Sanofi Showcases Hemophilia Pipeline at ISTH 2019

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New investigational data for Sanofi’s approved and hemophilia pipeline therapies will be presented at the XXVII Congress of the International Society on Thrombosis and Haemostasis (ISTH 2019) taking place July 6-10, 2019 in Melbourne, Australia.

“At ISTH, we look forward to sharing data that shows the breadth of Sanofi's hemophilia pipeline while adding to the growing body of evidence being generated in clinical trials for Eloctate and Alprolix,” said Karin Knobe, MD, PhD, Head of Development, Rare Blood Disorders, Sanofi. “We are focused on advancing transformational therapies that may help address serious unmet needs for people living with hemophilia through our unique patient-centered approach and scientific rigor.”

The data featured across 12 accepted abstracts will include presentations on two of Sanofi’s hemophilia pipeline programs: BIVV001, the first and only investigational von Willebrand-independent factor VIII therapy for people with hemophilia A; and fitusiran, a novel RNAi therapy currently in Phase 3 development with subcutaneous, monthly dosing for people with hemophilia A or B, with and without inhibitors.

“Our data underscore our dedication to raising the standard of care and improving outcomes for people with hemophilia and other rare blood disorders,” said Mouhamed Gueye, PharmD, MBA, Head of Global Medical Affairs, Rare Blood Disorders, Sanofi Genzyme. “While we believe that factor replacement therapy remains the cornerstone of hemophilia care, we are excited about the potential of fitusiran’s investigational RNAi approach to treat all patients with hemophilia, regardless of inhibitor status.”

**BIVV001**

Final results from the completed Phase 1/2a EXTEN-A trial of BIVV001 will be presented in an oral session. This open-label, multicenter study evaluated the safety, tolerability and pharmacokinetics of BIVV001 in both a 25 IU/kg dose and 65 IU/kg dose cohort of subjects aged 18-65 years with severe hemophilia A. Primary endpoints are pharmacokinetics, tolerability, and development of inhibitors. At ISTH, investigators will also present interim results from a BIVV001 Phase I repeat dosing study.

**Fitusiran**

Interim results from the Phase 2 open-label extension (OLE) study will also be shared in an oral presentation highlighting fitusiran’s potential long-term safety and efficacy profile. An investigational RNA interference therapy that targets antithrombin, fitusiran is designed to rebalance hemostasis in patients with hemophilia. A poster evaluating the effectiveness of acute bleed management guidelines with fitusiran will also be presented. The safety and efficacy of fitusiran is being further evaluated in the large global Phase 3 ATLAS program.

**Eloctate® and Alprolix®**

Sanofi, together with its collaboration partner Sobi™, will present for the first time interim results from verITI-8, a prospective, multicenter study of Eloctate® [Antihemophilic Factor (Recombinant), Fc Fusion Protein] for immune tolerance induction (ITI) in children with severe hemophilia A and high titer inhibitors. Treatment of inhibitors remains a significant unmet need in hemophilia and eradication of inhibitors through ITI is currently considered the standard of care. Eloctate is not currently approved for ITI in the United States and Canada.

Additional analyses of long-term studies of Eloctate and Alprolix® [Coagulation Factor IX (Recombinant), Fc Fusion Protein] will also be presented jointly with Sobi, contributing additional data to the growing body of evidence for these therapies.

Data presentations are as follows and all abstracts are available on the ISTH 2019 website.

**Sunday, July 7, 2019**

**Oral Presentations**

- BIVV001: The First Investigational Factor VIII (FVIII) Therapy to Break through the von Willebrand Factor (VWF) Ceiling, with Potential for More Optimal, Extended Protection in Hemophilia A (Abstract # OC 11.1, 10:45 – 12:00 AEST)
- Fitusiran, an RNAi Therapeutic Targeting Antithrombin to Restore Hemostatic Balance in Hemophilia: Interim Analysis from the Open-label Extension Study (Abstract # OC 11.3, 10:45. – 12:00 AEST)

**Poster Presentations**
- Safety, Tolerability, and Pharmacokinetics of Repeat Dosing with BIVV001 in Patients with Severe Hemophilia A: Results of an Interim Analysis from a Phase 1 Study (Abstract # PB0246, 18:30 - 19:30 AEST)

- Fitusiran, an RNAi Therapeutic Targeting Antithrombin to Restore Hemostatic Balance in Hemophilia: Management of Acute Bleeding Events (Abstract # PB0324, 18:30 - 19:30 AEST)

- Real-world Data of Immune Tolerance Induction Using Recombinant Factor VIII Fc Fusion Protein in Hemophilia A Patients with Inhibitors in Japan: Observational Fc Adolescent and Children Treatment Study (FACTs) First Interim Reports (Abstract # PB0277, 18:30 - 19:30 AEST)

- Improved Hemostasis and Joint Health Over Time in a Subset of Patients who Did Not Reach Optimal Hemostatic Control in the First Year of Recombinant Factor VIII Fc Fusion Protein (rFVIIIFc) Therapy (Abstract # PB0234, 18:30 - 19:30 AEST) – Joint with Sobi

- Systemically Administered LV-FVIII and LV-FIX Confers Normal Level of Clotting Factor Expression with no Evidence of Oncogenesis in Non-Human Primates (Abstract # PB0306, 18:30 - 19:30 AEST)

**Monday, July 8, 2019**

*Oral Presentation*

- rFVIII f for First-time Immune Tolerance Induction (ITI) Therapy: Interim Results from the Global, Prospective verITI-8 Study (Abstract # OC 32.1, 10:15 - 11:30 AEST) – Joint with Sobi

*Poster Presentation*

- Long-term Outcomes after Switch from On-demand Treatment to Prophylaxis with rFIXFc: Longitudinal Subgroup Analysis of the B-LONG and B-YOND Study Population (Abstract # PB0693, 18:30 - 19:30 AEST) – Joint with Sobi

**Tuesday, July 9, 2019**

*Oral Presentation*

- The Crystal Structure of Monomeric D'D3 Reveals Principles of VWF Concatemer Formation and its Interaction with FVIII (Abstract # OC 67.2, 14:45 - 16:00 AEST)

*Poster Presentation*

- Long-term Outcomes after Switch from On-demand Treatment to Prophylaxis with rFVIIIFc: Longitudinal Subgroup Analysis of the A-LONG and ASPIRE Study Population (Abstract # PB1410, 18:30 - 19:30 AEST) – Joint with Sobi

**Wednesday, July 10, 2019**

*Oral Presentation*

- Recombinant Factor VIII Fc Fusion Protein Inhibits Inflammatory Osteoclast Formation in vitro (Abstract # OC 75.5, 10:15 - 11:30 AEST)

About BIVV001

BIVV001 (rFVIIIFc-VWF-XTEN) is a novel and investigational recombinant factor VIII therapy that is designed to extend protection from bleeds with prophylaxis dosing of once weekly or longer for people with hemophilia A. BIVV001 builds on the company’s innovative Fc fusion technology by adding a region of von Willebrand factor and XTEN polypeptides to potentially extend its time in circulation. BIVV001 was granted orphan drug designation by the Food and Drug Administration in August 2017. BIVV001 has not been approved by the FDA, EMA or any other regulatory authority for any indication and no conclusions can or should be drawn regarding the safety or effectiveness of this investigational therapeutic.

About Fitusiran

Fitusiran is an investigational, once-monthly, subcutaneously administered RNA interference therapeutic targeting antithrombin (AT) in development for the treatment of hemophilia A and B, with and without inhibitors. Fitusiran also has the potential to be used for rare bleeding disorders. Fitusiran is designed to lower levels of AT with the goal of promoting sufficient thrombin generation to restore hemostasis and prevent bleeding. Fitusiran utilizes Alnylam’s ESC-GalNAc conjugate technology, which enables subcutaneous dosing with increased potency and durability. Fitusiran has not been approved by the FDA, EMA or any other regulatory authority for any indication and no conclusions can or should be drawn regarding the safety or effectiveness of this investigational therapeutic.

About Eloctate®

Eloctate® [Antihemophilic Factor (Recombinant), Fc Fusion Protein] is a recombinant clotting factor therapy developed for hemophilia A using Fc fusion technology to prolong circulation in the body. It is engineered by fusing factor VIII to the Fc portion of immunoglobulin G subclass 1, or IgG1 (a protein commonly found in the body), enabling Eloctate to use a naturally occurring pathway to extend the time the therapy remains in the body. Eloctate is manufactured using a human cell line in an environment free of animal and human additives.

**Indications**

Eloctate® [Antihemophilic factor (recombinant), Fc fusion protein] is a recombinant DNA derived, antihemophilic factor indicated in adults and children with Hemophilia A (congenital Factor VIII deficiency) for: on-demand treatment and control of bleeding episodes, perioperative management of bleeding, and routine prophylaxis to reduce the frequency of bleeding episodes.
Limitation of Use

Eloctate is not indicated for the treatment of von Willebrand disease.

Important Safety Information

CONTRAINDICATIONS: Eloctate is contraindicated in patients who have had life-threatening hypersensitivity reactions to Eloctate or its excipients.

WARNINGS AND PRECAUTIONS: Hypersensitivity reactions have been reported with Eloctate. Allergic-type hypersensitivity reactions, including anaphylaxis, have been reported with Factor VIII replacement products. Immediately discontinue Eloctate and initiate appropriate treatment if hypersensitivity reactions occur. Formation of neutralizing antibodies (inhibitors) to Factor VIII has been reported following administration of Eloctate, including in previously untreated patients. Patients using Eloctate should be monitored for the development of Factor VIII inhibitors. Clotting assays (e.g., one-stage) may be used to confirm that adequate Factor VIII levels have been achieved and maintained.

Adverse Reactions: The most frequently occurring adverse reactions (>0.5% of subjects) in clinical trials were arthralgia, malaise, myalgia, headache, and rash.

Please see enclosed Full Prescribing Information.

Eloctate is approved and marketed by Sanofi in the United States, Japan and Canada. It is also approved in Australia, New Zealand, Brazil, Saudi Arabia, Kuwait and other countries, and Sanofi has marketing rights in these regions. It is also approved as Elocta® in the European Union, Switzerland, Iceland, Liechtenstein, Norway and other countries where it is marketed by Sobi.

About Alprolix®

Alprolix® [Coagulation Factor IX (Recombinant), Fc Fusion Protein] is a recombinant clotting factor therapy developed for hemophilia B using Fc fusion technology to prolong circulation in the body. It is engineered by fusing factor IX to the Fc portion of immunoglobulin G subclass 1, or IgG1 (a protein commonly found in the body), enabling Alprolix to use a naturally occurring pathway to extend the time the therapy remains in the body (half-life). Alprolix is manufactured using a human cell line in an environment free of animal and human additives.

Indications

Alprolix® is a recombinant DNA derived, coagulation Factor IX concentrate indicated in adults and children with hemophilia B for: on-demand treatment and control of bleeding episodes, perioperative management of bleeding, and routine prophylaxis to reduce the frequency of bleeding episodes.

Limitation of Use

Alprolix is not indicated for induction of immune tolerance in patients with hemophilia B.

Important Safety Information

CONTRAINDICATIONS: Alprolix is contraindicated in patients who have a known history of hypersensitivity reactions, including anaphylaxis, to the product or its excipients.

WARNINGS AND PRECAUTIONS: Allergic-type hypersensitivity reactions, including anaphylaxis, are possible with factor replacement therapies, and have been reported with Alprolix. Discontinue use of Alprolix if hypersensitivity symptoms occur, and initiate appropriate treatment.

Formation of neutralizing antibodies (inhibitors) to Factor IX has been reported following administration of Alprolix, including in previously untreated patients. Patients using Alprolix should be monitored for the development of Factor IX inhibitors. Clotting assays (e.g., one-stage) may be used to confirm that adequate Factor IX levels have been achieved and maintained.

The use of Factor IX products has been associated with the development of thromboembolic complications.

Nephrotic syndrome has been reported following attempted immune tolerance induction in hemophilia B patients with Factor IX inhibitors and a history of allergic reactions to Factor IX. The safety and efficacy of using Alprolix for immune tolerance induction have not been established.

ADVERSE REACTIONS: Common adverse reactions (incidence ≥1%) observed in clinical trials were headache, oral paresthesia, and obstructive uropathy.

Please see Full Prescribing Information.

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About Hemophilia A and B

Hemophilia is a rare, genetic disorder in which the ability of a person's blood to clot is impaired. Hemophilia A occurs in about one in 5,000 male births annually, and more rarely in females. Hemophilia B occurs in about one in 25,000 male births annually, and more rarely in females. The World Federation of Hemophilia estimates that approximately 196,700 people are currently diagnosed with hemophilia A and B worldwide.[1]

People with hemophilia A or B experience significant bleeding episodes, some of which can be life-threatening. Prophylactic
infusions of factor VIII or IX can temporarily replace clotting factors that are needed to help control bleeding and prevent new bleeding episodes.[ii] The World Federation of Hemophilia recommends prophylactic factor replacement therapy for patients with hemophilia to help prevent bleeding.[iii]

About the Sanofi and Sobi Collaboration
Sanofi and Sobi collaborate on the development and commercialization of Alprolix and Eloctate®/Elocta® [Antihemophilic Factor (Recombinant), Fc Fusion Protein]. Sanofi has final development and commercialization rights in North America and all other regions in the world excluding the Sobi territory, and has manufacturing responsibility for Eloctate/Elocta and Alprolix. Sobi has final development and commercialization rights in the Sobi territory (essentially Europe, North Africa, Russia and most Middle Eastern markets). In September 2014, Sobi elected to add the rFVIIIc-VWF-XTEN fusion molecule for the potential treatment of hemophilia A to its collaboration agreement.


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