The Catalyst Biosciences subcutaneous solution

Our highly potent candidates:

- Quick & simple SQ injection
- Self-administered
- Ideal for pediatric patients
- Achieve higher & more stable factor levels
- Continuously at protective levels
Subcutaneous pharmacokinetics are complex

Absorption of subcutaneous injection

+ Creation of a depot at the injection site
+ Local catabolism at the injection site decreases bioavailability
+ Prolongation of observed half-life because of depot returning drug to circulation via Lymphatic and Venous systems
  - Slow subcutis convection and diffusion to Lymphatic and Venous capillaries results in absorption rate-limited PK and prolonged systemic exposure
  - GAG and negative charge barrier
  - SQ absorption of protein may be slow with Tmax up to 8 days in humans
  - Large proteins (>20 kDa) are mainly transported by Lymphatics
  - Transport in the Lymphatics is unlikely to be the rate-limiting step for the slow absorption after SQ injection
Subcutaneous pharmacokinetics are complex

**FIX subcutaneous pharmacokinetics**

+ Extravascular distribution and collagen IV binding further impact factor IX PK
  ▪ Decreases observed bioavailability
  ▪ Later release contributes to prolonged observed half-life
+ Competition for binding sites with CRIM positive FIX

**FVIIa subcutaneous pharmacokinetics**

+ Rapid absorption from compared with FIX

Redosing any agent within 3 half-lives results in accumulation of plasma levels
Marzeptacog alfa (activated): MarzAA rFVIIa

SQ prophylaxis and SQ treatment of a bleed are clear unmet needs in hemophilia and other bleeding disorders

- Four engineered amino acid substitutions within the FVIIa protein
- 9-fold more potent catalytic activity than NovoSeven RT
- Allows subcutaneous dosing
- Half-life prolonged when using subcutaneous dosing

Orphan Drug Designation in the US and EU
Subcutaneous Prophylaxis: Hemophilia A or B with inhibitors
**MarzAA phase 2/3 SQ clinical trial MAA-201 design**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose (µg/kg)</th>
<th>PK Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>MarzAA IV</td>
<td>18</td>
<td>24 hours</td>
</tr>
<tr>
<td>MarzAA SQ</td>
<td></td>
<td>48 hours</td>
</tr>
</tbody>
</table>

- **Patients with documented annual bleeding rate (ABR) >12**
- **Open label SQ study with individual dose escalation if needed in Hemophilia A or B with inhibitors**
- **Primary endpoint: reduction in annualized bleed rate at final dose level**
- **Secondary endpoints: safety and tolerability, inhibitor formation**

**Endpoint achieved if ABR decreases from ≥12 to ≤6**
MarzAA PK IV 18 µg/kg then SQ 30 µg/kg

- IV half-life of 3.65 hours
- SQ half-life of 17 hours
- Stable levels after SQ dosing for 48 hours without high peak after IV dosing
MarzAA SQ PK demonstrates prolonged half-life

SQ half-life increased to 17.0 hours from an IV half-life of 3.65 hours

<table>
<thead>
<tr>
<th>Route</th>
<th>Half-life alpha (hr)</th>
<th>Half-life beta (hr)</th>
<th>Mean Residence Time (hr)</th>
<th>Cmax (ng/mL)</th>
<th>Tmax (hr)</th>
<th>AUC₀₋₄ (ng/mL*hr)</th>
<th>AUC₀₋∞ (ng/mL*hr)</th>
<th>Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>1.47 ± 0.29</td>
<td>3.65 ± 0.23</td>
<td>4.05 ± 0.39</td>
<td>375 ± 54</td>
<td>0.5 ± 0.4</td>
<td>1076 ± 97</td>
<td>1102 ± 101</td>
<td>27 ± 6%</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SQ</td>
<td>17.0 ± 3.1</td>
<td>25.8 ± 4.5</td>
<td>24 ± 4.5</td>
<td>7 ± 0.8</td>
<td>473 ± 132</td>
<td>609 ± 190</td>
<td></td>
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</tr>
</tbody>
</table>
MarzAA: Robust reduction in annualized bleed rate (ABR)

*The width of each grey bar represents bleed duration: 1 to 9 days
Significant reduction in Proportion of Days with Bleeding (PDB)

**Median Proportion of Days with Bleeding reduced to zero**

<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>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-treatment</td>
<td>18%</td>
<td>11%</td>
<td>12%</td>
<td>11%</td>
<td>22%</td>
<td>4%</td>
<td>18%</td>
<td>9%</td>
<td>8%</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>82%</td>
<td>89%</td>
<td>88%</td>
<td>89%</td>
<td>78%</td>
<td>96%</td>
<td>82%</td>
<td>91%</td>
<td>92%</td>
<td>91%</td>
</tr>
<tr>
<td>On-treatment</td>
<td>1%</td>
<td>0%</td>
<td>0%</td>
<td>2%</td>
<td>0%</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
<td>0%</td>
<td>0%</td>
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<tr>
<td></td>
<td>99%</td>
<td>100%</td>
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</tr>
</tbody>
</table>

Orange denotes the Proportion of Days with Bleeding during period of observation

- Average **pre-treatment** proportion of days of bleeding was **12.3%** (SD 5.8%) [median = 11.0%]
- Average **on-treatment** proportion was reduced to **0.8%** (SD 0.9%) [median 0%]
- Analysis of these pairwise differences by Wilcoxon signed-rank test has p=0.009 for 93.8% reduction
Marzeptacog alfa (activated) Phase 2: Clinical efficacy

7 of 9 subjects had no bleeding (spontaneous or traumatic) at final dose level
Greater than 90% reduction in all bleeding; Median ABR zero; Median bleeding days zero

Mean Annualized Bleeding Rates (ABR) significantly reduced from 19.8 to 1.6
Mean Proportion of Days with Bleeding (PDB) significantly reduced from 12.3% to 0.8%

<table>
<thead>
<tr>
<th></th>
<th>6 m pre-treatment</th>
<th>On treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized Bleed Rate (n = 9)</td>
<td>19.8</td>
<td>1.6, p = 0.009</td>
</tr>
<tr>
<td>Proportion of Days with Bleeding (n = 9)</td>
<td>12.3%</td>
<td>0.8%, p = 0.009</td>
</tr>
</tbody>
</table>
MAA-201 safety

Safe & well tolerated

No anti-drug antibodies were detected

- One fatal unrelated SAE: intracerebral hemorrhage due to untreated hypertension
- 517 SQ injections were administered
  - 6 injection site reactions in 2 subjects
    - 1 moderate swelling that resolved without sequelae in one subject
    - 2 mild and 3 moderate redness that resolved without sequelae in the other subject and did not occur with subsequent SQ injections
The Potential for Subcutaneous Treatment of a Bleed
Preclinical evaluation of bleeding in hemophilia mice

Acute injury model with SQ dosing after the injury

Preclinical hemophilia A mouse model

- Standardized bleeding models are used to evaluate efficacy of hemostatic agents
- Represents a traumatic injury
- The standard acute injury model is IV treatment of the agent 5 min prior to injury to the tail that induces bleeding
- Two approaches to evaluate SQ MarzAA in a hemophilia A mouse model
  - SQ treatment prior to injury
  - SQ treatment after injury
Fast onset of action for SQ MarzAA in Hemophilia A mice

Acute mouse injury model with dosing prior to injury

SQ MarzAA normalizes bleeding

- SQ treatment of MarzAA 15 min prior to injury normalizes bleeding
- Normalization of bleeding demonstrated at comparable SQ and IV doses
- Clear dose dependent effect
- Fast onset of action
- These doses translate to the range of doses ($\mu$g/kg) being explored in clinical trials
SQ MarzAA reduces bleeding when dosed After the Injury

Acute mouse injury model with dosing after the injury

Reduced bleeding After Injury

+ Hemophilic mice bleed considerably more than normal mice
+ SQ treatment of MarzAA one min after traumatic bleeding has started significantly reduces blood loss and stops the bleed
+ The effect is dose dependent
+ Reduction in blood loss is similar to IV NovoSeven
Thrombogenicity risk can be evaluated *in vitro*

The thrombin generation assay is an effective model of coagulation
Potential to treat break through bleeds in patients on Hemlibra

MarzAA has a preferred coagulation profile that is similar to NovoSeven

+ MarzAA and NovoSeven behave similarly when combined with Hemlibra
+ MarzAA could allow hemophilia A patients to combine two SQ therapies - "sports prophylaxis" or treat breakthrough bleeds
+ MarzAA works well at plasma levels achievable with SQ dosing
Data supports SQ MarzAA for treatment of a bleed

SQ MarzAA rapidly reaches therapeutic concentrations in humans

SQ MarzAA reduces bleeding before and after an injury in preclinical models

Thrombin generation for MarzAA + Hemlibra is similar to NovoSeven + Hemlibra *in vitro*
MAA-102 Study Design

IPK assessment of intravenous (IV) and subcutaneous (SC) MarzAA

Primary:
+ Evaluate the pharmacokinetics (PK) of ascending subcutaneous (SC) doses of MarzAA

Secondary:
+ Determine if PK behaves in a dose proportional manner
+ Determine whether a split injection provides the same PK as a single injection
+ Determine the pharmacodynamics (PD) of SC MarzAA
+ Evaluate the safety of SC MarzAA

n=8 at each dose level

MarzAA IV
18 µg/kg

MarzAA SC
30 µg/kg

MarzAA SC
45 µg/kg

MarzAA SC
60 µg/kg

MarzAA SC
30 µg/kg

MarzAA SC
45 µg/kg

MarzAA SC
60 µg/kg

MarzAA SC
30 µg/kg

MarzAA SC
45 µg/kg

MarzAA SC
60 µg/kg

Different anatomical locations

Same anatomical location

Same subject
Marzeptacog alfa (activated) program

Moving forward in clinical development to address key unmet needs

- Robust SQ prophylaxis clinical efficacy demonstrated
- Safe and well tolerated
- No anti-drug antibodies detected
- Pivotal trial guidance obtained from EMA & MHRA
- PK study initiated to assess range of clinical doses
- Exploring the use of SQ MarzAA in treatment of a bleed
- Preparing for End of Phase 2 meeting 4Q 2019
- Moving forward with Phase 3 study planning
The new standard in hemophilia B prophylaxis

Patients in high mild range are protected from spontaneous bleeds

+ **Our concept** of prophylactic treatment is to keep severe & moderate hemophilia patients in the high mild range
+ **Subcutaneous factor** treatments build up over time, offering long-term stability in clotting levels

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**Normal clotting levels**

**Mild Hemophilia**
Protection from spontaneous hemarthrosis when activity >12%

**Moderate Hemophilia**
15-20 bleeds/year

**Severe Hemophilia**
~30 bleeds/year
Dalcinonacog alfa – DalcA

Novel clinical stage SQ FIX product candidate differentiated from IV market leaders

Phase 1/2 completed
+ 22-fold more potent than BeneFIX in man
+ **Allows subcutaneous dosing**
+ Half-life prolonged when using subcutaneous dosing
+ Maintains continuous protective FIX activity levels of 12 – 30%
+ Disruptive to all intravenous products

Orphan Drug Designation in US & EU
Dalcinonacog phase 1/2 open label design

Hemophilia B FIX

DalcA IV vs BeneFIX IV

Cohort 1 (n=3)

BeneFIX IV
70 IU/kg

DalcA IV
70 IU/kg

DalcA IV to SQ crossover ascending dose cohorts 2 - 3

Cohort 2 (n=3)

DalcA IV
70 IU/kg

Cohort 3 (n=3)

DalcA IV
70 IU/kg

DalcA IV to SQ crossover ascending dose cohorts 2 - 3

DalcA multi-dose SQ

Cohort 5 (n=5)

DalcA SQ
140 IU/kg
6 daily-doses

DalcA IV + multi-dose SQ*

Cohort 6 (n=2)

DalcA IV
70 IU/kg

DalcA SQ
140 IU/kg
9 daily-doses

*First SQ dose 30 min post-IV
SQ DalcA PK increases half-life by 3.6 fold over IV

Cohort 2 & 3: PK activity profiles after IV and SQ Dalcinonacog alfa administration

<table>
<thead>
<tr>
<th>Route</th>
<th>t-half alpha (hrs)</th>
<th>t-half beta (hrs)</th>
<th>Tmax</th>
<th>AUC 0-t (mU/mL*hr)</th>
<th>Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>Mean ± SD</td>
<td>9.4 ± 4.4</td>
<td>27.0 ± 2.2</td>
<td>16.7 ±11.3 mins</td>
<td>1026 ± 330</td>
</tr>
<tr>
<td>SQ</td>
<td>Mean ± SD</td>
<td>3.4 (n=1)</td>
<td>242.2 ± 365.5</td>
<td>29.0 ± 16.3 h</td>
<td>306 ± 148</td>
</tr>
<tr>
<td></td>
<td>Median [25%-75%]</td>
<td>3.4 (n=1)</td>
<td>98.7 [60.0-369.4]</td>
<td>24 h [19.5-48]</td>
<td>352 [138-410]</td>
</tr>
</tbody>
</table>
DalcA Phase 1/2 clinical trial FIX activity results

Trough levels >12% are sufficient to protect against spontaneous joint bleeds

IV Peak 75% FIX activity

Cohort 5:
- C4-01-S06
- C4-01-S05
- C4-01-S07
- C4-01-S01
- C4-01-S02

Cohort 6*:
- C5-01-S01
- C5-01-S02

*Mild 5-40%
*Moderate 1-5%
*Severe <1%

*Two nAbs observed, one transient
Conclusions on the dalcinonacog alfa program

Continuing clinical development after an extensive immunogenicity risk assessment

Preclinical immunogenicity assessment showed that dalcinonacog alfa is equivalent to that of competitors such as BeneFIX

A comprehensive evaluation of the drug product showed comparable quality to marketed rFIX products

KoLs and subject experts agree with the immunogenicity risk assessment and proceeding with the P2b to evaluate the safety and efficacy of dalcinonacog alfa
Dalcinonacog alfa phase 2b SQ clinical trial design

DLZ-201 enrolling

- Initial: 35 min Post-IV
- Daily SQ Dosing to Day 28
- Wash-out

- DalcA IV 50 IU/kg
- DalcA SQ 100 IU/kg

- Endpoint achieved with steady state FIX activity levels > 12%

+ Enrollment: 6 patients
+ Single IV dose followed by 28 day SQ dosing

+ Primary endpoint: Steady state FIX activity level above 12% with daily dosing
+ Secondary endpoints: safety, lack of neutralizing antibody formation, pharmacokinetics, pharmacodynamics
Dalcinonacog alfa program

Moving forward in clinical development to address key unmet needs

- Robust SQ prophylaxis clinical efficacy demonstrated
- Safe and well tolerated
- Two anti-drug antibodies detected but low risk of immunogenicity
- Expected Top line Phase 2 results 4Q 2019
Addressing unmet needs in orphan bleeding disorders

**Hemophilia A with inhibitors**
Anti-FVIII antibodies that neutralize activity
- 30% of Hem A patients
- Treatments: SQ Hemlibra®, IV FVIIa, FEIBA®

SQ treatment of bleeds & Hemlibra non-responders

**Hemophilia B with inhibitors**
Anti-FIX antibodies that neutralize activity
- 5% of Hem B patients
- Treatments: IV FVIIa, FEIBA

SQ prophylaxis & SQ treatment of bleeds

**Factor VII deficiency – Glanzmann Thrombasthenia**
Congenital lack of FVII – Platelet abnormality
- Treatments: IV plasma FVII or FVIIa

SQ prophylaxis in severe patients & SQ treatment of bleeds

**MarzAA & DalcA**

**Hemophilia B**
Congenital lack of functional FIX
- Treated with IV FIX products

SQ prophylaxis

**Hemophilia A**
Congenital lack of functional FVIII
- Treatments: IV FVIII or SQ Hemlibra

SQ treatment of bleed

**Acquired Hemophilia**
Rare disorder, caused by anti-FVIII nAbs
- Treated with immunosuppressants + IV FVIIa, FEIBA or Obizur®

SQ treatment of bleeds & SQ prevention of re-bleeds
THANK YOU