Phase 2B Trial to Evaluate the Safety and Factor IX Levels of a Daily Subcutaneous Prophylaxis Treatment Regimen of Dalcinonacog alfa in Hemophilia B

Johnny Mahlangu, Claude Negrier, Mathilde Fretigny, Frank Del Greco, Linda Neuman, Grant Blouse, Howard Levy

Haemophilia Comprehensive Care Centre, University of Witwatersrand and NHLS, Johannesburg, South Africa; Department of Haematology, Louis Pradel University Hospital, Brom, France; Catalyst Biosciences, South San Francisco, California, USA

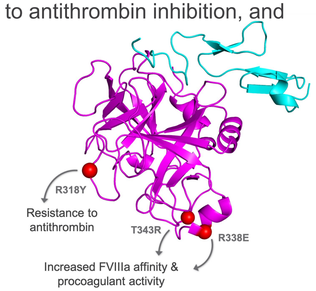
Conclusions

- **Subcutaneous dalcinonacog alfa (DalcA) prophylaxis provides continuously protective levels of Factor IX (FIX)**
- **Subcutaneous administration confers a major advantage over intravenous infusion with the potential for simple and rapid injection, improved quality of life, and reduction in health care burden**

Background

All marketed FIX products are infused intravenously (IV)

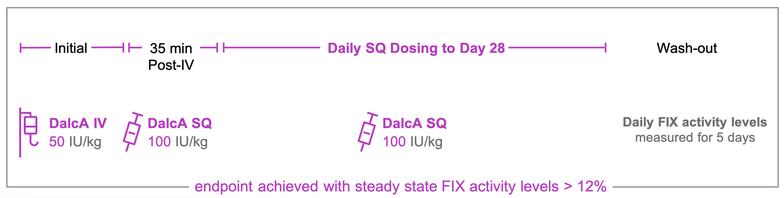
- DalcA is an engineered, novel recombinant FIX variant with 22-fold greater potency conferred by the enhanced functionality of substitutions that increase catalytic activity, increase resistance to antithrombin inhibition, and improve affinity for activated factor VIII
- DalcA is differentiated from marketed IV FIX products by:
  - Simple subcutaneous (SQ) administration
  - Small volume injection
  - Prolonged half-life with SQ injection
  - Potential to maintain continuous protective levels



Study Design

DLZ-201 is a Phase 2b open label study that evaluated the safety, FIX activity levels, and immunogenicity of SQ DalcA when given daily (NTC03995784).

- Male subjects >18 years with severe Hemophilia B were consented and enrolled
- On Day 1, subjects received a single IV dose of DalcA 50 IU/kg, followed by the first of 28 daily SQ doses of 100 IU/kg
- Half-life was calculated from daily FIX activity levels measured after the Day 28 dose



Primary Objective

- To evaluate the dose required to achieve a steady-state of >12% FIX levels

Secondary Objectives

- To determine pharmacokinetics and pharmacodynamics
- To evaluate markers of thrombogenicity
- To evaluate development of antibodies and determine if these are neutralizing
- To monitor and evaluate safety parameters

Study Population

Inclusion Criteria	Exclusion Criteria
Confirmed diagnosis of severe or moderate Hemophilia B	History or family history of FIX inhibitors
Male, age 18 years or older	Positive antibody to wild-type FIX at screening
Agreement to use highly effective birth control	Propeptide mutation genotype 128G>A
	History of other coagulation disorder

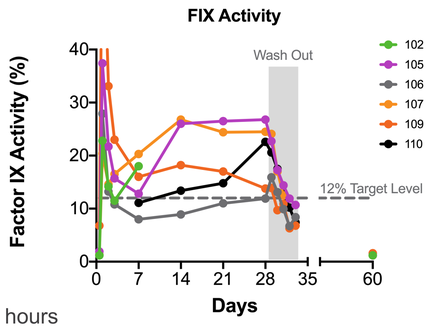
Subject Demographics and Study Parameters

Subject Number	Age (years)	Weight (kg)	Body Mass Index (kg/m^2)	SQ Injection Volume (mL)
102	30	66.8	22.8	0.83
105	36	72.7	26.7	0.9
106	19	57.8	21	0.72
107	40	62	22.2	0.77
109	29	61.8	19.1	0.76
110	53	63.6	19	0.79

Results

Pharmacokinetics and Immunogenicity

- Screened 11 patients with severe Hemophilia B
- Dosed 6 subjects
- Steady-state FIX levels observed after Day 14
- Consistent and stable FIX activity observed
- Mean FIX activity on Day 29: 19.4% (SD: 4.4; range: 13.9% to 24.1%)



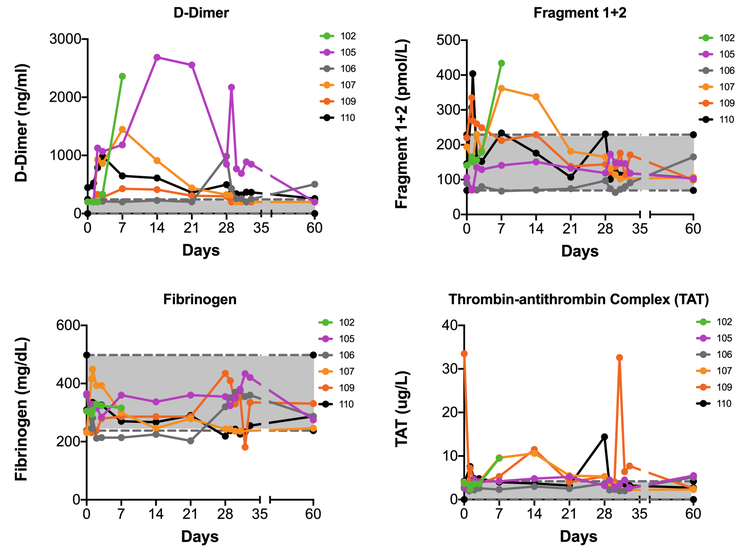
- Range of terminal half-life: 60 to 122 hours
- No breakthrough bleeds during dosing or washout
- No neutralizing ADA detected
- In subject 107, a non-neutralizing ADA to DalcA, with a 4-fold increase over baseline from the below cut point titer at screening, was observed, without clinical or pharmacokinetic effect

Summary of Pharmacokinetics* (n=5)

Parameter	Mean (SD)	Median	Min-Max
Area under curve (IU/dL x day)	126.0 (26.8)	122.2	99.1-170.5
Clearance (dL/day/Kg)	0.82 (0.2)	0.82	0.59-1
Maximum concentration (IU/dL)	20.74 (5.6)	22.6	13.9-26.8
Half-life beta (days)	3.9 (1.1)	4.2	2.5-5.1
Mean residence time (days)	6.2 (1.6)	6.7	3.8-8.1
Volume of distribution at steady state (dL/Kg)	5.0 (1.5)	4.1	3.8-6.7

Coagulation Markers

- Sporadic elevation of D-Dimers that decreased with continued dosing
- Highest D-Dimer levels observed in a subject who reported injection site hematomas
- Insignificant increases in F1+2 that resolved with continued dosing
- Sporadic TAT increases; did not correlate with D-Dimer increases
- No changes in Fibrinogen levels



Safety Profile

- No serious adverse events
- No thrombotic events
- Treatment-emergent adverse events: injection site reactions (ISR)
  - Subject 102 had moderate ISR resulting in premature discontinuation on Day 7
  - One subject had moderate hematomas that resolved without treatment or sequelae
- Some subjects reported mild ISR of pain and/or redness primarily with initial injections

Discussion

- Subcutaneous DalcA prophylaxis provided continuously protective levels of FIX
- In general, DalcA was well tolerated
- Absence of bleeding demonstrated the efficacy of SQ DalcA
- The prolonged half-life and stable high levels of FIX activity have the potential to allow for less frequent dosing

Bibliography

* Lee ML, Schroth P, Bray G, Gomperts ED. The use of robust regression techniques to obtain improved coagulation factor half-life estimates. XVIth Congress of the International Society for Thrombosis and Hemostasis, Florence, Italy, 1997.