Preliminary Results from a First-in-Human Phase I/II Gene Therapy Trial (FOCUS) of Subretinally Delivered GT005, an Investigational AAV2 Vector, in Patients with Geographic Atrophy Secondary to Age-Related Macular Degeneration

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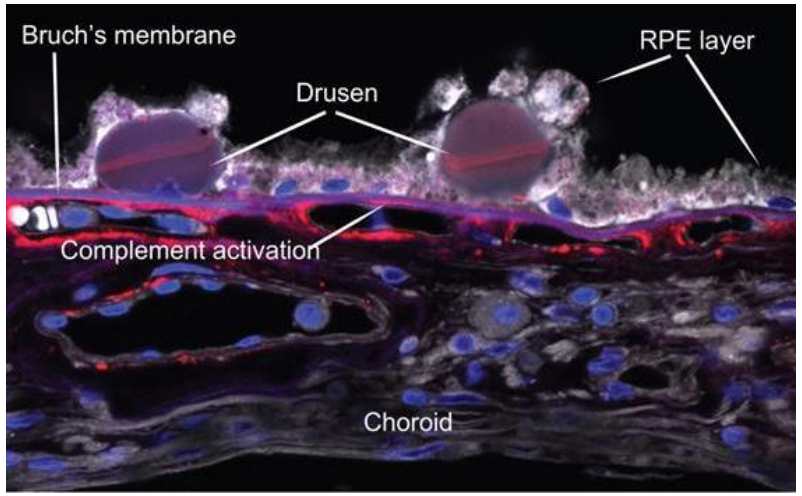
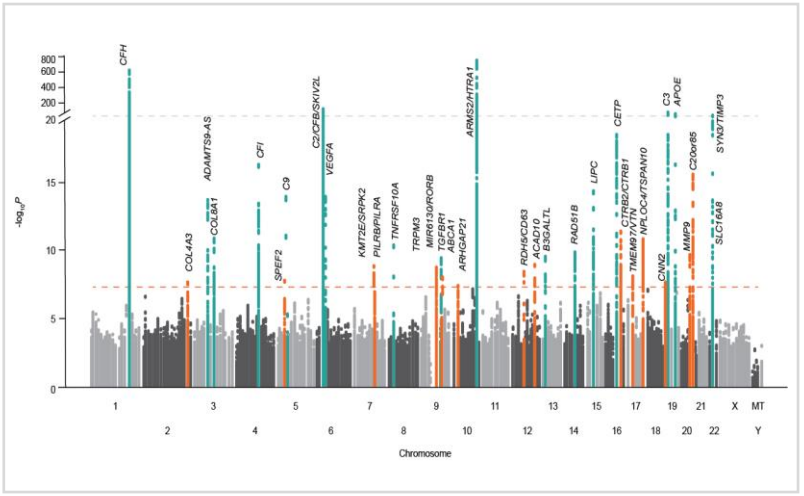
Complement Inhibition is a Validated Approach for Geographic Atrophy (GA)[1,2]

- Overactivation of the complement system leads to inflammation that can damage retinal tissues[3]
- Variants in multiple complement genes, including complement factor I (*CFI*), have been shown to be associated with an increased risk of developing age-related macular degeneration (AMD)[2,4]
- Clinical trials have shown that complement inhibition slows growth of GA[2,5,6]

Pathology[7]

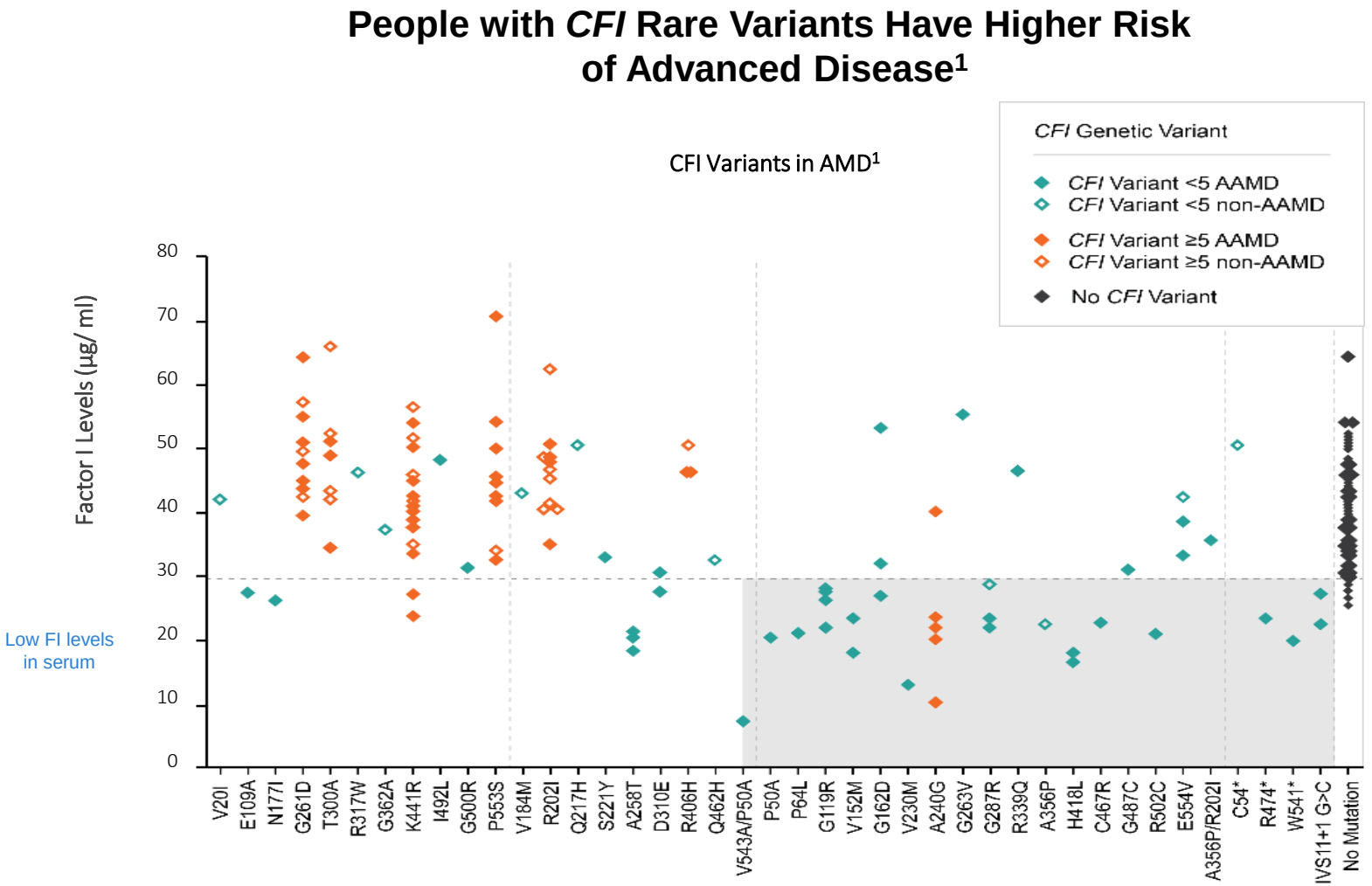


Genetics[8]



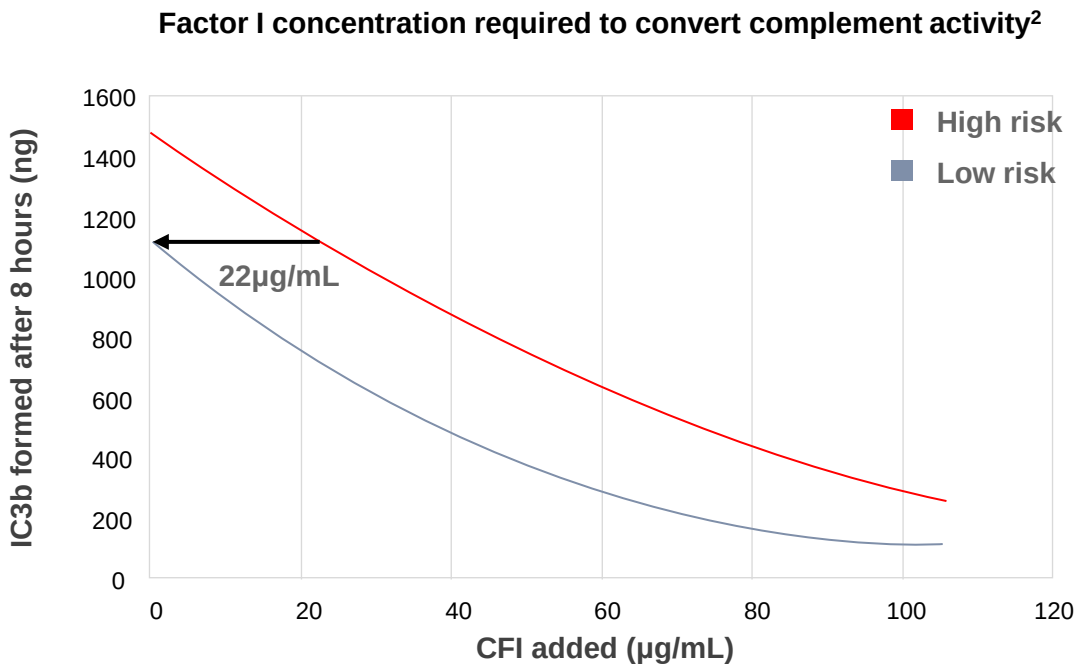
1. Boyer DS, et al. *Retina.* 2017;37:819-35. 2. Liao D, et al. *Ophthalmology.* 2020;127:186-95. 3. Lachmann PJ. *Adv Immunol.* 2009;104:115-49. 4. Harris CL, et al. *Trends Immunol.* 2012;33:513-21. 5. Jaffe GJ, et al. *Ophthalmology.* 2021;128:576-86. 6. Wykoff C. American Academy of Ophthalmology 2021, oral presentation. 7. Forest DL, et al. *Dis Model Mech.* 2015;8:421-7. 8. Fritsche LG, et al. *Nat Genet.* 2016;48:134-43.

Factor I (FI) is Strongly Associated with Development of AMD[1]

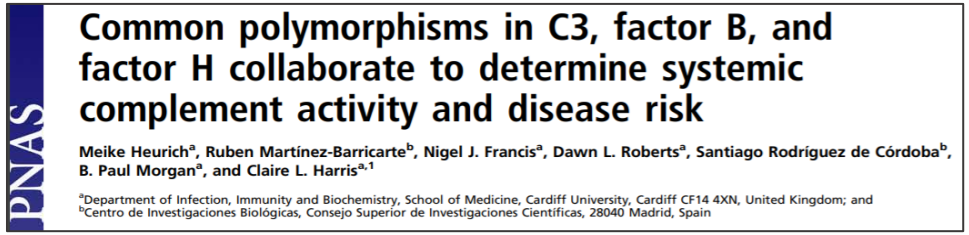


FI is Strongly Associated with Development of AMD[1,2]

FI Supplementation May Reduce Complement Activation, Regardless of Underlying Genetic Risk[2]



~80% increase in FI converts high-risk to low risk


PNAS

Common polymorphisms in C3, factor B, and factor H collaborate to determine systemic complement activity and disease risk

Meike Heurich[a], Ruben Martínez-Barricarte[b], Nigel J. Francis[a], Dawn L. Roberts[a], Santiago Rodríguez de Córdoba[b], B. Paul Morgan[a], and Claire L. Harris[a,1]

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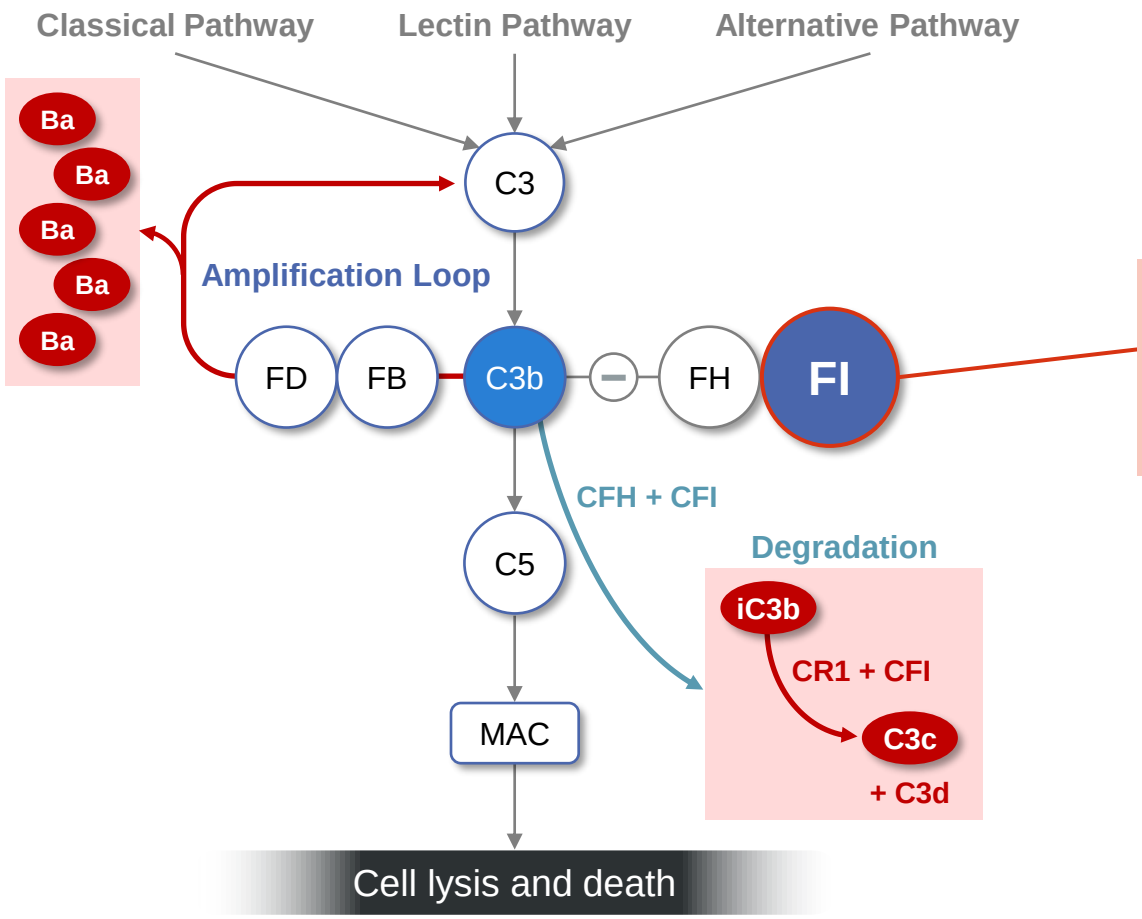
Proc Natl Acad Sci U S A. 2011 May 24;108(21):8761-6.

- Published data indicate that protective variants* in C3, CFB and CFH decrease complement activity by 48% when compared to common risk variants [PNAS (2011) 108(21):8761-6]

1. Kavanagh D, et al. *Hum Mol Genet*. 2015;24:3861-70. 2. Lachmann PJ, et al. *Clin Exp Immunol*. 2016;183:150-6.

FI: Key Downregulator of the Complement System



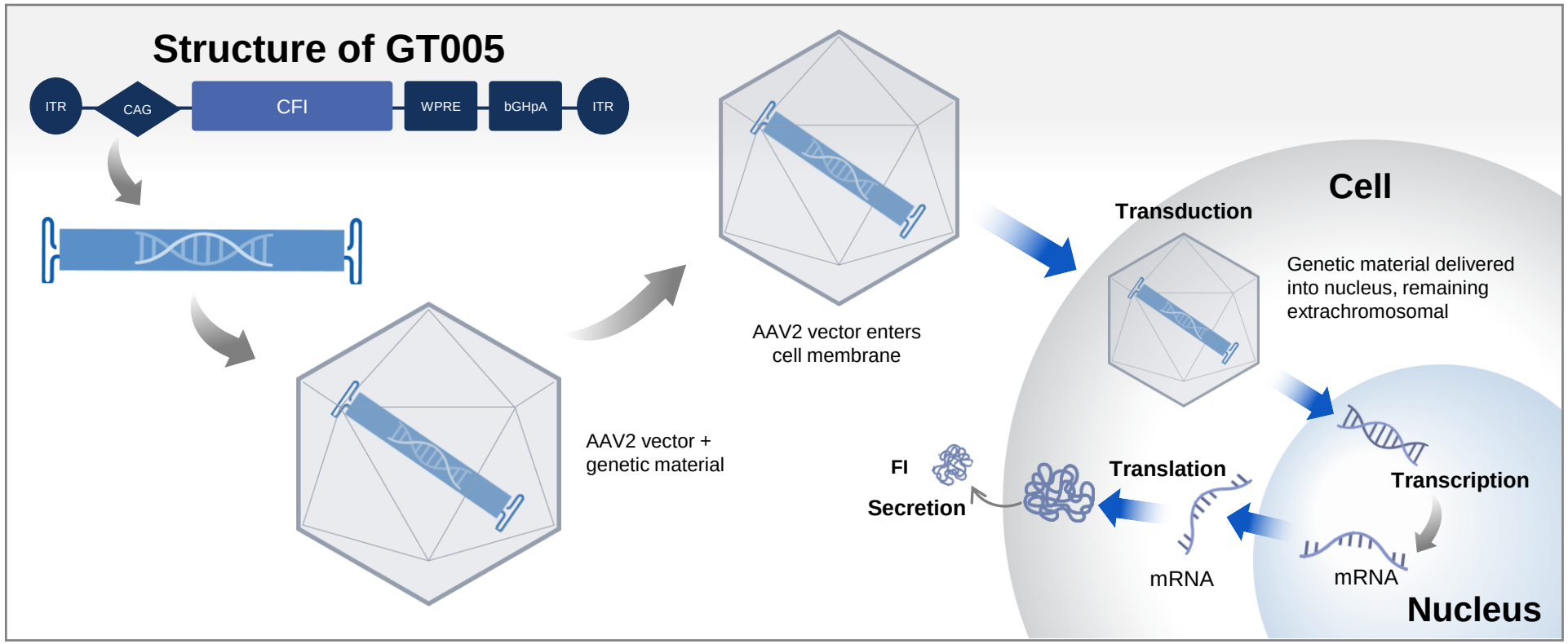
Adapted from Anderson DH, et al. *Prog Retin Eye Res*. 2010;29:95-112.

Recent studies have shown that complement system targets are highly implicated in AMD progression[1-3]

- Intrinsic protein produced by RPE cells
- Inducing FI expression leads to continual, sustained decreases in key proteins involved in complement overactivation (C3, Ba, C3b, iC3b)

1. Liao DS, et al. *Ophthalmology.* 2020;172:186-95. 2. Jaffe GJ, et al. *Ophthalmology.* 2020;1:S0161. 3. Wykoff C. American Academy of Ophthalmology 2021, oral presentation.

GT005* is an AAV2-Based Gene Therapy Designed to Induce Expression of FI[1,2]

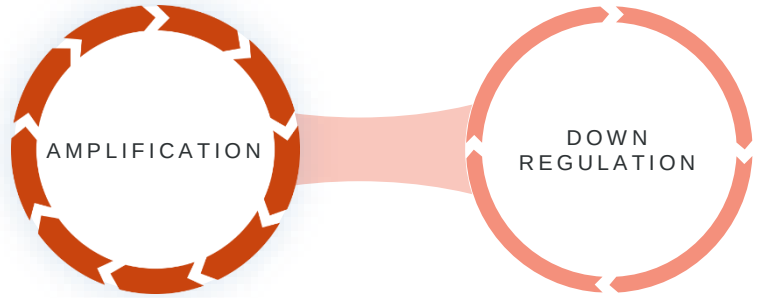


AAV=Adeno-associated virus. bGHpA=poly A signal. CAG=CAG promotor. ITR=Inverse terminal repeat. mRNA=Messenger ribonucleic acid. WPRE=Woodchuck Hepatitis Virus (WHV) Posttranscriptional Regulatory Element.

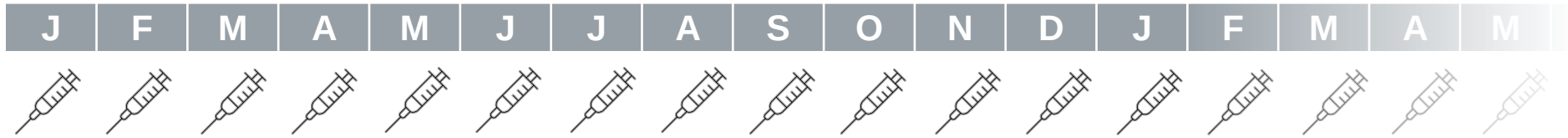
*GT005 is an investigational medication being studied as a treatment for geographic atrophy. It has not been approved for use by the FDA or any health authority and its efficacy and safety profiles have not been established. 1. Goswami R, et al. *Front Oncol.* 2019;9:297. 2. Wang D, et al. *Nat Rev Drug Discov*. 2019;18:358-78.

One-time Gene Therapy May Offer Durable Therapeutic Effect with Single Intervention

Complement system is always ‘on’



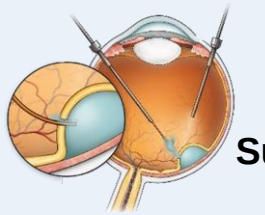
IVT therapies require repeat injections to maintain effect



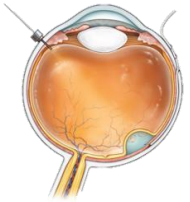
Gene therapy designed to provide durable effect with single administration

FOCUS Trial

Phase I/II Open-Label GT005 Safety and Dose Response Trial



Subretinal Transvitreal Delivery



Orbit™ Subretinal Delivery System

Dose Escalation (Dosing complete)	**Dose Expansion** (Dosing complete)	**Dose Escalation** (Dosing complete)	**Dose Expansion** (Enrolling)
Cohort 1 2E10 vg n=3			
Cohort 2 5E10 vg n=4		**Cohort 5** 5E10 vg n=3	
Cohort 3 2E11 vg n=4	**Cohort 4** 5E10 vg 2E11 vg n=20	**Cohort 6** 2E11 vg n=3	**Cohort 7** 2E11 vg n=up to 20

Interim safety and biomarker data reported

◆ =Safety Evaluation (after 3 participants complete 5 weeks follow-up)

FOCUS Trial

GT005 Dose Levels Have Been Well Tolerated in Cohorts 1–4

March 2022 Safety Analysis, N=31

GT005 well tolerated

- No GT005-related SAEs
- No safety signal on laboratory parameters
- RPE changes noted in some subjects in the high dose group; restricted to the bleb area with no significant visual changes

Most surgery-related TEAEs were mild (TEAEs with ‘unknown’ relationship are included)

- 20 mild
  - Most frequent TEAEs: 5 RPE changes, 3 cataracts
- 11 moderate
  - 6 cataracts; 1 allergy to surgical sutures, 1 choroidal neovascularization, 1 intra-ocular injection complication (sub-RPE injection), 1 RPE changes, 1 visual impairment

SAE=Serious adverse event
RPE=Retinal pigment epithelium
TEAEs = Treatment-Emergent Adverse Events

Interim Data Show No Clinically Significant GT005-Related Inflammation

- GT005 is associated with clinically benign immunogenicity
- No antibody-mediated immunogenicity to the FI transgene
- No significant association of immune responses with adverse events
- Vector shedding profile is aligned with other rAAV ocular therapies, with no viral vector detected at week 1 or week 5

Interim FOCUS Immunogenicity Data

- AAV2 neutralizing antibodies (n=20)
  - Pre-existing antibodies to AAV2 vector in 11 patients
  - 1 patient with a transient increase in anti-AAV2 titer at week 5
  - 19 patients show no change in anti-AAV2 titers post treatment
- T-cell immunogenicity (n=25)
  - Pre-existing T-cell immunogenicity to AAV2 vector in 1 patient
  - 2 patients with a low magnitude increase in T-cell response post treatment
- Anti-CFI antibodies (n=20)
  - No anti-CFI (transgene protein) antibodies to date
- AAV2 vector shedding (n=21)
  - No vector detected in urine or blood
  - Low levels of vector detected in saliva or tears of 5 patients 12–24 hours post-GT005; no vector detected at week 1 or 5

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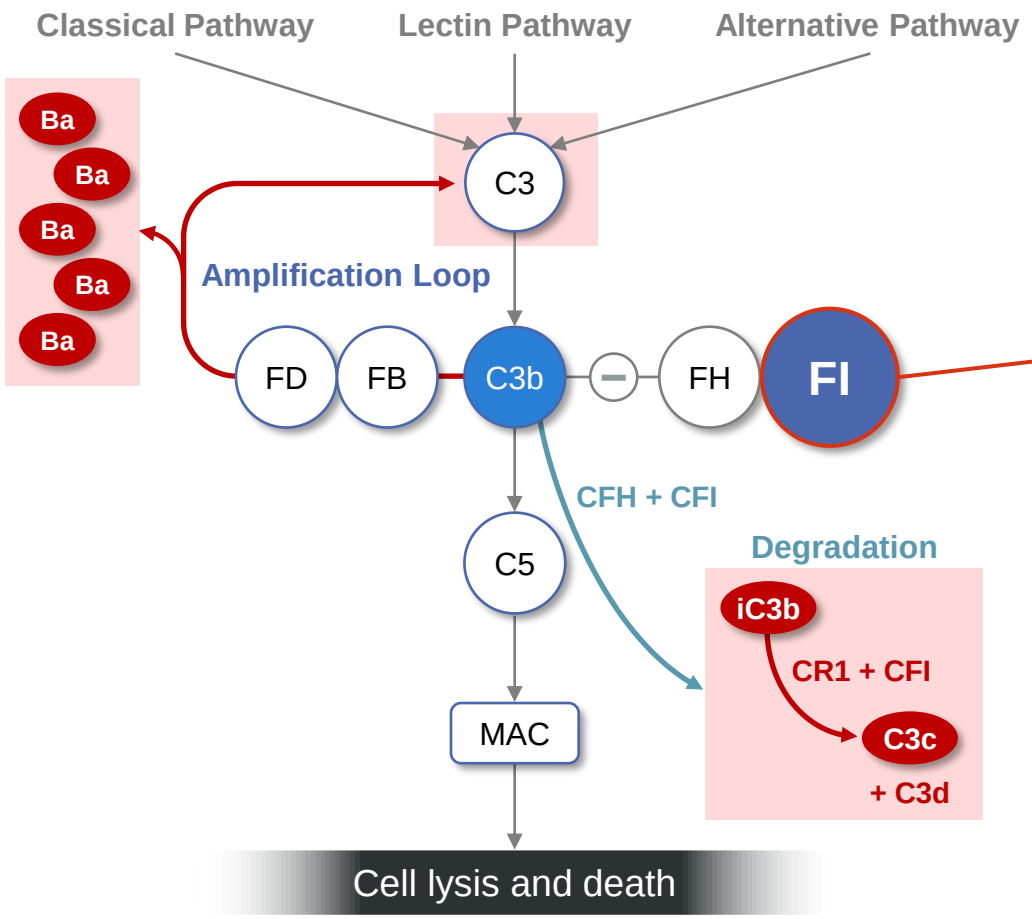

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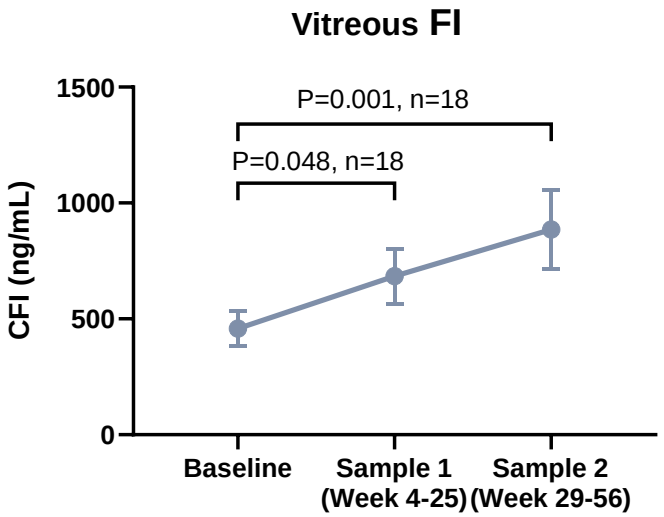
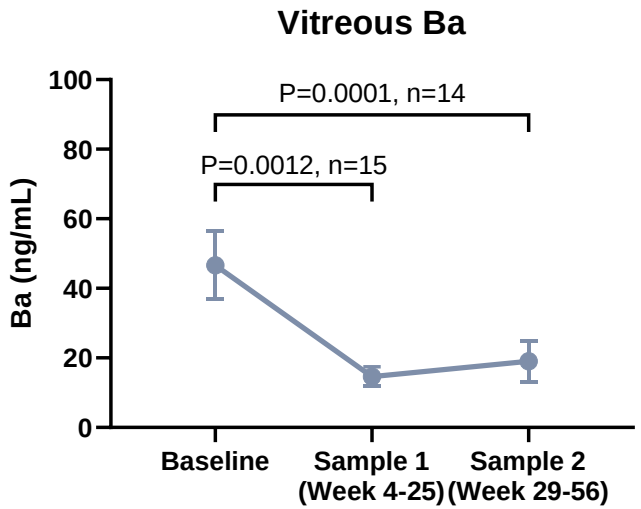
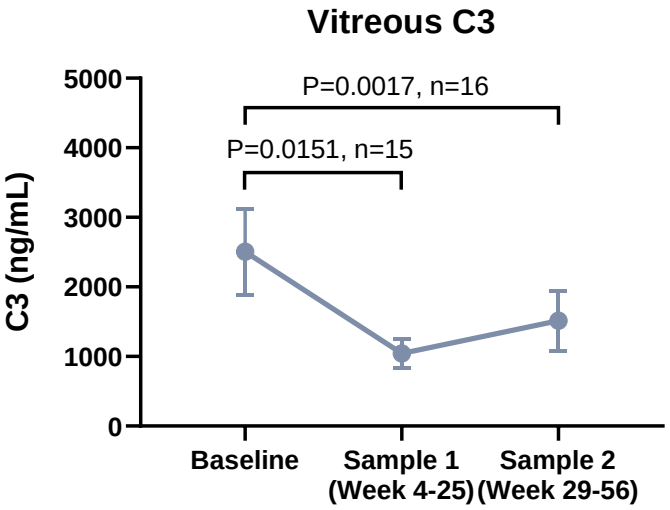
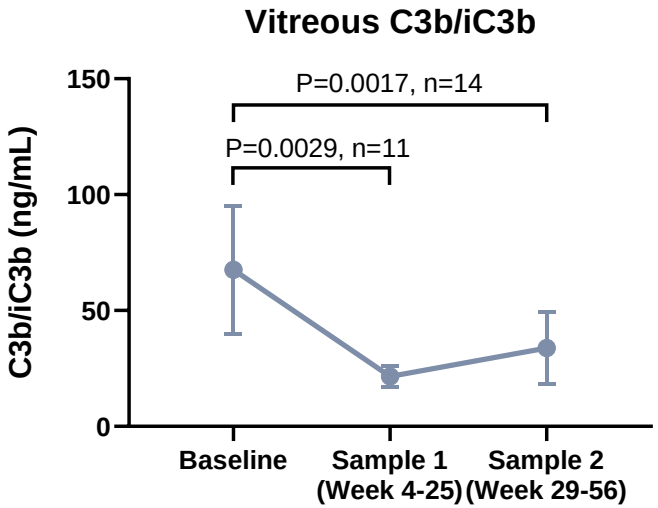
GT005 Generated Sustained Increases in Vitreous FI and Decreases in Downstream Proteins Involved in Overactivation of Complement System







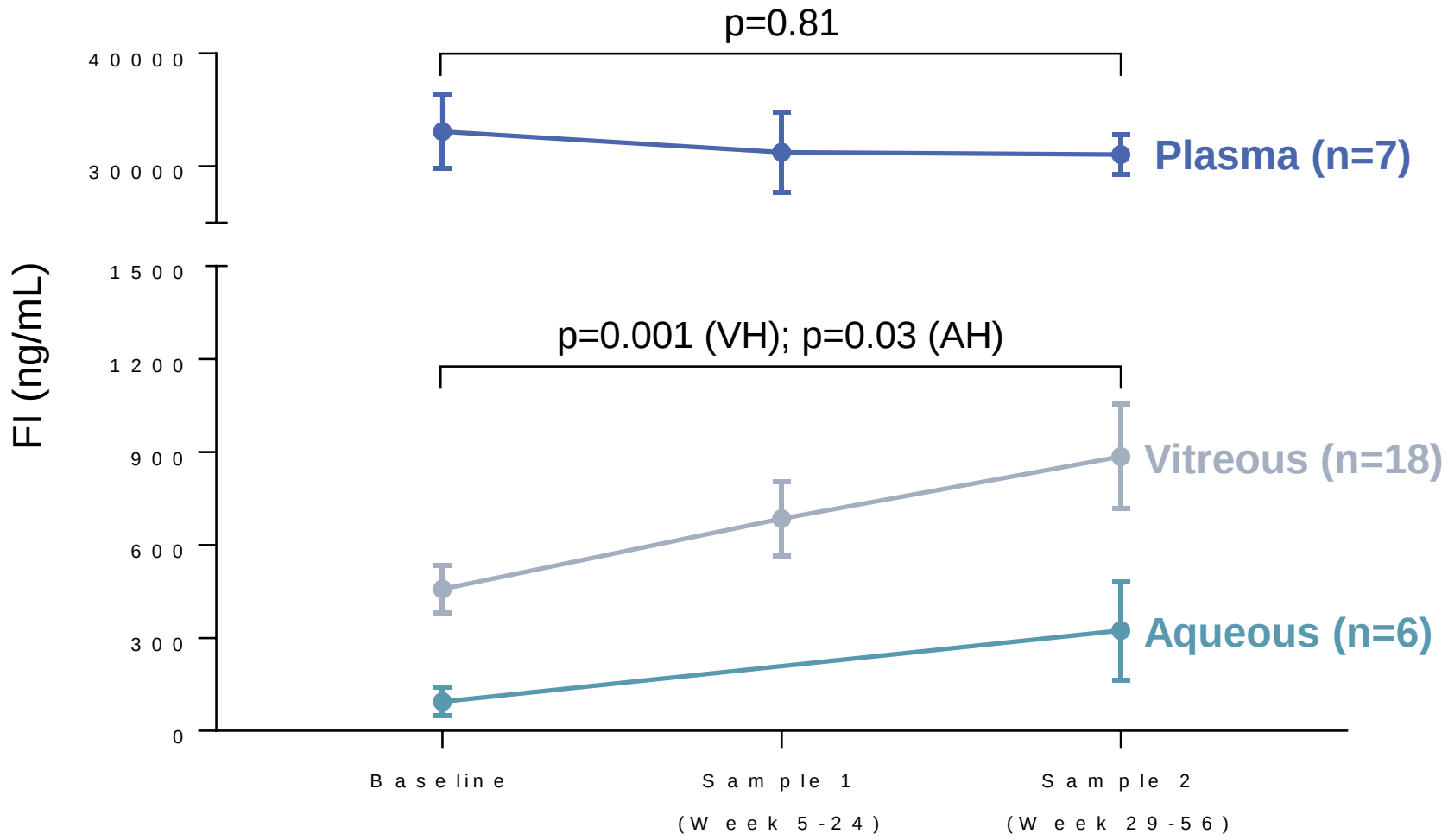


- Significant increases in vitreous FI post GT005

- GT005 not only impacts complement activation (Ba, C3b/iC3b) but also input of C3 to the ocular complement system
- Reduction of chronic inflammatory drive would result in an overall reduction in production of C3

Data shown as mean + SEM; Stats: Wilcoxon matched paired analysis. Data on file as of January 2022.

Elevation in Aqueous FI Mirrors Vitreous FI



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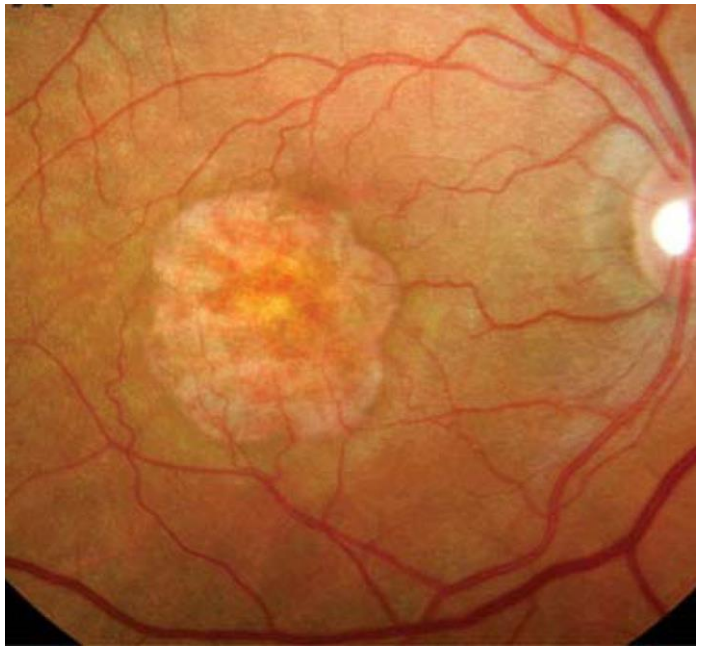
Take Home Messages

GT005*: Potential one-time gene therapy targeting complement activation is well tolerated with increased FI levels and downstream biomarker reduction

- FI is a natural regulator of the complement system[1,2]
- GT005 has been well tolerated to date in GA patients in the ongoing FOCUS Phase I/II trial
- Significant, sustained increases in vitreous FI occur after one treatment
- Early data show most patients experience increased vitreous FI and downstream modulation of complement biomarkers, consistent with reduced complement activity
- Randomized controlled Phase II trials evaluating safety and efficacy of GT005 are ongoing†



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1. Lachmann PJ. *Immunobiology*. 2019;224:511-17. 2. Lachmann PJ. *Adv Immunol*. 2009;104:115-49.

Acknowledgements

Participants

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Study Teams

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