Topline Results from a 2-year Phase 3 Study of Oral Tinlarebant in Adolescent Patients with Stargardt Disease

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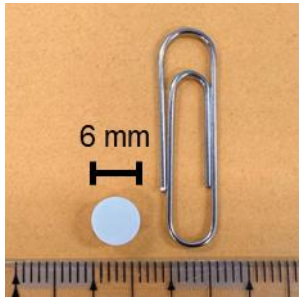
Tinlarebant

Introduction to Tinlarebant

- Patients with Stargardt disease (STGD1) carry pathogenic mutations in the *ABCA4* gene, resulting in dysfunction of the ABCA4 protein in photoreceptor cells, which disrupts normal vitamin A processing in the visual cycle resulting in the accumulation of cytotoxic vitamin A byproducts (*bisretinoids*) and progressive retinal cell death [1]

- Tinlarebant is a novel, **once-a-day oral tablet** designed to bind to serum retinol binding protein 4 (RBP4) as a means to specifically reduce retinol delivery to the eye in order **to slow or halt the accumulation of bisretinoids**

Tinlarebant Tablet



- Belite Bio believes that on **oral intervention directed at the underlying cause of retinal pathology** would be the best approach to potentially slow disease progression and preserve vision in STGD1 patients

[1] Mata NL, Weng J, Travis GH. Biosynthesis of a major lipofuscin fluorophore in mice and humans with ABCR-mediated retinal and macular degeneration. Proc Natl Acad Sci U S A. 2000, 20;97(13):7154-9.

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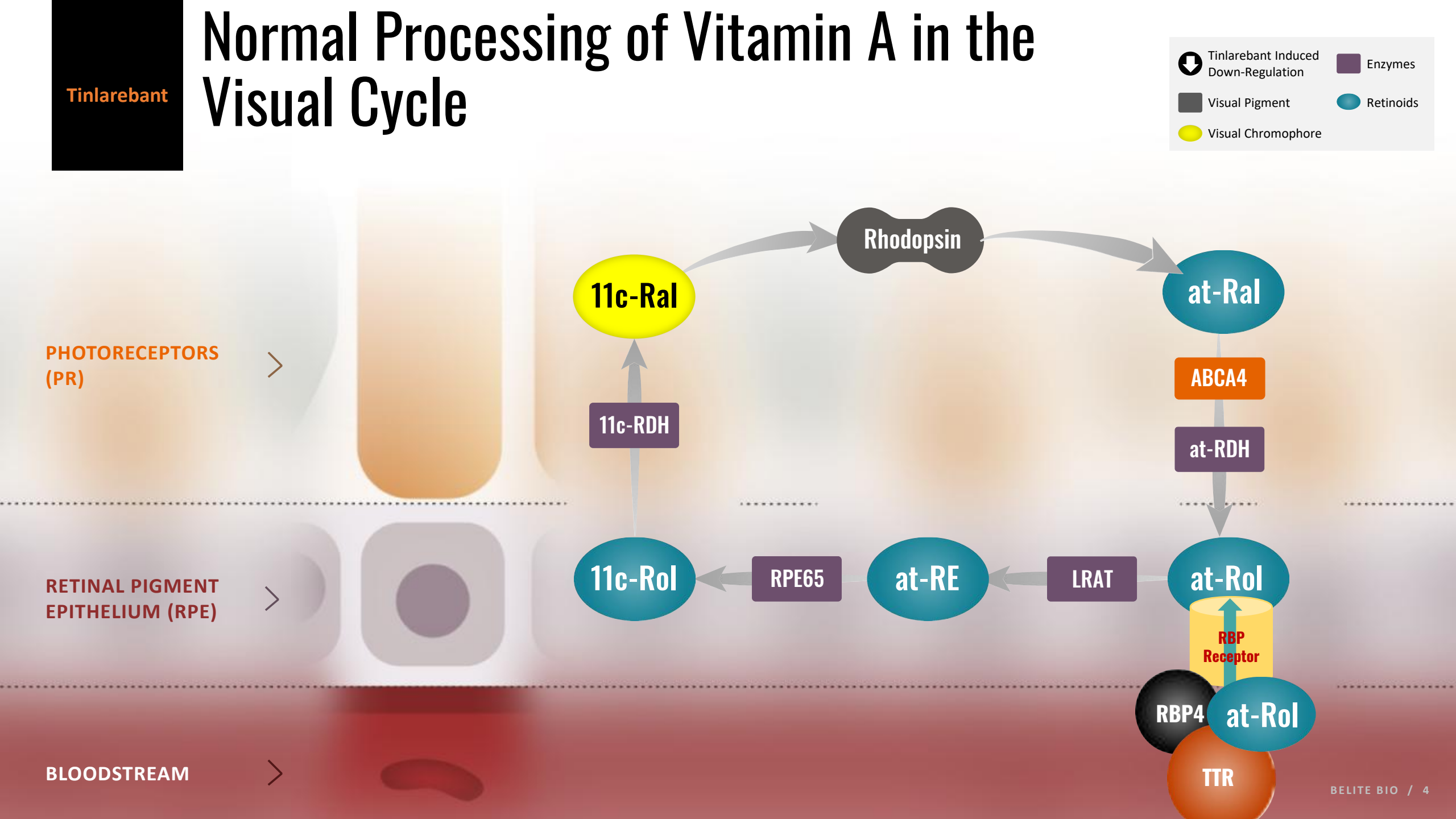
Tinlarebant Mechanism of Action

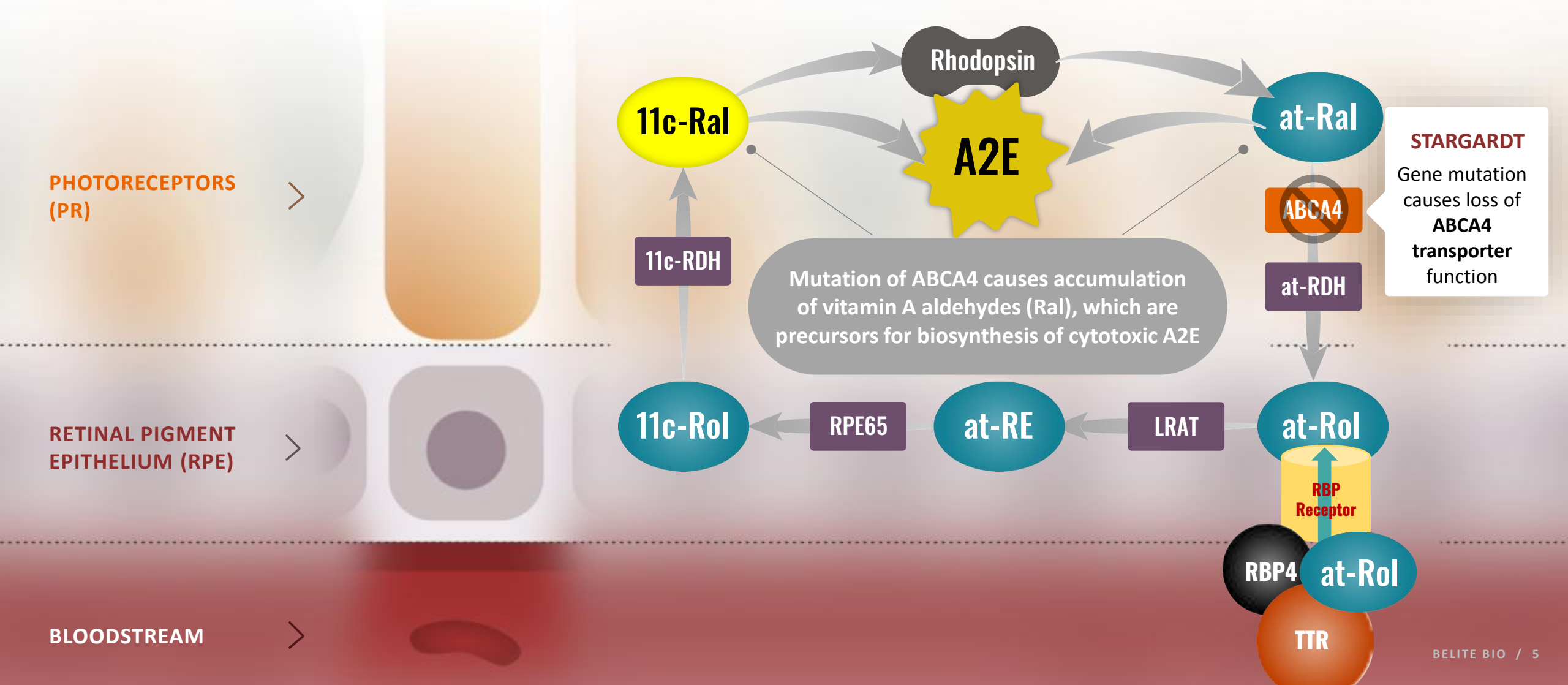
Tinlarebant

Normal Processing of Vitamin A in the Visual Cycle



Tinlarebant

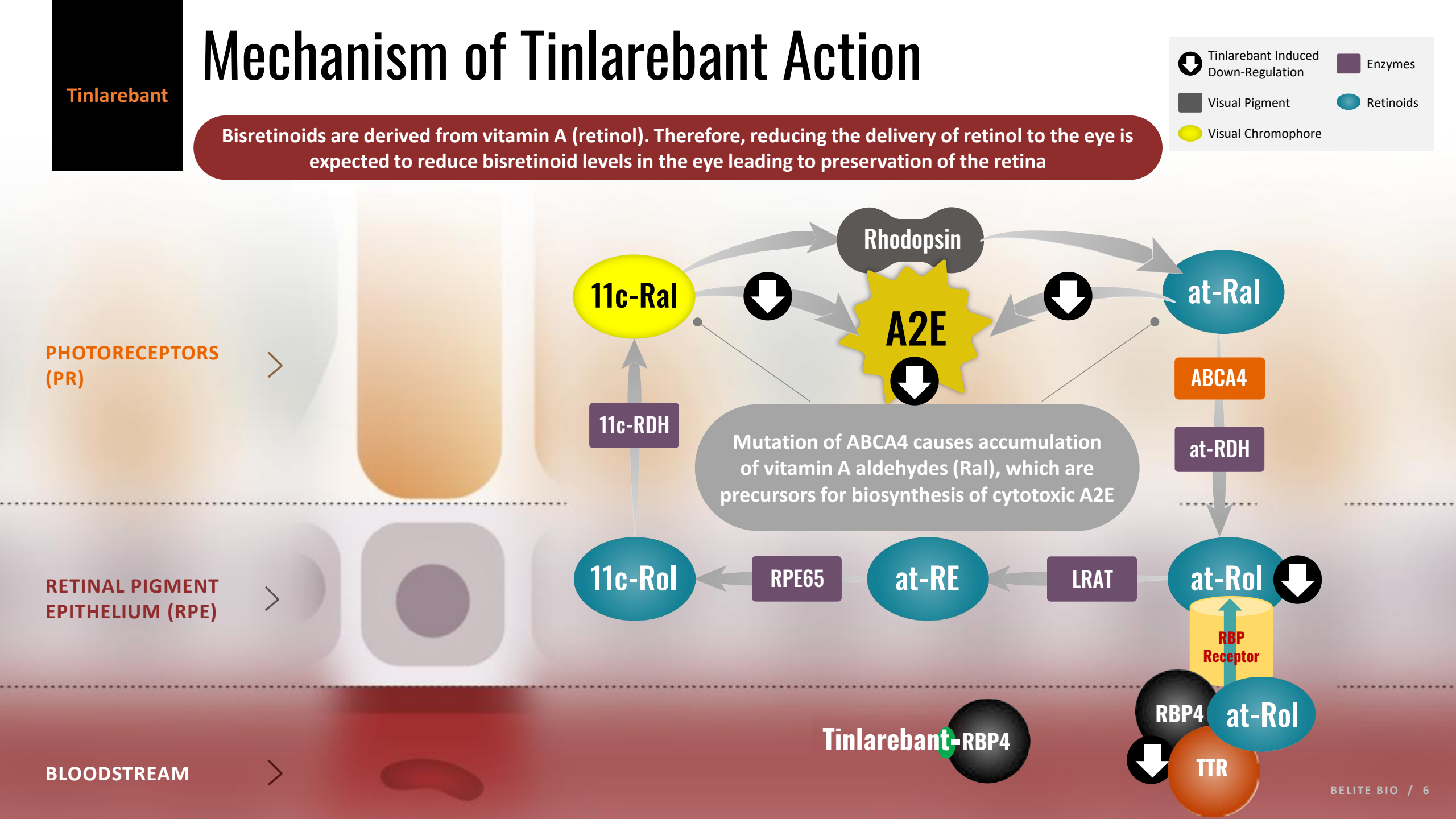
Formation of Toxic Vitamin A Byproducts in Stargardt Disease 1 (STGD1)



Tinlarebant

Mechanism of Tinlarebant Action

Bisretinoids are derived from vitamin A (retinol). Therefore, reducing the delivery of retinol to the eye is expected to reduce bisretinoid levels in the eye leading to preservation of the retina



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DRAGON Phase 3 Clinical Trial in Stargardt Disease

Study Design

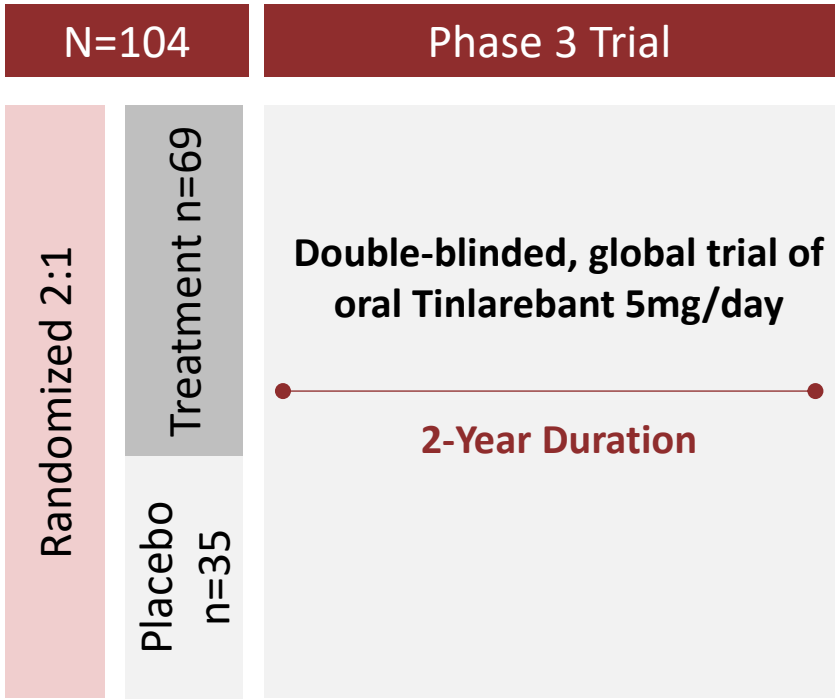
DRAGON Clinical Trial Design

Reduction in atrophic lesion growth rate as measured by fundus autofluorescence imaging is the FDA's accepted primary endpoint in Stargardt disease

DRAGON Design

Key Inclusion Criteria

- Clinical diagnosis of Stargardt disease
- 12-20 years old
- ≥1 mutation identified in the *ABCA4* gene
- Atrophic lesion size (DDAF) within 3 disc areas (7.62 mm^2)
- BCVA of 20/200 or better



Primary Measures

- *Slowing of atrophic lesion growth (DDAF)*
- *Safety and tolerability*

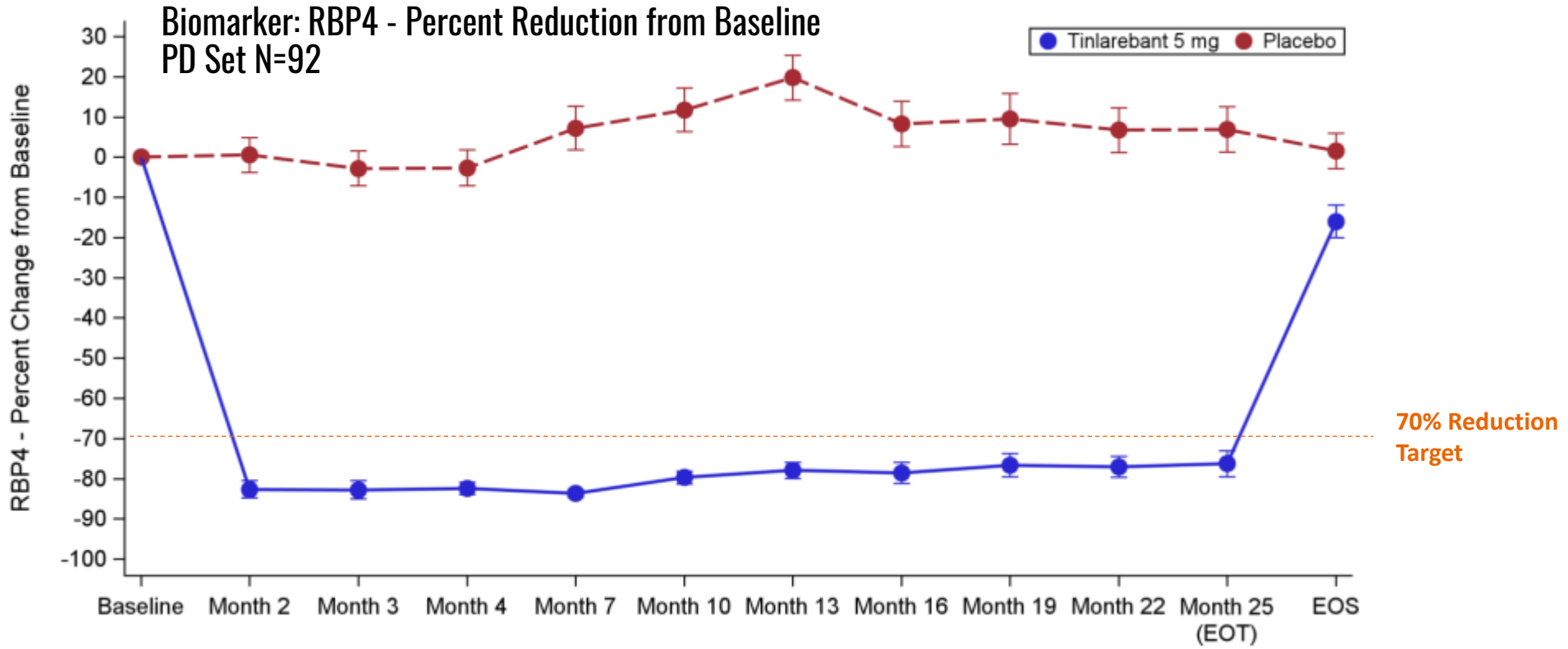
Secondary Measures

- *DAF*
- *BCVA*
- *SD-OCT*
- *Microperimetry*

DDAF = Definitely Decreased Autofluorescence; DAF = Decreased Autofluorescence; BCVA = Best-Corrected Visual Acuity; SD-OCT = Spectral-Domain Optical Coherence Tomography

PD Effect

Tinlarebant Produced an 80% Reduction of RBP4*



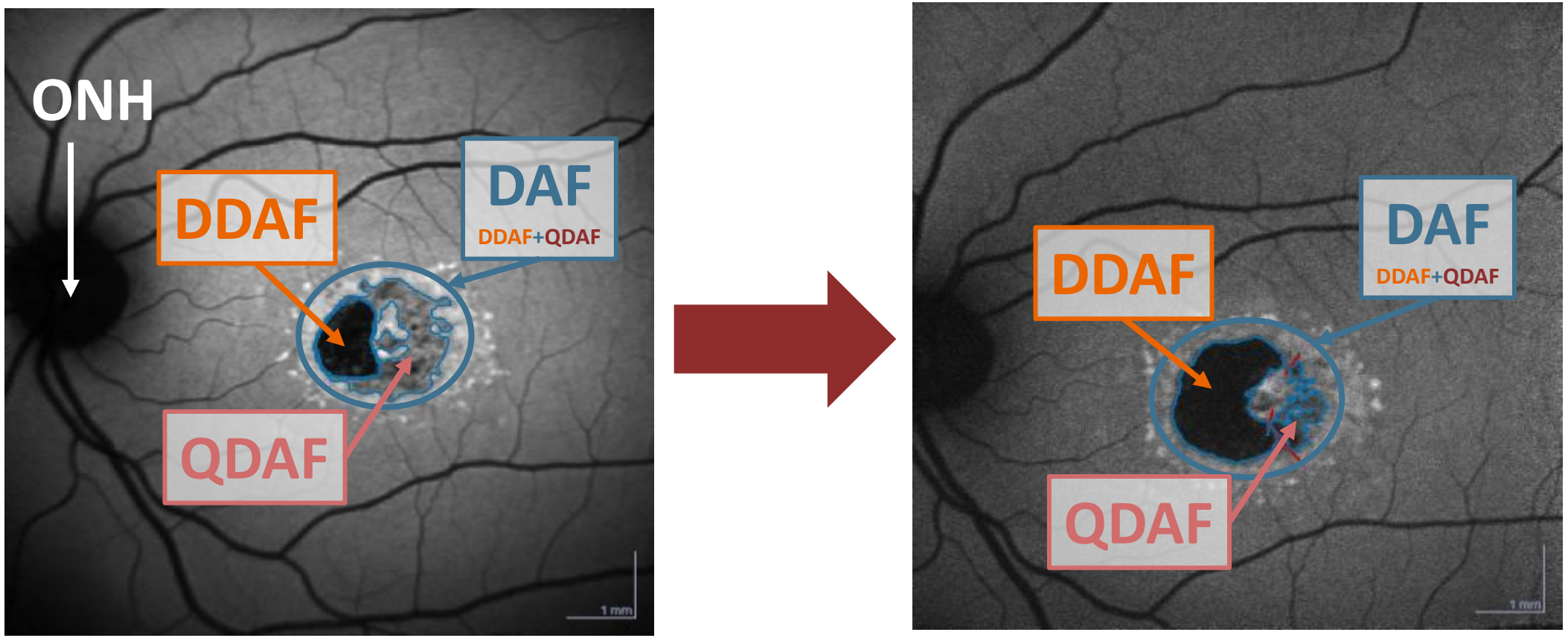
* In a prior study of a surrogate RBP4 antagonist (fenretinide) in patients with Geographic Atrophy, an RBP4 reduction of ≥70% was associated with a statistically significant slowing of lesion growth [Mata et al., Retina. 2013; 33(3): 498-507.]

Daily dosing of 5 mg/day Tinlarebant led to a sustained 80% reduction of RBP4 which returned to 84 % of the baseline value at the End of Study (28 days)

Lesion Types

DDAF Represents Well-demarcated Areas of Complete RPE Loss

- **DDAF** (definitely decreased autofluorescence): level of darkness close to 100% (at least 90%) relative to the ONH
- **QDAF** (questionably decreased autofluorescence): between 50% and 90% darkness
- **DAF** (decreased autofluorescence): the sum of DDAF and QDAF



Strauss RW, Ho A, Muñoz B, Cideciyan AV, Sahel JA, Sunness JS, Birch DG, Bernstein PS, Michaelides M, Traboulsi EI, Zrenner E, Sadda S, Ervin AM, West S, Scholl HPN; Progression of Stargardt Disease Study Group (2016) The Natural History of the Progression of Atrophy Secondary to Stargardt Disease (ProgStar) Studies: Design and Baseline Characteristics: ProgStar Report No. 1. Ophthalmology. 123: 817-28.

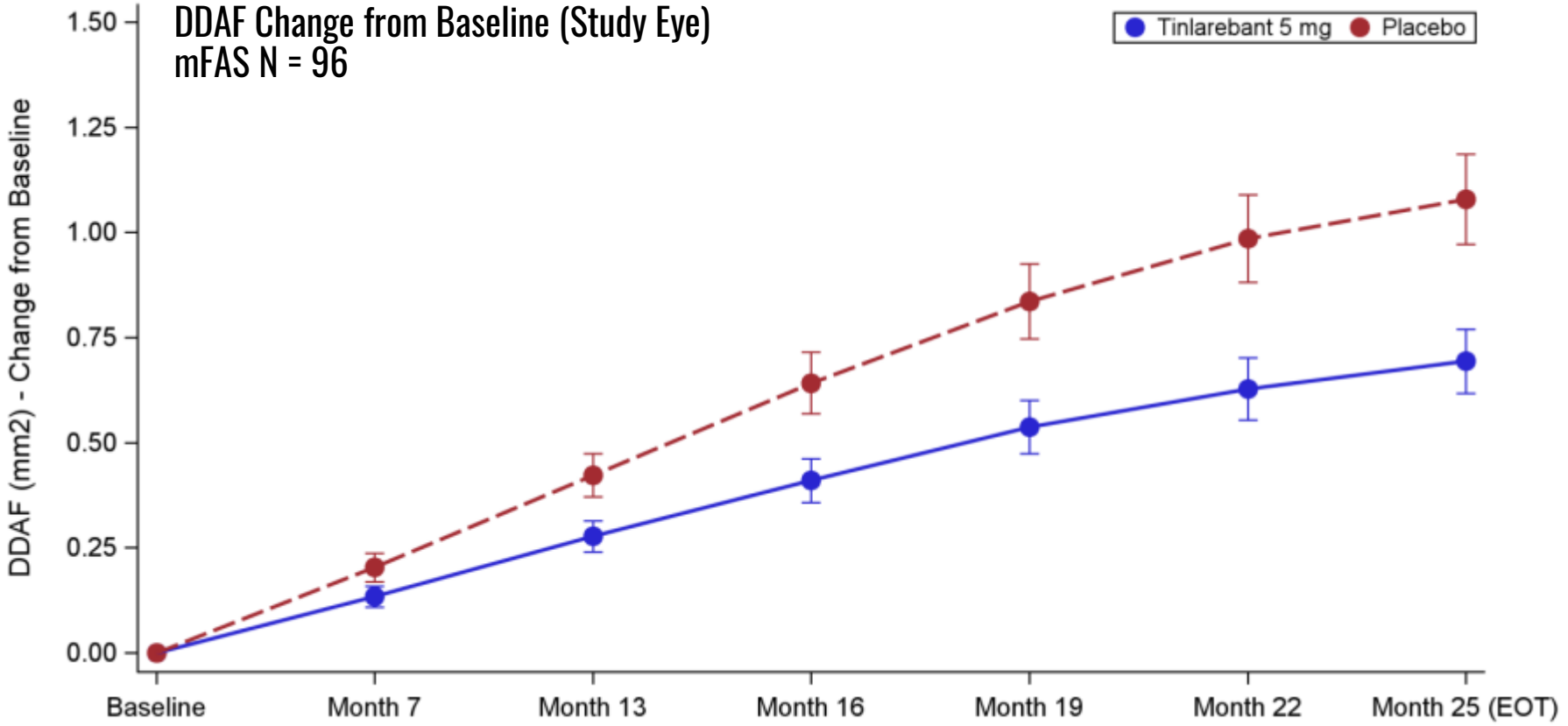
Efficacy Results

Primary Endpoint: DDAF Change in the Study Eye

- Annualized rate of lesion growth in the aggregate area of atrophy (DDAF) from baseline as assessed by fundus autofluorescence imaging through Month 25.
- Data is shown for the modified full analysis set (mFAS) which consists of all subjects who met the defined DDAF lesion eligibility criteria at baseline, having received at least one dose of study medication with at least one post baseline assessment.
- The Statistical Analysis Plan specified an unstructured covariance matrix for the Mixed Model for Repeated Measures (MMRM). The CRO also performed a post-hoc analysis using a first-order autoregressive covariance matrix to account for the longitudinal nature of the data and the relatively small sample size.

Efficacy Results

Tinlarebant Produced a Statistically Significant and Clinically Meaningful Reduction of DDAF Lesion Growth



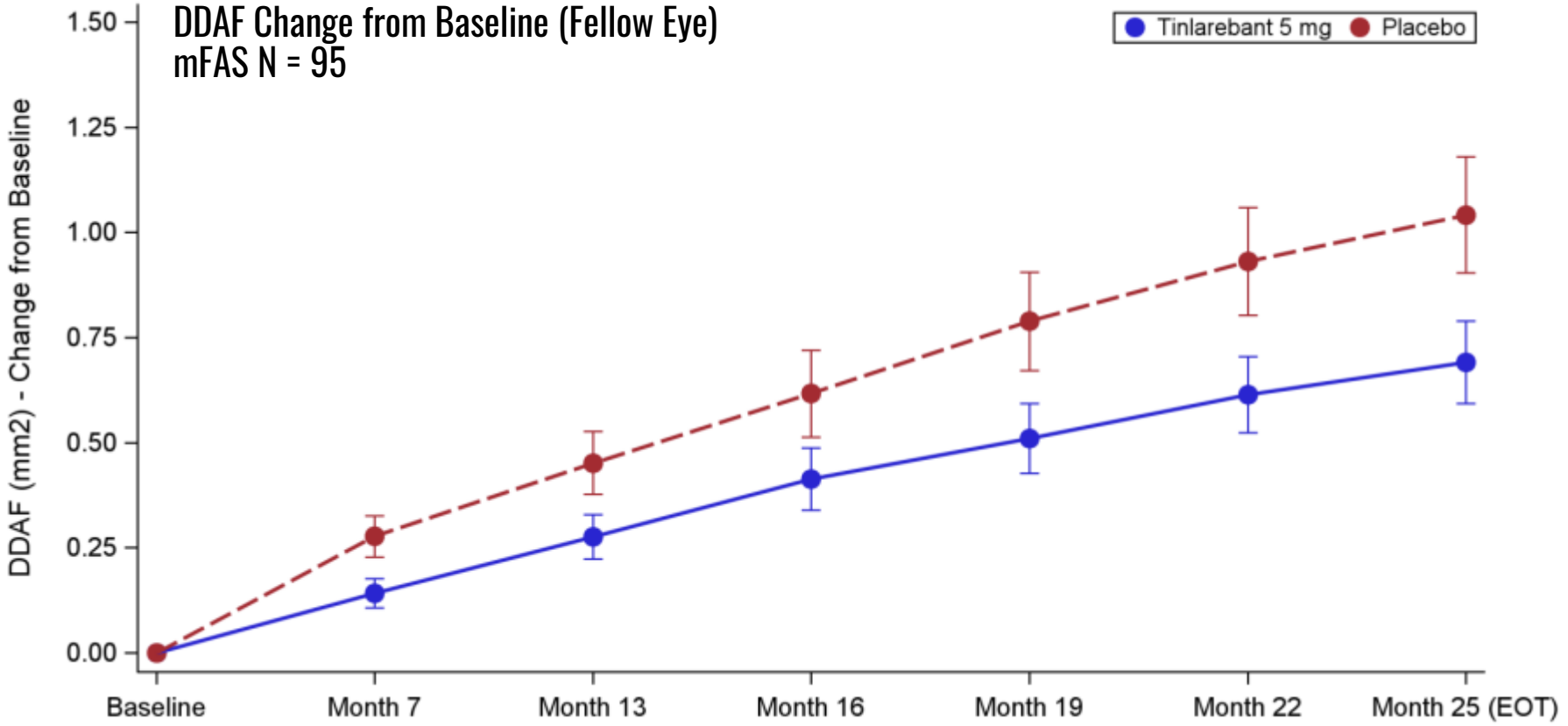
Applying an unstructured covariance matrix, the **treatment effect size was 35.7%** compared to placebo and yielded a **p-value of P = 0.0033**

With a first-order autoregressive covariance matrix, the **treatment effect size remained consistent (35.4%)** with **P <0.0001**

DDAF lesion growth was **slowed to 0.38 mm^2/year vs. 0.59 mm^2/year for placebo and 0.74 mm^2/year observed in ProgStar**

Efficacy Results

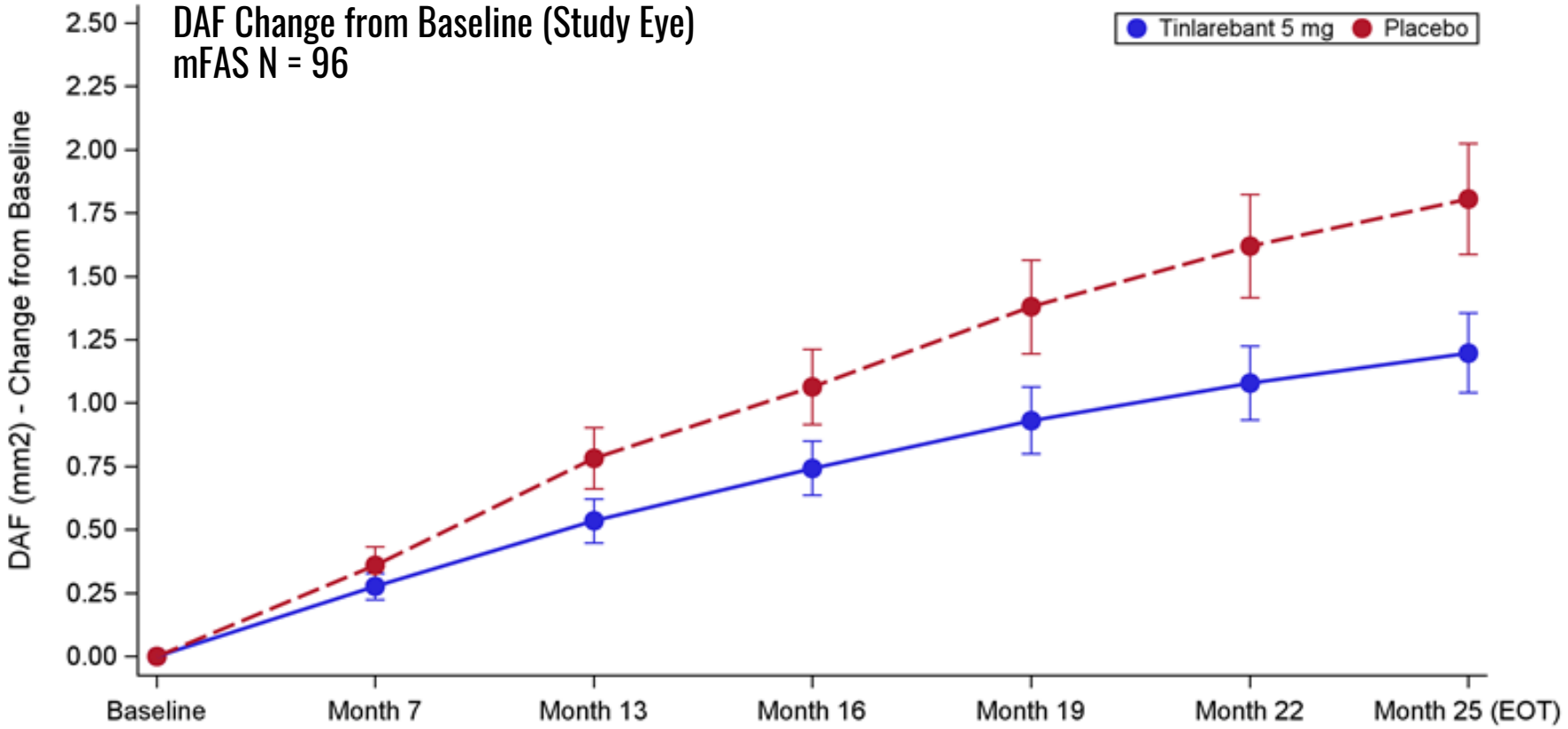
A Statistically Significant Reduction of DDAF Lesion Growth was Observed in the Fellow Eye



Tinlarebant slowed DDAF lesion growth in the fellow eye by 33.6% compared to placebo (P = 0.041)

Efficacy Results

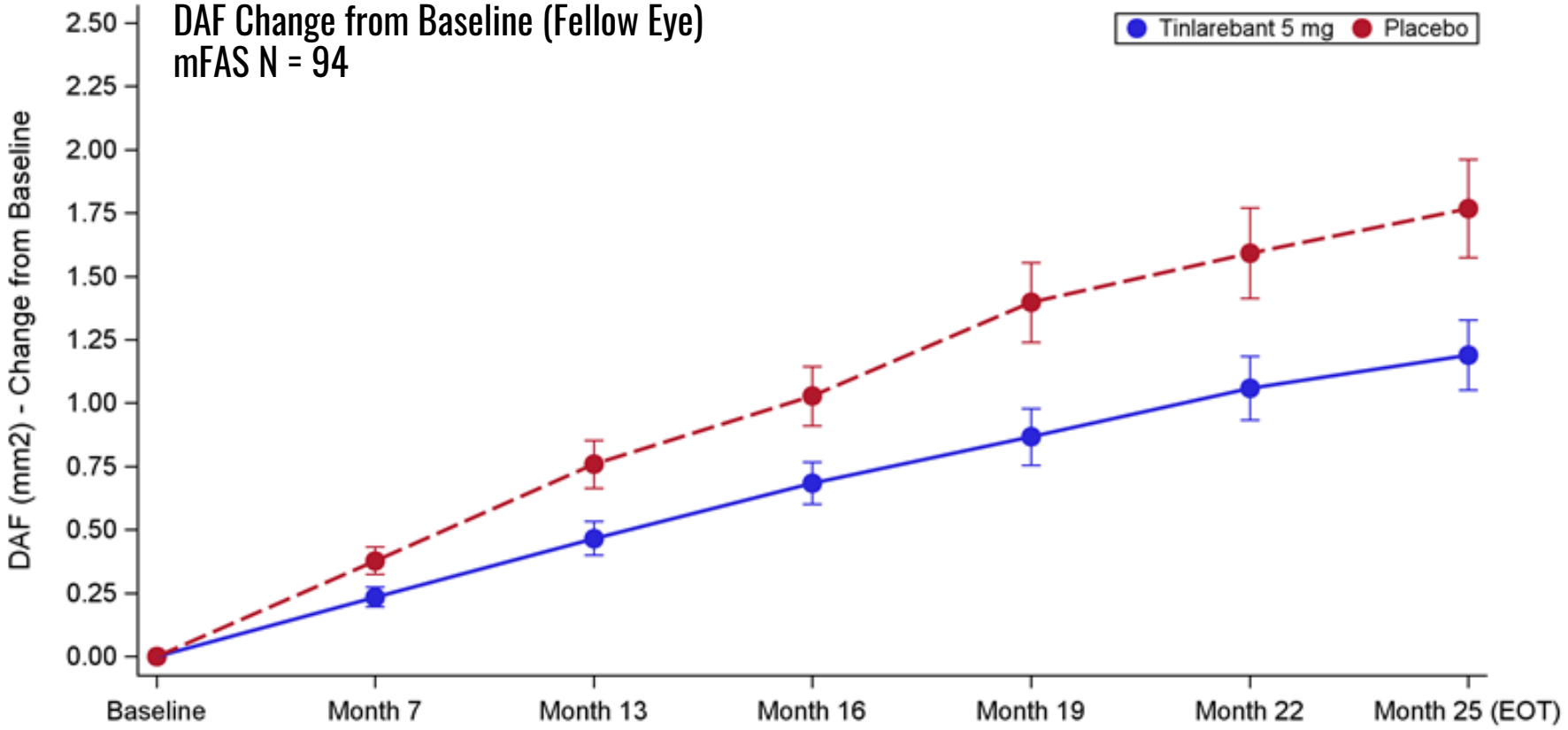
Tinlarebant Slowed DAF Lesion Growth in the Study Eye



Tinlarebant slowed DAF lesion growth by 33.7%
compared to placebo (P = 0.027)

Efficacy Results

Tinlarebant Slowed DAF Lesion Growth in the Fellow Eye



Tinlarebant slowed DAF lesion growth in the fellow eye by 32.7% compared to placebo (P = 0.017)

Efficacy Results

Change in BCVA was Consistent with Natural History

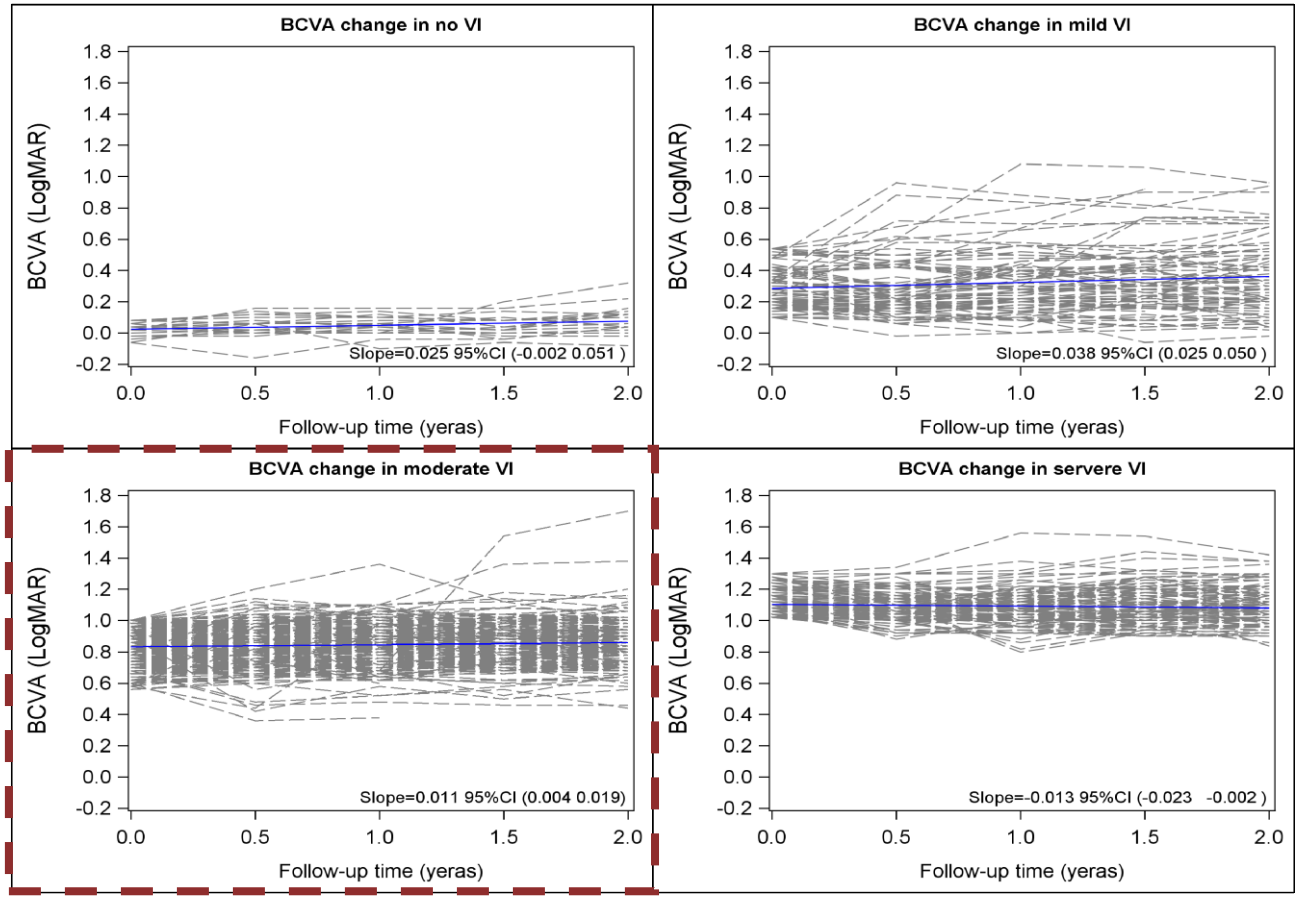
	Tinlarebant	Placebo
BCVA at Baseline	39.9	39.4
BCVA at EOS	39.7	40.0

- The overall change of visual acuity was minimal over the period of 24 months in both treatment groups
- Test–retest variability for ETDRS change scores in Stargardt disease are known to yield a repeatability coefficient ≈ 8 letters (1)
- Such minor changes in average visual acuity over two years are in line with the natural history of Stargardt disease and were observed in the ProgStar Study

(1) Parker MA, Choi D, Erker LR, Pennesi ME, Yang P, Chegarnov EN, Steinkamp PN, Schlechter CL, Dhaenens CM, Mohand-Said S, Audo I, Sahel J, Weleber RG, Wilson DJ. Test-Retest Variability of Functional and Structural Parameters in Patients with Stargardt Disease Participating in the SAR422459 Gene Therapy Trial. Transl Vis Sci Technol. 2016 Oct 1;5(5):10.

Natural History of VA Loss

ProgStar: Visual Acuity Change over 24 Months
Prospective Cohort (N=434)



- **Overall rate of BCVA loss was 0.55 letters/year over two years**
- **BCVA of eyes with baseline BCVA between 20/70 and 20/200 declined at a rate of 0.6 letters/year**

Kong X, Fujinami K, Strauss RW, Munoz B, West SK, Cideciyan AV, Michaelides M, Sahel JA, Ahmed M, Ervin AM, Schönbach EM, Cheetham JK, Scholl HPN; ProgStar Study Group (2018) Visual Acuity Change over 24 Months and its Association With Foveal Phenotype and Genotype in Individuals With Stargardt Disease: ProgStar Report Number 10. JAMA Ophthalmol. 136: 920-928.

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Safety Results

Safety Results

Tinlarebant Demonstrated a Well Tolerated Safety Profile

Safety Set N = 104

Subjects Who Experienced at Least One Non-Ocular Treatment-Emergent Adverse Event (TEAE), N (%)

Category	Tinlarebant 5mg (N=69)	Placebo (N=35)
TEAE	59 (85.5%)	27 (77.1%)
Severe TEAE	2 (2.9%)	1 (2.9%)
Serious TEAE	2 (2.9%)	4 (11.4%)
Study Drug-Related TEAE	14 (20.3%)	4 (11.4%)
Study Drug-Related Serious TEAE	0 (0.0%)	0 (0.0%)
TEAE Leading to Study Drug Discontinuation	0 (0.0%)	0 (0.0%)
TEAE Leading to Study Discontinuation	0 (0.0%)	0 (0.0%)
TEAE Leading to Death	0 (0.0%)	0 (0.0%)

- Total of 6 serious adverse events (SAEs) reported in the study – all events were non-ocular, with 4 assessed as unrelated and 2 assessed as unlikely related to the study treatment
- Most reported Non-Ocular adverse events (AEs): Nasopharyngitis (all cases were assessed as unrelated/unlikely related to treatment), Headache, and Acne – most events were mild and resolved during the study period

Safety Results

The Majority of Ocular Adverse Events were Mild

Safety Set N = 104

Subjects Who Experience at Least One Ocular TEAE, N (%)

Category	Tinlarebant 5mg (N=69)	Placebo (N=35)
TEAE	53 (76.8%)	8 (22.9%)
Severe TEAE	2 (2.9%)	0 (0.0%)
Serious TEAE	0 (0.0%)	0 (0.0%)
Study Drug-Related TEAE	49 (71.0%)	8 (22.9%)
Study Drug-Related Serious TEAE	0 (0.0%)	0 (0.0%)
TEAE Leading to Study Drug Discontinuation	4 (5.8%)	0 (0.0%)
TEAE Leading to Study Discontinuation	2 (2.9%)	0 (0.0%)
TEAE Leading to Death	0 (0.0%)	0 (0.0%)

- Most reported Ocular AEs: Xanthopsia, Delayed dark adaptation, and Night Vision Impairment
- The majority of the events were mild, and most resolved while on study
- There were no serious ocular TEAEs – 4 TEAEs lead to study drug discontinuation and 2 TEAEs lead to study discontinuation

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Summary

Summary

Summary Findings from the DRAGON Trial

- **The DRAGON trial met its primary endpoint:** A statistically significant slowing in DDAF lesion growth was observed in subjects treated with 5 mg/day compared to placebo
- The biomarker of tinlarebant treatment, **RBP4 reduction, showed a sustained mean 80% reduction with very little variability**
- **The treatment effect against DDAF lesion growth was 36% in Study Eyes** and should be considered **clinically meaningful**
- The observed treatment effect against DDAF was **supported by the key secondary endpoint: a reduction of DAF area growth,** and fellow eye data
- The **change in BCVA was minimal** in both the treatment and the placebo group – **consistent with natural history data**
- **Oral tinlarebant (5 mg/day) was well tolerated over 2-years** in adolescent STGD1 patients

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Thank You

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