TARGETED THERAPY OF UNCONTROLLEDERYTHROCYTOSIS IN POLYCYTHEMIA VERA WITHTHE HEPCIDIN MIMETIC, RUSFERTIDE: BLINDEDRANDOMIZED WITHDRAWAL RESULTS OF THEREVIVE STUDY

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Late Breaker Oral Presentation
DISCLOSURES

Protagonist Therapeutics, Inc (Advisory board)
Protagonist Therapeutics, Inc (Honoraria)
Phase 2 Study of Rusfertide in PV Patients (REVIVE)

**GOAL:** Maintain Hematocrit <45%

### Clinical Proof-of-Concept Study with Add-On Rusfertide

<table>
<thead>
<tr>
<th>Part 1 – Dose Finding</th>
<th>Part 2 – Blinded Randomized Withdrawal</th>
<th>Part 3 – Open Label Extension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically Effective Dose Finding Phase</td>
<td>Efficacy Evaluation Phase</td>
<td>Randomized Withdrawal Phase</td>
</tr>
<tr>
<td>Active Dose ± Titration*</td>
<td>Active Dose ± Titration*</td>
<td>Active/Placebo Dose (1:1)</td>
</tr>
<tr>
<td>Weeks 1 to 16</td>
<td>Weeks 17 to 28</td>
<td>Weeks 29 to 41</td>
</tr>
<tr>
<td><em>Titrated to maintain hematocrit &lt; 45%</em></td>
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</tbody>
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#### KEY ENDPOINTS:
- Safety
- **Part 1**
  - Number and rate of phlebotomies compared to historic experience
- **Part 2**
  - Proportion of Responders
    - Maintain Hematocrit <45%
    - Reduction in Phlebotomies
  - Patient Outcomes: MPN-SAF TSS

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**STUDY ELIGIBILITY:**
- Phlebotomy dependent PV patients diagnosed as per 2016 WHO criteria
- ≥3 phlebotomies in 6 months with or without concurrent cytoreductive therapy
- Rusfertide (PTG-300) doses of 10-120 mg administered subcutaneously weekly added to prior standard therapy
- All patients prior to first rusfertide dose were phlebotomized to HCT <45% to standardize the starting HCT
PURPOSE OF RESEARCH

• Polycythemia Vera is a myeloproliferative neoplasm characterized by excessive production of red blood cells (RBCs)\(^1\).
• Elevated hematocrit (HCT) is a hallmark of the disease, indicating overproduction of RBCs\(^2\).
• Uncontrolled HCT is associated with higher rates of death from cardiovascular causes or thrombotic events\(^3\).
• Maintaining HCT<45% is critical in PV, as per NCCN and ELN guidelines to decrease the risk of TE and CV events.
• Current standard of care does not maintain HCT <45% in a majority of patients\(^4,5\).
• Hepcidin is a peptide hormone that is the body’s main regulator of iron homeostasis and controls the availability of iron for formation of red blood cells.
• Rusfertide is a novel hepcidin mimetic that is designed to maintain iron homeostasis and normalize erythrocytosis.
• The REVIVE Phase 2 study evaluated the safety and efficacy of rusfertide in patients with polycythemia vera (PV) who had a high phlebotomy burden with current standard of care.

Phase 2 Study of Rusfertide in PV Patients (REVIVE)

Disposition

Part 1 (Dose Finding)
28 Weeks
n=70
- Discontinued early: 9
- Not Randomized: 2 (completed Part 1)
- AE: 3
- Withdrawal by Sub: 5+2
  Other: 1

Part 2
(Blinded Randomized Withdrawal)
12 Weeks
n=59
- Rolled to Part 3 after Clinical Hold: 6

Primary Efficacy Analysis
12 Weeks
n=53
- AE: 1

Part 3: 58 ongoing
- 52 subjects (74.3%) have exposure ≥1 y
- 32 subjects (45.7%) have exposure ≥1.5 y
- 10 subjects (14.3%) have exposure ≥2 y
**Baseline Demographics and Disease Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Randomized Part 2 (N=53)</th>
<th>Part 1 (N=70)</th>
<th>Placebo (N=27)</th>
<th>Rusfertide (N=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
<td>57.3±12.19</td>
<td>60.7±11.18</td>
<td>54.9±12.45</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>49 (70%)</td>
<td>17 (63%)</td>
<td>21 (80.8%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>21 (30%)</td>
<td>10 (37%)</td>
<td>5 (19.2%)</td>
<td></td>
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<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>29.6±5.36</td>
<td>30.1±5.76</td>
<td>28.7±4.55</td>
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</tr>
<tr>
<td><strong>Disease Characteristics</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>Age at Diagnosis, y</strong></td>
<td>52.3±13.49</td>
<td>55.9±12.15</td>
<td>50.3±11.75</td>
<td></td>
</tr>
<tr>
<td><strong>PV Duration, y</strong></td>
<td>5.1±6.21</td>
<td>5.0±4.77</td>
<td>4.6±5.70</td>
<td></td>
</tr>
<tr>
<td><strong>Risk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Risk</td>
<td>39 (55.7%)</td>
<td>17 (63%)</td>
<td>11 (42.3%)</td>
<td></td>
</tr>
<tr>
<td>Low Risk</td>
<td>31 (44.3%)</td>
<td>10 (37%)</td>
<td>15 (57.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Cytoreductive Therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>18 (25.7%)</td>
<td>9 (33.3%)</td>
<td>4 (15.4%)</td>
<td></td>
</tr>
<tr>
<td>Interferon</td>
<td>9 (12.9%)</td>
<td>5 (18.5%)</td>
<td>2 (7.7%)</td>
<td></td>
</tr>
<tr>
<td>JAK inhibitor</td>
<td>5 (7.1%)</td>
<td>2 (7.4%)</td>
<td>2 (7.7%)</td>
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</tbody>
</table>
REVIVE Study: Efficacy

Meaningful Reduction in Phlebotomy Frequency Following Rusfertide Administration

Phlebotomy Only (n=37)

Phlebotomy and Cytoreductives (n=33)

Data cutoff: Feb 15, 2023
REVIVE Study: Part 2, Blinded Randomized Withdrawal, Weeks 29-41

Rusfertide Met the Primary Endpoint of Efficacy

- **69.2% subjects** (18 out of 26) are responders. 8 non-responders as per protocol definition
  - 3 fulfilled the phlebotomy eligibility criteria
  - 5 discontinued treatment per patient/investigator discretion

- All 8 non-responders continued in part 3 open label extension of the study
  - 7 out of 8 are currently continuing treatment

- **92.3% subjects** (24 out of 26) in rusfertide arm did not receive phlebotomy in part 2, 12-week randomization part of the study

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**Responders definition as per protocol**
- Did not receive a phlebotomy
- Completed 12 weeks of treatment
- Hematocrit control maintained without phlebotomy eligibility, which is defined as
  - Hematocrit ≥45% that was ≥3% higher than Week 29 pre-randomization hematocrit value or
  - Hematocrit >48% or
  - An increase of ≥5% in hematocrit compared to Week 29 pre-randomization hematocrit value

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Highly significant Efficacy* in rusfertide arm vs. placebo

**Graph:**
- **Placebo (N=27):** 18.5% (n=5)
- **Rusfertide (N=26):** 69.2% (n=18)

*p=0.0003*
REVIVE Study: Efficacy
Efficacy over Placebo Demonstrated in Phlebotomy Alone and Phlebotomy + Cytoreductive Subgroups

Proportion of Subjects

<table>
<thead>
<tr>
<th></th>
<th>PHL (N=29)</th>
<th>PHL+Cyto (N=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rusfertide</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>Placebo</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

p=0.0209

p=0.0215
REVIVE Study: Consistent Efficacy
Rusfertide Significantly Delays Time to Treatment Failure on Multiple Outcomes Compared to Placebo

Responders

- Rusfertide (N=26)
- Placebo (N=27)

Absence of PHL Eligibility

- Rusfertide (N=26)
- Placebo (N=27)

HCT <45%

- Rusfertide (N=26)
- Placebo (N=27)
REVIVE Study: PV Symptoms in Part 1
Improvement in Patients Experiencing Moderate or Severe Symptoms at Baseline

- Part 1 is an open-label 28-week treatment with rusfertide that allows evaluation of symptom improvement

*In Part 2, subjects randomized to Placebo treatment do not remain on treatment for long (median 4.4 weeks), so it is not possible to compare effects on symptoms.

Individual symptoms assessed using MPN-SAF p-value are based on paired comparisons.
Rusfertide wasGenerally Well Tolerated

- 70 subjects were enrolled in the rusfertide REVIVE study
  - 52 subjects (74.3%) have exposure ≥1 y
  - 32 subjects (45.7%) have exposure ≥1.5 y
  - 10 subjects (14.3%) have exposure ≥2 y

- Rusfertide was generally well tolerated
  - A majority (83%) of TEAEs were Grade 1 or 2
  - 17% subjects reported Grade 3 TEAEs
  - There were no Grade 4 or 5 TEAEs
  - Most common TEAEs were injection site reactions (ISR)
    - Events were localized, Grade 1 or 2 in severity, and generally did not lead to treatment discontinuation
    - ISRs decreased in incidence with continued treatment
  - Symptoms associated with PV such as fatigue, pruritus, headache and dizziness were the second most common reported AEs
  - Two events related to treatment with rusfertide led to discontinuation (mild thrombocytosis and recurrent grade 1 injection site erythema)

<table>
<thead>
<tr>
<th>TEAEs by Preferred Term Noted at ≥15%</th>
<th>N=70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with at least one TEAE</td>
<td>70 (100%)</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>45 (64.3)</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>29 (41.4)</td>
</tr>
<tr>
<td>Injection site pruritus</td>
<td>28 (40.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>22 (31.4)</td>
</tr>
<tr>
<td>Injection site mass</td>
<td>18 (25.7)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>18 (25.7)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>17 (24.3)</td>
</tr>
<tr>
<td>Injection site swelling</td>
<td>17 (24.3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>16 (22.9)</td>
</tr>
<tr>
<td>Headache</td>
<td>16 (22.9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>16 (22.9)</td>
</tr>
<tr>
<td>Anemia</td>
<td>14 (20.0)</td>
</tr>
<tr>
<td>COVID-19</td>
<td>14 (20.0)</td>
</tr>
<tr>
<td>Injection site irritation</td>
<td>13 (18.6)</td>
</tr>
<tr>
<td>Injection site bruising</td>
<td>11 (15.7)</td>
</tr>
</tbody>
</table>

Data as of 15 February 2023
Phase 2 Study of Rusfertide in PV Patients (REVIVE)

Overall Summary

- Rusfertide is a first-in-class hepcidin mimetic that selectively targets uncontrolled erythrocytosis.
- The REVIVE study demonstrated a significantly higher efficacy with rusfertide compared to placebo in subjects with PV.
- The study met the efficacy endpoints (Proportion of Responders, Absence of phlebotomy eligibility, Hematocrit control).
- Rusfertide demonstrated favorable effects on several Patient-Reported Outcomes (fatigue, problems with concentration, pruritus, inactivity), particularly in patients who were burdened by these symptoms.
- Rusfertide was generally well tolerated. TEAEs were generally Grade 1 or 2. The most common TEAEs was ISRs. There were no Grade 4 or 5 TEAEs.
- Current standard of care therapy in PV does not consistently maintain hematocrit <45%, thereby increasing the risk of thromboembolic events. Rusfertide has the potential to consistently maintain hematocrit <45%.
- Rusfertide is currently being investigated in the ongoing placebo-controlled VERIFY Phase 3 study.
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PV Patients and caregivers
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