A Phase 1b/2 Study of the Safety and Tolerability of Tinlarebant in Adolescent Patients Affected by Stargardt Disease

18-Month Data from a 2-year, Phase 1b/2 Study of Oral Tinlarebant in Adolescent Stargardt Disease Patients

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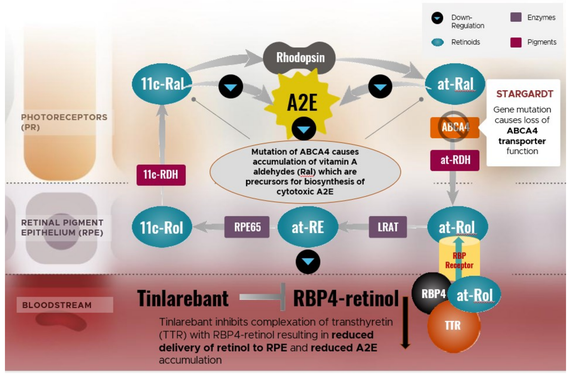
Pathology of Stargardt Disease (STGD1) and Mechanism of Tinlarebant Action

- In STGD1, mutations in the ABCA4 gene cause retinal disease due to the accumulation of cytotoxic by-products of vitamin A (A2E and related bisretinoids)
- Tinlarebant (LBS-008) is an orally administered, high-affinity antagonist of RBP4 which specifically reduces retinol delivery to the eye
- In STGD1 mouse models, Tinlarebant (5 mg/day, p.o.) was effective to reduce serum RBP4 leading to reduced accumulation of bisretinoids and prevention of photoreceptor degeneration

Figure 1. Mechanism of Tinlarebant Action in the Treatment of STGD1

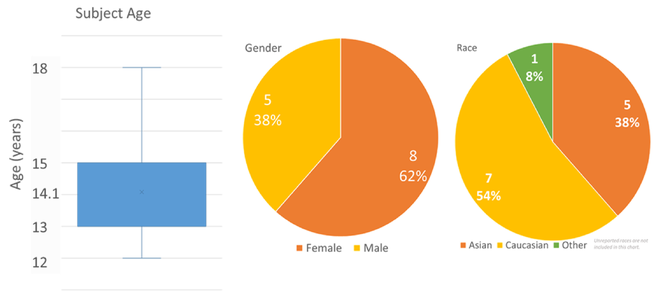


Overview of Study LBS-008-CT02 & Preliminary Efficacy Analysis

Study LBS-008-CT02 is a 2-year, open label study of oral Tinlarebant in 13 adolescent STGD1 patients aged 12-18 years [1]. Here, 18-month lesion growth and visual acuity data from Study LBS-008-CT02 and the ProgStar Prospective Study [2] are compared to evaluate trends toward efficacy. DDAF/QDAF lesion areas are as defined in the ProgStar Study [2, 3] where DAF area is the sum of QDAF and DDAF areas.

Age and Gender Demographics in Study LBS-008-CT02

Figure 2. Age, Gender and Race Composition in Study LBS-008-CT02



All LBS-008-CT02 subjects had pronounced QDAF lesions with no atrophic (DDAF) lesions at baseline, indicating a high risk for onset of DDAF lesions.

Tinlarebant is Safe and Well-Tolerated During 18 Months of Treatment

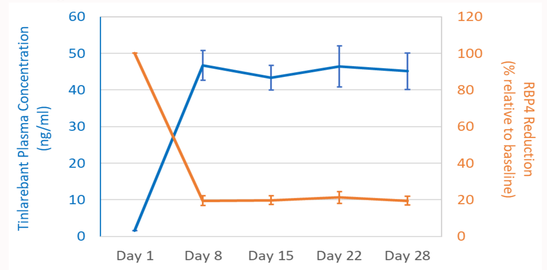
Table 1. Treatment-Related Adverse Events (AEs)

AEs	Severity	Frequency (#patients)	% Recovery
Xanthopsia/chromatopsia	Mild	9/12 (75%)	6/9 (66.7%)
Delayed dark adaptation	Mild	9/12 (75%)	1/9 (11.1%)
Night vision impairment	Mild	1/12 (8.3%)	0/1

All treatment-related AEs were mild in severity. There were no clinically significant findings in relation to vital signs, physical exams, cardiac health, or organ functions.

Tinlarebant is an Effective RBP4 Antagonist in Adolescent STGD1 Subjects

Figure 3. Mean Tinlarebant and RBP4 levels

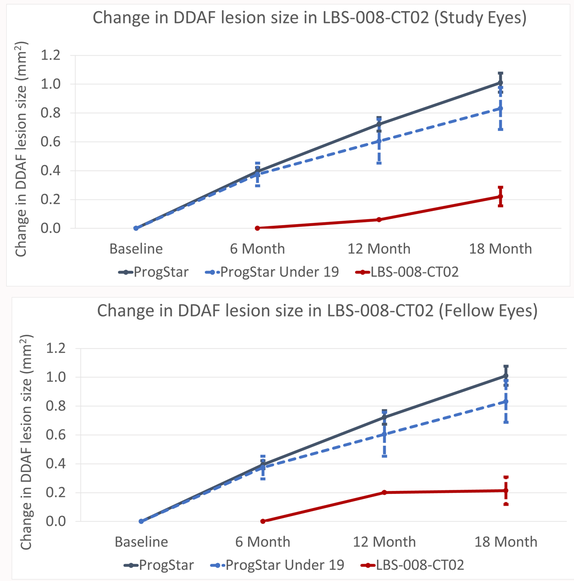


Tinlarebant (5 mg/day, p.o.) produces a sustained mean RBP4 reduction of ~80%.

Progression of DDAF Retinal Lesions in Study LBS-008-CT02

FAF imaging of subjects in LBS-008-CT02 with no DDAF at baseline showed **incident DDAF lesions in 1 subject at Month 12 and 5 subjects at Month 18. LBS-008-CT02 subjects showed a lower mean DDAF lesion growth compared to the ProgStar Study data (all subjects) and the cohort of subjects ≤18 years after 18 months of treatment (Figure 4, upper and lower panel, respectively).**

Figure 4. DDAF Lesion Size Change in ProgStar and Study LBS-008-CT02



All subjects in this analysis had DDAF lesions. LBS-008-CT02 subjects exhibited a smaller increase (0.2 ± 0.1 mm^2) in DDAF lesion size compared to ProgStar subjects (0.4 ± 0.3 mm^2) during an 18 month period.

Figure 5. FAF imaging case studies in Study LBS-008-CT02

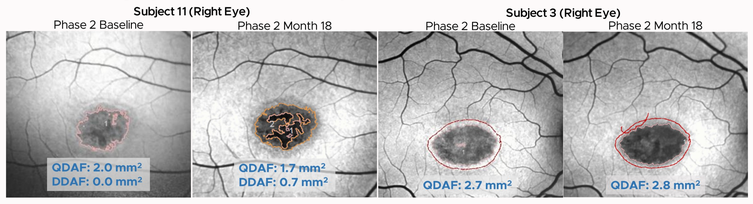


Figure 6. A Majority of LBS-008-CT02 Subjects had No Incident DDAF Lesions at 18 Months

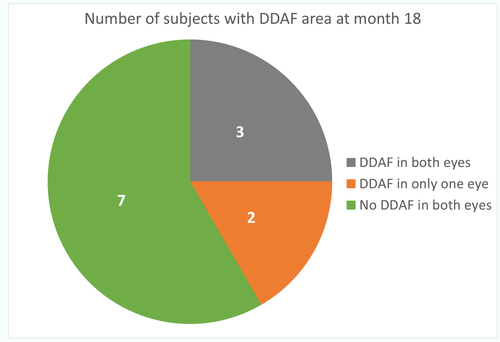
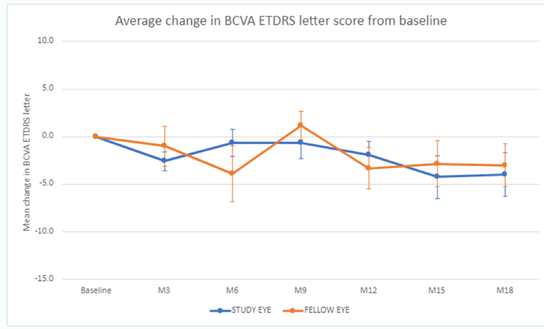


Figure 7. Best Corrected Visual Acuity (BCVA) is Stabilized in LBS-008-CT02 Subjects



Analysis of BCVA showed little change from baseline values during 18 months of Tinlarebant treatment.

Increased Retinal Thickness in LBS-008-CT02 versus ProgStar

SD-OCT analyses showed increased retinal thickness in the central subfield of LBS-008-CT02 subjects compared to ProgStar study subjects. Slower retinal thinning observed in LBS-008-CT02 is consistent with reduced DDAF lesion growth which was observed on FAF imaging.

Summary

- Tinlarebant (5 mg/day, p.o.) continues to be safe and well tolerated during 18 months of treatment
- Tinlarebant is effective to produce a sustained mean RBP4 reduction of ~80%
- Reported AEs were anticipated based on the mechanism of Tinlarebant action
- Comparisons of retinal imaging data between Study LBS-008-CT02 and ProgStar showed:
  - Progression of DDAF lesions among LBS-008-CT02 subjects who developed DDAF lesions was reduced compared to ProgStar study subjects
  - Central subfield retinal thickness was increased in LBS-008-CT02 subjects compared to ProgStar study subjects
- Visual acuity was stabilized in LBS-008-CT02 subjects during 18 months of Tinlarebant treatment.

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Abbreviations

DAF	Decreased autofluorescence (DDAF+QDAF)	QDAF	Questionably decreased autofluorescence
DDAF	Definitely decreased autofluorescence	RBP4	Retinol-binding protein 4

References

1. Grigg JR, Chen FK, Chen T-C, et al. Invest. Ophthalmol. Vis. Sci. 2022;63(7):3518
2. Strauss RW, Ho A, Munoz B, et al. Ophthalmology 2016;123:817-828.
3. Strauss RW, Kong X, Ho A, et al. JAMA Ophthalmol. 2019; 137(10):1134-1145.