A Phase 1B Study of the Safety and Tolerability of the Mineralocorticoid Fludrocortisone Acetate in Patients with Geographic Atrophy

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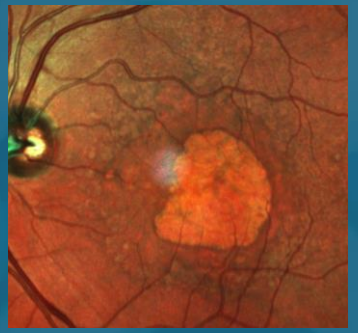
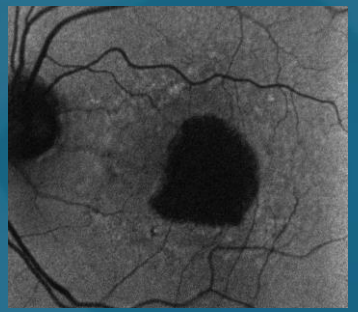
Background and Purpose

- **Geographic atrophy (GA)** is an advanced form of dry age-related macular degeneration (AMD) and the leading cause of severe vision loss in people over the age of 65 in western countries[1,2,].
- Steroids are commonly used to treat other retinal diseases; however, these are typically glucocorticoids and have previously been shown to increase intraocular pressure (IOP) and accelerate lens opacification[3].
- **Fludrocortisone acetate (FCA)** is a synthetic steroid possessing mineralocorticoid and glucocorticoid properties[4].
- This study assessed the safety and tolerability of a single dose of FCA among patients with GA over a 6-month period

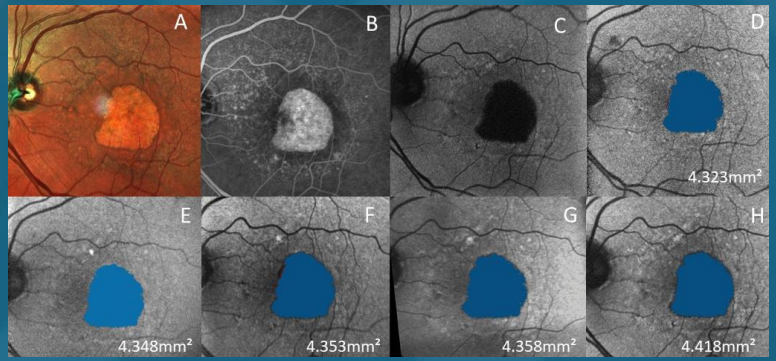




Methods

- A single-centered, phase 1b prospective, open-labelled, single-dose, dose escalation was conducted on patients with GA.
- The study was conducted in 2 parts with a sentinel subject assessed after 28 days by the data safety monitoring board before continuing to treat subsequent subjects.
- All participants were assessed at baseline, days **1, 7, 14, 28, 60, 90** and **150**.
- **Assessments** included
  - best-corrected visual acuity (BVCA)
  - low-luminance BCVA
  - IOP
  - Fundus autofluorescence (FAF)
- GA progression was assessed using region finder software comparing follow-up images to baseline

Part A (1mg/0.1mL FCA)	Part B (2mg/0.1mL FCA)
1 sentinel + 2 subjects	1 sentinel + 5 subjects



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Key Findings

- A total of 9 patients were enrolled
- **No significant** increases in IOP or vital measurements were observed
- Mean area of GA increased in both eyes, but the difference was **not** statistically significant between treated and non-treated eyes

Baseline Characteristic	N = 9
Age (years) Mean ± SD	79.73 ± 6.19
Female	55.5%
Right Eye	55.5%
Pseudophakic	55.5%
BCVA (letters) Mean ± SD	53.11 ± 10.01
LLVA (letters) Mean ± SD	39.33 ± 11.21
IOP Mean ± SD	13.33 ± 3.08
GA area (mm^2) Mean ± SD	9.53 ± 5.69

	Study Eye		Fellow Eye		P value
Variable	Mean Change from Baseline	P value	Mean Change from Baseline	P value	
BCVA(letters)	-2.63 ± 7.01	0.28	4.88 ± 8.37	0.69	0.07
LLVA (letters)	3.25 ± 9.23	0.38	4.5 ± 11.49	0.72	0.81
IOP (mmHg)	-0.25 ± 4.06	0.75	-0.625 ± 4.24	0.69	0.86
GA area (mm^2)	0.5 ± 5.69	0.003	0.62 ± 4.49	0.02	0.64

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Conclusions

- This study showed that intravitreal fludrocortisone acetate was clinically safe and well tolerated among this cohort of patients with geographic atrophy.
- **No** systemic/ocular adverse events or significant increase in IOP were noted.
- Our study findings indicate that GA progression was lower than natural history studies[5] in both the treated and fellow eyes over the study period which may indicate a possible treatment effect of FCA

1. Mitchell P, Smith W, Attebo K, *et al*. Prevalence of age-related maculopathy in Australia. The blue Mountains eye study. *Ophthalmology* 1995;102:1450–60. **2. Klein R, Klein BE, Linton KL.** Prevalence of age-related maculopathy. The Beaver dam eye study. *Ophthalmology* 1992;99:933–43. **3. Rittiphairoj T, Mir TA, Li T, *et al*.** Intravitreal steroids formacular edema in diabetes. *Cochrane Database Syst Rev* 2020;11:Cd005656. **4. Gomez-Sanchez, CE, Kirk DN, Farrant RD, *et al*.** 18-Substituted steroids: synthesis of 18-hydroxycortisol (11 beta,17 alpha,18,21-tetrahydroxy-4-pregnene-3,20-dione) and 18-hydroxycortisone (17 alpha,18,21-trihydroxy-4-pregnene-3,11,20-trione). *J Steroid Biochem* 1985;22:141–6. **5. Wang J, Ying G-S**. Growth rate of geographic atrophy secondary to age-related macular degeneration: a meta-analysis of natural history studies and implications for designing future trials. *Ophthalmic Res* 2021;64:205–15.

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