Phase 1 Clinical Study of MGTA-145 in Combination with Plerixafor Shows Rapid Single-Day Mobilization and Collection of CD34+ HSCs without G-CSF

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Disclosures

• **Consulting/Advisory Committees:** Cellworks, Tioma, Rivervest, Bioline, Asterias, Amphivena and Bluebird, Celgene, Incyte, NeoImuneTech, Macrogenics

• **Employment/Salary:** Washington University

• **Ownership Investment:** Magenta, WUGEN
Background

- MGTA-145 is a biologic agent that activates the CXCR2 pathway in neutrophils. In combination with plerixafor, a CXCR4 inhibitor, MGTA-145 can mobilize adequate numbers of HSCs for a successful transplant (≥2×10^6 CD34^+ cells/kg) [Stiff et al, BBMT 2011].

- MGTA-145 plus plerixafor has been shown to rapidly mobilize HSCs in mice and non-human primates within minutes to hours, respectively [Hoggatt et al, Cell 2018; Goncalves et al, Blood 2018; Karpova et al, JCI 2019].

Limitations to Current Mobilization Standard of Care:
- Requires 4-6 days
- Adverse events, some for the duration of mobilization
- Variable yields
- Contraindicated/precautions in certain diseases

Benefits of Novel Mobilization:
- Shorten mobilization phase
- Fewer/shorter duration of adverse events
- On demand mobilization enables more flexible scheduling
Objectives

- To assess the safety and tolerability of MGTA-145 ± plerixafor
- To assess CD34+ and CD34+CD90+ HSC mobilization after MGTA-145 ± plerixafor
- To assess the number of CD34+ HSCs mobilized and collected during apheresis with MGTA-145 + plerixafor
Study Design

MGTA-145-101 Healthy Volunteer Study Schema

Part A – Single Dose: MGTA-145
0.0075 - 0.3 mg/kg MGTA-145

Part B – Single Dose: MGTA-145 + plerixafor
0.015 - 0.15 mg/kg MGTA-145

Part C – 2 Daily Doses: MGTA-145 + plerixafor
0.03 and 0.07 mg/kg MGTA-145

Part D (Ongoing) – Apheresis
MGTA-145 + plerixafor
0.015 and 0.03 mg/kg MGTA-145
# Subject Demographics

<table>
<thead>
<tr>
<th>Part A</th>
<th>Part B</th>
<th>Part C</th>
<th>Part D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MGTA-145 (0.0075 – 0.3 mg/kg)</strong>&lt;br&gt;n=24</td>
<td><strong>MGTA-145 + plerixafor (0.015 – 0.15 mg/kg)</strong>&lt;br&gt;n=38</td>
<td><strong>MGTA-145 + plerixafor (0.03 – 0.07 mg/kg)</strong>&lt;br&gt;n=8</td>
<td><strong>MGTA-145 + plerixafor (0.015 – 0.03 mg/kg)</strong>&lt;br&gt;n=8*</td>
</tr>
<tr>
<td><strong>Age, years (range)</strong></td>
<td>43 (27 – 59)</td>
<td>39 (22 – 59)</td>
<td>35 (24 – 57)</td>
</tr>
<tr>
<td><strong>Male (%)</strong></td>
<td>20 (83)</td>
<td>30 (79)</td>
<td>8 (100)</td>
</tr>
<tr>
<td><strong>Weight, kg (range)</strong></td>
<td>85 (57 – 111)</td>
<td>82 (54 – 107)</td>
<td>77 (63 – 97)</td>
</tr>
<tr>
<td><strong>Race, n</strong>&lt;br&gt;White</td>
<td>14</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td><strong>Black/AA</strong></td>
<td>7</td>
<td>24</td>
<td>4</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

* A 9th subject enrolled in Part D but did not undergo leukapheresis
# Treatment Emergent Adverse Events

<table>
<thead>
<tr>
<th>Subjects with any drug related TEAE</th>
<th>Part A</th>
<th>Part B</th>
<th>Part C</th>
<th>Part D</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGTA-145 (0.0075 - 0.3 mg/kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>n=24</td>
<td>n=38</td>
<td>n=8</td>
<td>n=8*</td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td></td>
<td>19 (79.2)</td>
<td>31 (81.6)</td>
<td>6 (75.0)</td>
<td>8 (88.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>-</td>
<td>6 (15.8)</td>
<td>1 (12.5)</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>Nausea</td>
<td>-</td>
<td>7 (18.4)</td>
<td>2 (14.3)</td>
<td>4 (44.4)</td>
</tr>
<tr>
<td>Abdominal discomfort/pain</td>
<td>-</td>
<td>5 (13.2)</td>
<td>-</td>
<td>3 (33.3)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>-</td>
<td>3 (7.9)</td>
<td>1 (7.1)</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>Back pain / Musculoskeletal pain2</td>
<td>19 (79.2)</td>
<td>24 (63.2)</td>
<td>4 (50.0)</td>
<td>3 (33.3)</td>
</tr>
<tr>
<td>Dizziness / Lightheadedness</td>
<td>-</td>
<td>5 (15.6)</td>
<td>1 (7.1)</td>
<td>4 (44.4)</td>
</tr>
<tr>
<td>Headache</td>
<td>-</td>
<td>4 (10.5)</td>
<td>2 (14.3)</td>
<td>2 (22.2)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>-</td>
<td>-</td>
<td>1 (12.5)</td>
<td>-</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>-</td>
<td>2 (5.3)</td>
<td>-</td>
<td>1 (11.1)</td>
</tr>
</tbody>
</table>

There was no dose response in AEs, so data are aggregated.

1 All AEs are grade 1 except for grade 2 abdominal pain (1), nausea (1), and back pain (1) in the plerixafor + MGTA-145 0.075 mg/kg 2h stagger cohort (Part B) and grade 2 headache (1) in the plerixafor + MGTA-145 0.015 mg/kg cohort (Part D).

2 Back pain was associated with MGTA-145 infusion, lasted <20 minutes in most cases and did not require medical therapy.

* A 9th subject enrolled in Part D but did not undergo leukapheresis.
Pharmacokinetics of MGTA-145 Alone and in Combination with Plerixafor

**MGTA-145 Dose:**
- 0.0075 mg/kg
- 0.015 mg/kg
- 0.03 mg/kg
- 0.075 mg/kg
- 0.15 mg/kg
- 0.3 mg/kg

**Plasma Drug Concentration (ng/mL):**
- 0.03 mg/kg
- 0.075 mg/kg
- 0.15 mg/kg
- 0.3 mg/kg
- 0.015 mg/kg
- 0.0075 mg/kg
- 0.075 mg/kg MGTA-145 + plerixafor
- 0.15 mg/kg MGTA-145 + plerixafor

**Hours Post Administration:**
- 0
- 1
- 2
- 3
- 4

**Plasma Drug Concentration (ng/mL):**
- 0.03 mg/kg MGTA-145 + plerixafor
- 0.075 mg/kg MGTA-145 + plerixafor
- 0.15 mg/kg MGTA-145 + plerixafor
- 0.15 mg/kg MGTA-145

**LLQ:**
- Low Limit of Quantification
MGTA-145 has Rapid On-Target Neutrophil PD with Minimal Activation

Neutrophil Mobilization

CXCR2 Target Down-Modulation

MMP-9 Release

Minimal Neutrophil Activation

Dotted line represents the anticipated effect of 5 days of G-CSF [Falanga et al., Blood. 1999]
MGTA-145 Demonstrates Single Agent Activity and Leads to Robust Mobilization of CD34+ Cells in Healthy Subjects in Combination with Plerixafor

**MGTA-145 Monotherapy**

**MGTA-145 + plerixafor**

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**Graph A**

**Graph B**

**Graph C**

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**Legend**

- **A:** MGTA-145 Monotherapy
- **B:** MGTA-145 + plerixafor
- **C:** Historic peak for plerixafor monotherapy

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**Figure Details**

- **Graph A:** CD34+ cells over time post administration.
- **Graph B:** CD34+ cells over time post plerixafor administration.
- **Graph C:** CD34+ cells over time post plerixafor administration.
**MGTA-145 Reliably Mobilizes >20 CD34+ Cells per µL**

**Part B: Mobilization at 0.015 versus 0.03 mg/kg, 2h stagger**

<table>
<thead>
<tr>
<th>Mobilization Regimen</th>
<th>MGTA-145 dose (mg/kg)</th>
<th>Subjects (n)</th>
<th>Peak CD34+ (#/µL)</th>
<th>% ≥ 20 / µL</th>
<th>% ≥ 40 / µL</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGTA-145 + Plerixafor</td>
<td>0.015</td>
<td>6</td>
<td>35 (17-78)</td>
<td>83% (5/6)</td>
<td>33% (2/6)</td>
</tr>
<tr>
<td></td>
<td>0.03</td>
<td>6</td>
<td>40 (18-63)</td>
<td>83% (5/6)</td>
<td>50% (3/6)</td>
</tr>
<tr>
<td>Plerixafor</td>
<td>0</td>
<td>14</td>
<td>26 (13-78)</td>
<td>64% (9/14)</td>
<td>21% (3/14)</td>
</tr>
</tbody>
</table>
# MGTA-145 Enabled Reliable Collection of >2x10^6 CD34^+ Cells in One Day

## Part D: Apheresis Collection at 0.015 versus 0.03 mg/kg dose, 2h stagger

<table>
<thead>
<tr>
<th>MGTA-145 dose (mg/kg)</th>
<th>Subjects (n)</th>
<th>Total CD34^+ Yield (x10^6) Median (range)</th>
<th>CD34^+ / kg (x10^6) Mean</th>
<th>Median</th>
<th>Range</th>
<th>CD90^+ / kg (x10^6) Mean</th>
<th>Median</th>
<th>Range</th>
<th>CD90^+ (% of CD34^+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.015</td>
<td>4</td>
<td>310 (118-525)</td>
<td></td>
<td>4.0</td>
<td>3.7</td>
<td>1.5 - 7.0</td>
<td>1.4</td>
<td>1.2</td>
<td>0.5 – 2.8</td>
</tr>
<tr>
<td>0.03</td>
<td>4</td>
<td>321 (239-500)</td>
<td></td>
<td>4.1</td>
<td>4.3</td>
<td>2.7 – 5.3</td>
<td>1.3</td>
<td>1.5</td>
<td>0.5 – 1.8</td>
</tr>
</tbody>
</table>

Collection data reflect internal analysis.

a CD90^+ cells defined as CD34^+ CD90^+ CD45RA^- cells.
CD34+ CD90+ Cells Contain Hematopoietic Stem Cells Responsible for Robust Engraftment in Humans and Non-human Primates

Transplantation of Highly Purified CD34+Thy-1+
Hematopoietic Breast Cancer Cells

Transplantation with selected autologous peripheral blood CD34+Thy1+ hematopoietic stem cells (HSCs) in multiple myeloma: Impact of HSC dose on engraftment, safety, and immune reconstitution

A distinct hematopoietic stem cell population for rapid multilineage engraftment in nonhuman primates

Stefan Radtke1,2, Jennifer E. Adair1,3, Morgan A. Giese1, Yan-Yi Chan1, Zachary K. Norgaard1, Mark Enstrom1, Kevin G. Haworth1, Lauren E. Schefter1, and Hans-Peter Kiem1,3,4,*
MGTA-145 + Plerixafor Mobilizes Higher Numbers of Phenotype HSCs Capable of Robust Multilineage Engraftment than Standard-of-Care

Data expressed as mean±95% CI
MGTA-145 + plerixafor: n=7 donors (mobilized with 0.015 or 0.03 mg/kg MGTA-145)
G-CSF: n=3 donors
Significantly Higher Multilineage Engraftment of MGTA-145 + Plerixafor-Mobilized CD34\(^+\) Cells Compared to G-CSF-Mobilized CD34\(^+\) Cells in NSG Mice

Collect mobilized CD34\(^+\) cells

MGTA-145 + plerixafor Apheresis product (Part D)
vs.
G-CSF-mobilized peripheral blood

Limiting Dilution Transplant into NSG mice

CD34\(^+\) cell doses

Low
Mid
High

Donor #801

Donor #807

MGTA-145 + plerixafor: n=2 donors (at 0.03 mg/kg dose level)
G-CSF: n=3 donors
n=7-8 mice per cell dose

Week 12

10-fold
p < 0.001

hCD45
0.43%

mCD45

hCD45
0.19%

SRC ± 95% CI

Magenta Therapeutics
Summary

- MGTA-145 is well-tolerated in 79 subjects as monotherapy and in combination with plerixafor.
- MGTA-145 engages CXCR2 on neutrophils to mobilize CD34+ cells into peripheral blood with limited neutrophil activation.
- MGTA-145 in combination with plerixafor reliably mobilizes sufficient HSCs for a transplant.
- After dosing and apheresis, preliminary data suggest that MGTA-145 + plerixafor mobilizes HSCs enriched in functional CD34+ CD90+ cells.
Conclusions

- MGTA-145 administration is safe, as monotherapy or in combination with plerixafor, and led to an additive increase in CD34+ cell mobilization.
- Additional studies to fully characterize MGTA-145 + plerixafor apheresis products, including preclinical engraftment and graft versus host disease (GvHD) studies in mice, are ongoing.
- The number of functional stem cells mobilized by MGTA-145 + plerixafor provides a strong rationale for conducting mobilization studies of allogeneic and autologous transplant in autoimmune diseases, hematopoietic gene therapy and hematologic malignancies.

<table>
<thead>
<tr>
<th></th>
<th>G-CSF</th>
<th>MGTA-145 + plerixafor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Bone remodeling</td>
<td>Chemokine cell migration</td>
</tr>
<tr>
<td><strong>Time to mobilize and collect</strong></td>
<td>5+ days</td>
<td>&lt;1 day</td>
</tr>
<tr>
<td><strong>Tolerability</strong></td>
<td>Majority with bone pain, headache, myalgia, and/or fatigue (up to 1+ week)a</td>
<td>Majority with transient, grade 1 back pain (most &lt;20 minutes)</td>
</tr>
<tr>
<td><strong>Efficacy (≥2x10^6 CD34+/kg)</strong></td>
<td>78%b</td>
<td>100% (4/4 at 0.03 mg/kg dose)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75% (3/4 at 0.015 mg/kg dose)</td>
</tr>
<tr>
<td><strong>Functional CD34+ (% CD90+)</strong></td>
<td>10%</td>
<td>35%</td>
</tr>
<tr>
<td><strong>Engraftment of CD34+</strong></td>
<td>-</td>
<td>10x increased engraftment</td>
</tr>
</tbody>
</table>

Thank you

– Pat Falahee
– Kevin Goncalves
– Sharon Hyzy
– Katie Hammond
– Will Savage
– Glen Raffel
– Veit Schmelmer
– Haley Howell
– Jason Neale
– Tony Boitano
– John Davis

– Steve Devine

– David Scadden
– Jon Hoggatt
Backup1: PD data for all dose levels

A

- Neutrophils ($x 10^3/µL$)
- Hours Post Administration

B

- CXCRI2 Expression (% of baseline)
- Hours Post Administration

C

- Molar Ratio of MMP-9:TIMP-1
- Hours Post Administration
Backup2: Monotherapy data for all dose levels

MGTA-145 Monotherapy

0.0075 mg/kg
0.015 mg/kg
0.03 mg/kg
Placebo
0.075 mg/kg

CD34+ cells (#/µL)

0 5 10 15
0 2 4 6 8 10 12 14 16
0 2 4 6 8 10 12 14

Hours Post Administration

Magenta Therapeutics