CSL Behring Announces Results from Study of Recombinant Single-Chain Factor VIII (rVIII-SingleChain) for Treatment of Hemophilia A

Pharmacokinetic results indicate rVIII-SingleChain may have advantages over multi-chain rFVIII

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CSL Behring today announced that pharmacokinetic results for its novel investigational recombinant coagulation single-chain factor VIII (rVIII-SingleChain) showed improved half-life over octocog alfa (the comparator). It also demonstrated a safety and efficacy profile that supports advancement to late-stage clinical development. The data were presented at the International Society on Thrombosis and Haemostasis (ISTH) congress in Amsterdam.

CSL Behring, in collaboration with its parent company, CSL Limited (ASX:CSL), is developing rVIII-SingleChain for the treatment of hemophilia A as part of the AFFINITY clinical trial program.

"These data are promising and suggest that the recombinant single-chain design for Factor VIII may help address the need for a hemophilia A treatment with a longer half-life," said Professor Ingrid Pabinger-Fasching, M.D., of the Medical University of Vienna, Austria. "A treatment with an improved half-life has the potential to increase the quality of life for those with severe hemophilia A by reducing the number of factor VIII protein infusions required to restore normal blood clotting."

The CSL Behring rVIII-SingleChain design uses a strong, covalent bond shown to improve the stability and half-life of factor VIII (FVIII). The investigational treatment is currently being studied in a Phase III trial.

"As part of our commitment to developing effective therapies to treat hemophilia, we sought to develop a novel recombinant single-chain Factor VIII design that improves the stability and half-life of factor VIII," said Russell Basser, M.D., CSL Senior Vice President, Global Clinical Research & Development. "We are encouraged by these clinical results and very pleased that our investigation of rVIII-SingleChain molecule has progressed to Phase III."

About the Pharmacokinetic Study
The study enrolled 27 participants ≥18 years old with severe hemophilia A. Study participants had pharmacokinetic (PK) measurements performed over 72 hours for both octocog alfa and rVIII-SingleChain after they had received a single infusion of 50 IU/kg body weight of each of the compounds, respectively. In between study drug administration there was a 4-day minimum washout phase. Study objectives comprised the characterization of the PK profile of rVIII-SingleChain, the PK comparison of rVIII-SingleChain to octocog alfa and the characterization of the safety profile of rVIII-SingleChain.

The pharmacokinetics of rVIII-SingleChain and octocog alfa were assessed on the basis of FVIII activity. The following PK parameters were calculated for baseline-corrected FVIII activity using a non-compartmental model analysis with WinNonlin Phoenix (Version 6.3): The area under the plasma activity-time curve from time zero to the last quantifiable concentration (AUClast); the area under the plasma activity-time curve from time zero to infinity (AUCinf); the observed maximum plasma activity after drug administration (Cmax); incremental Recovery (IU/mL/IU/kg) defined as FVIII activity (IU/mL) obtained 30 minutes following infusion; clearance (CL), and terminal elimination half-life (t½).

About the AFFINITY Phase I/III Study
The AFFINITY Phase I/III study is an open-label, multi-center trial that examines the crossover safety, efficacy and pharmacokinetics of recombinant coagulation single-chain factor VIII compared with recombinant human antihemophilic factor VIII (octocog alfa).

In Part 1 of the study, 27 subjects received a single infusion of 50 IU/kg body weight (b.w.) of octocog alfa followed by a single infusion of 50 IU/kg b.w. rVIII-SingleChain. In Parts 2 and 3 of the study, subjects will receive infusions of rVIII-SingleChain to prevent and treat bleeding (if required), at a dose and frequency determined by their study doctor (based on the subject's underlying bleeding phenotype). More information about the study design can be found at www.clinicaltrials.gov.

About rVIII-SingleChain
Recombinant FVIII molecules so far available consist of a heavy and a light chain. Under certain conditions, these chains can dissociate, resulting in the formation of separated, or "dissociated," rFVIII chains that are not hemostatically active. The CSL Behring rVIII-SingleChain uses a strong, covalent bond that connects the light and heavy chains, thereby creating a stable single chain rFVIII.

In-house CSL Behring studies have shown that the molecular integrity of rVIII-SingleChain is significantly increased using the single-chain design, resulting in a homogenous product that is more stable than currently available FVIII products. In addition, in-vitro studies have shown that rVIII-SingleChain demonstrates a strong affinity for von Willebrand factor (VWF), resulting in a faster and more efficient binding to VWF. The FVIII/VWF complex plays an important role in the physiological activity and clearance of FVIII and has been shown to have an influence on the presentation of FVIII to the immune system.

The research leading to the initiation of the studies that CSL Behring is now conducting is the result of collaboration across the CSL Behring research sites in Marburg, Germany, in King of Prussia, USA, and at laboratories operated by CSL Limited in Melbourne, Australia.

About Hemophilia
Hemophilia is an inherited bleeding disorder characterized by prolonged or spontaneous bleeding, especially into the muscles and joints. In nearly all cases, it affects only males. The disease is caused by deficient or defective blood coagulation proteins known as

factor VIII or IX. The most common form of the disease is hemophilia A, or classic hemophilia, in which the clotting factor VIII is either deficient or defective. Hemophilia A affects approximately 1 in 5,000 to 10,000 people. Hemophilia B is characterized by deficient or defective factor IX. Hemophilia B affects approximately 1 in 25,000 to 50,000 people. The recommended treatment for patients who are factor deficient is to treat by replacement factor therapy.

About CSL Behring
CSL Behring is a leader in the plasma protein therapeutics industry. Committed to saving lives and improving the quality of life for people with rare and serious diseases, the company manufactures and markets a range of plasma-derived and recombinant therapies worldwide.

CSL Behring therapies are used around the world to treat coagulation disorders including hemophilia and von Willebrand disease, primary immune deficiencies, hereditary angioedema and inherited respiratory disease, and neurological disorders in certain markets. The company's products are also used in cardiac surgery, organ transplantation, burn treatment and to prevent hemolytic diseases in the newborn. CSL Behring operates one of the world's largest plasma collection networks, CSL Plasma. CSL Behring is a subsidiary of CSL Limited (ASX:CSL), a biopharmaceutical company headquartered in Melbourne, Australia. For more information, visit www.cslbehring.com.

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