Perioperative Management in Patients with Hemophilia Receiving Fitusiran, an Investigational RNAi Therapeutic Targeting Antithrombin for the Treatment of Hemophilia

Claude Negrier1, Margaret V Ragni2, Penelope Georgiou3, Toshio Lissitchkov4, Huy Van Nguyen5, Kate Madigan6, K John Pasi4
1Centre de Traitement de l'Hémostase, Bron, France; 2University of Pittsburgh, Pittsburgh, PA; 3University Multiprofile Hospital for Active Treatment “Svet Gorilj” and Medical University, Plovdiv, Bulgaria; 4University Hospital for Hematology, Sofia, Bulgaria; 5Amiryen Pharmaceuticals, Cambridge, MA; 6Royal London haemophilia Centre, Barlo and the London School of Medicine and Dentistry, London, United Kingdom

Background

Fitusiran (ALN-AT3SC-002) • SC-administered small interfering RNA (siRNA) targeting antithrombin (AT) o Non-biologic, chemically-synthesized, with targeting ligand to specifically deliver—i.e., AT3SC o harnesses natural siRNA interference (RNAi) mechanism for regulation of plasma AT levels
Therapeutic Hypothesis
• Hemophilia A and B are bleeding disorders characterized by ineffective clot formation due to insufficient thrombin generation • Fitusiran is designed to target AT, with goal of promoting sufficient thrombin generation to restore hemostasis and prevent bleeding • Observation of anorectic bleeding prevention in patients with co-inheritance of thrombophilic traits in hemophilia • Supported by pre-clinical data and emerging Phase 1 and Phase 2 open-label extension clinical results

Fitusiran Phase 1 and Phase 2 Open-Label Extension (OLE) Studies
• Phase 1 study (NCT02269060) included 42 patients with hemophilia A or B with or without inhibitors • 34 patients with hemophilia A or B with or without inhibitors have transitioned to Phase 2 OLE. Study currently on hold, sponsor aims to resume dosing as soon as possible, upon agreement with global regulatory authorities, and with appropriate protocol amendments for enhanced patient safety monitoring (NCT02269060)

Antithrombin Levels and Thrombin Generation in Phase 2 OLE

Results

Objectives & Methods

Perioperative Hemostatic Management in Patients Receiving Fitusiran • Hemophilia-related complications often require surgical intervention • Surgery in hemophilia patients may require management of both hemostasis and potential thrombotic risk • Management of operative procedures while on non-factor therapies like fitusiran is of clinical interest • Purpose of this presentation is to describe details as reported by study investigators on perioperative hemostatic management during surgical procedures in patients with hemophilia receiving fitusiran

Methods

Patient's inhibitor titer was rechecked and measured at the following visit in Phase 2 OLE: Day 11 (patient declined)

Outcomes

• Unremarkable with almost no blood loss and compared to what would have been expected in non-hemophilic patient

Thrombophilic Clotless Lysis: Details on Perioperative Management
• Patient had received fitusiran for 10 months in the Phase 2 OLE study & procedure occurred 18 days after procedure
• Patient's inhibitor titer increased; therapy changed to BPA
• No supplemental FVIII needed pre & post procedure
• Outcome: "Procedure went well with minimal blood loss"

Molar Tooth Extraction: Details on Perioperative Management
• Patient had received fitusiran for 10 months in the Phase 2 OLE study & procedure occurred 18 days after procedure
• Patient's inhibitor titer increased; therapy changed to BPA
• No supplemental FVIII needed pre & post procedure
• Outcome: "Procedure went well with minimal blood loss"

Day Medication Name Dose(s)
Day 0 FVIII 51 IU/kg X 1
Day 0 FVIII 32 IU/kg X 2
Day 1-4 FVIII 32 IU/kg Twice Daily
Day 5-6 FVIII 42 IU/kg Twice Daily
Day 7 FVIII 42 IU/kg
Day 7 aPCC 74 U/kg
Day 8-9 aPCC 74 U/kg Three Times Daily
Day 10 aPCC 74 U/kg
Day 10 FVIII 93 mcg/kg X 1
Day 11 FVIII 93 mcg/kg X 1
Day 12 FVIII 93 mcg/kg X 1

Outcomes

• Patient's inhibitor titer increased; therapy changed to BPA
• No supplemental FVIII needed pre & post procedure
• Outcome: "Procedure went well with minimal blood loss"

Acknowledgements & Disclosures

ABR, annualised bleeding rate; APOC, activated protein C complex concentrations; AT, antithrombin; BPA, bypassing agent; CVST, cerebral venous sinus thrombosis; FVIII, Factor VIII; HA, Hemophilia A; HB, Hemophilia B; INR, international normalized ratio; op, operative; rFVIIa, recombinant Factor VIIa

References