**Grading of age-related macular degeneration and its association with diabetic retinopathy in a diabetic retinopathy screening program**

**Purpose**
Age-related macular degeneration (AMD) is the leading cause of certified visual loss in England. Diabetes mellitus and diabetic retinopathy (DR) have been inconsistently related to the risk of AMD. The UK has universal photographic screening programmes for DR enabling the retrospective study of AMD in people with diabetes. In this study, we would aim to study the prevalence and the type of AMD in people with diabetes attending a DR screening program, with a view to identifying any associations between AMD and DR.

**Setting/Venue**
Retrospective, observational study in Liverpool, United Kingdom, utilising fundus photographs routinely collected by the Liverpool Diabetic Eye Screening Programme (LDESP). Patients are enrolled into this programme when their general practitioner makes the diagnosis of diabetes. We utilised patient data collected by the Individualised Screening for Diabetic Retinopathy (ISDR) Cohort Study, which included patients from LDESP unless they opted out of ISDR.

**Methods**
We randomly selected 1,500 subjects of 10,336 people aged ≥50 years who attended the LDESP in 2011 and were enrolled in the ISDR Cohort Study. One researcher (DFR) graded the retinal images taken from the LDESP database for AMD based on the Age-Related Eye Disease Study grading system. We modified the classification by including the non-central geographic atrophy into level 4 (late AMD) in our study. In the analysis, we used the eye with the worst AMD grading result. We randomly selected 10% of the images to be graded for AMD by a reading centre senior grader to assess the quality control. DR grading was performed for routine screening by trained accredited graders within LDESP following published national standards. For the purpose of this analysis, DR was categorised as: (1) no DR (R0M0 in both eyes or only assessable eye); (2) background/mild non-proliferative DR (NPDR) includes R1M0 in both eyes/R1M0_R0M0/R1M0 in one assessable eye; (3) sight-threatening DR (STDR) includes R2 (pre-proliferative/moderate/severe NPDR), R3 (proliferative), M1 (maculopathy), and P (photocoagulation). Multiple logistic regression with multiple imputation was used for data analysis, and some variables were discounted due to high proportion of missing values (≥20%).

**Results**
Gradable photographs were obtained in 1,492 subjects including 374 with background DR and 40 with STDR. Early, intermediate, and late AMD was seen in as follows: 221 (14.8%), 54 (3.6%), and 13 (0.9%) of all subjects; 166 (15.6%), 33 (3.1%), and 11 (1.0%) of those with no DR; 50 (13.4%), 17 (4.5%), and 1 (0.3%) of those with background DR; 4 (10.0%), 2 (5.0%), and 1 (2.5%) of those with STDR. There was no statistically significant association between the binary presence of DR and presence of AMD (p=0.5, chi-squared test). In multiple logistic regression analysis, and after adjusting for possible confounding factors, prevalence of AMD increased with increasing age (OR = 1.06; 95%CI: 1.04–1.08, p<0.001) as expected. No significant association was identified between any AMD and the presence of any DR (OR = 0.87; 95%CI: 0.63–1.19, p=0.4) or diabetes control (OR = 0.99; 95%CI: 0.98 - 1.01, p=0.4). The interobserver agreement for AMD severity level of the right eye (kappa=0.86) was “almost perfect agreement” and “substantial” for the left eye (kappa=0.76).

**Conclusions**
We found that detecting and grading AMD during routine DR screening is feasible and reliable, indicated by good interobserver agreement in our study. This could provide a model for adding AMD to DR screening programmes should a treatment for dry AMD be identified. We did not find any evidence that DR is a protective, or risk factor for AMD. This suggests the mechanisms of these prevalent retinal diseases are not shared.

**Financial Disclosure**
None
Purpose
To analyze the functional and morphological changes in patients discontinuing or suspending treatment with vascular endothelial growth factors (VEGF) for neovascular age-related macular degeneration (nAMD).

Setting/Venue
Retrospective, observational case series.

Methods
The medical records of eyes who received anti-VEGF therapy for nAMD were searched for eyes that discontinued, or suspended treatment for a minimum of 6 months. The visual acuity (VA) and central macular thickness (CMT) at treatment discontinuation and/or suspension were compared with VA at 1- and 2-years post discontinuation/suspension in treatment.

Results
A total of 187 eyes were identified and observed for up to 2-years post discontinuation/suspension in anti-VEGF treatment. The mean number in anti-VEGF injections before discontinuing treatment was 13.8±3.5 (95% CI 8.4 to 17.2 injections). Eighty-one (42%) eyes resumed therapy with a mean loss of 6.4±7.2 (95% CI -1.2 to -0.6 letters; P < 0.01) letters from their last injection before the suspension. These patients recovered +2.1 and +1.4 letters at years 1 and 2, respectively, resulting in a net loss of 5.0 letters [95% CI 2.9 – 7.2 letters; P < 0.01] from treatment suspension and +4.9 letters (95% CI -1.9 to 7.8 letters; P < 0.01) from diagnosis. The 106 eyes that permanently discontinued therapy had gained 6.2 letters (95% CI 4.3 to 8.1 letters; P < 0.01) after 1-year of treatment and lost 0.8 letters (95% CI -0.2 to 0.5 letters; P < 0.01) at discontinuation. After stopping treatment, these patients lost a further 3.4 and 7.0 letters at 1- and 2-years post-discontinuation, respectively. These eyes had a mean -1.6 letter loss (95% CI -4.5 to 1.3 letters; P < 0.01) from diagnosis.

Conclusions
Marked deterioration in visual acuity was noted in patients discontinuing anti-VEGF therapy after 1- and 2-years. The eyes that resumed treatment were able to regain some visual acuity and maintain this for up to 2-years post suspension of therapy; however, the visual acuity is mostly irreversible.

Financial Disclosure
K. Spooner: At time of writing research, KS was an employee of Sydney Retina, at time of presentation KS is an employee of Allergan Australia. S.Fraser-Bell is a consultant Novartis, Allergan, Roche and Bayer. A.Chang is a consultant for Novartis, Allergan, Roche and Bayer.
Avacincaptad Pegol, a novel C5 inhibitor, demonstrates continued reduction in geographic atrophy growth: 18-month results from GATHER1 clinical trial

Purpose
Avacincaptad pegol, a polyethylene glycol-conjugated oligonucleotide, is a potent C5 inhibitor delivered via a 100 µl intravitreal injection. The 18-month results of GATHER1, a prospective, randomized, double-masked, multinational, sham-controlled clinical trial evaluating avacincaptad pegol for the treatment of GA secondary to AMD, are reported here.

Setting/Venue
This study was a Phase 2/3 trial completed at 63 sites in the United States, Europe, and Israel.

Methods
Patients were randomized to avacincaptad pegol 1 mg, avacincaptad pegol 2 mg, avacincaptad pegol 4 mg or sham injection. In part 1, subjects were randomized to receive either 1 mg or 2 mg avacincaptad pegol or sham intravitreal (IVT) injections. In part 2, subjects received either 2 mg or 4 mg avacincaptad pegol or sham IVT injections. GA progression was evaluated as the change in lesion area as measured by fundus autofluorescence (FAF). Square-root transformation was applied to mitigate the impact of baseline factors on GA growth. Other assessments included visual function (best corrected visual acuity and low-luminance visual acuity) and safety.

Results
A total of 286 subjects were enrolled in this study. The pre-specified primary efficacy endpoint was the mean rate of change in GA over 12 months, measured by FAF. The reduction in the mean rate of GA growth (square root transformation) over 12 months was 27.4% (P = 0.0072) for the avacincaptad pegol 2 mg cohort and 27.8% (P = 0.0051) for the avacincaptad pegol 4 mg cohort, both statistically significant, compared with the corresponding sham cohorts. This is the first study in this patient population to have data to 18 months. These data are descriptive in nature. The least-squares mean change from baseline to month 18 in square-root GA lesion area was 0.599 mm in sham-treated subjects vs 0.430 mm in avacincaptad pegol 2 mg-treated subjects vs 0.430 mm in avacincaptad pegol 2 mg-treated subjects (28% reduction; P < 0.0014). The least-squares mean change from baseline to month 18 in square-root GA lesion area was 0.559 mm in sham-treated subjects vs 0.391 mm in avacincaptad pegol 4 mg-treated subjects (30% reduction; P < 0.0021). There were no significant differences in best corrected visual acuity or low-luminance visual acuity between avacincaptad pegol and sham-treated subjects. Avacincaptad pegol was generally well tolerated after 18 months of administration, with no trial discontinuations.

Conclusions
Intravitreal avacincaptad pegol resulted in a statistically significant decrease in the rate of GA lesion growth over 18 months of treatment versus sham injection. GATHER2, a second pivotal clinical trial comparing avacincaptad 2 mg versus sham, has been initiated and is currently enrolling subjects.

Financial Disclosure
Consultant (4DMT, Adverum, Aerie, Aerpio, Aldeyra, Allegro, Alzheon, Annexon, Apellis, Aprea, Asclepix, Aviceda, BVT, Dark Horse, DTx, Eloxx, Galimedix, Genentech, Graybug, Gyroscope, Iveric, jCyte, Kanghong, LensGen, NGM, Novartis, Ocular Therapeutix, OcUtera, Oxurion, Palatin, Regeneron, Regenerxbio, Stealth, Thea, Verseon, Vinci, Voyant) Research grants (Apellis, Asclepix, Bayer, Genentech, Graybug, Gyroscope, Hemera, Iveric, Kanghong, ...
Title
Association between visual acuity and intraretinal or subretinal fluid in patients with neovascular age-related macular degeneration treated with intravitreal aflibercept treat-and-extend: A post hoc analysis of the ARIES study

Purpose
Understanding the impact of the different fluid compartments is critical in developing anti-vascular endothelial growth factor treatment paradigms that optimize patients’ vision and reduce treatment burden. Therefore, the aim of this analysis was to explore the relationship between intraretinal fluid (IRF) and/or subretinal fluid (SRF) and best-corrected visual acuity (BCVA) in patients with neovascular age-related macular degeneration (nAMD) treated with intravitreal aflibercept (IVT-AFL) to guide treatment extension decisions.

Setting/Venue
ARIES (NCT02581891) was a multicenter, randomized, open-label, active-controlled, parallel-group, Phase 3b/4 study that compared the efficacy of IVT-AFL administered in two different proactive, individualized treat-and-extend (T&E) dosing regimens over 2 years in treatment-naïve patients with nAMD.

Methods
): All patients received three initial monthly doses of 2 mg IVT-AFL (Weeks [W] 0, 4, and 8), followed by an injection after an 8-week treatment interval (W16). At W16, patients were randomized 1:1 to an early-start T&E arm (IVT-AFL T&E regimen adjusted in 2-week steps) or a late-start T&E arm (IVT-AFL every 8 weeks in Year 1, followed by a T&E regimen starting from W48, adjusted in 2-week steps). The maximum treatment interval was 16 weeks. The primary endpoint was change in BCVA (Early Treatment Diabetic Retinopathy Study [ETDRS] letters) from randomization (W16) to W104. Fluid compartment status (presence/absence of SRF and IRF) was assessed by the central reading center at baseline (BL), W16 and at every treatment visit based on optical coherence tomography images. Treatment intervals were extended if IRF was absent, there was no new neovascularization, and SRF did not exceed 50 µm in thickness. This post hoc analysis explored the relationship between presence of fluid (SRF and IRF) and BCVA by describing absolute BCVA by fluid subgroups at BL and by fluid status at fixed visits (W4, W8, W16, W52, and W104) in the per-protocol set (two treatment arms combined).

Results
The per-protocol set comprised 210 patients. Absence of SRF at BL was associated with lower BCVA (5–10 less letters) than if SRF was present; a similar association was observed at every subsequent timepoint (no SRF vs SRF: 64.5 vs 67.2 [W4]; 66.3 vs 68.5 [W8]; 66.4 vs 70.7 [W16]; 68.3 vs 73.6 [W52]; 65.4 vs 72.9 [W104]). Presence of IRF at BL was associated with lower BCVA (7–9 less letters) than if IRF was absent; a similar association was observed at most subsequent timepoints (IRF vs no IRF: 61.2 vs 65.9 [W4]; 66.6 vs 66.8 [W8]; 59.0 vs 69.3 [W16]; 66.2 vs 70.0 [W52]; 70.1 vs 67.4 [W104]). The presence of both SRF and IRF at BL was associated with lower BCVA (6–8 less letters) than if only SRF was present, but was associated with a higher BCVA (3–9 more letters) than if only IRF was present. Absence of SRF and IRF was not associated with higher BCVA (letters) at any timepoint (no fluid vs fluid: 64.7 vs 66.8 [W4]; 66.5 vs 67.7 [W8]; 67.3 vs 69.2 [W16]; 68.5 vs 72.6 [W52]; 65.3 vs 71.9 [W104]).

Conclusions
In ARIES, proactive, individualized IVT-AFL T&E was effective at reducing fluid and improving vision in treatment-naïve nAMD eyes regardless of fluid type. Post hoc analyses showed that good functional outcomes were achieved in the presence of SRF, whereas IRF was consistently associated with poorer functional outcomes. These findings indicate the need to differentiate SRF and IRF as surrogate markers for BCVA, in order to guide treatment extension decisions and optimize patient outcomes.

Financial Disclosure
Sebastian Wolf: Steering Committee for Bayer; Consultant for Allergan, Bayer, Boehringer-Ingelheim, Chengdu Kanghong Biotech, Heidelberg Engineering, Novartis, Oxurion, Zeiss, and Roche Varun Chaudhary; Grant support from Allergan Inc., Bayer Healthcare, and Novartis ; Scientific advisor for Alcon Laboratories, Bayer Healthcare, and Novartis. Frank G. Holz: Steering Committee for Bayer; Consultant for Acucela, Apellis Pharmaceuticals, Bayer,
Hypothetical anti-vascular endothelial growth factor switch in neovascular age-related macular degeneration: A post hoc analysis of the ARIES study

**Purpose**
The purpose of this analysis was to explore functional and anatomic outcomes (best-corrected visual acuity [BCVA] and central retinal thickness [CRT]) in patients with treatment-naive neovascular age-related macular degeneration (nAMD) who were treated with intravitreal aflibercept (IVT-AFL) for up to 104 weeks, but who were identified retrospectively as meeting criteria for a hypothetical switch at Week 24.

**Setting/Venue**
This post hoc analysis was based on patient data from ARIES (NCT02581891): a randomized, open-label, active-controlled, Phase 3b/4 study that compared the efficacy of two different proactive, individualized treat-and-extend (T&E) regimens of IVT-AFL.

**Methods**
In ARIES, patients received three initial monthly doses of 2 mg IVT-AFL, followed by an injection after an 8-week treatment interval (Week 16). At Week 16, patients were randomized 1:1 to early-start T&E (IVT-AFL T&E from Week 16 adjusted in 2-week steps) or late-start T&E (IVT-AFL every 8 weeks until Week 48, then T&E from Week 48) with a maximum treatment interval of 16 weeks. Anatomic criteria for extending treatment intervals were the absence of intraretinal fluid (IRF), absence of new neovascularization or hemorrhage, and subretinal fluid (SRF) not exceeding 50 µm in thickness. The primary endpoint of the study was change in BCVA (Early Treatment Diabetic Retinopathy Study [ETDRS] letters) from randomization (Week 16) to Week 104. This post hoc analysis was conducted to describe BCVA and CRT up to Week 104 in patients in the early-start T&E arm who did and did not meet the criteria for a hypothetical switch at Week 24. Criteria for switch, based on clinical practice, were the presence of IRF and/or SRF with central involvement and a next planned treatment interval of ≤8 weeks at Week 24.

**Results**
In the per-protocol set (n=106), 41 patients (baseline: BCVA, 60.6 letters; CRT, 464.8 µm) met the criteria for a hypothetical switch at Week 24 and 65 patients did not (baseline: BCVA, 60.0 letters; CRT, 453.4 µm). In the switch group, at Week 24, SRF with central involvement was present in 33/41 (80.5%) patients and IRF with central involvement was present in 12/41 (29.3%) patients. Mean (95% CI) change in BCVA from baseline at Week 24 was +6.1 (3.4, 8.8) letters in patients meeting switch criteria and +6.6 (4.7, 8.6) letters in patients not meeting switch criteria; changes at Week 52 were +8.2 (5.0, 11.3) and +7.5 (5.3, 9.7) letters, respectively, and at Week 104 were +5.7 (1.3, 10.1) and +3.4 (0.1, 6.7) letters. Mean (95% CI) change in CRT from baseline in patients who did and did not meet switch criteria was -152.0 (-186.1, -117.9) and -173.1 (-203.5, -142.6) µm, respectively, at Week 52, and -138.3 (-175.7, -101.0) and -176.2 (-212.0, -140.4) µm, respectively, at Week 104.

**Conclusions**
In ARIES, patients with nAMD who could have hypothetically switched anti-VEGF treatment, initial improvements in BCVA were maintained with continued proactive, individualized T&E IVT-AFL therapy. Our results suggest that there is limited rationale for switching treatment-naïve nAMD patients on IVT-AFL during the early course of the therapy since, with continuous proactive treatment, comparable visual gains can be achieved by these patients compared with those who initially respond well on a T&E regimen. As the ARIES study follow-up was 104 weeks, further long-term studies are needed to determine the relevance of our findings over a longer time period.

**Financial Disclosure**
Gábor Márk Somfai: Consultant for Allergan, Bayer, and Novartis  Cengiz Türksever: Consultant for Allergan, Bayer, and Novartis  Susanne Oesch: Employee of Bayer (Schweiz) AG Tobias Machewitz: Employee of Bayer AG Sandrine Zweifel: Consultant: Bayer Healthcare Pharmaceuticals, Novartis Pharma AG, and Roche Diagnostics; Speaker: Bayer Healthcare Pharmaceuticals, and Novartis Pharma AG  Pascal W. Hasler: Speaker: Bayer, ...
### Title

How common are polypoidal choroidal vasculopathy and its associated features in the general population? — A population-based study employing validated OCT-diagnostic criteria

### Purpose

Polypoidal choroidal vasculopathy (PCV) is an important cause of neovascular AMD globally, and may account for up to half of all cases of neovascular AMD seen by ophthalmologists in Asia, and as many as 5–15% of cases seen in Caucasian populations. It remains unclear whether traditional early AMD features such as drusen and pigmentary changes are associated with an increased risk of developing PCV, while several other features have been suggested to predispose to PCV, including thickened choroid, pachydrusen, and shallow irregular retinal pigment epithelium elevation (SIRE). To date there are no studies comprehensively evaluating the prevalence of these features in the setting of a population study. Additionally, PCV prevalence in the general population remains unclear as the gold-standard for diagnosis is indocyanine green angiography (ICGA), which is impractical for large population-based studies. Recently a non-ICGA-based PCV diagnostic system was developed that utilized three OCT-based features (sharp peaked PED, sub-RPE ring-like lesions, and complex RPE elevations) that differentiate PCV from typical nAMD with high sensitivity and specificity. Here we report on the prevalence of PCV based on these validated criteria and also on the prevalence of traditional early AMD and PCV-associated features in a large ethnic Chinese population-based study.

### Setting/Venue

A population-based ethnic Chinese cohort from Singapore.

### Methods

Individuals from a population-based ethnic Chinese study cohort underwent multimodal imaging with spectral-domain OCT and color fundus photography (CFP), and were graded for the presence of features associated with typical AMD and PCV and also according to recently validated non-ICGA PCV diagnostic criteria. PCV was diagnosed based on the presence of at least 2 of 3 major diagnostic criteria (sharp peaked PED, sub-RPE ring-like lesion, and complex RPE elevations seen by en face OCT). The frequency of other PCV minor diagnostic criteria (central choroidal thickness of at least 300 microns, double layer sign, complex PED, and orange nodules), and retinal features associated with typical AMD and PCV were also assessed.

### Results

A total of 1,760 eyes from 961 individuals from the population-based cohort were included. Abnormalities were identified in 67.9% of eyes (42.9% of individuals) overall. The presence of any of the three major PCV diagnostic features was rare, occurring in only 0.2% of eyes. Most minor PCV diagnostic features were uncommon, occurring in 0.2–0.5% of eyes, although thickened choroid was common (40% of eyes). Pachydrusen were more common than soft drusen (5.5% of eyes vs. 0.9% of eyes), while pigmentary changes occurred in 8% of eyes. Features thought to predispose individuals to PCV, including thickened choroid, pachydrusen, double layer sign, complex PEDs, orange nodules, and macular pigmentary changes, were rarely present in combination — only 7% of eyes had two of these features, while less than 1% of eyes (1.6% of individuals) had three or more of these features. Applying the PCV diagnostic criteria to the study cohort, we identified three with PCV, giving an estimated population prevalence of 0.3% (95% CI, 0.06–0.91%). All cases had one or more sharp peaked PED and en face multilobular PED, while two cases additionally had sub-RPE ring-like lesion(s). Many supporting features (double layer sign, thick choroid, and orange nodule) were also present.

### Conclusions

PCV is an important component to the global burden of neovascular AMD but the absence of widely available ICGA often makes its diagnosis challenging. Here we have demonstrated the use of a newly validated OCT-based diagnostic system for identifying PCV cases in a population-based cohort. We have additionally shown that most imaging features associated with PCV are generally rare. Applying these validated PCV diagnostic criteria allows for a more accurate estimation of prevalence of this condition over prior studies. The importance of PCV as an important global cause of neovascular AMD makes this noninvasive and inexpensive diagnostic method an attractive alternative for both population-based screening and clinical diagnosis.

### Financial Disclosure

None to declare
Title
Choroidal neovascularization in old patients with pathologic myopia: Age-related macular degeneration (AMD) or myopic neovascularization

Purpose
To analyze the frequency and characteristics of choroidal neovascularization (CNV) in old patients with high myopia, as well as its response to treatment compared to published data. The aim of this study is also to determine whether the treatment with one single injection of Anti-VEGF on a Pro Re Nata (PRN) basis is effective in this subgroup of patients.

Setting/Venue
This retrospective study has been conducted at the retina unit of the Hospital Clínico Universitario de Valladolid (HCUV), Spain. Data collection from medical records for the period between 2014 and 2020 started after the approval of the Clinical Research Ethics Committee for the area of eastern Valladolid. Only patients previously diagnosed of high myopia were included.

Methods
A retrospective observational study in 91 patients with high myopia and choroidal neovascularization. Inclusion criteria were patients over 18 years who suffered from pathologic myopia and have been diagnosed of choroidal neovascularization. All patients underwent treatment with intravitreal Anti-Vascular Endothelial Growth Factor (Anti-VEGF) and were followed for a minimum period of 1 year and a maximum of 6 years. Best Corrected Visual Acuity (BCVA) and Central Retinal Thickness (CRT) progression was studied before and after treatment for patients exhibiting a CNV type 1 in Optical Coherence Tomography (OCT), as well as for patients with a type 2 CNV. Additionally, CNV phenotype and response to treatment in patients under 60 years was analyzed separately from older patients. The Anti-VEGF agent, as well as the number of injections administered in the first year and during the complete follow up period were recorded.

Results
CNV type 1 is higher than expected (n=40, 44%) in patients with high myopia. BCVA improved significantly one month after the first injection in both samples, although type 2 CNV demonstrated a better response to treatment (from 0,71 to 0,56) than type 1 CNV (from 0,75 to 0,62), p < 0.05. Mean (SD) age at onset is 67,9 years (14,4 years). Patients under 60 years (n=25, 27´47%) demonstrated a gain of 15 ETDRS letters after three months, while older patients showed a 5 ETDRS letters gain. (p=0,115). The first group received 2,59 injections in the first year and 2,96 during the whole period. On the other hand, 3,25 injections in the first year and 3,94 in total were administrated for the older group.

Conclusions
Patients with high myopia over 60 years are more likely to exhibit a CNV type 1, therefore altering the course and prognosis of a typical myopic CNV. It may be hypothesized that older people with morphological features of CNV due to ageing changes could benefit from a proactive therapy, with three initial injections followed by a PRN regimen.

Financial Disclosure
No financial relations
Shorter treatment intervals are associated with higher treatment compliance than longer treatment intervals in a treat-and-extend regimen for nAMD

Purpose
Continuous, indefinite treatment with anti-vascular endothelial growth factor (anti-VEGF) injections for neovascular age-related macular degeneration (nAMD) patients is essential to maintain visual acuity (VA) and prevent vision loss. However, this results in issues with long-term adherence to treatment. Patients treated under a treat-and-extend regimen will have variable treatment intervals based on disease activity of the choroidal neovascular (CNV) lesion, with shorter intervals (minimum 4 weeks) when disease is highly active and vice versa. It is plausible that patients on short treatment intervals, i.e., high treatment frequency, may be more likely to discontinue due to injection fatigue. Alternatively, the need for frequent treatment in high disease activity patients may indicate that discontinuing treatment would very quickly lead to vision loss and thus encourage them to adhere to treatment. We hypothesise that eyes with longer intervals would be more compliant as they are less susceptible to injection fatigue.

Setting/Venue
This was an observational study of real-world outcomes using data from the prospectively designed Fight Retinal Blindness! registry.

Methods
Treatment-naïve eyes in the Fight Retinal Blindness! registry initiating treatment for nAMD between 1st January 2013 and 31st December 2015 were identified. Eyes must have received a minimum of 4 injections with no large gaps between injections exceeding 365 days and treated for at least 18 months to reduce the likelihood of under-treatment. Eyes were grouped based on the number of injections received in the first 18 months: 4-6 injections, 7-9 injections, 10-12 injections, 13-15 injections, 16-18 injections, and 18-21 injections. The primary outcome was the proportion of dropouts between 18-60 months analysed using Kaplan-Meier survival curves. Hazard ratios were calculated using Cox proportional hazards models adjusted for gender, age, VA at 18 months, angiogenesis subtype, and clustering of outcomes within eyes from the same patient and patients treated by the same practitioner.

Results
There were 1706 eyes from 1564 patients eligible for the analysis. The proportion of eyes lost to follow-up was highest when fewer injections were administered in the first 18 months and lowest in eyes that received more injections in the first 18 months. Injection frequency at 18 months was significantly associated with risk of dropout (P = 0.003). The estimated dropout rate at 60 months was 82%, 84%, 76%, 71%, 64% and 63% for eyes receiving 4-6 injections, 7-9 injections, 10-12 injections, 13-15 injections, 16-18 injections, and 18-21 injections at 18 months, respectively. Other factors significantly associated with risk of dropout included age (P < 0.001) and VA at 18 months (P < 0.001). As expected, the proportion of visits in which the CNV lesion was graded as active was highest in eyes receiving more injections. The proportion of visits graded as active at 18 months was 51%, 55%, 54%, 64%, 75%, and 81% for eyes receiving 4-6 injections, 7-9 injections, 10-12 injections, 13-15 injections, 16-18 injections, and 18-21 injections at 18 months, respectively. Although the activity decreased for all injection frequency groups over time, eyes that received more injections at 18 months continued to have the most activity throughout.

Conclusions
Contrary to our hypothesis, we found that eyes were more likely to be adherent with more frequent injections. We believe this is because patients receiving frequent treatment have high disease activity leading to the perception that continuing treatment is still effective and necessary to control it. In contrast, eyes on longer intervals with low disease activity may be less likely to perceive the benefits of continuing treatment and discontinue as a result. Clinicians may need to be more vigilant in ensuring patients on long intervals do not get complacent as they are at greater risk of discontinuing treatment.
Assessment of central subfield thickness fluctuations and impact on vision in the Archway phase 3 trial of the port delivery system with Ranibizumab

Purpose

To evaluate changes in retinal thickness in participants enrolled in the Archway phase 3 trial, which compared continuous intravitreal delivery of ranibizumab using the Port Delivery System (PDS; an investigational device) against intravitreal injections of ranibizumab given monthly for neovascular age-related macular degeneration (nAMD). We analyzed the frequency of clinically significant alterations in retinal thickness (fluctuations) and association with visual acuity by study arm.

Setting/Venue

Archway (NCT03677934) was a phase 3, randomized, active treatment–controlled trial for the treatment of nAMD, conducted at 77 study locations in the United States.

Methods

Archway compared the PDS with ranibizumab 100 mg/mL with fixed 24-week refill-exchanges (PDS Q24W) versus intravitreal ranibizumab 0.5 mg every 4 weeks (monthly ranibizumab) in nAMD. At enrollment, before randomization, participants had received a mean of 5 anti–vascular endothelial growth factor (VEGF) injections. This post hoc analysis was confined to participants with ≥7 study visits with evaluable optical coherence tomography (OCT) images over 40 weeks and best-corrected visual acuity (BCVA) measurements at baseline and week 40. Central subfield thickness (CST) was measured from the internal limiting membrane to Bruch’s membrane. A fluctuation in retinal thickness was defined as a change in CST ≥ 50 µm in either direction. A fluctuation score was calculated using the cumulative changes in µm of CST measurements over 40 weeks; changes less than 50 µm were considered clinically insignificant and not included. Associations between CST fluctuations and vision outcomes at week 40 were analyzed.

Results

Analyses included 243 PDS Q24W and 163 monthly ranibizumab patients. Through week 40, 78.2% and 79.1% of patients in the PDS Q24W and monthly ranibizumab arms, respectively, did not experience any CST fluctuations ≥ 50 µm. In patients who experienced CST fluctuations ≥ 50 µm, the mean (95% CI) number of fluctuations through week 40 was 1.8 (1.5, 2.1) in the PDS Q24W arm and 2.3 (1.7, 2.9) in the monthly ranibizumab arm; the cumulative mean CST change through week 40 was 181.2 µm and 232.7 µm in the PDS Q24W and monthly ranibizumab arms, respectively. Mean (95% CI) BCVA change from baseline at week 40 in PDS Q24W versus monthly ranibizumab patients, respectively, was –1.6 (–3.6, 0.3) versus –1.0 (–3.4, 1.4) letters in patients who experienced CST fluctuations ≥ 50 µm through week 40 and +1.1 (0.0, 2.1) versus +1.0 (–0.2, 2.3) letters in patients who did not experience any CST fluctuations ≥ 50 µm through week 40.

Conclusions

In this study of retinal thickness fluctuations during the maintenance phase of anti-VEGF treatment, numerically fewer clinically significant fluctuation events were observed in the PDS Q24W arm compared with the monthly ranibizumab arm. This was accompanied by numerically reduced CST change in the PDS Q24W arm. However, these differences in CST did not result in clinically significant differences in visual acuity in the 2 arms. Further characterization of the approximately one-fifth of participants who experienced clinically significant fluctuations may yield valuable OCT biomarkers of responsiveness to anti-VEGF therapy.

Financial Disclosure

Usha Chakravarthy is a visiting Professor at F. Hoffmann-La Roche; consultant of and received speaker fees from Apellis, Alimera, Boehringer Ingelheim, Iveric Bio, Novartis, and Roche; and member of the data monitoring committee for Bayer and Gyroscope. Steven Blotner and Shamika Gune are employees of Genentech, Inc. Merce Morral is an employee of F. Hoffmann-La Roche. Carl Regillo is a consultant/advisor for Adverum Biotechnologies, Allergan, Chengdu HiiDii, Genentech, Inc., and Otsuka.
**Title**

Preliminary results from a first-in-human Phase I/II gene therapy study (FOCUS) of GT005, an investigational AAV2 vector encoding complement factor I, in patients with geographic atrophy

**Purpose**

Complement overactivation has been implicated in age-related macular degeneration (AMD) disease pathogenesis. Complement Factor I (CFI) protein regulates the activity of the complement system, and it is hypothesized that increasing CFI production could dampen the overactive complement system, thereby reducing AMD disease progression. We investigated the safety and dose response of subretinally administered GT005, an investigational recombinant adeno-associated viral (AAV2) vector encoding CFI, for the treatment of geographic atrophy (GA) secondary to AMD.

**Setting/Venue**

FOCUS (NCT03846193, EudraCT 2017-003712-39) is an ongoing first-in-human, open-label, Phase I/II study conducted at 9 centers in the United States and the United Kingdom. The study consists of 4 parts (dose-escalation/expansion using transvitreal delivery, and dose-escalation/expansion using Orbit subretinal delivery system [Orbit SDS]). Interim data from the transvitreal cohorts are presented herein.

**Methods**

All patients had bilateral GA at baseline. The study eye received a single subretinal administration of GT005. Part 1 explored three GT005 dose levels (2E10, 5E10 and 2E11 vector genomes [vg]) using transvitreal delivery with sentinel dosing between the first and second patient of each dose cohort. Part 2 is ongoing and further explores dose-levels that were shown to be safe and tolerable in Part 1. The primary endpoint is safety over 48 weeks, with secondary endpoints including immunogenicity, vector shedding, anatomical/functional outcomes, and changes in complement protein expression in the vitreous humor.

**Results**

As of February 2021, 20 patients had received GT005 via transvitreal delivery across Part 1 (n=11) and Part 2 (n=9), with a mean follow-up of 37.6 weeks (range: 1.1 to 94.0 weeks). All dose levels of GT005 were well-tolerated with no dose-related trends in the frequency and type of adverse events (AEs). There were no serious ocular AEs or signs of GT005-related inflammation. AEs of special interest will be presented. The mean change from baseline in best corrected visual acuity in the study eye and the fellow eye at Week 48 was -0.63 (n=8; 95% Confidence Interval [CI]: -8.85, 7.60) and -3.38 (n=8; 95% CI: -9.37, 2.62), respectively. Biomarker analyses showed elevated vitreous CFI levels in 9/10 patients, with an average increase of 146% compared to baseline (p=0.02). Reductions in vitreous Ba and C3 breakdown products were also observed at 24-56 weeks, with an average decrease of 41% and 42% compared to baseline (p-value less than 0.05), respectively. Increases in CFI levels correlated with decreases in Ba levels (R= -0.68, p= 0.03).

**Conclusions**

GT005 was well tolerated at doses of 2E10 to 2E11vg with no signs of GT005-related inflammation or change from baseline in visual acuity. Biomarker analyses demonstrate durable transgene expression through increased vitreous CFI levels, as well as evidence of target engagement through downstream modulation of complement proteins. FOCUS Parts 2 and 3 are continuing to enroll, and two randomized, controlled Phase II trials (EXPLORE, HORIZON) evaluating the safety and efficacy of GT005 are ongoing.

**Financial Disclosure**

Research funding and consultancy to Gyroscope Therapeutics Limited (with all fees paid to University of Oxford) and share options that might have future value.
Efficacy, safety and durability of Faricimab in neovascular age-related macular degeneration: Week 48 results from the phase 3 TENAYA and LUCERNE trials

Purpose
Dual inhibition of angiopoietin-2 (Ang-2) and vascular endothelial growth factor (VEGF)-A with faricimab, the first bispecific antibody designed for intraocular use, may promote vascular stability, resulting in increased durability and improved long-term outcomes beyond anti-VEGF treatment alone for neovascular age-related macular degeneration (nAMD). Here we report primary week 48 results of the ongoing phase 3 TENAYA and LUCERNE trials, designed to assess efficacy, safety and durability of faricimab up to every 16 weeks (Q16W) compared with aflibercept every 8 weeks (Q8W) in patients with nAMD.

Methods
Treatment-naïve patients were randomised 1:1 to receive faricimab 6.0 mg up to Q16W after 4 initial every-4-week (Q4W) doses or aflibercept 2.0 mg Q8W after 3 initial Q4W doses. Patients in the faricimab arm were assessed for protocol-defined disease activity at weeks 20 and 24. Patients with no evidence of active disease at weeks 20 and 24 received Q16W dosing through week 60; those with active disease at week 20 received Q8W dosing; patients with active disease only at week 24 received every-12-week (Q12W) dosing. The primary efficacy endpoint was non-inferiority of faricimab up to Q16W compared with aflibercept Q8W in mean change in best-corrected visual acuity (BCVA) from baseline averaged over weeks 40, 44 and 48 with faricimab up to Q16W (+5.8 and +6.6 ETDRS letters in TENAYA and LUCERNE, respectively) compared with aflibercept Q8W (+5.1 and +6.6 ETDRS letters). Notably, 79.7% (TENAYA) and 77.8% (LUCERNE) of patients in the faricimab up to Q16W arm were on ≥Q12W dosing intervals at week 48, with 45.7% and 44.9% of patients in TENAYA and LUCERNE, respectively, on a Q16W dosing interval. Reductions in CST from baseline averaged over weeks 40, 44 and 48 with faricimab up to Q16W (−136.8 and −137.1 µm in TENAYA and LUCERNE, respectively) were comparable with aflibercept Q8W (−129.4 and −130.8 µm). In both trials, faricimab was well tolerated; intraocular inflammation event rates were low and no cases of vasculitis or occlusive retinitis were reported.

Conclusions
TENAYA and LUCERNE met their primary endpoint, with consistent and reproducible results across both trials. Faricimab administered up to Q16W demonstrated non-inferior vision gains versus aflibercept Q8W in patients with nAMD, with ~80% of patients on dosing intervals of ≥Q12W and ~45% on Q16W fixed dosing intervals at week 48. Faricimab treatment also resulted in meaningful reductions in CST, and was well tolerated.
Purpose
Idiopathic SPEDs are thought to represent an early stage of central serous chorioretinopathy (CSCR), which may or may not progress into acute or chronic CSCR, a disease typically affecting young/middle-aged individuals. CSCR is more common in males, those with type-1 personalities, and is associated with the use of corticosteroids and anti-psychotic medication. The choroidal circulation is altered in CSCR, with increased choroidal vascular permeability, thickened choroid and dilated choroidal vessels. Acute CSCR presents as sub-retinal fluid, with or without SPEDs, and disruption of the outer retinal layers. It will often resolve spontaneously, although it recurs in up to 50% of cases, and can lead to secondary CNV or macular oedema. If fluid or RPE disruption occurs at the fovea irreversible visual loss may occur. Clinically, patients tend to present when visual changes occur, therefore generally at the acute stage. The grading of multiple subjects with idiopathic SPEDs during the ocular component of UKBB presented an opportunity to carry out a more detailed grading on these subjects. In particular, grading characterised SPED, choroidal thickness and vessel diameter compared to subjects with no CSCR pathology.

Methods
Individuals graded as having an idiopathic SPED in either eye during the UKBB image analysis were selected for more detailed grading. This was predominantly OCT based and included; the number of SPEDs, the height, base diameter and location of the largest SPED, including whether sub-, juxta- or extra-foveal, superior or inferior, and nasal or temporal. Where gradable, sub-foveal choroidal thickness (SFCT), using any scan, and greatest (vertical) choroidal vessel diameter (CVD) on the foveal scan. Those with characteristic acute stage CSCR changes in either eye were excluded from this sub-study, as were any subjects with AMD or any other notable pathology. Four eyes showed signs of past fluid in the fellow-eye and those were included. Colour images were used to confirm OCT findings, and rule out any other pathology outside the OCT-grid. If any additional distinct SPEDs were seen outside the OCT-grid on the colour images, these were included in the SPED number. A thickness measurement control-group of an equal number of eyes recorded as having no abnormalities, were graded using the same method. Paired T-tests were used to confirm OCT findings, and rule out any other pathology outside the OCT-grid. If any additional distinct SPEDs were seen outside the OCT-grid on the colour images, these were included in the SPED number.

Results
68527 participant image-sets were supplied, 99% of colour/OCTs were available, equating to 67995 colour/67935 OCTs for the right eye, and 67623 colours/67591 OCTs for the left eye. Approximately 90% of colour images and 99% of OCTs were gradable quality. 109 eyes (85 patients) had at least one idiopathic SPED, 12 patients had bilateral SPEDs. This equates to 0.08% of the gradable study population having unilateral SPEDs, and 0.009% having bilateral. In 76% of cases, one SPED was present, 17% had two SPEDs, 4% three, 2% two and 2% over 5. Mean SFCT was 265 (111-443) and mean base diameter 483 (197-1963). 80% of SPEDs were extra-foveal, 21% juxta-foveal (within or touching the foveal avascular zone) and 8% sub-foveal. 45.9% of SPEDS were located in the superior, 40.4% inferior and 13.8% located centrally. 56% were located nasally, 37.6% temporally, and 6.4% centrally. SPED-eyes had a mean MCT of 355µm (141-567), mean CVD of 314µm (190-567) and mean CVD of 191µm (108-439). For normal eyes SFCT, MCT and CVD were; 265 (111-443), 320 (176-458) and 165 (93-267) respectively. There was significant difference between the two groups for; SFCT (n=88, p<0.001), MCT (n=99, p<0.001), and CVD (n=84, p=0.001).

Conclusions
Choroidal thickness at the fovea, and maximum choroidal thickness of those with SPEDs were significantly higher than those of individuals with no pathology. Additionally vertical diameter of the largest (gradable) vessel on the foveal scan was significantly greater in those with SPEDs, signifying choroidal changes and vessel dilation in these subjects. There was a slight difference between superior and inferior location of SPEDs at 40 and 46% respectively, however there seems to be a propensity towards nasal occurrence of SPEDs with 56% occurring nasally, rather than 38% temporally. Idiopathic SPEDs often resolve themselves and unless sub-foveal are unlikely to cause any vision changes. Only 8% of SPEDs were sub-foveal and 21% juxta-foveal, therefore it is likely that most of these individuals were unaware of any eye problems at the time of image collection.
**Title**
A phase 1b multi-center, open label, single-arm safety study of intravitreal Pegcetacoplan supporting the phase 3 DERBY and OAKS studies for geographic atrophy

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-

**Purpose**
Describe the goals and findings from APL2-103, which evaluated the use of intravitreal pegcetacoplan for geographic atrophy (GA) secondary to age-related macular degeneration (AMD). Data from this phase 1b safety study supports two large phase 3 studies

**Setting/Venue**
This 24-month phase 1b, open-label, single-arm safety study of monthly pegcetacoplan was initiated in GA subjects with low vision (Snellen 20/200 to 20/800) to assess drug product lots before introduction into Phase 3 trials

**Methods**
The phase 3 DERBY and OAKS studies of intravitreal pegcetacoplan in GA were temporarily halted in December 2018 due to transient intraocular inflammation (IOI) in 4 patients after dosing with a new formulation developed for the phase 3 trials. An investigation into the potential causes for the IOI led to a quality review of the manufacturing procedures. The report revealed the presence of an impurity in the active pharmaceutical ingredient introduced during the scale-up process. Further steps were subsequently implemented to eliminate the impurity, and the resulting product was tested in several animal studies.

**Results**
A full recovery was observed in all four patients who experienced IOI during the phase 3 studies (mean BCVA before IOI event: 47.5 letters [range 38-67] and after resolution: 45.5 letters [29-68]). A 7-day follow-up evaluation across 4 clinical sites was then conducted in APL2-103. 10 subjects in Study 103 who were treated using a drug product lot free of the impurity showed no signs of investigator-assessed IOI after 7 days. Following these findings, the two phase 3 studies were re-initiated in March 2019, with continued drug product lot evaluation from APL2-103. After phase 3 re-initiation, safety findings in APL2-103 continued to be consistent with all previous and ongoing intravitreal pegcetacoplan programs. New-onset exudation was observed in 2 enrolled patients over 24 months. No cases of IOI have been observed with the phase 3 formulation during this time. An exploratory interim efficacy analysis of APL2-103 in bilateral GA patients revealed that the GA growth rate in pegcetacoplan-treated eyes was slower than untreated fellow eyes by 46% at 24 months (P=0.007).

**Conclusions**
The potential root cause of intraocular inflammation in phase 3 studies was detected and removed. These findings highlight the value of ensuring safety following manufacturing or formulation changes. The results of the phase 1b APL2-103 study support the ongoing and fully enrolled phase 3 studies, with an acceptable safety profile.

**Financial Disclosure**
FFB (F) and Novartis (F) - research grants to Duke Reading Center for RP studies.
Determinants of reading performance in geographic atrophy secondary to age-related macular degeneration

**Purpose**

Age-related macular degeneration (AMD) is the leading cause of blindness in the elderly in western countries. High prevalence, expected increase in patients, and lack of treatment options make especially its dry late-stage, i.e. geographic atrophy (GA), an important study subject. Hereby, enlargement of GA, detected by fundus autofluorescence (FAF) imaging, is accepted as endpoint for clinical trials. However, the impact of GA topography and enlargement on the reading performance is yet understudied. In this analysis, we investigated the complex relationship between the topography of GA lesions, the visual function, and the reading performance and we determined the longitudinal change of the reading performance.

**Setting/Venue**

150 eyes of 85 patients with a median age [IQR] of 78.9[9.6] years with GA participating in the longitudinal, non-interventional, prospective natural history study ‘Directional Spread in Geographic Atrophy’ (NCT02051998) at the Department of Ophthalmology, University of Bonn, Germany, were included in the analysis.

**Methods**

Clinical assessment included age, gender, best-corrected visual acuity (BCVA), low luminance visual acuity (LLVA), central visual field loss (foveal sparing), reading acuity, and speed. The BCVA, LLVA were assessed using the Early Treatment Diabetic Retinopathy Study. Reading acuity and reading speed were assessed using the RADNER-Charts. All patients underwent 30°x30° FAF imaging and infrared reflectance imaging (Heidelberg Engineering, Germany). The images were semi-automatically annotated for geographic atrophy followed by extraction of shape-descriptive variables. Linear mixed-effects models were applied to investigate the association of those variables with reading performance. Nested-resampling was applied to obtain estimates of the prediction accuracy. Hereby, the mean coefficient-of-determination (R2) served as measure of prediction accuracy.

**Results**

Reading performance was impaired with a monocular reading acuity of 0.90[0.9] logMAR and a reading speed of 52.82[123.0] words-per-minute. In the multivariable cross-sectional analysis, (i) best-corrected visual acuity, (ii) area of geographic atrophy in the central ETDRS-subfield, (iii) classification of non-center vs. center-involving geographic atrophy, and (iv) area of geographic atrophy in the inner-right ETDRS-subfield showed strongest associations with reading acuity (cross-validated R2(Reading Acuity)=0.69). Regarding reading speed, the most relevant variables were (i) best-corrected visual acuity, (ii) low luminance visual acuity, (iii) area of geographic atrophy in the central, (iv) in the inner-right, and (v) in the inner-upper ETDRS-subfield (cross-validated R2(Reading Speed)=0.67). In the longitudinal analysis, a similar prediction accuracy for reading performance was determined. Prediction accuracy did not improve when follow-up time was added as an independent variable. Binocular reading performance did not differ significantly from reading performance in the better eye.

**Conclusions**

Reading acuity and speed are significantly impaired in geographic atrophy patients. Its association with visual functional and structural biomarkers supports the validity of reading performance as a meaningful endpoint in clinical trials. To benefit patients in clinical and low vision care, measures should be focused primarily on the better eye.

**Financial Disclosure**

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### Title
Central serous chorioretinopathy in active endogenous Cushing’s syndrome

### Purpose
Multiple case series have provided evidence for a relatively high incidence of central serous chorioretinopathy (CSC) in patients with active Cushing’s syndrome (CS). To describe the ophthalmological status in detail of 11 consecutive patients with active endogenous CS.

### Setting/Venue
Academic Medical Center

### Methods
This prospective cohort study describes extensive ophthalmological phenotyping in a consecutive patient series with either de novo or recurrent active endogenous CS. All patients underwent complete ophthalmological examination, including multimodal imaging, which was performed shortly after establishing the diagnosis of active CS in hypercortisolemic state.

### Results
Eleven CS patients (4 men, 7 women) with active hypercortisolism were included. Abnormalities reminiscent of (subclinical) central serous chorioretinopathy were found in 3 patients (27%). Optical coherence tomography (OCT) revealed macular subretinal fluid in 1 patient, who was diagnosed as having active central serous chorioretinopathy (CSC) and successfully treated with half-dose photodynamic therapy. Two other patients showed CSC-like abnormalities: an unilateral pseudovitelliform lesion on OCT and hyperfluorescent changes on fluorescein angiography in one patient, and unilateral leakage on fluorescein angiography in the other patient. Mean subfoveal choroidal thickness on enhanced depth imaging OCT was 270 ± 40 μm (range, 178 – 357 μm).

### Conclusions
Retinal abnormalities resembling (subclinical) CSC may be more common than previously thought in patients with active Cushing’s syndrome, and may exist even in patients without visual complaints. Clinicians should have a low threshold for ophthalmological evaluation in case of a CS patient with visual symptoms since there may be therapeutic opportunities to prevent vision loss.

### Financial Disclosure
None
Long-term efficacy outcomes with Brolucizumab vs Aflibercept treatment in patients with early residual fluid presence in nAMD: post hoc analysis of pooled data from HAWK & HARRIER studies

Purpose
Retinal fluid is a key biomarker of anti-vascular endothelial growth factor (VEGF) efficacy in neovascular age-related macular degeneration (nAMD). Despite an initial loading dose of three (monthly) anti-VEGF injections, early residual fluid (ERF) is evident in some patients at Week 12 (four weeks post final loading injection). We compare the efficacy of brolucizumab versus aflibercept to Week 96 in nAMD patients who had ERF at Week 12.

Setting/Venue
HAWK and HARRIER were two 96-week, Phase 3, prospective, randomized, double-masked, multicenter studies comparing efficacy and safety of brolucizumab 3 mg (HAWK only) and 6 mg with aflibercept 2 mg in eyes with nAMD.

Methods
HAWK and HARRIER were two Phase III, prospective, randomized, double-masked, multicenter studies comparing the efficacy and safety of brolucizumab with aflibercept in treatment-naïve eyes with nAMD. In HAWK, patients were randomized 1:1:1 to brolucizumab 3 mg (n=358), brolucizumab 6 mg (n=360) or aflibercept 2 mg (n=360). In HARRIER, patients were randomized 1:1 to brolucizumab 6 mg (n=370) or aflibercept 2 mg (n=369). After three loading doses, brolucizumab patients received 12-weekly (q12w) dosing with an option to adjust to 8-weekly dosing (q8w) if disease activity (as identified by a masked investigator) was present; aflibercept was dosed q8w as per the label. This HAWK and HARRIER pooled analysis includes patients who were defined as having ERF (presence of intraretinal [IRF] and/or sub-retinal fluid [SRF] at Week 12) from the brolucizumab 6 mg (treated every 12 or 8 weeks; n=149) and aflibercept 2 mg (treated every 8 weeks; n=217) arms.

Results
The proportion of patients with ERF at Week 12 was lower in the brolucizumab 6 mg group (149/730; 20.4%) than with aflibercept 2 mg (217/729; 29.8%). In those patients with ERF, mean (SE) best corrected visual acuity (BCVA) change (letters) from baseline in the brolucizumab 6 mg group was 5.7 (0.9), 7.1 (1.1), 6.2 (1.2) and 6.5 (1.2) at Weeks 24, 48, 72 and 96, respectively, while in the aflibercept 2 mg group it was 4.8 (0.8), 5.2 (0.9), 4.0 (1.0) and 3.6 (1.0). Mean (SE) central subfield thickness (CST) change (µm) from baseline at Weeks 24, 48, 72 and 96 in the ERF brolucizumab 6 mg group was -162.2 (10.1) µm, -181.5 (10.2) µm, -184.5 (10.7) µm and -186.6 (10.8) µm, respectively, while in the ERF aflibercept 2 mg group it was -120.3 (8.3) µm, -133.1 (8.4) µm, -137.4 (8.9) µm and -144.1 (8.9) µm, respectively. The percentage of ERF brolucizumab 6 mg patients with IRF and/or SRF at Weeks 24, 48, 72 and 96 was 61%, 59%, 50% and 50%, respectively, while in the ERF aflibercept 2 mg group it was 76%, 76%, 62% and 58%.

Conclusions
In nAMD patients with ERF at Week 12, long-term vision gains and fluid resolution was higher in the brolucizumab-treated patients versus aflibercept.

Financial Disclosure
RG: Consultant and Financial Support: Novartis, Bayer, Roche, Alimera, Allergan
Clinical trial of Conbercept ophthalmic injection for the treatment of polypoidal choroidal vasculopathy (PCV) using two different administration methods.

Setting/Venue
This was a parallel-group, randomized, open-label, multi-center, phase IV clinical study, lasting 50 weeks (2-week screening period and 48-week treatment period).

Methods
304 subjects were screened and randomly assigned to the fixed-dosing group of 0.5 mg Conbercept (3+Q12W group) or the treat-and-extend group of 0.5 mg Conbercept (3+T&E group) in a 1:1 ratio. The primary endpoint was evaluated after 48 weeks of treatment. The main endpoints were the mean changes in best corrected visual acuity (BCVA), central retinal thickness (CRT), polyp lesion area, and polyp regression.

Results
A total of 304 subjects were randomized; 152 subjects in the 3+Q12W group and 152 subjects in the 3+T&E group. Baseline visual acuity was 61.54±13.96 and 60.4±14.58 letters, respectively, and baseline CRT was 422.94±152.69 µm and 411.12±141.35 µm, respectively. After 48 weeks, visual acuity in the 3+Q12W group and 3+T&E group increased by 5.67±16.38 and 6.54±14.58 letters respectively; the proportion of patients with visual acuity improvement of ≥15 letters were 26% and 23%, respectively; CRT decreased by 96.76±157.80 µm and 108.22±167.58 µm; respectively; the rate of complete polyp regression was 38% and 37% respectively; the proportion of polyps under effective control was 82% and 85% respectively; the polyp area decreased by 42% and 44%, respectively; the recovery rate of PDT was 11.38% and 7.14%, respectively. The average number of injections in the two groups was 6.55 and 9.37, respectively. The incidence of adverse events was 28.09%, the incidence of target-eye adverse events was 14.72%, and the incidence of serious adverse events was 0.33%.

Conclusions
The STAR study confirmed that 0.5 mg Conbercept 3+Q12W and 3+T&E are effective and safe in the treatment of PCV. Both treatments can significantly improve visual acuity and eliminate polyps. The 3+Q12W group needed fewer injections.
Analysis of retinal fluid and vision outcomes in the Archway phase 3 trial of the port delivery system with ranibizumab (PDS) in patients with nAMD

**Purpose**

The Port Delivery System with ranibizumab (PDS) is an investigational drug delivery system for the continuous delivery of ranibizumab into the vitreous, which was evaluated for the treatment of neovascular age-related macular degeneration (nAMD) in the Archway phase 3 trial. This analysis aims to determine the incidence of subretinal fluid (SRF) and/or intraretinal fluid (IRF) from baseline to week 40 in Archway and assess vision outcomes based on presence, type, and location of fluid.

**Setting/Venue**

Archway (NCT03677934) was a randomized, multicenter, open-label (visual assessor–masked), active treatment–controlled study in patients with nAMD.

**Methods**

Patients were randomized 3:2 to the PDS with ranibizumab 100 mg/mL with fixed 24-week refill-exchanges (PDS Q24W) or intravitreal ranibizumab 0.5 mg every 4 weeks (monthly ranibizumab). This post hoc analysis comprised patients from Archway with data on the presence/absence of SRF/IRF at baseline. The presence of retinal fluid was assessed using optical coherence tomography at each monthly visit, independently graded for SRF or IRF. Analysis outcomes included the proportion of patients with either SRF or IRF (and SRF and/or IRF in the center 1 mm [SRF/IRF 1 mm]) and change in best-corrected visual acuity (BCVA) from baseline (Early Treatment Diabetic Retinopathy Study [ETDRS] letters) in study eyes in the presence or absence of SRF/IRF up to week 40.

**Results**

Percentage of patients with either SRF or IRF was similar between the PDS Q24W and monthly ranibizumab treatment arms at baseline (47.6% [118/248] vs 50.9% [85/167]) and week 40 (50.6% [120/237] vs 48.4% [77/159]). Vision outcomes were comparable between treatment arms, regardless of presence/absence of any retinal fluid, including presence/absence of SRF in the center 1 mm (SRF 1 mm); mean (95% CI) BCVA change (ETDRS letters) from baseline at week 40 with PDS Q24W versus monthly ranibizumab: absence of SRF 1 mm, +0.9 (−0.1, 1.9; n = 182) versus +0.6 (−0.6, 1.8; n = 137); presence of SRF 1 mm, +0.2 (−1.6, 2.0; n = 51) versus +1.0 (−1.7, 3.8; n = 21). BCVA vision outcomes were also comparable between the PDS Q24W and monthly ranibizumab arms in the absence of IRF in the center 1 mm (IRF 1 mm): +0.8 (−0.1, 1.7; n = 216) versus +1.0 (−0.0, 2.0; n = 147), but appeared to be slightly reduced in the monthly ranibizumab arm in the presence of IRF 1 mm: PDS Q24W, +0.1 (−3.6, 3.8; n = 17); monthly ranibizumab, −3.5 (−11.8, 4.7; n = 11).

**Conclusions**

In Archway, the incidence of retinal fluid was generally similar in the PDS Q24W and monthly ranibizumab treatment arms and remained consistent over time. Vision outcomes were generally comparable in both treatment arms. Continuous delivery of ranibizumab with PDS Q24W maintained vision outcomes, regardless of the presence or absence of retinal fluid.
Title
REGATTA: A phase 2a, multiple dose study of IVT GEM103 (recombinant human Complement Factor H [CFH]) in genetically selected subjects with geographic atrophy (GA) secondary to dry AMD - Clinical study outline and available baseline characteristics

Purpose
Geographic atrophy is the most advanced form of dry AMD. Genetic variations coding for proteins in genes involved in the alternative complement pathway are strongly associated with risk of AMD. Based on the literature as well as data from Gemini natural history study, approximately 40% dry AMD patients have a loss of function variant in the CFH gene. GEM103 is a full length, recombinantly produced human CFH protein which provides a functional level of active CFH in AMD patients with loss of function mutations in the gene encoding CFH. CFH functions physiologically to restore complement activity and to restore retinal health. Results from the Phase 1 study of IVT GEM103 in subjects with central geographic atrophy (GA) secondary to non-neovascular (dry) age-related macular degeneration (AMD) show that single IVT doses from 50 to 500 µg were well tolerated, with no dose-limiting toxicities. GEM103-related adverse events, signs of ocular inflammation, or ADA. These results supported the enrollment of subjects into ReGAtta, a Phase 2a multiple ascending dose evaluation of GEM 103 in genetically selected subjects with geographic atrophy (GA) secondary to dry AMD for continued evaluation of the safety, supraphysiologic CFH maintenance over time, and effect on biomarkers of complement activation.

Setting/Venue
This is the first data presentation of an interim analysis from ReGAtta, a phase 2a, open-label, repeat dose, dose escalation study evaluating safety and total CFH levels and complement biomarkers through serial aqueous humor (AH) sampling following 6 months of IVT GEM103 at 250 or 500 µg, with 12 additional monthly 500 µg IVT doses in genetically selected subjects with geographic atrophy (GA) secondary to dry AMD (ClinicalTrials.gov Identifier: NCT04643886).

Methods
Genetically selected subjects with GA secondary to dry AMD Subjects, ≥50 years of age, total GA lesion size ≥1.25 and ≤17.5 mm2 (0.5- and 7-disc areas), best corrected visual acuity (BCVA) 24 to 83 Early Treatment Diabetic Retinopathy Study (ETDRS) letters (equivalent to Snellen visual acuity of approximately 20/25 to 20/320), no exudative AMD or CNV in study eye, and who met other eligibility criteria, were enrolled. Subjects were assigned to study cohorts based on genetic profile (either the common CFH variant [CFH402HH], Rare missense variants of CFH or complete complotype; or neither of these profiles). Outcome measures include AEs, signs of ocular inflammation, ADA, total CFH levels in AH, exploratory biomarkers in AH, and clinical effects including changes from baseline in visual acuity and anatomical measurements including GA lesion size.

Results
As of March 2021, preliminary baseline data were available for 62 subjects dosed with IVT GEM103: 36 with common CFH variant [CFH402HH], 13 with rare missense variants of CFH or complete complotype; and 13 neither of these genotypic profiles. Mean age was 78.03 years, 62.9% of subjects were female. Overall baseline GA lesion size (mean ± standard deviation) was 8.01 ± 5.62 mm² (n=62). Overall baseline BCVA and LLVA (mean ± standard deviation) was 60.77 ± 18.92 ETDRS letters and 37.80 ± 18.25 ETDRS letters respectively (n=62). Analyses of available data for safety, total CFH levels in AH and biomarkers in AH after repeat IVT dosing with GEM103 will be presented at the meeting.

Conclusions
Gemini uses a precision medicine strategy to identify and treat genetically defined dry AMD subjects who are likely to respond to GEM103 therapy. Phase 2a (REGATTA), repeat dose, dose escalation study evaluates safety, total CFH levels in AH, and measurement of complement biomarkers after repeat IVT dosing with GEM103. REGATTA study will confirm findings from Phase 1 single dose study relating to safety, achievement of supraphysiologic levels of CFH over time in AH and effect on biomarkers of complement activation in AH after repeat IVT dosing with GEM103 in genetically selected subjects with geographic atrophy (GA) secondary to dry AMD.
The safety-specific, next-generation optical coherence tomography analysis from HAWK: preliminary qualitative OCT findings associated with intraocular inflammation

Purpose
Intraocular inflammation (IOI), retinal vasculitis, or vascular occlusion have been reported in patients with neovascular age-related macular degeneration (nAMD) treated with intravitreal anti-vascular endothelial growth factor therapy. This current analysis is a preliminary comparative discovery assessment of eyes with IOI from the HAWK study to evaluate the presence of optical coherence tomography (OCT) features that may precede or develop in association with IOI, and which might serve as OCT biomarkers for IOI.

Setting/Venue
HAWK (NCT02307682) was a multicenter study conducted in North, Central, and South America; Europe; Asia; Australia; and Japan. The imaging analysis was completed at Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA.

Methods
HAWK was a randomized, double-masked, 96-week phase 3 study comparing brolucizumab to aflibercept in nAMD. A comparative higher-order discovery analysis was initiated evaluating 34 eyes with IOI and 34 propensity-matched controls from the HAWK study. This analysis includes comparative higher-order OCT, radiomics assessment, and machine learning feature assessment. This report provides an initial assessment of the comparative discovery assessment of the Safety-Specific Next-Generation imaging analysis (SaGe) from HAWK. Images were reviewed frame by frame for specific features prior to or during the IOI event.

Results
Initial comparative assessment of the 34 IOI eyes and the 34 propensity-matched control eyes demonstrated differential findings between the two groups. Qualitative assessment identified characteristic preretinal hyperreflective foci, “stalagmites,” in 20 of 34 eyes (59%) with IOI compared to 1 of 34 eyes (3%) in the control group. The one control subject was noted to have an adverse event secondary to floaters at the time the “stalagmites” were noted on OCT. The presence of the “stalagmites” was first identified at the time IOI was initially noted in 11 subjects. Of these 11 subjects, 8 eyes (72%) were defined as IOI + retinal vasculitis and/or vascular occlusive (IOI+RV/RO). In 9 subjects, the “stalagmites” were visualized at visits prior to the reported IOI event in all 9 eyes, and 7 of these 9 eyes (77%) were identified as having IOI+RV/RO. There were 14 out of 34 eyes (41%) with IOI that did not have the presence of “stalagmites”, of which 8 eyes (57%) were defined as IOI+RV/RO.

Conclusions
In this preliminary discovery evaluation for OCT biomarkers for IOI-related events in the HAWK data set, the presence of hyperreflective preretinal foci (i.e., preretinal “stalagmites”) appears to be a potentially important objective IOI-related OCT finding, and its utility as a signal for clinicians assessing for underlying posterior inflammation requires further investigation. This specific signal also appears to be a potential important biomarker for underlying IOI associated vasculitis/vascular occlusive events. Important limitations of this initial analysis include that the IOI assessment only included eyes treated with brolucizumab and not the aflibercept treatment arm and the analysis did not evaluate eyes from the HARRIER clinical trial. An expanded assessment to include additional eyes with IOI from both phase 3 trials is currently underway.

Financial Disclosure
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Dissecting inner and outer retinal contribution to retinal light sensitivity in AMD: a structure-function analysis

Purpose
Integrating structural and functional data is of key importance to characterise eye diseases. High resolution structural data can be acquired with spectral domain optical coherence tomography (SD-OCT), which allows accurate segmentations and measurement of different retinal layers. Functional maps of retinal sensitivity can instead be obtained with microperimetry, which incorporates live retinal tracking technology into standard perimetry to account for eye movements during the test. Both microperimetry and SD-OCT have been widely used to study age-related macular degeneration (AMD). Structural and functional changes in AMD are mainly thought to involve the outer retina. However, retinal ganglion cells (RGC) can also experience degeneration either from normal ageing or other diseases, such as glaucoma. RGC loss, especially when mild, can be partially gauged with SD-OCT and neural models provide a connection between estimates of stimulated RGCs and expected perimetric sensitivity. The purpose of this analysis is to use OCT-derived RGC estimates, within an established neural model for perimetry, to predict the expected sensitivity based on the structure of the inner retina. Deviations from the model, in patients with AMD, may indicate outer retinal damage in the absence of other pathology.

Setting/Venue
European multi-centre, low-interventional cohort study of age-related macular degeneration (MACUSTAR study) across seven European countries.

Methods
Microperimetry was performed using the MAcular Integrity Assessment device (MAIA, CenterVue, Padua, Italy). Both mesopic and scotopic tests (with a red stimulus) were performed on subjects with no AMD (controls), early AMD (eAMD) and intermediate AMD (iAMD). Scotopic testing was preceded by 30 minutes of dark adaptation. One eye of each participant was tested twice in separate sessions (within three weeks of each other). Dense macular scans (30x25°, 241 B-scans) were obtained by Spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany). Layer segmentations were obtained from a pre-trained and validated deep learning algorithm (based on DeepLab V3 architecture). Histology data were combined with Ganglion Cell Layer (GCL) thickness to obtain local structural estimates of RGC counts. Fundus images from the MAIA and the Spectralis were matched to accurately report the locations tested with perimetry onto the structural map. RGC displacement was applied to perimetric stimuli to measure the number of RGCs stimulated at each location. A bivariate normative linear mixed-effect model, accounting for both the local log10(RGC count) and age, was estimated for scotopic and mesopic microperimetry using the control group. Pointwise deviations from this model were quantified for the eAMD and iAMD group.

Results
The final dataset included data from (mesopic/scotopic): 43/41 eyes with no AMD (controls), 28/27 with early AMD (eAMD) and 150/151 with intermediate AMD (iAMD). The mean (standard deviation) age (years) was 69 (7) for controls, 72 (6) for eAMD and 71 (7) for iAMD. The relationship between log10(RGC count) and sensitivity was significant (p < 0.001) for both the mesopic and the scotopic test. In agreement with previous results, the coefficients were compatible with partial summation conditions, which justifies the use of a linear relationship. However, the relationship was much shallower for the scotopic test (1 dB/log10(RGC count)) than the mesopic test (1.72 dB/log10(RGC count)). No significant effect of age was found (p = 0.319 and 0.673 for the mesopic and scotopic tests respectively). Both eAMD and iAMD eyes showed a significant deviation from the normative model (p < 0.05 for both scotopic and mesopic tests), but there was no significant difference between the two groups. Both tests identified a similar percentage of abnormal locations (sensitivity < 5th normative percentile) in eAMD (18% mesopic; 17% scotopic) and iAMD (17% for both tests) eyes, with no significant differences.

Conclusions
Our analysis, in agreement with previous findings, shows that the expected retinal light sensitivity can be estimated from a healthy inner retina assuming partial summation conditions. This is valuable for AMD because it offers a generalisable structural benchmark for the expected normative sensitivity. The approach accounts for inner retinal changes due to normal ageing as well as any pathology, which are frequent in an elderly population (e.g., undiagnosed/early glaucoma). Such a relationship, however, is not expected to hold for advanced RGC loss, both because of the shortcomings of structural estimates and because of deviations from the partial summation regime. Further investigation is required for a more harmonious integration of advanced inner retinal damage, such as from glaucoma. Eyes with AMD showed significant deviation from the normative models, but no significant differences between eAMD and iAMD groups. Of note, the iAMD group showed a wider variation in sensitivity, which might be due to the much larger sample size. Further analyses focussed on more extreme normative cut-offs and on locations with detectable structural outer retinal changes might be helpful in identifying finer differences between eAMD and iAMD.

Financial Disclosure
Consultant - CenterVue, SpA
**Title**

Effect of pigment epithelial detachment thickness and variability on visual acuity outcomes in patients with neovascular age-related macular degeneration: 96-week pooled, treatment-agnostic data from the HAWK and HARRIER studies

**Purpose**

To investigate the effect of retinal pigment epithelial detachment (PED) thickness (i.e., height) and variability on best corrected visual acuity (BCVA) over 96 weeks of follow-up in anti-VEGF treated patients with neovascular age-related macular degeneration (nAMD).

**Setting/Venue**

Post hoc treatment-agnostic analysis of the pooled cohorts of the 96-week, randomized, double-masked, multicentre Phase III clinical trials HAWK (NCT02307682) and HARRIER (NCT02434328) of nAMD patients treated with either brolucizumab 6 mg or aflibercept 2 mg (n=1396 patients).

**Methods**

Optical coherence tomography images from anti-VEGF treated patients in the pooled HAWK and HARRIER (H&H) studies were assessed for the maximum PED thickness across the macula at baseline through to Week 96. The impact of PED thickness on BCVA outcomes was assessed by comparing BCVA change from baseline to Week 96 in the subgroups of patients with either less than 200 µm or ≥200 µm PED thickness at baseline and at Week 12 (the first visit when the full effect of the three loading injections could be observed). The impact of PED fluctuations on change in BCVA from baseline to Week 96 was evaluated by grouping the H&H cohort into four PED variability quartiles (Qv1–4) based on PED variability expressed as PED thickness standard deviation (SD) for each patient from Week 12 to Week 96. Furthermore, the association between PED thickness and the presence of other retinal fluids was probed by grouping the H&H cohort into four quartiles based on PED thickness (Qh1–4) at Week 48 (time of primary endpoint) and assessing the presence of intraretinal fluid (IRF) and subretinal fluid (SRF) in these quartiles at that specific time point.

**Results**

Patients with baseline PED thickness less than 200 µm (n=870) gained (mean ± standard error) 8.0±0.4 and 7.0±0.5 Early Treatment Diabetic Retinopathy Study (ETDRS) letters from baseline at Weeks 48 (p=0.0003) and 96 (p=0.004), respectively, versus 5.5±0.6 and 4.6±0.6 ETDRS letters for patients with baseline PED thickness ≥200 µm (n=513). Patients with Week 12 PED thickness less than 200 µm (n=1138) gained 7.5±0.4 and 6.5±0.4 ETDRS letters from baseline at Weeks 48 (p=0.03) and 96 (p=0.04), respectively, versus 5.5±0.9 and 4.3±1.0 ETDRS letters for patients with Week 12 PED thickness ≥200 µm (n=215). BCVA gains from baseline were lower for patients in the quartile Qv4, which had the highest variability (Week 48 ETDRS letter gains: Qv1: 7.1±0.7; Qv2: 8.4±0.7; Qv3: 8.1±0.7; Qv4: 5.0±0.7; Week 96 ETDRS letter gains: Qv1: 6.2±0.8; Qv2: 7.9±0.8; Qv3: 7.2±0.8; Qv4: 3.3±0.8). Compared with patients in Qh1, Qh2–4 patients showed a steadily increasing association (odds ratio [95% confidence interval]) of PED thickness with presence of both IRF (Qh2: 1.5 [0.9; 2.5]; Qh3: 1.9 [1.2; 3.2]; Qh4: 3.9 (2.4; 6.2]) and SRF (Qh2: 1.6 [1.0; 2.6]; Qh3: 2.3 [1.5; 3.6]; Qh4: 5.6 (3.6; 8.6)).

**Conclusions**

In this pooled, treatment-agnostic HAWK and HARRIER post hoc analysis, BCVA outcomes over 96 weeks were better in patients with PED thickness less than 200 µm at baseline or at Week 12 compared with patients with PED thickness ≥200 µm. Greater fluctuations in PED thickness from Week 12 through Week 96 were also associated with lower BCVA gains at Week 96, and increasing PED thickness at Week 48 was associated with an increasing presence of IRF and SRF, especially in the group with the greatest PED thickness. The results of this analysis therefore indicate that lower and less variable PED thickness is associated with reduced disease activity and improved visual outcomes in nAMD patients treated with anti-VEGF. PED thickness may thus represent a surrogate of neovascular activity.

**Financial Disclosure**

Consultant for Amgen, Bayer, Genentech, Iveric Bio, Novartis, Optovue; Research grants from Amgen, Genentech, Heidelberg, Optovue, Regeneron, Topcon; Speaker fees from Optovue
Purpose
Optimal vision outcomes with anti–vascular endothelial growth factor (VEGF) treatment for neovascular age-related macular degeneration (nAMD) require frequent injections and close monitoring. Real-world data suggest that this overall treatment burden creates a barrier to effective anti-VEGF treatment that contributes to many patients not achieving or maintaining vision outcomes seen in clinical trials. In addition, owing to the multifactorial nature of nAMD, there is a ceiling to the vision gains possible with anti–VEGF-A treatment alone. Dual inhibition of angiopoietin-2 (Ang-2) and VEGF-A with faricimab may promote vascular stability, resulting in increased durability and reduced treatment burden, and may improve long-term outcomes beyond anti-VEGF treatment alone for nAMD. Our goal was to design phase 3 studies to evaluate the efficacy, safety and durability of faricimab dosed up to every 16 weeks (Q16W) compared with aflibercept every 8 weeks (Q8W) in patients with nAMD.

Setting/Venue
In retinal and choroidal vascular diseases such as nAMD, Ang-2 and VEGF-A are upregulated, driving vascular instability. In the phase 2 STAIRWAY trial (NCT03038880), dual Ang-2/VEGF-A inhibition with faricimab demonstrated robust vision and anatomical improvements comparable with anti–VEGF-A treatment alone, but with fewer injections, providing evidence for potential increased durability and reduced treatment burden with extended faricimab dosing in nAMD. Informed by the phase 2 trial, we designed the phase 3, randomised, double-masked, active comparator–controlled, 112-week, TENAYA (NCT03823287) and LUCERNE (NCT03823300) trials of faricimab in nAMD to further evaluate the vascular-stabilising effects of dual Ang-2 and VEGF-A inhibition.

Methods
Treatment-naive patients with nAMD, aged ≥ 50 years, with choroidal neovascularisation lesions of any type and best-corrected visual acuity (BCVA) of 78–24 Early Treatment Diabetic Retinopathy Study letters, were randomised 1:1 to faricimab 6.0 mg up to Q16W after 4 initial every-4-week (Q4W) doses, or aflibercept 2.0 mg Q8W after 3 initial Q4W doses. Based on disease activity assessments (prespecified anatomical and functional criteria, and investigator opinion) at weeks 20 and 24, patients in the faricimab arm were allocated to receive Q8W, every-12-week (Q12W) or Q16W dosing through week 60. From week 60, faricimab-treated patients follow a personalised treatment interval (PTI), a protocol-driven treat-and-extend regimen, during which treatment intervals are adjusted based on individualised treatment response, assessed by prespecified anatomical and functional criteria at study drug dosing visits. To maintain masking, all patients receive active treatment or sham at Q4W study dosing visits to week 108. To assess the effect of COVID-19–related intercurrent events, resulting in study treatment discontinuation and missed doses with potentially major impact on efficacy, and their impact on data quality and integrity, sensitivity and supplemental analyses were conducted to assess the robustness of the primary analysis.

Results
To control for differences in time from last treatment between arms and inherent variabililty in BCVA, the primary efficacy endpoint, assessing noninferiority of faricimab up to Q16W versus aflibercept Q8W in mean change in BCVA from baseline, was averaged over weeks 40, 44 and 48. The faricimab initial dosing was informed by the phase 2 STAIRWAY trial, and intended to maximise Ang-2/VEGF-A suppression before extending treatment intervals up to Q16W. Secondary endpoints through week 48 included the proportion of patients on faricimab Q16W, Q12W and Q8W treatment intervals; the proportion of patients gaining or avoiding a loss of ≥ 15 letters from baseline; and changes in anatomic outcomes. Safety was assessed by the incidence and severity of ocular and nonocular adverse events. In the PTI phase, treatment interval is extended by 4 weeks in patients with stable disease; reduced by 4 or 8 weeks in patients with disease reactivation or intervals are maintained if extension or reduction criteria are not met. An automated interactive voice or web-based response (IxRS) system is used for treatment assignment. COVID-related missed visits were generally well balanced across treatment arms and trials, with no meaningful impact on the primary outcome and data integrity.

Conclusions
The phase 3 TENAYA and LUCERNE trials met their primary efficacy endpoint of noninferiority of faricimab up to Q16W versus aflibercept Q8W in visual acuity gains, with ~80% of patients on ≥ Q12W and ~45% on Q16W dosing intervals of faricimab at week 48, and showed that faricimab was well tolerated. The PTI phase is ongoing. The phase 3 trials of faricimab in nAMD were designed to tailor treatment intervals according to patients’ needs with individualised dosing up to Q16W, to reflect real-world treatment practice. Treatment durability driven by the vascular-stabilising effects of dual Ang-2 and VEGF-A could reduce treatment burden and improve outcomes for patients with nAMD.
Title

Efficacy and safety of intravitreal aflibercept treat-and-extend compared with fixed dosing for neovascular age-related macular degeneration: The AZURE study

Purpose

To compare the efficacy and safety of intravitreal aflibercept (IVT AFL) administered using a proactive, individualized treat-and-extend (T&E) regimen or a fixed-dosing regimen every 8 weeks (q8), for patients with neovascular age-related macular degeneration (nAMD) beyond the first year of treatment.

Setting/Venue

AZURE (NCT02540954) was a randomized, active-controlled, parallel-group, open-label, multicenter Phase 3b study to assess the non-inferiority of T&E to q8 dosing in patients with nAMD who had completed at least 1 year of IVT-AFL treatment.

Methods

Patients aged ≥51 years, with active subfoveal choroidal neovascularization lesions secondary to nAMD and best-corrected visual acuity (BCVA; Early Treatment Diabetic Retinopathy Study [ETDRS] letters) of 73–25 letters were eligible. All patients completed at least 1 year of IVT-AFL treatment prior to enrolment. Patients were randomized 1:1 to receive 2 mg IVT-AFL in a fixed q8 regimen (treatment every 8 weeks) or an individualized T&E dosing regimen (minimum treatment interval of 8 weeks with no upper limit; adjusted according to functional/anatomic criteria per the investigator’s judgment). The primary endpoint was mean change in BCVA from baseline (BL) to Week (W) 52; the prespecified margin for non-inferiority was 5 letters. Secondary endpoints at W52 included the proportion of patients maintaining vision, defined as losing <15 letters (key secondary) and mean change in central subfield thickness (CST) from BL. The proportion of patients for whom the treatment interval was extended and the total number of injections at W52 were exploratory endpoints. All endpoints were exploratory at W76. Safety (including treatment-emergent adverse events [TEAEs] in the study eye) was evaluated throughout the study.

Results

The full analysis set comprised 332 patients (q8: n=167; T&E: n=165). Mean±SD BCVA at IVT-AFL initiation (≥1 year before BL) was 60.9±9.9 (q8) and 59.4±10.5 (T&E) letters. At study BL, mean age was 74.7±7.0 (q8) and 76.2±8.3 (T&E) years; mean BCVA was 70.1±10.9 (q8) and 69.0±12.1 (T&E) letters. At W52, mean BCVA change from BL was −0.5±8.4 (q8) and −0.3±7.5 (T&E) letters. Least-squares mean difference (95% CI) of T&E versus q8 was 0.22 (−1.51; 1.96). T&E achieved a non-inferior change in mean BCVA at W52 versus q8 (p<0.0001). At W76, mean BCVA change from BL was −0.9±10.4 (q8) and −1.5±10.9 (T&E) letters. From BL to W52, 94.0% (q8) and 95.2% (T&E) of patients maintained vision. Mean CST change from BL at W52 and W76 was −33.4±47.1 and −37.8±51.1 (q8) and −24.4±55.2 and −21.7±57.0 (T&E) µm, respectively. Mean numbers of IVT-AFL injections at W52 and W76 were 6.8±0.8 and 9.6±1.4 (q8) and 6.0±1.0 and 8.0±1.8 (T&E). With T&E, the last treatment interval to W76 was ≥12 weeks for 37.0% (n=61) of patients (mean 11.1±3.6 weeks). Ocular TEAEs were similar: q8 (48.8%) and T&E (45.5%). Two patients (0.6%) experienced endophthalmitis and no cases of retinal vasculitis were reported.

Conclusions

In patients who previously received at least 1 year of IVT-AFL treatment for nAMD, proactive, individualized T&E dosing achieved similar functional outcomes as q8 dosing. Functional and anatomic improvements achieved during Year 1 were maintained in Year 2 and Year 3 of IVT-AFL treatment with both regimens. The treatment burden on patients was lower with proactive T&E dosing than with q8 dosing – fewer injections were required with T&E and more than one third of patients could be maintained on treatment intervals of ≥12 weeks. No new safety signals were identified, which is consistent with prior interventional studies.

Financial Disclosure

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Title
Scleral fixated and iris fixated intraocular lens implantation: A meta-analysis

Purpose
To compare the efficacy and safety outcomes following scleral fixated (SF) vs iris fixated (IF) intraocular lens (IOL) implantation in adults.

Setting/Venue
Meta-analysis.

Methods
A systematic literature search was conducted on Ovid MEDLINE, EMBASE, and Cochrane CENTRAL from 2005-2020. Inclusion criteria were as follows: adult patients, comparison of SF to IF IOL implantation or different techniques for SF or IF IOL implantation, sample size of at least 5 eyes in each group, and English language articles. Outcomes included corrected distance visual acuity (CDVA), endothelial cell density (ECD), and incidence of complications. Meta-analysis was conducted using a random effects model in which weighted mean differences (WMD) and risk ratios (RR) with 95% confidence intervals (95%CI) were computed. The Risk of Bias 2.0 (RoB 2.0) tool was completed for randomized controlled trials (RCTs) and the Risk of Bias in Non-randomized Studies – of Interventions (ROBINS-I) tool was completed for non-randomized studies. The certainty of evidence for outcomes was evaluated via the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) tool.

Results
1252 eyes from 7 RCTs and 14 cohort studies were included. Overall risk of bias was low to some concerns for RCTs and moderate for non-randomized studies. Mean follow-up was 14±12 months. There was no significant difference in mean CDVA between sutured SFIOL and IFIOL implantation (P=0.80) or sutureless SFIOL and IFIOL (P=0.43) at final follow-up. Absolute change in spherical equivalent (P=0.74) was not significantly different. Final ECD was significantly higher for sutured SFIOLs (WMD=283.30 cells/mm², 95%CI=[101.79,464.82], P=0.002) relative to IFIOLs. Risk of pupil distortion/ovalization was significantly higher in the IFIOL group (RR=0.05, 95%CI=[0.01,0.33], P=0.002) relative to sutureless SF IOLs.

Conclusions
There were no differences in visual acuity and refractive outcomes between SFIOL and IFIOL implantation. Final ECD was significantly higher in the sutured SFIOL group compared to IFIOL. A significantly greater proportion of patients experienced pupil distortion/ovalization following IFIOL relative to sutureless SFIOL implantation. Future RCTs are needed to confirm these findings.

Financial Disclosure
Conflicts of Interest: MMP: Financial support (to institution) – PSI Foundation. PJK: Advisory board – Novartis, Alcon, Bayer, Roche, Novelty Nobility; Financial support (to institution) – Allergan, Bayer, Roche, Novartis; Financial support – Novartis, Bayer; Equity owner – ArcticDx. RHM: Advisory board- Bayer, Novartis, Allergan, Roche; Financial Support (to institution)- Bayer, Novartis.
Gene expression profile prediction in uveal melanoma using deep learning

**Purpose**
Uveal melanoma (UM) is the most common intraocular tumor in adults, and the current gold standard prognostic test for metastasis and survival prediction is the gene expression profile (GEP) test [Castle Biosciences, Friendswood, TX]. UM patients can be divided into two classes by GEP, and there is a stark contrast in long-term survival between the two classes: the 92-month survival probability in class 1 patients is 95%, versus 31% in class 2 patients. However, the GEP test is costly and not available outside of the U.S. We aimed to develop a deep learning based algorithm to directly predict GEP status from H&E stained cytopathology slides.

**Setting/Venue**
Consecutive patients with uveal melanoma treated at a tertiary academic referral center.

**Methods**
Digital cytopathology slide images were generated from fine needle aspiration biopsies (FNAB) of UM tumors, smearing of tumor cells on glass slides, H&E staining and whole slide scanning at 40x magnification. Our training dataset included 65 slides from 58 patients (28 class 1 tumors; 30 class 2 tumors). Using a customized tool that combined unsupervised clustering and further refinements through human-computer interactions, 90,316 unique regions of interest (ROIs) containing UM cells were generated and used for training of a deep learning system (DLS). GEP status of each tumor was used as ground truth. The data label at the slide level was propagated to the its respective ROIs. The DLS was trained in a two-stage manner, involving first the ResNet-50 deep convolutional neural network (DCNN) and finally a two-layer artificial neural network for the binary classification task of distinguishing between GEP class 1 and class 2. The DLS was tested on a separate dataset of 24 slides from 24 patients (12 class 1 tumors; 12 class 2 tumors; 1 slide per patient).

**Results**
Our DLS correctly predicted the GEP status of 22/24 slides, thus achieving a 91.7% accuracy on a patient-level analysis. Of the two slides that were incorrectly predicted, one was generated from a class 1 tumor and one was generated from a class 2 tumor.

**Conclusions**
We have developed a DLS that is capable of robust predictions of GEP status based on H&E stained cytopathology slides alone. Such an algorithm has the potential to serve as an alternative to GEP testing, especially in areas of the world where GEP testing is not available. As the next step, we plan to prospectively validate this algorithm using data from a different institution and develop a similar DLS using actual metastasis status as the ground truth for training and testing.

**Financial Disclosure**
Amaros (consultant)
The association of retinal age gap with arterial stiffness and incident cardiovascular disease

Yifan Chen
United Kingdom

Purpose
To investigate associations of retinal age gap with arterial stiffness and incident cardiovascular disease (CVD).

Setting/Venue
The current study operates in accordance with the principles of the Declaration of Helsinki, with written informed consent from all participants, under the UK Biobank application number 62489.

Methods
A total number of 80,170 fundus images from 46,970 participants in the UK Biobank had reasonable image quality and were included. A deep learning (DL) model based on 19,200 fundus images of 11,052 disease-free participants was used to predict the retinal age via 5-fold cross-validation. Retinal age gap (retinal age predicted based on the fundus image from the right eye minus chronological age) was generated by the trained DL model for the remaining 35,917 participants. Arterial stiffness index (ASI) was derived from the analysis of digital volume pulse. Incident CVD was ascertained by self-reported questionnaire, hospital admission records or death records, whichever the earliest. Linear regression models were used to assess the association between retinal age gap and ASI. Cox proportional hazards regression models were used to explore the relationship between retinal age gap and incident CVD in the population free of CVD at the baseline.

Results
In the 35,541 participants with available ASI data, we found each one-year increase in the retinal age gap was significantly associated with ASI ($β = 0.0016$, 95% confidence interval [CI]: 0.001- 0.003, $P<0.001$). After a median follow-up of 5.83 years (interquartile range [IQR]: 5.73-5.97), 675 (2.00%) out of 33,817 participants who were deemed free of CVD had incident CVD. In the fully adjusted model, each one-year increase in retinal age gap was associated with a 3% increase in the risk of incident CVD (hazard ratio [HR]=1.03, 95% CI: 1.01-1.06, $P=0.012$). This association remained significant after further adjustment for ASI.

Conclusions
We found that retinal age gap was significantly associated with ASI and incident CVD, implying the potential of this biomarker in identifying individuals at high risks of CVD.

Financial Disclosure
none
Title
Development and external validation of an automatic segmentation model for detection and quantification of geographic atrophy from optical coherence tomography imaging

Purpose
Geographic atrophy (GA) is the defining atrophic lesion of advanced non-neovascular age-related macular degeneration (AMD). Detection and segmentation of GA from optical coherence tomography (OCT) imaging is necessary for diagnosis, monitoring, prognosis, and to inform therapy research for this orphan disease. The current standard of segmentation requires specialist manual effort, which is labour intensive and prone to inter-grader variability. There is a need for validated and fully automated deep-learning approaches to qOCT detection and segmentation of GA that are applicable in clinical care of non-neovascular AMD patients with GA and potential to facilitate therapy research.

Setting/Venue
Dataset for model development were selected from participants of the FILLY2 trial (NCT02503332) a 18-month prospective, multicenter, randomised, sham-controlled phase 2 study that enrolled patients at 46 sites in the United States (New England Institutional Review Board, University of Miami, Mayo Clinic, Institutional Review Board of the Cleveland Clinic Foundation, Duke University Health System Institutional Review Board, and Research Compliance Office, Stanford University), Australia (Bellberry Ltd), and New Zealand (Northern A Health and Disability Ethics Committee, Health and Disability Ethics Committees, and Ministry of Health). External validation cohort were recruited from Moorfields Eye Hospital NHS Foundation Trust (London, United Kingdom).

Methods
Segmentation models were trained on FILLY2 participant data 5049 OCT B-scans from 399 eyes (200 patients) with GA secondary to AMD were manually segmented. Using U-Net architecture, deep-learning models were trained for each of the constituent morphological features of GA: RPE (retinal pigment epithelium)-loss; photoreceptor degeneration; and hypertransmission. A fourth model was trained for direct segmentation of GA i.e. overlapping regions of RPE-loss, photoreceptor degeneration, and hypertransmission. Predictive performance was validated on an external dataset recruited from a cohort-independent in time and geography from the model development cohort-from a retrospective cohort of all patients who attended Moorfields Eye Hospital NHS Foundation Trust as part of routine clinical care. The dataset comprised 884 OCT B-scans from 192 eyes (110 patients), of which: 151 eyes with GA secondary to non-neovascular AMD; 31 eyes with neovascular AMD; 8 eyes with pigment epithelial detachment; 2 eyes with epiretinal membrane. Each OCT scan was annotated for the target features by two senior graders independently with adjudication by a senior ophthalmologist. The primary outcome is the agreement (DSC [dice similarity coefficient] and ICC [intraclass correlation coefficient]) between model GA prediction and consensus of the 2 independent graders on the external validation dataset.

Results
When evaluated on the external validation dataset, the resultant models accurately segmented each of the three constituent features of GA: RPE-loss (median DSC [dice similarity coefficient] ± SD [standard deviation] 0.95 ± 0.21), photoreceptor degeneration (0.96 ± 0.21), hypertransmission (0.97 ± 0.15), in addition to GA itself (0.96 ± 0.15). Model performance was greater than agreement between specialist human graders (RPE-loss 0.93 ± 0.31, photoreceptor degeneration 0.89 ± 0.20; hypertransmission 0.81 ± 0.30; GA 0.80 ± 0.30). Although the models were trained on annotated OCTs from patients with GA secondary to AMD, high performance was observed for each feature when considering OCTs also featuring other retinal pathologies including nAMD, PED, and ERM.

Conclusions
We report the development and validation of a deep-learning tool that can automatically process OCT scans for detection and quantification of GA that can be scaled across OCT volumes. The approach described: (i) performs fully automated segmentation of whole-volume OCT B-scans for GA; (ii) identifies and segments each of the retinal OCT features required to identify GA and its subtypes as per the CAM (Consensus of Atrophy Meetings) group consensus definitions; (iii) is trained and validated on the largest cohort size to-date; and critically, (iv) is externally validated on an independent dataset from real-world clinical practice. Here it is demonstrated that predictive performance equivalent to human specialist graders is robustly retained beyond the sample used for model development. Together, these features award this strategy the sophistication, resilience, and generalisability required to facilitate real-life clinical management of patients with GA, as well as, promote standardisation of clinical trial endpoints for GA research.

Financial Disclosure
Apellis Pharmaceuticals (Waltham, Massachusetts, United States) provided funding, input on the study design, and feedback on the manuscript.
Deep learning for automated stratification of ophthalmic images: Application to age-related macular degeneration and color fundus images

**Purpose**
Deep learning (DL) systems based on convolutional neural networks (CNNs) have achieved expert-level performance in different classification tasks, and have shown the potential to reduce current experts’ workload significantly. We explore this potential in the context of automated stratification of ophthalmic images. DL could accelerate the setup of clinical studies by filtering large amounts of images or patients based on specific inclusion criteria, as well as aid in patient selection for clinical trials. DL could also allow for automated categorization of entering images in busy clinical or screening settings, enhancing data triaging, searching, retrieval, and comparison. Automated stratification could also facilitate data collection and application of further DL-based phenotyping analysis, by generating useful sets of images for expert annotation, training, or testing of segmentation algorithms. In our work, we focus on the stratification of color fundus images (CFI) based on multiple features related to age-related macular degeneration (AMD) at different hierarchical levels. We further analyze the robustness of the automated stratification system when the amount of data available for development is limited. We performed our validation on two different population studies.

**Methods**
Automated stratification of CFI was performed based on the presence or absence of the following AMD features, following a hierarchical tree with different branches (Bi) and levels (Hi) from generic features (H0) to specific features (H3): AMD findings (H0); B1: drusen (H1), large drusen (H2), reticular pseudodrusen (H3); B2: pigmentary changes (H1), hyperpigmentation (H2), hypopigmentation (H2); B3: late AMD (H2), geographic atrophy (H2), choroidal neovascularization (H2). The automated stratification system consisted of a set of CNNs (based on the Inception-v3 architecture) able to classify the multiple AMD features (presence/absence) at higher and lower levels. This allowed to automatically stratify incoming CFI into the hierarchical tree. CFI from the AREDS dataset were used for development (106,994 CFI) and testing (27,066 CFI) of the CNNs. We validated the robustness of the system to a gradual decrease in the amount of data available for development (100%, 75%, 50%, 25%, 10%, 5%, 2.5%, and 1% of development data). An external test set (RS1-6) was generated with 2,790 CFI from the Rotterdam Study. This allowed to validate the performance of the automated stratification across studies where different CFI grading protocols were used.

**Results**
Area under the receiver operating characteristic curve (AUC) was used to measure the performance of each feature’s classification within the automated stratification. The AUC averaged across AMD features when 100% of development data was available was 93.8% (95% CI, 93.4%-94.2%) in AREDS and 84.4% (82.1%-86.5%) in RS1-6. There was an average relative decrease in performance of 10.0±4.7% between AREDS and the external test set, RS1-6. The performance of the system decreased gradually with each development data reduction. When only 1% of data was available for development, the average AUC was 81.9% (81.0%-82.8%) in AREDS and 74.0% (70.8%-77.0%) in RS1-6. This corresponded to an average relative decrease in performance of 12.7±13.2% in AREDS and 12.6±7.8% in RS1-6.

**Conclusions**
The automated stratification system achieved overall high performance in the classification of different features independently of their hierarchical level. This shows the potential of DL systems to identify diverse phenotypes and to obtain an accurate automated stratification of CFI. The results showed that automated stratification was also robust to a dramatic reduction in the data available for development, maintaining the average AUC above 80%. This is a positive observation, considering that the amount of data available for DL development can be limited in some settings, and the gradings can be costly to obtain. Nevertheless, variability in performance across features could be observed, especially for those with very low prevalence, such as reticular pseudodrusen, where performance became more unstable when few data were available. The external validation showed these observations held when the automated stratification was applied in a different population study, with an expected (but not drastic) drop of performance due to differences between datasets and their grading protocols. In conclusion, our work supports that DL is a powerful tool for the filtering and stratification of ophthalmic images, and has the potential to reduce the workload of experts while supporting them in research and clinical settings.
Purpose
Inherited retinal diseases (IRDs) are single-gene disorders caused by genetic mutations in any one of over 270 genes. They are a leading cause of blindness in children and working age adults globally. Identifying the causative gene through genetic testing is crucial for potential gene targeted treatments, recruitment to clinical trials, prognosis and family planning. However the prescription of appropriate genetic tests and the interpretation of genetic results requires phenotype-genotype recognition that only few IRD experts are currently capable of providing. Therefore we aimed to develop Eye2Gene, an AI algorithm, to predict the probable IRD causative gene from the retinal scans of suspected IRD patients.

Setting/Venue
Eye2Gene was trained and tested on retinal scans of 1,907 IRD patients with a known genetic diagnosis from Moorfields Eye Hospital and externally validated on a cohort of 37 IRD patients with a genetic diagnosis from the University Hospital Bonn. The training was limited to predicting the top 36 most common genes which represents 82% of all IRD cases at Moorfields.

Methods
Following quality control, the Moorfields training dataset consisted of 44,817 images from 1,907 IRD patients from Moorfields Eye Hospital, split into three different modalities: Fundus Auto-Flourescence (FAF), Infrared (IR), and Spectral-Domain Optical Coherence Tomography (SD-OCT). For each of the three modalities, five individual Inception v3 convolutional neural networks (CNNs) were trained on different samples of the training data using 5-fold cross validation. This resulted in Eye2Gene, an ensemble of fifteen different neural networks. Each network was trained to identify up to 36 gene classes. Per image predictions were obtained by combining the fifteen CNNs predictions. Per patient predictions were obtained by combining the prediction across multiple images from the same patient. In order to assess generalisability of Eye2Gene, we defined a held-out dataset consisting of 264 patients from Moorfields not used in the training and an external dataset of 37 patients from University Hospital of Bonn. From these a subset 50 FAF scans was extracted for human evaluation by eight ophthalmologists with varying levels of experience in IRDs in order to benchmark Eye2Gene against human performance. Ophthalmologists were asked to pick their top five gene choices per image out of the 36 genes.

Results
Eye2Gene yields a top-5 accuracy of 88% (i.e predicts the correct gene in the top 5 guesses 88% of the time) in the Moorfields held-out dataset and 83% in the external validation University Hospital of Bonn dataset. On the 50 FAF images that were used for the human benchmarking, Eye2Gene achieved a top-5 accuracy of 70% while the ophthalmologists obtained a maximum combined top-5 accuracy of 78% (at least one of the eight ophthalmologists included the correct gene in the top 5 guesses 78% of the time). However, the maximum top-5 accuracy for any single ophthalmologist was not higher than 36%.

Conclusions
We have developed an AI algorithm Eye2Gene, capable of predicting the 36 top most common IRD genes in the UK and German population to a top-5 accuracy of >80%. From our preliminary benchmarking, Eye2Gene achieves performance similar to a consensus of human experts on an external dataset. This makes Eye2Gene the most advanced AI system yet for the recognition of genes from IRD retinal scans. Future work will include increasing the training dataset through aggregation to achieve better performance and predict more gene classes. Additionally, segmentation of retinal features will also be necessary for obtaining interpretable outputs to satisfy explainability and transparency requirements. We expect Eye2Gene will eventually enable democratisation of IRD expertise, currently available in only a few centres in the world, which will facilitate the prescription and interpretation of genetic tests.

Financial Disclosure
I am a co-founder of Phenopolis Ltd, a software company.
Monitoring of retinal fluid using AI in real-world management of neovascular age-related macular degeneration (nAMD)

**Purpose**
To provide proof-of-principle of quantification of intra- (IRF) and subretinal fluid (SRF) volumes in OCT images from real-world management of neovascular age-related macular degeneration (nAMD) using an automated deep learning-based algorithm.

**Setting/Venue**
Retrospective analysis from the Vienna Imaging Biomarker Eye Study (VIBES) in patients with nAMD under routine anti-VEGF therapy from 2007-2018 at the Department of Ophthalmology, Medical University of Vienna.

**Methods**
Data from five databases (2 EHR, treatment database, 2 devices (Spectralis, Cirrus) including all patients treated in the out-patient clinic were matched. Filtering was performed for treatment-naive nAMD with a baseline (BSL) OCT image for automated IRF, SRF and CST segmentation and at least one follow-up examination. Visual acuity (VA) and OCT at BSL, month 1-3 and years 1-5, age, gender and treatment frequency were included. Main outcome measures were volumes of IRF and SRF in nanoliters (nl) as measured in the central 1, 3 and 6mm over time.

**Results**
A total of 1127 eyes were eligible and included into the analyses. Mean CST with 358μm at BSL and decreasing to 280-303μm during follow-up demonstrated a representative cohort. Maximum volumes for IRF and SRF were seen at BSL with an IRF volume of 21.5/76.6/107.1nl, a SRF volume of 13.7/86/262.5nl in the 1, 3, 6-mm area respectively. The course of retinal fluid response in real-world management demonstrated recurrent disease activity following the loading dose. IRF volume decreased to a mean of 5nl during the loading dose in the central mm, increased to 11nl at year 1 and 16nl at year 5. SRF decreased to a mean of 4nl after initial loading in the central mm and remained low with less than 7nl until year 5. In contrast to CST and SRF values, IRF was closely reflecting the visual acuity change over time.

**Conclusions**
The automated AI-based fluid algorithm precisely detected and quantified IRF and SRF volumes in OCT images from clinical routine over long-term follow-up. Reliable and fast AI tools will allow to introduce efficient decision support indicating disease activity and therapeutic response for the real-world management of exudative macular disease, improving clinical outcomes while saving resources.

**Financial Disclosure**
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Impact of structural changes on multifocal electroretinography in patients with use of hydroxychloroquine

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Purpose
To investigate the relationship between retinal structure and macular function in eyes screened for hydroxychloroquine (HCQ) toxicity.

Setting/Venue
San Raffaele Hospital, Milan, Italy

Methods
Subjects referred for hydroxychloroquine retinopathy screening with structural optical coherence tomography (OCT) and multifocal electroretinogram (mERG) testing completed on the same day were included in the analysis. Amplitude and implicit time of mERG N1 and P1 waves were included in the analysis. Ring ratios were computed for amplitude values as the ratio of rings 1–3:5. A control group of healthy subjects was included for comparison of structural OCT metrics.

Results
Sixty-three eyes screened for HCQ retinopathy and 30 control eyes were analyzed. The outer nuclear layer (ONL) was significantly thinner in HCQ patients in the foveal (p=0.008), parafoveal (p<0.0001), and perifoveal (p<0.0001) regions. The HCQ cohort was further divided into two subgroups according to the presence of structural clinically detectable retinopathy. HCQ eyes without retinopathy had a lower ONL thickness in the foveal (p=0.032), parafoveal (p<0.0001), and perifoveal (p<0.0001) regions, and a thinner inner nuclear layer (INL) in the parafoveal region (p=0.045 vs. controls). Structural changes in HCQ patients without retinopathy were significantly associated with macular function as R2:R5 ring ratio of mERG P1 amplitude was associated with INL (p=0.002) and ONL (p=0.044) thicknesses, and R3:R5 ring ratio of P1 amplitude was associated with ONL thickness (p=0.004).

Conclusions
Our results suggest that structural alterations secondary to HCQ toxicity may occur in absence of clinically detectable retinopathy and this may reflect in an impaired macular function.

Financial Disclosure
None
Comparison of mydriatic and nonmydriatic handheld retinal imaging with early treatment diabetic retinopathy study (ETDRS) 7-standard field photography for diabetic retinopathy (DR) and diabetic macular edema (DME).

Purpose
To compare mydriatic and nonmydriatic handheld retinal imaging with standard ETDRS 7-field color 30-degree fundus photography (ETDRS photos) for the assessment of diabetic retinopathy (DR) and diabetic macular edema (DME).

Setting/Venue
Images acquired during the same visit were collected from adult patients with diabetes mellitus (DM) at a tertiary hospital in Metropolitan Manila, Philippines.

Methods
This is a prospective, comparative instrument validation study. A total of 225 eyes from 116 patients clinically diagnosed to have DM were included in the study. Following a standard imaging protocol, nonmydriatic and mydriatic retinal images were acquired using handheld retinal cameras [Nonmydriatic (NM) – Aurora (AUNM), Smartscope (SSNM) and RetinaVue 700 (RVNM); Mydriatic (MD) – Aurora (AUMD), Smartscope (SSMD), RetinaVue 700 (RVMD) and iNview (NVMD)] and dilated ETDRS photos. Certified retinal imager-graders acquired all handheld retinal images and all ETDRS photos were acquired by clinical trials certified ophthalmic photographers. All images were evaluated at a centralized reading center using color-calibrated high-resolution HD computer displays. Grading was performed independently by 4 graders (2 certified retinal image graders, 1 ophthalmologist and 1 retina specialist) using the international DR/DME classification. Disagreements were adjudicated by a senior retina specialist. Kappa statistics [simple (K), weighted (Kw)] assessed the level of agreement for DR and DME. Sensitivity and specificity for any DR, referable DR ([refDR] moderate nonproliferative DR (NPDR) or worse, any DME or ungradable images) and vision threatening DR ([vtDR] severe NPDR or worse, clinically significant DME (CSME) or ungradable images) were calculated.

Results
Images from 225 eyes of 116 patients were evaluated. Severity by ETDRS photos: DR – no DR 33.3%, mild NPDR 20.4%, moderate 14.2%, severe in 11.6%, proliferative DR 20.4%; DME – no DME 68.0%, DME 9.3%, ciDME 17.3%, ungradable 5.3%. For nonmydriatic handheld retinal imaging, agreement for DR was highest with AUNM (Kw=0.73). DME agreement was highest with RVNM (Kw=0.81). Agreement for DR severity with ETDRS photos was highest with AUNM (55.6% exact, 80.0% 1-step). Ungradable images were associated with a higher rate of refDR and vtDR on corresponding ETDRS photos (AUNM: 2.1x/2.2x, SSNM: 2.1x/2.1x, and RVNM: 2.1x/2.4x, p-value 0.0003). For mydriatic handheld retinal imaging, agreement for DR was highest with AUMD and RVMD (Kw=0.75) and lowest with NVMD (Kw=0.68). DME agreement was highest for AUMD and RVMD (Kw=0.78). Agreement for DR severity with ETDRS photos was highest with AUMD (65.8% exact, 93.8% 1-step). The established standard for sensitivity (0.80) was met by SSNM, RVNM, AUMD, SSMD and RVMD for anyDR, refDR and vtDR. Specificity (0.95) was met by AUNM, SSNM, RVNM, AUMD and RVMD for anyDR, and by AUMD and RVMD for refDR. The standards for sensitivity (0.80) and specificity (0.95) were met by AUMD and RVMD for DME.

Conclusions
Following a standardized protocol, both nonmydriatic and mydriatic handheld retinal imaging devices have substantial levels of agreement for both DR and DME. With mydriasis, handheld retinal imaging devices meet standards for sensitivity and specificity in identifying any DR and refDR. The ungradable rates for DR and DME decreased by 15.1% (AU), 16.4% (SS) and 32.4% (RV) for DR, and by 16.8% (AU), 14.7% (SS) and 32.0% (RV) for DME after mydriasis. Similarly, there is increased exact agreement with ETDRS photos by 10.2% (AU), 8.4% (SS) and 20.0% (RV) for DR severity following pupil dilation. None of the handheld devices met the established 95% specificity for vtDR, suggesting that lower thresholds for referral when handheld devices are used. Additionally, sensitivity thresholds for DME were only achieved with mydriasis when using handheld devices, suggesting that pupil dilation enhances DME evaluation.

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Retinal toxicity secondary to high dose cefuroxime in a patient undergoing trabeculectomy

Purpose
To present a case of severe retinal toxicity secondary to high dose cefuroxime administered during trabeculectomy glaucoma surgery. We describe the clinical features and management and describe serial multimodal imaging and electroretinogram (ERG) findings. To the best of our knowledge, this is the first report of cefuroxime retinal toxicity in trabeculectomy surgery, instead of cataract surgery, which is of particular significance because of the possible differences in pharmacokinetics within the eye.

Setting/Venue
Cefuroxime is routinely administered during intra-ocular surgery to prevent post-operative endophthalmitis, with intra-cameral injection widely adopted in cataract surgery. Toxicity to both intra-cameral cefuroxime (ICC) and sub-conjunctival cefuroxime (SCC) during cataract surgery has been reported.

Methods
A 69-year-old male with primary open-angle glaucoma, underwent right trabeculectomy, augmented with mitomycin C (0.2mg/ml). The patient inadvertently received cefuroxime 12.5mg/0.1mls as an intracameral rather than a subconjunctival injection. Within 4 hours, the error was discovered and the patient underwent immediate anterior chamber (AC) washout. His right best-corrected visual acuity (BCVA) was hand movements, and he had pigment cells in the AC and dull macular reflex. Uveitis was observed with vitreous cells and haze. Optical coherence tomography (OCT) demonstrated serous macular detachment (SMD), characteristic schisis-like changes in the outer nuclear layer (ONL) and ellipsoid zone (EZ) disruption. He was managed with intensive topical steroid and non-steroidal therapy, subconjunctival dexamethasone (3.3mg/ml) and orbital floor depomedrone (40mg/1ml).

Results
Serial OCT, fundus autofluorescence and OCT-angiography images and ERG findings are presented in conjunction with clinical findings during 3-months follow-up. Initial full-field ERG showed decreased a-wave and b-wave amplitude, which normalised within 6 weeks while his multi-focal ERG showed reduced signals in all rings and gradual improvements at 6-weeks and 3 months. The OCT SMD and ONL schisis-like changes resolved after 5 days and EZ disruption resolved after 9 days. BCVA improved to near pre-operative levels (pre-op VA -0.06 logMAR, last follow-up 0.04 logMAR).

Conclusions
There have been reports of cefuroxime toxicity with standard (1mg/0.1ml) and high dose ICC (2-100mg) and SCC (31.25mg). As ICC and SCC are routinely used in intra-ocular surgery, ophthalmologists need to be aware of this potential complication and consider this in patients with unexplained reduced vision post-operatively. Theatre teams need to be vigilant about potential dilution and administration errors to ensure that the correct concentration and volume of cefuroxime is given. We highlight the risks of high dose intracameral injection, including uveitis and retinal toxicity, and the utility of serial OCT and full-field and multi-focal ERG in this condition. We report a favourable outcome with significant and rapid improvement in retinal structure and function observed during follow-up.

Financial Disclosure
No financial disclosures
**Title**
Microvascular impairment in COVID-19 bilateral pneumonia 6-months follow-up assessed by optical coherence tomography angiography

**Purpose**
The purpose of this study was to evaluate the presence of retinal and microvascular alterations in COVID-19 patients with bilateral pneumonia due to SARS-COV-2 that required hospital admission and compare this with a cohort of age and sex matched controls.

**Setting/Venue**
Cases were selected from a series of COVID-19 bilateral pneumonia patients, with at least one SARS-COV-2 positive polymerase chain reaction (PCR) test, and admitted at the Clínica Universidad de Navarra (Pamplona, Spain) during March and April 2020. Controls were obtained from a large optical coherence tomography angiography (OCTA) database at Hospital Clinic (Barcelona, Spain) from previous research projects.

**Methods**
Cross-sectional, consecutive case-control series. COVID-19 bilateral pneumonia patients underwent retinal imaging 14 days (n=25) and 6 months (n=17) after hospital discharge with structural optical coherence tomography (OCT) and OCTA measurements. Vessel density (VD) and foveal avascular zone (FAZ) area were evaluated in the superficial, deep capillary plexus (SCP, DCP), and choriocapillaris (CC)

**Results**
14 days after discharge, COVID-19 patients presented significantly thinner ganglion cell layer (GCL) (p = 0.003) and thicker retinal nerve fiber layer (RNFL) compared to controls (p = 0.048), and this RNFL thickening was greater in COVID-19 cases with cotton wool spots (CWS), when compared with patients without CWS (p = 0.032). In both SCP and DCP, COVID-19 patients presented lower VD in the foveal region (p < 0.001) and a greater FAZ area than controls (p = 0.007). 6 months after discharge, the parafoveal RNFL and GCL were significantly thinner in COVID-19 patients at 6 months compared to 0 months (p = <0.001 in both cases). In the optic nerve analysis, a significantly thinner RNFL was observed (p = 0.006) but persisted significantly thickened, compared to controls (p = 0.02). The vascular density (VD) at 6 months persisted significantly decreased when compared to the control group, and no significant differences were found with the 0 months evaluation; in addition, when analyzed separately, women showed a worsening in the VD. Moreover, a significantly greater FAZ (p = 0.003) was observed in COVID-19 patients at 6 months, compared to 0 months.

**Conclusions**
These findings confirm clinical findings suggesting that thrombotic and inflammatory phenomena happen in the retina of COVID-19 patients. These microvascular alterations can be detected and quantified by OCTA and they persist over time and are still evident 6 months after hospital discharge. Further research is warranted to analyze the longitudinal evolution of these changes over time as well as their correlation with disease severity.

**Financial Disclosure**
None to disclose
Optical coherence tomography angiography changes in heart failure with preserved ejection fraction

Heart Failure (HF) with preserved Ejection Fraction (HFpEF) constitutes a complex and poorly understood disease which is characterized by recurring exacerbations, often requiring frequent venous blood sample collection and serial echocardiography to guide therapy optimization. The development of easy-to-perform non-invasive biomarkers for HFpEF risk stratification and prognosis could translate in significant gains in quality of life and less direct and indirect health-related costs. Optical coherence tomography angiography (OCTA) is a fast, reproducible and non-invasive ocular exam that can produce a highly detailed vascular analysis at the capillary level. Since previous evidence has demonstrated significant OCTA changes in the retinal and choroidal microcirculations of patients with systemic cardiovascular diseases, we hypothesize that HFpEF may also lead to alterations in ocular microvascularity. The purpose of this work was to characterize the ocular microvasculature of HFpEF patients recurring to OCTA.

Methods
Fifty-seven HFpEF patients and twelve comorbidity-matched controls were recruited from the outpatient clinic. OCTA examination (Cirrus 5000, AngioPlex®, Carl Zeiss) was carried out by an experienced technician. Vessel densities (VD) were calculated in the superficial and deep retinal plexus as well as in the choriocapillaris and choroid layers of the disc centered images. Foveal avascular zone (FAZ) area and perimeter were also calculated on macula centered images. Only high-quality images (score higher than 7/10 and no major artefacts) were considered. Also, eyes were excluded if ocular pathologies besides minor refractive error/incipient cataract were present. Statistics were performed using SPSS version 27. Normality of the data were assessed. Independent sample T-test, Mann-Whitney or Kruskal-Wallis tests were applied to compare groups, when appropriate. P values lower than 0.05 were considered to be statistically significant.

Results
After excluding patients for concomitant ocular pathology or low-quality images, 56 eyes from 33 patients and 20 eyes from 10 controls were included. The sample included 17 women and 26 men. Among HFpEF patients, twelve were classified as New York Heart Association (NYHA) class 1, nineteen as class 2 and only two patients as class 3. No significant differences in peripapillary superficial and deep retinal capillary plexus were found between controls and patients (p=0.464 and p=0.869, respectively) neither between different NYHA classes (p=0.960 and p=0.772, respectively). However, nasal choriocapillaris VD was significantly lower in HFpEF patients than controls (p=0.008). Furthermore, choroid VD is not different between controls and HFpEF patients but is significantly different when comparing the different classes of NYHA (p=0.026). Results show a significant increase of choroidal VD from controls to NYHA class 1 followed by a significant decrease in more severe classes. Regarding macula-centered scans, FAZ area and perimeter were significantly higher in HFpEF patients than controls (p=0.013 and p=0.011 respectively). This difference holds when comparing the different NYHA classes of patients (p=0.031 and p=0.028, respectively), suggesting an enlargement of this zone with the severity of the disease.

Conclusions
Our results demonstrate an enlargement of FAZ area and perimeter in HFpEF patients in comparison to comorbidity-matched controls. These FAZ changes seem to also be correlated with NYHA class. Furthermore, we also show a significant decrease of VD in the nasal peripapillary area of the choriocapillaris and whole choroid layers. Significant differences were not identified in the peripapillary retinal plexus. It is known that HF is characterized by an autonomic dysregulation. The presence of changes in the choroidal circulation but not in the retinal plexus may reflect dysregulation of the autonomic system with preservation of the retinal autoregulation. However, we need to take into account that almost all included patients were classified as NYHA classes 1 or 2, which are the least severe classes. It is possible that more severe cases may already show retinal autoregulation impairment. To the best of our knowledge, this is the first work evaluating OCTA features on HFpEF patients. Although more robust evidence is needed to better understand these changes, we can conclude that OCTA could be a useful tool to assess vessel dysregulation in HFpEF.
Title
Computerized analysis of retinal vascular growth following intravitreal Bevacizumab monotherapy in retinopathy of prematurity until three years of age

Purpose
Anti-VEGF’s though help in inhibiting stage 3 ROP, the chronic arrest of the peripheral retinal vasculature as long-term complications has become a concern. We aim to measure the physiologic growth of the retinal vasculature over time on serial fluorescein angiographic (FA) imaging following intravitreal bevacizumab monotherapy in Retinopathy of Prematurity until three years of age.

Setting/Venue
A retrospective, observational clinical study

Methods
Seventy eyes in 35 infants treated for type-1 ROP were included, 63 eyes were treated with IVB and 7 eyes untreated. Serial angiographic images taken post-IVB on 4 serial examinations were analyzed starting at average 66 weeks post-menstrual age (PMA) with repeat imaging every 8 months until 3 years of age. The retinal vessel length was manually measured in ImageJ software from the temporal margin of the optic disc through the foveal center to the temporal vascular-avascular junction and vascular length at the different time points were compared.

Results
The mean retinal vessel length was 14.177 mm at time point #1 (66.2 weeks PMA) and 13.761 mm including all 4 FA sessions (range 44-234 weeks PMA). Paired t-tests compared the retinal vascular length of each individual eye over time and showed no statistically significant growth from the first FA at 66.2 weeks PMA until 3 years of chronological age. From time point #2 to #1 (N=30) the difference was -0.117 ± 0.785 mm (95% CI -0.416 to +0.176, p=0.42), from #3 to #1 (N=15) the difference was +0.060 ± 0.854 mm (95% CI -0.413 to +0.533, p=0.79), and from #4 to #1 (N=7) the difference was -0.404 ± 1.32 mm (95% CI -1.628 to +0.820, p=0.45). Even the eyes with recurrence (n=6) and untreated eyes (n=7) showed no significant change in vascular growth over time.

Conclusions
Retinal vascular length measured angiographically post-IVB monotherapy in ROP showed no significant vascular growth on serial examinations from 66 weeks PMA until three years of age. The persistent chronic vascular arrest and the inhibition of normal angiogenesis with anti-VEGF monotherapy accounts for a longitudinal study for dose titration and vascular growth and recovery until adulthood.

Financial Disclosure
None
Title
Neurovascular coupling in the human retina evaluated by adaptive optics ophthalmoscopy.

Purpose
Neurovascular coupling (NVC) is the capability of vessels in neural tissue to adapt to neuronal demand. It is generated through a chain of interdependent cells: neurons, glial cells, smooth muscle cells, pericytes and vascular endothelial cells. The stimulus for generating NVC in the retina is flickering light (12-15 Hz). Here we report the results of flicker-induced dilation of retinal arterioles in normal subjects using adaptive optics ophthalmoscopy (AOO).

Setting/Venue
The protocol was approved by an ethical committee (Comité de Protection des Personnes) in the National Center of Ophthalmology en Paris, France.

Methods
The command program of the internal fixation light of a commercially available flood-illumination adaptive optics camera (rtx1, Imagine Eyes, Orsay, France) was modified to accommodate a 28°x20° flickering yellow light emitting diode, which is the light used for fixation target. The clinical procedure comprises 3 basal images before stimulation (taken within ± 60 seconds), followed by 3 periods of flickering stimulation at 15Hz during 20 seconds each; the image was captured during the last 2 seconds of the stimulation cycle. AOO images of arterial segments of at least 250 µm long in the posterior pole were segmented offline using a custom software (AOV image, developed by Florence Rossant).

Results
Twenty one eyes of 21 controls (10 females and 11 males; mean age ±SD 38.4 years ±12.7) were examined. The average diameter of the arteries lumen was 85.1 µm (±20.4). The difference between the basal measurements ranged from -2.22% to +2.86% with an average of +0.17%. Flicker-elicited dilation ranged from +0.83% to +6.63% with an average of +2.98%. The average wall to lumen-ratio of the vessels was of 0.24. The percentage of dilation was independent from age and size of vessel, but there was a tendency of an inverted correlation with the wall to lumen ratio (WLR).

Conclusions
AOO-based NVC analysis offers a novel approach of the evaluation of the vasomotricity of retinal vessels. The vasodilation was found comparable to that reported using other methods, with the additional advantage of analyzing local changes and the concomitant measurement of the WLR. The latter as found to be inversely correlated to flicker-induced vasodilation. This may be an indication that microvascular tone may influence flicker response.

Financial Disclosure
None
**Title**
Vascular changes in the ageing retina as measured quantitative by swept source optical coherence tomography angiography

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**Purpose**
Recently, we reported in vivo a strong negative correlation between perfusion density (PD) and aging in the choriocapillaris of healthy subjects. However, less is known about the effect of aging on the topographical distribution of the capillaries of retinal plexuses. The aim of the current study is to evaluate the effect of aging on vascular parameters at foveal, parafoveal, and perifoveal region in the superficial capillary plexus (SCP) and deep vascular complex (DVC) of healthy subjects by using optical coherence tomography angiography (OCT-A).

**Setting/Venue**
This is a retrospective study of patients enrolled in Medical Retina and Imaging Unit of the Department of Ophthalmology, San Raffaele Scientific Institute in Milan, Italy.

**Methods**
In this observational cross-sectional study, consecutive healthy subjects underwent Swept Source OCT-A (PLEX Elite 9000, Carl Zeiss Meditec Inc., USA). 3x3-mm and 6x6-mm scans centered on the fovea were acquired and analyzed post-processed with thresholding and binarization processes. Main outcome measures included quantitative topographical OCT-A features (PD and vessel length density [VLD]) at the foveal (circle of radius of 0.5 mm), parafoveal (circular annulus around the fovea with radius of 1.5 mm) and parafoveal region (circular annulus around the fovea with radius of 3.0 mm) in both SCP and DVC, and their relationship with aging.

**Results**
Ninety-four eyes (94 patients, mean age 48.5±20.4 years old, range 19-84) were included. A strong negative correlation was found between PD and aging in the parafoveal area in both 3x3 mm images (r= -0.394, p<0.001) and 6x6 mm (r= -0.308, p=0.003). In detail, this reduction was driven by the reduction of PD and VLD in the nasal parafoveal subfield (r= -0.339, p<0.001 and r= -0.272, p=0.008, for PD and VLD, respectively). In the analysis of perifoveal area, there was no significant correlation between aging and PD/VLD of both SCP and DVC in the whole area. However, in the topographical subfield analysis, there was a significant correlation of aging with PD and VLD of the perifoveal nasal and temporal areas of SCP (r= -0.311, p=0.002 and r= -0.326, p=0.001, for PD and VLD of the nasal area; r= 0.326, p=0.001 and r= 0.313, p=0.002, for PD and VLD of the temporal area). Furthermore, a significant negative correlation was found between aging and PD of the perifoveal inferior area of the DVC (r= -0.300, p=0.003).

**Conclusions**
We reported in vivo a strong negative correlation between PD of the retinal vessels and aging of healthy subjects. This reduction seems related to a reduced number of capillaries (i.e. VLD). The age-related changes were higher in the parafoveal area compared to the perifoveal area.

**Financial Disclosure**
None
### Title

Multicolor confocal scanning laser ophthalmoscope imaging in posterior uveitis

### Purpose

To compare the clinical usefulness of MultiColor confocal scanning laser ophthalmoscope imaging (MCI) with conventional color fundus photography (CFP) in posterior uveitis

### Setting/Venue

Advanced Eye Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India

### Methods

Prospective cross-sectional study of consecutive patients with posterior uveitis who underwent concurrent imaging on MCI and CFP at a single tertiary referral centre. Clinical evaluation and multimodal chorioretinal imaging were used as gold standard. Two independent masked graders analyzed the images for the presence of vitreoretinal surface abnormalities, depth of lesions, presence of retinal fluid and hemorrhage, features of healed lesion, and disease activity on MCI with Multicolor 450 Spectralis HRA + OCT (Heidelberg Engineering, Heidelberg, Germany) and CFP on VISUPAC Digital Imaging System (Carl Zeiss Meditec, Jena, Germany). Inter-grader agreement was calculated using the Kappa (K) coefficient. Sensitivity and specificity were analyzed for each finding on CFP, MCI, infrared reflectance, green reflectance and blue reflectance images in reference to the gold standard.

### Results

This study included 69 eyes of 43 patients. For the parameters analyzed, K value ranged from 0.61 – 1.00 indicating good to very good inter-grader agreement. Sensitivity for detection of epiretinal membrane was 20% on MCI and 10% on CFP. Retinochoroiditis was detected in 16.7% of cases on MCI and in 100% on CFP. Choroiditis was seen in 84.5% on MCI and in 100% on CFP. Vasculitis was detected in 50% of cases on MCI and in 100% on CFP. Optic neuritis was detected in 70% of cases on CFP and in 100% on CFP. Intraretinal fluid was not detected on MCI but in 15% cases on CFP. Intraretinal hemorrhage was detected in 40% cases on MCI and in 100% on CFP. Subretinal fibrosis was identified in 76.2% of cases on MCI and in 100% on CFP. Scarring and atrophy was identified in 96.3% cases on MCI and in 100% on CFP. Intraretinal striae were detected in 66.7% of cases on MCI and in 50% on CFP. Choroidal neovascularization was seen in 0% eyes on MCI and in 11.1% on CFP. Active disease was identified in 56.6% cases on MCI and in 100% on CFP.

### Conclusions

Epiretinal membrane and inner retinal striae were better identified on MCI in comparison to CFP. For detection of depth of lesion, intraretinal hemorrhage and fluid, subretinal fibrosis, choroidal neovascularization and disease activity both for retinochoroiditis and choroiditis, MCI was inferior to CFP. Lesions of active posterior uveitis were poorly identified on MCI. MCI cannot be applied as standalone modality for posterior uveitis as it may lead to misinterpretation of pathology.

### Financial Disclosure

None
Title
Intraretinal vascular proliferation in macular telangiectasia type 2 (MacTel)

Purpose
To investigate the progression of vascular alterations using optical coherence tomography-angiography (OCT-A) in macular telangiectasia type 2 (MacTel).

Setting/Venue
Longitudinal, retrospective single center observational study.

Methods
Patients with a confirmed diagnosis of MacTel underwent annual ophthalmic examinations including best-corrected visual acuity (BCVA), color fundus photography (CFP), fluorescein angiography (FLA, if available), optical coherence tomography (OCT) and OCT angiography (OCT-A). Only eyes without subretinal/sub-RPE neovascular membranes and no signs of neovascular exudation at baseline were included and reviewed for ≥20 months. Grading was performed by two independent readers. Main outcome measures included vessel proliferation, vascular leakage, perivascular pigment accumulation, formation of subretinal/sub-RPE neovascular membranes, and neovascular exudation.

Results
A total of 124 eyes from 64 patients (mean age 62.4 years (range: 39-83 years); 37 females) were included and reviewed over a mean period of 23.3 months (range 20.5-40.5). A proliferation of vessels was observed in 68 eyes (55%), while 24 patients (38%) showed occurrence. Vascular proliferation was primarily observed at the level of the deep retinal plexus (n=48 (71%)). In eyes showing a formation of retinal-choroidal anastomoses (n=20 (29%)), a proliferation of vessels could also be observed within the outer retina-choriocapillaris (ORCC)-layer, possibly involving both choriocapillaris and displaced deep plexus vessels. Vascular proliferation was predominantly found in the temporal parafovea. In all cases vascular proliferation was associated with an increase in reflectivity on OCT and increased fluorescein leakage on FLA. Pigment plaques accumulated along proliferating vessels and vessels forming retinal-choroidal anastomoses. Fourty eyes (35%) showed a de novo development of perivascular pigment. A de novo formation of exudative subretinal/sub-RPE neovascular membranes was observed in 3 eyes (2%).

Conclusions
The results indicate intraretinal vessel proliferation as part of the natural course of MacTel in eyes that have been previously considered “non-proliferative”. Our findings indicate the need to reevaluate our current understanding and classification system of MacTel into “proliferative” and “non-proliferative” disease stages.
Foveal crack sign might predict macular hole development in fellow eyes of patients with full-thickness macular holes

Purpose
To investigate the prevalence and predictive value of the foveal crack sign (FCS) in fellow eyes of patients with full-thickness macular holes (FTMH) regarding future macular hole (MH) formation.

Setting/Venue
Institutional. Retrospective observational case series.

Methods
113 fellow eyes of 113 patients with FTMH have been observed during a mean follow-up time of 21 months. According to baseline SD-OCT images, patients were divided into 4 separate groups: patients with FCS and vitreous adhesion, patients with FCS and vitreous detachment, patients without FCS with vitreous adhesion, patients without FCS with vitreous detachment. Progression rate to MH formation, predictive value of FCS and of vitreous interface status were calculated and compared across the four groups.

Results
FCS was observed in 19 of 113 fellow eyes (17%) of patients with FTMH, 10 of them with progression to MH during the mean follow up time of 21 months. 2 other eyes with progression to MH showed no FCS at baseline. Progression rate was shown to be 77% (10 of 13 eyes) in patients with FCS and vitreous adhesion, 0% (none of 6 eyes) in patients with FCS and vitreous detachment, 4% (2 of 48 eyes) in patients without FCS with vitreous adhesion, 0% (none of 46 eyes ) in patients without FCS with vitreous detachment. FCS had sensitivity of 83.3% (95% CI: 50.9- 97.1%) and specificity of 91.1% (95% CI: 83.3- 95.6%) in predicting MH formation, positive predictive value of FCS was 52.6% (95% CI: 29.5-74.8%) and negative predictive value 97.9% (95% CI: 91.8- 99.6%).  Having simultaneously FCS and vitreous adhesion showed 83.3% (95% CI: 50.9- 97.1%) sensitivity and 97.1% (95% CI: 91.1-99.2%) specificity in predicting macular hole formation; positive predictive value was 76.9% (95% CI: 46.0-93.8%) and negative predictive value was 98.0% (95% CI: 92.4-99.7%).

Conclusions
Fellow eyes of patients with FTMH with foveal crack sign are at a very high risk (77%) of FTMH development, as long as posterior vitreous adhesion is present.
Automated analysis of uveitic retinal ischaemia using widefield optical coherence topography angiography

**Purpose**
To develop an automated method for quantifying retinal ischaemia in Optical Coherence Tomography Angiography (OCTA), with particular application for use in the assessment of uveitic retinal ischaemia.

**Setting/Venue**
Manchester Royal Eye Hospital, Manchester, United Kingdom. Patients with uveitis and retinal ischaemia on widefield OCTA, determined by clinical experts, were included.

**Methods**
This was a feasibility study involving a retrospective, observational case-control series comprised of 10 patients (10 eyes), with a diagnosis of intermediate, posterior, or panuveitis and 10 patients (10 eyes) without intraocular inflammation or vitreoretinal disease. 10x10mm OCTA scans of the superficial capillary plexus were captured and denoised using inbuilt software on the Canon OCTA-1 machine. The images were anonymised and exported in binary format using proprietary Canon software. The exported images were analysed using a custom algorithm written by the last author in MATLAB 2021 (Mathworks, Natick, MA), which is fully automated and avoids the need for manual segmentation. Major blood vessels were removed using morphological techniques to purely segment the capillary network. Non-perfused areas were identified when they matched predefined thresholds of size, that were defined iteratively through experimentation. The identified ischaemic areas were represented as images for each patient’s OCTA with ischaemic areas filled in and output as a percentage of the ratio of pixels associated with non-perfused capillaries to total pixels. Ischemic areas identified on the images were compared to those identified by an Ophthalmologist. A paired t-Test was carried out using IBM SPSS Statistics 25 to compare percentage ischaemia in ischaemic vs normal eyes.

**Results**
The algorithm was able to identify ischaemic areas in all 10 patients who had been previously determined to show clinical ischaemia. Mean percentage of ischaemic areas in uveitic eyes was 3.9% vs the mean percentage in normal eyes of 0.03%. A paired t-test showed a significance level of 0.014 (2-tailed).

**Conclusions**
We describe a rapid automated method for objectively quantifying retinal ischaemia on OCT-A, developed and demonstrated on a discrete small number of patients. Our next step is to validate this novel algorithm on a larger, independent data set to truly demonstrate its validity and to investigate the role of this analysis in specific uveitis diseases involving the retinal circulation. Automated OCTA indices may provide objective markers of retinal ischaemia, which may be used in the evaluation and monitoring of ocular inflammatory disease with retinal ischaemia.

**Financial Disclosure**
Research Funding provided by Canon Medical Systems, Europe
Title
Functional correlates of drusen remodeling in intermediate age-related macular degeneration using mesopic microperimetry

Purpose
To assess the effect of drusen remodeling on retinal sensitivity in the subfoveal and parafoveal retinal regions through mesopic microperimetry in eyes with intermediate age-related macular degeneration.

Setting/Venue
Tertiary referral center at Department of Ophthalmology, IRCCS-Fondazione Bietti, Rome.

Methods
A retrospective observational study of patients aged 50 or older, graded with intermediate AMD according to the Beckman classification and followed for a minimum of 12 months was conducted. Patients were included if they had complete medical records, fundus autofluorescence, spectral-domain optical coherence tomography (SD-OCT), and microperimetry evaluation at baseline and 12 months of follow-up. SD-OCT was obtained using Heidelberg Spectralis OCT (HRA2+OCT, Heidelberg Engineering, Heidelberg, Germany) with a minimum of a 20- x 15-degree (5.8 x 4.3 mm) rectangle centered on the fovea (25-lines cube). Automated segmentation of all retinal layers was performed using the dedicated software. All the b scans were consecutively checked for segmentation errors and eventually adjusted. The ‘outer retinal layers’ (ORL) map was generated by segmenting between the external limiting membrane and the Bruch’s membrane to calculate drusen volume. Microperimetry was performed using Macular Integrity Assessment system (MAIA; CenterVue S.p.A., Padova, Italy) under mesopic condition using a customized grid of 33 stimuli around central 10°, a white background illumination of 4 asb (1.27 cd/m2), Goldmann III stimuli with a projection time of 200 ms and a 4-2 staircase strategy. The thickness map was overlaid with the corresponding microperimetric map using Fiji software (version 2.1.0/1.53.c).

Results
A total of 18 eyes of 18 patients (11 females and 7 males) were consecutively included (68.4 +/- 8.6 years) in the present study. Drusen resorption was observed in 8/18 eyes (44.4%), and drusen growth was observed in 10/18 eyes (55.5%). Eyes with drusen resorption presented a significant decrease in the global retinal sensitivity (RS) than eyes with drusen growth (-0.81 dB vs. 0.26 dB, respectively, p=0.04). In eyes with drusen resorption, the greatest change in ORL thickness at 1 year was observed in the subfoveal region (-16.13 micron, 95%CI: 1.24, -33.5), corresponding to a significant loss of RS at the same anatomical level compared to eyes with drusen growth (-1.5 dB vs. 0.5 dB, p=0.02). A significant loss of retinal sensitivity at 1 year was observed in eyes with drusen resorption in the temporal parafovea when compared to eyes with drusen growth (-1.13 dB vs. 0.58 dB, p=0.04).

Conclusions
Spatial distribution of drusen and remodeling are well-known factors of progression into late-stage macular complications. The present study interpolates the anatomical changes in drusen volume with retinal sensitivity, demonstrating that the greatest morpho-functional fluctuations appeared in the subfoveal region. At this anatomical level, a reduction of drusen volume was responsible for a significant functional decline in the same region, and it also influenced global retinal sensitivity. By contrast, drusen growth is not associated with any functional decline. These findings suggest that the process of drusen resorption may be accompanied by fatal photoreceptor damage or retinal pigment epithelium impairment.

Financial Disclosure
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**Title**

In vivo intraocular biomarkers in uveal melanoma: An aqueous humor proteomic study

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P

**Purpose**

To evaluate, in vivo, the presence of specific aqueous humor (AH) biomarkers in eyes affected by uveal melanoma (UM) and to correlate them with genetic and clinical tumor characteristics.

**Setting/Venue**

This is a cross-sectional case–control study with prospective enrolment, performed at the Department of Ophthalmology of the University of Padova and IRCCS G.B. Bietti Foundation, Ocular Oncology and Toxicology Unit.

**Methods**

Thirty-six eyes affected by primary UM underwent full ophthalmic examination, including: ophthalmoscopy, fundus photography, ultrasonography and Spectral Domain OCT. During brachytherapy (Iodine-125) surgical procedure AH sample collection and 25-gauge transscleral fine needle aspiration biopsy (FNAB) were performed. AH samples were analyzed by microarray and western blotting techniques to detect the concentration of selected proteins. Cytologic material underwent fluorescence in situ hybridization for chromosome 3. Tumor thickness and largest basal diameter (LBD) were quantified. Tumors were staged using the 8th AJCC classification. The presence of peritumoral serous retinal detachment was categorized considering the number of retinal sectors involved (less than 1 quadrant; 1 to 2 quadrants; more than 2 quadrants). The AH of thirty-six normal eyes, scheduled for cataract surgery, was used as control. The specific concentration of selected proteins was quantified on the linearized standard curves.

**Results**

Compared with the control group, significantly higher levels of: SSTR1 (p=0.027), SF3B1 (p=0.026), BAP1 (p=0.012), GNAQ (p=0.024), HMB45 (p=0.017), IL-6 (p=0.049), IL-8 (p=0.007), RANTES (p=0.009), PEDF (p=0.049), Osteopontin (p=0.049), EGF (p=0.042), bFGF (p=0.018), MIF (p=0.008), MCP (p=0.022) were detected in eyes with UM. VEGF concentration difference between the two groups was statistically borderline (p=0.055). Comparison between clinical characteristics and biomarker concentrations showed a positive significant correlation between: tumor thickness and IL-8 (p = 0.032) and VEGF (p = 0.032), degree of serous retinal detachment and IL-6 (p = 0.021), LBD and RANTES (p = 0.031). Monosomy 3 was detected in 17 cases (47%) and disomy 3 in 19 cases (53%). No correlation was found between chromosome 3 status and: tumor dimensions (p= 0.30), and tumor location (ciliary body vs choroid) (p=0.25). Statistically significant higher levels of inflammatory proteins were detected in eyes with monosomy 3 UM (p=0.049).

**Conclusions**

The presence of selected biomarkers may be identified, in vivo, in the AH of eyes affected by UM. Furthermore, some inflammatory AH biomarkers are specifically correlated to the monosomy 3 pattern, and some clinical characteristics of the tumor itself. These findings not only confirm in vivo the possibilities offered by AH analysis in eyes harbouring a UM, but suggest that AH evaluation may represent the liquid biopsy approach in UM diagnosis and follow-up.

**Financial Disclosure**

N/A
Title
Development of a short form of the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25)

Purpose
The NEI VFQ-25 is widely used to assess vision-related functioning in clinical trials across a variety of retinal diseases, but the length of the questionnaire may make it cumbersome for use in clinical practice settings. The purpose of this study was to derive and psychometrically validate a short form of the NEI VFQ-25 that could be more easily integrated with routine clinical practice and amenable to digital assessment in patients with neovascular age-related macular degeneration (nAMD).

Setting/Venue
Study included secondary analyses of ANCHOR, MARINA, and PIER clinical trials data of intravitreal ranibizumab, a recombinant, humanized antibody antigen-binding fragment (Fab), designed for intraocular use in nAMD, macular edema following retinal vein occlusion (RVO), myopic choroidal neovascularization (mCNV), diabetic retinopathy (DR) and diabetic macular edema (DME) patients. ANCHOR was a phase 3 randomized, multicenter, double-masked, sham injection-controlled study of ranibizumab in nAMD (N = 716). MARINA was a phase 3 randomized, multicenter, double-masked, active treatment-controlled study of ranibizumab in nAMD (N = 432). PIER was a phase 3b multicenter, randomized, double-masked, sham injection-controlled study in nAMD (N = 184).

Methods
Statistical analyses were conducted on pooled data (total N = 1318) from the three clinical trials. A combination of Rasch modeling and principal component analysis (PCA) was employed to reduce the NEI VFQ-25 to a minimum number of items representing the composite score. Psychometric analyses of the short form were then conducted to ensure internal consistency, test-retest reliability, construct (known-groups and convergent/divergent) validity, and responsiveness to change. Distribution- and anchor-based methods were used to estimate thresholds of clinically meaningful change using best-corrected visual acuity (BCVA).

Results
Quantitative item reduction resulted in a seven-item short form (VFQ-SF) containing items from the near activities, distance activities, general vision, peripheral vision, and role difficulties scales. Psychometric analyses on the VFQ-SF demonstrated the questionnaire had excellent internal consistency (α = 0.88) and test-retest reliability (ICCs ranged 0.79 to 0.91), and correlated highly with the NEI VFQ-25 (NEI VFQ-25 composite r = 0.95; domain rs ranged 0.49 to 0.90). The VFQ-SF demonstrated moderate correlations with BCVA [r = 0.46 (worst seeing eye) and r = 0.68 (best seeing eye)] and with the exception of the HUI3 vision score (r = 0.72), smaller correlations with health-related quality of life questionnaires [HUI3 r range: -0.23 to 0.37; SF-36 r range: 0.10 to 0.30]. Correlations between the full NEI VFQ-25 and each of these constructs were highly similar. The VFQ-SF differentiated between BCVA severity groups and demonstrated responsiveness to change from baseline to 12- and 24-month follow-ups. Triangulating distribution- and anchor-based estimates determined a threshold for clinically meaningful improvement of 7 points.

Conclusions
This study applied quantitative item reduction methodology to reduce the NEI VFQ-25 from 25 to 7 items and validated the resulting questionnaire, the VFQ-SF. The VFQ-SF demonstrated robust psychometric properties that may support its use in place of the NEI VFQ-25 to generate a composite vision-related functioning score in nAMD patients when time is limited. This brief questionnaire could be suitable for use in clinical practice settings or remote monitoring of vision-related functioning, via electronic platforms such as web- or device-based apps.

Financial Disclosure
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Impact of Caffeinated and Decaffeinated Coffee Consumption on Retina and Choroid: An Optical Coherence Tomography Angiography Study

**Purpose**
To evaluate the impact of caffeinated and decaffeinated coffee consumption on the macular microcirculation in healthy individuals by using optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA).

**Setting/Venue**
This prospective, randomized, single-centered study enrolled healthy individuals who were randomly divided into two groups; a caffeinated coffee consumer group (study group), and age- and sex-matched decaffeinated coffee consumer group (control group).

**Methods**
Vascular densities of superficial capillary plexus (SCP) and deep capillary plexus (DCP), foveal avascular zone (FAZ) area, FAZ perimeter (PERIM) and vascular density 300 microns around the FAZ (FD-300), as well as outer retinal and choriocapillary flow areas were measured by OCTA. Meanwhile, central macular thickness (CMT), subfoveal choroidal thickness (CT) and optic nerve fiber layer thickness were measured by OCT. Measurements were carried out prior to consumption, and after the consumption at 30 minutes, 1st, 6th and 24th hours. Measured data were analyzed for statistical significance.

**Results**
Among 48 participants 24 were females and the other 24 were males. Mean age was 23.45 ± 0.92 in the caffeinated coffee consumer group and 22.73 ± 1.13 in the decaffeinated coffee consumer group. Compared to pre-consumption measurements, there were statistically significant reductions in the parafoveal and perifoveal SCP and DCP vascular densities, outer retinal and choriocapillary flow areas and CT during 30 minutes and one hour after the consumption of caffeinated coffee. There was no significant difference, however, in any parameters between consecutive measurements in the decaffeinated coffee consumers (p>0.05).

**Conclusions**
This study has shown that caffeinated coffee consumption temporarily can leads to a decline in the measurements of parafoveal and perifoveal vascular densities, outer retinal and choriocapillary flow areas as well as in the CT. Lack of these vascular changes after decaffeinated coffee consumption suggests potential resultant vasoactive nature of caffeine.

**Financial Disclosure**
none
Title
Anatomical and Visual Outcomes of Filipino Patients with Acute Central Serous Chorioretinopathy Treated with Intravitreal Ranibizumab vs. Observation vs. Intravitreal Aflibercept: A Retrospective Cohort Study

Presenter
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Purpose
This study aims to compare visual and anatomical outcomes of intravitreal anti-VEGF versus observation alone in the treatment of acute central serous chorioretinopathy among a cohort of Filipino eyes, within 4 months of follow-up.

Setting/Venue
In this retrospective comparative study, a dataset of a cohort of patients diagnosed with acute CSCR between January 2013 to June 2020 were reviewed and analyzed in a single tertiary hospital.

Methods
In this retrospective comparative study, a cohort of 49 eyes diagnosed with acute CSCR were reviewed and analyzed. Within the cohort are 29 eyes treated with intravitreal anti-VEGF (IVT group) and 20 eyes with observation. Best-corrected visual acuity (BCVA), central subfoveal retinal thickness (CSRT) measurement and subretinal fluid (SRF) optical coherence tomography (OCT), leakage in fundus angiography (FA) and presence of visual distortion at baseline and 4 months follow-up were collected and analyzed. Subjects with incomplete data were excluded. Furthermore, excluded in the study were subjects who received retinal laser therapy, those with coexisting retinal diseases and maculopathies capable of causing macular exudation such as age-related macular degeneration, diabetic or uveitic retinopathy, and non-retinal diseases that can contribute to central blurring of vision such as glaucoma, dense cataract and corneal opacity.

Results
All patients in both study groups demonstrated improvement in visual acuity at the end of 4 months. Comparison within groups regarding mean VA (p=0.816) and CSRT (p=0.177) improvement from baseline of were also comparable between groups. However, the IVT group had statistically lower CSRTs vs observation group (237 ± 32 um vs 339 ± 248 um, p=0.003) at month 4. Significant resolution of SRF (23 to 2 vs 19 to 12, p=0.000), FA leakage (26 to 3 vs 20 to 9, p=0.010) and visual distortion (24 to 4 vs 16 to 11, p=0.004) in the IVT group vs the observation group was noted at month 4. Subgroup analysis of the IVT group, aflibercept (10 eyes) vs ranibizumab (16 eyes) in terms of visual acuity (p=0.997) and CSRT (p=0.877), as well as, mean improvement in VA (p=0.254) and CSRT (p=0.827) from baseline at month 4 of follow-up showed comparable results.

Conclusions
Compared with observation alone, intravitreal anti-VEGF did not have positive effect in terms of the final visual acuity at 4th month of follow-up in a cohort of Filipino eyes diagnosed with acute CSCR. However, intravitreal anti-VEGF offered earlier improvement in visual acuity, resolution of visual distortion, subretinal fluid, and angiographic leakage.

Financial Disclosure
None
A safety study of ONS-5010 for the treatment of wet age-related macular degeneration, diabetic macular oedema and branch retinal vein occlusion.

To assess the safety of intravitreal ONS-5010 bevacizumab-vikg.

20 US retinal clinics.

This was a prospective, multi-center, open-label, single-arm, interventional clinical trial. Up to 3 doses of intravitreal 1.25 mg (50 µL) ONS-5010 were administered monthly with follow up to 3 months. The key inclusion criteria were treatment-naïve or previously-treated, active wet age-related macular degeneration (AMD), diabetic macular oedema (DMO), or branch retinal vein occlusion (BRVO) requiring anti-VEGF therapy, and best-corrected visual acuity of ≥ 20 ETDRS letters. The analysis included all participants who received at least one dose of ONS-5010. Follow-up data were collected monthly. The frequency of adverse events (AEs) was collected, as well as safety parameters from ocular and systemic safety assessments.

A total of 197 participants (65 with wet AMD, 108 DMO and 24 BRVO) received at least one dose of ONS-5010, with 192 (97.5%) completing the 3-month study. At least 1 AE was reported in 62 (31.5%) participants; 20 (10.2%) had study eye AEs of which 12 (6.1%) were deemed related to study treatment by the Investigator. AEs reported in ≥ 2% of participants comprised urinary tract infection, COVID-19, fall, and conjunctival hemorrhage. Conjunctival hemorrhage was the most commonly reported ocular AE (5 AEs in 4 participants). No AEs related to intraocular inflammation were reported. Eleven (5.6%) participants had serious AEs; none were related. One unrelated SAE was ocular (retinal hemorrhage). At day 90, 188 (97.9%) participants lost fewer than 15 letters compared to baseline.

The ONS-5010 safety profile is consistent with prior ophthalmic studies of bevacizumab. This supports the continued development of ONS-5010 for the treatment of wet AMD, DMO and BRVO. Subject to further testing and marketing authorization, an on-label, ophthalmic formulation of bevacizumab would increase the treatment options available to patients, clinicians and healthcare funders.

Consultant to Outlook Therapeutics (Brown, Jackson, Hu); Paid Medical Advisor to Outlook Therapeutics (Humayun).
**Title**
Fifty two Weeks Safety and Efficacy of Ambient light sensitive Multi-Characteristic Opsin enabled vision restoration in patients with ABCA4 mutation

**Purpose**
ABCA4 mutation leads to severe photoreceptor degeneration. Optogenetics therapy offers the potential for vision restoration in these patients by photosensitizing higher order neurons. Since this approach focuses on disease phenotype versus a specific genotype deficit, it is applicable to a wide range of patient population. Existing optogenetic tools utilize opsins, that do not generate adequate electrical current in ambient light requiring an external device for stimulation. Multi-Characteristic Opsin (MCO) is an engineered opsin that is activated at ambient light levels, thereby avoiding the need for an external amplifying device and associated phototoxicity. Hence, this novel technique can be utilized to improve the sight in advanced RP and related retinal degeneration involving ABCA4 gene.

**Setting/Venue**
After approval from Drug Controller General of India (DCGI) registered Institutional Ethical Committee of a tertiary eye care centre of eastern India, the clinically confirmed cases of Advanced Retinal Degeneration with poor vision (no better than PL and HM) were subjected for gene analysis to find out ABCA4 mutation and included in the study after satisfying the inclusion and exclusion criteria.

**Methods**
Four subjects with advanced vision loss were identified. After informed consent was obtained, subjects received prophylactic oral steroids prior to a single intravitreal injection of AAV2-MCO (vMCO). AAV2 was used to deliver MCO by a single investigator. Safety and exploratory efficacy of intravitreal vMCO injection was evaluated. These subject were monitored closely till 52 weeks to record any adverse events and final visual outcome.

**Results**
vMCO was well tolerated with no reported serious adverse events. There were no serious systemic as well as ocular adverse events (AE). Ocular AE were limited to inflammation and mild intraocular pressure rise, which were well controlled with topical medications. Furthermore, exploratory efficacy endpoints demonstrated improvement in visual acuity as well as vision function in the subjects. The improvement in vision was assessed by objective methods like Low Vision multi parametric tests and A-Y mobility test and the measured vision correlated with the patient reported outcome (assessed by Visual Function Questionnaire).

**Conclusions**
vMCO is well tolerated with no serious adverse events. vMCO appears to be safe and well tolerated and leads to improvement in visual function. This proof-of-concept study demonstrates promise in restoring vision of patients with ABCA4 mutation and may have potential in visual improvement in other related inherited retinal degenerations.

**Financial Disclosure**
NIL
Comparison of the results of subthreshold micropulse laser coagulation in patients with various forms of macular degeneration

Mariia Melikhova
Russian Federation

Purpose
Evaluation of the effectiveness of micropulse subthreshold laser coagulation (SML) in 3 groups: sclerogenic macular degeneration (SMD), acute and chronic central serous chorioretinopathy (CSR)

Setting/Venue
S. Fyodorov "Eye Microsurgery" Federal State Institution, St. Petersburg Branch

Methods
SML was performed in 3 groups of patients. Group 1 - 15 patients with SMD aged 28 to 63 years, the median age was 55.0 (40; 62) years. Group 2 with acute CSR included 16 patients aged 21 to 51 years, the median age was 37.0 (32; 42.5) years. Group 3 - a chronic form of CSR consisted of 15 people aged from 26 to 56 years, the median age was 43.0 (40; 51). In group 1, women predominated (93%), in groups 2 and 3, men (94% and 80%, respectively). SML was performed with a diode laser (810 nm). In the subthreshold mode, a 10% microimpulse was used, 2-3 sessions were performed with an interval of 2-4 months. The observation period was 6-12 months. The treatment was carried out according to the method of a dense "lattice" with an additional effect on the supposed points of dye leakage. The criterion of efficiency was the complete disappearance of the liquid. In the study, patient data were recorded at 5 time points, each subsequent point was compared with the baseline.

Results
In group 1 of patients, serous retinal detachment (SRD) completely adhered in 7 out of 15 people (46.7%), there were no relapses during the year of follow-up. In group 2, the treatment effect was achieved in 11 out of 16 people (68.8%), 3 relapses of SRD. In group 3 with chronic CSR, complete regression of SRD was achieved in 10 out of 15 people (66.7%) with 1 recurrence of SRD. Significant dynamics of BCVA and retinal thickness in the central zone were observed only in the group with acute CSR

Conclusions
SML accelerates the resorption of subretinal fluid as efficiently as possible in patients with acute CSR. In the other two groups, this method of treatment cannot be considered completely satisfactory due to the very slow rate of regression of SRD and the absence of a significant effect on visual acuity

Financial Disclosure
no
**Title**
Gene Therapy by Subretinal Delivery of RGX-314 for Neovascular AMD: End of Study Phase I/IIa Results

**Purpose**
Frequent intravitreal injections of anti-VEGF have been shown to reduce the risk of severe vision loss in clinical trials for neovascular AMD (nAMD). Real-world evidence demonstrates that patients lose visual acuity over time, in part, as a consequence of the high treatment burden of current therapy utilizing anti-VEGF injections. RGX-314 is designed as a single gene therapy intervention utilizing an AAV (adeno-associated virus) vector, AAV8, to deliver a transgene for a soluble anti-VEGF fab with the goal of producing continuous anti-VEGF therapy.

**Setting/Venue**
This Phase I/IIa, open-label, multiple-cohort, dose-escalation study of RGX-314 was conducted at ophthalmology surgical centers and clinical retina practices in the United States.

**Methods**
This Phase I/IIa trial evaluated five doses of RGX-314 administered via subretinal delivery in previously treated (average of 9.6 annualized anti-VEGF injections per year) patients with nAMD. Assessments of safety and efficacy are being conducted out to 2 years, and measurements include: ocular and systemic adverse events, RGX-314 aqueous protein level, best corrected visual acuity (BCVA), central retinal thickness, and supplemental anti-VEGF intravitreal injections needed post-RGX-314. Patients are then encouraged to enroll in a Long-Term Follow-Up (LTFU) study to assess safety and efficacy for up to a total of five years after RGX-314 administration. In the LTFU study, visits are scheduled every 6 months for the first year and then annually until end of study. Patient management during the LTFU is at the discretion of the physician.

**Results**
Cohorts 1 - 5 have completed enrollment (n=42). As of January 22, 2021, RGX-314 has been generally well-tolerated at all dose levels with 20 serious adverse events (SAEs) reported in 13 patients, including one possibly drug-related SAE of significant decrease in vision in Cohort 5. A durable treatment effect has been observed with stable visual acuity, decreased retinal thickness, and reductions in anti-VEGF injection burden in patients in Cohorts 4 and 5 at 1.5 years post RGX-314 administration. Patients in Cohort 4 experienced a 58.3% reduction in anti-VEGF treatment burden, while patients in Cohort 5 had a reduction in anti-VEGF treatment burden of 81.2%. A long-term, durable treatment effect over 3 years was demonstrated in the LTFU study for Cohort 3 patients, with a mean improvement in vision (+12 letters) and stable retinal thickness. Patients also demonstrated long-term reductions in anti-VEGF treatment burden over three years with a mean annualized rate of 2.4 anti-VEGF injections after administration of RGX-314. This is a reduction of 66.7% from the mean annualized injection rate during the 12 months prior to administration of RGX-314, and 50% of patients (3/6) remain anti-VEGF injection-free over three years. Updated data will be presented.

**Conclusions**
In the 42 subjects with nAMD, subretinal administration of RGX-314 has been generally well-tolerated and initial results out to three years show potential for a one-time administration of RGX-314 to provide sustained clinical outcomes in the treatment of nAMD.

**Financial Disclosure**
Research Funding: Gemini, Chengdu Kanghong, Genentech, Kodiak, Novartis, Adverum, Regeneron, REGENXBIO, Adverum, California Retina Research Foundation, Greybug, Ionis, Gemini, Stealth, Astellas, Apellis, NGM, Ophthea Consultant: Allegro, Genentech, Regeneron, Adverum, Gemini, Novartis, Kodiak, REGENXBIO
Purpose
A single-injection intravitreal (IVT) gene therapy that durably expresses intracellular anti-vascular endothelial growth factor (VEGF) could reduce the need for and burden of repeated anti-VEGF injections in patients with neovascular age-related macular degeneration (nAMD) whilst improving outcomes. The AAV.7m8 capsid was developed using directed evolution to enable efficient IVT delivery, increase transduction of retinal cells and to increase protein expression. ADVM-022 utilises the 7m8 capsid for consistent continuous delivery of aflibercept following a single in-office IVT injection.

Setting/Venue
OPTIC is an ongoing open-label, dose-ranging, multi-centre phase 1 study to evaluate the safety and tolerability of a single IVT injection of 3 dose levels of aflibercept-expressing ADVM-022, 2E11 and 6E11 vg/eye, through to 104 weeks in patients with nAMD who have demonstrated a prior response to anti-VEGF therapy. Additional objectives include evaluating best corrected visual acuity (BCVA), central subfield thickness (CST), intraretinal fluid (IRF), subretinal fluid (SRF), and the need for anti-VEGF supplemental therapy. The OPTIC study is being conducted at centers in the USA. All 4 planned cohorts are fully enrolled for a total of 30 patients.

Methods
Patients were administered a single IVT injection of ADVM-022 at 6E11 vg/eye for cohorts 1 (n=6) and 4 (n=9) and at 2E11 vg/eye for cohorts 2 (n=6) and 3 (n=9). Patients in cohorts 1 and 2 received oral steroid prophylaxis (60mg oral prednisolone for 6 days starting at day -3 followed by a 7 day taper), whilst those in cohorts 3 and 4 received steroid eye drop prophylaxis (QID difluprednate for 3 weeks starting at day 1, followed by a 3 week taper). Patients received supplemental aflibercept standard of care bolus IVT injections if any of the following criteria were met: 1) loss of > 10 letters in BCVA from baseline attributed to IRF or SRF observed by the investigator; 2) increase in CST >75 µm from baseline; 3) presence of vision-threatening haemorrhage due to AMD.

Results
As of October 15 2020, median follow-up for each cohort was 86 weeks (C1), 64 weeks (C2), 48 weeks (C3) and 16 weeks (C4). All enrolled patients previously required frequent anti-VEGF injections (mean 7.1–9.2 injections) in the 12 months prior to receiving ADVM-022 and had relatively good baseline BCVA (mean 65.0–65.9 ETDRS letters) and CST > 300 µm. ADVM-022 continues to be well tolerated with a favorable safety profile. All ADVM-022-related ocular adverse events were mild (78%) to moderate (22%). When observed, ocular inflammation was predominantly low grade and responsive to steroid eye drops. No cases of retinal involvement or vasculitis were reported. 80% of patients with nAMD treated with a single injection of ADVM-022 in OPTIC have remained supplemental anti-VEGF injection free; 14/15 patients receiving 6E11 vg/eye and 10/15 patients receiving 2E11 vg/eye ADVM-022. The mean annualised anti-VEGF injection frequency was reduced by 99% (6E11 vg/eye) and 85% (2E11 vg/eye) after ADVM-022. For C1–3, BCVA was maintained with a mean change of -2.5 to +0.2 ETDRS letters, and CST improved with a mean change of -19.7 to -132.7 µm.

Conclusions
ADVM-022 is designed to provide continuous stable expression of aflibercept following a single IVT injection. Data from OPTIC demonstrate that ADVM-022 is well-tolerated at both dose levels in patients previously requiring frequent anti-VEGF injections and has the potential to reduce treatment burden and improve long term visual and anatomical outcomes.

Financial Disclosure
Consultant for Adverum, Allergan, Apellis, Bayer, Heidelberg Engineering, Iveric Bio, Kanghong Pharmaceuticals, Novartis, Oxurion and Roche. Research funding from Novartis and Roche.
The impact of the OrCam device on the quality of life in patients with inherited retinal dystrophies

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Netherlands

Purpose
The aim of this study was to investigate the impact of the OrCam MyEye visual aid on the quality of life in patients with inherited retinal dystrophies (IRD). The OrCam is a portable visual aid, which is mounted to the frame of eyeglasses, that translates visual information to auditory feedback (e.g. text-to-speech, barcode and facial recognition).

Setting/Venue
An observational study performed at two Dutch rehabilitation centers from 15 October 2019 to 7 August 2020.

Methods
This prospective, observational study included 20 patients with low vision (BCVA< 20/200 Snellen) due to retinitis pigmentosa (n = 9; 45%) or cone-rod dystrophies (n = 11; 55%). After receiving extensive instructions on the OrCam, patients tested the OrCam for ± 5 weeks. Questionnaires were administered before and after OrCam testing, which included the Dutch version of the NEI-VFQ-25, a modified version of the Dutch Activity Inventory (D-AI), and the OrCam Function Questionnaire (OFQ).

Results
At final visit, a significant improvement in the 'near vision' subscale of the NEI-VFQ-25 was observed (p < 0.001), which did not differ between retinitis pigmentosa or cone-rod dystrophy patients (p = 0.446). No significant changes were seen in the priority scores of the different goals of the D-AI. The OFQ showed an overall improvement in performing vision-related tasks (p < 0.001), although patients reported more difficulty in using the OrCam during lower light situations.

Conclusions
The OrCam MyEye is a promising low vision aid in patients with IRD that have rehabilitation needs in the reading domain. Other functionalities of the OrCam, in the current state, were reported to be less effective, suggesting that these are areas for potential improvement.

Financial Disclosure
No financial disclosures
**Purpose**
To investigate the choroid in patients affected by PXE-related retinopathy using the Choroidal Vascularity Index (CVI).

**Methods**
PXE patients and controls were recruited at the Eye Clinic in Florence. High-resolution imaging OCT scans (12x9 mm) of 32 PXE patients and 20 age-matched control subjects were examined. Images were binarized using ImageJ software and Subfoveal Choroidal Thickness (SFCT), Luminal Area (LA), Stromal Area (SA), Total Choroidal Area (TCA) and CVI were measured.

**Results**
Sixty-four eyes of 32 PXE patients (mean age 45.65 ± 16.12; range 14-69) and 40 eyes of 20 control subjects (mean age 47.3 ± 13.7; range 18-71) were included in the study. SFCT was significantly lower in PXE patients compared to control subjects. LA, SA and TCA of the PXE patients were significantly reduced in comparison with those obtained for controls. On the contrary, the CVI did not significantly differ between patients and controls. In young subjects, we did not detect differences regarding OCT parameters.

**Conclusions**
In PXE-related retinopathy the choroidal impairment appears secondary to the Bruch’s membrane calcification and progressive with age, and there is a simultaneous, proportional impairment of both the stromal and the vascular components of the choroid.
### Title
Clinical and genetic spectrum of patients with GUCY2D-associated retinal dystrophies

### Purpose
To describe the spectrum of retinal dystrophies associated with GUCY2D, and to identify potential clinical endpoints and optimal patient selection for future (gene) therapy.

### Setting/Venue
This multicenter retrospective study included patients from from the Delleman archive, a large database for inherited eye diseases at the Amsterdam University Medical Centers (Amsterdam, the Netherlands), and various Dutch expertise center within RD5000 consortium, a national consortium for registering patients with retinal dystrophies. Data from additional patients were included from the University Hospital Ghent (Ghent, Belgium), as well as the Moorfields Eye Hospital (London, United Kingdom) and 3 other academic tertiary referral centers in the United Kingdom.

### Methods
This study reviewed medical records of 52 affected patients from 30 unrelated families for medical history, symptoms, best-corrected visual acuity (BCVA), ophthalmoscopy, visual field, full-field electroretinography and retinal imaging (fundus photography, spectral-domain optical coherence tomography (SD-OCT), fundus autofluorescence).

### Results
Patients had autosomal dominant cone-rod dystrophy (CORD; n=39; 75%) and autosomal recessive Leber congenital amaurosis (LCA; n=13; 25%). The mean follow-up time was 11.4±11.8 years for CORD and 5.7±4.4 years for LCA. The mean age at onset was 21.5±18.7 years and 0.4±1.0 years, respectively. For CORD, the mean Snellen BCVA at first visit was 0.25±0.22 (0.60±0.65 logMAR), and on average decreased with 0.07 (1.15 logMAR) per 10 years (p<0.003). In LCA patients, Snellen BCVA ranged from no light perception to 0.10 (1.00 logMAR). In CORD patients, the integrity of the ellipsoid zone (EZ) and external limiting membrane (ELM) on SD-OCT were significantly correlated with BCVA (Spearman’s r=-0.685 p=0.001 and r=-0.61 p=0.004, respectively).

### Conclusions
LCA associated with GUCY2D mutations resulted in severe congenital visual impairment. GUCY2D-associated CORD showed a later onset and a relatively slow decrease of visual acuity, possibly suggesting a relatively large window of opportunity for future (gene) therapy. Severe visual impairment in the CORD group was generally reached in the 5th decade of life. The integrity of ELM and EZ may be suitable structural endpoints for future gene therapeutic studies in CORD.

### Financial Disclosure
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Purpose
Inherited retinal dystrophies (IRDs) are rare heterogeneous disorders which are caused by more than 250 genes. The RPE65 gene is critical for the visual cycle as it encodes the RPE65 protein necessary for vitamin A absorption in photoreceptor cells. Mutations in the RPE65 gene are associated with several clinical manifestations including nyctalopia and decreased visual field and visual acuity. Individuals carrying these mutations exhibit vision loss that substantially limits major life activities, often during childhood or adolescence, and ultimately progresses to total blindness. Voretigene neparvovec (VN) is a genetically-modified non-replicating adeno-associated virus which enables the expression of the human RPE65 transgene. It is the first approved ocular gene therapy for patients with visual impairment due to biallelic RPE65 mutation–associated IRD having sufficient viable retinal cells. Current evidence on the effect of VN is from randomized controlled trials conducted on a limited number of patients, with no real-world data on its safety and effectiveness. The PERCEIVE study was therefore designed to assess the long-term safety and effectiveness of VN in a real-world setting. Findings from patients enrolled in the study to August 2020 are presented here.

Setting/Venue
PERCEIVE is a prospective, longitudinal, multicenter, multinational (ex-US), observational, registry-based study, which commenced in December 2019. The study does not impose a therapy protocol, diagnostic/therapeutic procedure, or a visit schedule. The study aims to enroll a minimum of 40 VN-treated patients in the enrollment period of 5 years.

Methods
Participation in the study was voluntary; it was strongly encouraged that all patients treated with VN be enrolled. Patients who are planning to or have received VN in at least 1 eye, provided informed consent; and who had not previously participated, or are currently participating, in an interventional clinical trial with VN were included. Patients are being treated as per local prescribing information and followed up according to routine clinical practice for 5 years. The primary objective is to collect safety information including adverse events (AEs) of special interest (AESI) and any other AEs. The secondary objectives are to follow pregnancy outcomes in VN-treated patients (and their female partners), and to assess visual function over time (e.g., as measured by full-field light sensitivity threshold [FST; white light], visual field, optical coherence tomography [OCT], and best-corrected visual acuity [BCVA]). Vision outcomes are presented for the first- and second-treated eye (FTE and STE, respectively) separately. The full analysis set (FAS), which includes all enrolled patients who received VN in at least 1 eye, was used to summarize all data. Data collected until August 2020 (data cut-off) are presented here.

Results
Until data cut-off, 15 patients were enrolled; 10 (16 eyes) received VN (6 bilateral; 4 unilateral). Patients were aged (mean, standard deviation [SD]) 27.6 (9.81) years. Seven (70%) are female. At baseline, central OCT revealed 36–74 µm thick outer nuclear layer in 11 eyes (n=9); absent in 4 (n=4). The ellipsoid zone line was disrupted in 9 eyes (n=6) and undetected in 6 (n=4). Baseline mean (SD) FST was −4.45 (11.24) dB for FTE and −4.08 (5.01) dB for STE. Four patients (4 eyes) experienced 6 events of ocular treatment-emergent AE (TEAE) including 4 events of AESIs: foveal degeneration (reported term: foveal thinning [AESI], n=3), dyschromatopsia (n=1), glare (n=1) and macular scar (AESI; n=1). Two patients reported non-ocular TEAEs (headache). No serious AEs occurred. The mean (SD) change from baseline in FST for FTE and STE at Month 6 was −15.57 (6.63) dB (n=3) and −16.03 dB (n=1), respectively. The mean (SD) change in foveal thickness at Month 6 was −0.7 (32.06) µm (n=2) and −22.0 µm (n=1) for FTE and STE, respectively. The mean (SD) change in BCVA (LogMAR) from baseline at Month 6 was −0.23 (0.17) (n=4) and 0.16 (n=1) for FTE and STE, respectively.

Conclusions
Baseline characteristics of the majority of VN-treated patients in this real-world study are similar to those of patients included in randomized clinical trials of VN. Till date, the findings on safety and tolerability of VN in these enrolled and evaluated patients are consistent with the established safety profile of VN. As more data are being collected, PERCEIVE will provide valuable insights on the characteristics of patients with biallelic RPE65 mutation–associated IRD, and the long-term clinical effect of VN in a real-world setting.
Updated Results From the NIGHT Study: Natural Progression of Choroideremia

Purpose
Choroideremia is a rare inherited retinal disease that leads to progressive vision loss and eventual blindness, with no currently approved treatments. A clearer understanding of the natural progression of choroideremia is critical for appreciating the potential impact of investigational therapies. Previously, we reported results from an interim cut of the data from 2019. Here, we report results from an interim cut of the data from 2020, which includes the full study population.

Setting/Venue
NIGHT (NCT03359551) was a 2-year, prospective, multicenter, observational study investigating the natural progression of choroideremia.

Methods
NIGHT enrolled adult males with genetically confirmed choroideremia and active disease visible within the macula. At baseline, eyes were classified into 3 cohorts by best-corrected visual acuity (BCVA): ≥74 Early Treatment of Diabetic Retinopathy Study (ETDRS) letters (197 eyes), 34-73 ETDRS letters (381 eyes), and <34 ETDRS letters (53 eyes). Visits occurred at 4-month intervals; BCVA, preserved ellipsoid zone (EZ) area, preserved area of autofluorescence (PAF), microperimetry (MP), contrast sensitivity, color vision, and reading-speed tests were assessed periodically. Endpoints other than BCVA were assessed through 12 months.

Results
NIGHT enrolled adult males with genetically confirmed choroideremia and active disease visible within the macula. At baseline, eyes were classified into 3 cohorts by best-corrected visual acuity (BCVA): ≥74 Early Treatment of Diabetic Retinopathy Study (ETDRS) letters (197 eyes), 34-73 ETDRS letters (381 eyes), and <34 ETDRS letters (53 eyes). Visits occurred at 4-month intervals; BCVA, preserved ellipsoid zone (EZ) area, preserved area of autofluorescence (PAF), microperimetry (MP), contrast sensitivity, color vision, and reading-speed tests were assessed periodically. Endpoints other than BCVA were assessed through 12 months.

Conclusions
Updated analyses of all enrolled participants in the NIGHT study were consistent with initial results describing gradual vision loss in individuals with choroideremia. Older participants tended to experience a greater decline in vision by BCVA over 20 months compared with younger participants. Microperimetry sensitivity, preserved EZ area, and PAF decreased over 12 months in all cohorts. These results reaffirm the importance of BCVA, MP, preserved EZ area, and PAF as measures of the natural progression of choroideremia.

Financial Disclosure
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The contribution of different pathologic alterations characterizing Best Vitelliform Macular Dystrophy on retinal sensitivity.

Purpose
Best Vitelliform Macular Dystrophy (BVMD) is an extremely heterogeneous genetic retinal dystrophy characterized by the presence of different pathologic alterations, including lipofuscin deposition, fluid accumulation, atrophy, and neovascular complications. Although progression through Gass’ stages is generally associated with a worse visual prognosis, scant data are available regarding the impact of each pathologic alteration on retinal functional deterioration, in terms of sensitivity and fixation stability. The main aim of the present study is to investigate the influence of clinical and imaging parameters on retinal sensitivity by means of micropereimetry, structural optical coherence tomography (OCT), blue-light fundus autofluorescence (BAF), and OCT-Angiography (OCTA).

Setting/Venue
Observational and cross-sectional study on a consecutive series of patients affected by genetically confirmed BVMD, enrolled in the Retinal Heredodystrophies Unit of San Raffaele Hospital in Milan, Italy.

Methods
Enrolled patients underwent a complete ophthalmologic examination including macular integrity assessment (MAIA) microperimetry, OCT, BAF, and OCTA. Eyes that satisfied the inclusion criteria were classified into five subtypes, according to the tomographic aspect of the lesion: subclinical, solid vitelliform deposition, mixed (combination of solid and fluid accumulation), subretinal fluid (vitelliform material entirely reabsorbed and replaced by fluid), atrophic. Eyes were also categorized as having a hyper-autofluorescent, patchy or hypo-autofluorescent pattern on BAF. The mean threshold of testing points within the area of the lesion was calculated in order to assess the sensitivity of the affected retina. 63% and 95% Bivariate Contour Ellipse Area (BCEA) were used as outcome variables for fixation stability. We calculated area of ellipsoid zone (EZ) integrity, thickness of the outer nuclear layer (ONL), and central macular thickness (CMT) using structural OCT. Presence of non-exudative MNVs and values of vessel density (VD), and tortuosity (VT) were assessed using OCTA. The primary outcome was the analysis of retinal sensitivity among lesion subtypes and BAF patterns. The secondary outcome was to analyze the influence of ONL thickness, CMT, area of EZ integrity, presence of non-exudative MNV, vessel density, and tortuosity on retinal sensitivity, fixation stability, and visual acuity.

Results
57 eyes of 30 patients were included in the analysis. The subclinical stage displayed the highest retinal sensitivity (24.44 dB; p < 0.01) while eyes characterized by atrophic areas the lowest one (11.85 dB; p < 0.01). Lesions showing solid vitelliform deposition had higher retinal sensitivity (21.97 dB) than subtypes with partial or total substitution with fluid (17.27 dB; p < 0.01). Lesions totally composed of subretinal fluid had a lower retinal sensitivity (15.68 dB) than mixed ones (18.73 dB; p < 0.05). The hyper-autofluorescent pattern was associated with a better sensitivity (21.96 dB) than patchy (16.24 dB; p < 0.01) and hypo-autofluorescent patterns (14.53 dB; p < 0.01). The presence of a non-exudative MNV marked a worse functional outcome (14.96 dB; p < 0.01). A larger area of preserved EZ (p < 0.01) was associated with a more stable fixation and a higher visual acuity. A thicker ONL and a larger area of EZ integrity were associated with better retinal sensitivity (both p < 0.01). Vessel tortuosity correlated positively with retinal sensitivity (p < 0.01) while vessel density correlated negatively with 63% BCEA and 95% BCEA (p < 0.05).

Conclusions
The present study expands the knowledge on retinal sensitivity variation in different subtypes of BVMD lesions. In particular, we assessed the contribution of different pathological features in determining retinal function deterioration, as assessed by micropereimetry. We found that the morphological composition had a remarkable influence on the sensitivity of BVMD lesions. In detail, our results suggest that retinal sensitivity deteriorates in a linear fashion as lipofuscin reabsorbs progressively and an area of subretinal fluid takes its place until atrophy ensues. On the other hand, fixation stability and visual acuity showed a relationship with ellipsoid zone status, rather than with lesion subtype or autofluorescence pattern. Lastly, we found that thickness of ONL, integrity status of EZ, and vascular perfusion at superficial and deep retinal capillary plexuses are valuable imaging markers of good retinal sensitivity in BVMD.

Financial Disclosure
None
**Epidemiology and clinical characteristics of scleritis in a Latin American eye care reference center**

**Purpose**
To evaluate demographic characteristics, clinical features, systemic disease associations and visual outcomes of patients with scleritis in a Colombian tertiary care referral center.

**Setting/Venue**
Medical records of patients who were diagnosed with scleritis at the Ocular Uveitis service in Fundación Oftalmológica de Santander Carlos Ardila Lule (FOSCAL) a tertiary eye care center in Floridablanca, Santander, Colombia were reviewed.

**Methods**
Data from 48 patients with scleritis followed from 2015 to 2020 were retrospectively evaluated. The main outcome measures were demographics, ocular disease characteristics and complications, presence of systemic associated disease and treatment regimen.

**Results**
In a series of 48 patients, women were overrepresented among scleritis patients with a relation of 2.4 : 1 corresponding to a 70.8% (n=34). Scleritis were found bilaterally in 20.8% (n=10) of patients. Scleritis was diffuse in 19, nodular in 21, necrotizing in 2, and posterior in 4 patients. Anterior uveitis (37%; n=17), Panuveitis (4.3%; n=2), ocular hypertension (4.3%; n=2), Macular Edema (2.3%; n=1) and Peripheral ulcerative keratitis (6.5%; n=3) were encountered as ocular complications in patients with scleritis. An associated systemic disease was found in 25% of patients with scleritis among which Rheumatoid Arthritis was the most prevalent systemic disease (72% n=8). 13.3% (n=6) of patients with scleritis required Intravenous corticosteroids, 35.6%(n=16) oral corticosteroids, 20% (n=9) immunosuppressive drugs, and 6.6% (n=3) Biologic medication.

**Conclusions**
Scleritis is a vision-threatening condition that requires prompt diagnosis, systemic assessment, and accurate treatment in order to prevent ocular and systemic complications. This study provides an insight about the scleritis distribution and characterization, ocular complications and associated diseases in a Latin American population. To our knowledge this is the first study that presents information of this entity in our population.

**Financial Disclosure**
We have no financial relations or interests.
Purpose
The DRAKO study aimed to evaluate the effectiveness and safety of standard-of-care intravitreal aflibercept (IVT-AFL) injections for the treatment of patients with diabetic macular edema (DME) within the UK over a 2-year follow-up period. Here we describe the change from baseline at Month 12 (M12) for best-corrected visual acuity (BCVA) and central subfield thickness (CST) when local standard-of-care posologies were applied. We also assess patient quality of life (QoL), summary of product characteristics (SmPC) adherence, and fellow eye involvement at M12. All results pertain to the anti-vascular endothelial growth factor (VEGF) treatment-naïve patient cohort.

Methods
Data were analyzed following an interim database lock at M12 (19 Jun 2019) for patients with BCVA or CST results available at baseline and M12 within a ±1-month window. Summary statistics were used to describe the change from baseline at M12 for all outcomes. The primary endpoints were change from baseline at M12 in QoL assessed using the National Eye Institute Visual Function Questionnaire 25-item version (NEI VFQ-25), evaluation of the number of injections and SmPC adherence, and evaluation of fellow eye involvement. Where both eyes were affected with DME, the study eye was defined as the eye with worse baseline visual acuity. Where appropriate, outcomes were stratified by baseline measures. Safety events were coded using the Medical Dictionary for Regulatory Activities and summarized. All outcomes were stratified by baseline measures. Safety events were coded using the Medical Dictionary for Regulatory Activities and summarized. All results were calculated using SAS 9.4.

Results
A total of 507 anti-VEGF treatment-naïve patients were enrolled. Subsequently, 388 patients were included in this analysis based on predefined criteria. Fellow eye involvement was confirmed for 53.9% patients. At baseline, mean (standard deviation [SD]) BCVA was 71.4 (12.0) letters and CST was 448.7 (88.7) µm. At M12, mean (SD) change from baseline gain of 2.5 (12.2) BCVA letters and reduction of 119.1 (116.4) µm in CST was reported. Patients with baseline BCVA <70 letters (36.9%) experienced a mean (SD) gain of 7.3 (12.9) letters at M12. At site initiation, 27 of 35 sites (77.1%) intended to adhere to DME SmPC for 5 initial monthly injections, and 21 of 35 sites (60.0%) planned to subsequently perform bi-monthly injections in Year 1 (as per SmPC). At M12, the mean number (SD) of injections administered was 6.4 (2.1). A mean gain of 4.2 letters was observed in patients receiving 5 initial injections (30.2% patients), with mean 1.1-letter gain in those being treated as per SmPC (2.3% patients). The mean number (SD) of fellow eye injections was 4.5 (2.5), with 69.3% occurring on the same day as study eye treatment. The safety profile of IVT-AFL was noted as consistent with previous studies.

Conclusions
The DRAKO study 12-month results indicate that IVT-AFL was effective for the treatment of anti-VEGF treatment-naïve DME in this UK real-world population by maintaining or improving functional and anatomical outcomes, despite patients being under-treated compared with SmPC, and a wide range of treatment posologies being applied. Patients adhering to SmPC posology initial dosing experienced vision gains above the mean for the study. Of note, mean baseline BCVA was high for most patients, supporting the effectiveness of the UK diabetic retinopathy screening program. The potential increased burden on the patient and the center for patients with bilateral disease was also ameliorated, with over two-thirds of bilateral treatments conducted on the same day. In addition, a trend towards improvement from baseline in QoL was seen, with similar outcomes for patients with or without fellow eye involvement.
Title
Twelve-month outcomes of ranibizumab versus aflibercept for macular oedema in branch retinal vein occlusion: data from the FRB! registry

Purpose
To compare the efficacy of ranibizumab (0.5mg) to aflibercept (2mg) in the treatment of cystoid macular oedema (CMO) due to branch retinal vein occlusion (BRVO) over 12 months in a real-world setting.

Setting/Venue
A multicentre, international, database observational study recruited 322 eyes initiating therapy in real-world practice over 5 years utilising data from the Fight Retinal Blindness registry.

Methods
The main outcome measure was mean change in EDTRS letter scores of visual acuity (VA). Secondary outcomes included anatomic outcomes, percentage of eyes with VA > 6/12 (70 letters), number of injections and visits, time to first inactivity, switching or non-completion.

Results
Generalised mixed effect models demonstrated that mean (95% CI) adjusted 12-month VA changes for ranibizumab and aflibercept were similar (+10.8 [8.2, 13.4] versus +10.9 [8.3, 13.5] letters respectively, p = 0.59). The mean adjusted change in central subfield thickness (CST) was greater for aflibercept than ranibizumab (-170 [-153, -187] μm versus -147 [-130, -164] μm respectively, p = 0.001). The overall median (Q1, Q3) of 7 (4, 8) injections and 9 (7, 11) visits was similar between treatment groups. First grading of inactivity occurred sooner with aflibercept (p = 0.01). Switching was more common from ranibizumab (37 eyes, 23%) than from aflibercept (17 eyes, 11%; p = 0.002).

Conclusions
Visual outcomes at 12 months in this direct comparison of ranibizumab and aflibercept for BRVO in real world practice were generally good and similar for the 2 drugs, despite a greater effect of aflibercept on CST and time to first grading of inactivity.

Financial Disclosure
I have received speaker fees from Allergan and travel sponsorship from Bayer and Novartis - all of which is outside of the submitted work.
Twelve-Month Treatment Outcomes of Macular Edema Following Central Retinal Vein Occlusion using Aflibercept or Ranibizumab in Routine Clinical Practice – Data from the Fight Retinal Blindness! Project

Purpose
To compare 12-month treatment outcomes of eyes receiving aflibercept or ranibizumab for macular edema secondary to central retinal vein occlusion (CRVO) in routine clinical practice.

Setting/Venue
This was a retrospective analysis from a prospectively designed observational outcomes registry: the Fight Retinal Blindness! Project. Practitioners from Australia, the United Kingdom, France and Switzerland contributed data.

Methods
Treatment-naïve eyes receiving either aflibercept (2mg) or ranibizumab (0.5mg) for macular edema secondary to CRVO from 1st of June 2014 to 1st of June 2019. Visual acuity (VA) and central subfield thickness (CST) were analyzed from baseline through 12 months. The primary outcome measure was the mean change in VA (number of letters read on a logarithm of the minimum angle of resolution (LogMAR) chart and change in CST (in µm) from baseline to 12 months.

Results
We identified 296 patient eyes (171 aflibercept; 125 ranibizumab) of 291 patients. Baseline VA (SD) was somewhat higher in aflibercept vs. ranibizumab treated eyes (42.5±25.5 letters vs. 36.9±26 letters; p=0.07) with similar CST (614 (240) µm vs. 616 (234) µm: p=0.95). The 12-month adjusted mean (95%CI) VA improvement was +16.6 (12.9, 20.4) letters for aflibercept vs. +9.8 (5.5, 14.1) letters for ranibizumab (p=0.001). The mean (95%CI) adjusted reduction in CST was significantly higher in aflibercept- vs ranibizumab-treated eyes: -304 (-276, -333) µm vs. -252 (-220, -282) µm, p<0.001. Both groups had a median (Q1, Q3) of 7 (5, 9) injections and 10 (8,13) visits.

Conclusions
Both aflibercept and ranibizumab improved VA and reduced CST in routine clinical practice, with aflibercept showing greater improvements in this comparative analysis.

Financial Disclosure
Novartis and Bayer support this research.
The role of complete or partial peripheral capillary non-perfusion on macular impairment in central and branch retinal vein occlusion

Purpose
The term retinal vein occlusion (RVO) includes a complex spectrum of vascular retinal disorders. Although it was largely demonstrated that peripheral capillary non-perfusion (PCN-P) is a negative phenomenon which may occur both in central RVO (CRVO) and branch RVO (BRVO), its pathogenetic contribution on macular morphofunctional deterioration has been partially understood. The aim of the present study is to investigate the influence of PCN-P on the macular region of the retina in eyes affected by BRVO and CRVO by using ultra widefield fluorescein angiography (UWFFA), optical coherence tomography (OCT) and OCT-angiography (OCTA).

Setting/Venue
The study was designed as a case series with a planned follow-up of 2 years. Consecutive CRVO and BRVO patients and a corresponding control group of healthy subjects were recruited at the Ophthalmology Department of San Raffaele Hospital in Milan from January 2016 to January 2018.

Methods
Overall, 28 patients underwent a complete ophthalmologic examination including best corrected visual acuity (BCVA) measurement using standard ETDRS charts, slit-lamp biomicroscopy of anterior and posterior segments, ultra widefield fluorescein angiography (UWFFA), OCT and OCTA. OCT scans were used to measure central macular thickness (CMT). High resolution 4.5x4.5 and 9x9 mm OCTA images collected at the end of the 2-year follow-up were used for an automatic segmentation into superficial capillary plexa (SCP), deep capillary plexa (DCP) and choriocapillaris (CC) at the level of macular (m) and optic nerve head (n). OCTA images were binarized on The ImageJ software to calculate vessel density (VD), after excluding the manually segmented foveal avascular zone (FAZ), and FAZ area. We compared OCTA quantitative findings of healthy subjects. We assessed the presence of collateral vessels (CVs) in both CRVO and BRVO patients with an age- and sex-matched control group.

Conclusions
In this study we quantitatively assessed the impact of PCN-P on morpho-functional macular status both in CRVO and BRVO. Our analysis reveal that ISI correlates with FAZ and BCVA in CRVO eyes, but not in BRVO eyes, probably due to a greater extent of retinal involvement in CRVO. No correlation with the extension of collateral vessels was registered both in CRVO and BRVO eyes. Our data indicate that ISI greater than 25% and cISI correlate respectively with baseline and final CMT, in CRVO. Conversely, only pISI unveils a correlation with baseline CMT in BRVO eyes. OCTA findings showed in both RVO types a lower macular VD with respect to healthy subjects. Additionally, VD did not correlate with ISI in CRVO, but correlated with macular DCP in BRVO. The reasons underlying this response may be referred to the uniformly low VD found in CRVO eyes, which cannot allow a positive correlation with the severity of ISI. Indeed, when PCN-P is present in CRVO eyes, VD is always reduced, resulting in a kind of off/on response. By contrast, in BRVO a conspicuous extent of the retina is not damaged by the vascular impairment, making the correlation between PCNP and VD more readable.

Results
Mean baseline BCVA was 0.69 ± 0.17 logMAR in CRVO and 0.43 ± 0.25 logMAR in BRVO, improving to 0.09 ± 0.12 logMAR and 0.15 ± 0.18 logMAR, respectively. Mean CMT at baseline was 512.50 ± 132.71 µm in CRVO and 463.83 ± 200.85 µm in BRVO, improving to 305.75 ± 89.25 µm and 353.17 ± 108.85 µm, respectively. All the quantitative OCTA parameters resulted significantly worse in CRVO and BRVO, with respect to controls. In CRVO, ISI correlated with FAZ, baseline and final BCVA; in BRVO, cISI >25% correlated with BCVA and CMT at baseline and final CMT (p<0.05). cISI correlated with baseline BCVA and cISI >25% correlated with final CMT (p<0.05). A worse final BCVA correlated with lower VD in mSCP (p<0.05). In BRVO eyes ISI did not show any correlation with the extension of CVs. In CRVO only, baseline CMT correlates with baseline and final BCVA (p<0.05).

Financial Disclosure
All authors have no conflict of interests to declare.
**Design and Rationale of the YOSEMITE and RHINE Trials: Two Phase 3 Studies of Faricimab in Patients With Diabetic Macular Edema**

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**Purpose**
Diabetic macular edema (DME) is a multifactorial disease, and best-achievable visual responses to anti-vascular endothelial growth factor (VEGF) monotherapy are difficult to achieve and maintain in clinical practice. Dual inhibition of angioptiin-2 and VEGF-A with faricimab, the first bispecific antibody designed for intraocular use, may synergistically promote vascular stability and improve outcomes in DME. Herein we describe the design and rationale of the phase 3 YOSEMITE and RHINE trials, which assessed the safety, efficacy, and durability of faricimab in patients with DME.

**Setting/Venue**
YOSEMITE (NCT03622580) and RHINE (NCT03622593) are identical, randomized, double-masked, active comparator–controlled, 100-week, phase 3 trials of faricimab in DME.

**Methods**
Treatment-naïve or previously anti-VEGF–treated patients with center-involving DME were randomized 1:1:1 to faricimab 6.0 mg every 8 weeks (Q8W) after 6 initial Q4W doses; faricimab 6.0 mg per personalized treatment interval (PTI) after 4 initial Q4W doses; or aflibercept 2.0 mg Q8W after 5 initial Q4W doses. Dosing intervals in the PTI arm were determined by an automated algorithm, and could be reduced or extended by 4-week increments (from Q4W up to Q16W) according to prespecified best corrected visual acuity (BCVA) and central subfield thickness (CST) criteria at active dosing visits. The PTI algorithm is based on the treat-and-extend concept, and was designed to enable personalized therapy for DME, reduce injection frequency, and potentially optimize real-world outcomes.

**Results**
Safety and efficacy were assessed Q4W through week 100. To account for differences in time from last treatment and BCVA variability, the primary efficacy endpoint was mean change in BCVA from baseline averaged over weeks 48, 52, and 56. Secondary endpoints included the proportion of patients with ≥2-step Early Treatment Diabetic Retinopathy Study-Diabetic Retinopathy Severity Scale improvement at week 52, change in CST from baseline, and the proportion of patients in the PTI arm receiving Q4W, Q8W, Q12W, or Q16W dosing at 1 year. Safety outcomes included the incidence and severity of ocular and nonocular adverse events. Both studies met their primary endpoint of noninferiority of faricimab dosed Q8W or per PTI versus aflibercept Q8W in visual acuity gains, and greater than 50% of patients in the faricimab PTI arms achieved Q16W dosing at 1 year. Faricimab was generally well tolerated, with no new safety signals identified.

**Conclusions**
YOSEMITE and RHINE were designed to evaluate whether dual inhibition of angioptiin-2 and VEGF-A with faricimab may improve outcomes beyond anti-VEGF monotherapy in patients with DME. The PTI arm will examine the potential for individualized faricimab therapy, tailored according to patient needs, to reduce treatment burden while maintaining efficacy.

**Financial Disclosure**
Marta S. Figueroa: (Consultant) Alcon, Allergan, Bayer, Novartis, Roche, Zeiss.  
Jeffrey Willis: (Employee) Genentech, Inc.  
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Purpose
The aim of the CENTERA study was to evaluate the efficacy and safety of intravitreal aflibercept (IVT-AFL) administered using a proactive, individualized treat-and-extend (T&E) dosing regimen in patients with macular edema secondary to central retinal vein occlusion (CRVO). The primary results, including safety, of the CENTERA study have been previously published. This post hoc analysis of the CENTERA study assessed baseline (BL) characteristics, treatment intervals, as well as functional (best-corrected visual acuity [BCVA]) and anatomic (central retinal thickness [CRT]) outcomes of patients who achieved treatment success based on study criteria similar to LEAVO (BCVA of ≥83 letters achieved at any point during treatment).

Methods
Patients with macular edema secondary to CRVO received 2 mg IVT-AFL injections at BL and every 4 weeks until disease stability criteria were met, or until Week 20, whichever occurred first (initiation phase). The treatment interval was adjusted in 2-week increments based on functional and anatomic outcomes, as assessed by the investigator (T&E phase). Monitoring occurred at each injection and mandatory visit (Weeks 24, 52, and 76). Co-primary endpoints were the proportion of patients who gained 15 letters from BL to Week 76 and the proportion of patients with a mean treatment interval of ≥8 weeks from the last initiation phase visit to Week 76. Safety was assessed throughout the study. A post hoc sensitivity analysis of the second co-primary endpoint was conducted based on study criteria similar to LEAVO for treatment success. In this sensitivity analysis, patients who achieved ≥83 letters at any point were considered treatment successes and, therefore, to have met the second co-primary endpoint of achieving a mean treatment interval of ≥8 weeks. The proportion of patients who maintained robust vision gains (achieved ≥83 letters and did not lose >5 letters thereafter) was also assessed.

Results
The full analysis set (FAS) comprised 160 patients (n=74 ≥83 letter group; mean±SD BL BCVA 61.2±12.3) and n=86 (<83 letter group; BL BCVA 44.0±16.2)). Overall, 65.6% (n=105; 95%CI, 57.7–72.9, p<0.0001 [test against 40% threshold]) of patients in the FAS gained ≥15 letters from BL to Week 76. During the T&E phase, 45.0% (n=72; 95%CI, 37.1–53.1, p=0.8822 [threshold of 50%]) of patients in the FAS achieved a mean treatment interval of ≥8 weeks. In the sensitivity analysis of the second co-primary endpoint, where patients who achieved ≥83 letters at any point were considered treatment successes and therefore to have met this endpoint, 66.3% (n=106; 95%CI, 58.4–73.5, p<0.0001 [test against 50% threshold]) of patients achieved a mean treatment interval ≥8 weeks or treatment success during the T&E phase. Of the patients who achieved ≥83 letters at any point, 54.1% (n=40) maintained vision. Mean change in BCVA from BL to Week 76 was +23.9±13.6 (≥83 letter group) letters and +17.3±23.1 (<83 letter group) letters. At BL, mean CRT was 695.6±226.4 (≥83 letter group) µm and 816.6±249.9 (<83 letter group) µm. Mean change in CRT from BL to Week 76 was −419.8±235.0 (≥83 letter group) µm and −563.4±249.3 (<83 letter group) µm.

Conclusions
In the CENTERA study, clinically meaningful and significant improvements in functional and anatomic outcomes were achieved with IVT-AFL administered using a proactive, individualized T&E regimen in patients with macular edema secondary to CRVO. An appreciable proportion of patients in CENTERA achieved high BCVA (≥83 letters) following IVT-AFL T&E treatment. This sensitivity analysis indicated that, if similar criteria to LEAVO for treatment success had been used, most patients could have achieved a mean treatment interval of ≥8 weeks or treatment success during the T&E phase. Of the patients who achieved ≥83 letters at any point during the study, over half not only achieved, but also remained at ≥83 letters. In addition, patients who achieved ≥83 letters at any point during the study had higher BCVA and lower CRT at BL, compared with those who did not achieve ≥83 letters. In both groups, patients demonstrated BCVA gains and improved CRT, demonstrating that IVT-AFL administered using a proactive, individualized T&E regimen optimizes visual acuity gains and normalizes CRT irrespective of BL status.
Changes in macular perfusion following treatment of diabetic macular edema with intravitreal anti-vascular endothelial growth factor agents

To investigate the effect of treatment in eyes having center-involving diabetic macular edema (ciDME) with intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy on macular perfusion measured using optical coherence tomography angiography (OCT-A).

In a prospective interventional cohort study, 22 patients with at least 1 eye having ciDME referred to the Medical Retina service were recruited. All patients enrolled received 3 consecutive monthly loading doses of intravitreal anti-VEGF injections starting at baseline. All patients had OCT-A and spectral-domain optical coherence tomography (SD-OCT) scans performed at baseline and subsequently at month 3, after the completion of the anti-VEGF therapy. The 3x3 mm macular scans on OCT-A were used in this analysis. Using the in-built manufacturer software, average vessel density and size of the fovea avascular zone (FAZ) measurements in the superficial capillary plexus were generated. Central retinal thickness (CRT) in the central 1-mm Early Treatment Diabetic Retinopathy Study (ETDRS) standard subfield measured on SD-OCT were also recorded. These imaging parameters were correlated with baseline patient demographics and disease parameters such as the severity of background diabetic retinopathy to investigate their relationships.

Twenty-two patients (11 males and 11 females) were enrolled into the study. The mean age was 62.1 years old (range 50-81 years). Of the 44 eyes, 32 eyes had ciDME and received anti-VEGF injections while 12 eyes did not have ciDME. Four (9.1%) eyes had background mild non-proliferative diabetic retinopathy (NPDR), 19 (43.2%) eyes had moderate NPDR, 10 (22.7%) eyes had severe NPDR, 5 (11.4%) eyes had proliferative diabetic retinopathy (PDR) and 6 (13.6%) eyes were status post panretinal photocoagulation (PRP). At baseline, average vessel density was significantly higher in the group with mild-moderate NPDR compared to the group with severe NPDR-PDR and status post PRP (44.0% vs. 40.5%, p=0.007). However, there is no difference in size of the FAZ when the two groups based on background retinopathy were compared (0.380 mm² vs. 0.387 mm², p=0.865). CRT in eyes with ciDME at baseline (mean CRT 441.7um) decreased significantly after anti-VEGF therapy at month 3 (mean CRT 377.3um, p=0.001). Despite a significant decrease in CRT after anti-VEGF injections, there was no significant difference between average vessel density (42.2% vs. 43.2%, p=0.145) and size of the FAZ (0.404 mm² vs. 0.419 mm², p=0.504) at baseline and month 3 after treatment.

At baseline, there is an association between the average vessel density at the macula with the severity of background retinopathy. Following treatment of ciDME with 3 consecutive monthly loading doses of intravitreal anti-VEGF injections, there is significant decrease in CRT and edema. Despite this, the average vessel density at the macula and size of the FAZ remained statistically unchanged in the short-term after injections.
Evaluation of incidence of retinopathy of prematurity in Germany for the revision of German screening criteria

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Purpose
To evaluate current screening criteria for retinopathy of prematurity (ROP) by investigating the incidence of ROP requiring treatment in infants with gestational age (GA) ≥30 weeks or postmenstrual age (PMA) <32 weeks in Germany.

Setting/Venue
Epidemiological study

Methods
Three patient databases were analyzed, including the German Quality Assurance Procedure in Neonatology (years 2011–2017; n=52,461 infants screened for ROP, 1505 infants treated for ROP), the German Retina.net ROP Registry (years 2011–2018; n=281 treated infants) and the ROP screening program of two German university hospitals (years 2012–2016; n=837 screened infants).

Results
In the analyzed cohorts, infants with GA ≥30 weeks represented 33.1%–38.5% of the screening populations but only 1.40%–1.42% of the cases requiring ROP treatment. The number needed to screen increased from 4 for infants with GA 23 weeks to 1,788 for infants with GA 31 weeks. In a cohort of 281 infants treated for ROP, all 4 infants with GA ≥30 weeks had additional risk factors for ROP including prolonged oxygen supplementation and/or significant comorbidities. Five infants (1.8%) were treated at 32 weeks PMA and none at PMA <32 weeks.

Conclusions
In the investigated cohorts, preterm infants with GA ≥30 weeks carried a very low or no risk for developing treatment-requiring ROP unless additional risk factors were present, and no treatment was performed earlier than 32 weeks PMA. These findings contributed to the recent revision of the German ROP screening criteria.

Financial Disclosure
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**Purpose**
Angiopoietin-2 (Ang-2) and vascular endothelial growth factor-A (VEGF-A) act synergistically to drive angiogenesis, with Ang-2 first destabilising vessels and VEGF-A driving proliferation. Faricimab, a bispecific antibody that targets both Ang-2 and VEGF-A, demonstrated improvement in best-corrected visual acuity and durability up to every 16 weeks versus intravitreal anti-VEGF monotherapy in phase 2 and ongoing phase 3 clinical trials in patients with neovascular age-related macular degeneration (TENAYA: NCT03823287; LUCERNE: NCT03823300) and diabetic macular edema (YOSEMITE: NCT03622580; RHINE: NCT036222593). However, little is known regarding the role for Ang-2 in vascular permeability and inflammation. To explore the therapeutic potential of targeting Ang-2 and VEGF-A in diseases with vessel destabilisation and retinal inflammation, we explored the use of a dual Ang-2/VEGF-A inhibitor in 2 in vivo animal models: the retinal ischaemia/reperfusion (I/R) injury mouse model to assess vascular permeability, and the JR5558 mouse model of spontaneous neovascularisation (sCNV) to investigate inflammation.

**Methods**
In the I/R mouse model, immunoglobulin G (IgG) control antibody, anti–VEGF-A, anti–Ang-2 and dual anti–Ang-2/VEGF-A antibodies were intravitreally injected 2 days before I/R injury. Retinal ischaemia was transiently induced by injection of saline into the anterior chamber to raise the intraocular pressure of C57BL/6J mice for 75 minutes followed by natural reperfusion. Sham treatment was needle puncture. Retinal accumulation of fluorescein isothiocyanate—labelled bovine serum albumin at 48h after I/R injury was used as a measure of retinal vascular permeability. A DNA fragmentation assay was used to evaluate ongoing cell death at 48h after injury. In regards to retinal inflammation, JR5558 sCNV mice were treated intraperitoneally at postnatal days P45 and P52 with mouse cross-reactive tool antibodies against VEGF-A, Ang-2, or both (bispecific anti–Ang-2/VEGF-A antibody), and IgG as control. Subretinal inflammatory cell infiltration, detected by Iba1, CD45 and CD11b immunostaining, was evaluated by flat-mounted retinal pigment epithelium (RPE)/choroid histology at 1, 3, and 5 weeks post treatment to assess immediate and long-term effects on the number of inflammatory cells around lesions.

**Results**
After I/R injury, Ang-2/VEGF-A dual inhibition acted synergistically to significantly prevent retinal vascular permeability by 64%, whereas anti–VEGF-A produced a 37% reduction and anti–Ang-2 monotherapy produced no statistically significant change in leakage prevention. Likewise, Ang-2/VEGF-A dual inhibition significantly reduced ongoing cell death by 47%, whereas VEGF-A and Ang-2 monotherapies provided no significant protection. In the JR5558 sCNV model, treatment with the bispecific anti–Ang-2/anti–VEGF-A antibody significantly reduced the number of Iba1+ microglia/macrophages on the RPE/choroid and around lesions versus IgG control at 1 and 3 weeks post treatment, whereas the effect of anti–VEGF-A and anti–Ang-2 mono-target therapies was not significant. At 5 weeks post treatment, only anti–Ang-2- and anti–Ang-2/VEGF-A–treated mice showed significant reductions in the number of Iba1+ microglia/macrophages versus IgG control. Anti–VEGF-A treatment alone did not prevent subretinal infiltration of Iba1+ immune cells. Similarly, the number of CD45+ and CD11b+ inflammatory cells on the RPE/choroid and around lesions was significantly reduced only with Ang-2/VEGF-A inhibition relative to untreated control.

**Conclusions**
In conclusion, these results indicate that inhibiting Ang-2 and VEGF-A simultaneously produced synergistic effects in the retinal I/R injury model in preventing retinal vascular leakage and cell death that were superior to Ang-2 and VEGF-A mono-target therapies. In the sCNV model, experiments further elucidated the potential role of Ang-2 inhibition alone and in combination with anti–VEGF in reducing inflammation in the retina, and demonstrated that the prolonged anti-inflammatory effect was driven by Ang-2 neutralisation. Indeed, dual Ang-2/VEGF-A inhibition was superior to VEGF-A monotherapy in causing sustained prevention of subretinal cellular infiltration on the RPE/choroid and around lesions. The sustained anti-inflammatory effects of the dual therapy during CNV suggest that the prolonged inflammation might also be driven by Ang-2. In summary, dual Ang-2/VEGF-A neutralisation may lead to a more sustained stabilisation of vessels as opposed to VEGF-A inhibition alone, which would be in line with the recent phase 3 clinical data that demonstrated sustained efficacy of faricimab versus intravitreal anti-VEGF mono-target therapy and extended durability up to every 16 weeks.
Efficacy, Safety, and Durability of Faricimab in Diabetic Macular Edema: One-Year Results From the Phase 3 YOSEMITE and RHINE Trials

Purpose
Faricimab is a novel bispecific antibody designed to inhibit both angiopoietin and vascular endothelial growth factor (VEGF)-A, reduce vascular leakage and inflammation, promote vascular stability, and improve outcomes and durability beyond anti-VEGF monotherapy for diabetic macular edema (DME). The phase 3 YOSEMITE and RHINE trials aim to assess the efficacy, safety, and durability of intravitreal faricimab versus aflibercept in patients with DME.

Setting/Venue
YOSEMITE (NCT03622580) and RHINE (NCT03622593) are identical, randomized, double-masked, active comparator-controlled, 100-week, phase 3 trials of faricimab in treatment-naïve and previously anti-VEGF-treated patients with DME.

Methods
Patients were randomized 1:1:1 to faricimab 6.0 mg every 8 weeks (Q8W) after 6 initial Q4W doses, faricimab 6.0 mg per personalized treatment interval (PTI) after 4 initial Q4W doses, or aflibercept 2.0 mg Q8W after 5 initial Q4W doses. The PTI algorithm is a protocol-driven regimen based on the treat and-extend concept, with dosing intervals adjusted in 4-week increments (Q4W up to Q16W) using prespecified best corrected visual acuity (BCVA) and central subfield thickness (CST) criteria. The primary efficacy endpoint was mean change in BCVA from baseline at 1 year, averaged over weeks 48, 52, and 56. Noninferiority in the intention-to-treat (ITT) population, followed by superiority in treatment-naïve patients, was assessed for each faricimab arm against aflibercept. Secondary endpoints included the proportion of patients with ≥2-step Early Treatment Diabetic Retinopathy (ETDRS)-Diabetic Retinopathy Severity Scale improvement from baseline, the proportion of patients gaining or avoiding a loss of ≥15 ETDRS letters from baseline, change in CST from baseline, and the proportion of patients in the PTI arm on Q4W, Q8W, Q12W, or Q16W dosing at 1 year. Safety was assessed by the incidence and severity of ocular and nonocular adverse events.

Results
In total, 1891 patients with DME were enrolled in YOSEMITE (N = 940) and RHINE (N = 951). Baseline characteristics were well balanced across treatment arms. Both trials met the primary endpoint; mean BCVA gains from baseline at 1 year with faricimab Q8W (+10.7 and +11.8 ETDRS letters in YOSEMITE and RHINE, respectively) or faricimab PTI up to Q16W (+11.6 and +10.8 ETDRS letters) were noninferior to aflibercept Q8W (+10.9 and +10.3 ETDRS letters). In treatment-naïve patients, mean BCVA gains at 1 year were consistent with the ITT population and no faricimab arm showed superiority to aflibercept. Mean change in CST over 1 year consistently favored faricimab over aflibercept. Similarly, absence of protocol-defined DME (CST < 325 µm) and absence of intraretinal fluid during year 1 were achieved by more patients treated with faricimab versus aflibercept. Notably, 52.8% (YOSEMITE) and 51.0% (RHINE) of patients in the faricimab PTI arm achieved Q16W dosing at week 52, while 73.8% and 71.1%, respectively, achieved ≥Q12W dosing. In both trials, faricimab was well tolerated; intraocular inflammation event rates were low and no cases of vasculitis or occlusive retinitis were reported.

Conclusions
Faricimab Q8W or per PTI, a personalized regimen based on individual responses to treatment, offered noninferior vision gains compared with aflibercept Q8W, while demonstrating improvements in anatomic outcomes and the potential for extended (up to Q16W) dosing at 1 year.
**Title**

Faricimab Personalised Treatment Interval (PTI) Dosing Dynamics Illustrated With Patient Case Profiles: YOSEMITE and RHINE Phase 3 Diabetic Macular Edema (DME) Trials

**Purpose**

Faricimab is a novel bispecific antibody designed to inhibit angiopoietin-2 (Ang-2) and vascular endothelial growth factor (VEGF)-A. Dual Ang-2/VEGF-A inhibition promotes enhanced vascular stability, which can translate to anatomic and durability benefits beyond that achievable with VEGF-A inhibition alone. Here, we present a visualisation of the faricimab PTI dosing dynamics, illustrated with profiles of patients with DME from the phase 3 YOSEMITE/RHINE trials. Faricimab PTI dosing aimed to tailor treatment intervals per individual patient needs to improve and maintain vision gains, while reducing treatment burden. Durability of faricimab effect in the PTI arm was a key objective of YOSEMITE/RHINE.

**Setting/Venue**

YOSEMITE (NCT03622580) and RHINE (NCT03622593) are identical, randomised, double-masked, active comparator-controlled, 100-week, phase 3 trials of faricimab in patients with DME. Eyes were randomised (1:1:1) into 3 arms: faricimab 6.0 mg every 8 weeks (Q8W), faricimab 6.0 mg PTI or the control arm, aflibercept 2.0 mg Q8W.

**Methods**

The PTI algorithm is a protocol-driven regimen based on the treat-and-extend concept, with dosing intervals adjusted in 4-week increments (up to Q16W) using prespecified central subfield thickness (CST) and best-corrected visual acuity (BCVA) criteria. Treatment intervals could be extended after week 12 if a reference CST value below the threshold of 325 μm was achieved. Thereafter, dosing interval decisions by automated interactive voice/web response system (IxRS) were based on change in CST from this reference value, with intervals extended by 4 weeks, reduced by 4 or 8 weeks or maintained based on both CST assessed by masked harmonised central reading centre graders and BCVA assessed by masked study site assessors. Only CST and BCVA at treatment visits, not sham visits, were considered by the IxRS. To maintain masking, eyes received sham injections at study visits when not receiving treatment. Additional anatomical endpoints were evaluated using optical coherence tomography (OCT), colour fundus photography and fundus fluorescein angiography, with optional OCT angiography. Achievement of extended treatment intervals was assessed at week 52.

**Results**

Overall, 1891 patients were enrolled in YOSEMITE and RHINE (N = 940 and 951, respectively). Among patients assigned to the faricimab PTI arm, greater than 70% achieved ≥Q12W treatment intervals and greater than 50% achieved the Q16W treatment interval at week 52, whereas 12% and 16% of patients were on the Q4W and Q8W treatment intervals, respectively, at week 52. Here, we present a post hoc analysis of the overall dynamics of faricimab PTI dosing from baseline up to week 52. Specifically, representative cases will be described and associated retinal images presented for the following PTI scenarios: (A) CST threshold met at week 12 and rapid, immediate extension to Q16W by week 32; (B) criteria for extension met at a later timepoint, with Q16W interval reached more slowly; and (C) scenario where patients fluctuate between extended and more frequent treatment intervals throughout the first year.

**Conclusions**

This post hoc analysis of individualised treatment frequency dynamics illustrates how the faricimab PTI algorithm was used effectively to optimise treatment intervals according to the heterogeneous needs of patients with DME. The PTI faricimab arm demonstrated strong durability of faricimab effect, with 52% of patients on the Q16W treatment interval and 72% of patients on the Q12W or Q16W treatment intervals at week 52.
The German ROP Registry – data from treated retinopathy of prematurity between 2011 and 2020

Purpose
Retinopathy of prematurity (ROP) can be a blinding disease with lifelong impact. Over the last decade, anti-VEGF treatment has been investigated in several randomized controlled trials and has evolved into a new treatment option for ROP. Real-life data on anti-VEGF in ROP, however, is scarce. The low incidence of treatment-requiring ROP makes it difficult for individual hospitals alone to make scientific use of their clinical data. To address this situation, the German Retina.net ROP Registry was launched in 2011 with the aim of analyzing treatment patterns, demographic parameters and long-term outcomes of treated ROP. The current analysis presents the registry data of children born between 2011 and 2020.

Setting/Venue
19 German centers contributed data to the non-interventional Retina.net ROP registry. Before a child was included in the prospective, pseudonymized part of the registry, parents were informed about the registry and their written informed consent was obtained. Patients could also be entered retrospectively, in which case the data was entered anonymized.

Methods
Registry data from all infants born between 2011 and 2020 was included in the current analysis. We examined whether demographic parameters (gestational age at birth, birth weight, postmenstrual age at treatment, weight at treatment, weight gain from birth to treatment) as well as the applied treatment patterns changed during this 10-year period. Descriptive statistics were used to analyze the data, which include number (N), mean and standard deviation (SD).

Results
A total of 353 infants (691 eyes) with treated ROP were documented in the registry. 157 children were female (45%; N=351) and 158 were transferred from an external hospital to the documenting center for ROP treatment (45%; N=348). Treated infants had a mean gestational age of 25.3 weeks (±1.8) (N=352) and a mean birth weight of 691 g (±223) (N=346). At treatment, mean postmenstrual age was 37.7 weeks (±3.2) (N=352), mean postnatal age 12.4 weeks (±3.1) (N=353) and mean weight 2310 g (±746) (N=159), with weight gain from birth to treatment averaging 19 g per day (±6.2) (N=158). Over the observed ten-year period the described demographic and treatment parameters remained stable. In contrast to the demographic parameters, the type of treatment changed significantly over the observed ten-year period. While in 2011 anti-VEGF treatments accounted for only 14% of all treatments, the proportion of anti-VEGF treatments increased to 61% in year 2020. While bevacizumab was predominantly used for anti-VEGF therapy from 2011 - 2018, all but two documented anti-VEGF treatments in 2019 and all anti-VEGF treatments in 2020 were performed with ranibizumab.

Conclusions
To our knowledge this is next to the Swedish SWEDROP registry the longest period of multi-center real-life data on treated ROP. A major change over this 10-year period was seen in the treatment patterns used. While laser treatment rates declined, anti-VEGF treatment rates increased significantly. Following the approval of ranibizumab for ROP in Europe in 2019, all anti-VEGF treatments in the registry were performed with ranibizumab. These results may be representative for Germany but may not reflect treatment patterns in other countries. To address this situation, we are currently working on opening the registry for other countries. For reference please see www.eu-rop.org.

Financial Disclosure
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Impact of Foveal Eversion on Functional and Morphological Outcomes in Patients with Central and Branch Retinal Vein Occlusion

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Purpose
To investigate the influence of the OCT biomarker foveal eversion (FE) on treatment response and persistence of macular edema (ME) due to retinal vein occlusion.

Setting/Venue
Department of Ophthalmology, Scientific Institute San Raffaele Hospital, University Vita-Salute, Milan, Italy.

Methods
We retrospectively studied 168 eyes with Central Retinal Vein Occlusion (CRVO) and 116 eyes with Branch Retinal Vein Occlusion (BRVO). The inclusion criterion was the presence of a clinically relevant macular edema. All patients received treatment with intravitreal anti-VEGF, dexamethasone, or both. From structural Optical Coherence Tomography images (Spectralis HRA, Heidelberg Engineering; Heidelberg, Germany), we extracted the presence of foveal eversion, defined as a complete convex profile of the central fovea, the behavior of macular edema and central macular thickness (CMT) during 24 ± 30 months of follow-up.

Results
64 out of 168 CRVO eyes (38%) and 25 out of 116 BRVO eyes (22%) showed foveal eversion. Eyes with and without foveal eversion resulted in age- and sex-matched (p > 0.05), as the percentage of iRVO and laser treatment was similar between the two groups (p > 0.05), as the percentage of eyes underwent cataract surgery (p > 0.05). In CRVO eyes, the mean number of injections required from the FE eyes was higher (12 ± 8 vs. 6 ± 7) (p < 0.001). The mean baseline LogMAR BCVA was similar with 12-month follow-up (p > 0.05), while the last LogMAR BCVA showed a significant worsening in eyes with FE (p < 0.001). The mean CMT was significantly higher in eyes with FE at baseline, after 12 months, and at last follow-up (p < 0.001). Comparably, in BRVO eyes, the mean number of injections required from the FE eyes was higher (10 ± 9 vs 5 ± 5), the mean LogMAR BCVA was higher in eyes with FE at baseline and after 12-months follow-up (p < 0.01), as the mean CMT was significantly higher in eyes with FE at baseline, after 12 months and at last control (p < 0.001).

Conclusions
The eversion of the foveal profile is a poorly investigated structural OCT biomarker. We showed a clinical relevance of FE, associated with higher percentage of ME persistence in retinal vein occlusion. In the perspective of even more optimized and personalized therapeutic strategies, foveal eversion might represent an easily evaluable biomarker for the management of CRVO and BRVO eyes. The anatomical explanation of a chronic complete eversion of the foveal profile is not completely clear; it could be the final effect of a combination of significant retinal structural loss. Considering the role of intraretinal glial cells, in particular Müller cells, in the metabolic functions of the retina, including regulation of permeability, release of growth factors and other inflammatory mediators, this process might be related to a strong involvement of these cells. This specific cytotype is densely present in the fovea, and it might be responsible for a remarkable loss of foveal structural and functional integrity, leading to the onset of foveal eversion.

Financial Disclosure
None
Intravitreal aflibercept for the treatment of patients with diabetic macular edema in routine clinical practice in Latin America: The AQUILA study

**Purpose**
The purpose of AQUILA was to evaluate the clinical effectiveness (functional and anatomic outcomes) and safety of intravitreal aflibercept (IVT-AFL) in patients with diabetic macular edema (DME) and with neovascular age-related degeneration (nAMD) in routine clinical practice in Latin America. The study was also designed to understand how patients with DME and nAMD are treated with IVT-AFL in Latin America, including treatment regimens utilized and the reasons for changes in treatment regimens or treatment discontinuation. The results for the patients with DME are presented here.

**Methods**
Treatment-naïve and pre-treated patients with DME (aged ≥18 years) were enrolled from April 2018 to September 2019. Patients became eligible for the study once the decision was made to treat with IVT-AFL according to routine clinical practice and local prescribing information. Decisions regarding IVT-AFL treatment were made at the discretion of the prescribing physician, according to their medical practice. The primary efficacy endpoint was change in best-corrected visual acuity (BCVA; Early Treatment Diabetic Retinopathy Study [ETDRS] letters) from baseline, number of visits and IVT AFL injections, mean duration of treatment intervals, and the proportions of patients with no fluid on optical coherence tomography, a Snellen equivalent of 20/40 or better (~70 ETDRS letters), and ≥15 ETDRS letter gain. Patients who received at least one IVT-AFL injection and had a BCVA assessment in the study eye at both baseline and at least one follow-up visit were included in the full analysis set (FAS: Argentina, n=136; Mexico, n=95; Colombia, n=18; Costa Rica, n=9).

**Results**
Of 319 patients, 258 (181 treatment-naïve; 77 pre-treated) were included in the FAS (mean age: 64 years; male: 56%; type 2 diabetes: 93%) and 216/319 patients (68%) completed 12 months’ follow-up. Median duration from diagnosis to IVT-AFL treatment was 1.8 months (treatment-naïve) and 16.0 months (pre-treated) and the mean±SD number of IVT AFL injections by M12 was 3.7±1.8 (treatment-naïve) and 4.0±2.2 (pre-treated). Overall, 32/258 patients (12%) received ≥5 initial monthly IVT-AFL injections (13/181 treatment-naïve; 19/77 pre-treated) and 14/258 (5%) received ≥8 injections by M12 (7/181 treatment-naïve; 7/77 pre treated). Mean BCVA improved from baseline to M12 by +8.1±17.7 (treatment-naïve; baseline: 54.5±19.4) and +4.6±15.4 letters (pre-treated; baseline: 52.9±18.6). BCVA changes from baseline to M12 were +11.0±8.1 (treatment-naïve) and +11.5±14.4 (pre treated) in patients who received ≥5 initial monthly doses and +7.8±18.2 (treatment-naïve) and +2.3±15.2 (pre-treated) in patients who received <5 injections. By M12, 33% of patients had BCVA improvements of ≥15 letters (35% treatment-naïve; 27% pre-treated) and 45% had a BCVA ≥70 letters (treatment-naïve: 51% [from 28% at baseline]; pre-treated 32% [from 22% at baseline]). By M12, mean CRT decreased by -106.1±158.2 μm (treatment-naïve; baseline: 387.7±144.6) and -86.7±154.6 μm (pre treated; baseline: 422.7±146.1). No new safety signals were observed.

**Conclusions**
AQUILA is the first study to assess the use of IVT-AFL in routine clinical practice in Latin America. In AQUILA, 12% of patients with DME received ≥5 initial monthly doses of IVT-AFL, and 5% received ≥8 injections in the first year of treatment. Functional and anatomic outcomes improved during 12 months’ treatment with IVT-AFL. Improvements in BCVA were numerically greater in treatment-naïve patients than pre-treated patients and in patients who received ≥5 initial monthly injections than those who did not. Thus, in real-world studies, patients treated regularly and proactively with IVT-AFL have the potential to achieve outcomes consistent with those observed in interventional studies. The safety profile of IVT-AFL was consistent with previous studies.

**Financial Disclosure**
Francisco J. Rodriguez: Consultant: Bayer, Novartis, and Roche; Speaker: Bayer, Novartis, and Roche; Research funds: Novartis
Tobias Machewitz: Employee: Bayer AG, Berlin, Germany
Margarete Mueller: Employee: Bayer AG, Berlin, Germany
### Title
OCTA metrics monitor severity progression of Diabetic Retinopathy – 3-year longitudinal study

### Purpose
To examine retinal vessel closure metrics and neurodegenerative changes occurring in the initial stages of nonproliferative diabetic retinopathy (NPDR) and severity progression in a three-year period.

### Setting/Venue
Clinical Trial Center – AIBILI, Coimbra - Portugal

### Methods
Three-year prospective longitudinal observational cohort of eyes/patients with type 2 diabetes (T2D) using spectral domain-optical coherence tomography (SD-OCT) and OCT-Angiography (OCTA). Eyes were examined four times with one-year intervals. OCTA vessel density maps of the retina were used to quantify vessel closure. Thickness of the ganglion cell inner plexiform layer (GCL+IPL) was examined to identify retinal neurodegenerative changes. Diabetic retinopathy ETDRS classification was performed using the seven-field ETDRS protocol.

### Results
A total of 78 eyes/patients, aged 52 to 80 years, with T2D and ETDRS grades from 10 to 47 were followed for 3 years with annual examinations. A progressive increase in retinal vessel closure demonstrated by higher decreases in vessel density (VD) correlated with retinopathy worsening identified by step-changes in ETDRS severity scale (p < 0.001). This decrease in VD varied between different individuals. No apparent correlation was found between neurodegenerative changes and retinopathy progression.

### Conclusions
Retinal vessel closure in NPDR correlates with DR severity progression. Our findings provide evidence to support that OCTA metrics of vessel closure may be used as a surrogate for DR severity progression.

### Financial Disclosure
Consultant: Carl Zeiss Meditec, Ciana Therapeutics, Alimera Sciences, Boehringer Ingelheim, Allergan, Bayer, Gene Signal, Novartis, Pfizer, Oxular, Roche, Sanofi, Vifor Pharma, Adverum Biotechnologies.
**Title**
Targeting plasma kallikrein with a novel bicyclic peptide inhibitor (THR-149) reduces retinal inflammation and reactive gliosis in a diabetic rat model

**Purpose**
Anti-VEGF therapies are the current mainstay treatment for diabetic macular edema (DME), although it is now established that a significant number of patients respond sub-optimally or not at all to VEGF inhibition. Alternative therapeutic strategies for anti-VEGF treatment for DME are therefore urgently needed. Elevated plasma kallikrein (PKal) is a known pathogenic factor in DME where it drives VEGF-independent retinal inflammatory processes and vasopermeability. In the current study, we determined the potential of THR-149, a novel potent and highly specific peptide inhibitor for PKal, to prevent key pathologies associated with DME in diabetic rats, especially in relation to elements of the neurovascular unit, such as retinal inflammation and loss of normal Müller cell homeostatic function.

**Setting/Venue**
The efficacy of intravitreal (IVT) administration of THR-149 was evaluated in a diabetic streptozotocin (STZ)-induced rat model, in which the impact on glial and immune cell function in the diabetic retina was explored. This preclinical study was conducted at Oxurion, NV (Leuven, Belgium).

**Methods**
Following STZ-induced diabetes in the rat, THR-149 (12.5 µg/eye) and its vehicle was administered in both eyes either via a single or via 3 consecutive IVT injections (with 1-week interval, n=7 rats/group). Untreated, non-diabetic rats served as a control (n=5 rats). At 4 weeks post-diabetes, the effect of all groups was compared by histological analysis of the retina for Iba1-positive immune cells, vimentin-positive Müller cells, potassium- and water homeostasis-related channels (Kir4.1 and AQP4, respectively) at the glio-vascular interface. The Iba1-, vimentin- and Kir4.1-positive area in the retina was investigated by measuring the ratio of the immuno-positive area over the retinal area per image, whereas the AQP4-positive area was measured over the ONL area and expressed as percentage. Iba1-positive cells were also counted, and further classified as activated or non-activated cells, based on their morphology. Statistical analysis was performed with a one-way analysis of variance using a Bonferroni multiple comparison test.

**Results**
Analysis of the Iba1 staining in the retina following 4 weeks of diabetes showed a significant increase in the Iba1-positive area and cell number when compared to non-diabetic controls (p-value smaller than 0.05). Single and repeated administration of THR-149 reduced the inflammatory positive area (p-value smaller than 0.05) when compared to vehicle, as well as the total number and activation state of immune cells, a key readout of retinal inflammation. Repeated administration of THR-149 also reduced the diabetes-induced increase of vimentin-positive cells (reactive gliosis) at 4 weeks after diabetes onset (p-value smaller than 0.05) versus vehicle, whereas no significant difference following a single administration of THR-149 was seen (p=0.99) versus vehicle. At the molecular level, reduced Kir4.1-channel levels in the diabetic retina were restored to control non-diabetic levels in the presence of repeated THR-149 (p-value smaller than 0.01) compared to vehicle. In contrast, little to no effects were observed on the diabetes-induced AQP4-channel levels by THR-149.

**Conclusions**
These data demonstrate that repeated administration of THR-149, a novel bicyclic peptide inhibitor of PKal, reduced several DME-related key pathologies, such as activation of retinal microglia/macrophages and Müller cells in the diabetic rat retina and restored the reduced expression of Müller cell Kir4.1-positive channels. These observations indicate that modulation of the PKal-pathway using THR-149 has clinical potential to treat patients with DME and that potentially repeated IVT injections are needed to achieve a more complete therapeutic effect in elements of the neurovascular unit.

**Financial Disclosure**
Tine Van Bergen, Isabelle Etienne, Jean H.M. Feyen, Alan Stitt report direct financial relationship with Oxurion NV.
Exploring Ang-2 Signalling in Vascular Stability in Patients With DME Receiving Faricimab in Phase 2 and Phase 3 Trials

Faricimab, a bispecific antibody currently in year 2 of phase 3 trials, targets both angiopoietin-2 (Ang-2) and vascular endothelial growth factor-A (VEGF-A), which are key drivers of vascular instability. Faricimab demonstrated improvement in best-corrected visual acuity and sustained efficacy up to every 16 weeks (W) versus anti-VEGF monotherapy in phase 2 and 3 clinical trials in patients with diabetic macular edema (DME). The purpose of these analyses is to explore the impact of dual inhibition of Ang-2 and VEGF-A by faricimab on vascular stability.

Methods
In BOULEVARD, treatment-naive patients were randomised 1:1:1 to intravitreal ranibizumab 0.3 mg, faricimab 1.5 mg or faricimab 6.0 mg, administered every 4W for 20W, followed by a 16W off-treatment observation period to assess durability. In a post hoc analysis of BOULEVARD, sustained retinal stability, defined as the occurrence and maintenance (< 10% worsening) of CST ≤ 325 µm to W24 was assessed in the intent-to-treat population. In a separate analysis of a subset of patients from BOULEVARD, inflammatory biomarker (ICAM-1) levels in aqueous humor were assessed from baseline to W28. Vascular stability was also assessed in the phase 3 trials. In a new set of preclinical experiments, JR5558 mice were treated intraperitoneally with antibodies against Ang-2, VEGF-A or both (bispecific anti–Ang-2/anti–VEGF-A antibody [VA2]). Untreated and immunoglobulin G (IgG)-treated mice were used as controls. Vascular stability was evaluated by examining neovascular leakage, subretinal infiltration of inflammatory cells (Iba1+, CD11b+, CD45+) and fibrosis using fluorescein angiography (FA) and fibronectin staining on the retinal pigment epithelium/choroid at baseline and 1W (PT1), 3W (PT2) and 5W (PT3) post treatment.

Results
In a post hoc analysis of BOULEVARD, > 50% of patients achieved sustained retinal stability through W24 beginning at W8, W16 (faricimab 6.0, 1.5 mg) and W20 (ranibizumab). In a separate analysis, mean (SD) % ICAM-1 levels versus baseline increased by 50 (75) (ranibizumab) and decreased by 56 (20) (faricimab 1.5 mg) and 42 (54) (faricimab 6.0 mg) at W28. Phase 3 vascular stability data will be presented. In preclinical experiments, significant reduction of FA-evaluated CNV leakage (P<0.05 to P<0.001) was observed in JR5558 mice treated with Ang-2, VEGF-A or VA2 versus controls at PT1; only Ang-2– and VA2–treated mice showed significant reduction in CNV leakage versus controls (P<0.05 to P<0.001) at PT2/PT3. Treatment with VA2 antibody, not anti–VEGF-A or anti–Ang-2 alone, significantly reduced Iba1+ cell infiltration versus IgG control at PT1/PT2 (P<0.05) and CD45+ CD11b+ cell infiltration versus untreated control at PT1 (P<0.05). At PT3, only anti–Ang-2– and VA2–treated mice showed significant reduction in number of Iba1+ macrophages (P<0.0001) versus IgG control. There was significant reduction in fibronectin+ area with VA2 (P<0.01) and anti–Ang-2 (P<0.001) versus IgG at PT1, not with anti–VEGF-A alone. This was maintained only with VA2 at PT2 (P<0.01) and PT3 (P<0.05).

Conclusions
We present post hoc analyses of the phase 2 BOULEVARD trial, in which patients receiving faricimab achieved sustained retinal stability earlier than those receiving ranibizumab, and showed reductions in inflammatory biomarkers versus ranibizumab. In phase 3, faricimab showed greater anatomic improvement versus aflibercept and potential for improved durability up to every 16W due to vascular stability by Ang-2 inhibition. Furthermore, research suggests that Ang-2 blockade drives vascular stability. These data support the involvement of Ang-2 signalling in vascular stability in patients with DME.
A Novel Bicyclic Peptide Inhibitor of Plasma Kallikrein, THR-149, for the Treatment of Diabetic Macular Edema (DME): Clinical and Pre-Clinical Evidence

Levels of plasma kallikrein (PKal) have been found to be elevated in the eyes of patients with diabetic macular edema (DME) and have been shown to drive DME-related pathogenic inflammatory processes and vascular permeability in a vascular endothelial growth factor (VEGF)-independent fashion. THR-149, a novel bicyclic peptide inhibitor of PKal, is being developed as a potential treatment for patients with center-involved DME (CI-DME). A phase 1 clinical study has shown that a single intravitreal (IVT) injection of THR-149 is safe and well tolerated. Preliminary evidence of efficacy was also demonstrated, especially with regard to improvements in best-corrected visual acuity (BCVA). Revisions in central subfield thickness (CST), however, were inconclusive. Using a streptozotocin (STZ)-induced rat model of diabetes, the effects of single versus multiple injections of THR-149 on retinal thickness were examined. These clinical and preclinical results have supported the design of the ongoing phase 2 clinical trial.

Methods
The phase 1 study of THR-149 was conducted in adult subjects with CI-DME with previous response to anti-VEGF agents and/or corticosteroids. The study used an open-label, 3+3 dose-escalation design which included 3 dose cohorts of THR-149 (0.005, 0.022 and 0.13 mg) with a 3-month follow-up period after a single IVT administration. The primary endpoint was the incidence of dose-limiting toxicities (DLTs). The secondary endpoints included incidence of adverse events (AEs) and occurrence of laboratory abnormalities. Preliminary evidence of efficacy was assessed through the examination of changes from baseline in BCVA and CST. In preclinical studies, the effects of THR-149 and aflibercept on retinal thickness (RT) were examined (n=7 rats/group). Following the induction of diabetes with STZ, THR-149 (12.5 µg/eye) or its vehicle was administered via a single or 3 weekly IVT injections. As an active control, diabetic rats were intraperitoneally administered aflibercept (2 mg/kg) or its vehicle 3 times per week for 3 weeks. RT was quantified at 4 weeks after diabetes onset, and also in untreated, nondiabetic control animals (n=5), by measuring the thickness of the total retina on FITC-BSA perfused histological tissue sections. Data were analyzed via one-way ANOVA and Bonferroni multiple comparison tests.

Results
In the phase 1 study of THR-149, 3 subjects each in the two lower dose cohorts and 6 subjects in the high dose cohort were enrolled. There were no DLTs or serious AEs and all subjects completed all study visits. Mean change from baseline in BCVA was rapid with an increase of 3.9 ETDRS letters at Day 1 after injection, peaking at 7.5 letters at Day 14 with gains maintained at 6.4 letters at Month 3. A mean decrease in CST from baseline of 18 µm was seen at Day 1. At all later time points, mean increases from baseline of 10-30 µm were observed. In diabetic rats, a single IVT administration of THR-149 did not have a significant effect on total RT versus vehicle-treated eyes, whereas, three weekly IVT administrations of THR-149 reduced RT by 50 µm (p<0.05) versus vehicle-treated eyes. RT was also reduced by 42 µm compared to vehicle in the active control rats receiving repeated intraperitoneal administrations of aflibercept (p<0.001). Given these findings, the phase 2 clinical study of THR-149 is examining the safety and efficacy of three monthly IVT injections of THR-149 in subjects with CI-DME.

Conclusions
The phase 1, first-in-human study of THR-149 evaluated its safety and preliminary efficacy in the treatment of subjects with CI-DME who had previously been treated with anti-VEGF agents or corticosteroids. At all dose levels tested, a single IVT injection of THR-149 was found to be safe and well tolerated. Preliminary evidence of efficacy was shown by a rapid gain in BCVA which was maintained up to the end of the study (Month 3), however, CST changes were inconclusive. While a single administration of THR-149 in STZ diabetic rats did not have an effect on RT, three weekly administrations of THR-149 produced a significant decrease in RT. Based on these clinical and preclinical results, an ongoing phase 2 study is examining the safety and efficacy of three monthly injections of THR-149 in subjects with CI-DME with a history of suboptimal response to anti-VEGF agents, including aflibercept.

Purpose
Evidence of efficacy was also demonstrated, especially with regard to improvements in best-corrected visual acuity (BCVA). Reductions in central subfield thickness (CST), however, were inconclusive. Using a streptozotocin (STZ)-induced rat model of diabetes, the effects of single versus multiple injections of THR-149 on retinal thickness were examined. These clinical and preclinical results have supported the design of the ongoing phase 2 clinical trial.

Setting/Venue
The prospective, phase 1 clinical study of THR-149 was conducted at six retina practices in the United States. The preclinical study of the effects of THR-149 in a STZ diabetic rat model was conducted at Oxurion, NV (Leuven, Belgium). The phase 2 clinical study is being conducted in eight countries in Europe and the United States.

Financial Disclosure
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Title
Retrospective review of persistent subretinal fluid following surgery in patients with rhegmatogenous retinal detachment

Purpose
To describe the incidence, characteristics and possible factors associated of persistent subretinal fluid (SRF) following surgery of rhegmatogenous retinal detachment (RRD).

Setting/Venue
Single-center, multi-surgeon retrospective analysis of case series with SRF following RRD repair, either with 23 G pars plana vitrectomy (PPV) or 23G PPV combined with a scleral buckle, at a major tertiary hospital in Barcelona, Spain.

Methods
160 consecutive patients with RRD underwent either 23G PPV or 23PPV combined with a scleral buckle in Santa Creu i Sant Pau Hospital (Barcelona) were retrospectively reviewed. Different parameters were analysed regarding RRD characteristics, type of surgery, localization, SRF extension and course length. Postoperative outcomes including visual acuity (VA) and anatomical changes, using spectral domain optical coherence tomography (SD-OCT) and fundus autofluorescence (FAF) images, were also reported. All patients were treated intraperatively with endophotocoagulation and gas tamponade with 24% SF6 at the end of surgery except for one who was treated with scleral buckle and cryopexy.

Results
A total of 24/160 eyes were identified with persistent SRF (15%) with an average age of 61.5y (range 40-81y). 11 of these eyes were treated with 23G VPP alone, 12 were treated with 23GVPP and scleral buckle combined and just 1 was treated with scleral buckle alone. Of all these patients, 19/160 were macula-off RRD (11.9%) and 5/160 were macula-on RRD (3.1%). SRF was observed clinically and in SD-OCT in an average of 1.9 months after surgery (range 1-5.5 months). Subfoveal localization was detected in 6/24 patients (25%), extrafoveal localization in 6/24 patients (25%) and a combination of the two in 12/24 patients (50%). FAF images were obtained from some of the patients, showing complete SRF extension. SRF of all patients resolved starting at the fourth month, with an average of 8.7 months (range 4-21 months). Statistical significative difference was found between different treatment groups, presenting resolution in 10 months in those treated with 23G VPP and only in 5 months in those treated with 23G VPP combined with scleral buckling (p<0.026, U Mann-Whitney). Finally, the average VA (logMAR) improvement at SRF resolution was of 0.15.

Conclusions
Persistent SRF is frequently found after RRD surgery, in our study the incidence was 15%, and it slowly resolves without any treatment with a good visual prognosis, and it does more rapidly in patients treated with 23G VPP combined with scleral buckling. SD-OCT is strongly recommended in postoperative visits of patients who underwent a previous RRD surgery to exclude SRF. In those patients with extramacular SRF, FAF imaging could have an important role in determining total fluid extension and in monitoring progressive resolution.
Quantification of aerosol production during pars plana vitrectomy and phacoemulsification.

Purpose
Pars plana vitrectomy (PPV) and phacoemulsification are common intraocular surgical procedures that utilise high-speed devices. High-speed devices have the potential to generate aerosols, yet there are few studies demonstrating whether these procedures generate aerosols. This is a pertinent question to answer since there is increasing evidence that the SARS-CoV-2 virus may be transmitted via aerosols. We used an optical particle counter to quantify the degree of aerosol production during simulated PPV and phacoemulsification.

Setting/Venue
Department of Ophthalmology, Royal Derby Hospital, University Hospitals of Derby and Burton NHS Foundation Trust, Derby, UK.

Methods
All procedures were performed on advanced model eyes. The PPV was performed with a 25-gauge set up, using the Alcon CONSTELLATION System. A divide and conquer technique for phacoemulsification was performed with the Alcon CENTURION System. Aerosol production was measured during sculpting and quadrant removal. An optical particle counter was used to measure particle concentration. For each of the three procedures, the particle count was measured at baseline with the vitrector or phaco handpiece deactivated, and then during the procedure with the instrument activated. This was repeated five separate times.

Results
The mean concentration of particles sized 1–5 μm was compared with the corresponding baseline for each procedure. There was no statistically significant change (p=0.14) in the particle concentration during PPV compared to baseline (mean change -129 counts/ft³, SD 174). During sculpting, there was a 193% increase (mean change 1932 counts/ft³, SD 1451) in the particle concentration from the baseline, which was statistically significant (p=0.04). For quadrant removal there was an 83% increase (mean change 817 counts/ft³, SD 697) in the particle concentration from the baseline (p=0.04).

Conclusions
This is one of the first studies to demonstrate that PPV does not generate aerosols under simulated conditions. This may be because the procedure is performed through valved port cannulas, within a closed system, such that any aerosol generated is contained within the eye. Our findings suggest that aerosols may be produced during simulated phacoemulsification, although it is important to note currently there is no evidence demonstrating the presence of SARS-CoV-2 in aqueous humour.

Financial Disclosure
I have no financial relations with any company.
Title
The effect of supervision and out-of-hours surgery on the outcomes of primary macula-on retinal detachments operated by vitreoretinal fellows: A review of 576 surgeries

Purpose
During Bank Holidays and Weekends (BHWE), many primary macula-on retinal detachments (RD) across the United Kingdom are performed unsupervised by experienced vitreoretinal (VR) fellows. We aimed to determine whether fellows in their first year (F1) and second year (F2) could safely operate out of hours independently with remote supervision on primary macula-on retinal detachments.

Setting/Venue
The Birmingham and Midlands Eye Centre in the United Kingdom

Methods
Retrospective consecutive case series of patients attending Birmingham and Midlands Eye Centre from January 2017-July 2020. We evaluated: i) 6-month retinal re-detachment rate and ii) visual outcomes, of F1, F2 and consultants during office hours and BHWE as well as the effects of supervision (consultant present and scrubbed in the operating theatre) versus non-supervision.

Results
For retinal re-detachment rate, no statistical significance was found between: grade of surgeon (p=0.821), whether supervised (p=1.000), whether BHWE (p=1.000), unsupervised-BHWE and supervised-midweek (p=0.757) and unsupervised F1 and F2 (p=1.000). The lack of significance was maintained across a multivariate Cox survival regression analysis that identified high myopia (p=0.041) and C3F8 vs. C2F6 (p=0.028) as risk factors for re-detachment. No difference was detected in level of supervision (15.7% of all cases) between F1 and F2 during BHWE (p=0.761), mid-week (p=0.295), and overall (p=0.228). No difference was found between surgeon grade and logMAR letters gained pre-postoperatively (p=0.834).

Conclusions
A safe VR service can be provided by experienced VR fellows during office-hours, BHWE, supervised or unsupervised, with similar primary-success and visual outcomes to consultants. In our unit, initial intensive supervision and feedback, followed by a gradually increasing degree of independence are fundamental for VR fellows to gain confidence and become safe independent surgeons.

Financial Disclosure
none
**Choroidal morphological and vascular characteristics in patients with macular holes**

**Purpose**
We aimed to evaluate choroidal morphological and vascular features of patients with macular holes compared to contralateral fellow eyes and healthy eyes.

**Setting/Venue**
A retrospective comparative study at a single tertiary center.

**Methods**
Twenty-one patients with macular holes who underwent 25-G vitrectomy surgery between May 2018 and October 2020 were reviewed. The choroid was imaged using enhanced depth imaging (EDI) mode of Spectralis SD-OCT (Heidelberg Engineering, Heidelberg, Germany). Subfoveal, nasal, and temporal choroidal thickness (CT) were measured in foveal (1.5 mm centered on the fovea) regions. The choroidal areas and choroidal vascularity index (CVI) were calculated with ImageJ (National Institutes of Health, Bethesda) software. All choroidal parameters were used to compare with fellow eyes and the eyes of age-, gender-, and systemic comorbidity-matched controls.

**Results**
The macular hole patients include 14 females (66.7%) and 7 males (33.3%) with a mean age of 69.1 ± 4.7 years. The hole size and basal hole diameter were 536.8 ± 131.9 µm and 977.2 ± 230.3 µm, respectively. Successful macular hole closure was achieved after surgery in 18 patients (85.7%). The mean follow-up duration was 14.9 ± 4.1 months. The mean final best-corrected visual acuity (BCVA) values were improved compared with the baseline BCVA from 1.07 ± 0.17 to 0.78 ± 0.35 logMAR. The mean CT and CVI of eyes with macular holes were lower than both fellow eyes and healthy control eyes (p = 0.004 and p = 0.000, respectively). The CVI values had correlation with postoperative logMAR visual acuity (r = −0.498, p= 0.022).

**Conclusions**
This study shows that the mean CT and CVI values decrease in eyes with macular holes. Relatively high CVI values were associated with more significant improvement in final BCVA after macular hole surgery.

**Financial Disclosure**
The authors declared no potential conflicts and funding source.
Title
Contribution of using epiretinal human anterior lens capsule cut by femtosecond laser to treat complex macular holes: about 3 cases

Purpose
Very large and/or old macular holes (MH), recurrent or persistent MH after conventional treatment including internal limiting membrane (ILM) inverted flap, or MH complicating severe rhegmatogenous retinal detachment (RRD) have poor prognosis, resulting in permanent loss of vision, or recurrent RRD. To close complex MH, using subretinal human anterior or posterior lens capsule (HALC/HPLC) has been reported but remained confidential. Aim: first-time report of epiretinal HALC cut by Femtosecond laser (fsl) to close complex MH with minimum 1-year follow-up.

Setting/Venue
Ophthalmology Department, University Hospital of Saint-Etienne, France
Corneal Graft Biology, Engineering and Imaging Laboratory, EA2521, Jean Monnet University, Saint-Etienne, France

Methods
Consecutive prospective 3 cases series: 1 patient with RRD recurrence by persistent MH on highly myopic (HM) eye previously treated by epiretinal lyophilised hAM which moved early postoperatively, 2 with persistent MH post RRD healed. All patients had patent cataract. Our IRB approved the study and all the patients signed an informed consent. All patients underwent a 23G pars plana vitrectomy and standardized procedure. A 6mm diameter disc of HALC cut by fsl, stained with 0.06% trypan blue, and decellularized, was inserted with a catheter through a sclerotomy, after partial fluid-air exchange, and unfolded over the MH widely as a patch (i.e. overlay) with a silicon tip backflush cannula. Gas (C2F6 18%, Arceole) (n=2) or heavy silicone oil tamponade (Densiron 68, Fluoron) (n=1) was used. All patients enrolled underwent complete examination including SD-OCT (Spectralis, Heidelberg) and fundus photography and when possible autofluorescence imaging (CR2-AF, Canon). At 1 year, the main outcome was anatomic success defined as complete MH closure. Secondary outcomes were best corrected visual acuity (BCVA) recovery, changes in ellipsoid zone (EZ) and external limiting membrane (ELM) defects, potential surgical complications. Mean follow-up was 13±1.7 months (range, 12-15).

Results
Mean baseline data on 3 eyes of 3 patients were: mean age 62 ±13 years, minimum and maximum diameters, respectively 1048±148 and 1237±33 μm; axial length 28.01±3.77 mm with 2 HM eyes; number of prior surgeries 2±1; mean duration from previous surgeries 2.5±2.18 months. At 1 year, anatomic success was achieved in 3 eyes (100%), with MH closed type 1B (n=2), type 2A (n=1). HALC remained stable on the surface of retina, and in one case (type 2A closure) it appeared like interposed "filling" tissue which plugs the foveolar dehiscence throughout all layers. Mean logMAR far BCVA improved from 1.67±1.10 to 0.73±0.46, with 3 eyes (100%) achieving ≥0.3 logMAR improvement. Mean EZ and ELM defects decreased in all patients, without reaching normal anatomical contour (i.e. type 1A closure). The RRD was reattached without recurrence. All colored HALC were bleached after 1 day. No serious adverse event occurred: no displacement, no rejection, no retraction of HALC.

Conclusions
Using epiretinal HALC cut by fsl may be useful for complex MH without alternative in eyes with patent cataract requiring combined procedure. Fsl may standardize HALC preparation, with a wide circular colored patch. Long-term (1 year) anatomic profile and recovery of visual function are encouraging. Larger sample of population with longer follow-up needs to be investigate, and randomised study should be necessary but difficult to realize for these cases hopefully rare.

Financial Disclosure
NONE
**Title**
Characterisation of retinal detachment after post-operative endophthalmitis

**Purpose**
To characterise cases of rhegmatogenous retinal detachment (RD) occurring after postoperative endophthalmitis (PE), describe outcomes and identify risk factors.

**Setting/Venue**
Tertiary referral centre.

**Methods**
Retrospective analysis of electronic patient and laboratory records from consecutive patients with RD occurring after PE, identified after cross-referencing clinical audit databases of PE and RD for the period between 01/01/2013 and 01/07/2020. Fungal, chronic and endogenous endophthalmitis or cases following trauma were excluded. The main outcome measure was best corrected visual acuity (BCVA) in logMAR units. Secondary measures were proportion of patients achieving 0.3 logMAR or better, 1.0 logMAR or worse, proportion requiring eye removal and proportion of phthisis. Putative univariate risk factors studied were bacterial taxonomy, initial mode of treatment, delay to antibiotic delivery, pars plana vitrectomy (PPV) surgery, inciting operation, and grade of surgeon performing PPV. Continuous variables were analysed for normal distribution with the Kolmogorov-Smirnov test and the Mann-Whitney rank-sum test was used to compare means. Discrete variables were analysed using the Fisher’s exact and Chi-squared tests as appropriate.

**Results**
During the study period, 103 cases of PE were treated at our centre. Two cases of fungal and one case of chronic endophthalmitis were excluded. Six patients were postoperatively managed at their distant area of residence and were excluded. Amongst the remaining 94 eyes, the frequency of RD was 21 (22%). The average age was 70 years and there were 14 male patients. The commonest inciting intervention leading to RD was intravitreal injection ([IVI] 8/21, 38%) followed by cataract surgery (7/21, 33%). Eight eyes (38%) presented with macula-involving RD and three had total RD (14%). Nine cases (43%) had RDs confined to one quadrant. Sixteen cases had one retinal break (76%) and in two cases no breaks were found (10%). Only 1 case (5%) had PVR at the time of presentation. Twenty cases underwent surgical repair with PPV and one patient declined surgery. In 16 cases (76%) silicone oil was used and 12 cases (57%) received a dose of antibiotics at the time of surgery. Seven cases (35%) experienced a recurrent RD. Eight eyes (40%) had one operation alone, with a mean number of operations of 2.1. In 13 cases (62%) the RD was identified during PPV where the indication was PE. In 6 cases (30%) the retinal break was iatrogenic. Seven eyes (35%) were left with permanent silicone oil fill. All 21 RD eyes had had PPV as part of the treatment for PE. None of the patients treated with intravitreal antibiotics developed RD (0%), whereas 13/38 (34%) patients receiving intravitreal antibiotics followed by PPV and

**Conclusions**
The outcomes of retinal detachment after endophthalmitis are poor in many cases and worse than those of endophthalmitis cases without this complication. In our sample, risk factors for RD after endophthalmitis included: initial mode of antibiotic delivery, performance of vitrectomy, seniority of surgeon carrying out vitrectomy and potentially the virulence of the bacterium.

**Financial Disclosure**
University Hospitals Bristol and Weston NHS Foundation Trust, employment Newmedica Bristol, partner Alcon, educational grants received Bausch and Lomb, educational grants received Daybreak Medical, educational grants received DORC, educational grants received
Correlation between retinal displacement and outer retinal tomographic changes after retinal detachment surgery

**Purpose**
To analyze tomographic changes in outer retinal layers after vitrectomy for rhegmatogenous retinal detachment (RD) and its association with the presence of retinal displacement.

**Setting/Venue**
Retrospective study that included outer retina tomographic analysis of 42 patients with RD who underwent RD surgery in 2018 and 2019 at Albacete University Hospital Complex (Spain).

**Methods**
Tomographic images obtained with spectral-domain optical coherence tomography (SD-OCT) at 3, 6 and 12 months after RD surgery were analyzed according to the presence or absence of alterations in outer retinal layers (external limiting membrane, ellipsoid zone and interdigitation zone). Autofluorescence images at 6 months were also observed to detect retinal displacement. Exclusion criteria were: Presence of previous retinal pathology, age under 18 years and images of insufficient quality.

**Results**
The mean age was 60.14 ± 10.71. Any grade of retinal displacement was detected in 50% of autofluorescence images. Alterations in external limiting membrane (ELM) layer at 3, 6 and 12 months were detected in 45.2%, 19% and 14.3% of images respectively. Changes in ellipsoid zone (EZ) were observed in 69%, 38.1% and 28.6% and changes in the interdigitation zone (IZ) were detected in 73.8%, 42.9% and 31% respectively. Improvement in ELM layer occurred in 31% of images after 12 months, in EZ was observed in 45.2% and 47.6% in IZ. Of the total of patients with retinal displacement detected at 3 months, 17 (85%) showed alterations in the EZ, with a statistically significant difference (Chi-squared-test, p = 0.038). IZ layer showed alterations in similar proportion but no significant differences were detected (p=0.144). Association between the presence of retinal displacement and improvement of EZ at 6 and 12 months was observed (Chi-squared-test, p = 0.014 and 0.004 respectively). No other significant differences were observed at different times.

**Conclusions**
Retinal displacement after retinal detachment surgery is associated with higher rate of tomographic alterations in the EZ at 3 months, as with an increased probability of improvement of those changes at 6 and 12 months.
**Title**
Increased mortality after intravitreal injections of anti-VEGF for neovascular AMD among patients with prior stroke or acute myocardial infarction

**Purpose**
To evaluate whether intravitreal injections (IVI) of antivascular endothelial growth factor (anti-VEGF) in neovascular age-related macular degeneration (nAMD) patients with prior stroke or acute myocardial infarction (AMI) are associated with increased mortality.

**Setting/Venue**
Retrospective, population-based cohort study.

**Methods**
From 2005 to 2013, nAMD patients in the Taiwan National Health Insurance Research Database who received IVI of anti-VEGF and had a diagnosis of stroke/AMI prior to their first injections were defined as the IVI group. The mortality of the IVI group during the study period was compared to that of the non-IVI group, which consisted of nAMD patients who had prior stroke/AMI but were never exposed to anti-VEGF. The IVI group and the non-IVI group were 1 to 4 matched according to propensity score (PS), which was derived from age, sex, date of stroke/AMI, and comorbidities. PS-adjusted Cox regression analyses were used to estimate the hazard ratio (HR) for mortality associated with IVI of anti-VEGF. Subgroup analyses were also performed according to the interval between stroke/AMI and IVI (< 6 months, 6 months–1 year, 1–2 years, >= 2 years).

**Results**
There were 3384 individuals in the IVI group and 13536 individuals in the non-IVI group. The IVI group had a significantly higher mortality risk (adjusted HR = 2.37; 95% confidence interval [CI], 2.14–2.62) than the non-IVI group. Subgroup analyses revealed that elevated mortality was significant when anti-VEGF was injected within one year after stroke/AMI.

**Conclusions**
We found an increased mortality risk associated with IVI of anti-VEGF in nAMD patients with prior stroke/AMI compared to the mortality risk of nAMD patients with prior stroke/AMD but without exposure to anti-VEGF.

**Financial Disclosure**
Nil
Comparison of air versus 10% SF6 tamponade for the management of idiopathic macular holes

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Purpose
To compare air versus 10% SF6 tamponade in vitrectomies for idiopathic macular holes.

Setting/Venue
Explorative, prospective, randomized, single-center case series.

Methods
Patients with idiopathic macular holes were vitrectomized (27-gauge) and received either air or 10% SF6 tamponades after electronic randomization. Gass macular hole stages Ia, Ib, II, III and IV were included, provided the minimum linear diameter was under 600 μm (relevant for stages III and IV). Exclusion criteria were myopia over 6 diopters, glaucoma, diabetes, macular pseudoholes, epiretinal membranes, previous vitrectomy, patient age under 18 and other pathologic ocular conditions except cataract. Primary macular hole closure two weeks after surgery was assessed using spectral-domain optical coherence tomography and served as the main outcome parameter. Metric parameters were descriptively summarized using mean and standard deviation (SD). Both groups were compared using the unpaired Student’s t-test and a p value below 0.05 was considered significant.

Results
18 eyes of 18 patients (13 women; 72%) were recruited and mean patient age at the time of surgery was 67.4 years (range 56 - 85, SD 8.7). Mean preoperative macular hole minimum linear diameter was 171 μm (range 0 - 355 μm, SD 140 μm) and 181 μm (range 0 - 336 μm, SD 116 μm) for the air and 10% SF6 group, respectively (p = 0.87). There were no statistically significant differences in pre- (air mean 0.27 Snellen, range 0.1 - 0.5, SD 0.1; 10% SF6 mean 0.35 Snellen, range 0.25 - 0.5, SD 0.07) or postoperative (air mean 0.46 Snellen, range 0.22 - 0.78, SD 0.15; 10% SF6 mean 0.59 Snellen, range 0.22 - 0.8, SD 0.19) visual acuity or axial eye length (air mean 23.77 mm, range 22.82 - 24.4, SD 0.5; 10% SF6 mean 24.53 mm, range 23.42 - 26.63, SD 1.2) between both groups. All 18 patients were vitrectomized successfully with primary macular hole closure two weeks after surgery confirmed by spectral-domain optical coherence tomography.

Conclusions
Air tamponade showed comparable anatomic results to 10% SF6 in our series. Future trials should include more patients and use multimodal imaging to confirm our results.

Financial Disclosure
None.
**Title**
Evaluation of Emulsification Rates Using Densiron® XTRA in Patients with Retinal Detachments

**Purpose**
Inferior retinal detachments (RD) may be accompanied with numerous complexities including post-operative positioning, recurrence, and predilection for proliferative vitreoretinopathy. Although high-density silicone oils (heavier than water) are ideal endotamponades for the aforementioned scenario, they have been documented to emulsify leading to potential complications. Densiron® XTRA is a novel heavy oil that has not been studied in a clinical setting, to the best of our knowledge. The purpose of this study is to review the incidence of emulsification as well as the surgical outcomes of patients with retinal detachments treated with Densiron® XTRA as an endotamponade.

**Setting/Venue**
This study was carried out at the Calgary Retina Consultants in the Southern Alberta Eye Centre associated with the University of Calgary, as well as Rockyview General Hospital in Calgary, Alberta, Canada.

**Methods**
A non-comparative, retrospective chart review of patients aged 18 to 90 years of age that underwent treatment of RD with the intraocular agent Densiron® XTRA. Seventy-four eyes (43 right, 31 left) of 74 patients (50 male, 24 female) were included. Standard 3-port pars plana vitrectomy (PPV) was performed in all patients. Three patients required cryotherapy, 21 patients required a scleral buckled (SB), 71 patients required the use of perfluoro-N-octane (PFO), 29 patients required peeling, and 18 patients underwent retinectomy. The primary outcome was anatomical success (retinal reattachment) at time of oil removal and 6 months post-oil removal. Secondary outcomes were visual acuity (VA) at 6 months and complications including emulsification.

**Results**
The mean age of patients at presentation was 62y (SD 17). Fifty patients previously underwent an intraocular procedure for RD including three pneumatic retinopexies, five SBs, 37 PPVs, and five combined SB and PPVs. There were 14 macula-on, nine macula-split and 51 macula-off RDs. Silicone oil was removed in 64 of 74 (86.5%) eyes with average duration of 18.03 weeks of tamponade (95% CI: 14.63-21.43). At time of oil removal, 50 eyes (78.1%) remained anatomically attached, while 14 eyes (21.9%) re-detached. Of the 14 eyes, four required additional surgery within 6 months of oil removal for recurrent detachments. Average follow-up time was 16 months. Comparing pre and post VA, 66% demonstrated improvement, 14% declined, and 20% exhibited no change in vision. One patient developed recalcitrant macular hole in a silicone-filled eye, one eye had corneal decompensation, one eye developed phthisis and one eye was eviscerated for pain following a central retinal artery occlusion. Intraocular pressure elevation (> 25 mm Hg) requiring treatment was noted in 27 eyes (36.5%), with 15 needing prolonged treatment. There were zero cases of emulsification. Of the 58 patients with 6 months post-oil removal data, 43 (74.1%) were successfully reattached with one surgery with Densiron® XTRA.

**Conclusions**
Densiron® XTRA is a safe and effective heavy-silicone oil for the use of retinal detachments, particularly inferior detachments. There were zero cases of emulsification identified. The retinal re-attachment rate at time of oil removal was 78.1%, with a 74.1% rate of successful anatomic reattachment at 6 months post-oil removal.

**Financial Disclosure**
None.
Clinical characteristics of retinal detachment following pediatric open globe injuries

**Purpose**
To determine the clinical characteristics and outcomes of retinal detachments associated with pediatric traumatic open-globe injuries.

**Setting/Venue**
A total of 23 eyes in 23 pediatric patients diagnosed with retinal detachment following open globe injuries between August 15, 2012 and February 15, 2020 at one academic institution.

**Methods**
Patient demographics, injury characteristics, presenting signs and symptoms, surgical management, and anatomic and functional outcomes were documented. Univariate and multivariate analysis were conducted to identify presenting factors that impacted final visual outcomes. The primary functional outcome was Best Corrected Visual Acuity (BCVA) of the injured eye at last follow up. The anatomic outcomes were single surgery and final anatomic success.

**Results**
The median time between initial injury and detection of retinal detachment was 18 days. The macula was detached in 15 (68%) patients. Surgical treatment of the retinal detachment was attempted in 14 of the 23 patients (61%). Pars plana vitrectomy (PPV) was the initial treatment in 13 of 14 patients (93%). Silicone oil was used for initial PPV tamponade in ten (77%). Single surgery anatomic success rate and final anatomic success were 50% and 86% in patients for whom treatment was attempted, respectively. Of all 23 patients, six (26%) recovered vision greater than or equal to 20/200 at last follow up, and only one (4%) was greater than 20/40. In univariate analysis, patient age at the time of injury (p = 0.004), macular attachment (p = 0.032), and recurrent retinal detachment (p = 0.006) were found to have a statistically significant relationship with final visual acuity. In a multivariate analysis, only patient age remained a statistically significant predictor of final visual acuity (p = 0.0174).

**Conclusions**
We characterized the presenting features, treatment, and outcomes for pediatric patients with retinal detachment following open globe injury. Final anatomic success rates after surgical intervention were 86%, though single surgery success rates were lower (50%). Functional outcomes were poor. Patient age was found to be the most important factor in predicting final vision.
Purpose
Rhegmatogenous retinal detachment (RRD) can be managed via scleral buckling (SB) alone or in combination with pars plana vitrectomy (PPV+SB). This meta-analysis aims to elucidate the comparative efficacy and safety of these commonly used surgical procedures.

Methods
We conducted a systematic literature search of Ovid MEDLINE, EMBASE, and Cochrane CENTRAL from January 2000 to June 2020. English-language, peer-reviewed, comparative randomized controlled trials (RCTs) and observational studies reporting on the efficacy and/or safety outcomes of SB in comparison to PPV+SB in eyes with RRD were included. Critical appraisal was performed using Cochrane risk of bias 2 tool for RCTs and the ROBINS-I tool for observational studies. GRADE guidelines were used to assess the certainty of evidence. The primary endpoint was final best corrected visual acuity (BCVA). Secondary outcomes were primary and final reattachment rates and the incidence of ocular adverse events. All outcomes were collected at last follow-up. Random effects meta-analyses were conducted for all outcomes. Categorical outcomes were reported as risk ratios (RR) and continuous outcomes were reported as weighted mean differences (WMD). A 95% confidence interval (CI) was calculated in all analyses and a p-value less than 0.05 was considered significant. Number needed to treat (NNT) and number needed to harm (NNH) were also reported.

Results
Across 13 studies, 6715 baseline eyes (3247 SB and 3468 PPV+SB) were included. Compared to PPV+SB, SB alone achieved a significantly better final BCVA (0.29 ± 0.46 vs. 0.51 ± 0.58 logMAR, respectively; WMD, −0.17 logMAR; 95%CI, −0.30 to −0.04; P=0.007; GRADE: moderate certainty of evidence) and final reattachment rate (98.1% vs. 95.2%, respectively; RR, 1.02; 95%CI, 1.01 to 1.04; P=0.001; NNT, 50; GRADE: high certainty of evidence). However, the primary reattachment rate was similar between PPV+SB and SB (87.2% vs. 88.1%, respectively; RR, 0.99; 95%CI, 0.94 to 1.03; P=0.54; GRADE: moderate certainty of evidence). Eyes with SB alone had a significantly lower risk of cataract development or progression compared with PPV+SB (7.3% vs. 32.8%, respectively; RR, 0.28; 95%CI, 0.22 to 0.36; P<0.00001; NNH, 4; GRADE: moderate certainty of evidence). There were no significant differences between SB alone and PPV+SB in the incidence of epiretinal membrane formation (P=0.53), macular edema (P=0.62), elevated intraocular pressure (IOP; P=0.66), and development or progression of proliferative vitreoretinopathy (PVR; P=0.36).

Conclusions
Compared to PPV+SB, SB alone offers significantly better final BCVA and final reattachment rate along with reduced risk of cataract development or formation in RRD eyes (GRADE: high certainty of evidence). The primary reattachment rate and the incidence of epiretinal membrane formation, macular edema, elevated IOP, and development or progression of PVR were similar between SB alone and PPV+SB (GRADE: low-moderate certainty of evidence).

Financial Disclosure
Conflicts of Interest: PN: None. ASD: None. AE: None. APS: None. MMP: Financial support (to institution) - PSI Foundation PJK: Consultant – Novartis, Alcon, Bayer, Novelty Nobility; Financial support (to institution) – Allergan, Bayer, Roche, Novartis; Financial support – Novartis, Bayer; Equity owner – ArcticDx. RHM: Consultant – Bayer, Novartis, Allergan, Roche; Financial Support (to institution)- Bayer, Novartis.
What are the risk factors for developing bilateral rhegmatogenous retinal detachment? A study of 3,020 patients

**Presenter**
James Neffendorf
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**Purpose**
The risk of fellow eye rhegmatogenous retinal detachment (RRD) is important when counselling patients and determining follow-up. Pseudophakic retinal detachment (PPRD) also forms a substantial proportion of RRD. We sought to further investigate these risks based on baseline characteristics such as age at presentation and fellow eye lens status.

**Setting/Venue**
All surgical procedures were performed by the same surgical team at 3 sites in London.

**Methods**
This was a retrospective audit of prospectively collected EMR data of 3,020 patients who underwent RRD surgery by the same surgical team between 1998 and 2020. The main outcome measure was the rate of fellow eye RRD, with a stratification of risk based on age decade at presentation, sex, and lens status in the fellow eye.

**Results**
The rate of fellow eye RRD was 5.7% (172/3020) over a total follow-up of 23,159 patient-years. The cumulative proportional hazard estimates for the development of fellow eye RRD were as follows (5th decade – 3.6% at 1 year, 8.4% at 5 years, 11.4% at 10 years; 8th decade – 1.4% at 1 year, 3.2% at 5 years, 3.6% at 10 years). For those in their fifth or sixth decade, the fellow eye RRD risk was significantly higher at 1, 5 and 10 years if the fellow eye was pseudophakic versus phakic (6.5 vs 3%, 13.5% vs 6.5%, 15.1% vs 8.3%, respectively; p=0.001).

**Conclusions**
The risk of bilateral RRD is significantly higher in younger patients. This risk is amplified if the fellow eye is pseudophakic at the time of first RRD.

**Financial Disclosure**

n/a
Prevalence and risk factors of ellipsoid zone damage after pars plana vitrectomy for idiopathic epiretinal membrane

**Purpose**
To assess the factors associated with external limiting membrane (ELM)/ellipsoid zone (EZ) damage after pars plana vitrectomy (PPV) for idiopathic epiretinal membrane (ERM) and evaluate their impact on the functional and anatomic recovery rate.

**Setting/Venue**
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**Methods**
Single-center, retrospective cohort study. Consecutive patients who underwent PPV with ERM ± inner limiting membrane (ILM) peeling were analyzed. Best-corrected visual acuity (BCVA) and central macular thickness (CMT) were collected at baseline and for one year. Demographic data, surgical details, and baseline features were included as covariates in a multivariable logistic regression model having ELM/EZ loss as binary outcome. Odds ratio (OR) and 95% confidence intervals (CI) were calculated. Factors influencing BCVA and CMT recovery rates were explored with linear regression models.

**Results**
Overall, 179 eyes of 171 patients were included. Thirty-four eyes (19%) had ELM/EZ loss after surgery; in 9 eyes (5%) ELM/EZ loss persisted at 12 months. Phacoemulsification at the time of PPV (OR=6.97, 95% CI 1.22-33.08, p=0.007) and presence of ELM/EZ damage before PPV (OR=6.91, 95% CI 1.74-31.10, p=0.007) were risk factors for postoperative ELM/EZ disruption. Thicker outer nuclear layer (p=0.002), thicker ectopic inner foveal layer (p<0.001), and high endoillumination power (p=0.03) were associated with slower visual recovery. ILM peeling (p=0.04) was associated with slower anatomic recovery.

**Conclusions**
Additional procedures during PPV and ERM peeling are associated with ELM/EZ defects after surgery and slower rate of anatomic improvement, but do not preclude good visual outcomes.

**Financial Disclosure**
none
# Real-Time In Vivo Assessment of Retinal Reattachment in Humans using Swept-Source Optical Coherence Tomography

**Purpose**
To assess the in vivo physiology of retinal reattachment in humans using swept-source optical coherence tomography (SS-OCT) in real-time.

**Setting/Venue**
A prospective consecutive case series of fovea-involving rhegmatogenous retinal detachment (RRD) undergoing pneumatic retinopexy (PnR) at St Michael's Hospital/Unity Health Toronto, Toronto, Canada between July 1, 2020 and September 30, 2020. This study was approved by the Research Ethics Board at St. Michael’s Hospital/Unity Health Toronto in Toronto, Canada, and adhered to the Declaration of Helsinki.

**Methods**
Fifteen consecutive patients with a single or multiple retinal break(s) within 3 clock hours in detached retina above the 8 and 4 o'clock meridians with any number, location and size of retinal breaks or lattice degeneration in the attached retina, proliferative vitreoretinopathy ≤ grade B, undergoing treatment with PnR were eligible for the study. All patients underwent PnR as described in the PIVOT randomized trial. SS-OCT was performed at presentation and every 2 hours for the first six hours after gas injection, at day 1, 2, 5, and at week 1, 2, 4 and 6 after PnR. The primary outcome was the longitudinal assessment of early post-operative SS-OCT to establish stages of reattachment.

**Results**
93.3% (14/15) achieved successful reattachment at the median follow-up duration of 13 weeks (IQR 7.5-18.0). Reattachment occurred in five specific stages: Stage 1, redistribution of fluid and approach of the neurosensory retina towards the retinal pigment epithelium (RPE) occurred in 100% (15/15). Stage 2, reduction in cystoid macular edema and improvement of outer retinal corrugations was achieved in 100% (15/15). Stage 3, initial contact of the neurosensory retina to the RPE occurred completely in 66.7% (10/15). Stage 4, deturgescence of the inner and outer segments of the photoreceptors occurred in 66.7% (10/15). Stage 5, recovery of photoreceptor integrity occurred in three specific sub-stages, 5A: external limiting membrane (ELM) recovery (10/15, 66.6%), 5B: ellipsoid zone (EZ) recovery (9/15, 60%), 5C: interdigitation zone (IDZ)/foveal bulge recovery (3/15, 20%). 20% (3/15) had delayed progression through Stage 2, characterized by the formation of outer retinal folds. Similarly, 33.3% (5/15) developed residual subfoveal fluid blebs (delayed progression to stage 3).

**Conclusions**
This study characterizes the in vivo physiology of retinal reattachment in humans using high-resolution SS-OCT that occurs in five specific stages. Delayed progression through certain stages was characterized by post-operative anatomic abnormalities such as outer retinal folds and residual subfoveal fluid blebs.
Euretina 2021 Virtual Abstracts

**Title**
Time from Presentation to Surgical Repair of Rhegmatogenous Retinal Detachments: A Meta-Analysis

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**Purpose**
Visual outcomes of surgical repair for rhegmatogenous retinal detachment (RRD) may be influenced by the time from presentation to surgical repair. The conventional approach recommends treating macula-on RRDs urgently and allows for macula-off RRDs to be delayed for several days. However, recent studies cast doubts on whether this approach leads to optimal results. This meta-analysis investigates the relationship between time to surgical repair and visual acuity (VA) outcomes for macula-on and macula-off RRDs.

**Setting/Venue**
Meta-analysis.

**Methods**
We searched MEDLINE, EMBASE, and Cochrane CENTRAL from inception to September 2020. We included controlled studies that recorded both the time to RRD repair and VA outcomes. Studies published in languages other than English, unpublished studies, case reports, narrative reviews, editorials, and articles with repeat data from the same patient sample were excluded. We conducted a random-effects meta-analysis using an empirical Bayesian estimator for all outcomes. Sensitivity analyses included leave-one-out and influence analyses for all outcomes. Continuous outcomes were reported as mean difference (MD) with 95% confidence interval [CI], and RR outcomes were reported as a pooled RR with 95% CI. Primary outcomes were final VA, change in VA (∆VA), and relative risk (RR) of final VA >0.4 logMAR between macula-off RRD repair in 1-3 days versus 4-7 days and macula-on repair in ≤ 24 hours versus >24 hours. Secondary outcomes examined other timepoints and RR of reattachment success for macula-on repair in ≤ 24 hours versus >24 hours.

**Results**
39 articles (1 RCT, 38 observational) reported on 7030 patients. Macula-off RRD repair in 1-3 days was superior to 4-7 days for final VA (MD [95% CI]: -0.06 [-0.09, -0.03] logMAR, p<0.001), but was not different for ∆VA (0.03 [-0.18, 0.25], p=0.05) or for the RR of VA >0.4 logMAR (RR [95% CI]: 1.28 [0.99, 1.67], p=0.06). Macula-off repair in ≤ 7 days was superior to >7 days for final VA (-0.20 [-0.30, -0.10], p<0.001), ∆VA (-0.29 [-0.46, -0.13], p<0.001), and RR of VA >0.4 logMAR (1.34 [1.01, 1.78], p<0.05). Macula-off repair in ≤ 10 days was superior to >10 days for final VA (-0.48 [-0.65, -0.31], p<0.001) and ∆VA (-0.42 [-0.66, -0.17], p<0.001). There was no difference between ≤ 15 days and >15 days for final VA (-0.06 [-0.23, 0.11], p>0.05) or ∆VA (-0.02 [-0.43, 0.38], p>0.05). Macula-on RRD repair in ≤ 24 hours was superior to >24 hours for final VA (-0.02 [-0.03, -0.01], p<0.01), but was not different for ∆VA (0.00 [-0.02, 0.02], p>0.05) or the RR of VA >0.4 logMAR (1.09 [0.91, 1.31], p>0.05). Reattachment success was similar between macula-on repair in ≤ 24 hours and >24 hours (RR [95% CI]: 0.97 [0.90, 1.03], p<0.05).

**Conclusions**
Macula-off and macula-on RRDs have the best visual outcomes when repaired in ≤ 3 days and ≤ 24 hours, respectively. Further studies should aim to investigate whether the relationship between time to RRD repair and visual outcome is affected by the type of repair performed or endotamponade used.

**Financial Disclosure**
MMP: Financial support (to institution) – PSI Foundation. PJK: Advisory board – Roche, Novartis, Alcon, Bayer, NovoTis; Financial support (to institution) – Allergan, Bayer, Roche, Novartis; Financial support – Novartis, Bayer; Equity owner – ArcticDx. RHM: Advisory board- Bayer, Novartis, Allergan, Roche; Financial Support (to institution)- Bayer, Novartis.
Title
The PRECISE study; Peeling of the inner limiting membrane (ILM) from the retinal surface in patients with idiopathic macular holes with finesse forceps.

Purpose
ILM peeling is known to be associated with a number of changes in the inner retina including retinal nerve fibre layer loss (RNFL), sub-acute nerve fibre layer swelling (SANFL), and a disassociated nerve fibre layer appearance (DONFL). Alcon/Grieshaber Finesse ‘shark skin’ forceps have been developed to specifically improve the ease of picking up the ILM atraumatically during membrane peeling. This may reduce inner retinal damage during ILM peeling by reducing associated retinal trauma but this is unproven. Similarly, it is known that surgeon and local ocular factors may be important, but the magnitude and significance of these variables is unknown.

Setting/Venue
Five experienced surgeons in 3 vitreoretinal surgical centres in the UK

Methods
Pilot masked randomised controlled trial of 66 patients undergoing ILM peeling for idiopathic macular hole with conventional ILM peeling forceps as compared to the new Finesse ‘shark skin’ forceps. The study concentrated on objective signs of retinal trauma assessed by masked image assessors of pre and postoperative spectral domain optical coherence tomography, infrared and auto-fluorescent imaging but also assessed surgeon related factors in a questionnaire as well as functional endpoints including visual acuity and visual fields after surgery. Surgeons, postoperative vision and imaging assessors were masked to the type of forceps used. The study also assessed appropriateness of trial design including masking procedures, recruitment, endpoints and adverse events to assess the feasibility and sample size for a definitive study.

Results
66 patients (66 eyes) have been recruited. The mean age was 71 years and 77% of participants were female. The mean minimum linear diameter of the holes was 458 microns, with 40% stage 2, 50% stage 3 and 10% stage 4 holes. 32% had vitreo-foveal attachment. The median hole duration was 6 months, with a mean preoperative visual acuity of 50 ETDRS letters. Primary hole closure was achieved in 63/66 eyes (95%) and mean final visual acuity was 67 letters. No adverse events related to the forceps were recorded. Data on RNFL changes, SANFL, DONFL and visual fields will be presented and related to masked topographical analysis of intraoperative video images. The effect of surgeon, hole phenotype and forceps type will be reported.

Conclusions
The study has fully recruited and will provide key data relating to inner retinal trauma after ILM peeling. Specifically, it will assess whether the use of Finesse 'Shark skin' forceps reduces the occurrence of inner retinal changes after ILM peeling, as compared to conventional ILM forceps. It will also allow discrimination between surgeon, ocular and forceps factors related to inner retinal changes after ILM peeling for idiopathic macular hole.

Financial Disclosure
The study was funded as an IIS by Alcon, with payment to Newcastle University.
Outer Retinal Folds following Pars Plana Vitrectomy vs Pneumatic Retinopexy for Rhegmatogenous Retinal Detachment Repair: Post Hoc Analysis from the PIVOT trial.

Purpose
To assess the incidence of post-operative outer retinal folds (ORFs) following pneumatic retinopexy (PnR) vs pars plana vitrectomy (PPV) with en face and cross-sectional spectral-domain optical coherence tomography (SD-OCT) following rhegmatogenous retinal detachment (RRD) repair and to determine the association of ORFs with visual acuity (ETDRS letter score) and metamorphopsia (M-CHARTS) at 12 months post-operatively.

Setting/Venue
This study is a post hoc analysis of macula-off patients from The Pneumatic Retinopexy vs Vitrectomy for the Management of Primary Rhegmatogenous Retinal Detachment Outcomes randomized trial ('PIVOT') conducted at St. Michael's Hospital, Toronto, Canada.

Methods
The incidence and morphological features of the ORFs were assessed with en face and cross-sectional OCT at 1 month post-operatively by two masked graders. Quantitative assessment of morphological features was performed with Image J. Visual acuity (ETDRS letter score) and quantitative metamorphopsia score (using M-CHARTS) were measured at 1 year. The primary outcome of this post hoc analysis was the difference in the proportion of patients with macula-off RRD with early post-operative ORFs (1 month post-operatively) in eyes undergoing PPV vs PnR. The secondary outcomes included the association of ORFs with functional outcomes including visual acuity (ETDRS letter score) and quantitative metamorphopsia measurement (M-CHARTS) at 12 months. We assessed the correlation of ORFs morphological features (height, distance from fovea, total area, perimeter, length and angulation) with functional outcomes.

Results
Eighty-eight of the 176 participants enrolled in PIVOT were macula-off RRD. 94.3% (83/88) of these had month 1 post-operative OCT scans that weregradable, 93.2% (41/44) in the PPV group and 95.5% (42/44) in the PnR group. The incidence of ORFs was 34.1% (14/41) in the PPV group and 14.3% (6/42) in the PnR group (p=0.034). ETDRS letter score at 1 year was 65.7±6.6 and 75.1±1.4 letters in patients with and without ORFs respectively (difference=9.4 letters, 95% CI=7.5-11.3, p=0.047). In the PPV group only, ETDRS letter score at 1 year was 62.8 ± 24.7 letters and 75.4 ± 9.2 letters in patients with and without ORFs respectively (difference=12.6 letters, 95% CI=0.05-24.59, p=0.04). Horizontal and vertical metamorphopsia scores were similar in patients with vs without ORFs: horizontal: 0.35 ± 0.12 vs 0.29 ± 0.07 (difference=0.06, 95% CI=0.01-0.11, p=0.69) and vertical: 0.25±0.07 vs 0.29±0.07 (difference=0.04, 95%CI=0-0.08, p=0.60) respectively. There was a negative correlation between the shortest distance of an ORF from the fovea with vertical metamorphopsia score (r=-0.507, p=0.045). The other quantitative measurements of ORF maximum height, total area, perimeter, length, angulation and total number of folds were not correlated with any of the functional outcomes.

Conclusions
In conclusion, this post-hoc analysis of the PIVOT trial demonstrated a higher risk of ORFs in PPV vs PnR at one month post-operatively with worse ETDRS visual acuity at one year in patients with ORFs compared to those without. This study provides further evidence that different surgical treatments for RRD repair result in varying integrity of retinal reattachment.

Financial Disclosure
No financial relation