Zilucoplan in Generalized Myasthenia Gravis

*Top-line Results of a Phase 2 Study*

December 10, 2018
Introduction
Myasthenia Gravis Disease Overview
Phase 2 Results
Closing Remarks
Q&A
Forward-Looking Statements

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Topics

- Introduction
- Myasthenia Gravis Disease Overview
- Phase 2 Results
- Closing Remarks
- Q&A
Generalized Myasthenia Gravis (gMG) Is a Rare, Debilitating, C5-Mediated Disease

Autoantibodies and complement-mediated destruction of the neuromuscular junction cause pathology in gMG

**FREQUENCY**
150-250/Million, ~60,000 (US), ~100,000 (EU), ~24,000 (JP)

**CAUSE**
Autoantibodies block signals from nerves to muscles and complement activation destroys the neuromuscular junction

**DIAGNOSIS**
Acetylcholine receptor antibody positive

**CONSEQUENCES**
Serious and progressive
- Significantly impacts quality of life
- ~80% progress to generalized muscle weakness
- ~20% experience crisis

**TREATMENT**
Sporadic, expensive, and often non-specific
- Cholinesterase inhibitors, corticosteroids, ISTs, thymectomy
- IVIG, PLEX total maintenance costs ~$150,000 per year
- Eculizumab (Soliris®; Alexion), bi-weekly IV therapy approved in 2017; ~$700,000 per year

References:
Zilucoplan: A Subcutaneously Self-administered, Macro cyclic Peptide Inhibitor of Complement C5

Multiple validated indications, pipeline-in-a-product potential

**Alternative Pathway**
Activated by non-self cells

**Classical Pathway**
Activated by antibody-antigen complexes

**Lectin Pathway**
Activated by pathogen surfaces

**Multiple Indications**
- PNH: Phase 2 positive ✅
- gMG: Phase 2 positive ✅
- aHUS/LN: Phase 1b positive ✅
- Neuropathies and Myopathies: TBA

PNH – paroxysmal nocturnal hemoglobinuria; gMG – generalized myasthenia gravis; aHUS – atypical hemolytic uremic syndrome; LN – lupus nephritis
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Phase 2 Study Targets Broad gMG Patient Population

**Broad Patient Population:**
- Generalized MG (Myasthenia Gravis Foundation of America class II-IVa)
- AChR-antibody positive
- Quantitative Myasthenia Gravis (QMG) score of ≥ 12
- Stable doses of corticosteroids and/or immunosuppressants
- No requirement to be “refractory” or have failed multiple prior therapies

**Endpoints:**
- **Primary:** Change in QMG score from baseline to week 12
- **Key Secondary:** Change in MG-ADL score from baseline to week 12
- Pre-specified significance testing at 1-sided alpha of 0.1

**Enrollment:** 44 Patients (vs. target of 36)

Randomized, double-blind, placebo-controlled, multi-center study followed by an open-label long-term extension (LTE)
## Baseline Characteristics Confirm Breadth of gMG Study Population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n=15)</th>
<th>Zilucoplan 0.1 mg/kg (n=15)</th>
<th>Zilucoplan 0.3 mg/kg (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years (± SD)</td>
<td>48 (15.7)</td>
<td>46 (15.7)</td>
<td>55 (15.5)</td>
</tr>
<tr>
<td>Male, n(%)</td>
<td>4 (27%)</td>
<td>7 (47%)</td>
<td>10 (71%)</td>
</tr>
<tr>
<td>Race, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• White</td>
<td>12 (80%)</td>
<td>13 (87%)</td>
<td>11 (79%)</td>
</tr>
<tr>
<td>• Asian</td>
<td>1 (7%)</td>
<td>0 (0%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>• Black or African American</td>
<td>2 (13%)</td>
<td>2 (13%)</td>
<td>2 (14%)</td>
</tr>
<tr>
<td>MGFA Class at Screening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• II</td>
<td>7 (47%)</td>
<td>5 (33%)</td>
<td>5 (36%)</td>
</tr>
<tr>
<td>• III</td>
<td>8 (53%)</td>
<td>10 (67%)</td>
<td>5 (36%)</td>
</tr>
<tr>
<td>• IVa</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>4 (29%)</td>
</tr>
<tr>
<td>Duration of Disease, mean years (min, max)</td>
<td>8.0 (0.1, 20.9)</td>
<td>8.7 (1.6, 24.1)</td>
<td>8.3 (0.5, 26.0)</td>
</tr>
<tr>
<td>Baseline QMG Score, mean (± SD)</td>
<td>18.7 (4.0)</td>
<td>18.7 (4.0)</td>
<td>19.1 (5.1)</td>
</tr>
<tr>
<td>Baseline MG-ADL Score, mean (± SD)</td>
<td>8.8 (3.6)</td>
<td>6.9 (3.3)</td>
<td>7.6 (2.6)</td>
</tr>
<tr>
<td>Baseline MG Composite Score, mean (± SD)</td>
<td>18.7 (5.7)</td>
<td>14.5 (6.3)</td>
<td>14.6 (6.3)</td>
</tr>
<tr>
<td>Baseline MGQoL15r Score, mean (± SD)</td>
<td>15.9 (7.4)</td>
<td>19.1 (5.0)</td>
<td>16.5 (7.3)</td>
</tr>
<tr>
<td>Prior MG Therapies (Standard of Care)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pyridostigmine, n(%)</td>
<td>14 (93%)</td>
<td>15 (100%)</td>
<td>14 (100%)</td>
</tr>
<tr>
<td>• Corticosteroids, n(%)</td>
<td>13 (87%)</td>
<td>13 (87%)</td>
<td>14 (100%)</td>
</tr>
<tr>
<td>• Immunosuppressants, n(%)</td>
<td>12 (80%)</td>
<td>12 (80%)</td>
<td>9 (64%)</td>
</tr>
<tr>
<td>Prior IVIG, n(%)</td>
<td>9 (60%)</td>
<td>8 (53%)</td>
<td>10 (71%)</td>
</tr>
<tr>
<td>Prior Plasma Exchange, n(%)</td>
<td>7 (47%)</td>
<td>9 (60%)</td>
<td>7 (50%)</td>
</tr>
<tr>
<td>Prior Thymectomy, n(%)</td>
<td>5 (33%)</td>
<td>8 (53%)</td>
<td>7 (50%)</td>
</tr>
<tr>
<td>Prior MG Crisis Requiring Intubation, n(%)</td>
<td>3 (20%)</td>
<td>4 (27%)</td>
<td>2 (14%)</td>
</tr>
</tbody>
</table>

**High Unmet Medical Need**

Non-Refractory Patients Included
- 9% no prior steroids
- 25% no prior ISTs
- 39% no prior IVIG
- 48% no prior PLEX
Primary and Key Secondary Endpoints Met with 0.3 mg/kg Zilucoplan Dose: Rapid, Clinically Meaningful, and Statistically Significant Reductions in QMG and MG-ADL

![Graphs showing change from baseline in QMG and MG-ADL over study weeks]

Pre-specified significance testing at 1-sided alpha of 0.1 with LOCF ANCOVA p values shown; error bars denote standard errors of least squares mean; mITT
Primary and Key Secondary Endpoints Also Met with 0.1 mg/kg Zilucoplan Dose

Pre-specified significance testing at 1-sided alpha of 0.1 with LOCF ANCOVA p values shown; error bars denote standard errors of least squares mean; mITT
Pre-specified Pooled Analysis of Approval Endpoint (MG-ADL) Satisfies 2-Sided $p<0.05$

Change from Baseline in MG-ADL

Zilucoplan in Phase 2 met approvable endpoint (MG-ADL) at 12 weeks with similar magnitude and statistical significance as eculizumab in Phase 3 REGAIN study at 26 weeks*

LOCF ANCOVA 2-sided $p$ value shown; error bars denote standard errors of least squares mean; mITT
* Placebo-corrected change in MG-ADL at 26 weeks in REGAIN study: $-1.9$ LOCF ANCOVA $p=0.039$; ref. Howard et al AANEM 2016
Responder Analysis: Robust and Meaningful Improvements over Placebo

Zilucoplan arm favored overall and in patients exhibiting largest point improvements.
Patients Can Achieve Minimal Symptom Expression by Week 12

Minimal symptom expression (MSE) = Achieving MG-ADL score of 0 or 1

23% of patients (placebo-corrected) achieved MSE in 12 weeks in 0.3 mg/kg zilucoplan arm

### Safety and Tolerability Profile Supports Continued Development

<table>
<thead>
<tr>
<th>Patients requiring rescue with IVIG or PLEX</th>
<th>Placebo (n=15)</th>
<th>Zilucoplan 0.1 mg/kg (n=15)</th>
<th>Zilucoplan 0.3 mg/kg (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients requiring rescue with IVIG or PLEX</td>
<td>3 (20%)</td>
<td>1 (7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Patients with adverse events (AEs)</td>
<td>12</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Patients with related AEs</td>
<td>3</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Patients with serious AEs</td>
<td>3</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Patients with related serious AEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Patients with most common related AEs:**

- **Nausea**: 0, 2, 2
- **Injection site bruising**: 1, 2, 0
- **Injection site scab**: 0, 3, 0
- **Contusion**: 0, 1, 1
- **Headache**: 1, 4, 2
- **Patients with injection site reactions**: 3, 4, 3

- No meningococcal infections
- Profile consistent with Ph1 and Ph2 PNH studies

- All 44 subjects completed 12-week study; No early withdrawals
- 43/44 subjects (98%) entered long-term extension

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No patients required rescue in 0.3 mg/kg zilucoplan arm.
Zilucoplan in gMG: Phase 2 Top-line Data Summary

- Positive Phase 2 study in broad gMG population (not restricted to “refractory”)
- Primary and key secondary endpoints met with clinically meaningful and statistically significant reductions in QMG and MG-ADL in both 0.3 mg/kg and 0.1 mg/kg dose groups
- Magnitude and speed of effect, no rescue therapy required, and higher rate of minimal symptom expression all favor 0.3 mg/kg dose over 0.1 mg/kg dose for Phase 3
- Favorable safety and tolerability profile with no early withdrawals in the study; Safety and PK/PD profile consistent with Phase 1 healthy volunteer and Phase 2 PNH studies
- End-of-Phase 2 meetings with FDA and other regulatory agencies planned for 1H19 to confirm Phase 3 design
- Expanded dataset, including pharmacodynamics and extension data, planned for 1H19
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### Zilucoplan: A Convenient Complement Inhibitor for a Broad gMG Population

<table>
<thead>
<tr>
<th>Administration</th>
<th>Tx Time</th>
<th>Population</th>
<th>Mechanism</th>
<th>QMG, ADL</th>
</tr>
</thead>
<tbody>
<tr>
<td>~0.5 mL (3 kDa) SC daily self-admin</td>
<td>5-8 sec.</td>
<td>Uncontrolled MG (~30k)</td>
<td>C5 Cyclic Peptide</td>
<td>@ 12wks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>≥7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>43%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Eculizumab³</th>
<th></th>
<th>Refractory MG (~3-5k)</th>
<th>C5 mAb</th>
<th>@ 26wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>120 mL (140 kDa) Intravenous infusion every 14 days</td>
<td>45 min.</td>
<td></td>
<td></td>
<td>≥7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>34%</td>
</tr>
</tbody>
</table>

Market Opportunity: Extend Complement Inhibition to More Patients

MG Diagnosis → Acetylcholinesterase Inhibitor → Steroids → Immunosuppressive Therapies → IVIG/PLEX (Crises or Chronic)

>20K pts ~ 35%

<10K pts ~ 15%

Zilucoplan Phase 2 Population

Target Complement-Mediated Damage Earlier (~50% of MG patients are uncontrolled)

Opportunity to Treat ~30K Patients (U.S. Only) with AChR+ gMG

US Prevalence: ~200 per million (~60K pts)

Data source: IQVIA market projections (93% retail, 1.5B LRx & Dx claims, CDM ~350 hospitals, PharMetrics health plan 150M pts)

Jan 2016 – Dec 2017 selection period (patients with at least 1 MG diagnosis claim ICD-10 G70.00 or G70.01); 5 years history for treatment and procedures (starting Jan 2013)

Applied best practice eligibility controls and apply appropriate pre-screener/end-treater rules

Used Rx/Dx intersection to project Rx and office-based treatments, and projected hospital utilization of relevant therapies (ie. IVIG, PLEX) using CDM

Segment size projected with Pharmetrics Plus data, therapy usage does not use Pharmetrics Plus; therapy analysis on steroid dosage used to allocate patients on high dose steroid to uncontrolled
Zilucoplan: Designed for Everyday Complement Control

**Efficacious:** Rapid and meaningful reductions in QMG & MG-ADL with high proportion of patients achieving MSE; Favorable safety and tolerability

**Convenient:** 5-8 sec push, ~0.5 mL, room temperature; Experience comparable to daily insulin injection

**Easy to Use:** BD UltraSafe Plus™ PFS with >13,000 doses administered in zilucoplan clinical trials; 91% of gMG patients interested in daily self-administered SC complement inhibitor\(^1\)

**Accessible:** Pricing expected to enable broader access; Non-refractory and refractory patients

**Positioned for Earlier Use:** Targets complement-mediated damage at all stages of treatment paradigm

\(^1\)Data on file: market research with MGFA (n=372)
Array of C5 Inhibitor Assets Provides an Opportunity to Build a Transformative Franchise in Neurology

**Neurology Disease Targets**
Systemic & Local C5

- Neurodegenerative
- Neuropathies/Myopathies
- Neuromuscular

**C5 Lifecycle**

- **Oral Small Molecule C5 Inhibitor**
  - Highly potent, orally available
- **Zilucoplan XR**
  - Added convenience of SC once weekly
- **Zilucoplan QD**
  - SC once daily, small peptide inhibitor, designed to inhibit C5 systemically and locally

Potential of a Peptide Inhibitor in Tissue-Based C5 diseases and a First-in-Class Oral Small Molecule
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