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Alkeus is Addressing the Root Cause of Stargardt Disease

Gildeuretinol
(ALK-001) has Breakthrough Therapy
Designation

We are Building a Team to Launch Gildeuretinol and Transform
Lives

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LATEST NEWS TRANSFORMING SIGHT

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STARGARDT DISEASE

Stargardt disease, which affects more than 30,000 people in the United States, is one of the most common genetic causes of blindness in children and young adults. No treatment exists.

WITH MORE THAN 30,000 PEOPLE IN THE U.S. STARGARDT DISEASE IS MORE COMMON THAN OTHER GENETIC DISEASES SUCH AS CF, PKU AND SMA

Of the six most common genetic, autosomal recessive diseases, Stargardt disease is the only one without a treatment.

Disease	US Patients	Incidence
Alpha-1 antitrypsin deficiency (A1AT)	~100,000	~3:10,000
Sickle cell disease (SCD)	~90,000	1:500-1,200 births
Stargardt disease* (STGD1)	>30,000	~1:8,000
Cystic fibrosis (CF)	30,000	~1:3,500 births
Phenylketonuria (PKU)	16,500	~1:16,000
Spinal muscular atrophy (SMA)	9,000	~1:8,000 births

*Reference: Worldwide carrier frequency and genetic prevalence of autosomal recessive inherited retinal diseases, 2019. Approximately 5% of the population is a carrier for an ABCA4 variant

THE ROOT CAUSE: DEFECTS IN THE ABCA4 GENE

Sight is made possible by a biochemical chain reaction in the eye: Vitamin A enables photoreceptors in the eye to convert light into electrical signals that are sent to the brain. Vitamin A is essential to the eye's ability to see but also has a propensity to form dimers – or clumps – that are toxic to retinal pigment epithelium (RPE) layer.

Mutations in the *ABCA4* gene were identified as the cause of Stargardt disease in 1997. The normal role of the ABCA4 protein is to ensure the flow of n-retinylidene-PE, a vitamin A isomer, through the photoreceptor membrane.

In Stargardt patients the ABCA4 protein is defective or absent, which allows excess vitamin A concentration and dimerization, and results in toxic by-products that irreversibly damage the RPE layer, leading to progressive vision loss.

GILDEURETINOL (ALK-001),

A ONCE-A-DAY ORAL, INVESTIGATIONAL THERAPY FOR THE TREATMENT OF STARGARDT DISEASE

Gildeuretinol (ALK-001) is the first and only medicine in clinical development to selectively address the underlying mechanism of Stargardt disease, by reducing the rate of vitamin A dimerization in the eye.

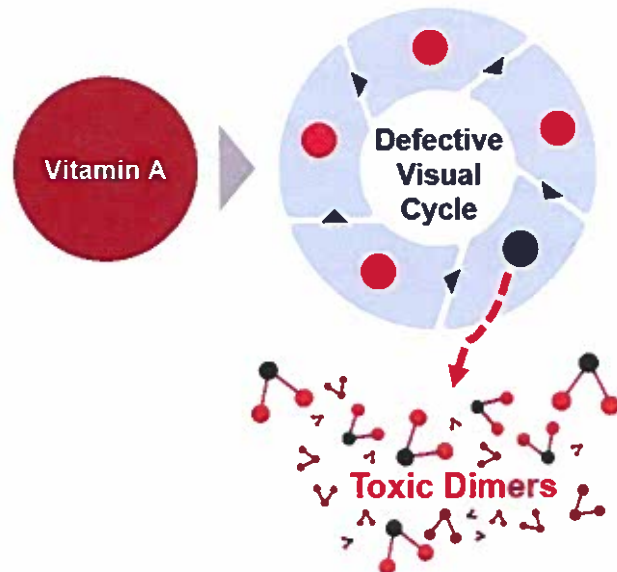


Toxic vitamin A aggregates (“dimers”) have been implicated in the pathophysiology of Stargardt and dry-AMD. Gildeuretinol is a chemically-modified vitamin A and is taken once daily by mouth. In *in vitro* studies, researchers have demonstrated that gildeuretinol slowed dimerization of vitamin A by 4-5 fold, and in *in vivo* models, gildeuretinol has reduced vitamin A dimer formation in the eye by 80%, leading to preservation of visual function in animal models of Stargardt disease.

Gildeuretinol was designed to perform all of the functions of vitamin A needed to support sight, but without the tendency to dimerize or clump, thus avoiding the toxic by-products that damage the retina. Researchers engineered gildeuretinol as a novel, selectively modified version of vitamin A, where three hydrogen atoms are replaced with deuterium atoms, a stable, non-radioactive isotope of hydrogen. This modification is what dramatically reduces the rate of dimerization.

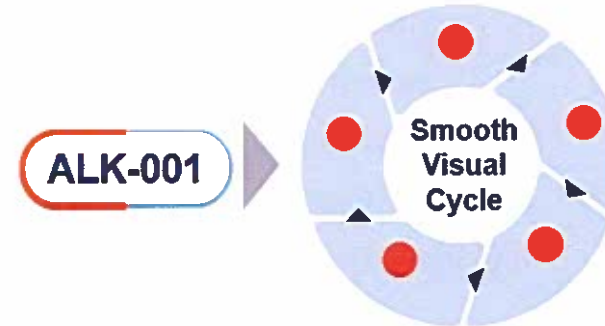
THE PROBLEM

Vitamin A is essential for vision but forms toxic byproducts as a result of the visual cycle



THE ALK-001 SOLUTION

ALK-001 **substitutes vitamin A** and **retains vitamin A natural functions** while safely reducing the production of toxic byproducts, thereby preserving retinal health and vision. All future treatment approaches will be add-ons to ALK-001



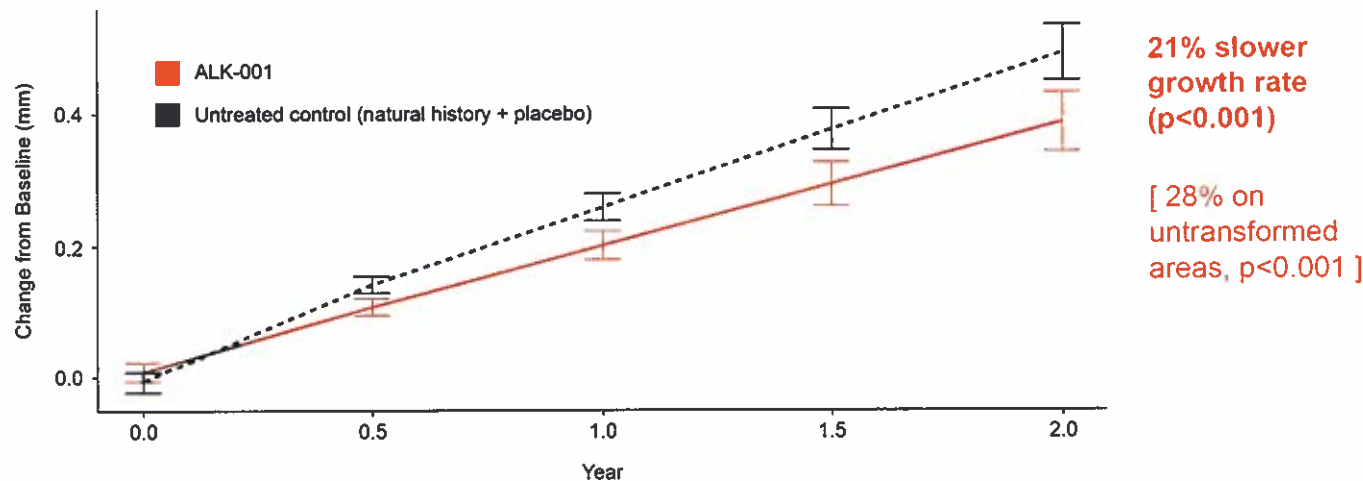
PUBLICATIONS

GILDEURETINOL CLINICAL RESULTS: A FIRST FOR STARGARDT PATIENTS

In 2022, clinical investigators reported results from a double-masked, placebo-controlled, randomized Phase 2 study of gildeuretinol (ALK-001) in 50 patients with advanced Stargardt disease at the American Academy of Ophthalmology.



GILDEURETINOL SLOWS THE GROWTH RATE OF ATROPHIC LESIONS IN STARGARDT PATIENTS



Gildeuretinol met the pre-specified primary efficacy endpoint with high statistical significance, with a consistent trend of clinical benefit seen in secondary efficacy analyses.

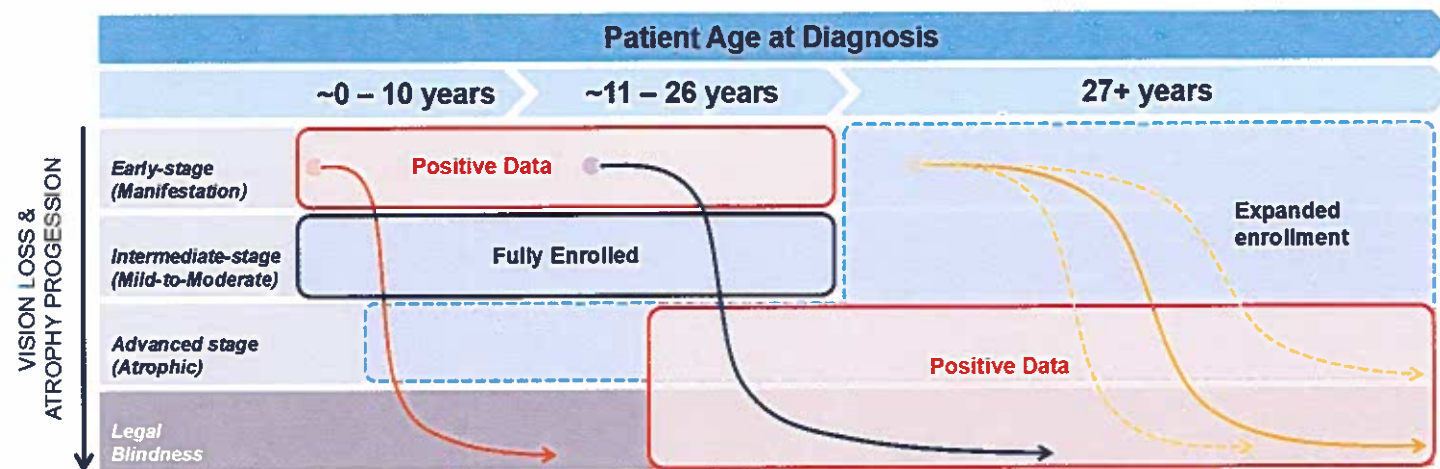
In the clinical trial known as TEASE-1, gildeuretinol dosed once a day resulted in decreased retinal damage as compared to placebo, based on observed growth rates in atrophic lesions as measured by fundus autofluorescence (FAF).

Gildeuretinol was well-tolerated with a safety profile consistent with the well-characterized safety profile of vitamin A.

In addition, an innovative, open-label study in children, known as TEASE-3, has indicated an ability for gildeuretinol, when given early, to halt the disease process before progressive retinal damage and vision loss occurs. Results from this clinical trial are anticipated to be presented in an upcoming medical forum.



ALKEUS' CLINICAL PROGRAM WITH GILDEURETINOL IS DESIGNED TO SUPPORT BROAD USE IN STARGARDT DISEASE



References: Visual acuity loss and clinical observations in a large series of patients with Stargardt disease, 2003;
Visual Acuity Change over 12 Months in the Prospective Progression of Atrophy Secondary to Stargardt disease (ProgStar) Study, 2016.

Four clinical trials of gildeuretinol in Stargardt Disease are ongoing or completed, with the first two data readouts demonstrating positive clinical efficacy data.

PURSuing A RAPID PATH TO MARKET

The U.S. FDA has granted Breakthrough Therapy Designation and Orphan Drug Designation to gildeuretinol (ALK-001) for the treatment of Stargardt disease. Alkeus is engaged in discussions with regulatory authorities to define the most appropriate path to bring gildeuretinol to Stargardt disease patients as rapidly as possible. Alkeus plans to submit an NDA for approval of gildeuretinol in Stargardt disease in 2024.

BROAD POTENTIAL TO TREAT EYE DISEASE

The pathological features of Stargardt disease—lesions in the retinal pigmental epithelium (RPE) layer, visible using high-resolution optical imaging —are common across several degenerative eye diseases.

There is mounting scientific evidence that the same process—excessive vitamin A dimerization, leading to toxic by-products that irreversibly damage photoreceptors in the retina—drives the progressive lesion growth not just in Stargardt disease but in these other diseases as well.

In addition to Stargardt disease, gildeuretinol is being evaluated in *Geographic Atrophy (GA)*, an advanced form of dry age-related macular degeneration (dry AMD). More than 1 million people in the United States and more than 5 million people worldwide have GA.

Dry AMD is common in people over the age of 50. In dry AMD, layers of the retina slowly deteriorate over time. GA may occur in later-stage dry AMD patients, and is characterized by discrete areas of damage to the RPE layer, which leads to a progressive decline in central vision.

Although multiple mechanisms are associated with dry AMD and GA, it is clear that the toxic by-products of vitamin A are significant drivers of damage to the RPE layer.

In 2019, Alkeus initiated a Phase 3 study of gildeuretinol in Geographic Atrophy, with a primary goal of measuring ALK-001's ability to slow the growth rate of GA lesions. The trial is fully enrolled with 200 patients.

In addition to Stargardt disease, gildeuretinol is being evaluated *Geographic Atrophy (GA)*, an advanced form of dry age-related macular degeneration (dry AMD). More than 1 million people in the United States and more than 5 million people worldwide have GA.



ABOUT ALKEUS

Alkeus was co-founded by Leonide Saad, Ph.D. and Ilyas Washington, Ph.D. with the goal of treating degenerative eye diseases in a completely new way: developing a molecule that could reduce the potential for toxicity when vitamin A dimerizes —clumps —in the eye. This dimerization is a key underlying

contributor to the irreversible retinal damage that is common to a number of eye diseases.

Alkeus has steadily progressed its lead molecule gildeuretinol (ALK-001), demonstrating its tremendous promise and advancing a comprehensive clinical program.

Alkeus is co-founded by Ilyas Washington, Ph.D and Leonide Saad, Ph.D



2010

2011



Publication of preclinical studies demonstrating that gildeuretinol (ALK-001) significantly reduces formation of vitamin A dimers, and slows retinal damage in genetic models of Stargardt disease



Gildeuretinol enters Phase I clinical development



2014

2015



First Phase 2 clinical study of gildeuretinol begins, for patients with advanced Stargardt disease

Phase 2 studies of gildeuretinol begin in children and young adults with early-stage and moderate disease



2017

2019



Alkeus initiates a Phase 3 study of gildeuretinol in Geographic Atrophy (GA) secondary to dry AMD



FDA grants breakthrough therapy designation to gildeuretinol for Stargardt disease



2021

2022



Phase 2 results presented at American Academy of Ophthalmology Annual Meeting show that gildeuretinol slows the growth rate of atrophic lesions in patients with advanced Stargardt disease

Alkeus secures \$150 million in Series B funding to support rapid registration path for gildeuretinol in Stargardt disease; Joshua Boger, Ph.D. named Executive Chairman



2023



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Topline Results from Alkeus Pharmaceuticals' Study of Oral Gildeuretinol Demonstrate Significant Trend in Slowing GA Progression and Visual Function Improvement

October 23, 2024 | [Press Release](#)

Alkeus Pharmaceuticals Announces Data Presentations at the American Academy of Ophthalmology (AAO) 2024 Annual Meeting, October 18-21 in Chicago

October 17, 2024 | [Press Release](#)

Alkeus Pharmaceuticals Announces Results from the SAGA Study of Oral Gildeuretinol in Patients with Geographic Atrophy Secondary to Age-Related Macular Degeneration

September 17, 2024 | [Press Release](#)

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