Phase 2b Trial of Subcutaneous Engineered FIX Dalcinonacog alfa: Pharmacokinetics and Safety

PB0312

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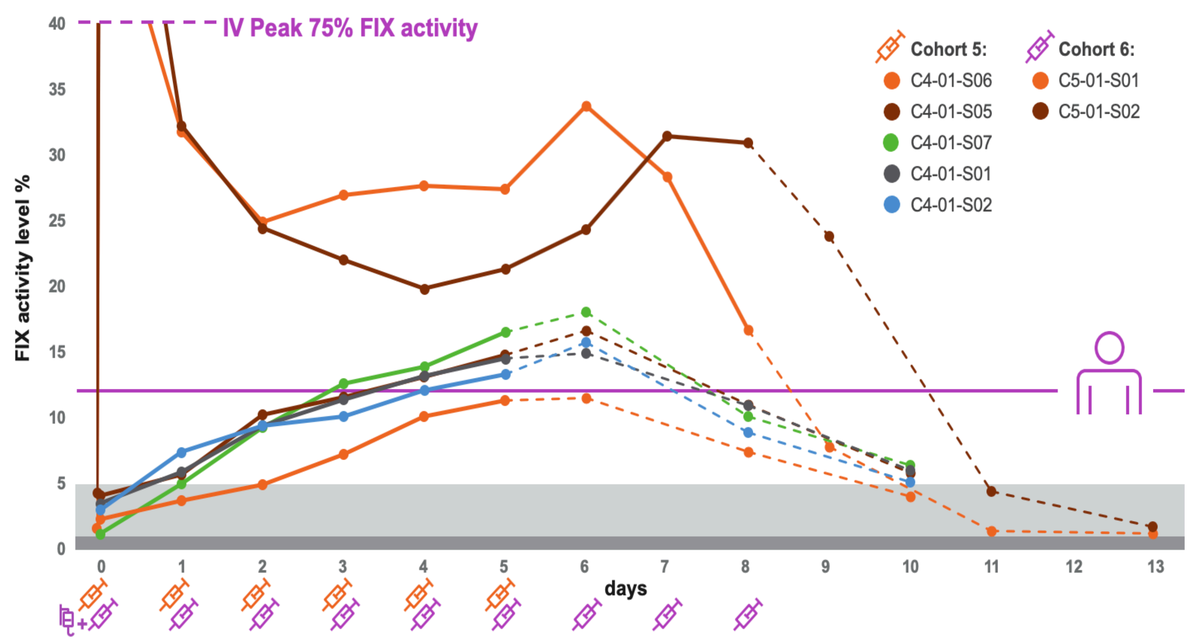
Key Messages

+ Phase 1/2 trial ISU304-001 demonstrated clinical efficacy and tolerability with subcutaneous dosing of dalcinonacog alfa (DalcA) an engineered FIX with 22-fold increased potency over wild-type FIX
+ An *in silico* and *in vitro* risk assessment of DalcA and wild-type FIX showed similar and low predicted immunogenicity (see PB0315)
+ No subjects developed inhibitors to wild-type Factor IX in the Phase 1/2 trial
+ Final data from the Phase 2b DLZ-201 trial is expected in Q4 2019
+ Prophylactic subcutaneous DalcA has the potential to maintain continuous protective levels in Hemophilia B patients to provide effective prophylaxis

Background

+ Clinical experience and quantitative analysis In patients with Hemophilia B show that maintenance of FIX levels above a trough of 10% is associated with a clinically significant reduction in annualized bleeding rate of greater than 80%[1]
+ All currently approved factor IX replacement products require venous access to administer
+ The need for recurrent venous access for lifetime replacement therapy can be a significant technical, social, economic and time-consuming challenge in patients of all ages
+ A reduction in the frequency of intravenous infusions, can result in wide variations in circulating levels of FIX activity increasing bleeding risk
+ DalcA, a novel rFIX variant was developed using a rational design approach, has three point mutations in two loops of the FIX protein
+ Amino acid substitutions prolong the half-life and increase the potency 22-fold, allowing for convenient subcutaneous dosing and effective prophylaxis
+ A dose ranging Phase 1/2 trial (ISU 304-001) demonstrated that daily subcutaneous dosing of 140 IU/kg achieved levels >12% after 6 doses at 140 IU/kg and greater than 30% after 9 daily doses (figure 1)
+ Two related subjects developed neutralizing antibodies to DalcA
+ Neither subject developed an inhibitor to wild-type FIX and both subjects successfully returned to their prior FIX prophylaxis
+ Transient mild to moderate injection site reactions were reported and all resolved without sequelae
+ A comprehensive immunogenicity risk assessment using state-of-the-art *in silico* and *in vitro* analyses showed that DalcA was no more immunogenic than wild-type FIX (see PB0315 for further details)
+ The promising data support the continuing development of subcutaneous DalcA for prophylaxis in Hemophilia B patients with the Phase 2b trial DLZ-201 (figure 2)

Figure 1. Phase 1/2 PK Results Study ISU304-001



Trial Methodology

Figure 2. Phase 2b Trial Schema Study DLZ-201

Enrollment

+ Six adult subjects with severe hemophilia B and without genotype 128 G>A

Treatment

+ Single intravenous dose of 50 IU/kg followed by 28 daily subcutaneous doses of 100 IU/kg

Primary endpoint

+ Number of subjects who achieve steady-state FIX activity level above 12%

Secondary endpoints:

+ Occurrence of antibodies to DalcA and to determine if these are neutralizing
+ Pharmacokinetics of subcutaneous DalcA
+ Pharmacodynamics of subcutaneous DalcA
+ Levels of thrombogenicity markers after subcutaneous DalcA
+ Safety parameters of subcutaneous regimens of DalcA

Trial status

+ The trial is enrolling and dosing is continuing

References

1. Roberts J, Fosser C, Tortorici M, Veldman A, Jacobs I C, Sidhu J. Blood 2016 **128**:1411;