Topline Results from the Phase 3 DRAGON Study of Tinlarebant for Adolescent Stargardt's Disease

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Tinlarebant

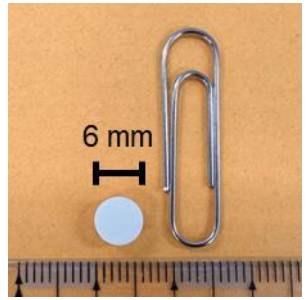
Introduction to Tinlarebant

- Patients affected with Stargardt Disease (STGD1) harbor genetic mutations in a key protein within the retina which interferes with normal vitamin A processing in the visual cycle; this results in the accumulation of cytotoxic byproducts of vitamin A (*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 cytotoxic bisretinoids**.

- Belite Bio believes that **intervention directed at emerging retinal pathology**, which is not primarily mediated by complement activation/inflammation, would be the best approach to potentially slow disease progression in STGD1 & GA.

Tinlarebant Tablet



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

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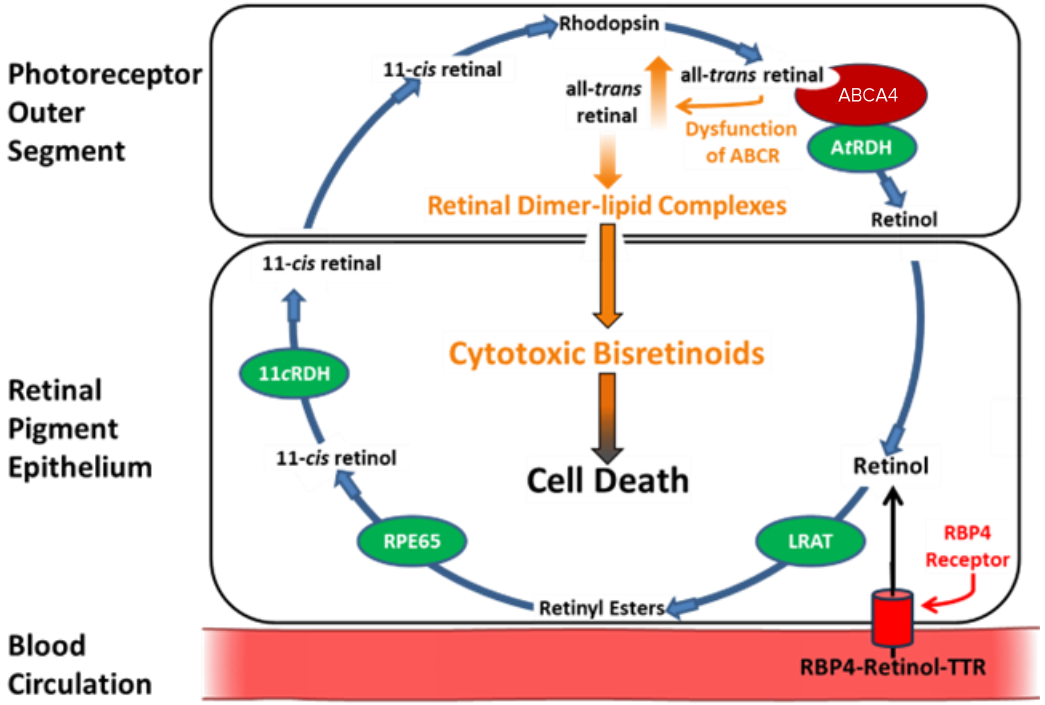
Formation of Bisretinoids in STGD1 Patients

- Vitamin A (retinol) travels through the circulation as a ternary complex bound to RBP4 and transthyretin (TTR); this is a large sized complex which cannot be eliminated through the kidney
- Unlike other extra-hepatic target tissues, the eye has a unique requirement for uptake of retinol bound to RBP4 due to the abundant expression of an RBP4 receptor
- Retinol taken into the eye goes through a series of enzymatic reactions resulting in the formation of rhodopsin in the retina
- Photoactivation of rhodopsin liberates all-*trans* retinal which is transported out of the retina by the ABCA4 protein
- In STGD1 patients, dysfunction of the ABCA4 protein results in accumulation of all-*trans* retinal which spontaneously reacts with other retinal species and lipids producing Retinal Dimer-lipid Complexes (aka, *bisretinoids*)
- Deposition of these complexes into the RPE results in the formation of cytotoxic bisretinoids which have been shown to kill RPE cells through diverse mechanisms.



Abbreviations: ABCA4, ATP-binding cassette sub-family A member 4 ; A*t*RDH, all-*trans* retinol dehydrogenase; LRAT, lecithin retinol acyltransferase; RPE65, retinal pigment epithelium protein 65kDa; 11*c*RDH, 11-*cis* retinol dehydrogenase.

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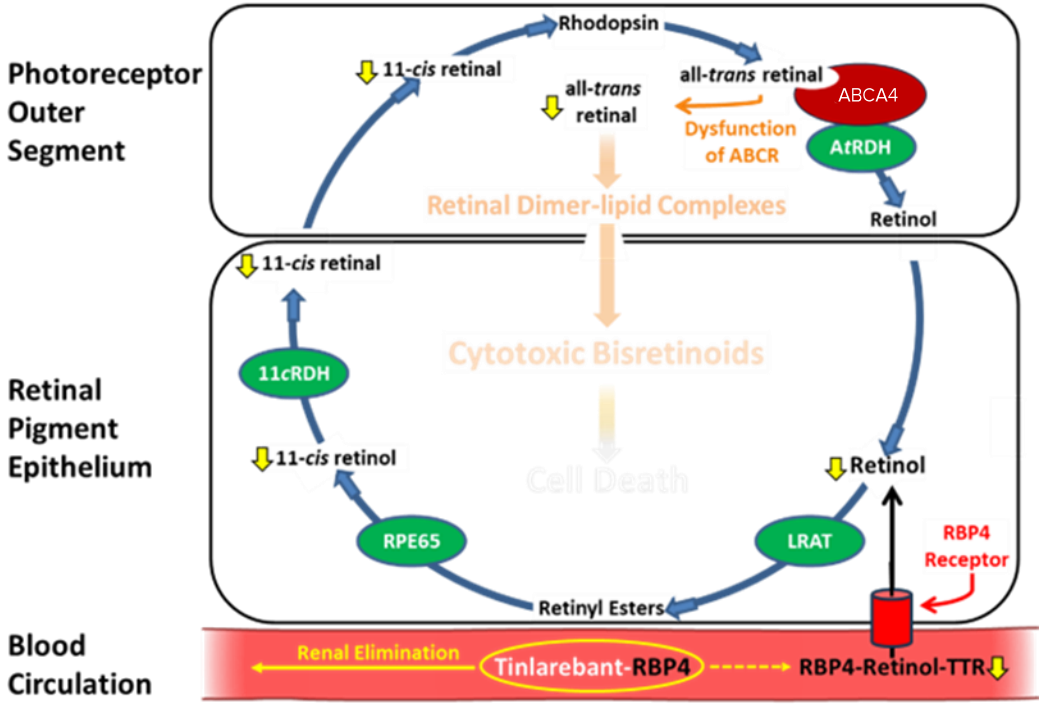
Mechanism of Tinlarebant Action

- Tinlarebant is a small molecule RBP4 antagonist which has a 100-fold greater affinity for RBP4 compared to retinol
- Tinlarebant competes with retinol for binding to RBP4 and does not allow the binding of TTR
- The tinlarebant-RBP4 complex is liberated into the circulation and is readily eliminated through the kidney due its small size
- The net effect is a reduction in the native ternary complex of RBP4-retinol-TTR resulting in reduced retinol delivery to the eye
- Reduced retinol delivery to the eye results in a reduction of all retinoids cascading through the visual cycle, including retinaldehyde species
- Reduction of retinaldehyde levels, in turn, results in reduced formation of Retinal-Dimer-lipid complexes, reduced accumulation of cytotoxic bisretinoids, and preservation of retinal tissue



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Phase 3 DRAGON Trial in Stargardt Disease

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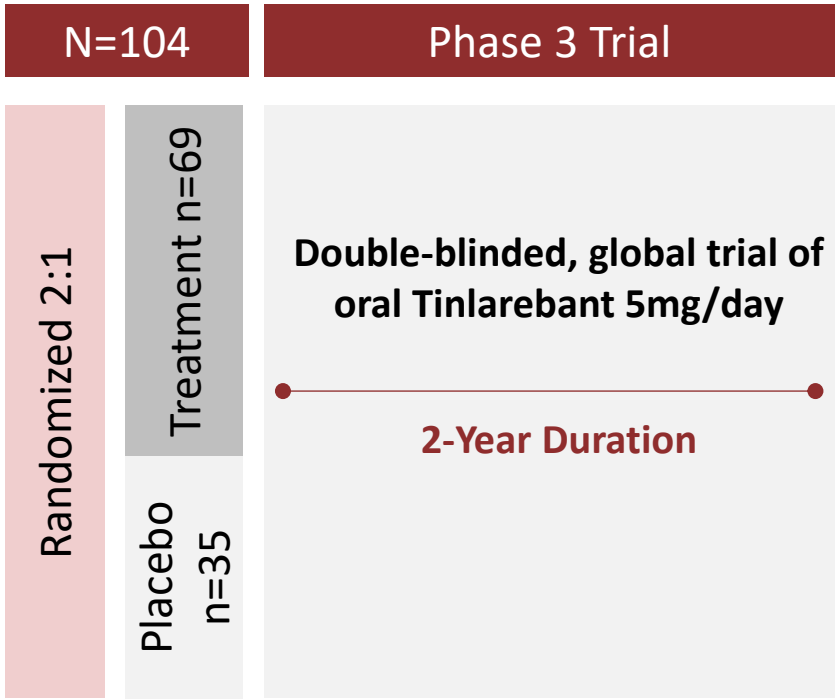
DRAGON Clinical Trial Design in Stargardt Disease

Reduction in atrophic lesion growth rate as measured by fundus autofluorescence imaging is the FDA's accepted primary endpoint in Stargardt disease and geographic atrophy secondary to age-related macular degeneration

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

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DRAGON Clinical Trial Demographics and Baseline Characteristics

	Mean (SD), Total N=104
Age (Years)	15.4 (2.47)
Baseline Height (cm)	168.12 (10.349)
Baseline Weight (kg)	61.75 (16.891)
Baseline BMI (kg/m2)	21.62 (4.578)

	N (%), Total N=104
Sex	
Male	65 (62.5%)
Female	39 (37.5%)
Race	
White	38 (36.5%)
Asian	58 (55.8%)
Multiple	1 (1.0%)
Other	7 (6.7%)

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Phase 3 DRAGON Trial in Stargardt Disease

-Data from DRAGON Topline Report

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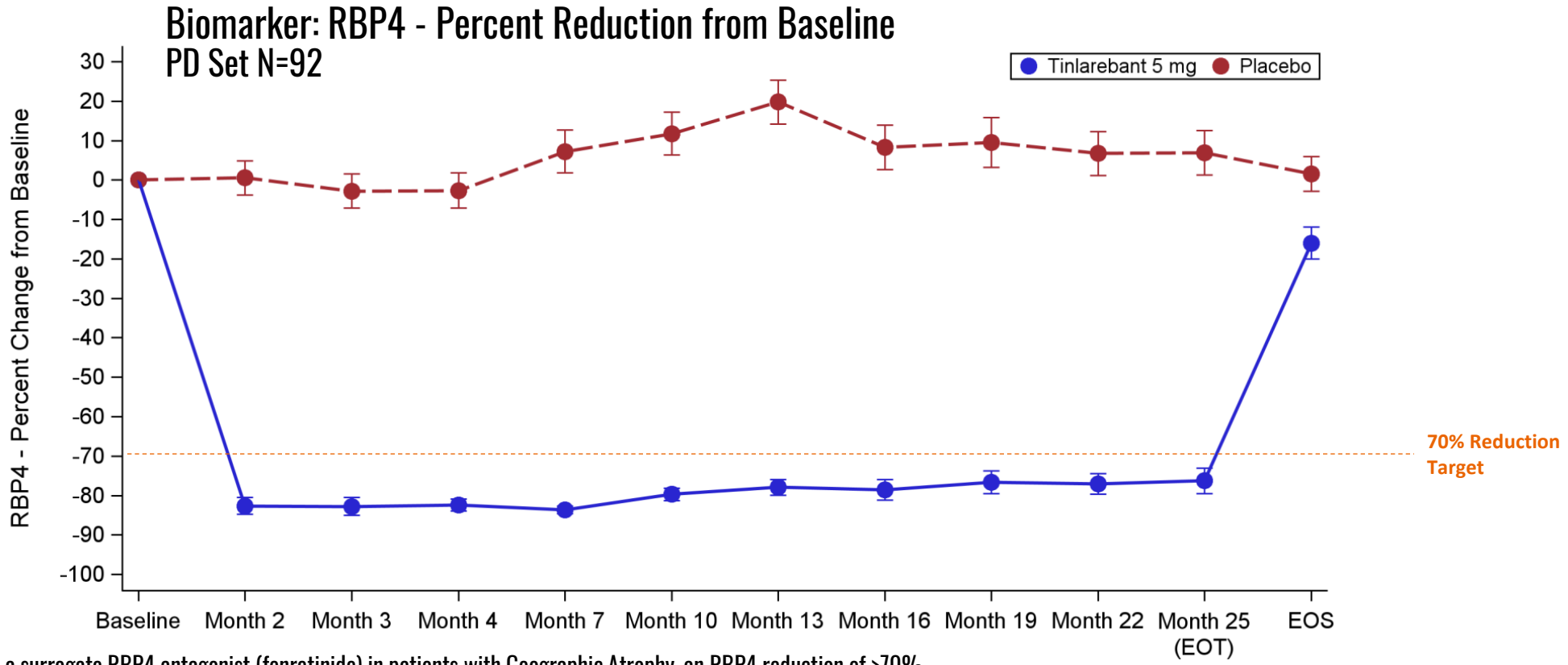
Tinlarebant Treatment Led to 80% Reduction in RBP4, Well Above Goal of 70%*



* 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 and RBP4 levels returned to 84 % of the baseline value at the End of Study (EOS)

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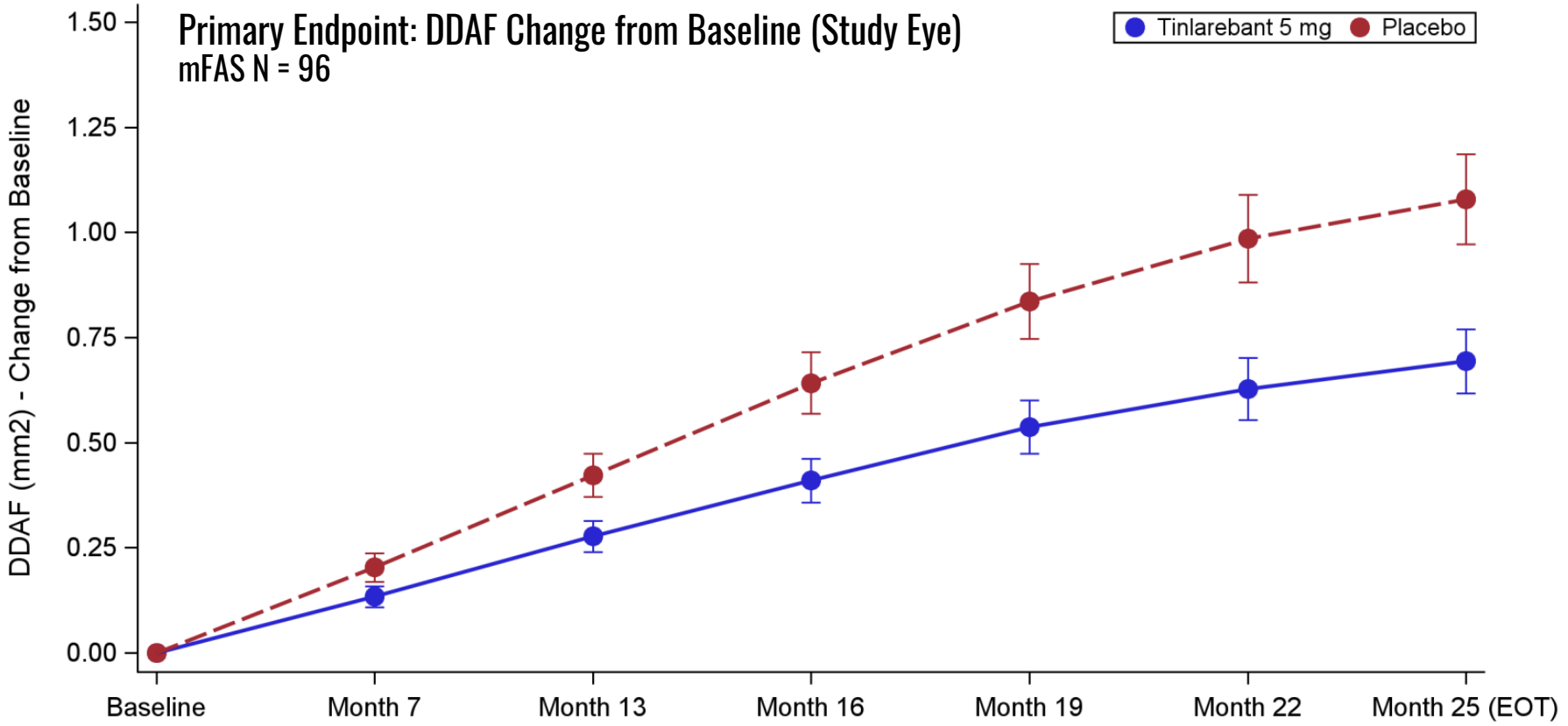
Primary Endpoint Showed a Statistically Significant & Clinically Meaningful Outcome



- 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 mm²/year vs. 0.59 mm²/year for placebo and 0.74 mm²/year observed in ProgStar**

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As Expected, BCVA in Study Eye Did Not Show Any Significant Change

	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.

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Tinlarebant Demonstrated a Well Tolerated Safety Profile

*TEAE=Treatment-emergent adverse event

Category	Tinlarebant 5mg (N=69)	Placebo (N=35)
Ocular 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%)
Non-Ocular 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%)

- Ocular TEAE: **Xanthopsia, Delayed Dark Adaptation, and Night Vision Impairment** are the most reported
  - The majority of the events were mild, and most resolved while on study.
- Non-ocular TEAE: **Nasopharyngitis (unrelated/unlikely related to treatment), Headache, and Acne** are the most reported
  - Most events were mild and resolved during the study period.
- Total of 6 Serious TEAEs were reported in the study
  - All events were non-ocular, with 4 assessed as unrelated and 2 assessed as unlikely related to the study treatment.
- No serious ocular TEAEs were reported; 4 TEAEs led to study drug discontinuation, and 2 led to study discontinuation.

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Summary

- **The DRAGON trial met its primary endpoint:** A highly statistically significant slowing in DDAF lesion growth was observed in subjects treated with 5 mg/day oral Tinlarebant as compared to placebo
- **The treatment effect was 36%** and is considered **clinically meaningful**
- The **change in best-corrected visual acuity was minimal** in both the treatment and the placebo group – and is **in-line with natural history data**
- The biomarker of tinlarebant treatment, **RBP4 reduction, showed a sustained 80% reduction with very little variability**
- **Tinlarebant (5 mg p.o., daily) was safe and well tolerated** in adolescent STGD1 patients

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THANK YOU