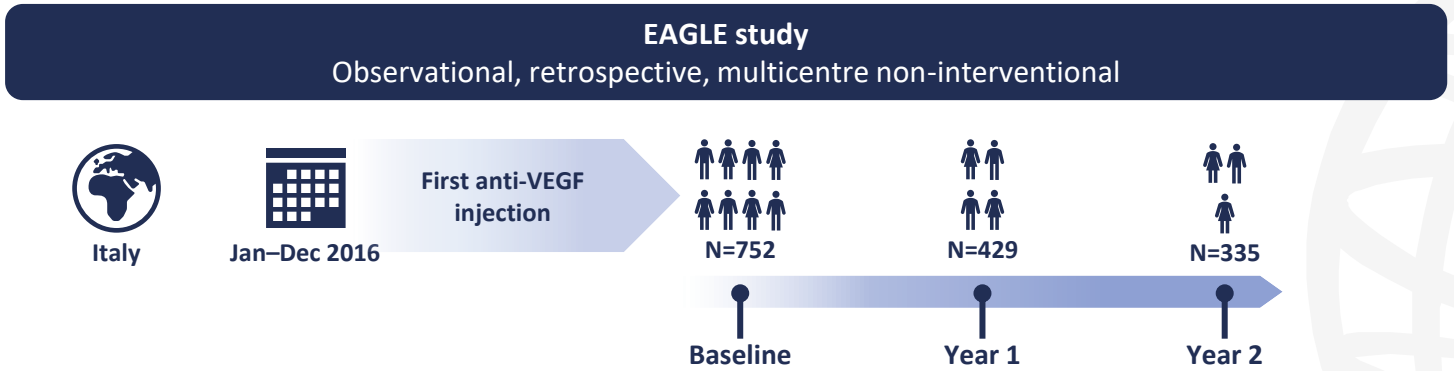
Anti-VEGF in real life experience (EAGLE)

Study design



Primary endpoint:
- Mean number of injections/year and overall

Secondary endpoints:
- Changes in VA
- Factors associated with VA outcomes

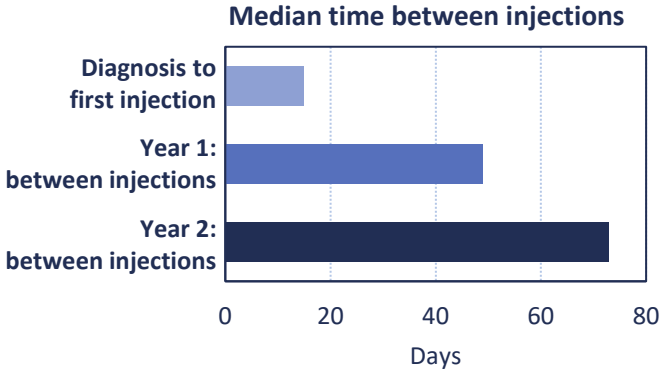
- **To assess the real life management of naive patients with nAMD receiving anti-VEGF**
- **To evaluate the effectiveness of licensed anti-VEFG drugs for intraocular use**

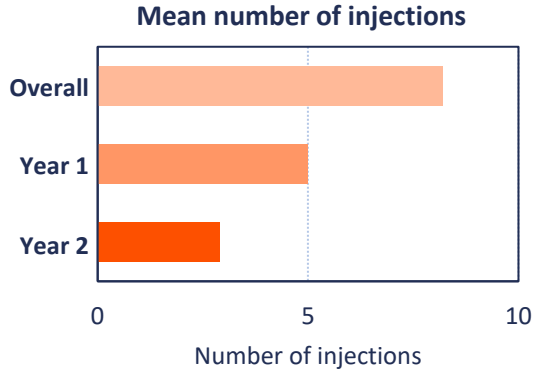
nAMD, neovascular age-related macular degeneration; VA, visual acuity; VEGF, vascular endothelial growth factor.

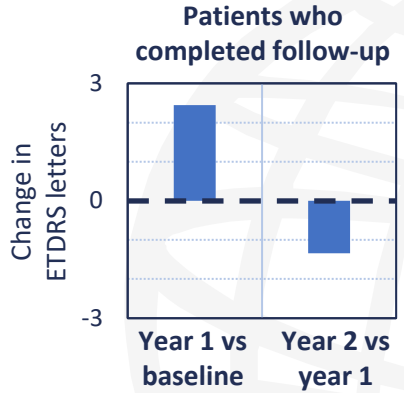
"Evidence of anti-VEGF use in real life experience (EAGLE) - a large retrospective cohort study from secondary data source in Italy" by G. Staurenghi. EURETINA 2020 Virtual, 2-4 October 2020.

Anti-VEGF in real life experience (EAGLE)

Study outcomes







Baseline VA: 58 letters

Patients with baseline VA above 58 letters **received 1–2 injections more** than patients with baseline VA below 58 letters	Patients with baseline VA above 58 letters **gained around 10 letters more** than patients with baseline VA below 58 letters

- **The number of injections was lower than what has been reported in clinical trials**
- **A large number of patients were lost to follow-up**
- **Patients with low VA at baseline were more frequently lost to follow-up**

ETDRS, Early Treatment Diabetic Retinopathy Study; VA, visual acuity; VEGF, vascular endothelial growth factor.

"Evidence of anti-VEGF use in real life experience (EAGLE) - a large retrospective cohort study from secondary data source in Italy" by G. Staurenghi. EURETINA 2020 Virtual, 2-4 October 2020.

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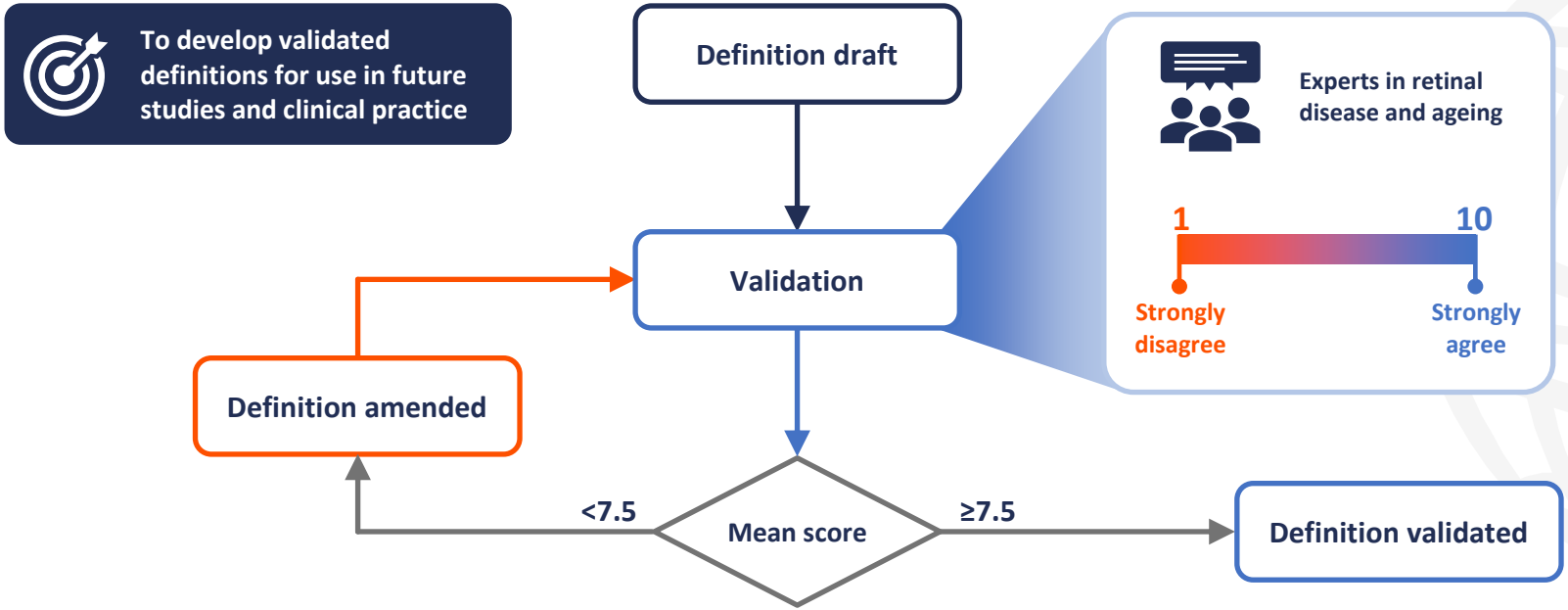
Anti-VEGF therapy: Adherence and persistence

Validation process



VEGF, vascular endothelial growth factor.
"Defining adherence and persistence to anti-vascular endothelial growth factor (VEGF) therapies in neovascular age-related macular degeneration (nAMD)" by A. Loewenstein. EURETINA 2020 Virtual, 2-4 October 2020.

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Anti-VEGF therapy: Adherence and persistence

Validated definitions

Adherence

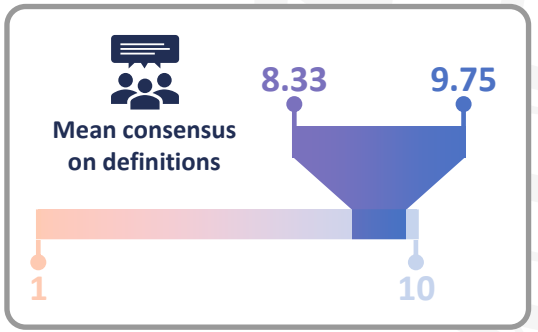
- **Fully adherent patient**
  Attends every treatment or monitoring visit
- **Adherent patient**
  Misses no more than one treatment or monitoring visit
- **Non-adherent patient**
  Misses no more than two treatment or monitoring visits over a period of 1 year

Persistence

- **Persistent patient**
  Maintains treatment or monitoring as advised by the physician
  and
  attended most recent appointment
- **Non-persistent patient**
  Does not attend any treatment or monitoring visit
  and/or
  follow-up appointments are not scheduled for a period of 6 months

Missed visit

The recommended appointment date is exceeded by more than two weeks



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"Defining adherence and persistence to anti-vascular endothelial growth factor (VEGF) therapies in neovascular age-related macular degeneration (nAMD)" by A. Loewenstein. EURETINA 2020 Virtual, 2-4 October 2020.

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Home monitoring of nAMD: MyVision

Study design and outcomes

MyVision trial
Clinical follow-up of the MultiBit vision test

Denmark, Norway, Sweden

12 months

To compare MultiBit results and nAMD disease activity

MultiBit vision test

- Mobile app
- Displays numbers in various resolutions in different parts of the central vision
- Tests the function of the macula
- Results automatically sent to the eCRF

N=45

- Newly diagnosed nAMD patients treated with anti-VEGF in a T&E or PRN regimen
- Trained to perform the MultiBit test
- Completed the test daily or weekly

19 centres

- Investigators performed disease activity assessments in the clinic
- Data manually entered into the eCRF

- MultiBit results were compared with clinical examinations outcomes
- Disease sequences were classified into:
  - Deterioration
  - Improvement
  - No change

Specificity 52%

45% Sensitivity

MultiBit needs further development and validation

eCRF, electronic case report form; nAMD, neovascular age-related macular degeneration; PRN, pro re nata/as required; T&E, treat and extend.
"A multicenter, prospective 12-months non-interventional study to investigate an automated alarm system for home monitoring of wet AMD based on trends in MultiBit vision test" by M. Larsen. EURETINA 2020 Virtual, 2-4 October 2020.

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Home monitoring of AMD: Notal OCT

Study design

Notal OCT
Tele-connected OCT in patients' homes

- Consecutive eyes with dry and wet AMD
- VA ≥20–400
- Subjects imaged on commercial OCT and then self-imaged own eyes with Notal OCT (two instruments: V2.5 and V3)
- Notal OCT images were compared with commercial OCT:
  - IRF and SRF in the central 10-degree visual field of the macula

- **To evaluate self-operability of Notal OCT by elderly patients**
- **To compare image assessment for disease activity between commercial and Notal OCT**

Benefits of home OCT self-monitoring

Personalized AMD management

- **Avoid undertreatment**
- **Improve outcomes**
- **Reduce treatment burden**
- **Increase patient satisfaction**

AMD, age-related macular atrophy; IRF, intra-retinal fluid; OCT, optical coherence tomography; SRF, sub-retinal fluid; VA, visual acuity.
"Improving adherence and outcomes in AMD therapy: Home monitoring" by A. Lowenstein. EURETINA 2020 Virtual, 2-4 October 2020.

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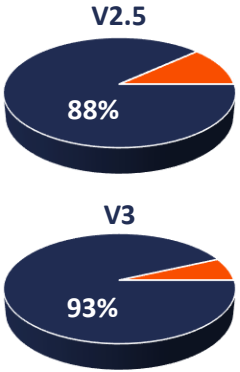
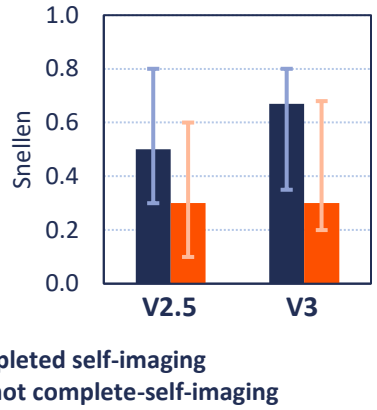
Home monitoring of AMD: Notal OCT

Study outcomes

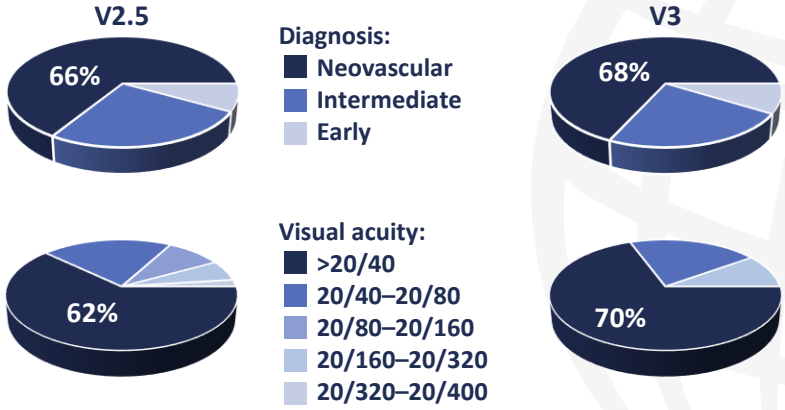
Ability to self image



Median visual acuity



Eye characteristics and self-imaging success



In a patient survey, 96% of patients agreed or strongly agreed with statements on the simplicity and comfort of Notal OCT V2.5

PPA and NPA between commercial and Notal OCT were consistently over 90% for IRF and SRF measurement

IRF, intra-retinal fluid; AMD, age-related macular atrophy; NPA, negative percent agreement; OCT, optical coherence tomography; PPA, positive percent agreement; SRF, sub-retinal fluid.

"Improving adherence and outcomes in AMD therapy: Home monitoring" by A. Lowenstein. EURETINA 2020 Virtual, 2-4 October 2020.

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EURETINA 2020 Virtual
Holistic approaches to patient care in nAMD

Optimal dosing of anti-VEGF in nAMD: Clinical trials and real-world experience

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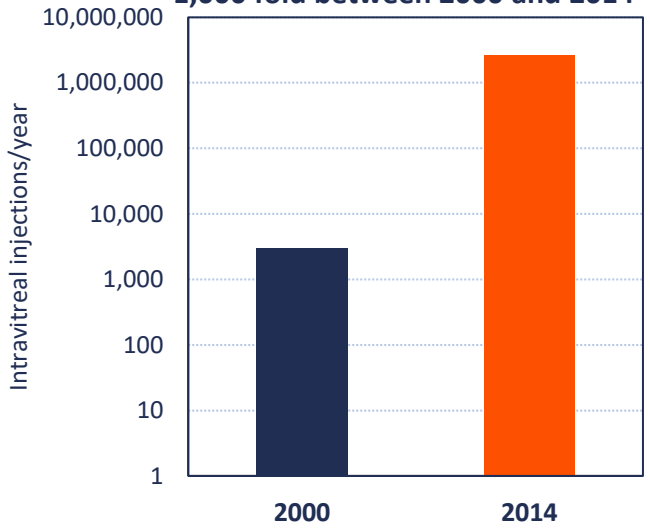
Impact of anti-VEGF on nAMD

The number of anti-VEGF injections/year increased nearly 1,000 fold between 2000 and 2014[1]



Real-world outcomes lag behind those documented in clinical trials:[1]

- Patients with newly diagnosed nAMD receive fewer anti-VEGF injections
- More than 20% of patients receiving an anti-VEGF agent discontinue treatment and do not follow up

To reduce treatment burden and improve real-world outcomes

nAMD, neovascular age-related macular degeneration; VEGF, vascular endothelial growth factor.

1. Holekamp NM. *Am J Manag Care*. 2019;25:S172–81.

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The MATE study

Study design

MATE study
(EudraCT Number: 2015-002302-36)
Prospective, multicentre, pilot, RCT

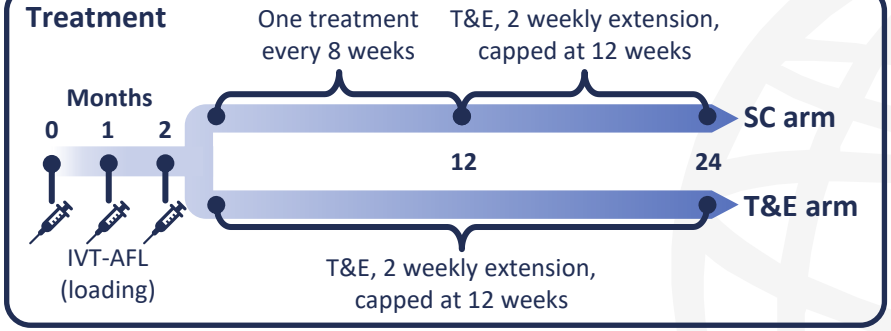
UK

N=39

6 centres

Dec 2015–
Mar 2019

To measure the impact of anti-VEGF treatment on the quality of life of patients with nAMD



Assessment

- Visual acuity
- Number of treatments

- **MacDQoL** – enables participants to indicate which aspects of their life are affected by nAMD
- **MacTSQ** – measures participant treatment satisfaction

MacDQoL, macular disease dependent quality of life; MacTSQ, macular disease treatment satisfaction questionnaire; nAMD, neovascular age-related macular degeneration; RCT, randomized controlled trial; SC, standard care; T&E, treat and extend; VEGF, vascular endothelial growth factor.

"The MATE study: a 24-month, pilot, randomised controlled trial comparing standard care with individualized treat and extend regimen with intravitreal aflibercept for neovascular age - related macular degeneration MacTSQ and MacDQOL outcomes" by S. Burns. EURETINA 2020 Virtual, 2-4 October 2020.
Clinical trial listed by identifier at: www.clinicaltrialsregister.eu (accessed October 2020).

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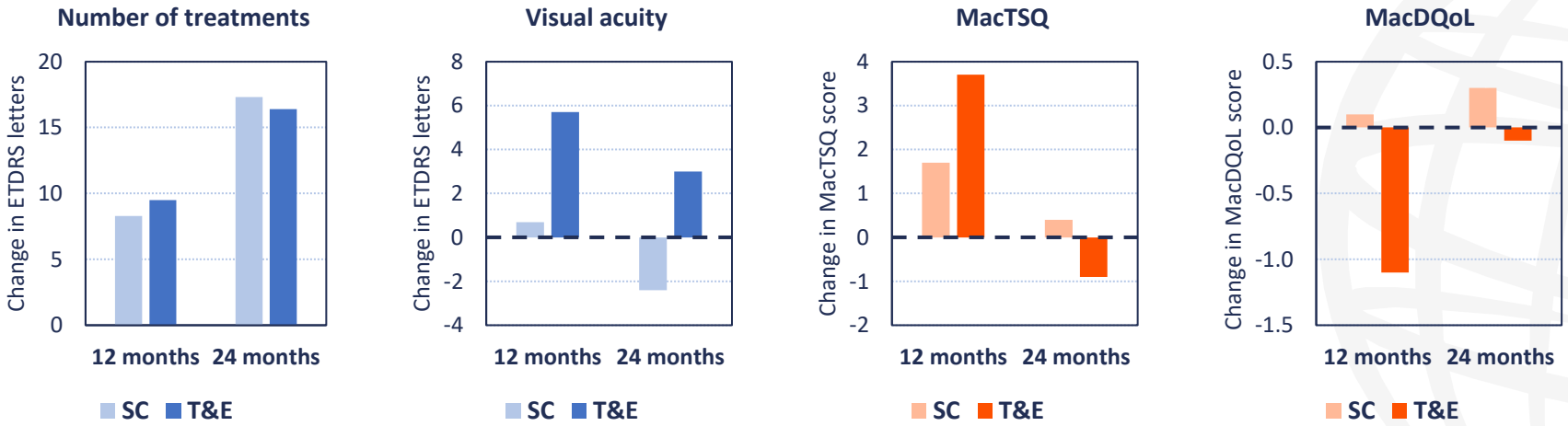
The MATE study

Study outcomes

Changes compared to baseline values



Measures of treatment satisfaction and quality of life do not correlate with number of treatments or visual acuity

ETDRS, Early Treatment Diabetic Retinopathy Study; MacDQoL, macular disease dependent quality of life; MacTSQ, macular disease treatment satisfaction questionnaire; SC, standard care; T&E, treat and extend.

"The MATE study: a 24-month, pilot, randomised controlled trial comparing standard care with individualized treat and extend regimen with intravitreal aflibercept for neovascular age - related macular degeneration MacTSQ and MacDQOL outcomes" by S. Burns. EURETINA 2020 Virtual, 2-4 October 2020.

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COVID-19 and enrolment of XTEND

Study design

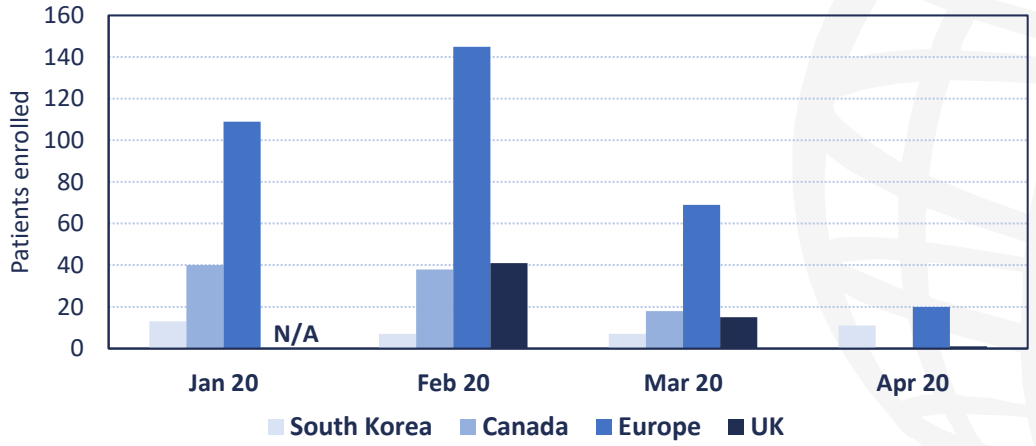
XTEND study (NCT03939767)
Multicentre, observational, prospective, cohort study

- Europe
- Latin and North America
- Asia-Pacific
- Enrolment started in May 2019
- Treatment-naïve patients aged ≥50 years

To examine the effectiveness of proactive IVT-AFL regimens in a routine clinical practice setting in patients with nAMD

Study sub-analysis outcomes

To evaluate national differences of the effect of the COVID-19 pandemic on patient enrolment into the XTEND study



Due to the COVID-19 pandemic, patient enrolment declined across all countries in early 2020, and as of April 2020, enrolment was almost completely halted

COVID-19, coronavirus disease 2019; IVT-AFL, intravitreal aflibercept; N/A, not available; mAMD.

"Impact of COVID-19 on the enrollment of XTEND, a global non-interventional study investigating intravitreal aflibercept proactive dosing in patients with neovascular age-related macular degeneration" by V. Chaudhary. EURETINA 2020 Virtual, 2-4 October 2020.
Clinical trial listed by identifier at: ClinicalTrials.gov (accessed October 2020).

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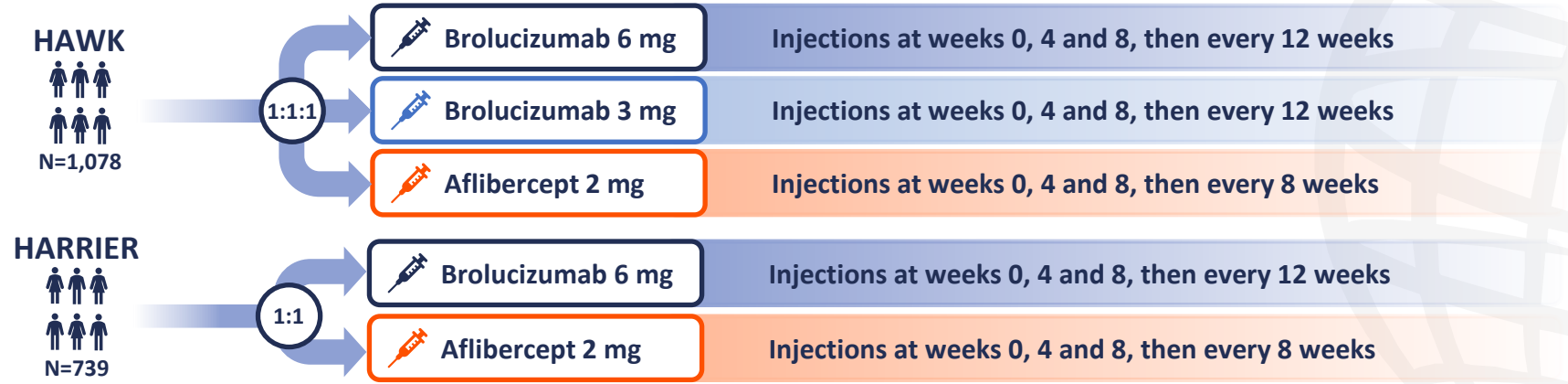
Brolucizumab vs aflibercept

Study design

HAWK (NCT02307682) and **HARRIER** (NCT02434328)



To assess the number of injections and time to dry analysis of brolucizumab vs aflibercept in patients with nAMD

Sustained dryness defined as three consecutive fluid-free (IRF and SRF) visits

IRF, intra-retinal fluid; nAMD, neovascular age-related macular atrophy; SRF, sub-retinal fluid.

"Number of injections and time to dry analysis of brolucizumab vs aflibercept in patients with neovascular age-related macular degeneration: 96-week data from HAWK and HARRIER" by Y. Yang. EURETINA 2020 Virtual, 2-4 October 2020.

Clinical trials listed by identifiers at: ClinicalTrials.gov (accessed October 2020).

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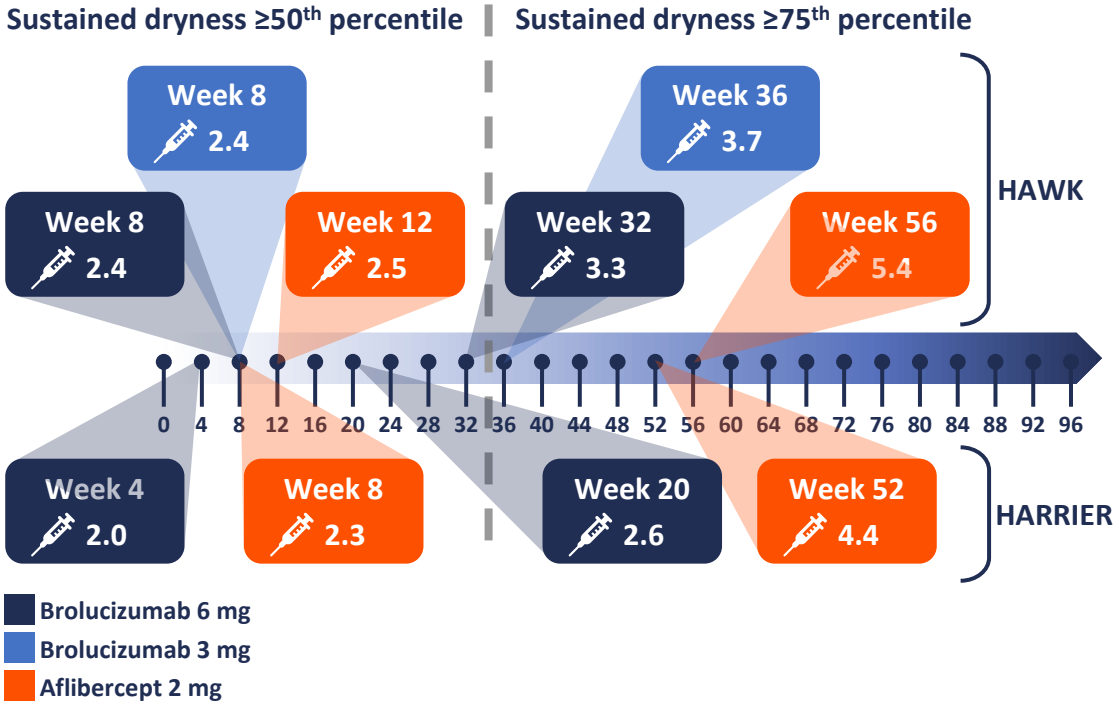
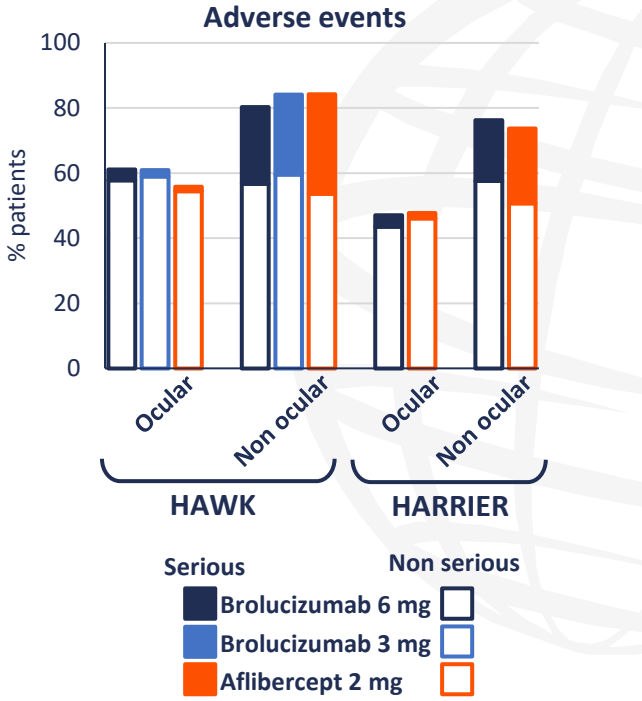
Brolucizumab vs aflibercept

Study outcomes





"Number of injections and time to dry analysis of brolucizumab vs aflibercept in patients with neovascular age-related macular degeneration: 96-week data from HAWK and HARRIER" by Y. Yang. EURETINA 2020 Virtual, 2-4 October 2020.

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Port delivery system with ranibizumab

Study design

Ladder trial (NCT02510794)
Phase II, randomized, active treatment-controlled trial

49 centres

USA

N=220

Sampling schedule

PDS arms (10, 40 and 100 mg/mL)

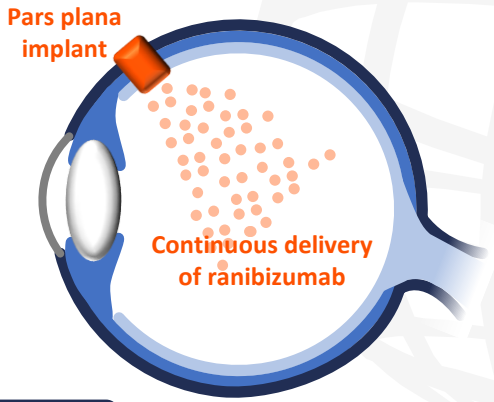
Serum:
- Randomization
- Day 1 (60 min or more after implant insertion)
- 1, 7 and 14 days after implant insertion
- At each monthly study visit
- At 1 and 7 days after each refill

Aqueous humour (optional)
- Randomization
- Before or immediately after implant refill
- At 7 days after refill

IVT arm 0.5 mg/month

Serum:
- Randomization
- Months 1, 3, 6 and 9
- At the final study visit

Port delivery system (PDS)



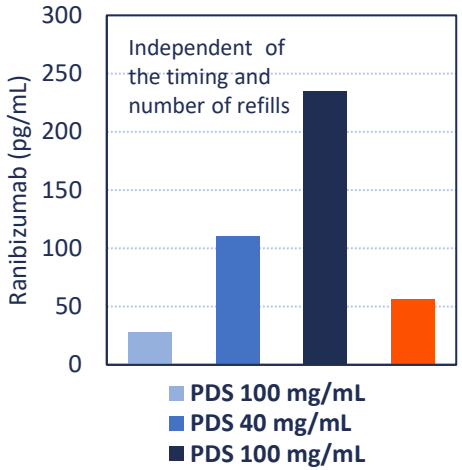
To characterize the pharmacokinetics of ranibizumab after the initial fill and subsequent refills of the PDS implant

IVT, intravitreal; PDS, port delivery system.
"Pharmacokinetic profile of the port delivery system with ranibizumab (PDS) in the phase 2 ladder trial" by A. Khanani. EURETINA 2020 Virtual, 2-4 October 2020.
Clinical trial listed by identifier at: ClinicalTrials.gov (accessed October 2020).

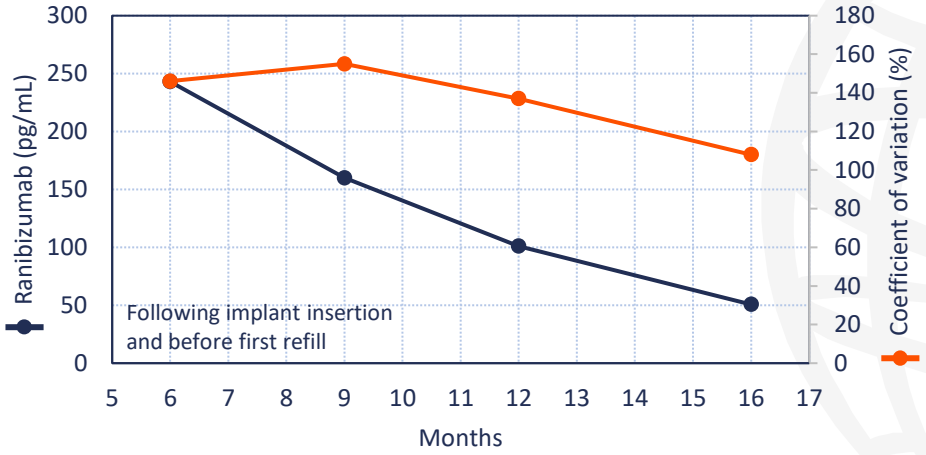
Port delivery system with ranibizumab

Study outcomes

Median serum ranibizumab concentrations at month 9



Geometric mean and coefficient of variation of serum ranibizumab in the PDS 100 mg/mL arm



Aqueous humour concentrations of ranibizumab correlated with serum ranibizumab concentrations (PDS arms)

! PK data support the median time to first refill of 15.8 months observed in patients in the PDS 100 mg/mL arm, which was associated with sustained visual gains comparable with monthly IVT ranibizumab

IVT, intravitreal; PDS, port delivery system.

"Pharmacokinetic profile of the port delivery system with ranibizumab (PDS) in the phase 2 ladder trial" by A. Khanani. EURETINA 2020 Virtual, 2-4 October 2020.

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