OR11: Phase 2/3 Trial of Subcutaneous Engineered FVIIa Marzeptacog Alfa (Activated) in Hemophilia A or B with Inhibitors: Pharmacokinetics, Pharmacodynamics, Efficacy and Safety

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Marzeptacog alfa (activated)

Four engineered amino acid substitutions within the FVIIa protein

+ Catalytic activity increased
+ 9-fold more potent than NovoSeven RT
+ Allows subcutaneous dosing
+ Half-life prolonged when using subcutaneous dosing

Orphan Drug Designation in US
MarzAA phase 2/3 SQ clinical trial design

+ Individualized dose escalation if needed

+ Enrollment completed

- Open label SQ study with individual dose escalation if needed
- Hemophilia A or B with inhibitors
- Adult patients with documented annual bleeding rate (ABR) >12

- Primary endpoint: reduction in annualized bleed rate at final dose level
- Secondary endpoints: safety and tolerability, no inhibitor formation

MarzAA IV PK 24 hours
MarzAA SQ PK 48 hours

if bleed occurs, then dose escalation

if bleed occurs, then dose escalation

if bleed occurs, then dose escalation

50 days

50 days

50 days

50 days

endpoint achieved if no bleeds for 50 days

MarzAA SQ 30 µg/kg
MarzAA SQ 60 µg/kg
MarzAA SQ 90 µg/kg
MarzAA SQ 120 µg/kg
## Subject demographics & disposition

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Age</th>
<th>Highest Inhibitor level BU</th>
<th>Age when inhibitor diagnosed</th>
<th>Hem A or B</th>
<th>Subject Status</th>
<th>ABR</th>
<th>ABR on treatment</th>
<th>Proportion of days with bleeding</th>
<th>Proportion of days with bleeding on treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2680101</td>
<td>36</td>
<td>16</td>
<td>15</td>
<td>A</td>
<td>Revoked consent</td>
<td>12.2</td>
<td>n/a</td>
<td>6%</td>
<td>n/a</td>
</tr>
<tr>
<td>2680301</td>
<td>18</td>
<td>5</td>
<td>14</td>
<td>A</td>
<td>Complete</td>
<td>26.7</td>
<td>Zero at 60 µg/kg</td>
<td>18%</td>
<td>Zero at 60 µg/kg</td>
</tr>
<tr>
<td>2680302</td>
<td>30</td>
<td>2.7</td>
<td>26</td>
<td>A</td>
<td>Fatal unrelated SAE</td>
<td>18.3</td>
<td>n/a</td>
<td>11%</td>
<td>n/a</td>
</tr>
<tr>
<td>6430201</td>
<td>29</td>
<td>4.7</td>
<td>27</td>
<td>A</td>
<td>Complete</td>
<td>15.9</td>
<td>Zero</td>
<td>12%</td>
<td>Zero</td>
</tr>
<tr>
<td>6430202</td>
<td>35</td>
<td>4.7</td>
<td>35</td>
<td>A</td>
<td>Complete</td>
<td>16.6</td>
<td>Zero</td>
<td>11%</td>
<td>Zero</td>
</tr>
<tr>
<td>0510101</td>
<td>43</td>
<td>5.5</td>
<td>39</td>
<td>A</td>
<td>Complete</td>
<td>22.2</td>
<td>Untreated traumatic hematoma Day 4.</td>
<td>22%</td>
<td>2%</td>
</tr>
<tr>
<td>6430203</td>
<td>23</td>
<td>4.5</td>
<td>21</td>
<td>A</td>
<td>Complete</td>
<td>15.2</td>
<td>Zero</td>
<td>4%</td>
<td>Zero</td>
</tr>
<tr>
<td>0510104</td>
<td>31</td>
<td>1.7</td>
<td>31</td>
<td>B</td>
<td>Complete</td>
<td>21.2</td>
<td>Zero at 60 µg/kg</td>
<td>18%</td>
<td>Zero at 60 µg/kg</td>
</tr>
<tr>
<td>6430204</td>
<td>18</td>
<td>56</td>
<td>6</td>
<td>A</td>
<td>Complete</td>
<td>15.9</td>
<td>Treated traumatic hematoma Day 36.</td>
<td>9%</td>
<td>2%</td>
</tr>
<tr>
<td>0510106</td>
<td>47</td>
<td>1.07</td>
<td>40</td>
<td>A</td>
<td>Dosing</td>
<td>20.5</td>
<td>n/a</td>
<td>8%</td>
<td>n/a</td>
</tr>
<tr>
<td>6160101</td>
<td>31</td>
<td>27.5</td>
<td>10</td>
<td>A</td>
<td>Dosing</td>
<td>24.3</td>
<td>n/a</td>
<td>9%</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Patients can have a very different proportion of days with bleeding despite similar ABR.
Subject status to date

Clinical efficacy demonstrated

+ 17 subjects have been consented and 12 enrolled; 3 active subjects; is no longer recruiting
+ ABR: Mean 19.0; Range 12.2-26.7
+ Proportion of days with bleeding: Mean 12.2%; Range 4-22%
+ 7 subjects have completed dosing
  • Clinically significant reduction in ABR
  • 2 subjects had dose escalation to 60 µg/kg
  • 5 subjects had no bleeds (traumatic or spontaneous) at their final dose level
  • Statistically significant reduction in proportion of days with bleeding
MarzAA reduces annualized bleed rate (ABR)

The width of each red bar represents bleed duration: 1 to 9 days

6-month recorded bleeds

Treatment Period

Follow-up Period

MarzAA 30 µg/kg & 60 µg/kg
Significant reduction in ABR on-treatment
## Pre- and on-treatment proportion of bleeding days efficacy

<table>
<thead>
<tr>
<th>Subject</th>
<th>2680301</th>
<th>2680302</th>
<th>6430201</th>
<th>6430202</th>
<th>0510101</th>
<th>6430203</th>
<th>0510104</th>
<th>6430204</th>
<th>0510106</th>
<th>6160101</th>
<th>Subject</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre-treatment</strong></td>
<td><img src="chart1.png" alt="Chart" /></td>
<td><img src="chart2.png" alt="Chart" /></td>
<td><img src="chart3.png" alt="Chart" /></td>
<td><img src="chart4.png" alt="Chart" /></td>
<td><img src="chart5.png" alt="Chart" /></td>
<td><img src="chart6.png" alt="Chart" /></td>
<td><img src="chart7.png" alt="Chart" /></td>
<td><img src="chart8.png" alt="Chart" /></td>
<td><img src="chart9.png" alt="Chart" /></td>
<td><img src="chart10.png" alt="Chart" /></td>
<td><img src="chart11.png" alt="Chart" /></td>
</tr>
<tr>
<td><strong>On-treatment</strong></td>
<td><img src="chart12.png" alt="Chart" /></td>
<td><img src="chart13.png" alt="Chart" /></td>
<td><img src="chart14.png" alt="Chart" /></td>
<td><img src="chart15.png" alt="Chart" /></td>
<td><img src="chart16.png" alt="Chart" /></td>
<td><img src="chart17.png" alt="Chart" /></td>
<td><img src="chart18.png" alt="Chart" /></td>
<td><img src="chart19.png" alt="Chart" /></td>
<td><img src="chart20.png" alt="Chart" /></td>
<td><img src="chart21.png" alt="Chart" /></td>
<td><img src="chart22.png" alt="Chart" /></td>
</tr>
</tbody>
</table>

Red denotes the proportion of days with bleeding during period of observation.

+ The average percentage of days of bleeding in the pre-treatment period was 12.2% (SD 5.2%) [median = 11.0%]
+ In the treatment period, these percentages were reduced to 1.0% (SD 5.2%) [median 1.0%]
+ The analysis of these pairwise differences by a randomization paired t-test yields p=0.016 (and p=0.0001 by Wilcoxon signed-rank test)
High pre-treatment ABRs reduced to a median of zero on treatment

+ 7 subjects have completed dosing with clinically significant reduction in ABR
+ 5 subjects had no bleeds at their final dose level
+ SQ half-life increases to 13.1 hours from an IV half-life 3.9 hours in Part 1
+ No anti-drug antibodies have been detected to date
+ More than 450 SQ injections have been administered
  - 6 injection site reactions in 2 subjects
    - Moderate swelling that resolved without sequelae
    - Mild or moderate redness that resolved without sequelae
Conclusions on the marzeptacog alfa (activated) program

Moving forward in clinical development after clinical proof of concept

Clinical efficacy and tolerability demonstrated

Additional clinical data at ISTH 2019

Pivotal trial guidance obtained from EMA & MHRA and we will confirm with FDA at end-of-phase 2 meeting in late 2019