Phase 1/2 Trial of Subcutaneously Administered Factor IX Variant CB 2679d/ISU304: Pharmacokinetics and Activity

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87 Session 322. Disorders of Coagulation or Fibrinolysis: Novel Therapies and Clinical Trials in Bleeding Disorders

ASH
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Disclosure

- Employee and Stockholder of Catalyst Biosciences
Factor IX Modified with 3 Point Mutations

- Rapid clearance of FIX necessitates frequent intravenous administrations to achieve effective prophylaxis
- Subcutaneous administration is the preferred route of administration but has been limited by low bioavailability and potency of the marketed FIX products
- Designed as best-in-class high potency recombinant FIX product
- Orphan Drug Designation in US and EU

Factor IX: CB 2679d/ISU304

- R318Y
- R338E
- T343R
CB 2679d/ISU304 Potency Advantage over wt-FIX

- 20-fold increased potency of CB 2679d over wild-type FIX in tail clip model
Normalization of FIX Activity and Rapid Whole Blood Clotting Time Correction with Daily SQ Dosing of CB 2679d/ISU304 (300 IU/kg) in Hemophilia B Dogs


*Levy et al. EAHAD 2017 Haemophilia (2017), 23 (Suppl. 2), 29-140
Design of Ongoing Phase 1/2 Trial

- ISU Abxis is executing the Phase 1/2 trial
- Cohort 3 has been completed

<table>
<thead>
<tr>
<th>Cohort 1 (n=3)</th>
<th>Cohort 2 (n=3)</th>
<th>Cohort 3 (n=3)</th>
<th>Cohort 4 (n=3)</th>
<th>Cohort 5 (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BeneFIX 75 IU/kg IV</td>
<td>ISU304/CB 2679d 75 IU/kg IV</td>
<td>ISU304/CB 2679d 75 IU/kg IV</td>
<td>ISU304/CB 2679d 75 IU/kg IV</td>
<td>ISU304/CB 2679d SQ</td>
</tr>
<tr>
<td>ISU304/CB 2679d 75 IU/kg SQ</td>
<td>ISU304/CB 2679d 75 IU/kg IV</td>
<td>ISU304/CB 2679d 150 IU/kg SQ</td>
<td>ISU304/CB 2679d 300 IU/kg SQ</td>
<td></td>
</tr>
</tbody>
</table>

Six Daily-Doses

- ISU304/CB 2679d IV to SQ Crossover – Ascending Dose Cohorts 2 - 4

- ISU304/CB 2679d Multi-Dose
Methods

- IV PK was sampled at predose, 0, 0.25, 0.5, 1, 3, 6, 9, 24, 48 and 72 hours
- SQ PK was sampled at predose, 1, 2, 4, 6, 8, 10, 12, 24, 48 and 72 hours
- A safety follow-up was done 3 weeks after dosing
- FIX antigen and FIX activity, anti-drug antibody to BeneFIX and ISU304 and neutralizing antibody were measured at Haematologic Technologies
- FIX antigen was measured using VisuLize™ Factor IX Antigen KitAG (Affinity Biologicals) and FIX activity was measured using a one-stage clotting assay using ACL TOP 700 and Instrumentation Laboratories reagents
- Calculation of AUC was based on the trapezoidal rule
- Calculation of half-life used Demitasse 2000 which uses an iterative piecewise fitting algorithm based on a robust (M-regression) log-linear model
- All activity data were adjusted for baseline assuming exponential falloff after IV administration and a half-life of 20 hours
Cohort 1, 2 & 3: IV BeneFIX & IV CB 2679d/ISU304 75 IU/kg
### PK profiles after IV administration (mean ± SD)

<table>
<thead>
<tr>
<th>Group</th>
<th>t-half alpha (hrs)</th>
<th>t-half beta (hrs)</th>
<th>MRT (hrs)</th>
<th>Cmax (mU/mL)</th>
<th>AUC 0-t (mU/mL*hr)</th>
<th>AUC 0-inf (mU/mL*hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BeneFIX</td>
<td>5.3 ± 0.8</td>
<td>21.0 ± 1.1</td>
<td>25.1 ± 1.5</td>
<td>70.2 ± 16.0</td>
<td>855 ± 163</td>
<td>933 ± 177</td>
</tr>
<tr>
<td>CB 2679d/ISU304</td>
<td>8.5 ± 4.0</td>
<td>27.0 ± 2.2</td>
<td>35.8 ± 2.5</td>
<td>70.0 ± 46.9</td>
<td>973 ± 274</td>
<td>1148 ± 334</td>
</tr>
<tr>
<td>P-value by two-sample t-test*</td>
<td>0.22</td>
<td>0.0014</td>
<td>0.00004</td>
<td>0.995</td>
<td>0.50</td>
<td>0.32</td>
</tr>
</tbody>
</table>

*ignoring the matching from Cohort 1

- IV CB 2679d has a significantly longer half-life and mean residence time than BeneFIX
Cohort 2: 75 IU/kg IV then 75 IU/kg SQ CB 2679d/ISU304
Cohort 3: 75 IU/kg IV then 150 IU/kg SQ CB 2679d/ISU304
**CB 2769d – ISU304-001 PK: SQ vs IV has 3.6-fold Increase in Half-life**

### Cohort 2 & 3: PK activity profiles after IV and SQ CB 2679d/ISU304 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</td>
<td>3.4 (n=1)</td>
<td>242.2 ± 365.5</td>
<td>29.0 ± 16.3 hrs</td>
<td>306 ± 148</td>
</tr>
<tr>
<td></td>
<td>Median [25%-75%]</td>
<td>98.7 [60.0-369.4]</td>
<td>24 hrs [19.5-48]</td>
<td>352 [138-410]</td>
<td>18.5% [15.4-24.7%]</td>
</tr>
</tbody>
</table>

- 98.7 hour SQ CB 2679d half-life is similar to IV agents dosed biweekly or weekly:
  - Alprolix  86.52 hours
  - Idelvion  104-118 hours
  - Rebinyn/Refixia  114.9 hours
• One subject had a mild general reaction within 1 hour of injection
  – Fatigue/Boredom
  – Headache
  – Dizziness

• Transient mild AEs were reported in cohorts 2 and 3 and all resolved without sequelae:
  – Itching
  – Tenderness
  – Erythema
  – Solidification
  – Injection site discomfort
  – General ache [moderate severity]
Modeling of Daily 75 IU/kg SQ $t_{1/2} = 36$ hours

- Modeling demonstrates that CB 2679d could achieve **stable** FIX minimum levels in the high mild hemophilia or normal range >50%
Modeling of Daily 60 IU/kg SQ $t_{1/2} = 100$ hours

- Normal FIX activity levels of >50% are reached after 7 daily doses of CB 2679d
- No difference between peak and minimum levels when Tmax is 24 hours
- Lower doses of CB 2679d will maintain levels above 50% at all times
- Less frequent dosing is also a possibility
Modeling predicts subcutaneous administration may be a superior prophylaxis regimen compared with IV agents. Time in mild to normal levels predicts protection from spontaneous bleeds.

Illustrative clotting agent activity level:
- Normal clotting levels
- Mild hemophilia
- Moderate hemophilia
- Severe hemophilia

SQ CB 2679d/ISU304

Time after dosing:
- SQ: Subcutaneous drug administration
- IV: Intravenous drug administration
CB 2679d/ISU304 Program Conclusions

• CB 2679d is designed as best-in-class high potency recombinant Factor IX product
• 22-fold potency advantage allows subcutaneous administration
• Normal trough factor IX blood levels achieved after 6 daily subcutaneous doses in hemophilia B dogs
• Phase 1/2 subcutaneous trial is ongoing
  – Cohort 3 (150 IU/kg SQ) has been completed
  – Multi-dose SQ data anticipated Q1 2018
• IV CB 2679d has a longer half-life of 27 hours than 21 hours of wt-FIX
• SQ delivery significantly increases half-life 3.6-fold to 98.7 hours
• SQ dosing may provide superior prophylaxis to IV extended half-life agents
• Orphan drug designations have been granted in US and EU