A Phase 2, Open-label Study to Evaluate the Safety and Hematopoietic Stem Cell Mobilization of TG-0054 (burixafor) Alone or in Combination with G-CSF in Patients with Multiple Myeloma, Non-Hodgkin’s Lymphoma and Hodgkin’s Lymphoma

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• Burixafor is a potent antagonist of CXCR4 and blocks the interaction between the cell surface receptor CXCR4 and its only ligand SDF-1

• The blockage of the interaction causes rapid mobilization of stem cells from bone marrow into peripheral blood
Synergistic Stem Cell Mobilization Activities with G-CSF

- Additive or synergistic effects in mobilizing HSCs were observed when burixafor was combined with G-CSF.

### Table: Cell number of:
- Total WBCs
- CXCR4+ cells
- CD34+ cells

<table>
<thead>
<tr>
<th>Compound</th>
<th>Fold increase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WBC</td>
</tr>
<tr>
<td>G-CSF (100 ug/kg/day)</td>
<td>10.3</td>
</tr>
<tr>
<td>Plerixafor (3.6 mg/kg)</td>
<td>2.4</td>
</tr>
<tr>
<td>G-CSF+Plerixafor</td>
<td>11.0</td>
</tr>
<tr>
<td>Burixafor (5mg/kg)</td>
<td>3.2</td>
</tr>
<tr>
<td>G-CSF+Burixafor (5mg/kg)</td>
<td>15.4(^b)</td>
</tr>
<tr>
<td>Burixafor (50mg/kg)</td>
<td>8.2</td>
</tr>
<tr>
<td>G-CSF+Burixafor (50mg/kg)</td>
<td>23.0(^b)</td>
</tr>
</tbody>
</table>

*Tolerant dose of plerixafor via IV administration is 3.6 mg/kg  a: additive  b: synergistic
Burixafor is a potent CXCR4 antagonist and shows good selectivity against other human chemokine receptors.

In *in vitro* studies with major human liver microsomal cytochrome P450s, burixafor did not inhibit the activities of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 enzymes.

Burixafor was tested against 68 selected targets of lead profile screening at 100 uM. No significant off-target activities were observed.
Stem Cell Mobilization by Burixafor

Comparison of in vivo Activities of Burixafor vs. Plerixafor Administered Intravenously to Mice

<table>
<thead>
<tr>
<th></th>
<th>Minimal effective dose (mg/Kg)</th>
<th>Fold increase at 1 mg/Kg</th>
<th>Max. fold increase (at tolerant dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>WBC</td>
<td>CXCR4+</td>
</tr>
<tr>
<td>Plerixafor</td>
<td>1.0</td>
<td>1.9</td>
<td>4.8</td>
</tr>
<tr>
<td>Burixafor</td>
<td>1.0</td>
<td>2.9</td>
<td>3.4</td>
</tr>
</tbody>
</table>

The IV MTD of burixafor–HBr salt in mice is 50 mg/kg.
The IV MTD of plerixafor–HCl salt in mice is 3.6 mg/kg.
Phase I Study in Healthy Volunteers

Study Results
Phase I Study Overview

- **Study Design**
  - Randomized, Double-Blind, Placebo-Controlled, Sequential Ascending Single IV Dose

- **Objectives**
  - Safety and tolerability; Maximum tolerated dose (MTD)
  - PK and PD (Circulating CD34+, CD133+, and WBC cells counts)

- **Dosage**
  - Placebo, 0.10, 0.14, 0.28, 0.56, 1.12, 2.24, 3.14, and 4.40 mg/kg

- **Number of Subjects**
  - 64 subjects in 8 cohorts (8 subjects in each cohort)
  - Active : Placebo = 6:2 in each cohort

- **Study Center** - Parexel Clinical Pharmacology Research Unit, Baltimore, MD, USA
Mean plasma concentrations (ng/mL) of burixafor in log-linear scale vs. time.

- **Cohort 1 (0.10 mg/kg)**
- **Cohort 2 (0.14 mg/kg)**
- **Cohort 3 (0.28 mg/kg)**
- **Cohort 4 (0.56 mg/kg)**
- **Cohort 5 (1.12 mg/kg)**
- **Cohort 6 (2.24 mg/kg)**
- **Cohort 7 (3.14 mg/kg)**
- **Cohort 8 (4.40 mg/kg)**

- **Median T\text{\textsubscript{max}}**
  - 15 to 18 mins
- **Mean t\textsubscript{1/2}**
  - 2.53 to 5.17 hrs
- **C\textsubscript{\text{\textsubscript{\text{max}}} and AUC increased with dose.**
Ph I Study: Safety Summary

- Good tolerability was observed up to 4.40 mg/kg; All subjects completed the study procedures.
- All Adverse Events (AEs) were mild in severity and recovered spontaneously.
- The most commonly reported AEs were abdominal pain, diarrhea, dizziness, nausea and sweating.
- No significant abnormalities in physical examinations, vital signs, pulse oximetry, ECG, cardiac telemetry, and safety laboratory panel.
**Ph I Study: PD Results**

### Circulating CD34\(^+\) cell counts at peak time

<table>
<thead>
<tr>
<th>Cell Type (Units)</th>
<th>Mean Cell Numbers (±SD)</th>
<th>Burixafor Dose Level (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD34(^+) (cells/µL)</td>
<td>9.1 (±2.5)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

- **Circulating CD34\(^+\) Counts:**
  - Dose-dependent increase from baseline between 0.10 and 3.14 mg/kg.
  - Plateau over 2.24 to 3.14 mg/kg
  - Optimal CD34\(^+\) cell mobilization: 1.12 to 4.40 mg/kg (p>0.05), circulating CD34\(^+\) counts > 20 cells/µL
  - At peak time, burixafor caused a 3 - 14 fold increase in circulating CD34\(^+\) cells from baseline over the dose range
Mean Circulating CD34+ Cells After Burixafor Administration

CD34+ cells peaked at 4-6 hours and returned to baseline at 24 hours post dosing.
### Circulating CD133⁺ and WBC Cell Counts

<table>
<thead>
<tr>
<th>Cell Type (Units)</th>
<th>Mean Cell Numbers</th>
<th>Burixafor Dose Level (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.10</td>
</tr>
<tr>
<td>CD133⁺ (cells/µL)</td>
<td>Mean (∆SD)</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(±5.9)</td>
</tr>
<tr>
<td>WBC (cells/µL)</td>
<td>Mean (∆SD)</td>
<td>10467</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(±2594)</td>
</tr>
</tbody>
</table>

- **Circulating CD133⁺ and WBC Counts:**
  - Both CD133⁺ and WBC counts increased after burixafor administration. The trend is similar to that observed for CD34⁺
  - Plateau over 1.12 to 3.14 mg/kg
  - No AEs were deemed to be associated with WBC increases.
Phase 1 Study Overall Conclusions

- Burixafor administered as a single IV dose in healthy subjects was well tolerated at doses up to 4.40 mg/kg.
- Due to parasympathetic symptoms observed (grade 1), 4.40 mg/kg was deemed to be the MTD.
- PK parameters showed dose proportionality over the dose range studied.
- CD34⁺, CD133⁺ cells and WBC count generally increased with increase in burixafor dose from 0.10 to 3.14 mg/kg; at peak time, burixafor caused a 3 - 14 fold increase in circulating CD34⁺ cells from baseline.
12 patients (1 HD, 7 MM, and 4 NHL) were given single agent, intravenous burixafor over 15 minutes on day 1 of collection.

Peripheral blood CD34 counts were assessed at 2 hours, 4 hours and 6 hours after study drug administration.

If the CD34 count was $\geq 10/\mu l$, stem cell collection was initiated.

If CD34 count never reached $10/\mu l$ by 6 hours, G-CSF was started on day minus 4 before collection and patient was given G-CSF and burixafor additionally on each day of collection.
Schema for Study TG-0054-03

Eligible patients -> TG-0054 infusion and PB CD34+ counts

**Day 1**
- PB CD34+ ≥ 10 cells/µL at 2- or 4-hr post-dose
  - Day 1: Leukapheresis
- PB CD34+ < 10 cells/µL at both 2- and 4-hr post-dose, but ≥ 10 cells/µL at 6-hr post-dose
  - Day 2 to Day 5:
    - TG-0054 infusion and leukapheresis
- PB CD34+ < 10 cells/µL at 2-, 4-, and 6-hr post-dose
  - Day 4 to Day 10:
    - G-CSF 10 µg/kg/day SC injection
  - Day 8 to Day 11:
    - TG-0054 infusion and leukapheresis
Inclusion Criteria

- Patients diagnosed with multiple myeloma, non-Hodgkin’s lymphoma or Hodgkin’s lymphoma needing autologous stem cell transplantation
- Last chemo > 4 weeks prior to 1st dose of burixafor
- WBC count $\geq 3.0 \times 10^9$/L and platelet count $\geq 100k \times 10^9$ cells/L
- Patient ages 18-70
- ECOG 0-1
- AST and ALT < 2 x ULN
- Cr < 2.2
Exclusion Criteria

- Prior pelvic irradiation
- Greater than 6 cycles of Revlimid
- Prior stem cell transplantation
- History of other malignancies (except for basal cell carcinomas)
- Uncontrolled cardiac, pulmonary or infectious disease
- History of retinal proliferative disease
- Known HIV disease
- Investigational drug within 1 month of study entry
Primary Study objective

• To determine the total number of hematopoietic stem cells (HSCs) collected within four leukapheresis sessions after TG-0054 (3.14 mg/kg) alone or in combination with G-CSF mobilization in patients with multiple myeloma (MM), non-Hodgkin lymphoma (NHL) or Hodgkin disease (HD)
Secondary Objectives

- To determine the average number of leukapheresis sessions required to collect $2.5 \times 10^6$ CD34+ cells/kg
- To evaluate the safety of TG-0054 in patients with MM, NHL or HD
- To evaluate engraftment
- To evaluate the pharmacodynamics (PD) of TG-0054 by determining circulating CD34+ cell counts in peripheral blood
Demographics

- 7 myeloma, 4 non-Hodgkin’s lymphoma (NHL) and 1 Hodgkin’s lymphoma (HL)
- 5/7 myeloma patients had received 6 cycles of lenalidomide
- 4 NHL patients and 1 HL patient had received 2 lines of prior therapy including 2 cycles of DICE salvage chemotherapy
Results

• Seven patients (1 HD, 6 MM) were successfully mobilized with TG0054-03 as a single agent achieving a cumulative dose of CD34 of \(4.0 \times 10^6\) to \(10.4 \times 10^6\)/kg over 1-4 leukapheresis sessions.

• Five patients (4 NHL, 1 MM) required the addition of G-CSF after failing to achieve a peripheral blood CD34 count \(\geq 10\) on day 1 after burixafor infusion.
## Tiagen Mobilization and CD34+ Dose

<table>
<thead>
<tr>
<th>Patient</th>
<th>CD34+ 10^6/kg</th>
<th>Number of Leukaphereses</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.211</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>5.207</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>3.037</td>
<td>4</td>
</tr>
<tr>
<td>4*</td>
<td>21.03</td>
<td>2</td>
</tr>
<tr>
<td>5*</td>
<td>2.235</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>6.45</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>4.068</td>
<td>4</td>
</tr>
<tr>
<td>8*</td>
<td>3.253</td>
<td>4</td>
</tr>
<tr>
<td>9*</td>
<td>5.005</td>
<td>2</td>
</tr>
<tr>
<td>10*</td>
<td>7.641</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>9.421</td>
<td>4</td>
</tr>
<tr>
<td>12</td>
<td>10.423</td>
<td>4</td>
</tr>
</tbody>
</table>

* Indicates combination mobilization with G-CSF
Cells infused

- Within 5 weeks of the last apheresis, the patients underwent high-dose chemotherapy and transplantation using the collected autologous CD34+ cells

- The minimum number of CD34+ cells for transplantation was $2 \times 10^6$ cells/kg (actual body weight)

- Actual (mean CD34 infusion was $3.76 \times 10^6$ cells/kg (range 2.3-6.2)
## Engraftment Data

<table>
<thead>
<tr>
<th>Subject #</th>
<th># of collections</th>
<th>Days to neutrophil engraftment success</th>
<th>Days to platelet engraftment success</th>
</tr>
</thead>
<tbody>
<tr>
<td>001 A-M</td>
<td>4</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>002 H-S</td>
<td>4</td>
<td>12</td>
<td>23</td>
</tr>
<tr>
<td>003 E-M</td>
<td>4</td>
<td>11</td>
<td>22</td>
</tr>
<tr>
<td>004 A-M</td>
<td>2</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>005 M-A</td>
<td>3</td>
<td>14</td>
<td>27</td>
</tr>
<tr>
<td>006 J-H</td>
<td>4</td>
<td>12</td>
<td>17</td>
</tr>
<tr>
<td>007 B-V</td>
<td>4</td>
<td>12</td>
<td>23</td>
</tr>
<tr>
<td>008 T-J</td>
<td>4</td>
<td>12</td>
<td>37*</td>
</tr>
<tr>
<td>009 M-N</td>
<td>2</td>
<td>11</td>
<td>18</td>
</tr>
<tr>
<td>010 G-O</td>
<td>1</td>
<td>12</td>
<td>36*</td>
</tr>
<tr>
<td>011 S-B</td>
<td>4</td>
<td>12</td>
<td>22</td>
</tr>
<tr>
<td>012 M-B</td>
<td>4</td>
<td>11</td>
<td>17</td>
</tr>
</tbody>
</table>
Engraftment Results

- Median days to WBC engraftment were 12
- Median days to platelets of 50k were 22
- All patients have now been followed for 6 months or more and have been noted to have stable engraftment
• No grade 3-4 toxicity was seen in any of the patients

• The 2 most common AE’s reported were loose stools and worsening of peripheral neuropathy (myeloma patients) in 4 patients each

• Single patients reported abdominal cramping, nausea, nasal congestion, cough and joint pain
Conclusions

• Burixafor was well tolerated in patients undergoing stem cell collection

• 7 patients mobilized stem cells with single agent burixafor (including 5 myeloma patients who had received 6 cycles of lenalidomide)

• All 12 patients engrafted promptly after receiving conditioning regimens (BEAM for the lymphoma patients and melphalan 200 for the myeloma patients) followed by a stem cell infusion of at least 2.3 x10^6 CD34+ cells/kg

• A second phase of the protocol will assess the number of leukaphereses required to mobilize adequate numbers of stem cells using combination burixafor/G-CSF