Thrombocytopenia and Chronic Liver Disease

- Severe thrombocytopenia (platelet count <50 x 10^9/L) common in patients with chronic liver disease and cirrhosis¹
- Platelet transfusions current standard of care to reduce risk of bleeding during invasive procedures in these patients
  - associated with risk of transfusion reactions, infections and induction of platelet refractoriness
- No pharmacological treatments are currently licensed for this indication

Avatrombopag- an oral, small molecule TPO receptor agonist being developed to provide a measured increase in platelet count as an alternative to platelet transfusions

¹Giannini EG. Aliment Pharmacol Ther. 2006; 23(8): 1055-1065
³Hod E and Schwartz J. Br J Haematol. 2008; 142(2): 348-360
⁵Rebulla P. Haematologica. 2005; 90(2): 247-253
Acutrombopag Phase 3 Studies- ADAPT-1 & ADAPT-2

Two global Phase III studies of acutrombopag in patients with thrombocytopenia and chronic liver disease undergoing scheduled procedures

- Identically-designed, randomized, double-blind, placebo-controlled, parallel-group studies
- In total, 435 patients recruited from over 20 countries (blue)
Avatrombopag Phase 3 Study Design

ADAPT-1 & ADAPT-2

**PRE-RANDOMIZATION**
- **VISIT 1**
  - Screening Period
  - Day -14 to -1

**RANDOMIZATION**
(2:1 avatrombopag:placebo)
- **VISIT 2**
  - BASELINE
  - DAY 1
- **VISIT 3**
  - TREATMENT
  - DAY 2–5
- **VISIT 4**
  - PROCEDURE*
  - DAY 10–13
  - 5–8 days after last dose of study drug
- **VISIT 5**
  - 7 DAYS POST
  - PROCEDURE
- **VISIT 6**
  - DAY 35
  - 30 days after last dose of study drug

*Platelet transfusions were not mandatory

**Low Baseline Platelet Count Cohort**
- mean Baseline PC <40 X 10^9/L
- **R 2:1**
- 60 MG AVATROMBOPAG
  - *qd x 5 Days*
- PLACEBO

**High Baseline Platelet Count Cohort**
- mean Baseline PC 40 to <50 X 10^9/L
- **R 2:1**
- 40 MG AVATROMBOPAG
  - *qd x 5 Days*
- PLACEBO
## Avatrombopag Phase 3 Study Populations

### ADAPT-1 & ADAPT-2

<table>
<thead>
<tr>
<th>MAIN INCLUSION CRITERIA</th>
<th>MAIN EXCLUSION CRITERIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aged $\geq 18$ years</td>
<td>History of arterial or venous thrombosis, hematologic disorders, or cardiovascular disease</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>Known medical history of genetic pro-thrombotic syndromes</td>
</tr>
<tr>
<td>Mean Baseline platelet count $&lt;50 \times 10^9$/L*</td>
<td>Platelet transfusion or use of erythropoietin-stimulating agents within 7 days of screening</td>
</tr>
<tr>
<td>MELD score $\leq 24$ at screening</td>
<td>Portal vein flow $&lt;10$ cm/sec at Screening</td>
</tr>
<tr>
<td>Scheduled to undergo an invasive procedure</td>
<td>Hemoglobin $\leq 8$ g/dL or $\geq 18$ g/dL (males) or $&gt;15$ g/dL (females)</td>
</tr>
<tr>
<td></td>
<td>Hepatocellular carcinoma (HCC) allowed if Barcelona Clinic Liver Cancer Stage A or B</td>
</tr>
</tbody>
</table>

*Platelet counts were measured on 2 separate occasions: During the Screening Period and at Baseline, and performed at least 1 day apart with neither platelet count $>60 \times 10^9$/L
ADAPT-1 & ADAPT-2: Outcome Measures

PRIMARY EFFICACY ENDPOINT:

- Proportion of patients not requiring platelet transfusion or any bleeding rescue procedure up to 7 days post-procedure
  - Rescue procedures included: platelet transfusion, fresh frozen plasma (FFP), cryoprecipitate, vitamin K (phytonadione), desmopression, recombinant activated factor VII, aminocaproic acid, tranexamic acid, whole blood transfusion, packed red cell transfusion, surgical intervention or interventional radiology

SECONDARY EFFICACY ENDPOINTS:

- Proportion of patients achieving the target platelet count (≥50 x 10⁹/L)
- Magnitude of change in platelet count from Baseline to Procedure Day

SAFETY ENDPOINTS:

- Adverse events, serious adverse events, Adverse Events of Special Interest (AESI)
**APAPT-1 & ADAPT-2: Disease Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>ADAPT-1</th>
<th></th>
<th>ADAPT-2</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Baseline Platelet Count Cohort</td>
<td>High Baseline Platelet Count Cohort</td>
<td>Low Baseline Platelet Count Cohort</td>
<td>High Baseline Platelet Count Cohort</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;40 x 10^9/L</td>
<td>40 to &lt;50 x 10^9/L</td>
<td>&lt;40 x 10^9/L</td>
<td>40 to &lt;50 x 10^9/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo (n=48)</td>
<td>Placebo (n=34)</td>
<td>Avatrombopag 60 mg (n=90)</td>
<td>Placebo (n=43)</td>
<td>Avatrombopag 60 mg (n=70)</td>
<td>Placebo (n=33)</td>
<td>Avatrombopag 40 mg (n=58)</td>
<td></td>
</tr>
<tr>
<td><strong>Baseline Platelet Count Cohort</strong></td>
<td>Mean (± SD)</td>
<td>31 ± 7</td>
<td>45 ± 3</td>
<td>44 ± 3</td>
<td>33 ± 6</td>
<td>33 ± 5</td>
<td>45 ± 3</td>
</tr>
<tr>
<td><strong>Disease Etiology, %</strong></td>
<td></td>
<td>Alcoholic Liver Disease</td>
<td>15</td>
<td>14</td>
<td>6</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic Viral Hepatitis</td>
<td>63</td>
<td>56</td>
<td>79</td>
<td>63</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nonalcoholic Steatohepatitis</td>
<td>8</td>
<td>7</td>
<td>0</td>
<td>7</td>
<td>12</td>
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<tr>
<td></td>
<td></td>
<td>Other</td>
<td>15</td>
<td>22</td>
<td>15</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatocellular Carcinoma, %</td>
<td>23</td>
<td>24</td>
<td>21</td>
<td>9</td>
<td>33</td>
</tr>
<tr>
<td><strong>MELD Score</strong></td>
<td>Mean (SD)</td>
<td>11.1 (3.37)</td>
<td>10.4 (2.74)</td>
<td>11.5 (3.75)</td>
<td>11.4 (3.08)</td>
<td>11.1 (3.25)</td>
<td>10.5 (3.61)</td>
</tr>
<tr>
<td><strong>Child-Turcotte-Pugh Grade, %</strong></td>
<td></td>
<td>Grade A</td>
<td>63</td>
<td>55</td>
<td>61</td>
<td>53</td>
<td>49</td>
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<tr>
<td></td>
<td></td>
<td>Grade B</td>
<td>35</td>
<td>43</td>
<td>36</td>
<td>38</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Grade C</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>9</td>
<td>2</td>
</tr>
</tbody>
</table>
## ADAPT-1 & ADAPT-2: Scheduled Procedures by Bleeding Risk

<table>
<thead>
<tr>
<th>Bleeding Risk</th>
<th>ADAPT-1</th>
<th>ADAPT-2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Baseline Platelet Count Cohort</td>
<td>High Baseline Platelet Count Cohort</td>
</tr>
<tr>
<td></td>
<td>&lt;40 x 10^9/L</td>
<td>40–50 x 10^9/L</td>
</tr>
<tr>
<td>Placebo (n=48)</td>
<td>Placebo (n=34)</td>
<td>Placebo (n=43)</td>
</tr>
<tr>
<td>Avatrombopag 60 mg (n=90)</td>
<td>Avatrombopag 40 mg (n=59)</td>
<td>Avatrombopag 60 mg (n=70)</td>
</tr>
<tr>
<td>Low %</td>
<td>68</td>
<td>66</td>
</tr>
<tr>
<td>Moderate %</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td>High %</td>
<td>13</td>
<td>25</td>
</tr>
</tbody>
</table>

### Low Bleeding Risk Procedures
- Thoracentesis
- Paracentesis
- Endoscopy
- Upper GI endoscopy +/- biopsy
- Upper GI endoscopy +/- variceal banding, +/- sclerotherapy
- Colonoscopy +/- polypectomy/biopsy

### Moderate Bleeding Risk Procedures
- Liver biopsy
- Bronchoscopy +/- biopsy
- Ethanol ablation
- Chemoembolization for HCC

### High Bleeding Risk Procedures
- Biliary Interventions
- Dental procedures
- Transjugular intrahepatic portosystemic shunt
- Laparoscopic Interventions
- Nephrostomy Tube placement
- Radiofrequency ablation
- Renal Biopsy
- Vascular catheterization
ADAPT-1 & ADAPT-2: Primary Endpoint

Proportion of Patients Who did NOT Require Platelet Transfusion or Any Rescue Procedure for Bleeding*

**Low Baseline Platelet Count Cohort**
- <40 x 10⁹/L

**High Baseline Platelet Count Cohort**
- 40 to <50 x 10⁹/L

- **ADAPT-1**
  - Placebo: 23%
  - Avatrombopag: 66%
  - p<0.0001

- **ADAPT-2**
  - Placebo: 38%
  - Avatrombopag: 69%
  - p<0.006

- **ADAPT-1 & ADAPT-2: Primary Endpoint**
  - Placebo: 88%
  - Avatrombopag: 89%
  - p<0.0001

*Full Analysis Set*
Proportion of Patients Who Achieved Platelet Counts ≥ 50 x 10⁹/L on Procedure Day*

- **Low Baseline Platelet Count Cohort**
  - <40 x 10⁹/L
  - Placebo: 4%
  - Avatrombopag: 69%
- **High Baseline Platelet Count Cohort**
  - 40 to <50 x 10⁹/L
  - Placebo: 4%
  - Avatrombopag: 88%

Magnitude of Change in Platelet Count from Baseline to Procedure Day*

- **Low Baseline Platelet Count Cohort**
  - <40 x 10⁹/L
  - Placebo: 31 x 10⁹/L
  - Avatrombopag: 32 x 10⁹/L
- **High Baseline Platelet Count Cohort**
  - 40 to <50 x 10⁹/L
  - Placebo: 27 x 10⁹/L
  - Avatrombopag: 30 x 10⁹/L

*Full Analysis Set
ADAPT-1 & ADAPT-2: Change in Platelet Count Over Time

- Platelet counts reproducibly increased from Day 4, peaked at Day 10-13, and returned to Baseline levels by Day 35

- Only 3 (1.1%) patients had a platelet counts >200 x10⁹/L at any time during the study; all were asymptomatic

![Graph showing changes in platelet counts over time for ADAPT-1 and ADAPT-2](image-url)
# ADAPT-1 & ADAPT-2: Treatment Emergent Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>ADAPT-1 Low Baseline Platelet Count Cohort &lt;40 x 10^9/L</th>
<th>ADAPT-1 High Baseline Platelet Count Cohort 40 to &lt;50 x 10^9/L</th>
<th>ADAPT-2 Low Baseline Platelet Count Cohort &lt;40 x 10^9/L</th>
<th>ADAPT-2 High Baseline Platelet Count Cohort 40 to &lt;50 x 10^9/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>65</td>
<td>56</td>
<td>51</td>
<td>46</td>
</tr>
<tr>
<td>Avatrombopag 60 mg</td>
<td>60</td>
<td>53</td>
<td>51</td>
<td>49</td>
</tr>
<tr>
<td>Placebo</td>
<td>15</td>
<td>6</td>
<td>21</td>
<td>6</td>
</tr>
<tr>
<td>Avatrombopag 40 mg</td>
<td>14</td>
<td>7</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>TEAEs</td>
<td>17</td>
<td>8</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Treatment-related TEAEs</td>
<td>23</td>
<td>11</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>TEAE with CTCAE Grade 3 or Above</td>
<td>19</td>
<td>11</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Serious TEAEs</td>
<td>17</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Deaths</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Other SAEs</td>
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<td>11</td>
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<td>Life threatening</td>
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<td>Hospitalization</td>
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<td>1</td>
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<tr>
<td>Important Medical Events</td>
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<td>0</td>
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<tr>
<td>TEAEs leading to study drug dose adjustment</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TEAEs leading to study drug withdrawal</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Full Analysis Set (FAS) all randomized subjects; Treatment-emergent Adverse Event (TEAE) an adverse event that started on or after the date of first dose of study drug, up to 30 days after the last dose of study drug. For each row category, a subject with two or more adverse events in that category is counted only once.
ADAPT-1 & ADAPT-2: Deaths & Adverse Events of Special Interest

Deaths:
- N=2 in ADAPT-1 → Both in the 40 mg avatrombopag group; not considered to be study drug-related
- N=1 in ADAPT-2 → In the placebo group; not considered to be study drug-related

AEs Leading to Study Drug Discontinuation:
- N=2 in ADAPT-1 → Both occurred in the 60 mg avatrombopag group
- Only one subject discontinued due to study drug-related TEAEs of myalgia and anemia

Medically Significant Events:
- N=1 in ADAPT-2 TEAE of portal vein thrombosis in a 71 yo male in the 40 mg avatrombopag group
  - Platelet count 45 x 10^9/L at Baseline that increased to 77 x 10^9/L on Procedure Day, and then decreased to 61 x 10^9/L at Visit 5 and 45 x 10^9/L at Visit 6
  - Scheduled procedure: upper gastrointestinal endoscopy with variceal banding
  - Partial portal vein thrombosis identified 14 days after the last dose of avatrombopag
  - Event was judged as non-serious and potentially drug-related, although causality assessment confounded by concomitant medication (ie, bisoprolol- associated with mesenteric thrombosis)
Summary and Conclusions

- Avatrombopag was superior to placebo in:
  - Reducing the need for platelet transfusion or any rescue procedure for bleeding following a scheduled procedure
  - Increasing the proportion of patients achieving the target platelet count (≥50 x 10⁹/L)
  - The magnitude of change in platelet count from Baseline to Procedure Day

- Pharmacodynamics were predictable & durable
  - Platelet counts reproducibly increased after 4 days, peaked after 10-13 days, and returned to Baseline by Day 35

- The safety profile of avatrombopag was similar to placebo

- No hepatotoxicity or increase in thromboembolic or bleeding events, no rebound thrombocytopenia

Avatrombopag offers an effective and safe alternative to platelet transfusion for patients with thrombocytopenia and chronic liver disease undergoing scheduled procedures