Safety, Tolerability, and Efficacy of Tinlarebant from a 24-Month, Phase 2 Study in Adolescent Patients Affected by Stargardt Disease

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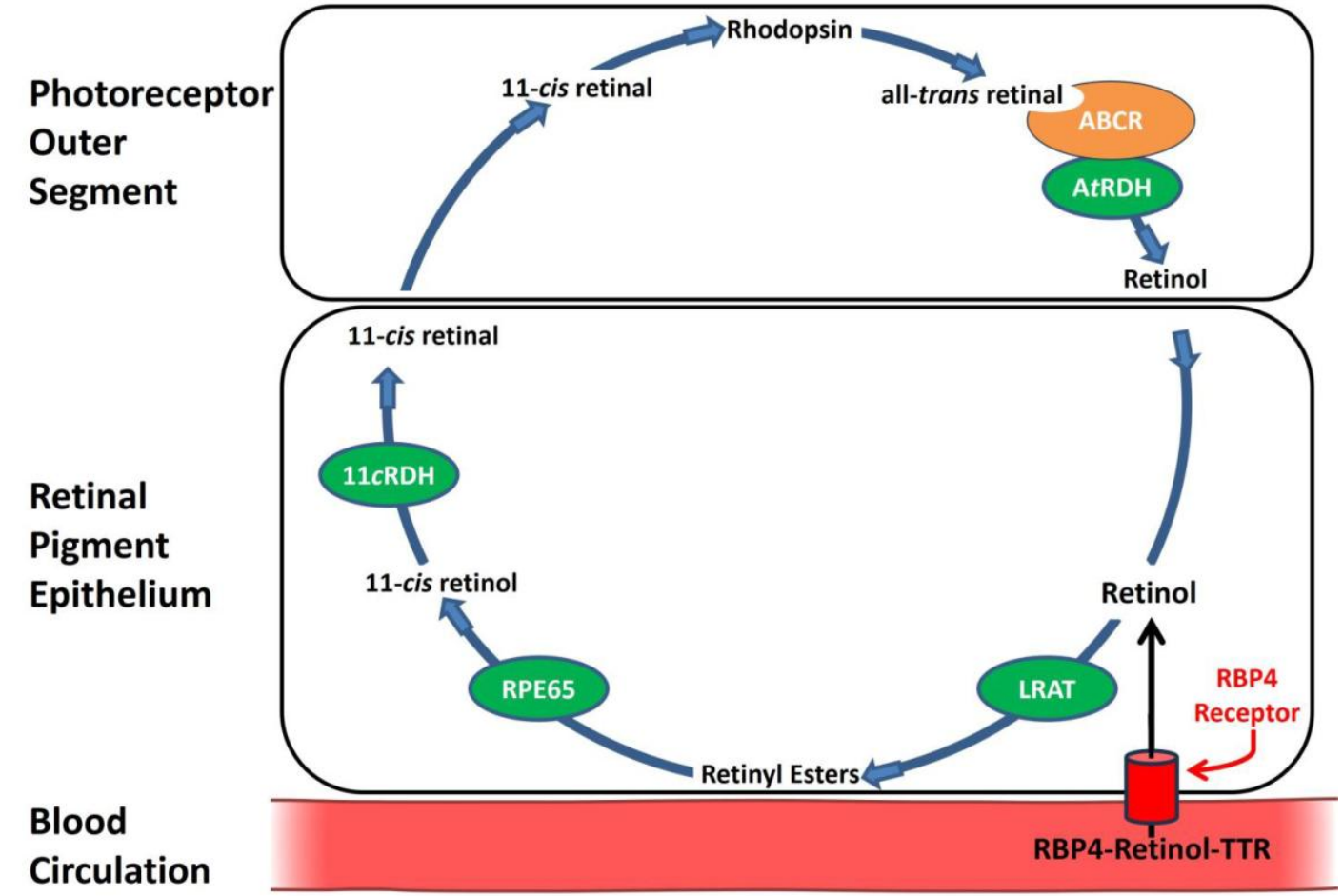
Characteristics of Autosomal Recessive Stargardt Disease (STGD1)

- **STGD1** – Mutations in a retina-specific ATP-binding cassette (ABC) transporter gene (*ABCA4*) which encodes a protein (ABCR) involved in removal of vitamin A aldehyde from the retina[1]
- **Disease Onset** – Typically during childhood, although diagnosis during adulthood is not uncommon and is generally associated with a less severe disease progression[2]
- **Pathology** – Characterized by
  - excessive accumulation of autofluorescent, cytotoxic, vitamin A byproducts (*bisretinoids*)
  - cellular debris (lipofuscin)
  - which leads to onset/growth of atrophic retinal lesions and loss of vision[3]

1. Molday RS, et al. The role of the photoreceptor ABC transporter ABCA4 in lipid transport and Stargardt macular degeneration. Biochim Biophys Acta. 2009;1791(7):573–83.
2. Tanna P, et al. Stargardt disease: Clinical features, molecular genetics, animal models and therapeutic options. Br J Ophthalmol. 2017;101(1):25–30.
3. Lambertus S, et al. Early-onset Stargardt disease: Phenotypic and genotypic characteristics. Ophthalmology. 2015;122(2):335–44.

Vitamin A Uptake and the Role of ABCR in the Visual Cycle

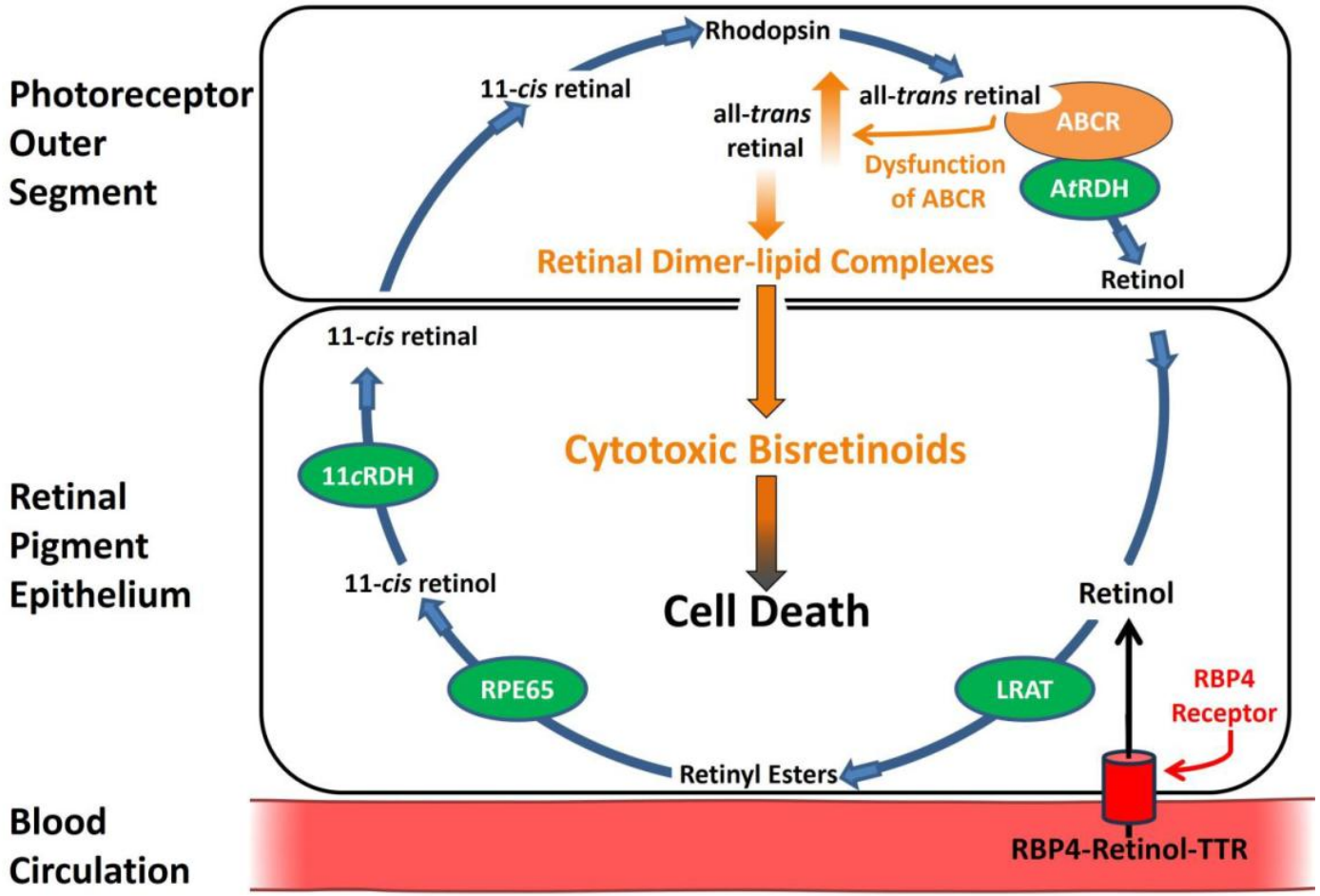
- Vitamin A (retinol) transported to eye in a protein complex with RBP4 & Transthyretin (TTR)
- Stra6 receptor on RPE binds specifically to retinol- RBP4- TTR complex
- Internalized retinol joins the visual cycle



Abbreviations: ABCR, ATP-binding cassette retina; A*t*RDH, all-*trans* retinol dehydrogenase; LRAT, lecithin retinol acyl transferase; RPE65, retinal pigment epithelium protein 65; RBP4, retinol binding protein 4; TTR, transthyretin; 11*c*RDH, 11-*cis* retinol dehydrogenase.

Accumulation of Bisretinoids and Retinal Cell Death in STGD1

- Dysfunction of ABCR
  - leads to accumulation of all-*trans* retinal within photoreceptor outer segments
- Reactivity of all-*trans* retinal promotes
  - formation of retinal dimer lipid complexes
  - deposited into the RPE during normal diurnal phagocytosis[6]
- Within the RPE
  - retinal dimer lipid complexes are converted to cytotoxic bisretinoids (e.g., A2E)
  - promote retinal cell death through diverse mechanisms[7,8]
- Continued retinol delivery to the eye drives bisretinoid accumulation



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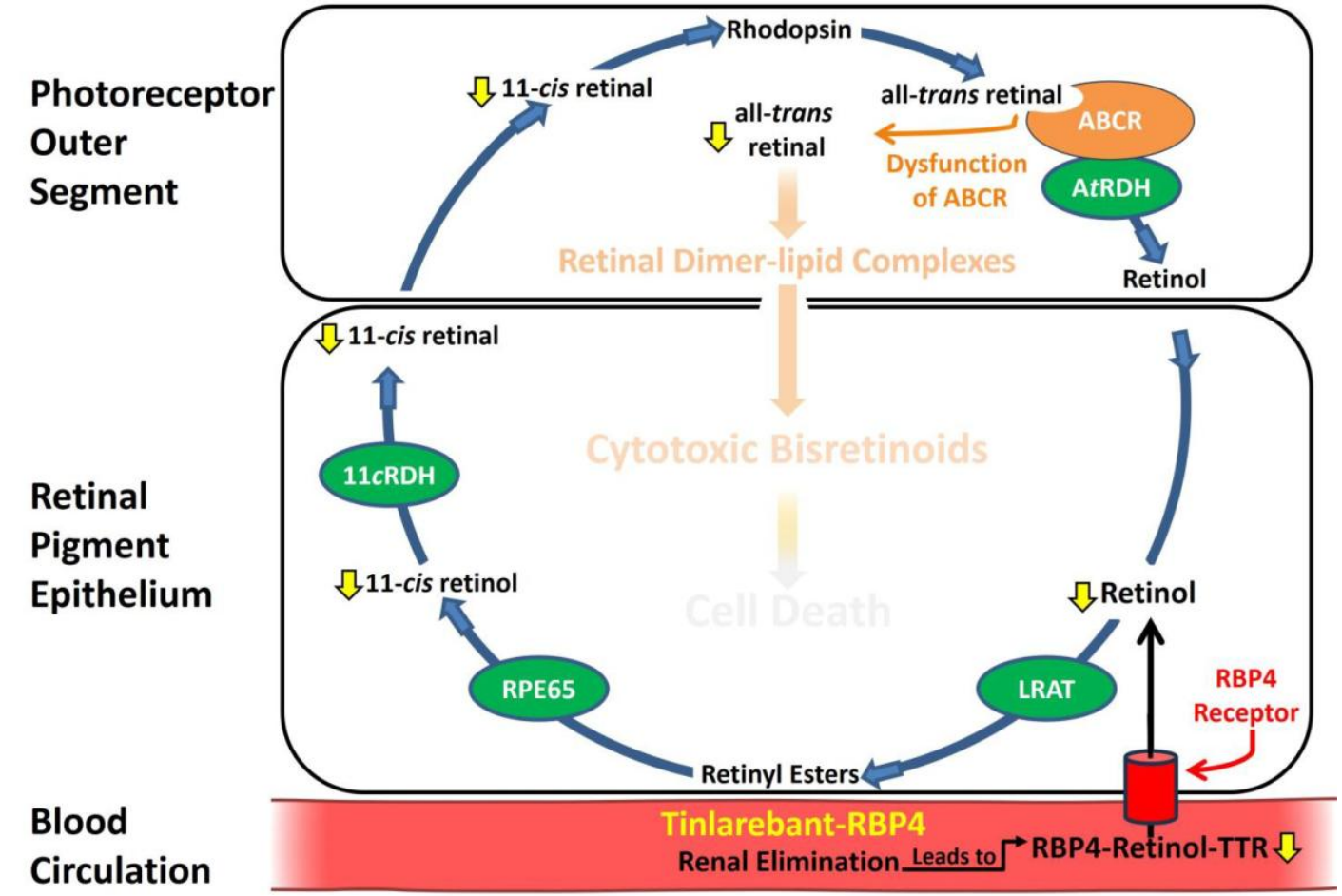
4. Sparrow JR, et al. The bisretinoids of retinal pigment epithelium. Prog Retin Eye Res. 2012; 31(2):121-35.
5. Parmar VM, et al. A2E-associated cell death and inflammation in retinal pigmented epithelial cells from human induced pluripotent stem cells. Stem Cell Res. 2018 Mar;27:95-104.
6. Sparrow JR. Bisretinoids of RPE lipofuscin: trigger for complement activation in age-related macular degeneration. Adv Exp Med Biol. 2010;703:63-74.

Therapeutic Approach: Reduce Retinol Delivery to the Eye

- Tinlarebant
  - Tinlarebant
    - binds to RBP4 with a 100-fold greater affinity than retinol
    - does not allow TTR binding
    - reduces retinol delivery to the eye
    - Doesn't impact vitamin A delivery to other tissues



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Phase 2 Trial Design

- The Phase 2 study of Tinlarebant in adolescent STGD1 patients is the 24-month extension of a Phase 1b/2 study

Phase 2 Study Design

- Open label study of confirmed STGD1 patients aged 12-18 years; n = 13, 11 from Phase 1b + 2 additional patients

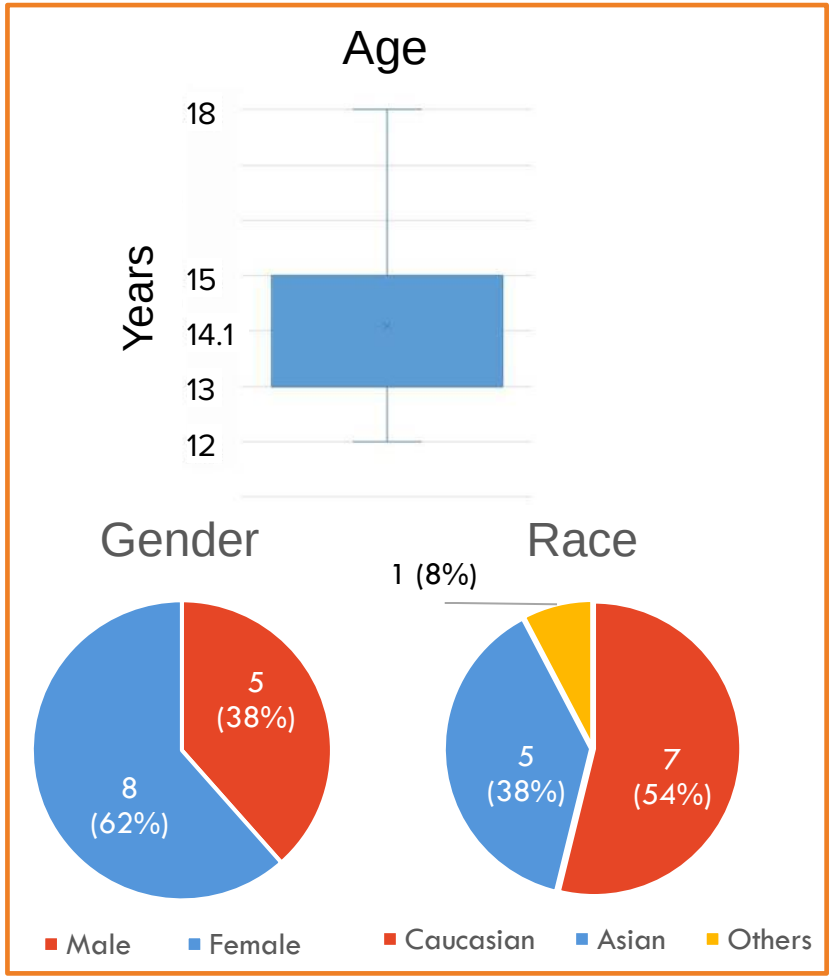
*All subjects showed only questionably decreased autofluorescence (QDAF) lesions at baseline (most were foveal-involved)

Primary Endpoints

- Ocular and systemic safety and tolerability

Secondary Endpoints

- Change in lesion size as assessed by Fundus Autofluorescence (FAF) photography
  - Definitely decreased autofluorescence (DDAF)
  - Questionably decreased autofluorescence (QDAF)
- Change in retinal thickness and morphology by SD-OCT
- Change in retinal sensitivity by microperimetry
- Change in BCVA
- Correlation between reduction in RBP4 level and the rate of DDAF lesion growth



Analysis of *ABCA4* Mutations in the Phase 2 Study Cohort

- Severe biallelic *ABCA4* mutations were found in 11 of 13 subjects
- (Subjects 3 and 5 harbored one moderate allele each)

Subject	cDNA change	Protein change	CADD v1.6 [1]	Assessment	Function tested *in vitro*	ClinVar
1	c.1922G>C	p.Cys641Ser	25.7	likely severe		not provided
1	c.2905A>G	p.Lys969Glu	28.9	likely severe		Pathogenic
2	c.768G>T	p.(Leu257Valfs*17)	23.1	severe	yes	Pathogenic/Likely pathogenic
2	c.[1532G>A;6006-1G>C]	p.[Arg511His;?]	15.3; 34	severe		not provided
3	c.4539+2028C>T	p.[=,Arg1514Leufs*36]	1.79	moderate	yes	Pathogenic/Likely pathogenic
3	c.2894A>G	p.Asn965Ser	24.8	severe	yes	Pathogenic
4	c.2576del	p.Gln859Argfs*41	N/A	severe		Pathogenic
4	c.[2588G>C;5603A>T]	p.[Gly863Ala;Asn1868Ile]	31; 23.3	moderate/severe	yes; yes	Likely pathogenic
5	c.3260A>G	p.Glu1087Gly	29.5	likely severe		Pathogenic
5	c.5714+5G>A	p.[=,Glu1863Leufs*33]	19.1	moderate	yes	Pathogenic/Likely pathogenic
6	c.5461-10T>C	p.[Thr1821Aspfs*6,Thr1821Valfs*13]	16.8	severe	yes	Pathogenic
6	c.6079C>T	p.Leu2027Phe	27.6	severe	yes	Pathogenic/Likely pathogenic
7	c.634C>T	p.Arg212Cys	26.3	severe	yes	Pathogenic/Likely pathogenic
7	c.2894A>G	p.Asn965Ser	24.8	severe	yes	Pathogenic
8	c.161G>A	p.Cys54Tyr	33	severe	yes	Pathogenic/Likely pathogenic
8	c.4139C>T	p.Pro1380Leu	25.3	moderate/severe	yes	Pathogenic/Likely pathogenic
9	c.1804C>T	p.Arg602Trp	24.7	severe	yes	Pathogenic/Likely pathogenic
9	c.5645T>C	p.Met1882Thr	24.8	likely severe		Uncertain significance
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Combined Annotation–Dependent Depletion (CADD)

Variants with CADD score >20 predicted to be among the 1% most deleterious
https://cadd.gs.washington.edu/

N/A: Not available

Analysis of *ABCA4* Mutations in the Phase 2 Study Cohort

- Subjects 1, 3, 4, 12, and 13
  - Did not develop atrophic lesions during the Phase 2 study
  - Despite harboring severe or likely severe alleles

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N/A: Not available

Analysis of *ABCA4* Mutations in the Phase 2 Study Cohort

- Subjects 9 & 10 (brothers)
- Subjects 12 & 13 (brother/sister)
  - Harbor identical mutations
  - Different phenotypes

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N/A: Not available

Visual acuity outcomes - background

- A subgroup of 6 subjects
  - mean bilateral BCVA loss of ~10 letters/year prior to enrollment
- The natural history would predict significant visual loss over 2 yrs
- Foveal-involved QDAF leads to visual acuity compromise

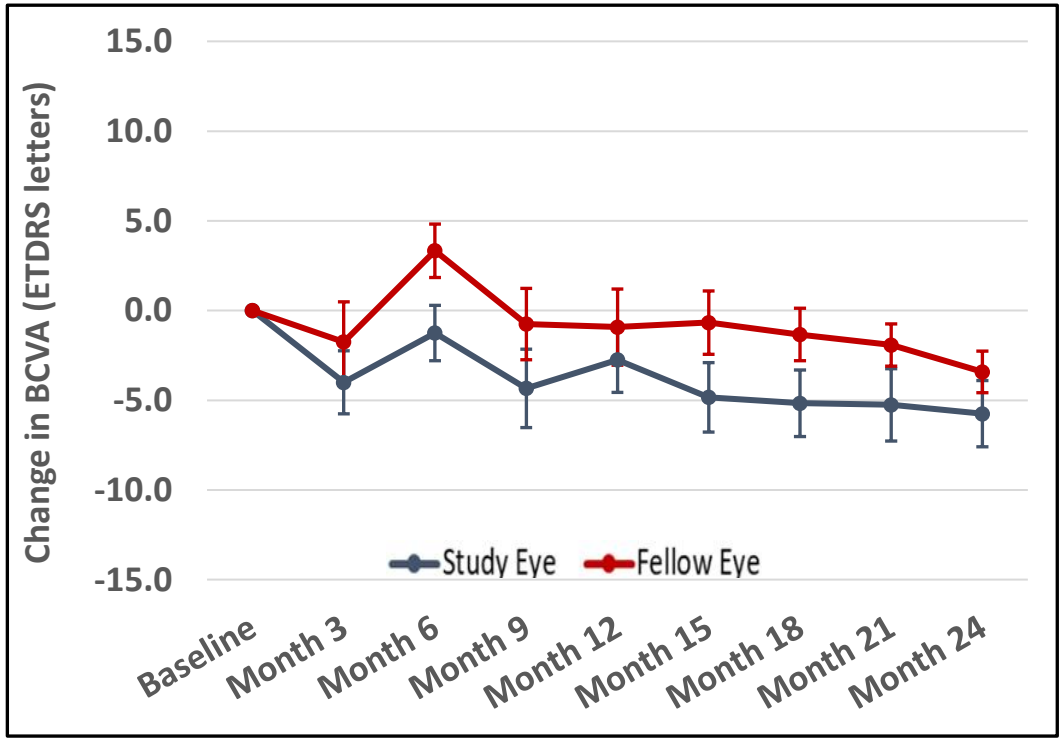
Subject	Race	Gender	Age at First Exam	Age at Enrollment	Disease Duration (yrs)	BCVA at Diagnosis Exam (Right / Left)	BCVA at Enrollment (Right/Left)	Annual Letter Loss (Right/Left)
1	Caucasian	Female	13	15	2	36/37	34/36	-
2	Caucasian	Female	11	12	1	33/39	40/42	-
3	Asian/ Caucasian	Female	13	13	<1	49/44	49/48	-
4	Caucasian	Female	14	15	1	39/44	45/45	-
5*	Caucasian	Female	12	13	1	70/61	45/55	25/6
6*	Caucasian	Female	13	18	5	70/65	35/36	7/6
7	Caucasian	Male	15	15	<1	59/75	69/40	-
8*	Caucasian	Male	8	13	5	57/57	31/31	5/5
9	Asian	Male	12	13	1	50/35	45/35	-
10*	Asian	Male	11	12	1	50/59	45/35	5/24
11*	Asian	Female	13	14	1	59/59	50/50	9/9
12	Asian	Female	10	18	8	35/44	35/35	-
13*	Asian	Male	10	12	2	59/59	35/35	12/12

*Subjects showing annual bilateral BCVA loss prior to Phase 2 enrollment; BCVA loss for subjects with <1 year disease not considered

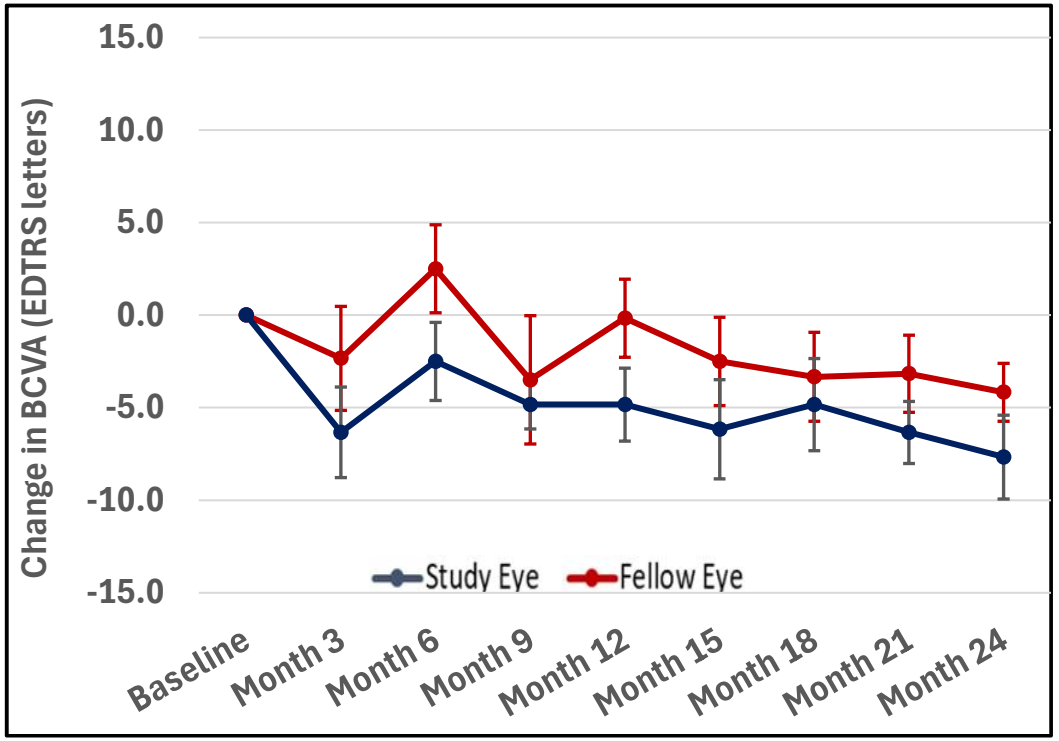
Change in Best Corrected Visual Acuity

- Visual acuity was stabilized during the study with a mean loss of 5 letters in the cohort over 24 months of treatment (equivalent to 2.5 letters lost/year, left panel)*
- For the 6 subjects:
  - Pre-enrollment mean bilateral loss of ~10 letters/year
  - 24-month data mean BCVA loss was 3.8 letters (equivalent to 1.9 letters lost/year, right panel)*

All Subjects



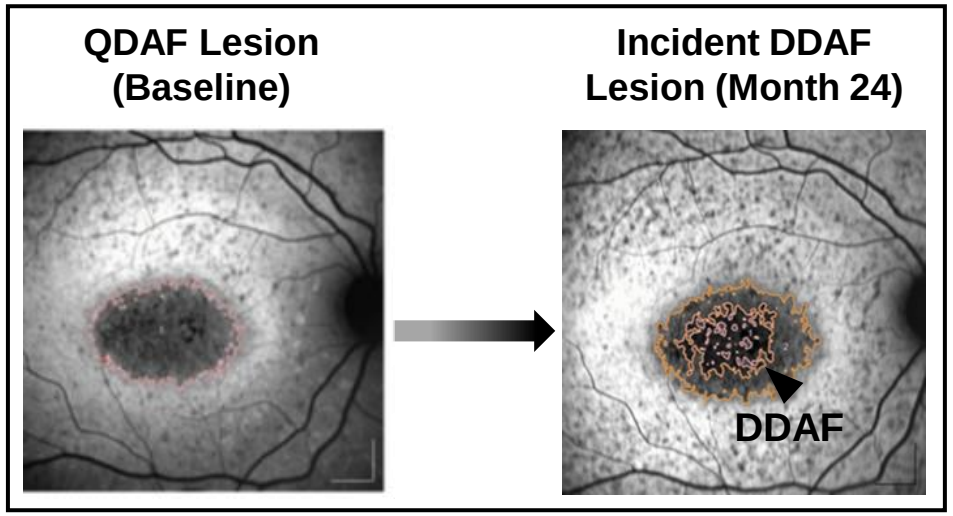
Subjects with Bilateral VA Loss Pre-Enrollment

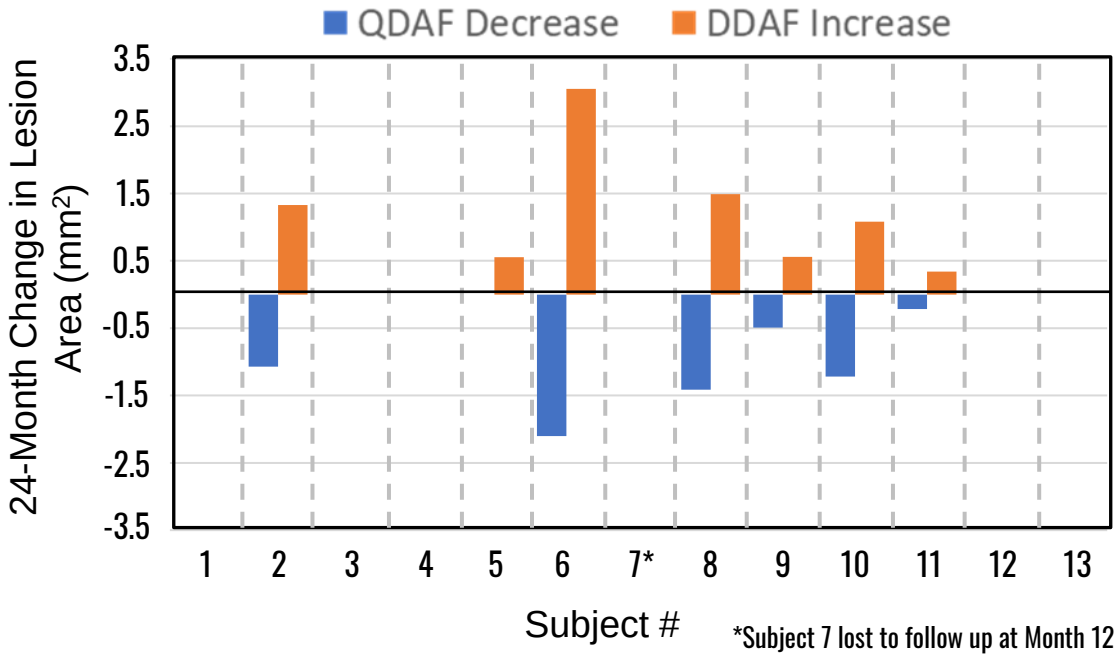


*Mean BCVA values at each timepoint were used to calculate the mean BCVA change over 24 months

24-Month Change in QDAF and DDAF Lesion Size

- Transition to, and growth of, incident DDAF in cohort
- In 5 of 12 subjects (42%),
  - no change in QDAF lesion size
  - no incident DDAF lesion growth observed
- In 7 of 12 subjects (58%)
  - DDAF lesions were relatively small
  - DDAF occurred with QDAF lesions
  - mean DDAF lesion size growth among all subjects over 24 months was 1.2 mm^2
- Only 1 subject (#5) showed a new DDAF lesion (0.5 mm^2) which was outside of the QDAF lesion area that was identified at Baseline
- Sibling subjects with identical *ABCA4* mutations and similar disease duration (9, 10, 13) showed different disease progression based on BCVA loss and QDAF/DDAF lesion growth



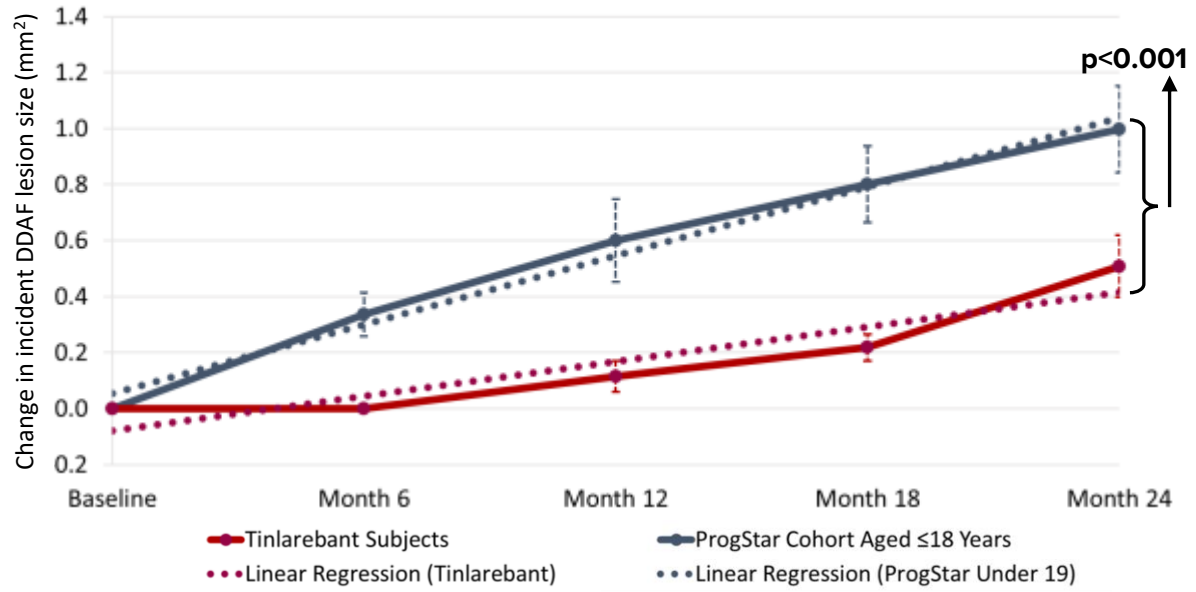


*Subject 7 lost to follow up at Month 12

Mean Growth Rate of Incident DDAF Lesions & Comparison to Natural History

- Incident DDAF lesions appeared in 7 subjects at different timepoints over 24 months; 4 of these subjects developed DDAF lesions after Month 12
- The mean DDAF lesion growth at Month 24 was 0.51 ± 0.4 mm^2
- Comparison of the mean DDAF lesion growth in Tinlarebant-treated subjects to natural history data from patients possessing similar baseline characteristics (from the ProgStar study) showed significantly lower growth in Tinlarebant-treated subjects ($p<0.001$)

Growth of Incident DDAF Retinal Lesions



	LBS-008-CT02	ProgStar Cohort [1, 2]
Patient Pool	**N=12**	**N=51* (aged ≤18 years)**
Mean change in incident DDAF lesion size at Month 24	**0.51± 0.4 mm^2**	**1.00 ± 1.3 mm^2**

Note:

** Only 50 patients from ProgStar Cohort (aged ≤18) were included in the analysis due to one subject having ungradable screening FAF data*

1. Strauss RW, Ho A, Muñoz B, et al. ProgStar Report No. 1. Ophthalmology. 2016;123(4):817-28.

2. Strauss RW, Muñoz B, Ho A, et al. ProgStar Report No. 9. JAMA Ophthalmol. 2017; 135(11):1232-1241.

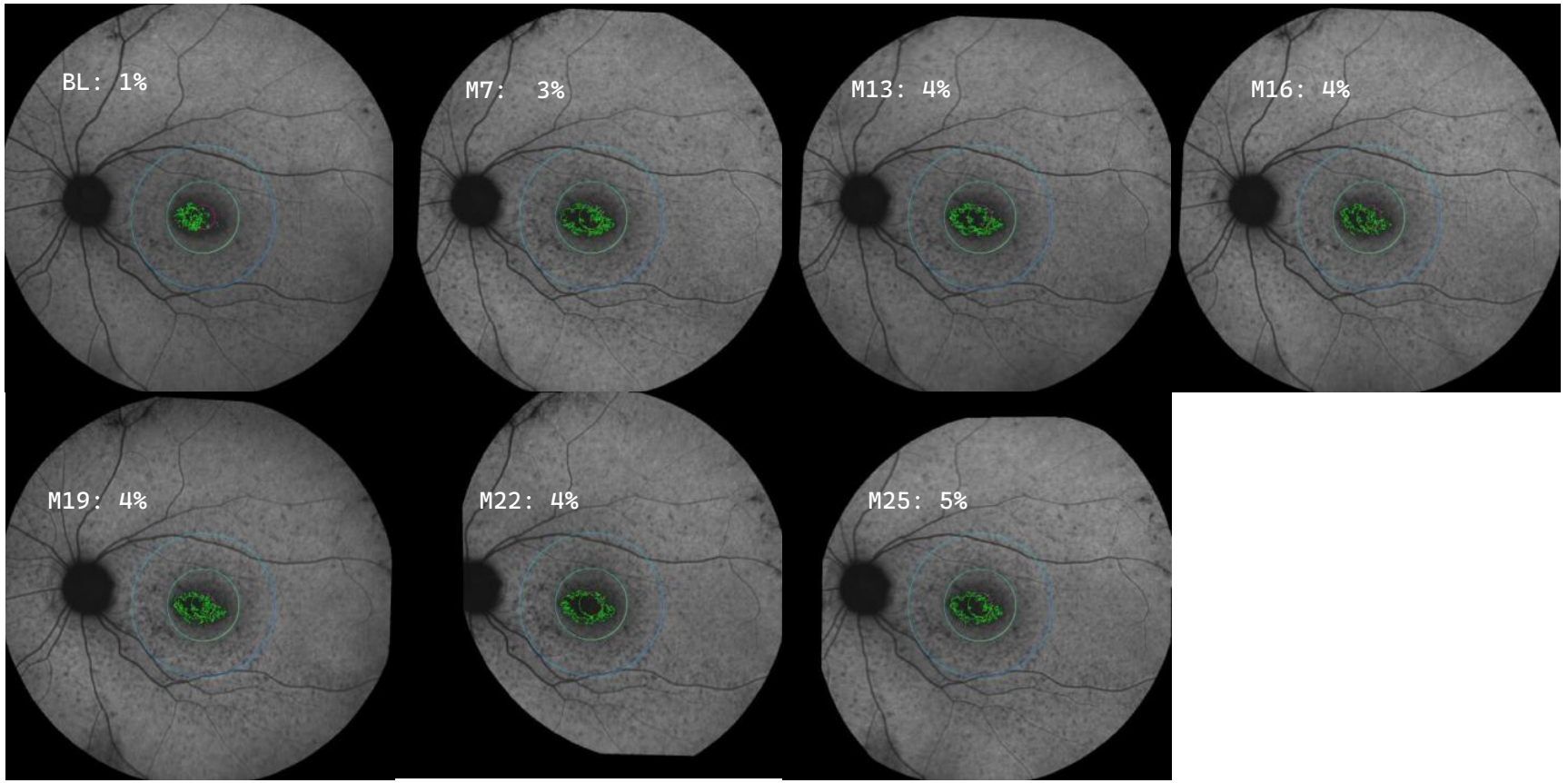
Measurement of DDAF - Region Finder

- Relies heavily on the grader's ability to visually determine the types and boundaries of areas with different levels of disc-derived autofluorescence (DDAF, DAF, QDAF).
- There is intra- and inter-grader variability
  - due to subjective assessment of lesion grayscale compared to the optic disc.
- General assessment without specific focus on key regions
  - potentially leading to less precise measurements.

Novel Lesion Size Quantification Method

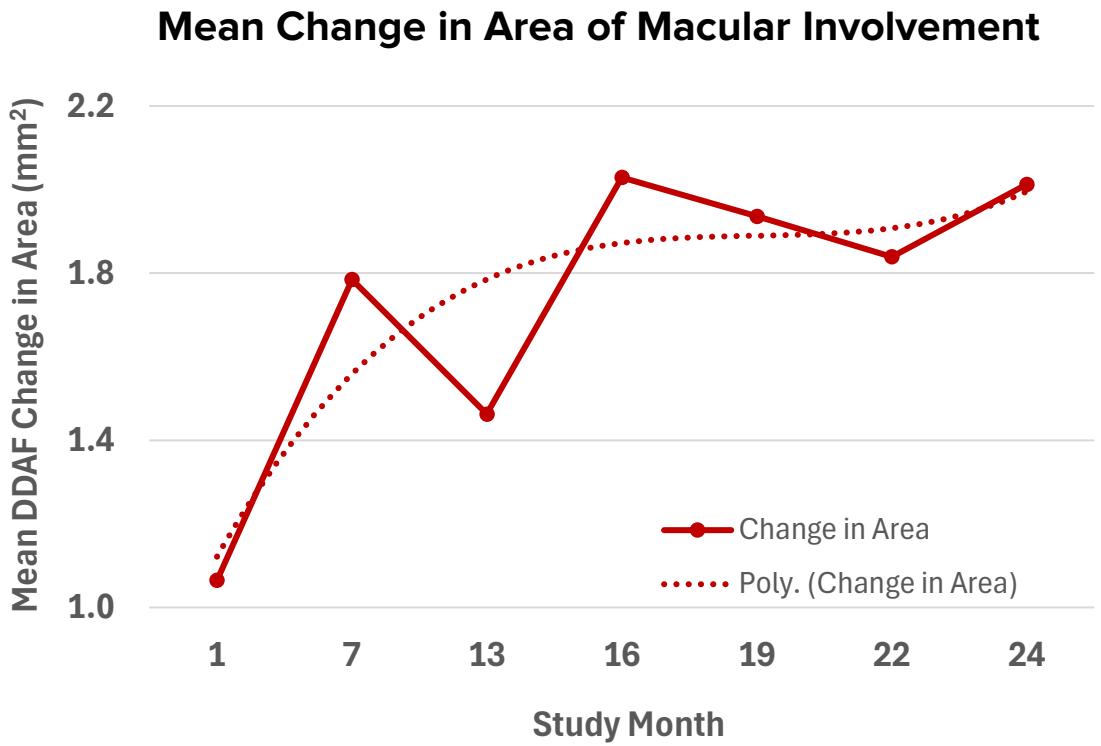
- Utilizes mathematical classification of lesions based on the proximity of their gray values to that of the optic disc, reducing subjective bias.
- Focuses on specific regions (macular area within central 6mm diameter and smaller zones of 1mm and 3mm ETDRS), enhancing the accuracy of localization and quantification.
- Independent of initial lesion size, employing a pixel-based method that consistently evaluates the percentage of a region affected at specified DAF thresholds.

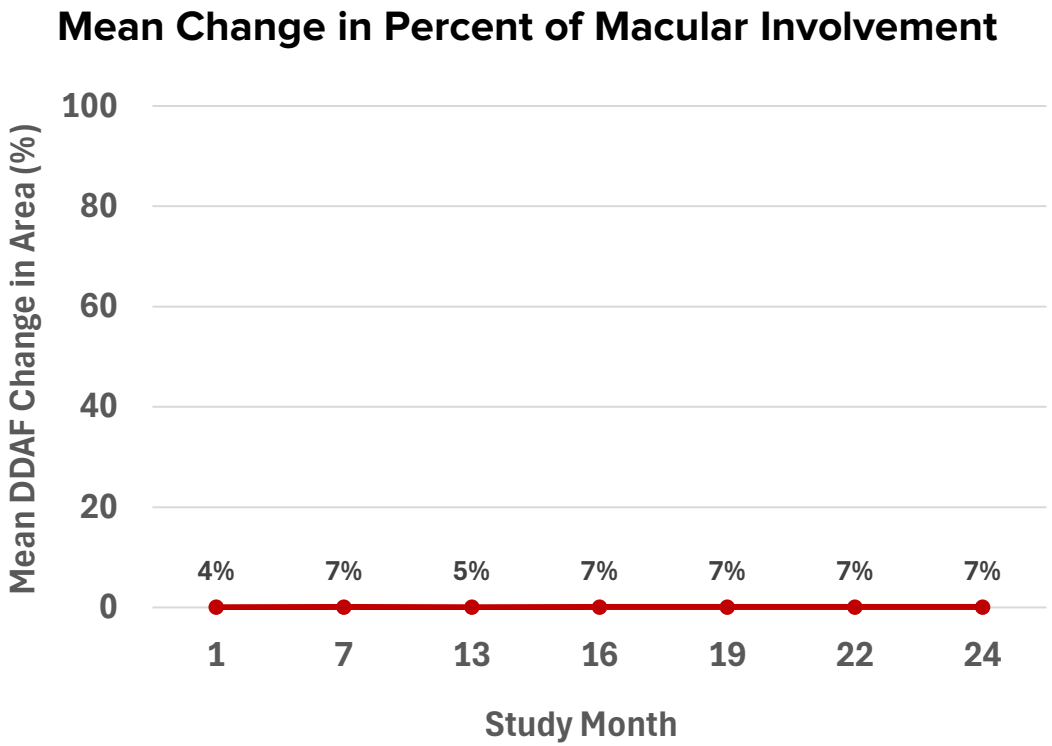
DAF @ >90 %



A Newly Developed Grading Algorithm Reveals Atrophic Macular Lesions

- FAF Analysis using new grading methodology showed atrophic lesions within the macula (6 mm outer ring) in 12 eyes of 8 subjects at Baseline
- In these subjects, growth of atrophic macular lesions was stabilized from Months 16 – 24
  - left panel; a 3rd order polynomial function of the lesion area data is shown
  - The extent of macular lesion involvement was ≤ 7% involvement over 24 Months (right panel)



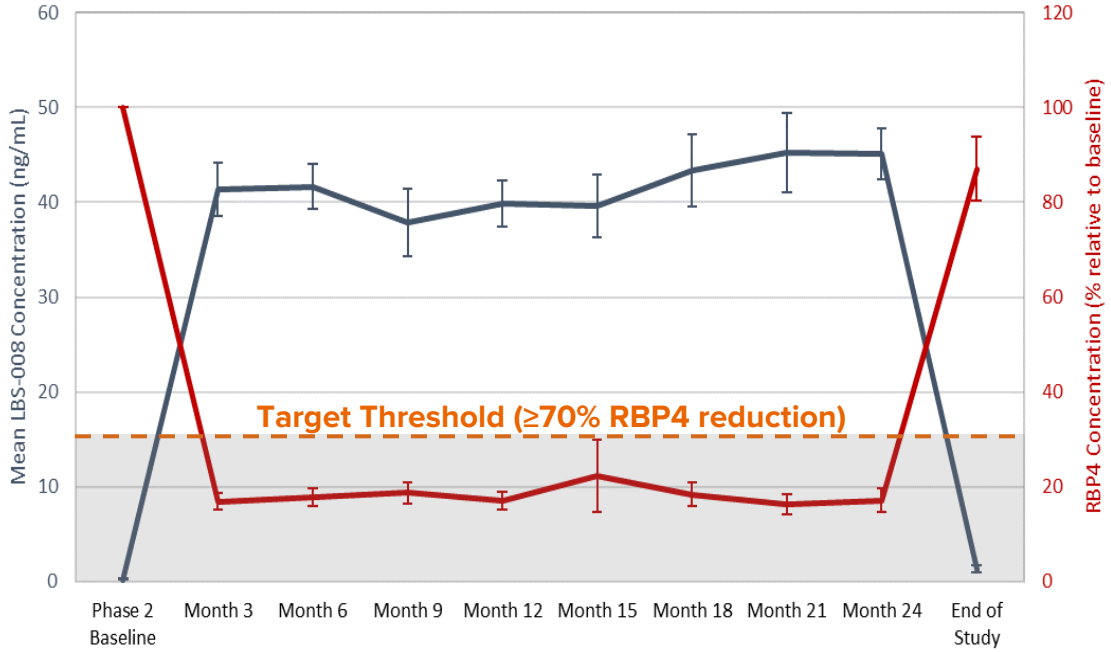


Drug-related Adverse Events (AEs)

Adverse Events	Severity	Frequency (# and % of patients)
Xanthopsia/ Chromatopsia	Mild	10/13 (76.9%)
Delayed Dark Adaptation	Mild	9/13 (69.2%)
Night Vision Impairment	Mild	1/13 (7.7%)
Increasing error score in FM100	Mild	1/13 (7.7%)
Intermittent headaches	Mild	2/13 (15.4%)

- Tinlarebant (5 mg p.o., daily) was safe and well tolerated over 24 months
- No systemic drug-related AEs, no clinically significant findings, No severe or moderate drug related AEs were reported, and no AEs required discontinuation of treatment

PK/PD Profile of Tinlarebant (5 mg/day, p.o.)



- ⬆ tinlarebant in blood (blue line) ➔ ⬇ RBP4 (red line)
- The 5 mg daily dose reduced RBP4 by a mean ~80%
- Cessation of tinlarebant at Month 24 corresponded with increased RBP4 which returned to 87% of the baseline value over 28 days

Tinlarebant Phase 2 Clinical Study - Summary

- Tinlarebant (5 mg/day) produced a sustained reduction of RBP4 (~80%) over 24 months, which was reversible after 28 days of drug cessation, and was found to be safe and well tolerated
- No incident DDAF lesions were formed in 5 of 12 subjects (42%) over 24 months despite severity of *ABCA4* mutations
- Mean incident DDAF lesion growth rate in 7 of 12 subjects was significantly lower (~50%) than the natural history growth rate observed in adolescent STGD1 subjects with similar baseline characteristics ($p<0.001$)
- Profound slowing of growth during the second year. In subjects with atrophic lesion involvement within the macula at Baseline
- Sibling subjects with identical *ABCA4* mutations showed different rates of QDAF and DDAF lesion growth
- Best corrected visual acuity was stabilized over 24 months with a mean loss of 2.5 letters/year
- Delayed dark adaptation and chromatopsia were the most common drug related ophthalmic AEs and were reported as mild and transient; there were no drug-related systemic AEs
- Collectively, data from the Phase 2 study indicate that reduction of retinol delivery to the eye with Tinlarebant is a promising approach for the treatment of STGD1