MGTA-145, In Combination with Plerixafor in a Phase 1 Clinical Trial, Mobilizes Large Numbers of Human Hematopoietic Stem Cells and a Graft with Immunosuppressive Effects for Allogeneic Transplant

Steven M. Devine, MD
MGTA-145 + Plerixafor Enables Rapid and Robust Mobilization of Hematopoietic Stem Cells (HSCs)

Limitations to Current Mobilization Standard of Care:
• Requires 5+ days
• Variable yields
• Adverse events, some for the duration of mobilization
• 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

65,000 transplants annually
70% use mobilized peripheral blood
MGTA-145, In Combination with Plerixafor, Rapidly Mobilizes HSCs

NOVEL MOBILIZATION AGENT

MGTA-145 (GroßT) + plerixafor (AMD3100)

CXCR2 agonist
CXCR4 antagonist

KEY FEATURES

- Rapid & robust mobilization of HSCs in mice and non-human primates
  [Hoggatt et al, Cell 2018; Goncalves et al, Blood 2018; Karpova et al, JCI 2019]
- Single-day dosing and collection
- Well-tolerated
- Mimics physiological response
MGTA-145-101 Healthy Volunteer Study Schema

Part A
Single Dose: MGTA-145

Part B
Single Dose: MGTA-145 + Plerixafor

Part C
2 Daily Doses: MGTA-145 + Plerixafor

Part D
Apheresis: MGTA-145 + Plerixafor

DiPersio et al. TCT 2020
## Treatment Emergent Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Part A</th>
<th>Part B</th>
<th>Part C</th>
<th>Part D</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subjects with any drug related TEAE</strong></td>
<td>19 (79.2)</td>
<td>31 (81.6)</td>
<td>8 (57.1)</td>
<td>6 (75.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>-</td>
<td>6 (15.8)</td>
<td>5 (35.7)</td>
<td>1 (12.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>-</td>
<td>7 (18.4)</td>
<td>2 (14.3)</td>
<td>1 (12.5)</td>
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<tr>
<td>Abdominal discomfort/pain</td>
<td>-</td>
<td>5 (13.2)</td>
<td>4 (28.6)</td>
<td>-</td>
</tr>
<tr>
<td>Vomiting</td>
<td>-</td>
<td>3 (7.9)</td>
<td>1 (7.1)</td>
<td>-</td>
</tr>
<tr>
<td>Back pain / Musculoskeletal pain</td>
<td>19 (79.2)</td>
<td>24 (63.2)</td>
<td>2 (14.3)</td>
<td>4 (50.0)</td>
</tr>
<tr>
<td>Dizziness / Lightheadedness</td>
<td>-</td>
<td>5 (15.6)</td>
<td>1 (7.1)</td>
<td>-</td>
</tr>
<tr>
<td>Headache</td>
<td>-</td>
<td>4 (10.5)</td>
<td>1 (7.1)</td>
<td>2 (25.0)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>-</td>
<td>-</td>
<td>2 (14.3)</td>
<td>-</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>-</td>
<td>2 (5.3)</td>
<td>-</td>
<td>1 (12.5)</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.
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 Enables Reliable Collection of $>2 \times 10^6$ CD34$^+$ Cells in One Day

### 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) Median (range)</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>

### 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$^6$)</th>
</tr>
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<tbody>
<tr>
<td></td>
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<td></td>
<td>Mean</td>
</tr>
<tr>
<td>0.015</td>
<td>4</td>
<td>310 (118-525)</td>
<td>4.0</td>
</tr>
<tr>
<td>0.03</td>
<td>4</td>
<td>321 (239-500)</td>
<td>4.1</td>
</tr>
</tbody>
</table>
CD34+ CD90+ Cells Contain HSCs Responsible for Robust Engraftment in Humans and Non-human Primates
MGTA-145 + Plerixafor Enables Greater Collection of HSCs after Apheresis in a Phase 1 Healthy Volunteer Study

**MGTA-145 + plerixafor:** n=7 donors (mobilized with 0.015 or 0.03 mg/kg MGTA-145)

**G-CSF:** n=3 donors

**CD34+ NUMBER**

- MGTA-145 + plerixafor
- G-CSF

**CD34+CD90+CD45RA- FREQUENCY**

5-fold p<0.001

**CD34+CD90+CD45RA- NUMBER**

3-fold p<0.05

MGTA-145 + plerixafor: n=7 donors (mobilized with 0.015 or 0.03 mg/kg MGTA-145)

G-CSF: n=3 donors
**EXPERIMENTAL SCHEMA**

- **Collect mobilized CD34+ cells**
  - MGTA-145 + plerixafor Apheresis product (Part D) vs. G-CSF or plerixafor mobilized blood

- **Transplant NSG Mice at Limit Dilution**
  - CD34+ cell doses: Low, Mid, High
MGTA-145 + Plerixafor CD34+ Cells from Phase 1 Healthy Volunteer Study Show Higher Multilineage Engraftment Compared to G-CSF and Plerixafor Mobilized CD34+ Cells in Primary and Secondary NSG Mouse Transplants

**WEEK 16 ENGRAFTMENT**
**PRIMARY NSG RECIPIENTS**

SRC per 1x10^6 cells ± 95% CI
n=3-4 donors
n=7-8 mice per cell dose

**WEEK 16 ENGRAFTMENT**
**SECONDARY NSG RECIPIENTS**

23-fold
p<0.001

11-fold
p<0.001

2-fold
p<0.05

21-fold
p<0.001

7-fold
p<0.001

3-fold
p<0.05

**WEEK 16 LINEAGE COMPOSITION**
**SECONDARY NSG RECIPIENTS**

Mean ± SEM
n=3-4 donors
n=7-8 mice per donor
**MGTA-145 + Plerixafor CD34+ Cells from Phase 1 Healthy Volunteer Study Can Be Efficiently Gene Modified and Engraft in NSG Mice**

**EXPERIMENTAL SCHEMA**

Collect mobilized CD34+ cells

MGTA-145 + plerixafor Apheresis product

CD34+ Selection

Gene Modify and Transplant

Pre-stimulate 1 Day

CRISPR/Cas9 Knockout of Beta-2 microglobulin (B2M)

Culture 1 Day

Phenotype & Transplant

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**IN VITRO GENE EDITING**

<table>
<thead>
<tr>
<th>Number</th>
<th>CD34+CD90+CD45RA-</th>
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<tr>
<td>Editing Rate</td>
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<tr>
<td>Mock Edited</td>
<td>Edited</td>
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Mean ± SD (n=2)

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**WEEK 16 NSG ENGRAFTMENT**

<table>
<thead>
<tr>
<th>Peripheral Blood Engraftment</th>
<th>Editing Rate</th>
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<tbody>
<tr>
<td>Mock Edited</td>
<td>Edited</td>
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</tbody>
</table>

ns

n=7-8 mice
MGTA-145 + Plerixafor Mobilized Blood Can Be Gene-Modified at the Same Rate as G-CSF Mobilized Blood

**IN VITRO EDITING FOR G-CSF AND MGTA-145 + PLERIXAFOR MOBILIZED BLOOD**

<table>
<thead>
<tr>
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<th>Editing Rate (%)</th>
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<tbody>
<tr>
<td>Mock Edited G-CSF</td>
<td>0</td>
</tr>
<tr>
<td>Edited G-CSF</td>
<td>100</td>
</tr>
<tr>
<td>Mock Edited MGTA-145 + Plerixafor</td>
<td>0</td>
</tr>
<tr>
<td>Edited MGTA-145 + Plerixafor</td>
<td>100</td>
</tr>
</tbody>
</table>

Mean ± SD (n=2)
ns=not significant, as indicated
### MGTA-145 + Plerixafor Grafts Are Enriched for Hematopoietic Stem/Progenitor Cells

<table>
<thead>
<tr>
<th>CD34⁺ (x10⁶/kg)</th>
<th>Median (range)</th>
<th>145-HV-101 Part D</th>
<th>Devine et al., Blood 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGTA-145 + plerixafor n=7</td>
<td>4.1 (1.5-7.0)</td>
<td>2.9 (1.2-6.3)</td>
<td>4.2 (2.5-18.7)</td>
</tr>
<tr>
<td>CD3⁺ (x10⁹/kg)</td>
<td>4.0 (3.3-6.2)</td>
<td>4.6 (1.5-7.8)</td>
<td>1.3 (1.2-6.8)</td>
</tr>
<tr>
<td>CD4⁺ (x10⁹/kg)</td>
<td>3.7 (3.0-5.0)</td>
<td>3.2 (1-5.7)</td>
<td>1.1 (0.7-3.2)</td>
</tr>
<tr>
<td>CD8⁺ (x10⁹/kg)</td>
<td>0.2 (0.0-0.6)</td>
<td>1.3 (0.4-3.4)</td>
<td>0.4 (0.3-3.4)</td>
</tr>
<tr>
<td>CD19⁺ (x10⁹/kg)</td>
<td>1.8 (1.1-1.9)</td>
<td>1.0 (0.2-2.4)</td>
<td>-</td>
</tr>
<tr>
<td>CD56⁺ (x10⁹/kg)</td>
<td>0.5 (0.2-1.0)</td>
<td>0.3 (0.1-1.0)</td>
<td>0.2 (0.1-0.5)</td>
</tr>
</tbody>
</table>
MGTA-145 + Plerixafor Grafts From Phase 1 Healthy Volunteer Study Are Immunosuppressive in a Xenograft Mouse Model

EXPERIMENTAL SCHEMA

Collect PBMCs

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

Transplant NSG Mice

6x10⁶ PBMCs per recipient TBI

SURVIVAL AFTER XENOTRANSPLANT OF MOBILIZED BLOOD

Edward Asmar, PhD

Median Survival (Days)

Whole Blood: 13
G-CSF: 25
Plerixafor alone: 15
145-p: 60+

LOG RANK TEST
145-p vs G-CSF: p<0.01
145-p vs plerixafor: p<0.001

Unmobilized: n=3 donors, n=6-7 mice/donor
Mobilized: n=3-6 donors per regimen, n=8 mice/donor
MGTA-145 + Plerixafor Mobilizes a Graft with High Numbers of Functional HSCs and the Potential for Reduced GvHD

• 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.

• MGTA-145 administration is safe, as monotherapy or in combination with plerixafor, and leads to robust CD34+ cell mobilization.

• Ph1 graft characterization of MGTA-145 + plerixafor mobilized blood demonstrates:
  – Collection of high numbers of CD34+ and CD34+CD90+ cells
  – Significantly higher multilineage engraftment compared to G-CSF or plerixafor mobilized CD34+ cells in primary and secondary NSG mouse recipients
  – Efficient gene modification and NSG engraftment of MGTA-145 + plerixafor CD34+ cells
  – Potent immunosuppression compared to G-CSF or plerixafor mobilized blood in a xenotransplant mouse model
Summary

<table>
<thead>
<tr>
<th></th>
<th>G-CSF</th>
<th>MGTA-145 + plerixafor</th>
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</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Bone remodeling</td>
<td>Chemokine cell migration</td>
</tr>
<tr>
<td>Time to mobilize and collect</td>
<td>5+ days</td>
<td>&lt;1 day</td>
</tr>
<tr>
<td>Tolerability</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>Efficacy (≥2x10(^6) CD34(^+)/kg)</td>
<td>78(^b)</td>
<td>88% (7/8)</td>
</tr>
<tr>
<td>Quality of CD34(^+) (% CD90(^+))</td>
<td>6.9%</td>
<td>33%</td>
</tr>
<tr>
<td>Function of CD34(^+)</td>
<td>-</td>
<td>&gt;10x increased engraftment</td>
</tr>
</tbody>
</table>


The number of functional hematopoietic 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.
## Acknowledgments

<table>
<thead>
<tr>
<th>MAGENTA THERAPEUTICS R&amp;D TEAM</th>
<th>MASSACHUSETTS GENERAL HOSPITAL</th>
<th>WASHINGTON UNIVERSITY, ST. LOUIS</th>
</tr>
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<tbody>
<tr>
<td>Kevin Goncalves</td>
<td>Jonathan Hoggatt</td>
<td>John DiPersio</td>
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<td>David Scadden</td>
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