INTRODUCTION

- In hemophilia patients with inhibitors, hemostasis can be achieved using bypass agents: activated plasma-derived prothrombin complex concentrates (aPCC), recombinant Factor VIIIa (FVIIa), or emicizumab that can only treat hemophilia A
- Marzepiscof alfa (activated) (MarzAA) has four amino acid substitutions that were introduced using rational design and has enhanced biological properties including 7-fold increased catalytic activity, measured by the rate of Factor Xa generation in vitro, in presence of tissue factor, and prolonged duration of effect in vivo compared with wild-type rFVIIa
- A human intravenous (IV) single-dose escalation study up to 30 µg/kg showed a half-life of 3.5 hours and dose-dependent pharmacodynamic effects on prothrombin time, aPTT and thrombin generation with a good safety profile (NCT01439871)

AIMS

- Phase 2 Study MAA-201 complies with the Declaration of Helsinki, is approved by recognized medical ethics committee, will enroll 12 subjects with inhibitors and annual bleeding rate (ABR) ≥12 who sign informed consent to determine if SQ MarzAA can provide effective prophylaxis (NCT03407651)
- The objective is to find an individualized dose that provides prophylaxis without spontaneous bleeding

METHODS

Part 1
- 18 µg/kg MarzAA was infused IV and pharmacokinetics (PK) and coagulation parameters were measured for 24 hours
- 30 µg/kg MarzAA was injected SQ and PK, bioavailability and coagulation parameters were measured for 48 hours

Part 2
- Daily 30 µg/kg MarzAA SQ therapy was injected for up to 50 days
- If no spontaneous bleeding events occurred the subject proceeded to safety follow up 3 weeks after the last dose
- If spontaneous bleeding was reported, then dose escalation occurred sequentially to 60, 90 or 120 µg/kg for 50 days, as needed
- Subjects were tested for anti-drug antibodies to MarzAA, as well as FVII levels (>50% reduction defined as significant) at screening and every 7 days during treatment
- Annualized Bleed Rate (ABR) was be compared to the subjects prior ABR

RESULTS

- 13 subjects have been consented and 7 enrolled (Median ABR 18.2; Range 12.2-26.7)
- 5 subjects have completed dosing clinically significant reduction in ABR
- 4 subjects had no bleeds at their final dose level
- IV half-life of 3.8 hours was increased to SQ half-life of 9.5 hours
- No anti-drug antibodies have been detected to date
- After more than 300 SQ injections, a single moderate injection site hematoma that resolved without sequelae, was reported

SUBJECT DEMOGRAPHICS AND DISPOSITION

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Height (m)</th>
<th>Weight (kg)</th>
<th>Sex</th>
<th>MarzAA SQ (µg/kg)</th>
<th>SQ 500 µg/kg</th>
<th>MarzAA SQ (µg/kg)</th>
<th>SQ 500 µg/kg</th>
<th>MarzAA SQ (µg/kg)</th>
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<th>MarzAA SQ (µg/kg)</th>
<th>SQ 500 µg/kg</th>
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PHARMACOKINETICS OF INTRAVENOUS OR SUBCUTANEOUS ADMINISTRATION OF MARZEPISCOF ALFA (ACTIVATED)

<table>
<thead>
<tr>
<th>Route</th>
<th>Cmax (ng/mL)</th>
<th>Tmax (hr)</th>
<th>Half-life (h)</th>
<th>Half-life half (h)</th>
<th>Max Residence Time (hr)</th>
<th>AUCinf (ng·h/mL)</th>
<th>MRT (h)</th>
<th>Mean Residence Time (h)</th>
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<tr>
<td>IV</td>
<td>833.1 ± 333.1</td>
<td>0.1 ± 0.1</td>
<td>15</td>
<td>7.3</td>
<td>3.3</td>
<td>32.6 ± 18.1</td>
<td>14.7</td>
<td>12.2 ± 7.5</td>
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<tr>
<td>SQ</td>
<td>471 ± 161</td>
<td>2.8 ± 0.2</td>
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<td>11.7</td>
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<td>453 ± 184</td>
<td>16.3</td>
<td>15.9 ± 9.4</td>
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</tbody>
</table>

**CONCLUSION**

- Increased potency of MarzAA and these pharmacokinetic and clinical results support a target of achieving zero ABR with individualized dosing using daily subcutaneous injections

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