New Clinical Results with Fitusiran

2017 International Society on Thrombosis and Haemostasis (ISTH) Congress
July 10, 2017

Alnylam® PHARMACEUTICALS

Fitusiran is an investigational medicine. Its safety and efficacy have not been established by any health authorities.

Agenda

Welcome

- Christine Lindenboom
  Vice President, Investor Relations & Corporate Communications

Introduction

- John Maraganore, Ph.D.
  Chief Executive Officer

Fitusiran Clinical Results

- Pushkal Garg, M.D.
  Chief Medical Officer

Q&A Session

Alnylam Forward Looking Statements

This presentation contains forward-looking statements, within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. There are a number of important factors that could cause actual results to differ materially from the results anticipated by these forward-looking statements. These important factors include our ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of our product candidates; pre-clinical and clinical results for our product candidates; actions or advice of regulatory agencies; delays, interruptions or failures in the manufacture and supply of our product candidates; our ability to obtain, maintain and protect intellectual property, enforce our intellectual property rights and defend our patent portfolio; our ability to obtain and maintain regulatory approval, pricing and reimbursement for products; our progress in establishing a commercial and ex-United States infrastructure; competition from others using similar technology and developing products for similar uses; our ability to manage our growth and operating expenses, obtain additional funding to support our business activities and establish and maintain business alliances; the outcome of litigation; and the risk of government investigations; as well as those risks more fully discussed in our most recent quarterly report on Form 10-Q under the caption “Risk Factors.” If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements.

John Maraganore, Ph.D.
Chief Executive Officer

Introduction

Pushkal Garg, M.D.
Chief Medical Officer

Fitusiran Clinical Results

Fitusiran

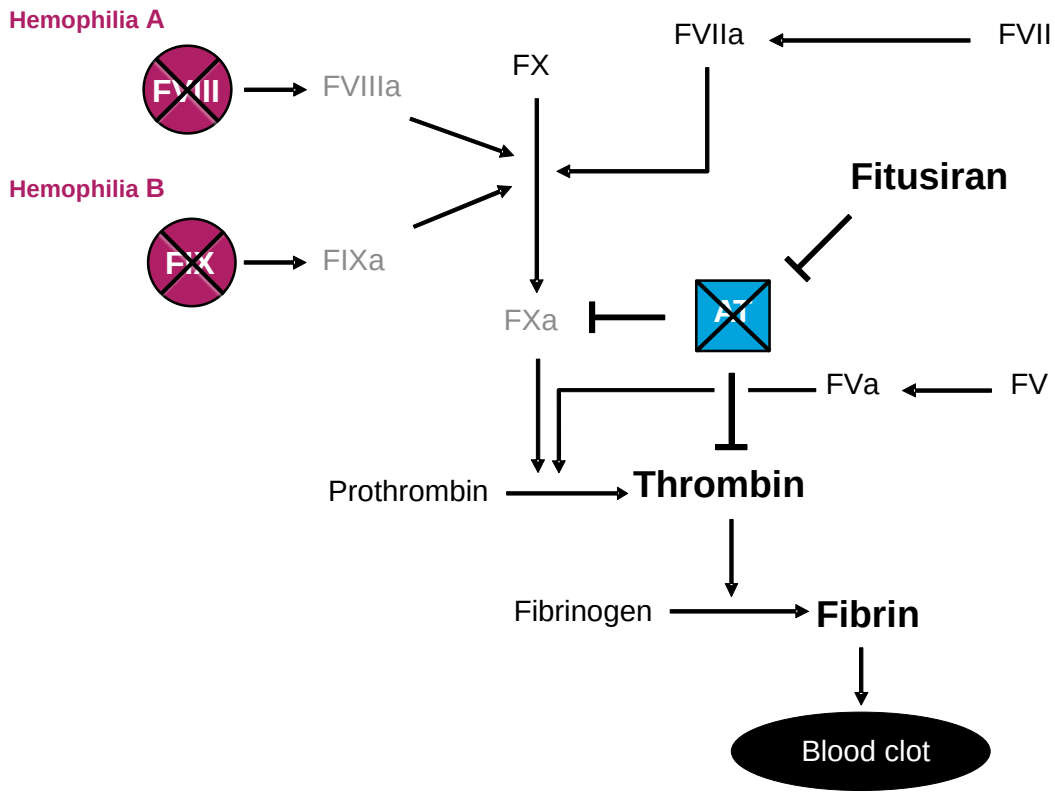
Investigational RNAi Therapeutic for Treatment of Hemophilia

Fitusiran (ALN-AT3)

- SC-administered small interfering RNA (siRNA) therapeutic 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 clinical results[6-7]



The clinical significance of fitusiran's mechanism of action is under investigation.

[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. *Blood*. 2016, 128: 1397; [7]Pasi KJ, et al. *N Engl J Med. 2017; epub ahead of print.*

Fitusiran is an investigational medicine. Its safety and efficacy have not been established by any health authorities.

Fitusiran Phase 2 Open-Label Extension (OLE)

Study Design & Patient Disposition

Patients previously dosed in Phase 1* study eligible to roll over onto Phase 2 OLE^ study

Phase 1, Part B (N=12 patients with HA or HB)

15, 45, 75 mcg/kg weekly x 3 SC

Phase 1, Part C (N=18 patients with HA or HB)†

225, 450, 900, 1800 mcg/kg, or 80 mg monthly x 3 SC

Phase 1, Part D (N=16 patients with HA or HB with inhibitors)

50, 80 mg monthly x 3 SC

Phase 2 OLE‡ (n= 33)

50 mg monthly SC

80 mg monthly SC

- Individual patient dose adjustment may be allowed (per SRC)
- Days between doses in Phase 1 and Phase 2 OLE ranged from 30 (no interruption in dosing) to 461

OLE, open-label extension; SC, subcutaneous

*ClinicalTrials.gov Identifier:NCT02035605; EudraCT: 2013-003135-29; Pasi KJ, et al. *N Engl J Med. 2017; epub ahead of print.*; Pasi KJ et al. *Blood*. 2016, 128: 1397

^ClinicalTrials.gov Identifier: NCT02554773; EudraCT: 2015-001395-21

†5 patients participating in Part C previously participated in Part B

‡3 patients started Phase 2 OLE at their original Phase 1 dose; later they were converted to 50 mg or 80 mg

Fitusiran is an investigational medicine. Its safety and efficacy have not been established by any health authorities.

Interim Fitusiran Phase 2 Open-Label Extension (OLE) Study Results*

Patient Demographics & Exposure

	Patients without Inhibitors		Patients with Inhibitors	
	50 mg† N=10	80 mg† N=9	50 mg† N=3	80 mg† N=11
Age, years; mean (range)	36 (19 – 61)	40 (24 – 58)	31 (22 – 36)	34 (21 – 41)
Weight, kg; mean (range)	78 (58 – 94)	73 (58 – 80)	82 (70 – 100)	72 (52 – 108)
Hemophilia A Hemophilia B	7 3	7 2	3 -	10 1
Severe Moderate	9 1	7 2	3 -	11 -
Positive Medical history for hepatitis C	8	8	2	9
Exposure, months; median (range)	13 (5 – 20)	14 (3 – 18)	11 (5 – 12)	6 (0 – 12)

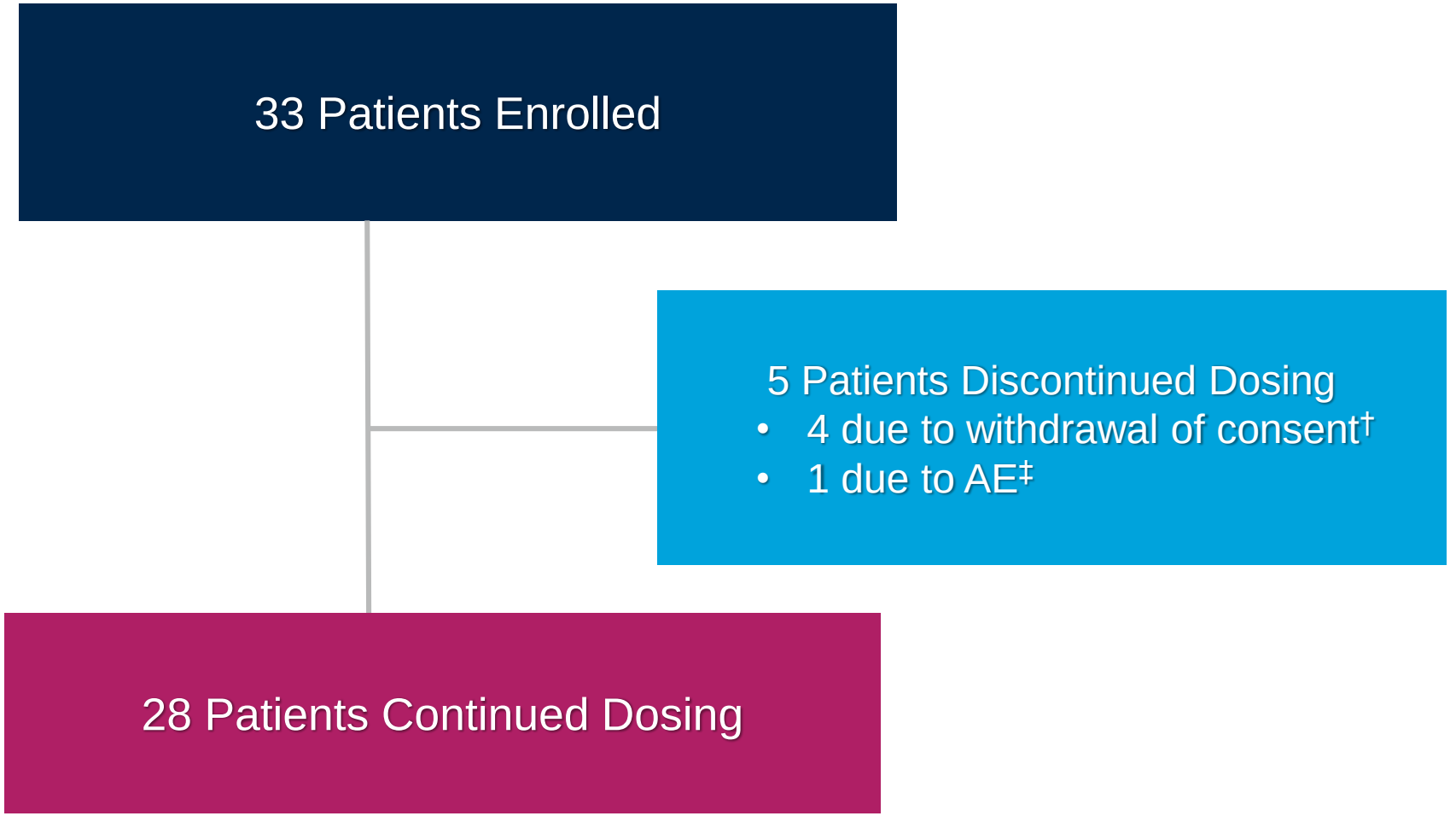
Maximum of 20 months (median 11 months) of fitusiran dosing in Phase 2 OLE

- Total of 359 months of patient exposure to fitusiran

*Data transfer 15June2017
†Doses denote current dose
Fitusiran is an investigational medicine. Its safety and efficacy have not been established by any health authorities.

Interim Fitusiran Phase 2 Open-Label Extension (OLE) Study Results*

Patient Disposition



*Data transfer 15June2017
† Withdrawal of consent due to: incarceration (1), to receive DAA therapy for HCV (1), following seizure (1), following hypertension (1)
‡ Discontinuation due to AE: AST and ALT elevation in patient with chronic HCV infection
Fitusiran is an investigational medicine. Its safety and efficacy have not been established by any health authorities.

Interim Fitusiran Phase 2 Open-Label Extension (OLE) Study Results*

Safety/Tolerability

- 6 patients reported SAEs†
  - 2 with SAEs considered possibly related to study drug
    - ALT and AST elevation in patient with chronic HCV infection; led to discontinuation
    - Seizure with confusion in patient with history of seizure disorder
- 70% of patients reported an AE
  - Majority of AEs were mild or moderate in severity and unrelated to study drug
  - Non-laboratory AEs reported in >2 patients: injection site reactions (ISRs) 6/33 (18%), abdominal pain 3/33 (9%), diarrhea 3/33 (9%) headache 3/33 (9%)
  - ISRs all mild and transient
- ALT increases >3x ULN observed in 11 patients (all confirmed HCV antibody positive)
  - All asymptomatic; no elevations of bilirubin >2x ULN
  - All cases are resolved (10) or resolving (1)
    - 8 without dose interruption
- No thromboembolic events
  - No clinical or laboratory evidence of pathologic clot formation
  - All bleed events successfully managed with replacement factor or bypassing agent
- No instances of drug-induced anti-drug antibody formation

*Data transfer 15June2017

†5 Patients with unrelated SAEs: acute gastroenteritis and cholecystitis (1), gastroesophageal reflux disease, asthma and infective exacerbation of asthma (1), COPD (1), Duodenal ulcers (1), lab test (1; same patient as ALT and AST SAE above)

Fitusiran is an investigational medicine. Its safety and efficacy have not been established by any health authorities.

Context for Transaminase Elevations

Fitusiran is a liver-directed therapy and low frequency of ALT changes with other molecules in our platform have been reported

However, chronic HCV infection has been associated with elevated ALT and thus represents an important confounder

Transaminase elevations have been observed in populations with chronic HCV infection

- In a study of 280 asymptomatic blood donors with chronic HCV infection†
  - 17% had normal ALT levels
  - 45% had ALT elevations >1-2x ULN
  - 16% had ALT elevations >2-5x ULN
  - 22% had ALT elevations >5x ULN
- In a 2015 report of ledipasvir-sofosbuvir treatment for chronic HCV infection‡, LFT monitoring of 77 patients treated with placebo over 12 weeks showed
  - 74% with normal ALT levels
  - 3% with ALT elevations >1-3x ULN
  - 14% with ALT elevations >3-5x ULN
  - 9% with ALT elevations >5x ULN

Phase 3 studies will exclude patients with chronic HCV infection; such patients may be enrolled after curative treatment

†Alter HJ, Conry-Cantilena C, Melpolder J, et al. Hepatology 1997;26:29S-33S.
‡Bourlière M, Bronowicki JP, de Ledinghen V, et al. Lancet Infect Dis 2015;15:397-404. (see Supplementary Table 7)
Fitusiran is an investigational medicine. Its safety and efficacy have not been established by any health authorities.

Interim Fitusiran Phase 2 Open-Label Extension (OLE) Study Results*

Safety/Tolerability

- 6 patients reported SAEs†
  - 2 with SAEs considered possibly related to study drug
    - ALT and AST elevation in patient with chronic HCV infection; led to discontinuation
    - Seizure with confusion in patient with history of seizure disorder
- 70% of patients reported an AE
  - Majority of AEs were mild or moderate in severity and unrelated to study drug
  - Non-laboratory AEs reported in >2 patients: injection site reactions (ISRs) 6/33 (18%), abdominal pain 3/33 (9%), diarrhea 3/33 (9%) headache 3/33 (9%)
  - ISRs all mild and transient
- ALT increases >3x ULN observed in 11 patients (all confirmed HCV antibody positive)
  - All asymptomatic; no elevations of bilirubin >2x ULN
  - All cases are resolved (10) or resolving (1)
    - 8 without dose interruption
- No thromboembolic events
  - No clinical or laboratory evidence of pathologic clot formation
  - All bleed events successfully managed with replacement factor or bypassing agent
- No instances of drug-induced anti-drug antibody formation

*Data transfer 15June2017

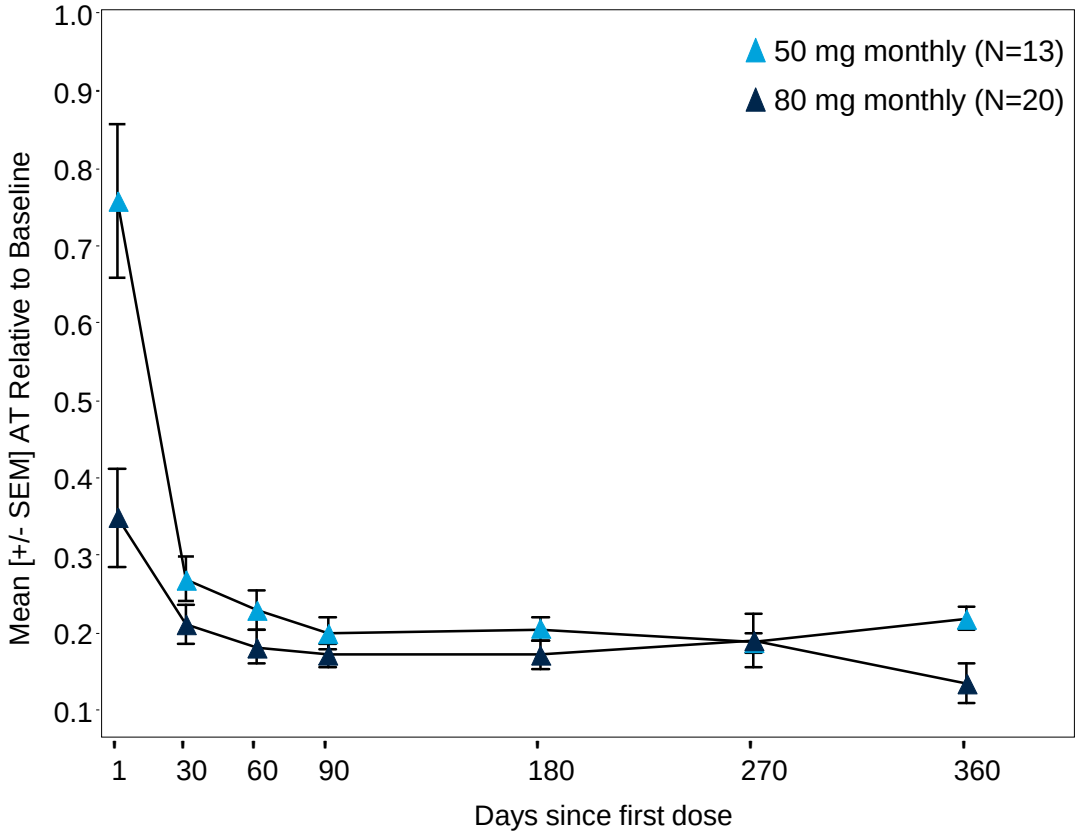
†5 Patients with unrelated SAEs: acute gastroenteritis and cholecystitis (1), gastroesophageal reflux disease, asthma and infective exacerbation of asthma (1), COPD (1), Duodenal ulcers (1), lab test (1; same patient as ALT and AST SAE above)

Fitusiran is an investigational medicine. Its safety and efficacy have not been established by any health authorities.

Interim Fitusiran Phase 2 Open-Label Extension (OLE) Study Results*

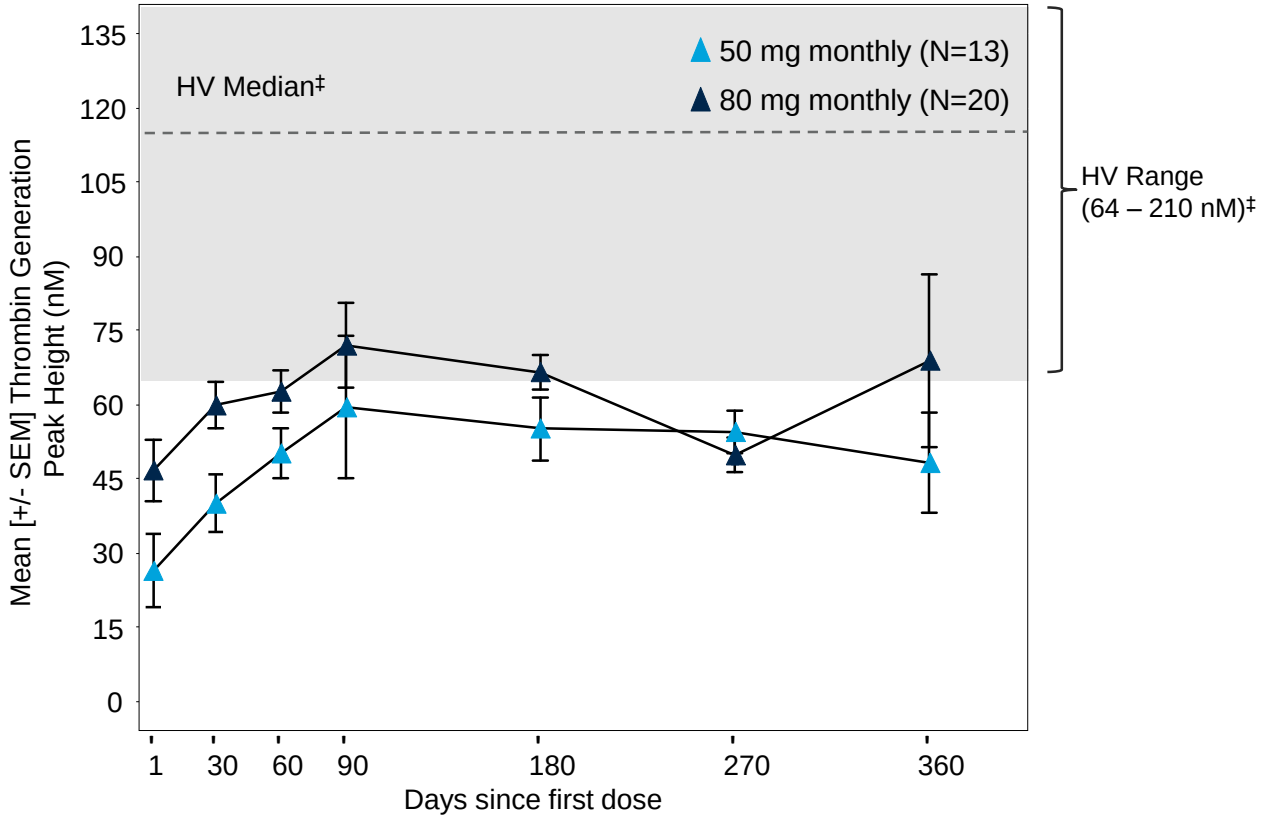
Antithrombin Levels and Thrombin Generation

Antithrombin Levels



Days since first dose:	1	30	60	90	180	270	360
▲ N†=	13	13	13	13	10	10	6
▲ N†=	19	19	17	16	12	9	4

Thrombin Generation



Days since first dose:	1	30	60	90	180	270	360
▲ N†=	12	10	11	11	9	8	5
▲ N†=	17	17	15	13	12	7	4

*Data transfer 15June2017

OLE, open-label extension; AT, antithrombin; SEM, standard error of the mean; HV, Healthy Volunteer

†Only patients with >56 days in OLE included in analysis; patients excluded from TG analysis if theyadministered factor or bypassing agent within 48 hours

‡Healthy volunteers with AT lowering <25% (Pasi KJ, et al. *N Engl J Med. 2017; epub ahead of print.*)

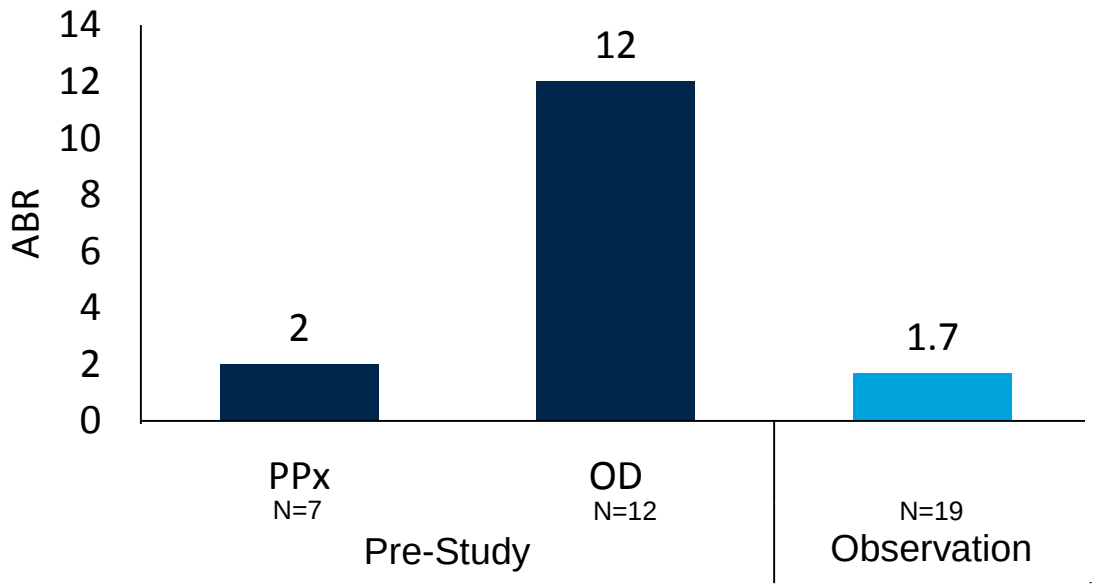
Interim Fitusiran Phase 2 Open-Label Extension (OLE) Study Results*

Exploratory Analysis of Bleed Events

Summary of Median ABRs in all Patients

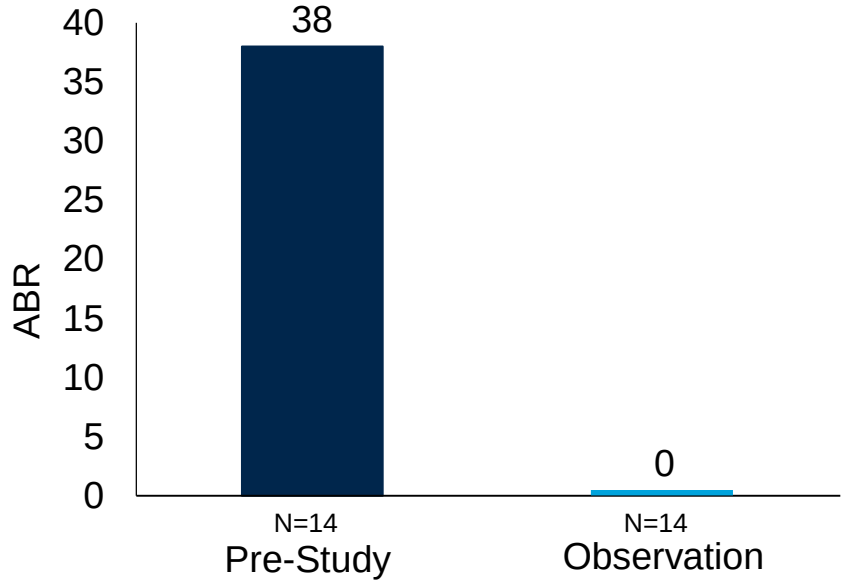
- 48% (16/33) of patients bleed free during observation period†
  - Overall median ABR in observation period = 1 (IQR: 0-3)
- 67% (22/33) of patients reported no spontaneous bleeds
  - Overall median AsBR in observation period = 0 (IQR: 0-2)

Summary of Median ABRs in Patients without Inhibitors



- Median duration in observation period: 13 months [range: 2 –19]
- Mean AT activity in observation period (relative to baseline): 22%

Summary of Median ABRs in Patients with Inhibitors



- Median duration in observation period: 6 months [range: 1 –11]
- Mean AT activity in observation period (relative to baseline): 18%

*Data transfer 15June2017
†Observation period defined as day 29 of treatment to earlier of data transfer or 56 days after last dose
ABR, annualized bleeding rate; AsBR, annualized spontaneous bleeding rate; PPx, prophylaxis; OD, on demand

Interim Fitusiran Phase 2 Open-Label Extension (OLE) Study Results*

Characteristics of Bleed Events During Treatment with Fitusiran

Bleed events evaluated in patients when antithrombin lowering was >75%

Characteristic	Patients without Inhibitors (n=19)	Patients with Inhibitors (n=14)
Total bleeds, n	25	68
Patients experiencing bleed(s), n	10	5
Causality		
Spontaneous	8	50
Traumatic	16	18
Other†	1	-
Location		
Joint	19	54
Muscle	1	14
Internal	2	-
Skin/mucosa	3	-

*Data transfer 15June2017
†Patient took factor treatment for abdominal pain
Fitusiran is an investigational medicine. Its safety and efficacy have not been established by any health authorities.

Interim Fitusiran Phase 2 Open-Label Extension (OLE) Study Results*

Management of Bleed Events with Factor Replacement in Patients without Inhibitors*

Treatment of Bleeds	FVIII (n=8)	FIX (n=2)
Recommendation from Protocol	No more than 30 IU/kg; re-dose after 24 hours if symptoms not relieved	No more than 50 IU/kg; re-dose after 24 hours if symptoms not relieved
Total bleeds, n	18	7
Total administrations, n	20	27
Mean administrations per bleed, (median; range)	1.1 (1; 1-2)	3.9 (3; 1-8)
Mean dose per injection	17 (5 – 31) IU/kg	18 (9 – 27) IU/kg
% using less than or same amount of factor per bleed as prior to fitusiran	100%	100%
Mean total amount of factor per bleed	19 IU/kg	70 IU/kg

*Data transfer 15June2017
FVIII, factor VIII; FIX, factor IX
Replacement Factor Products Used: Advate, Aimafix, Benefix, Eloctate, Haemate, Helixate, Immunate, Immunine, Octanate, Recombinate, Refacto
Fitusiran is an investigational medicine. Its safety and efficacy have not been established by any health authorities.

Interim Fitusiran Phase 2 Open-Label Extension (OLE) Study Results*

Management of Bleed Events with Bypassing Agents in Patients with Inhibitors*

Treatment of Bleeds	aPCC (n=4)	rFVIIa (n=1)
Recommendation from Protocol	Up to 75 U/kg for minor to moderate bleeds and up to 100 U/kg (no more than 200 U/kg/day) for major bleeds at 12-hour intervals; to be continued until clear signs of clinical improvement	Up to 90 µg/kg every 2 hours, adjustable based on severity of bleeding until hemostasis is achieved. For severe bleeds, up to 90 µg/kg every 3-6 hours after hemostasis is achieved
Total bleeds†, n	56	3
Total administrations, n	82	8
Mean administrations per bleed, (Median; range)	1.5 (1; 1-3)	2.7 (3; 2-3)
Mean dose per injection	27 (14 – 37) U/kg	59 (37 – 62) µg/kg
% using less than or same amount of BPA per bleed as prior to fitusiran	95% (53)	100% (3)
Mean total amount of BPA used per bleed	40 U/kg	156 µg/kg

*Data transfer 15June2017
aPCC, activated prothrombin complex concentrates; rFVIIa, Recombinant factor VIIa; BPA, bypassing agent
Bypassing agents used: FEIBA, NovoSeven,
†9 bleeds treated with Prothromplex not detailed on this slide

PB 1982: “The Combined Use of Bypassing Agents with Antithrombin Reduction in Plasma of Hemophilia A and B Patients with Inhibitors” to be presented **Wednesday, 12 July, 12:00-13:15, Hall 4.2**

Interim Fitusiran Phase 2 Open-Label Extension (OLE) Study Results*

Summary

Increasing patient safety experience, with up to 20 months of dosing in Phase 2 OLE

- Majority of AEs were mild or moderate in severity; ISRs most common non-laboratory AE, all mild and transient
- No thromboembolic events; no clinical or laboratory evidence of pathologic clot formation
- Asymptomatic ALT increases >3X ULN observed in HCV Ab+ patients; most cases improved without dose interruption; 1 case led to discontinuation

Encouraging results in patients with hemophilia A and B, with and without inhibitors

- Approximately 80% AT lowering with low inter-patient variability achieved with once-monthly subcutaneous dosing
- Exploratory post-hoc analysis of bleed events demonstrates median ABR = 1 for all patients†
  - 48% (16/33) patients bleed-free and 67% (22/33) patients experiencing zero spontaneous bleeds

All bleed events in patients successfully managed with replacement factor or BPA

*Data transfer 15June2017

†During observation period; defined as day 29 of treatment to earlier of data transfer or 56 days after last dose

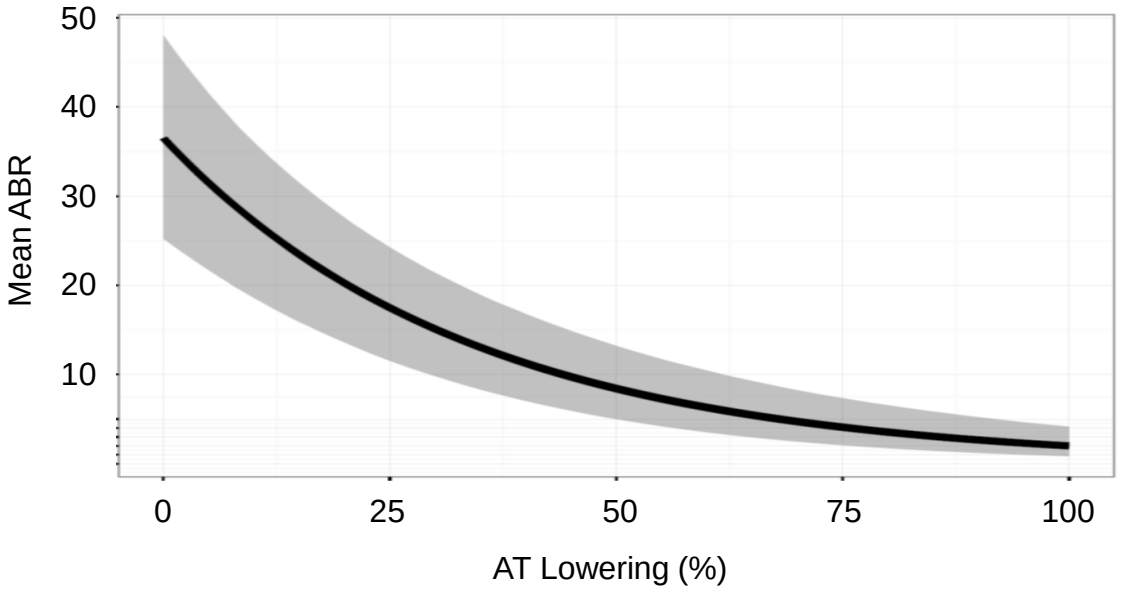
OLE, open-label extension; SAE: serious adverse events; AE, adverse events; ISR, injection site reactions; AT, antithrombin; ABR, annualized bleeding rate

Fitusiran is an investigational medicine. Its safety and efficacy have not been established by any health authorities.

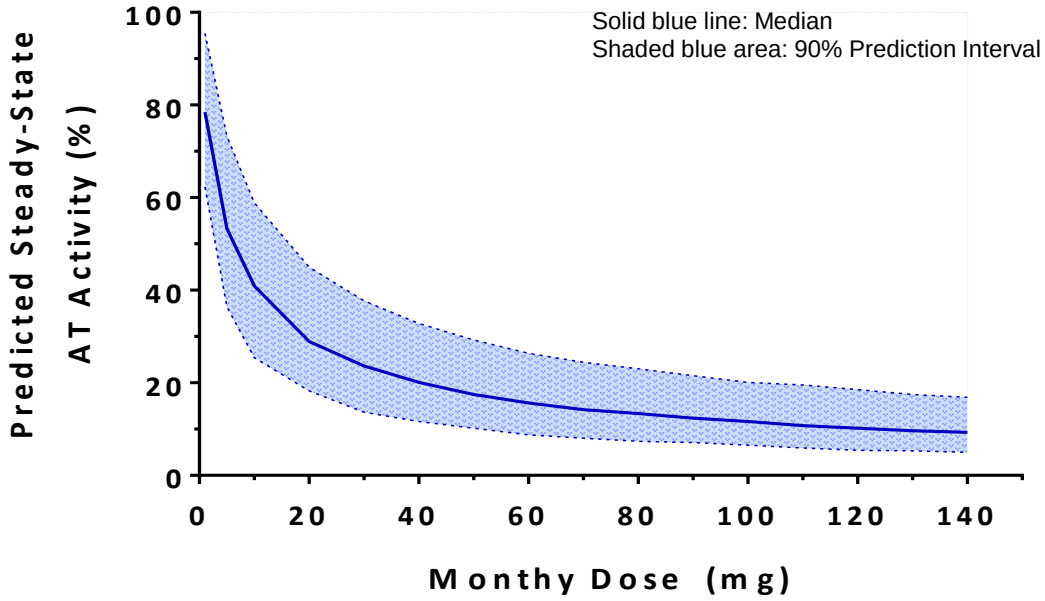
Next Steps

Modeling Based on Clinical Data Supports 80 mg as Phase 3 Dose

Simulation of mean ABR as a function of AT suggests a target of ~80% AT lowering



Modeled Dose-AT Relationship

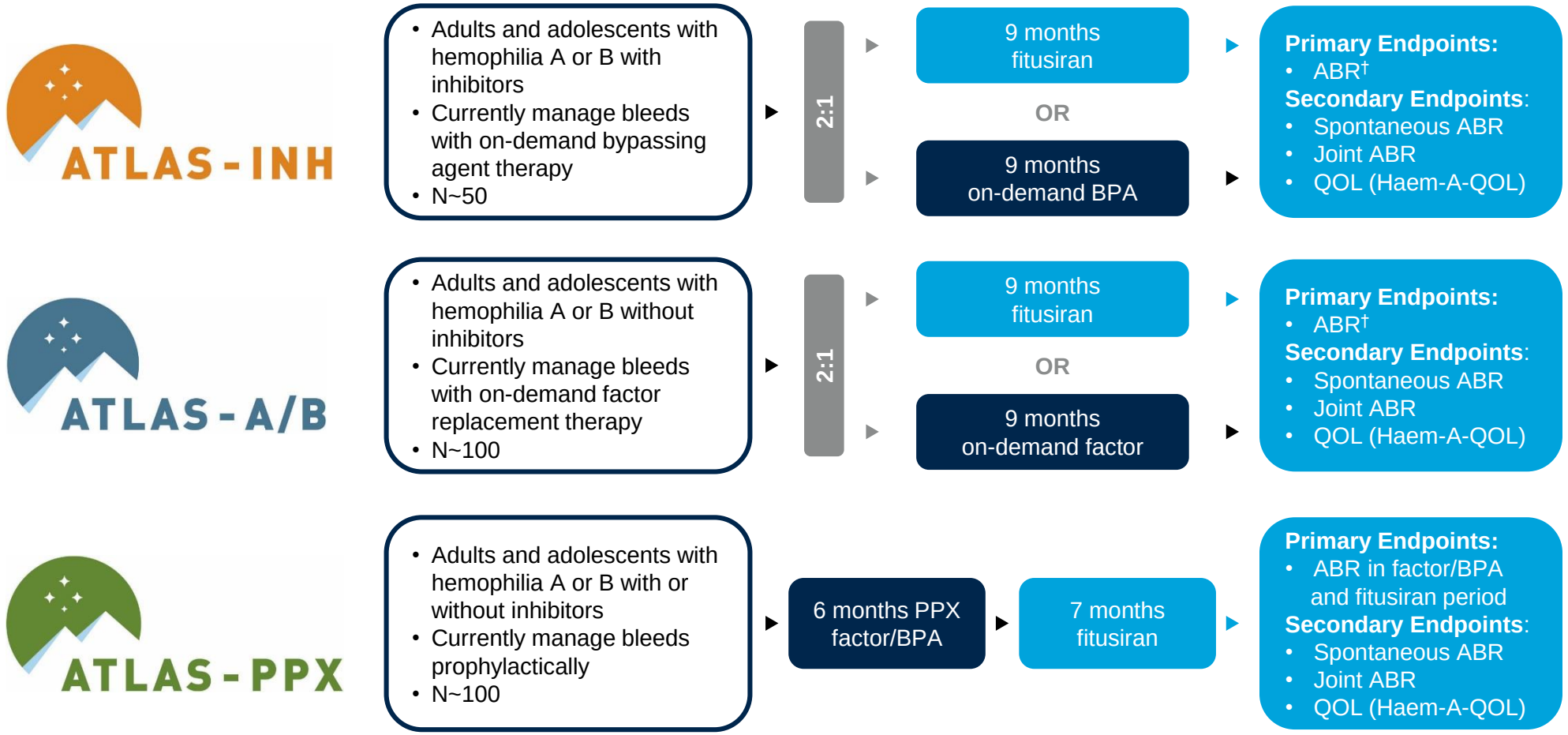


Larger proportion of patients at 80 mg maintain target AT throughout dosing interval

% of Patients with >80% AT Lowering at Steady-State	50 mg QM	80 mg QM
Peak	72	92
Trough	66	88

Next Steps

ATLAS Phase 3 Program Initiated



Patients who complete the study may be eligible for fitusiran treatment in ATLAS-OLE study

†Powered to detect as little as a 60% reduction from control to fitusiran
‡Powered to detect as little as a 50% reduction from control to fitusiran.
Fitusiran is an investigational medicine. Its safety and efficacy have not been established by any health authorities.

Q&A

Samantha
Regulatory Affairs, Alnylam

Thank You!

Alnylam® PHARMACEUTICALS

Fitusiran is an investigational medicine. Its safety and efficacy have not been established by any health authorities.