PHASE 1/2 TRIAL OF SINGLE AND MULTIPLE DOSE SUBCUTANEOUSLY ADMINISTERED FACTOR IX VARIANT CB2679D/ISU304: PHARMACOKINETICS AND SAFETY

PB159

Chur Woo You, Howard Levy, Martin L Lee, June Park, Seung-Beom Hong, Suyeong Kim, Ho-Jin Shin, Do Young Kim, Jung Woo Han, Soo-Jeung Kim

Eulji University Hospital, Daejon, Republic of Korea; Catalyst Biosciences, South San Francisco, CA, United States; UCLA Fielding School of Public Health, Biostatistics, Los Angeles, CA, United States; ISU Abxis, Sungnam-Si Gyeonggi-do, Republic of Korea; Pusan National University Hospital, Busan, Republic of Korea; Yonsei University College of Medicine, Severance Hospital, Seoul, Republic of Korea

INTRODUCTION

- CB 2679d / ISU304 was developed using rational protein design to increase resistance to ATIII inhibition and catalytic activity as well as to improve affinity for FVIIIa. Together these improvements resulted in a 22-fold enhanced potency enabling administration by subcutaneous (SQ) injection for routine prophylaxis
- Orphan drug designations have been granted in the US and EU

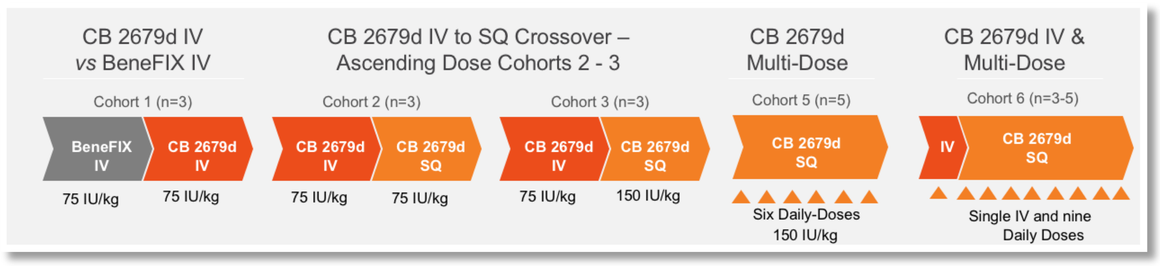
AIMS

- The Phase 1/2 Study ISU304-001 complies with the Declaration of Helsinki, is approved by recognized medical ethics committees, will enroll up to 15 subjects with severe hemophilia B who sign informed consent (NTC03186677) to determine if SQ CB 2679d can provide effective prophylaxis

METHODS

- Cohort 1 received 75 IU/kg intravenous (IV) BeneFIX followed by 75 IU/kg IV CB 2679d
- Cohort 2 and 3 received CB 2679d 73 IU/kg IV followed by 75 or 150 IU/kg SQ
- Cohort 4 was omitted as a greater SQ dose was not needed
- Cohort 5 received 150 IU/kg SQ daily for 6 days
- Cohort 6 was added by amendment and subjects received 75 IU/kg IV followed by 150 IU/kg SQ daily for 9 doses, beginning half an hour later
- Safety measures were performed 2 weeks after dosing
- FIX activity (one-stage clotting assay by ACL TOP 700 and Instrumentation Laboratories reagents), anti-drug antibody (ADA) and neutralizing antibody (nAb) were measured at Haematologic Technologies
- Half-life ($t_{1/2}$) calculation was by Demitasse 2000 that uses an iterative piecewise fitting algorithm based on a robust (M-regression) log-linear model

ISU304-001 TRIAL SCHEMA



RESULTS

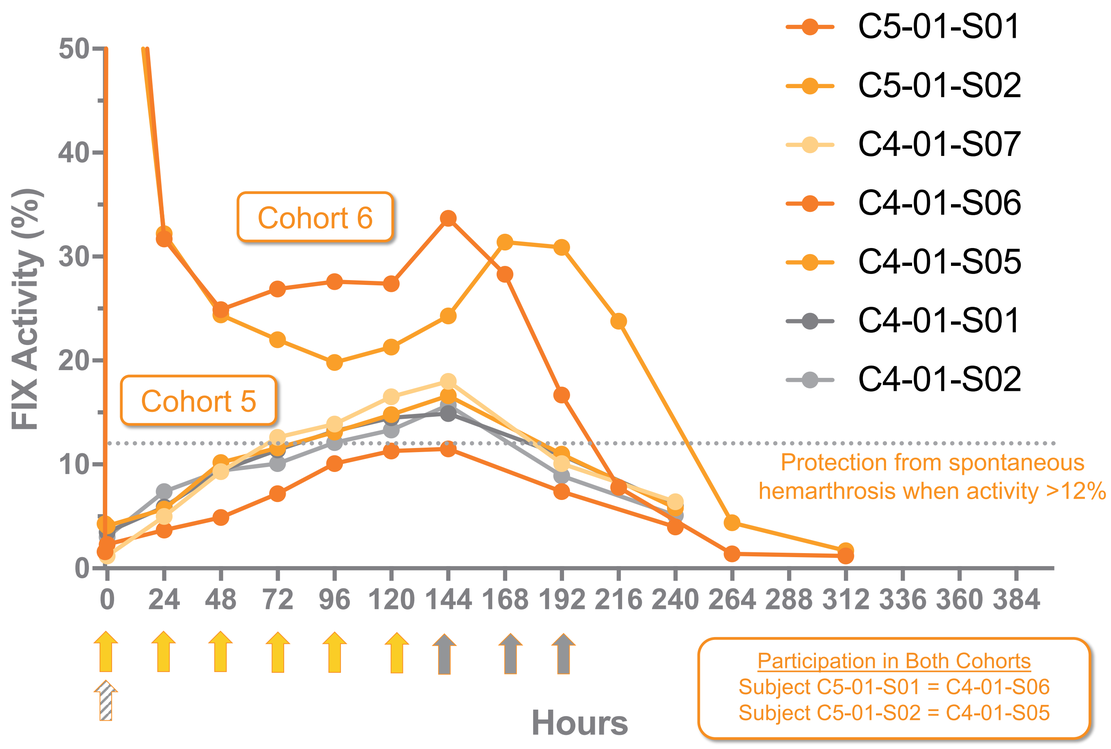
- 11 subjects were dosed, with 5 subjects participating in 2 cohorts
- Cohort 1: IV CB 2679d has 22-fold greater potency, longer $t_{1/2}$ 27.0±2.2 vs 21.0±1.1 hours (p=0.0014) and mean residence time 35.8±2.5 vs 25.1±1.5 hours (p=0.0004) compared with BeneFIX
- Cohort 2 & 3: SQ bioavailability was 19.8±5.2%; $t_{1/2}$ 98.7 hours
- Cohort 5: Median [25-75%] peak activity 24 hours after the 6th dose was 15.7% [14.9-16.6%] and median $t_{1/2}$ 63.2 [60.2-64.0] hours was 2.3-fold longer than IV
- Cohort 6 (N=2 and both participated in Cohort 5): Nadir of 20% after IV injection and 3-5 daily SQ injections; activity levels progressively increased to 31.4 and 33.7% before decreasing due to nAb; $t_{1/2}$ 24.4 and 26.9 hours
- Saturation of the extravascular compartment with an IV load results in substantial increase in activity levels achieved with daily SQ injection beyond mere summation of activity levels of IV+SQ (see figure comparing Cohort 5 and 6 FIX activity)

SAFETY

- No subjects experienced a bleed during the study period
- Four subjects developed ADAs, two were deemed neutralizing (nAb)
  - The nAbs bind to CB 2679d, but not wild-type FIX
- The subjects in Cohort 6 who developed a nAb to ISU304 were cousins
- The nAb in subject C5-01-S01 fell below 1 BU at the follow up visit 8 weeks after the last dose
- The nAb in subject C5-01-S02 was transient and below LLOQ at the follow up visit 8 weeks after the last dose
- Both Cohort 6 subjects returned to their prior prophylaxis treatment (BeneFIX® or RIXUBIS) with continued efficacy

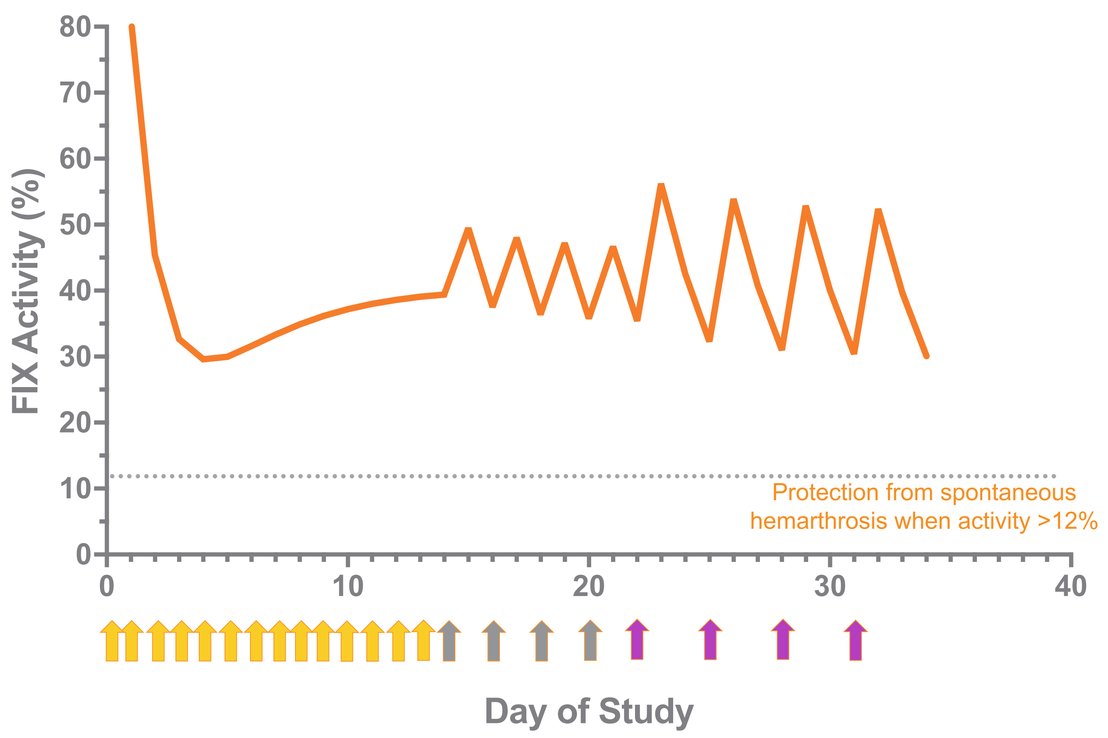
- Mild SQ injection site adverse events that resolved without sequelae were reported in Cohorts 2-5:
  - Pain, Itching, Erythema, Redness, Tenderness, Solidification
  - One subject reported moderate pain, erythema and redness for the initial 2 injections, and mild for the third, and none for subsequent injections
- Cohort 6:
  - C5-01-S01 had inconsistent mild pain, erythema and solidification from some injections that resolved without sequelae
  - C5-01-S02 had severe erythema from one injection, and moderate pain, erythema and solidification after some of the first few injections, that were mild thereafter and resolved without sequelae, except solidification that was continuing

COHORT 5 AND 6 FIX ACTIVITY



- Cohort 5 (n=5): Median [25-75%] peak activity 24 hours after the 6th dose was 15.7% [14.9-16.6%] and median $t_{1/2}$ 63.2 [60.2-64.0] hours (SQ dosing: orange arrows)
- Cohort 6 (n=2): Nadir of 20% after IV injection (IV dose: grey striped arrow) and 3-5 daily SQ injections; activity levels progressively increased to 31.4% and 33.7% before decreasing due to presence of nAb; $t_{1/2}$ 24.4 and 26.9 hours (SQ dosing: orange arrows + additional 3 arrows in grey)
- Cohort 5 subjects are coded as C4-01-SXX and cohort 6 subjects are coded as C5-01-SXX

MODELLING OF FIX ACTIVITY LEVELS FOR PLANNED PHASE 2B STUDY



SQ dosing at arrowheads:

- Single 70 IU/kg IV followed by 140 IU/kg and daily 140 IU/kg SQ for 14 days (orange)
- Alternate day dosing of 280 IU/ kg for 4 injections (grey)
- Every third day dosing 520 IU/kg for 4 injections (purple)

CONCLUSIONS

- Daily SQ dosing of 150 IU/kg for 6 days resulted in median of 15.7% FIX activity
- Daily SQ dosing of 150 IU/kg for 9 days following an IV loading dose resulted in a median >30% FIX activity
- Results suggest that long-term dosing of CB 2679d/ISU304 has the potential to maintain FIX activity in the high-mild hemophilia to normal range
- nAbs detected in 2 subjects, one transient, and do not cross react with wild-type FIX, BeneFIX® or RIXUBIS
- The cause of nAbs is being investigated
- Decreased dose or dosing frequency is feasible once target activity level achieved
- A phase 2b study will explore reduced frequency and longer-term dosing following resolution for the cause of observed nAbs

Scan to download a copy of the poster

Disclosures:

H. Levy is an employee of CATALYST BIOSCIENCES. S-B Hong and S. Kim are employees and J. Park, a former employee, of ISU Abxis.