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

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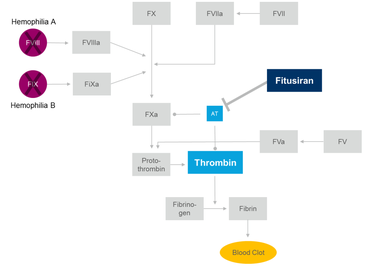
Background

Fitusiran (ALN-AT3)

- SC-administered small interfering RNA (siRNA) targeting antithrombin (AT)
  - Non-biologic, chemically-synthesized, with targeting ligand to specifically deliver to liver—site of AT synthesis
  - Harnesses natural RNA interference (RNAi) mechanism for regulation of plasma AT levels

Therapeutic Hypothesis

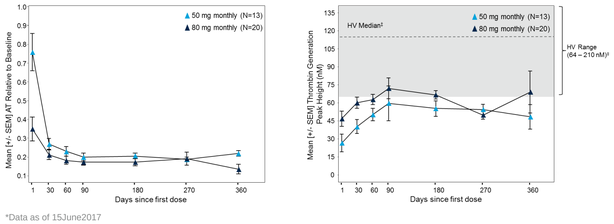
- Hemophilia A and B are bleeding disorders characterized by ineffective clot formation due to insufficient thrombin generation
- Fitusiran is designed to lower AT, with goal of promoting sufficient thrombin generation to restore hemostasis and prevent bleeding
  - Observation of ameliorated bleeding phenotype in patients with co-inheritance of thrombophilic traits in hemophilia[1-4]
  - Supported by pre-clinical data[5] and emerging Phase 1 and Phase 2 open-label extension clinical results[6-8]



Fitusiran Phase 1 and Phase 2 Open-Label Extension (OLE) Studies

- Phase 1 study (NCT02035605) 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[8]. 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 (NCT02554773)
- Monthly dosing with 50 mg or 80 mg of fitusiran resulted in consistent AT lowering and increased TG*
- 4 patients required 5 surgical procedures while on study, when AT lowering was in effect

Antithrombin Levels and Thrombin Generation in Phase 2 OLE*



*Data as of 15June2017

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

- Data on perioperative hemostatic treatment were collected for patients undergoing surgical procedures during the study while AT was lowered
- All cases were managed at discretion of respective investigator
- Assessment of hemostatic response was provided by investigators, although no formal reporting was required per protocol

Results

Surgical Procedures in Patients Receiving Fitusiran

Patient Demographics	AT Level†; ABR‡	Dose, Total Time on Fitusiran^; Timing of Surgery	Procedure	Perioperative Hemostatic Treatment	Outcome#
30 year-old Hemophilia A, with inhibitors; Pre-study ABR: 20	AT=19%; ABR: 0	80 mg, approximately 9 months; procedure occurred 11 days after 2nd fitusiran dose in Phase 1	Pre-Molar Tooth Extraction	**None**	"Unremarkable with almost no blood loss and considered comparable to a non-hemophilia patient"
27 year-old* Hemophilia A, No inhibitor; Pre-study ABR: 0	AT=15%; ABR: 2	50 mg, approximately 17 months; procedure occurred 26 days after 4th fitusiran dose in Phase 2 OLE	Nasal septoplasty	**Reduced dosing**	Hemostatic response excellent per ISTH scale
53 year-old Hemophilia A, No Inhibitor; Pre-study ABR: 0	AT=15.7%; ABR: 2	80 mg, approximately 16 months; procedure occurred 18 days after 10th fitusiran dose in Phase 2 OLE	Molar tooth extraction x 2	**None** (patient declined)	"Procedure went well with minimal blood loss"
36 year-old Hemophilia A, with inhibitors; Pre-study ABR: 20	AT=10.7%; ABR: 0	80 mg, approximately 10 months; procedures occurred 40 days after 3rd fitusiran dose in Phase 1	Thoracotomy and partial lung segmentectomy	**Standard dosing**	"Perioperative blood loss similar to what would have been expected in non-hemophiliac patient"
27 year-old* Hemophilia A, No inhibitor; Pre-study ABR: 0	AT=13.3%; ABR: 2	50 mg, approximately 17 months; procedure occurred 38 days after 10th fitusiran dose in Phase 2 OLE	Endoscopic cholecystectomy	**Reduced dosing**	No procedure-related bleeds or AE (hemostasis rating not provided)

*Same patient underwent two separate procedures
†Last measurement available prior to procedure
‡ABR during entire Observation Period defined as day 29 of treatment to earlier of data transfer or 56 days after last dose; as of Data transfer of 15June2017
^Total time on fitusiran as of 15June2017 combined from both studies ALN-AT3SC-001 and ALN-AT3SC-002
#As reported by investigator; no formal reporting per protocol

Pre-Molar Tooth Extraction: Details on Perioperative Management

- Patient had received fitusiran for 2 months in Phase 1, Part D; procedure occurred 11 days after 2nd dose of fitusiran
- No prophylaxis given before or during procedure
- Patient noticed bleeding 3-4 hours later at home; administered first dose of rFVIIa
- Third dose administered as prophylaxis so patient could go to work

Day	Medication Name	Dose(s)
Day 0	rFVIIa	95 mcg/kg X 1
Day 1	rFVIIa	95 mcg/kg X 2

Outcome: "Unremarkable with almost no blood loss and considered comparable to a non-hemophilia patient"

Nasal Septoplasty: Details on Perioperative Management

- Patient had received fitusiran for 4 months in the Phase 2 OLE; procedure occurred 26 days after 4th dose in Phase 2 OLE

Day	Medication Name	Dose(s)
Day 0 (Pre-op)	FVIII	28 IU/kg X 1
Day 0 (Post-op)	FVIII	14 IU/kg X 1
Day 2	FVIII	14 IU/kg X 1
Day 3	FVIII	14 IU/kg X 1
Day 7	FVIII	14 IU/kg X 1

- Surgical procedure completed with no reports of complications or blood loss greater than expected
- First post-op FVIII dose given 12 hours after procedure
- Patient seen by investigator on post-op days 3 and 7; reported no bleeding on either day; patient was administered FVIII prophylactically
- **Outcome: Hemostatic response excellent per ISTH scale**

Molar Tooth (X 2) Extraction: Details on Perioperative Management

- Patient had received fitusiran for 10 months in the Phase 2 OLE; procedure occurred 18 days after 10th dose in Phase 2 OLE
- Investigator recommended use of aminocaproic acid and tranexamic acid for hemostatic management; patient refused
- Patient received penicillin VK, lidocaine 2%, articaine 4%
- Patient reported no bleeding
- No supplemental FVIII needed pre or post procedure

Outcome: "Procedure went well with minimal blood loss"

Thoracotomy and Partial Lung Segmentectomy: Details on Perioperative Management

- Patient had received fitusiran for 3 months in Phase 1, Part D; procedure occurred 40 days after 3rd dose of fitusiran
- No prophylaxis given pre-procedure
- Inhibitor titer low at screening (0.33 NBU); initiated treatment with FVIII
- Post-operative inhibitor titer increased; therapy changed to BPA

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

† Patient's inhibitor titer was rechecked and investigator reported titer showing an increase in inhibitors
‡ Patient was switched to rFVIIa from aPCC due to supply issue

- Patient admitted for inpatient management for 14 days around the procedure
- **Outcome: "Perioperative blood loss similar to what would have been expected in non-hemophiliac patient"**

Results, continued

Endoscopic Cholecystectomy: Details on Perioperative Management

- Patient had received fitusiran for 10 months in the Phase 2 OLE; procedure occurred 38 days after 10th dose in Phase 2 OLE

Day	Medication Name	Dose(s)
Day 0 (Pre-op)	FVIII	28 IU/kg X 1
Day 0 (Post-op)	FVIII	14 IU/kg X 2
Day 1	FVIII	14 IU/kg X 2
Day 2	FVIII	14 IU/kg X 2
Day 3	FVIII	14 IU/kg X 1
Day 4	FVIII	14 IU/kg X 1
Day 5	FVIII	14 IU/kg X 1

- Patient admitted for in-patient management for 5 days following the procedure

Outcome: No procedure-related bleeding or adverse events reported

Perioperative Management of Surgical Procedures in Patients Receiving Fitusiran

- 4 major surgical procedures in clinical trials of fitusiran when AT lowering was ≥ 75%
  - 1 minor dental procedure when AT lowering was ≥ 75%
- Amount and duration of perioperative hemostatic treatment coverage varied depending on type of procedure
  - 3 cases managed with reduced or standard supplemental factor or bypassing agent; 2 received no additional hemostatic agent
- No thromboprophylaxis used in any procedure
- All procedures rated by respective investigators as resulting in minimal blood loss or blood loss similar to patients without hemophilia

Conclusions & Next Steps

Successful perioperative hemostatic management of patients in context of AT lowering with fitusiran has been observed

These cases suggest that hemostatic capacity conferred by fitusiran may allow reduced dosing of factor or BPA for perioperative management

Number of surgical procedures is limited and additional data are needed

Perioperative treatment, response, and biomarkers pre- and post-op, pre- and post-dose of factor or BPA will also be collected formally in Phase 3

Acknowledgements & Disclosures

ABR, annualized bleeding rate; aPCC, activated prothrombin complex concentrate; AT, antithrombin; BPA, bypassing agent; CVST, cerebral venous sinus thrombosis; FVIII, Factor VIII; HA, Hemophilia A; HB, Hemophilia B; NBU, Nijmegen Bethesda unit; op, operative; rFVIIa, recombinant Factor VIIa

Acknowledgements: Thank you to the patients, investigators & study staff who participated in these studies

Disclosures: Fitusiran is an investigational RNAi therapeutic targeting antithrombin. In September 2017, Alnylam temporarily suspended dosing in studies of fitusiran following the observation of a fatal thrombotic serious adverse event in the Phase 2 OLE study. All ongoing studies were placed on clinical hold. Alnylam, study investigators and the FDA have now aligned on safety measures and a risk management strategy for further advancement of fitusiran. Following regulatory and institutional review and approval of amended study protocols and other clinical materials implementing these measures, Alnylam intends to resume fitusiran studies as soon as possible

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References: [1]Kurnik K, et al. *Haematologica*. 92:982-985 (2007); [2]Ettingshausen E, et al. *Thromb Haemost*. 85:218-220 (2001); [3]Negrier C, et al. *Blood*. 81:690-695 (1993); [4]Shetty S, et al. *Br J Haematol.* 138:541-544 (2007); [5]Seghal A, et al. *Nat Med*. 21:492-497 (2015); [6]Pasi KJ, et al. *ASH.* (2016); [7]Pasi KJ, et al. *N Engl J Med*. 377(9):819-828 (2017); [8]Pasi KJ, et al. *Res Pract Thromb Haemost*. 2017;1(Suppl. 1):25.