MGD010: B-cell Inhibitory DART® Molecule Targeting CD79B & CD32B

Ph 1 First-in-Human, Double-Blind, Placebo-Controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, PK / PD & Immunogenicity of MGD010 in Healthy Subjects

[Abstract OP0201]

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DISCLOSURES

- Employee of MacroGenics
Introduction

• B cells play an important role in immune tolerance and autoimmunity
  – CD32B (FcγRIIb): a checkpoint molecule on B cells
  – CD79B: signal transducing component of B-cell receptor

• MGD010, a bi-specific Dual-Affinity Re-Targeting (DART®) molecule, inhibits B-cell activation
  – Co-ligation of CD32B with CD79B leverages a natural physiologic B-cell inhibitory loop, delivering a negative signal that limits B-cell activation

• **MGD010 provides a novel therapeutic approach to autoimmune disorders**
  – Non-depleting intervention (*vs* rituximab)
  – Rapid onset of activity (*vs* belimumab)
MGD010-mediated Inhibition of B-cell Function

*Inhibition of B-cell Proliferation in vitro and Immunoglobulin Secretion in vivo*

- Co-ligation of both targets is essential for functional activity of MGD010
  - Monospecific engagement of CD32B does not result in B-cell inhibition
  - Preclinical models confirm inhibitory properties of MGD010 with a decrease in B-cell proliferation and suppression of immunoglobulin secretion
Study Objectives

• Primary Objective
  – Assess safety and tolerability of single dose of MGD010 in healthy adult subjects

• Secondary Objectives
  – Evaluate single MGD010 dose pharmacokinetics
  – Assess pharmacodynamics effects of MGD010 on humoral immune responses
  – Evaluate potential anti-drug antibodies

• Exploratory Objectives
  – Evaluate MGD010 binding to CD32B and CD79B on peripheral B cells
  – Evaluate activation status of peripheral B cells and B-cell subsets
  – Assess immune phenotype, including modulation of B-cell subsets
  – Assess response of peripheral B cells to ex-vivo BCR stimulation
Eligibility

• **Key Inclusion criteria**
  – Age: 18 – 50 years
  – BMI: 18 – 30 kg/m²

• **Key Exclusion criteria**
  – Women of child bearing potential or who are pregnant and/or breastfeeding
  – Medical history and concurrent diseases
    • Any significant acute or chronic medical illness (use of any prescription drugs within 4 wks of dosing or OTC drugs within 1 wk of dosing)
    • Major surgery within 4 wks of dosing
    • Smoking > 10 cigarettes per day
    • Infectious disease (TB, Hep B, Hep C, HIV)
    • Known history of autoimmune or vascular disorders
    • Physical and lab findings:
      – QTc > 450 msec, HR < 45 bpm or > 120 bpm, SBP > 140 mmHg, DBP > 90 mmHg
      – AST/ALT > 1.25 > ULN, Tbili > 1.25 x ULN, abnormal PT/PTT
      – Positive urine drug screen
Study Design

• Enrolled healthy volunteers in six escalation cohorts
  – Healthy volunteers represent homogeneous population to ascertain safety and pharmacodynamics effects of MGD010

• Eight subjects to enroll at each dose cohort
  – Six subjects were treated with MGD010 and two were treated with Placebo

• Staggered dosing at each dose cohort to assess safety & tolerability
  – Randomized 6 subjects in double-blind manner after treating two sentinel subjects with MGD010

<table>
<thead>
<tr>
<th>Dose Cohort</th>
<th>MGD010 Dose (mg/kg)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>0.01</td>
</tr>
<tr>
<td>2</td>
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<td>3</td>
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<td>4</td>
<td>1.0</td>
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<tr>
<td>5</td>
<td>3.0</td>
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<tr>
<td>6</td>
<td>10.0</td>
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## Study Enrollment

<table>
<thead>
<tr>
<th>Baseline Demographics</th>
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<tbody>
<tr>
<td>N</td>
<td>49&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>33.4 ± 7.4</td>
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<tr>
<td>Gender (M:F)</td>
<td>48:1</td>
</tr>
<tr>
<td>Race:</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>12</td>
</tr>
<tr>
<td>Black</td>
<td>35</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
</tr>
<tr>
<td>Mean Weight (kg)</td>
<td>78.0 ± 12.1</td>
</tr>
<tr>
<td>Mean Height (cm)</td>
<td>177.5 ± 7.8</td>
</tr>
</tbody>
</table>

<sup>a</sup>Forty-nine subjects were treated in Dose Escalation: 0.01, 0.1, 0.3, 1, 3 or 10 mg/kg MGD010
### Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event*</th>
<th>All Events</th>
<th>Related</th>
<th>Adverse Event*</th>
<th>All Events</th>
<th>Related</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All ≥ Gr 3</td>
<td>All ≥ Gr 3</td>
<td></td>
<td>All ≥ Gr 3</td>
<td>All ≥ Gr 3</td>
</tr>
<tr>
<td>Conjunctival Haemorrhage</td>
<td>1 - -</td>
<td>-</td>
<td>Periorbital contusion</td>
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<tr>
<td>Ocular Hyperemia</td>
<td>1 -</td>
<td>-</td>
<td>Muscle twitching</td>
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<td>-</td>
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<tr>
<td>Pupils Unequal</td>
<td>1 -</td>
<td>-</td>
<td>Headache</td>
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<tr>
<td>Nausea</td>
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<td>Somnolence</td>
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<td>Chills</td>
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<td>Terminal insomnia</td>
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<tr>
<td>Vessel puncture site bruise</td>
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<td>Nasal congestion</td>
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<tr>
<td>Folliculitis</td>
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<td>-</td>
<td>Rhinorrhea</td>
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<td>Upper respiratory tract infection</td>
<td>2 - 2</td>
<td>-</td>
<td>Dry skin</td>
<td>1 -</td>
<td>-</td>
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<tr>
<td>Viral upper respiratory tract infection</td>
<td>2 -</td>
<td>-</td>
<td>Night sweats</td>
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<tr>
<td>Contusion</td>
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<td>Pruritus</td>
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<td>Ligament sprain</td>
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<td>-</td>
<td>Rash</td>
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<td>Limb injury</td>
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<td>Hypertension</td>
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<tr>
<td>Muscle strain</td>
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<td>-</td>
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</tbody>
</table>

*MedDRA Preferred Term

AEs assessed by 2007 FDA Guidance of Toxicity Grading Scale for healthy adult & adolescent volunteers enrolled in preventive vaccine clinical trials.
Pharmacokinetics and Circulating B-cell Occupancy

- MGD010 serum concentrations increase linearly with dose
  - Half-life: ~8 days at ≥1mg/kg
- Maximum B-cell occupancy at doses ≥1 mg/kg
  - Sustained receptor occupancy beyond one week at doses ≥ 1 mg/kg
- No B-cell depletion or cytokine release (data not shown) at any dose levels
Treatment with MGD010 Inhibited B-Cell Activation

- PBMCs from enrolled subjects collected longitudinally after MGD010 treatment
  - Ca\(^{2+}\) flux (hallmark of B-cell activation) induced \textit{ex vivo} by B-cell receptor ligation using anti-IgM
    - Data normalized to maximum Ca\(^{2+}\) permeability (maximum induction) via ionomycin

- Dose dependent B-cell inhibition demonstrated with increasing doses of MGD010
  - Inhibition sustained for several weeks at highest dose levels
MGD010 Modulated Cell Surface BCR and Serum Ig Levels

**MGD010 Down-Regulation of Cell Surface Ig Expression**

- **mlgD**
  - CD27⁻ Naïve B Cells
  - Dose-dependent down modulation of cell surface BCR expression on both naïve and memory B cells
  - *p<0.05 (Paired t-test compared to baseline)

- **mlgG**
  - CD27⁺ Memory B Cells

**MGD010 Modulation of Circulating Serum Ig Levels**

- **Serum IgM**
  - Dose-dependent modulation of circulating serum IgM

- **Serum IgG**
  - Dose-dependent modulation of circulating serum IgG

- **Serum IgA**
  - Dose-dependent modulation of circulating serum IgA

**MGD010 Dosing:**

- Placebo
- 1 mg/kg
- 3 mg/kg
- 10 mg/kg
A single MGD010 dose in healthy volunteers:

- Modulated naïve and mature B-cell signal transduction via signaling blockade and/or down-regulation of surface Ig
- Decreased serum IgM levels, suggesting an impact on plasmablasts
  - Lack of CD79B expression on plasma cells is consistent with no effect on other serum Ig
MGD010 Reduced B-cell CD40 Expression

- MGD010 has potential impact on B-cell : T-cell interactions
  - Decreased cell surface expression of CD40, a B cell co-stimulatory molecule
  - No effect on other cell surface markers observed
- HLA-DR (as shown), CD80/86, CD69, CD25

* p<0.05 (Paired t-test compared to baseline)
Summary

MGD010 is well tolerated as single dose up to 10 mg/kg in healthy subjects

1. No B-cell activation or cytokine release
2. No depletion of peripheral B cells
3. BCR saturated at ≥ 1mg/kg dose levels with sustained receptor occupancy with increasing doses

MGD010 down-modulated B-cell function at multiple levels

1. Reduction in BCR-induced Ca\(^{2+}\) mobilization
2. Decrease surface Ig expression
3. Decrease serum IgM levels

Data supports continued development of MGD010 in patients with autoimmune disorders
Acknowledgements

• In sincere appreciation to all volunteer subjects enrolled in this study for their contributions

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