

Gildeuretinol Enables the Vitamin A Cycle

Hendrik P Scholl; Leonide Saad; Gabrielle DeBartolomeo; Neil M Bressler; Stephen H Tsang; Kimberly E Stepien; Paul S Bernstein; Byron L Lam; Michael B Gorin; Ilyas Washington; Christine Nichols Kay

+ Author Affiliations & Notes

Investigative Ophthalmology & Visual Science June 2024, Vol.65, 6438. doi:

Abstract

Purpose : Gildeuretinol (formally ALK-001 and C20D3-Vitamin A) is a vitamin A substitute, designed to inhibit the pathological dimerization of vitamin A, a process thought to contribute to the development of Stargardt disease and blindness. We hypothesized that gildeuretinol could effectively replace retinol (vitamin A) in the vitamin A cycle to enable dark adaptation and vision.

Methods : In a multicenter double-masked, placebo-controlled, randomized clinical trial, subjects with Stargardt disease were assigned to gildeuretinol acetate 14 mg capsules, gildeuretinol acetate 24 mg capsules, or placebo capsules, taken once daily orally for 8 weeks. Plasma retinol and gildeuretinol levels were determined at 8 weeks. We evaluated mean change from baseline at 8 weeks in dark adaptation parameters, as measured by full field, psychophysical dark-adaptation testing acquired on an Espion 3. A six-question dark adaptation questionnaire was administered at baseline and week 8.

Results : Fifty-three patients were screened; 50 were assigned to gildeuretinol 14 mg capsule (n =15), gildeuretinol 24 mg capsule (n =15) or placebo capsule (n = 20). At the 8-week pharmacokinetic analysis, 87% and 92% of plasma vitamin A was in the form of gildeuretinol in the 14 and 24 mg cohorts, respectively. Because both treated cohorts had the same percentage of plasma gildeuretinol, the two doses were pooled for outcome analyses. Thirty nine patients underwent dark adaptation measurements (gildeuretinol n=21 and placebo n=18). We found no difference in dark adaptation parameters between gildeuretinol-treated and placebo cohorts (Table 1), despite plasma retinol being approximately 10% that of normal levels in the gildeuretinol cohort, normally defined as

severe vitamin A deficiency. Forty-nine patients answered the dark adaptation questionnaire. There were no reported difficulty seeing at night or in dim light associated with gildeuretinol. There were no adverse events associated with gildeuretinol intake.

Conclusions : Gildeuretinol effectively substituted retinol, and enabled dark adaptation and vision just as retinol would in the vitamin A cycle. Gildeuretinol holds promise as a disease-modifying therapeutic that addresses the underlying cause of Stargardt disease, with the safety profile of a vitamin.

This abstract was presented at the 2024 ARVO Annual Meeting, held in Seattle, WA, May 5-9, 2024.

Parameter (relative units)	Gildeuretinol (n = 21)	Placebo (n = 18)	Difference	p-value
Cone threshold	0.017	-0.009	0.027 (0.1411)	0.852
Cone coefficient	0.211	-0.78	0.991 (1.2223)	0.426
Cone time constant	-2.442	-2.496	0.054 (2.0337)	0.979
Second rod recovery rate	-0.071	-0.657	0.586 (0.4894)	0.246
Cone rod breakpoint	0.169	1.048	-0.879 (0.5218)	0.104
Third rod recovery rate	0.077	0.622	-0.545 (0.4680)	0.258
Rod-rod breakpoint	-0.078	-0.056	-0.022 (0.5342)	0.967

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Table 1. Dark adaptation parameters, during 60 minutes of dark adaptation. P-value as determined from a two-sample t-test with unequal variances.

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