



## **A Post Hoc Analysis of Intravitreal Aflibercept–Treated nAMD Patients from ARIES & ALTAIR: Predicting Patient-Individualized Treatment Interval for Aflibercept Treat-and-Extend Therapy Regimen by Adapting AI Algorithms Trained on Pro Re Nata Data**

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# Disclosures

## Disclosures: Presenting author

**Matthias Gutfleisch:** Study participation: Amgen, Apellis, Iveric Bio, Kodiak, Neurotech, Novartis, Regeneron, Roche; Shareholder: deepeye Medical GmbH; Travel support: DORC; Consultant: Bayer.

## Disclosures: Co-author group

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# Purpose

- Prediction of potential treatment need/expected therapy response and neovascular age-related macular degeneration (nAMD) disease course using artificial intelligence (AI)
- ARIES<sup>1</sup> and ALTAIR<sup>2</sup>
  - Randomized, controlled, Phase 3b/4 trials
  - Treat & Extend (T&E) regimens in newly diagnosed nAMD patients
  - Three loading doses (initial monthly injections), followed by injection after 8 weeks with 2 mg intravitreal aflibercept (IVT-AFL)
  - Treatment intervals assessed based on prespecified spectral domain optical coherence tomography (SD-OCT) criteria at each injection visit over 2 years

## Methods – Data

- AI analysis based on available SD-OCT images at Weeks 8 and 16
  - ARIES: SD-OCT images from 224 of 237 patients
  - ALTAIR: SD-OCT images from 112 of 246 patients
- Clinical patient documentation (visit intervals and injections as prediction targets)

1. Mitchell P, et al. *Retina*. 2021;41:1911–1920. Erratum in: *Retina*. 2022;42:e43.

2. Okada AA, et al. *Adv Ther*. 2022;39:2984–2998.

# Methods – criteria for interval adaptation

Criteria for interval adaptation for ARIES & ALTAIR interventional studies (see Table)



Extend



Maintain



Shorten

## ARIES T&E extension criteria

Maximum interval: 16 weeks

Minimum interval: 8 weeks\*

Absence of IRF

**AND**

Absence of new neovascularization or hemorrhage

**AND**

SRF  $\leq 50 \mu\text{m}$  in thickness

Any IRF

**OR**

New neovascularization or hemorrhage

**OR**

SRF  $> 50 \mu\text{m}$  in thickness

## ALTAIR T&E extension criteria<sup>1</sup>

Maximum interval: 16 weeks

Minimum interval: 8 weeks

No fluid present<sup>†</sup>

**AND**

No loss of  $\geq 5$  ETDRS letters<sup>‡</sup>  
No increase in CRT  $\geq 100 \mu\text{m}$ <sup>§</sup>  
No new neovascularization  
No new macular hemorrhage

Residual but decreased fluid<sup>†</sup>

**AND**

No loss of  $\geq 5$  ETDRS letters<sup>‡</sup>  
No increase in CRT  $\geq 100 \mu\text{m}$ <sup>§</sup>  
No new neovascularization  
No new macular hemorrhage

New fluid present<sup>†</sup>

**OR**

Persistent unchanged or increased fluid<sup>†</sup>

**OR, any of the following:**

Loss of  $\geq 5$  ETDRS letters<sup>‡</sup>  
Increase in CRT  $\geq 100 \mu\text{m}$ <sup>§</sup>  
New neovascularization  
New macular hemorrhage

\*Patients could receive more frequent treatment if identified as injection-intensive and were excluded from the per-protocol set; <sup>†</sup>Assessed by OCT; <sup>‡</sup>Loss of  $\geq 5$  ETDRS letters from the last treatment visit, in conjunction with recurrent fluid on OCT; <sup>§</sup>Increase in CRT of  $\geq 100 \mu\text{m}$  compared with the lowest previous value by OCT.

CRT, central retinal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; IRF, intraretinal fluid; SRF, subretinal fluid.

1. Ohji M, et al. *Adv Ther.* 2020;37:1173–1187.

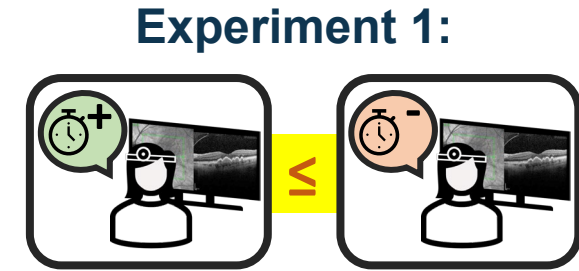
# Methods – AI pipeline

- Evaluation and adaptation of the existing AI models in the deepeye<sup>®</sup> research tool<sup>1–3</sup>
- AI architecture
  - Input: SD-OCT images from Weeks 8 and 16 from ARIES & ALTAIR studies
  - Two AI networks: Biomarker segmentation (i) and prediction model (ii)
  - Use of AI model trained on SD-OCT data of real-world pro re nata (PRN) cohort<sup>1</sup>
  - Retrain model (ii) and apply AI model to T&E datasets from ARIES & ALTAIR SD-OCT
- Assess agreement between AI model and study results (5-fold cross-validation)

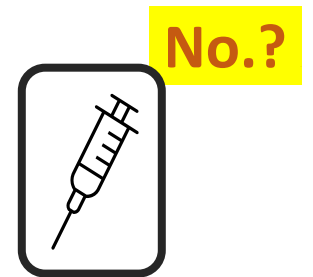


# Methods – experiments

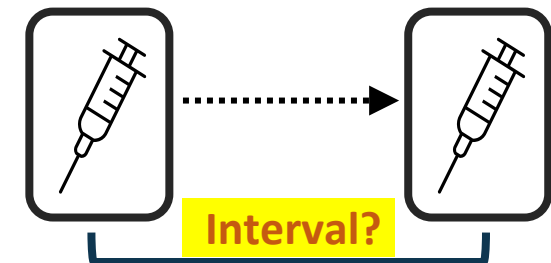
- Prediction of treatment frequency and interval
  - Experiment 1: Prediction of potential adequate first injection interval:  $<3$  vs  $\geq 3$  interval extensions in the first four visits after initiation\*
  - Experiment 2: Prediction of injection frequency in first and second years
  - Experiment 3: Prediction of treatment interval after second year (end of study)
- Documented study data served as ground-truth
- **In this presentation, we show detailed results of Experiment 3:**
  - Ground-truth: Intended patient individual treatment interval after 2 years
  - AI task: Prediction of this interval (see above), binarized into two classes
    - Short intervals ( $<12$  weeks)
    - Long intervals ( $\geq 12$  weeks)



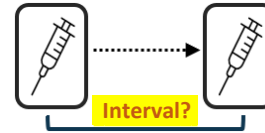
## Experiment 2:



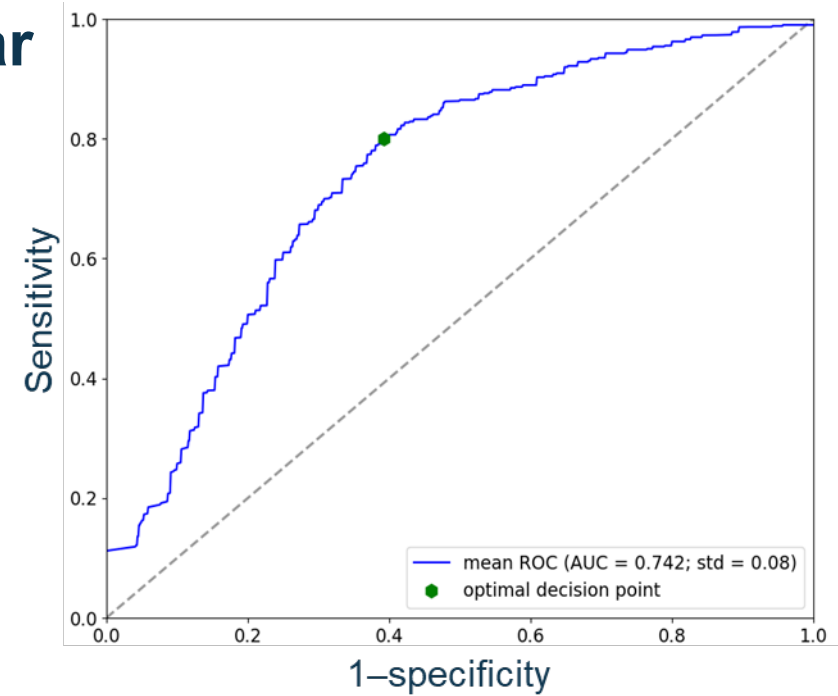
## Experiment 3:



# Results of Experiment 3 – interval after second year



- ARIES:
  - **Sensitivity:** Patients identified as needing a ‘short’ interval: From study data: 116 patients; from model: 93 patients (80% sensitivity)
  - **Specificity:** Patients identified as needing a ‘long’ interval: From study data: 105 patients; from model: 66 patients (63% specificity)
  - **Overall accuracy** of the algorithm in this case was 71%
- ALTAIR: Results with machine learning (not deep learning) approaches
  - **Sensitivity:** 34 of 43 (81%)
  - **Specificity:** 24 of 34 (71%)



ROC of Experiment 3 for ARIES. Threshold for accuracy chosen as 0.5 (not equal to the optimal decision point).

|         | AUC  | Accuracy | Sensitivity  | Specificity  | No. of short intervals | No. of long intervals |
|---------|------|----------|--------------|--------------|------------------------|-----------------------|
| ARIES*  | 0.74 | 71%      | 80% (93/116) | 63% (66/105) | 116                    | 105                   |
| ALTAIR* | 0.77 | 76%      | 81% (34/43)  | 71% (24/34)  | 43                     | 34                    |

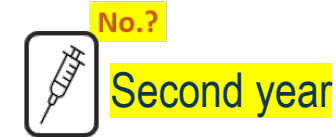
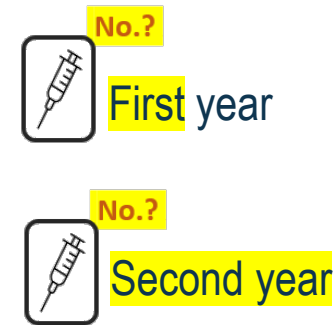
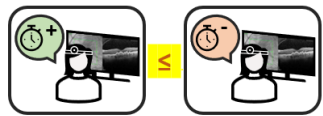
Short interval: Intended patient individual treatment interval after 2 years <12 weeks. Long interval: Intended patient individual treatment interval after 2 years ≥12 weeks.

\*Numbers of patients differ from total numbers (Slide 3). ARIES: Three images excluded due to too poor image quality for segmentation. ALTAIR: 35 cases excluded due to missing reading-center proved annotations.

ROC, receiver operator characteristic; AUC, area under the curve

# Results – additional experiments

- Experiment 1: <3 interval extensions in the four visits after treatment initiation\* (starting from Week 16)
- Experiment 2 (first year): ≥8 injections
- Experiment 2 (second year): ≥5 injections



| Experiment                 | Study  | AUC  | Accuracy | Sensitivity  | Specificity  | No. of Positives | No. of Negatives |
|----------------------------|--------|------|----------|--------------|--------------|------------------|------------------|
| Experiment 1               | ARIES  | 0.87 | 77%      | 83% (59/72)  | 71% (26/36)  | 72               | 36               |
| Experiment 1               | ALTAIR | 0.78 | 78%      | 85% (31/37)  | 71% (36/46)  | 37               | 46               |
| Experiment 2 (first year)  | ARIES  | 0.84 | 75%      | 81% (52/64)  | 70% (31/44)  | 64               | 44               |
| Experiment 2 (first year)  | ALTAIR | 0.79 | 79%      | 79% (27/35)  | 78% (42/54)  | 35               | 54               |
| Experiment 2 (second year) | ARIES  | 0.79 | 73%      | 75% (79/105) | 71% (82/116) | 105              | 116              |
| Experiment 2 (second year) | ALTAIR | 0.78 | 78%      | 87% (34/39)  | 69% (26/38)  | 39               | 38               |

Experiment 1: Predict first potential adequate injection interval.

Experiment 2: Predict injection frequency in first and second treatment years.

\*Treatment initiation with initial monthly injections.

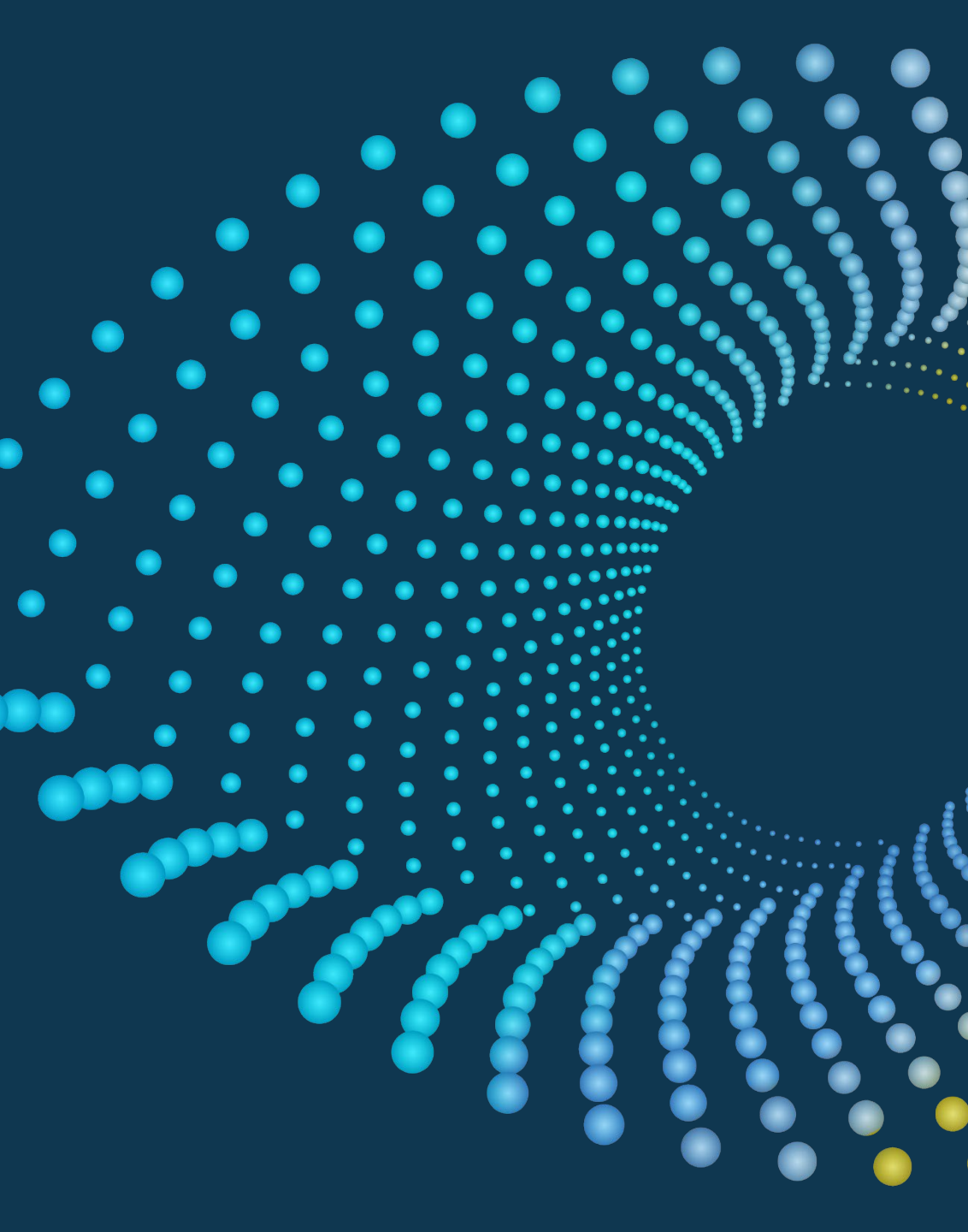


# Conclusions

- AI models successfully adapted from PRN to T&E prediction
- New AI algorithm accurately assigns a percentage between 71% and 76% of patients to the <12 weeks or ≥12 weeks interval extension groups (→ Experiment 3)
- Further experiments achieved a good\* prediction accuracy, between 73% and 78%; AUC of 0.78–0.84
- Potential clinical benefits for prediction of future treatment need
  - Informing patients about the expected need for therapy
  - Support ophthalmologists in optimizing treatment regimens
  - Reduce risk of under- and overtreatment
  - Reduce treatment burden for patients and caregivers
  - Improve therapy adherence
- AI models can potentially mitigate the variability among medical experts
- The limitations are the use of controlled study data with a preselected cohort of patients

\*Bogunović H, et al. prediction of “extendable treatment interval group”: AUC 0.71.<sup>1</sup>

1. Bogunović H, et al. *Front Med (Lausanne)*. 2022;9:958469.



**Thank you for your attention**