7/14/2022 08:05 am

Wet AMD 1 Symposium

Higher Order OCT Feature Assessment of the Impact of Fluid Dynamics on Visual Acuity in Neovascular AMD in a Phase III Clinical Trial: The Importance of Outer Retinal Integrity

- Justis Ehlers, MD, FASRS
- Leina Lunasco
- Sari Yordi, MD
- Hasan Cetin, MD
- Katherine Talcott, MD
- Robert Zahid, PharmD, MBA
- Joanne Hu, OD
- Peter Kaiser, MD FASRS
- Arshad Khanani, MD, MA, FASRS
- Sunil Srivastava, MD

Objective:
To assess the association of best corrected visual acuity (BCVA) with retinal fluid, exudative volatility, and ellipsoid zone (EZ) integrity in eyes with neovascular age-related macular degeneration (nAMD) using a machine learning-enhanced feature extraction system in a phase III clinical trial.

Purpose:
To provide a next-generation in-depth feature assessment to comprehensively characterize the relationship of fluid and visual acuity in patients with nAMD.

Methods:
In this treatment agnostic analysis of the Phase III HAWK nAMD clinical trial (n=652), fluidic compartment (intraretinal fluid [IRF] volume, subretinal fluid [SRF] volume) status and central subfield EZ integrity (mean thickness from the EZ to the retinal pigment epithelium [EZ-RPE]) were measured using a machine learning-enhanced feature-extraction platform with manual verification. EZ integrity maintenance was defined as EZ-RPE >20 µm; partial EZ attenuation as >0 µm to ≤20 µm; total attenuation as 0 µm. IRF and SRF volatility was calculated as the volumetric standard deviation (SD) from Week 12–48. BCVA (ETDRS letters) was assessed at Week 48 based on (1) the presence/absence of fluid (IRF or SRF), (2) underlying central subfield EZ integrity, and (3) retinal fluid volatility.

Results:
The best BCVA outcomes was achieved in eyes without fluid and maintenance of EZ integrity (78 letters), which was significantly better than eyes with SRF (68 letters, $P<0.0001$). Among eyes without fluid, eyes with partial EZ attenuation had a BCVA of 67 letters. Eyes with IRF (61 letters) had lower BCVA than eyes without fluid (70 letters, $P<0.0001$). Eyes without fluid with total EZ attenuation had the worst visual acuity outcomes (56 letters).

Among eyes with SRF, eyes with low SRF volatility (SD≤Q1) had greater BCVA than eyes with high volatility (SD≥Q3) (72 vs 63 letters, $P=0.04$). No difference was found between eyes with low and high IRF volatility among eyes with IRF (60 vs 58 letters, $P=0.58$).

Conclusion:
EZ integrity appears to be a key driver for visual acuity outcomes in eyes without fluid. The best overall outcomes were achieved in eyes without fluid and EZ integrity preservation. This is an important consideration for fluid tolerance in the management of nAMD. Achieving a dry retina with EZ maintenance may provide the optimal outcome. If SRF is persistent, understanding the volatility of the SRF is important due to the negative impact of high fluctuation on outcomes. Treatment approaches that minimize volatility should be considered.

IRB APPROVAL Yes

7/14/2022 08:09 am

Wet AMD 1 Symposium

Faricimab in Neovascular Age-Related Macular Degeneration: Year 2 Efficacy, Safety, and Durability Results From the Phase 3 TENAYA and LUCERNE Trials

- Arshad Khanani, MD, MA, FASRS
- Anna-Maria Demetriades, MD, PhD
- Aachal Kotecha, PhD
- David Silverman, MSc, MBChB
- Balakumar Swaminathan
- Vaibhavi Patel, BPharm
- Hugh Lin, MD

Objective:
To assess efficacy, safety, and durability of faricimab, a dual angiopoietin (Ang)-2 and vascular endothelial growth factor (VEGF)-A inhibitor, in patients with neovascular age-related macular degeneration (nAMD).

Purpose:
Year 1 data from the phase 3 TENAYA/LUCERNE trials support the hypothesis that dual inhibition of the Ang-2/VEGF-A pathways with faricimab, the first bispecific antibody designed for intraocular use, may promote vascular stability and durable efficacy beyond current anti-VEGF therapies for nAMD. Year 2 of TENAYA/LUCERNE will inform the longer-term efficacy, durability, and safety of faricimab in patients with nAMD.

Methods:
TENAYA (NCT03823287) and LUCERNE (NCT03823300) were identical, randomized, double-masked, active comparator–controlled, 112-week, phase 3 trials of faricimab in nAMD. Treatment-naïve patients were randomized 1:1 to receive faricimab 6.0 mg up to every 16 weeks (Q16W) based on protocol-defined disease activity assessments at weeks 20 and 24 after 4 initial every-4-week (Q4W) doses, or aflibercept 2.0 mg every 8 weeks (Q8W) through week 108 after 3 initial Q4W doses. From week 60, faricimab-treated patients followed a personalized treatment interval based on a protocol-driven treat-and-extend regimen through week 108.

Results:
At 1 year, faricimab up to Q16W offered durable vision gains that were noninferior to aflibercept Q8W, with ~80% of patients on ≥ Q12W and ~45% on Q16W dosing intervals at week 48. Even with reduced injection frequency, decreases in central subfield thickness (CST) were comparable between arms. Faricimab up to Q16W was well tolerated, with low rates of intraocular inflammation. Selected key year 2 outcomes will be presented at the meeting for the first time, including best-corrected visual acuity and anatomical outcomes, treatment interval distribution, and safety.

Conclusion:
Following positive year 1 results, year 2 results from the TENAYA/LUCERNE trials will explore whether early vision gains, reductions in CST, and extended (up to Q16W) dosing with faricimab are maintained over 2 years in patients with nAMD.

IRB APPROVAL Yes

7/14/2022 08:15 am

Wet AMD 1 Symposium

UBX1325, A Novel Senolytic Therapy for Treatment-Experienced Patients With Chronic DME or Wet AMD: 24-Week Results of a Phase 1 Study

- Raj Maturi, MD
- Sharon Klier, MD, MPH
- Hani Salehi-Had, MD
- Jamie Dananberg, MD

Objective:
Could a senolytic agent improve visual outcomes in treatment experienced patients with wet -Age Related Macular Degeneration (AMD) or Diabetic Macular Edema (DME)?

Purpose:
Cellular senescence is implicated in retinal microvascular pathology that drives disease in DME and wet AMD. UBX1325, a novel small molecule BclxL inhibitor, is a potent senolytic agent. This prospective study assessed the safety, tolerability, and disease relevant activity of a single intravitreal (IVT) injection of UBX1325 in subjects with chronic DME and wet AMD.

Methods:
A phase 1, open label, single ascending dose study (www.clinicaltrials.gov NCT04537884) was conducted in 4 cohorts at 0.5, 1, 5, and 10 µg, respectively. 12 subjects, 2 with DME and 1 with wet AMD in each cohort, were enrolled. 7 additional subjects with wet AMD were enrolled in the 10 µg cohort. Patients with DME or wet AMD meeting best corrected visual acuity (BCVA) criteria, and with macular fluid or, for AMD, subretinal (SR) and/or intraretinal (IR) fluid were eligible to be enrolled. All DME subjects and 4 of the AMD subjects had a 90 days washout, other AMD subjects were allowed standard of care treatment 28 day prior to screeening. Subjects received UBX1325 IVT once and followed through 24 weeks. Safety, change from baseline in BCVA and CST through study end were analyzed.

Results:
UBX1325 was well tolerated with a favorable safety profile throughout. No dose limiting toxicities or evidence of inflammation, infection, hemorrhage, or increase in intraocular pressure were observed. Amongst 8 subjects with DME, BCVA improved in 6 at Week 12, and in 5 at Week 24. At Week 24, 62.5% of subjects gained ≥5 letters and 50% gained ≥10 letters. CST remained stable through 24 weeks in most subjects with DME. Through 24 weeks, 62.5% of subjects did not meet rescue criteria (≥75 µm CST increase from trough or ≥10 ETDRS letters decrease from peak) after UBX1325. Amongst 10 evaluable subjects (of 11) with wet AMD, visual acuity was improved in 7 at 4 weeks and in 5 at Week 12 and CST remained stable through 12 weeks. 80% of subjects did not meet rescue criteria through 12 weeks. Reduction in SR and IR fluid was also observed. Additional 24 week data will be available for presentation.

Conclusion:
A single IVT injection of UBX1325 up to 10 µg was safe and well tolerated in subjects with advanced DME or wet AMD, through 24 weeks. Improvements in BCVA, CST, and IR and SR fluid, were observed in treated subjects. These data support further development of UBX1325, a novel senolytic small molecule, for DME and wet AMD.

IRB APPROVAL Yes

7/14/2022 08:31 am

Wet AMD 1 Symposium

Analysis of the Long-term Visual Outcomes of ForeseeHome Remote Telemonitoring.

- Michael Elman, MD
- Mariam Mathai
- Shivani Reddy
- Byron Ladd
- Richard Garfinkel, MD
- Alan Wagner, MD, FACS
- George Sanborn, MD
- Jennifer Jacobs
- Miguel Busquets

Objective:
To evaluate the performance and long-term outcomes of a home monitoring strategy for early detection of conversion to Neovascular AMD

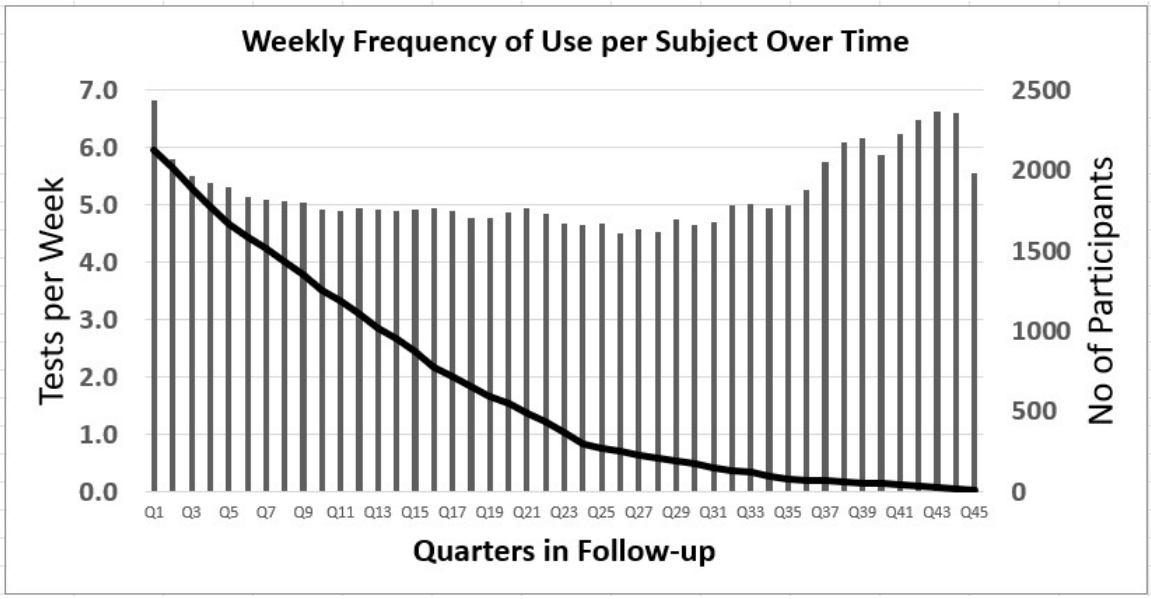
Purpose:
Evaluation of long-term visual acuity (VA) and performance of a monitoring strategy that includes a self-operated artificial intelligence enabled home monitoring system in conjunction with standard care for early detection of neovascular age related macular degeneration (nAMD) (ForeseeHome (FSH), Notal Vision Monitoring Center)

Methods:
A retrospective review was performed of all iAMD patients monitored with FSH from 5 clinics from 8/2010-07/2020. Data included visual acuity (VA) at baseline, VA at conversion to nAMD during the monitoring period, VA at most recent visit, frequency of use (FOU), duration of monitoring, modality of CNV diagnosis (system alert vs detection by standard care means), and duration and number of treatments since conversion to most recent visit.

Results:
3334 eyes of 2123 patients were reviewed with a mean (SD) age of 74(8) years, monitored for mean (SD) duration of 3.1(2.4) years, with a total of 1,706,433 tests in 10,474 eye-monitoring years. A Kaplan-Meyer survival analysis predicted a mean (95%CI) 4.5(4.3-4.7) years of monitoring. The mean (SD) weekly FOU per patient was 5.2(3.4) and it was persistent over the usage period. 285 eyes converted while monitored at an annual rate of 2.72% and were treated with mean (SD) 17.3(16.5) injections over mean (SD) 2.7(2.0) years, with 6.4(3.1) injections per year for eye treated for > 1 year. The median VA at baseline and recent visit for eyes that did not convert were 20/27 and 20/34 with a median change of 0.0 letters. The median VA at baseline, conversion and recent visit for eyes that converted during the monitoring period were 20/30, 20/39 and 20/32 with a median change from baseline to conversion, baseline to recent and conversion to recent of -4, -4 and 0 letters, respectively. 52% of the conversions detected had a system alert prior to conversion. 48% of patients were detected by symptoms or routine visit. Patients experienced a non-nAMD alert on average every 4.6 years. At conversion and at recent visit the proportion (95% CI) of eyes that maintained ≥20/40 was 84%(78%-88%) and 82%(76%-86%) respectively

Conclusion:
Patients in the FSH monitoring program showed excellent long-term visual acuity years after conversion to nAMD, emphasizing the importance of early detection

IRB APPROVAL No - exempt



Average Weekly Frequency of Use per Quarter of Participation in the Program

			Eyes that converted while monitored	Eyes that did not convert while monitored	p-value***	All eyes
No. of eyes	N		285	3049		3334
At baseline	n (%) of eyes with VA data		279 (98)	1134 (37)		1413 (42)
	VA	Mean (SD) - LogMAR	0.19 (0.16)	0.17 (0.17)		0.17 (0.17)
		Mean - Snellen Eq.	20/31	20/30		20/30
		Median (*IQR) - LogMAR	0.18 (0.1-0.3)	0.13 (0.02-0.26)	0.014	0.14 (0.04-0.3)
		Median - Snellen Eq.	20/30	20/27		20/28
	**% with VA ≥20/40 (95% CI)		86 (81-90)	87 (85-89)		87 (85-88)
At conversion to NV-AMD	n (%) of eyes with VA data		282 (99)	N/A		N/A
	VA	Mean (SD) - LogMAR	0.28 (0.22)	N/A		N/A
		Mean - Snellen Eq.	20/38	N/A		N/A
		Median (*IQR) - LogMAR	0.29 (0.1-0.4)	N/A		N/A
		Median - Snellen Eq.	20/39	N/A		N/A
	**% maintained VA ≥20/40 (95%		84 (78-88)	N/A		N/A
	VA change from baseline	Mean(SD) - LogMAR	-0.09 (0.23)	N/A		N/A
		Mean - Letters***	-4.5 (11.5)	N/A		N/A
		Median(IQR) - LogMAR	-0.08 (-0.2-0.0)	N/A		N/A
		Median - Letters	-4.0 (-10.0-0.0)	N/A		N/A
	Time from baseline (years)	Mean (SD)	2.3 (1.9)	N/A		N/A
		Median (IQR)	1.8 (0.8-3.2)	N/A		N/A
At recent visit	n (%) of eyes with VA data		283 (99)	901 (30)		1184 (36)
	VA	Mean (SD) - LogMAR	0.32 (0.36)	0.23 (0.29)		0.25 (0.31)
		Mean - Snellen Eq.	20/42	20/34		20/36
		Median (*IQR) - LogMAR	0.2 (0.1-0.41)	0.18 (0.1-0.3)	<0.001	0.18 (0.1-0.3)
		Median - Snellen Eq.	20/32	20/30		20/30
	% maintained VA ≥20/40 (95% CI)		82 (76-86)	85 (82-87)		84 (82-86)
	VA change from baseline	Mean(SD) - LogMAR	-0.14 (0.36)	-0.07 (0.31)		-0.09 (0.32)
		Mean- Letters	-7.0 (0.18)	-3.5 (15.5)		-4.5 (16.0)
		Median(IQR) - LogMAR	-0.08 (-0.22-	0.00 (-0.18-	0.004	0.00 (-0.18-
		Median - Letters	-4.0 (-11.0-3.0)	0.0 (-9.0-4.0)		0.0 (-9.0-4.0)
	Time from baseline (years)	Mean (SD)	5.0 (2.3)	4.3 (2.4)		4.4 (2.36)
		Median (IQR)	4.5 (3.1-6.6)	4.2 (2.4-6.1)		4.3 (2.57-
	VA change from conversion	Mean(SD) - LogMAR	-0.04 (0.35)	N/A		N/A
		Mean - Letters	-2.0 (17.5)	N/A		N/A
		Median(IQR) - LogMAR	0.00 (-0.1-0.1)	N/A		N/A
		Median - Letters	0.0 (-5.0-5.0)	N/A		N/A
	Time from conversion (years)	Mean (SD)	2.7 (2.0)	N/A		N/A
		Median (IQR)	2.3 (1.0-3.7)	N/A		N/A

VA= Visual acuity; N/A= Not applicable; *IQR: Interquartile range; **LogMAR cutoff for VA≥ 20/40 is 0.35.

Visual acuity outcomes at baseline, at conversion and at recent visit

7/14/2022 08:37 am

Wet AMD 1 Symposium

Conversion Rates from Nonexudative to Exudative Age-Related Macular Degeneration: An AAO IRIS® Registry Analysis

- Dan Gong, MD
- Connor Ross
- Nathan Hall
- Tobias Elze
- Lucia Sobrin, MD, MPH
- Joan Miller, MD
- Alice Lorch, MD, MPH
- John Miller, MD

Objective:
To assess whether certain types of patients with non-exudative age-related macular degeneration convert to exudative age-related macular degeneration at higher rates using a real-world data registry.

Purpose:
This study examined conversion rates from non-exudative (dry) to exudative (wet) age-related macular degeneration across different patient populations using real-world data from the AAO IRIS® Registry (Intelligent Research in Sight).

Methods:
A retrospective cohort analysis was conducted using the IRIS Registry spanning 2016-2019. A total of 2,664,789 patients with dry AMD in at least one eye were included in this study. Observed patient characteristics including age, sex, race, geographic region, and smoking status; dry and wet AMD stage; and conversion time from dry to wet AMD. Descriptive statistics and hazard ratios (HRs) from a Cox proportional hazard model were conducted across these characteristics.

Results:
Overall conversion rates from dry to wet AMD were 2.0, 6.1, and 6.7% for early, intermediate, and advanced stages respectively ($p<0.001$). Among those converting to wet AMD, there was decreased risk for males relative to females (HR 0.89, 95% CI [0.88, 0.89]) and Asians (HR 0.52, 95% CI [0.50, 0.54]) or Blacks/African-Americans (HR 0.39, 95% CI [0.37, 0.40]) relative to Caucasians. Relative to patients with bilateral dry AMD, those with wet AMD in one eye and dry in the other eye (HR 5.65, 95% CI [5.56, 5.75] and those with unilateral dry AMD (HR 3.60, 95% CI [3.57, 3.63] had a higher risk of conversion for the eye with dry AMD. Relative to patients with early dry AMD, those with intermediate dry AMD (HR 2.46, 95% CI [2.41, 2.51] and advanced dry AMD (HR 2.69, 95% CI [2.61, 2.77]) had a higher risk of conversion. Among patients with dry AMD in one eye and wet AMD in the other eye, compared with having active choroidal neovascularization in one eye, those with wet AMD with inactive choroidal neovascularization (HR 0.60, 95% CI [0.56, 0.64]) and wet AMD with inactive scar (HR 0.58, 95% CI [0.53, 0.62]) in one eye had a lower risk of conversion to wet AMD in the fellow eye.

Conclusion:
In this cohort analysis of the IRIS Registry, females, Caucasians, and smokers had higher risk of conversion from dry to wet AMD. Patients with one eye with wet AMD and one eye with dry AMD and patients with unilateral dry AMD were more likely to convert than patients with bilateral dry AMD. More advanced stages of dry AMD and active choroidal neovascularization in the fellow eye were associated with higher risk of conversion.

IRB APPROVAL No - no IRB or exemption

7/14/2022 08:41 am

Wet AMD 1 Symposium

Subretinal Pneumatic Displacement Without Tissue Plasminogen Activator for Submacular Hemorrhage: One-year Outcomes

- Marwan Abdulaal, MD
- Jacobi Robertson
- Lewis Shawn, MD
- David Miller, MD
- Jerome Schartman, MD, FASRS
- Sean Platt, MD
- Richard Donkor, OD, MSc, PhD
- Joseph Coney, MD, FASRS

Objective:
To evaluate whether a rapid subretinal displacement of submacular hemorrhage without the use of tissue pasminogen activator can be effective and safe.

Purpose:
To evaluate the outcome of eyes who received subretinal displacement for submacular hemorrhage (SMH) using Balanced Saline Solution (BSS) without tissue plasminogen activator (tPA).

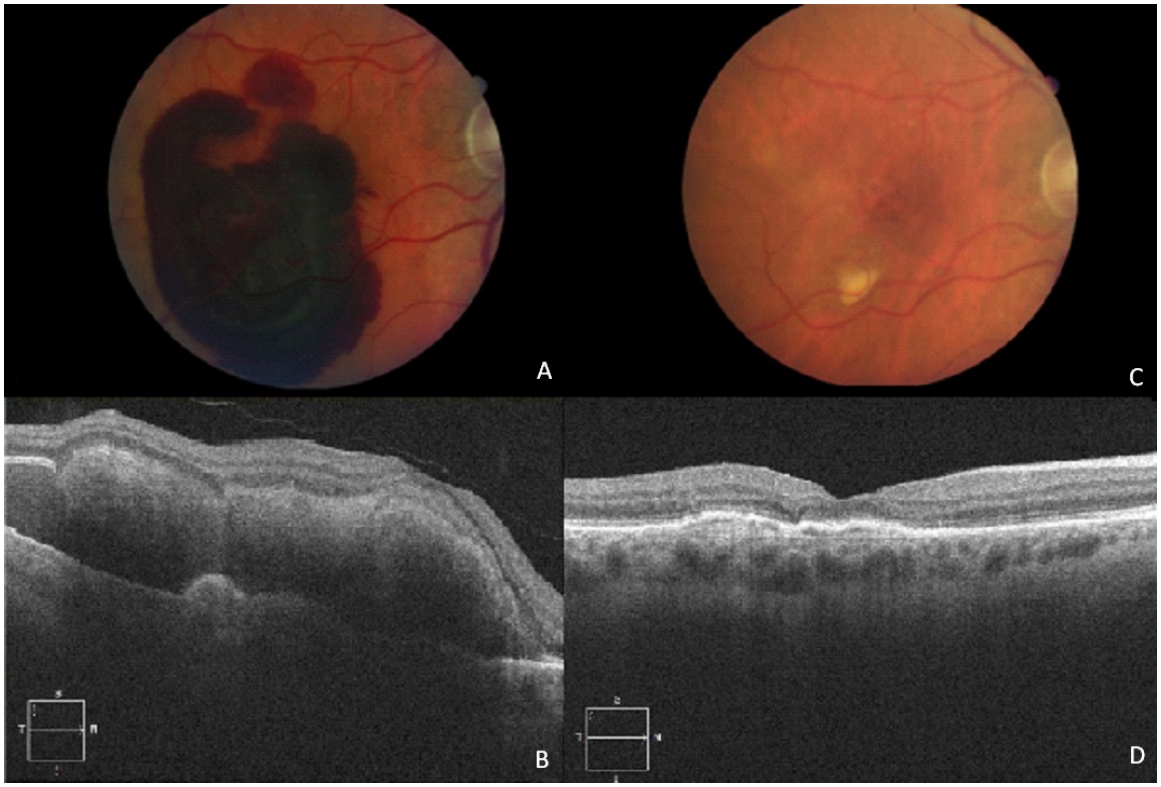
Methods:
A retrospective, comparative, and interventional study.Twenty-four patients with large SMH and at least 52 weeks of follow-up. Analysis of large SMH patients who underwent a pars plana vitrectomy (PPV) and subretinal fluid displacement without tPA from 2015 and 2020. Surgical intervention included a standard small gauge PPV with subretinal displacement using BSS with/without subretinal sterile air and a partial gas fluid exchange. Data collected included all medical records, color fundus photographs and Optical Coherence Tomography (OCT) images. **Main outcome**: To evaluate the change in best visual acuity (BCVA) and total resolution of SMH in eyes with subretinal displacement after a single surgery.

Results:
Neovascular age-related macular degeneration (nAMD) was the most common etiology associated with thick SMH (92%). Complete blood displacement was observed within one month in 79% of the cases. There was significant improvement of mean logMAR BCVA in the affected eye from 1.65 ± 0.6 (Snellen 20/800 at baseline) to 1.12 ± 0.6 letters (Snellen 20/250; p = 0.01) at 8-12 months follow-up. Most patients (75%) gained at least 1 line by 8-12 months follow-up. A reliable improvement of mean central retinal thickness (CRT) was observed in the affected eye from 569µ ± 220 at baseline to 252µ ± 63 by 8-12 months follow up (P<0.001). BSS with or without subretinal sterile air had similar impact on extent of SMH displacement and visual outcome. We did not find reliable positive correlation between final visual outcome and risk factors for poor visual outcome such as duration of hemorrhage and level of initial visual acuity (Spearman

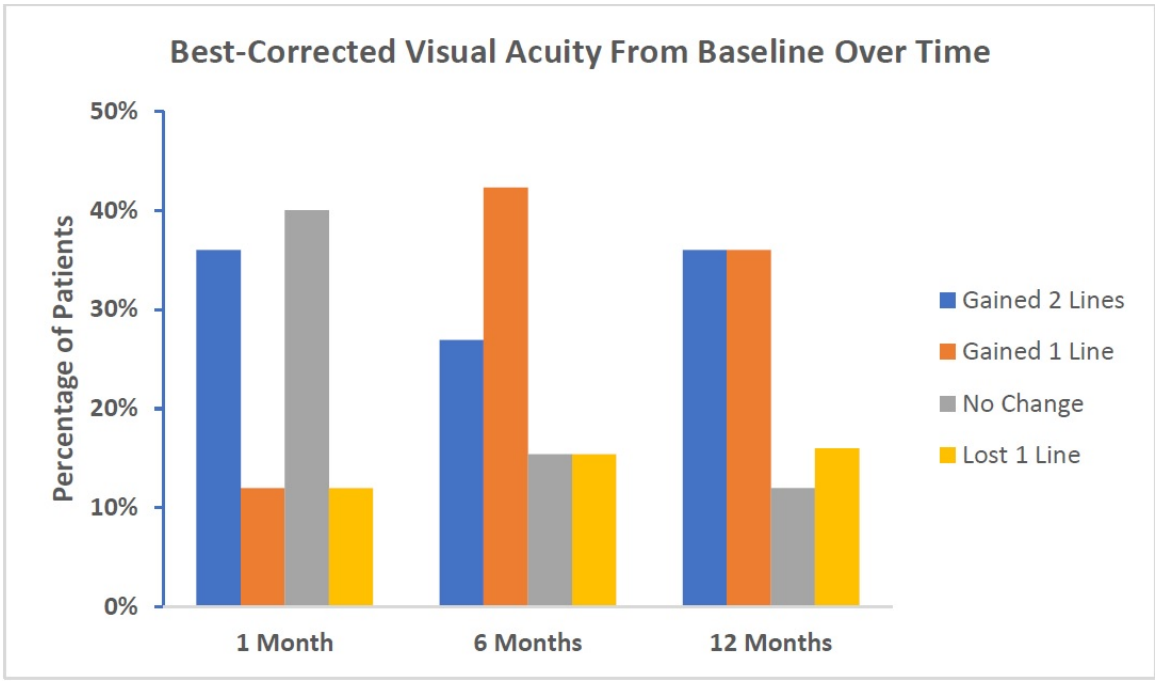
Rank Correlations: P=0.27, P=0.20 respectively). Factors such as oral anti-coagulation prior to surgery and crystalline lens status did not affect the outcome measures. Early postoperative complications included two vitreous hemorrhage cases and retinal detachment in one patient.

Conclusion:
Vitrectomy with subretinal BSS/sterile air injection without tPA injection was found effective for displacement of thick SMH with improvement in retinal function, visual acuity and CRT.

IRB APPROVAL No - no IRB or exemption



A & B-Preoperative fundus photos and OCT macula of a thick SMH; C & D- six



Percentage of patients showing improvement in BCVA with regards to number o

7/14/2022 08:45 am

Wet AMD 1 Symposium

Real World Efficacy, Durability and Safety of Faricimab in Neovascular Age-Related Macular Degeneration: The TRUCKEE Study

- Carl Danzig, MD
- Arshad Khanani, MD, MA, FASRS
- Hannah Khan, BS
- Aamir Aziz, BS
- David Almeida, MD, PhD, MBA
- Robert Avery, MD
- Himanshu Banda, MD
- Mark Barakat, MD
- Ramanath Bhandari, MD
- Nikolas London, MD, FACS, FASRS
- Veeral Sheth, MD, MBA, FASRS, FACS
- Jeremy Wolfe, MD, MS
- Michael Singer, MD

Objective:
This retrospective study evaluates the efficacy, safety and durability of faricimab in real-world patients afflicted by neovascular age-related macular degeneration (nAMD).

Purpose:
The FDA approved faricimab for the treatment of nAMD in early 2022. Current anti-VEGF agents improve patient outcomes but real-world patients show decline in visual acuity due to high treatment burden. Faricimab is intended to function with comparable efficacy to current agents while demonstrating increased durability, and is being investigated in the real-world by this retrospective study.

Methods:
Retrospective chart review conducted on patients treated with faricimab for nAMD. Treatment-naïve patients and patients switched to faricimab from other anti-vascular endothelial growth factor (VEGF) agents are evaluated. Demographics, previous treatment interval, early treatment diabetic retinopathy study (ETDRS) visual acuity (VA), central subfield thickness (CST) and changes in pigment epithelial detachments (PED) are collected. VA, CST, and sub/intraretinal fluid (SRF/IRF) improvements are evaluated as averages. Adverse events are collected and reported.

Results:
Data collection is currently ongoing. Thus far, 21 nAMD eyes (71% female, 29% male) were evaluated at baseline faricimab treatment. Mean age is 81.1 years. Adjusted mean baseline ETDRS and CST values are 54.1 [0.7] letters and 440.7 [7.1] µm, respectively, with the previous treatment interval at 34.8 days. 12 patients completed at least one follow-up visit with an interval of 36.8 days. Patients saw an average of +5.7 ETDRS letter improvement and mean CST reduction of -91.7 µm. No adverse events have been reported.

Conclusion:
VA and CST improvements have been noted in Phase III clinical trials, demonstrating durability of faricimab in nAMD patients. Real-world patients are showing improvements in visual acuity and anatomic parameters but are still at an early timepoint. Faricimab will continue to be evaluated in real-world patients to evaluate efficacy and safety.

IRB APPROVAL