Results of the Randomized, Double-Blind, Placebo-Controlled, Phase 3 Hercules Study of Caplacizumab in Patients with Acquired Thrombotic Thrombocytopenic Purpura

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for the HERCULES Investigators
Acquired Thrombotic Thrombocytopenic Purpura (aTTP)

- Acute, life-threatening thrombotic microangiopathy

- Disseminated vWF-platelet microthrombi caused by a deficiency in the vWF-cleaving enzyme ADAMTS13
  - tissue ischemia and end organ damage
  - mortality >90% if untreated

Tsai HM Int J Hemat 2010
# aTTP - Current Treatment and Issues

**Current therapy is based on two pillars**

<table>
<thead>
<tr>
<th>Daily plasma exchange (PE)</th>
<th>Immunosuppression (corticosteroids and/or rituximab)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- removes ULvWF</td>
<td>inhibits autoantibody formation</td>
</tr>
<tr>
<td>- removes autoantibodies</td>
<td></td>
</tr>
<tr>
<td>- replenishes ADAMTS13</td>
<td></td>
</tr>
</tbody>
</table>

The unmet medical need remains high

- Mortality of 10-20%
- Refractoriness to treatment (associated with poor outcomes)
- Disease exacerbations within weeks after stopping plasma exchange
- PE-related complications
Caplacizumab in aTTP

Ultra-Large (UL) vWF multimers

endothelium

ADAMTS13 activity is impaired

UL-vWF multimers cause platelet string formation

Caplacizumab (anti-vWF Nanobody) binds to A1 domain of vWF and inhibits platelet string formation

Caplacizumab blocks the binding of vWF to platelets which has an immediate effect on platelet aggregation and the ensuing formation of microthrombi
Caplacizumab - Phase III HERCULES study design

- Randomized, double-blind, placebo-controlled, multi-national study

- **TREATMENT PERIOD**
  - **PE**
  - **Placebo**\(^*\) N=73
  - **Caplacizumab**\(^*\) N=72

- **EXTENSION**
  - **Recurrence**
    - daily PE & open label caplacizumab
  - **PE**
  - **Extension based on ADAMTS13 <10%**

\(^*\) * i.v. bolus (10mg) followed by daily s.c. dose (10mg)

*PE = plasma exchange*
Key study endpoints

- **Primary endpoint:** time to confirmed platelet count response

- **Key secondary endpoints (hierarchically tested)**
  1. aTTP-related death, recurrence of aTTP, or at least one major thromboembolic event during the study drug treatment period
  2. recurrence of aTTP in the overall study period
  3. refractoriness to treatment
  4. time to normalization of 3 organ damage markers

- **Safety**

- **PK/PD and anti drug antibodies**

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1. Platelet count response was defined as initial platelet count ≥ 150x10⁹/L with subsequent stop of daily PE within 5 days

2. Data not yet available
Recruitment flow

- Screened: N=149
  - Randomised: N=145
    - Placebo: N=73
      - Treated with Placebo: N=73
        - Open-label Caplacizumab: N=26
          - Completed: N=50 (68.5%)
    - Caplacizumab: N=72
      - Treated with Caplacizumab: N=71
        - Open-label Caplacizumab: N=2
          - Completed: N=58 (80.6%)

Not eligible at screening (N=4)
Discontinued prior to study drug administration (N=1)
## Demographics and baseline disease characteristics

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<thead>
<tr>
<th></th>
<th>Placebo N=73</th>
<th>Caplacizumab N=72</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)</td>
<td>47.3 (14.1)</td>
<td>44.9 (13.5)</td>
</tr>
<tr>
<td>Females – N (%)</td>
<td>51 (69.9)</td>
<td>49 (68.1)</td>
</tr>
<tr>
<td>Baseline platelet count (10⁹/L) - mean (SD)</td>
<td>39.1 (29.1)</td>
<td>32.0 (27.2)</td>
</tr>
<tr>
<td>Previous aTTP episode(s) – N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- initial</td>
<td>34 (46.6)</td>
<td>48 (66.7)</td>
</tr>
<tr>
<td>- recurrent</td>
<td>39 (53.4)</td>
<td>24 (33.3)</td>
</tr>
<tr>
<td>ADAMTS13 activity at baseline – N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- &lt;10%</td>
<td>65 (90.3)</td>
<td>58 (81.7)</td>
</tr>
<tr>
<td>- ≥10%</td>
<td>7 (9.7)</td>
<td>13 (18.3)</td>
</tr>
<tr>
<td>Disease severity at baseline – N (%)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Less severe</td>
<td>48 (65.8)</td>
<td>42 (58.3)</td>
</tr>
<tr>
<td>- Very severe</td>
<td>25 (34.2)</td>
<td>30 (41.7)</td>
</tr>
</tbody>
</table>

* Very severe was defined as: French severity score ≥3 (cerebral involvement: yes=1 / no=0, LDH: >10xULN=1 / ≤10xULN=0, age: >60 years=2 / >40 and ≤60 years=1 / ≤40 years=0), or severe neurological involvement at baseline, or cardiac involvement (cTnI > 2.5 x upper limit of normal)
Primary endpoint: time to platelet count response*

- Platelet count response was defined as initial platelet count ≥ 150×10⁹/L with subsequent stop of daily PE within 5 days.

Percentage of patients without platelet count normalization

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<th>Placebo N = 73</th>
<th>Caplacizumab N = 72</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet normalisation rate ratio (95% CI)</td>
<td>1.55 (1.10, 2.20)</td>
<td></td>
</tr>
<tr>
<td>Stratified log-rank test p-value</td>
<td>&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

* Time (days) since first dose of study drug
First key secondary endpoint
Subjects with aTTP-related death, aTTP recurrence or a major thromboembolic event during the study drug treatment period

<table>
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<tr>
<th>Number of subjects (%)</th>
<th>Placebo N=73</th>
<th>Caplacizumab N=72*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total number of subjects with at least one of the events</strong>¹</td>
<td>36 (49.3)</td>
<td>9 (12.7)</td>
</tr>
<tr>
<td>aTTP-related death²</td>
<td>3 (4.1)</td>
<td>0</td>
</tr>
<tr>
<td>recurrence (exacerbation) of aTTP³</td>
<td>28 (38.4)</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>at least one treatment emergent major thromboembolic event²:</td>
<td>6 (8.2)</td>
<td>6 (8.5)</td>
</tr>
<tr>
<td>- cerebrovascular accident</td>
<td>3 (4.1)</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>- myocardial infarction</td>
<td>1 (1.4)</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>- pulmonary embolism</td>
<td>0</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>- deep venous thrombosis (spontaneous)</td>
<td>1 (1.4)</td>
<td>0</td>
</tr>
<tr>
<td>- deep venous thrombosis (catheter-associated)</td>
<td>2 (2.7)</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

* percentages are based on 71 subjects entering the study drug treatment period; ¹ patients could have more than 1 event; ² adjudication of aTTP-related death and major thromboembolic events by a blinded independent committee; ³ recurrence = recurrent thrombocytopenia after initial recovery of platelet count, requiring re-initiation of daily PEX
Second key secondary endpoint
Subjects with aTTP recurrence during the overall study period

<table>
<thead>
<tr>
<th>Number of subjects (%)</th>
<th>Placebo N=73</th>
<th>Caplacizumab N=72*</th>
</tr>
</thead>
<tbody>
<tr>
<td>aTTP recurrence¹</td>
<td>28 (38.4)</td>
<td>9 (12.7)</td>
</tr>
<tr>
<td>During the study drug treatment period (exacerbations)</td>
<td>28 (38.4)</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>During the follow-up period (relapses)</td>
<td>0</td>
<td>6 (9.1)²</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

* percentages are based on 71 subjects entering the study drug treatment period and 66 subjects in the follow-up period
¹ recurrence = recurrent thrombocytopenia after initial recovery of platelet count, requiring re-initiation of daily PEX
² ADAMTS-13 activity levels were <10% at the end of the study drug treatment period in all of these patients
Third key secondary endpoint
Percentage of subjects with refractory aTTP

- Protocol-specified key secondary endpoint (Benhamou et al., 2015)

<table>
<thead>
<tr>
<th>Number of subjects (%)</th>
<th>Placebo N=73</th>
<th>Caplacizumab N=72</th>
</tr>
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<tbody>
<tr>
<td>Refractory aTTP¹</td>
<td>3 (4.2)</td>
<td>0</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td>0.057</td>
</tr>
</tbody>
</table>

¹ refractory TTP = absence of platelet count doubling after 4 days of standard treatment and LDH > ULN

- International TTP working group consensus definition (Scully et al., 2017)

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<th>Number of subjects (%)</th>
<th>Placebo N=73</th>
<th>Caplacizumab N=72</th>
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<tr>
<td>Refractory aTTP²</td>
<td>5 (7.0)</td>
<td>0</td>
</tr>
<tr>
<td>p-value</td>
<td></td>
<td>0.018</td>
</tr>
</tbody>
</table>

² refractory TTP = persistent thrombocytopenia, lack of a sustained platelet count increment or platelet counts of <50 x 10⁹ L⁻¹ and a persistently raised LDH level (> 1.5 ULN) despite five plasma exchanges and steroid treatment
Fourth key secondary endpoint
Time to normalization of organ damage markers

<table>
<thead>
<tr>
<th>% of subjects with organ damage markers &gt;ULN at baseline</th>
<th>All subjects N=145</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactate Dehydrogenase</td>
<td>87.1%</td>
</tr>
<tr>
<td>Cardiac Troponin I</td>
<td>53.8%</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>22.7%</td>
</tr>
</tbody>
</table>

ULN = Upper Limit of Normal

Graph showing time (days) since first dose of study drug.

- Placebo (N=66)
- Caplacizumab (N=66)
Other secondary endpoints
Plasma exchange parameters, duration of ICU stay and overall hospitalization

<table>
<thead>
<tr>
<th>Overall study drug treatment period (mean±SE)</th>
<th>Placebo N=73</th>
<th>Caplacizumab N=71</th>
<th>% relative reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of days of Plasma Exchange</td>
<td>9.4±0.8</td>
<td>5.8±0.5</td>
<td>↓38%</td>
</tr>
<tr>
<td>Volume of plasma (L)</td>
<td>35.9±4.2</td>
<td>21.3±1.6</td>
<td>↓41%</td>
</tr>
<tr>
<td>Number of days in Intensive Care Unit</td>
<td>9.7±2.1</td>
<td>3.4±0.4</td>
<td>↓65%</td>
</tr>
<tr>
<td></td>
<td>(n=27)</td>
<td>(n=28)</td>
<td></td>
</tr>
<tr>
<td>Number of days in Hospital</td>
<td>14.4±1.2</td>
<td>9.9±0.7</td>
<td>↓31%</td>
</tr>
</tbody>
</table>
## Safety

**Overall summary of Treatment-Emergent Adverse Events (TEAEs)**

<table>
<thead>
<tr>
<th>Number of subjects (%) with</th>
<th>Placebo N=73</th>
<th>Caplacizumab N=71</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one TEAE</td>
<td>71 (97.3)</td>
<td>69 (97.2)</td>
</tr>
<tr>
<td>At least one study drug-related TEAE</td>
<td>32 (43.8)</td>
<td>41 (57.7)</td>
</tr>
<tr>
<td>At least one TEAE leading to study drug discontinuation</td>
<td>9 (12.3)</td>
<td>5 (7.0)</td>
</tr>
<tr>
<td>At least one SAE</td>
<td>39 (53.4)</td>
<td>28 (39.4)</td>
</tr>
<tr>
<td>At least one study drug-related SAE</td>
<td>4 (5.5)</td>
<td>10 (14.1)</td>
</tr>
<tr>
<td>At least one SAE leading to death</td>
<td>3 (4.1)</td>
<td>1 (1.4)¹</td>
</tr>
</tbody>
</table>

¹ adverse event occurred during the follow-up period of the study and was assessed by the investigator as not related to study drug treatment
Safety
Bleeding-related TEAEs*

<table>
<thead>
<tr>
<th>Bleeding-related TEAEs (by SMQ)¹</th>
<th>Placebo - n (%)</th>
<th>Caplacizumab - n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>17 (23.3)</td>
<td>33 (45.6)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>1 (1.4)</td>
<td>17 (23.9)</td>
</tr>
<tr>
<td>Gingival bleeding</td>
<td>0</td>
<td>8 (11.3)</td>
</tr>
<tr>
<td>Bruising</td>
<td>3 (4.1)</td>
<td>5 (7.0)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>1 (1.4)</td>
<td>4 (5.6)</td>
</tr>
<tr>
<td>Vaginal hemorrhage</td>
<td>1 (1.4)</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>1 (1.4)</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>Catheter site hemorrhage</td>
<td>3 (4.1)</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>Injection site bruising</td>
<td>2 (2.7)</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>Hematochezia</td>
<td>0</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>Hematoma</td>
<td>0</td>
<td>2 (2.8)</td>
</tr>
</tbody>
</table>

* Treatment emergent adverse events occurring in at least 2 subjects in either group

¹ Standardized MedDRA Query “Hemorrhage”
Caplacizumab Phase III HERCULES study – Conclusions

Caplacizumab addresses the pathophysiological platelet aggregation that leads to the formation of microthrombi and the resultant mortality and morbidity seen in aTTP

• Faster resolution of an aTTP episode with significantly shorter time to platelet count response
• Clinically relevant reduction in aTTP-related death, exacerbation of aTTP, or a major thromboembolic event
• Prevention of aTTP relapses when treatment is extended until resolution of underlying disease
• Potential to prevent refractory disease and speed normalization of markers of organ damage
• Striking reduction in use of plasma exchange and length of stay in the ICU and hospital
• Safety profile in line with previous study results and mechanism of action
Ablynx thanks the Patients, Investigators and Site Staff who participated in the HERCULES trial

United Kingdom
- Scully, M.
- Dutt, T.
- Clark, A.

United States
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