FOCUS Interim Results: GT005 Gene Therapy Phase I/II Study for the Treatment of Geographic Atrophy

Angiogenesis, Exudation, and Degeneration 2021

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Take Home Messages

- Complement over-activation has been implicated in AMD disease pathogenesis
- Complement Factor I (CFI) is a natural down-regulator of the complement system
- GT005 is an investigational gene therapy designed to induce expression of CFI after subretinal delivery
- GT005 has been well tolerated to date in the FOCUS Phase I/II trial in patients with GA
- Early data show majority of patients had increased vitreous CFI and downstream modulation of complement biomarkers
- Randomized controlled Phase II trials evaluating safety and efficacy of GT005 are ongoing
## Strong Evidence of Role of Overactive Complement System in AMD

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Genetics</th>
<th>Clinical Data</th>
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<tbody>
<tr>
<td><img src="image" alt="Pathology Image" /></td>
<td><img src="image" alt="Genetics Image" /></td>
<td><img src="image" alt="Clinical Data Image" /></td>
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- Biochemical analysis of drusen shows presence of multiple components of the complement pathway
- Variants in multiple complement genes (including CFI) shown to be associated with increased risk of developing AMD

*Investigational complement inhibitors have shown a 28-29% reduction in GA progression (vs sham) in recent Phase 2 studies*

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*Liao DS et al, 2020, Ophthalmology.127(2):186-195*

Jaffe GJ et al, 2020, Ophthalmology.1:S0161-6420(20)30845-9
CFI: A Natural Inhibitor of the Alternative Pathway

• CFI’s function is to keep the complement system in balance
• Given this critical role, we believe CFI is well suited for gene therapy
• GT005 is designed to induce production of this natural regulator
GT005: Using Clinically Proven AAV2 Vector to Produce CFI

- Designed to enable cellular transduction and induce secretion of CFI
- Potential to allow for constitutive expression of CFI after single administration
- Potential to avoid saw tooth dynamics of repeated intravitreal injections of medications
- AAV2 clinically predicated with persistent durability at 3 years in other programs*

ITR = inverse terminal repeat; CAG = CAG promoter; CMV = CMV promoter; CFI = complement factor I; WPRE = Woodchuck Hepatitis Virus (WHP) Posttranscriptional Regulatory Element which is a DNA sequence that, when transcribed creates a tertiary structure enhancing expression; bGHpA = poly A signal.

*Maguire AM et al, 2019, Ophthalmology; 126:1273-1285
FOCUS Phase I/II Open-Label Study to Evaluate GT005 Safety and Tolerability

- Completed dose escalation and currently enrolling dose-expansion cohort
- 22 patients dosed as of December 2020; data collection ongoing
- Measuring transgene expression and pharmacodynamic markers by vitreous sampling
- Interim data available from patients in Cohorts 1, 2, 3 and initial patients dosed in Cohort 4

**Dose escalation (Transvitreal)**
First patient dosed January 2019
Dosing complete

- Cohort 1
  - Dose 1
  - n=3

- Cohort 2
  - Dose 2
  - n=4

- Cohort 3
  - Dose 3
  - n=4

**Dose expansion (Transvitreal)**
First patient dosed March 2020
Enrolling

- Cohort 4
  - Doses 1, 2, 3
  - n=up to 20

- Cohort 5
  - Dose 2
  - n=3

**Orbit™ Subretinal Delivery System Integration**
First patient dosed October 2020
Cohort 5 complete

- Cohort 6
  - Dose 3
  - n=3

- Cohort 7
  - Dose TBD
  - n=up to 20

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

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- 22 patients dosed as of December 2020; data collection ongoing
- Measuring transgene expression and pharmacodynamic markers by vitreous sampling
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3 Dose Levels of GT005 Were Well Tolerated in Initial Cohorts

Ocular Treatment-Emergent Adverse Events (TEAEs) in Cohorts 1-4

<table>
<thead>
<tr>
<th>Cohort 1 (n=3) Dose: (2E10 vg)</th>
<th>Cohort 2 (n=4) Dose: (5E10 vg)</th>
<th>Cohort 3 (n=4) Dose: (2E11 vg)</th>
<th>Cohort 4 (n=8) Dose: (5E10-2E11 vg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAEs (n=4)</td>
<td>TEAEs (n=7)</td>
<td>TEAEs (n=6)</td>
<td>TEAEs (n=4)</td>
</tr>
<tr>
<td>• Cataract</td>
<td>• Age-related macular degeneration*</td>
<td>• Cataract</td>
<td>• Cataract</td>
</tr>
<tr>
<td>• Cataract (fellow eye)</td>
<td>• Blepharitis (both eyes)</td>
<td>• Choroidal neovascularisation</td>
<td>• Hallucination</td>
</tr>
<tr>
<td>• Dry eye</td>
<td>• Cataract</td>
<td>• Eye contusion (fellow eye)</td>
<td>• Intraocular pressure increased</td>
</tr>
<tr>
<td>• Eye Oedema</td>
<td>• Conjunctivitis viral (both eyes)</td>
<td>• Iridocyclitis</td>
<td>• Intracocular pressure increased</td>
</tr>
<tr>
<td>• Dry age-related macular degeneration (fellow eye) †</td>
<td>• Dry age-related macular degeneration (fellow eye) †</td>
<td>• Retinal haemorrhage</td>
<td>• Intracocular pressure increased</td>
</tr>
<tr>
<td>• Glaucoma (fellow eye)</td>
<td>• Glaucoma</td>
<td>• Vitreous floaters</td>
<td>• Intracocular pressure increased</td>
</tr>
</tbody>
</table>

- No dose-related trends in frequency/type of AEs
- No GT005-related SAEs
- No safety signal on laboratory parameters
- 1 possible GT005-related adverse event
  - Choroidal neovascularization treated with anti-VEGF (moderate severity)
- 12 surgery-related adverse events
  - 9 mild (1 corneal abrasion post op causing vision decrease)
  - 3 moderate (2 cataracts; 1 sub-RPE injection)
- Other ocular AEs in study eye of note
  - 2 study eye AEs reported with increased IOP
  - 1 with history of glaucoma, Tmax 27, resolved with drops
  - 1 with IOP elevation at wk1 visit. Tmax 29, resolved at 5 weeks

*Miscoded (Sub-RPE injection)
†BCVA drop in fellow eye secondary to GA progression

Data as of December 2020
Interim Data Shows No Signs of GT005-Related Inflammation

- GT005 associated with clinically benign immunogenicity
- No antibody-mediated immunogenicity to the CFI transgene
- No association of immune responses with adverse events

### Interim FOCUS Immunogenicity Data

- **AAV2 antibodies (n=12)**
  - Pre-existing antibodies to AAV2 vector in 9 patients
  - No increases in AAV2 antibody titers post-treatment

- **T-cell immunogenicity (n=11)**
  - Pre-existing T-cell immunogenicity to AAV2 vector in 2 patients
  - Increases in T-cell response post-treatment that were transient in nature and at a low magnitude

- **Anti-CFI antibodies (n=8)**
  - No anti-CFI antibodies seen in patients tested to date

Data as of December 2020
Secondary Endpoints Data

Visual Acuity Preserved at 48 Weeks Post Treatment

Data as of December 2020
Transgene Expression: Consistent and Durable Increase in Vitreous CFI levels

- 9/10 patients had elevated CFI levels post-GT005 administration; average increase of 146% from baseline
- 1st patient treated continues to have sustained CFI increase at 84 weeks
- Increases in vitreal CFI seen in both RV and non-RV patients

Data as of December 2020
It is unclear whether the relationship between Ba levels and lytic activity is linear

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]

Ba is a direct readout of the amplification loop**

Inhibition of the amplification loop by CFI (GT005) leads to a 41% drop in vitreal Ba levels, indicating significant inhibition of the amplification loop
Significant Decreases in Ba and C3 Breakdown Product Vitreous Levels After GT005 Administration

Average Decrease of 41% in Ba and 42% in C3 Breakdown Product Vitreous Levels

Data as of December 2020
The assay used for Ba and C3 breakdown products measurements are standard and validated
Statistical analysis: Wilcoxon matched pairs test (post-treatment compared to baseline); Data shown as Mean ± SD
Significant Correlation Between Increases in Local CFI Levels and Decreases in Ba with GT005

Correlation $\Delta$CFI and $\Delta$Ba (post-Treatment)

Notes:
Data as of December 2020
Statistical analysis: Spearman correlation; Data used: latest available data point up to week 56 for individual patients
Phase II Studies Evaluate Two Patient Populations

Primary Endpoint: GA Progression at 48 Weeks

**EXPLORE**
- 75 GA patients with CFI rare variants
- Arm 1: Low dose
- Arm 2: High dose
- Arm 3: Untreated control

**HORIZON**
- 180 GA patients (broad GA population)
- Arm 1: Medium dose
- Arm 2: High dose
- Arm 3: Untreated control

All participants enrolling in HORIZON and EXPLORE genotyped; participants in HORIZON being stratified by AMD genotype subgroup.
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Acknowledgements

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Study Teams

Participants