

ALK-001 (C20-D3-Vitamin A) slows the growth of atrophic lesions in *ABCA4*-related Stargardt Disease: Results of a Phase 2 placebo-controlled clinical trial (TEASE study)

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Abstract

Purpose : To study the effects of ALK-001 on the progression of Stargardt Disease (STGD1). STGD1 is the most prevalent inherited macular dystrophy and results from defects in the *ABCA4* gene that cause accelerated formation of vitamin A dimers in the retina. No treatment exists.

Methods : The TEASE study is a multicenter two-year Phase 2 double-masked, randomized, placebo-controlled clinical trial that randomized 50 patients with STGD1 and a well-delineated area of RPE atrophy. The investigational drug ALK-001 is a selectively deuterated vitamin A used as vitamin A replacement and taken orally once-a-day. Deuterium slows vitamin A dimer formation 4-5 fold without inhibiting the visual cycle. Patients were randomized 2:1 ALK-001:placebo during the first year, with 50% of placebo randomly crossed over to ALK-001 for the second year of treatment. The prespecified primary efficacy outcome measure is the rate of growth of the square root of atrophic lesions, as measured on short wavelength fundus autofluorescence imaging, and evaluated using a linear mixed model. The study was performed at 7 centers in the USA. 50 patients (38 white; 28 female) were randomized. Median age was 46 years (range, 18-60) and disease duration 9 years (0-36). Atrophic lesions were bilateral in 74% of cases with a ~5 mm² median area.

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Results : The growth rate of the *square root* of atrophic lesions in the ALK-001 treated group was 21% slower than in the untreated arm ($p < 0.001$). When using *untransformed areas*, the growth rate was 28% slower in the ALK-001 arm than the untreated arm. There were no clinically-significant changes in BCVA in either treated and untreated arms after 2 years as expected in this patient population. On average, ~90% of vitamin A was replaced with deuterated vitamin A, which was maintained over time. ALK-001 was well-tolerated with no unexpected adverse reactions, no report of night blindness or impaired dark adaptation, and no clinically-significant increases in liver enzymes.

Conclusions : These data represent the first time that a therapeutic intervention slows the progression of STGD1 in a clinically and statistically meaningful way. In addition, the data provides clinical evidence that vitamin A dimers contribute to the pathophysiology of STGD1, and that slowing vitamin A dimerization is beneficial even in advanced stages of STGD1.

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