A Subcutaneously Administered Investigational RNAi Therapeutic (Fitusiran, ALN-AT3) Targeting Antithrombin for Treatment of Hemophilia: Interim Weekly and Monthly Dosing Results in Patients with Hemophilia A or B

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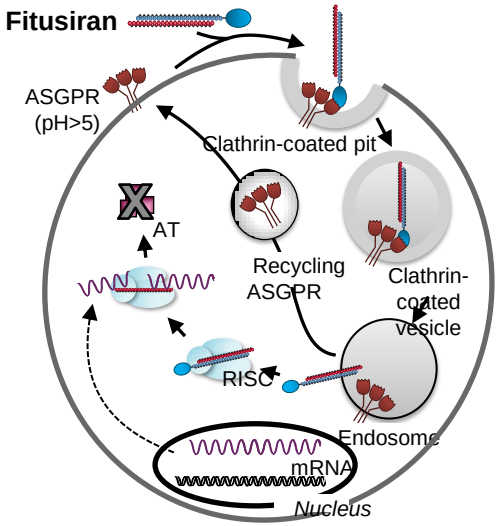
Alnylam® PHARMACEUTICALS

Fitusiran

Investigational RNAi Therapeutic for the Treatment of Hemophilia

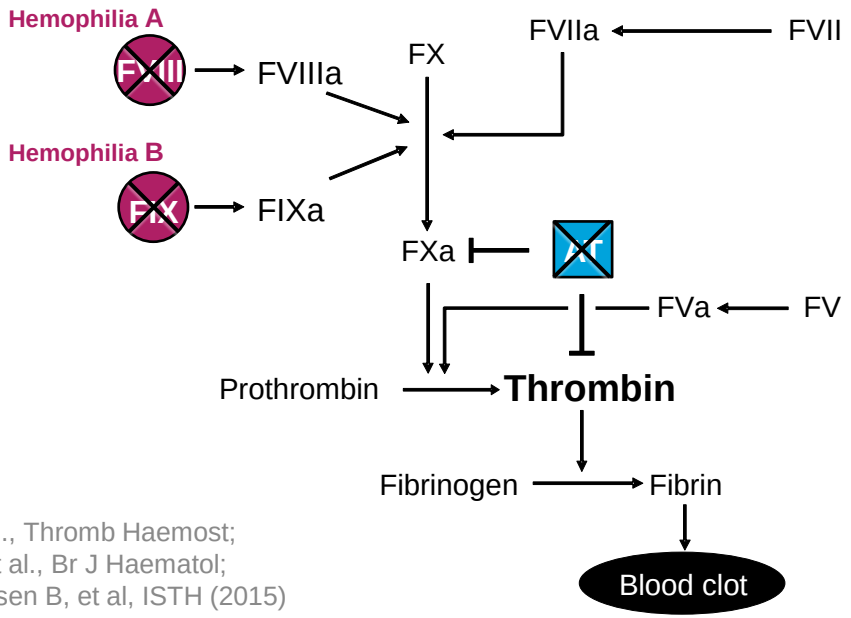
Fitusiran (ALN-AT3)

- SC-administered small interfering RNA (siRNA) therapeutic targeting antithrombin (AT)
  - Non-biologic, chemically-synthesized, with targeting ligand to specifically deliver to liver—the 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 the 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]



[1]Kurnik et al., Haematologica; 92:982-5 (2007); [2]Ettingshausen et al., Thromb Haemost; 85:218-20 (2001); [3]Negrier et al., Blood; 81:690-5 (1993); [4]Shetty et al., Br J Haematol; 138:541-4 (2007); [5]Seghal et al., Nat Med, 21:492-7 (2015); [6]Sorensen B, et al, ISTH (2015)

Fitusiran Phase 1 Study
Dose-Escalation Study in Three Parts

Primary objectives
- Safety, tolerability

Secondary objectives
- AT lowering, thrombin generation

Part A: Single-Ascending Dose (SAD) | Randomized 3:1, Single-blind, Placebo-controlled, Healthy volunteers

30 mcg/kg x 1 SC, N=4 ✓

Presented January 2015[1]

Part B: Multiple-Ascending Dose (MAD) – Weekly dosing | Open-label, Patients with Hemophilia A or B

15 mcg/kg qW x 3 SC, N=3 ✓

45 mcg/kg qW x 3 SC, N=6 ✓

75 mcg/kg qW x 3 SC, N=3 ✓

Presented June 2015[2]

Part C: Multiple-Ascending Dose (MAD) – Monthly dosing | Open-label, Patients with Hemophilia A or B

225 mcg/kg qM x 3 SC, N=3 ✓

450 mcg/kg qM x 3 SC, N=3 ✓

900 mcg/kg qM x 3 SC, N=3 ✓

1800 mcg/kg qM x 3 SC, N=3

Ongoing

Up to 2 additional cohorts

[1]Akinc A et al, Goring Coagulation Conference (2015)
[2]Sorensen B, et al, ISTH (2015)

Interim Fitusiran Phase 1 Study Results*
Demographics & Baseline Characteristics, Parts B & C

	Part B SC, Weekly × 3			Part C SC, Monthly × 3			
	15 mcg/kg N=3	45 mcg/kg N=6	75 mcg/kg N=3	225 mcg/kg N=3	450 mcg/kg N=3	900 mcg/kg N=3	1800 mcg/kg N=3
Age, mean (SD)	27 (9)	42 (14)	39 (4)	37 (21)	37 (15)	37 (17)	46 (12)
Hemophilia A Hemophilia B	2 1	6 0	2 1	2 1	2 1	3 0	3 0
Severe Moderate	3 0	6 0	3 0	2 1	3 0	2 1	3 0
Weight (kg), mean (SD)	76 (10.1)	80 (21.7)	82 (8.5)	85 (12.3)	76 (16.0)	76 (1.6)	71 (11.8)

*Data as of 12 November 2015

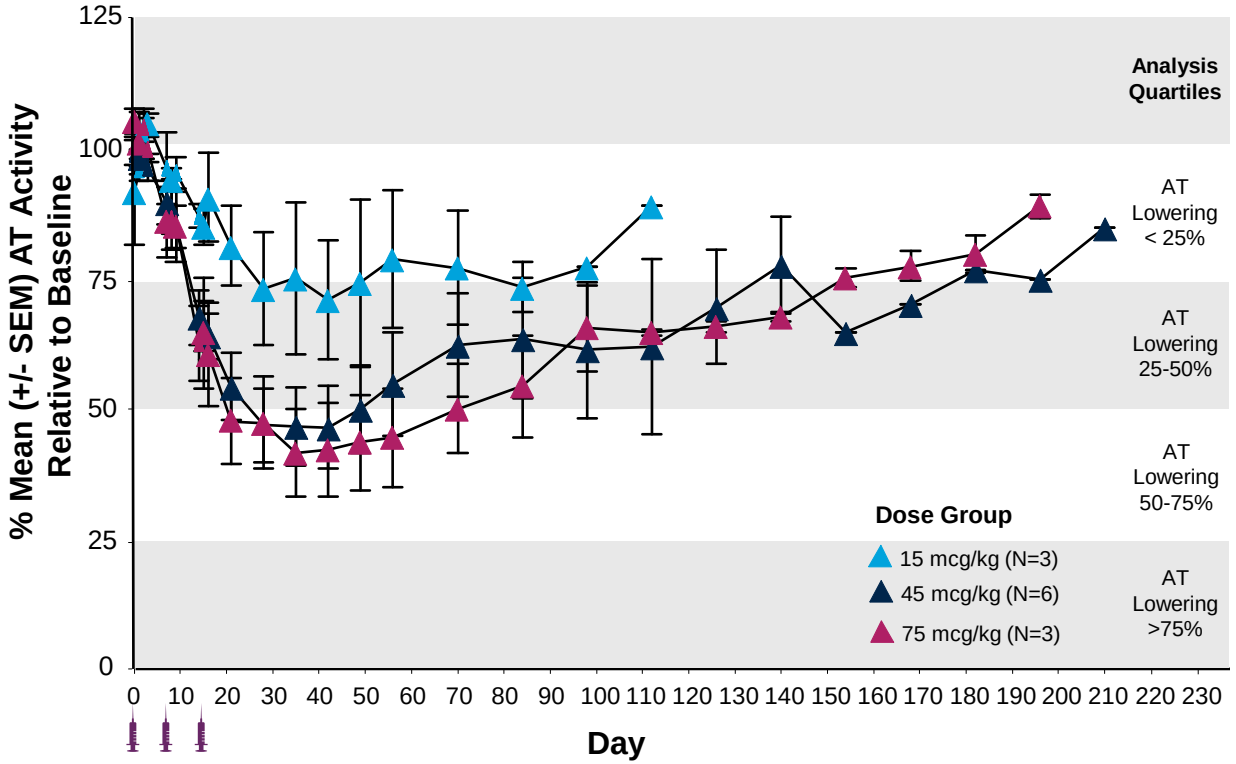
Interim Fitusiran Phase 1 Study Results*
Safety/Tolerability, Parts B & C†

- No SAEs related to study drug and no discontinuations
  - One subject was hospitalized due to re-activation of hepatitis C, not drug related
- AEs reported
  - Total of 35 AEs occurred in 14 patients
    - 33 single AEs + 2 AE episodes of arthritis
    - 34 Mild/Moderate, 1 Severe‡
  - 3 drug related AEs were observed – all mild:
    - Injection site reactions:
      - One patient (45 mcg/kg) experienced mild transient pain
      - One patient (1800 mcg/kg) experienced mild transient erythema & pain
    - Other:
      - Headache, transient
  - No thromboembolic events or clinically significant D-dimer increases
  - No drug related clinically significant changes in physical exams, vital signs, ECG or laboratory parameter (LFTs, CBC, coagulation)
  - Bleed events successfully managed with standard replacement factor administration
- No instances of anti-drug antibody (ADA) formation

*Data as of 12 November 2015:
†Adverse event grouping based on MedDRA-coded terms, excluding bleed events
‡Hypertriglyceridemia

Interim Fitusiran Phase 1 Study Results*
AT Lowering, Part B

AT lowering after weekly dosing in patients with hemophilia A and B

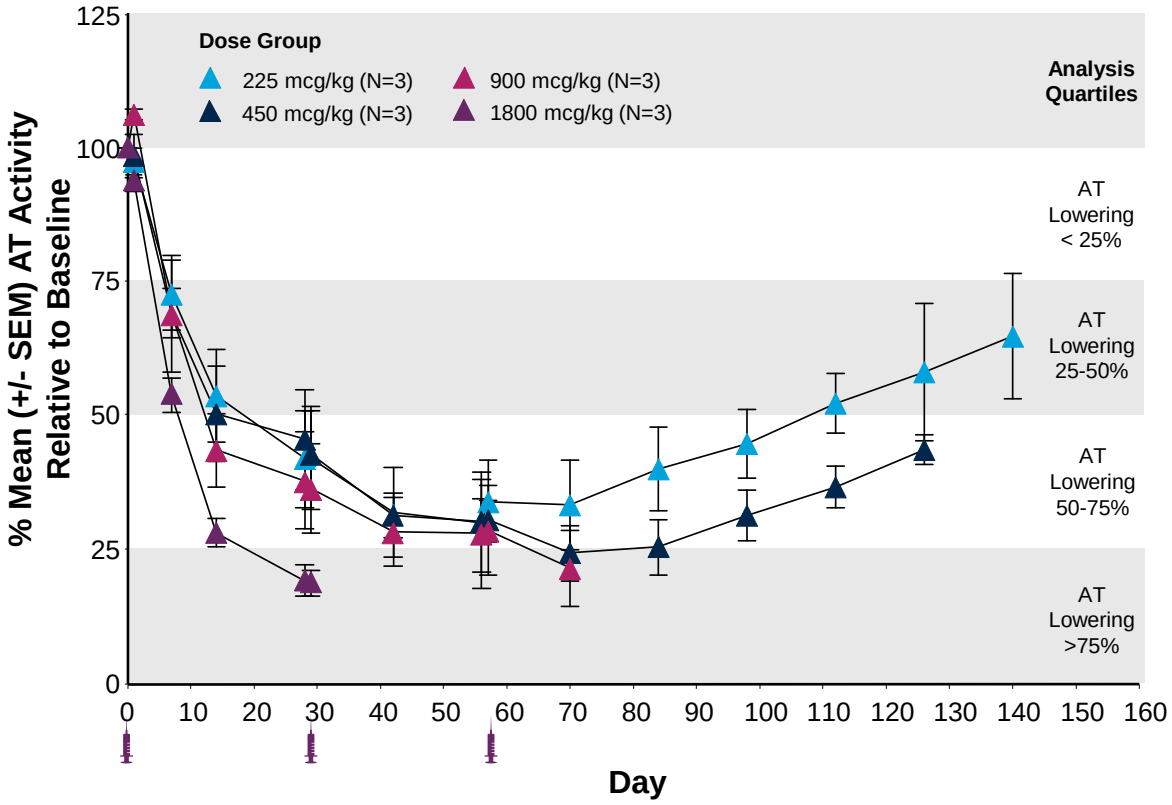


	Mean Max AT Lowering ± SEM	Max AT Lowering
15 mcg/kg (N=3)	29 ± 12%	53%
45 mcg/kg (N=6)	55 ± 9%	86%
75 mcg/kg (N=3)	61 ± 8%	74%

*Data as of 12 November 2015

Interim Fitusiran Phase 1 Study Results*
AT Lowering, Part C

AT lowering after monthly dosing in patients with hemophilia A and B

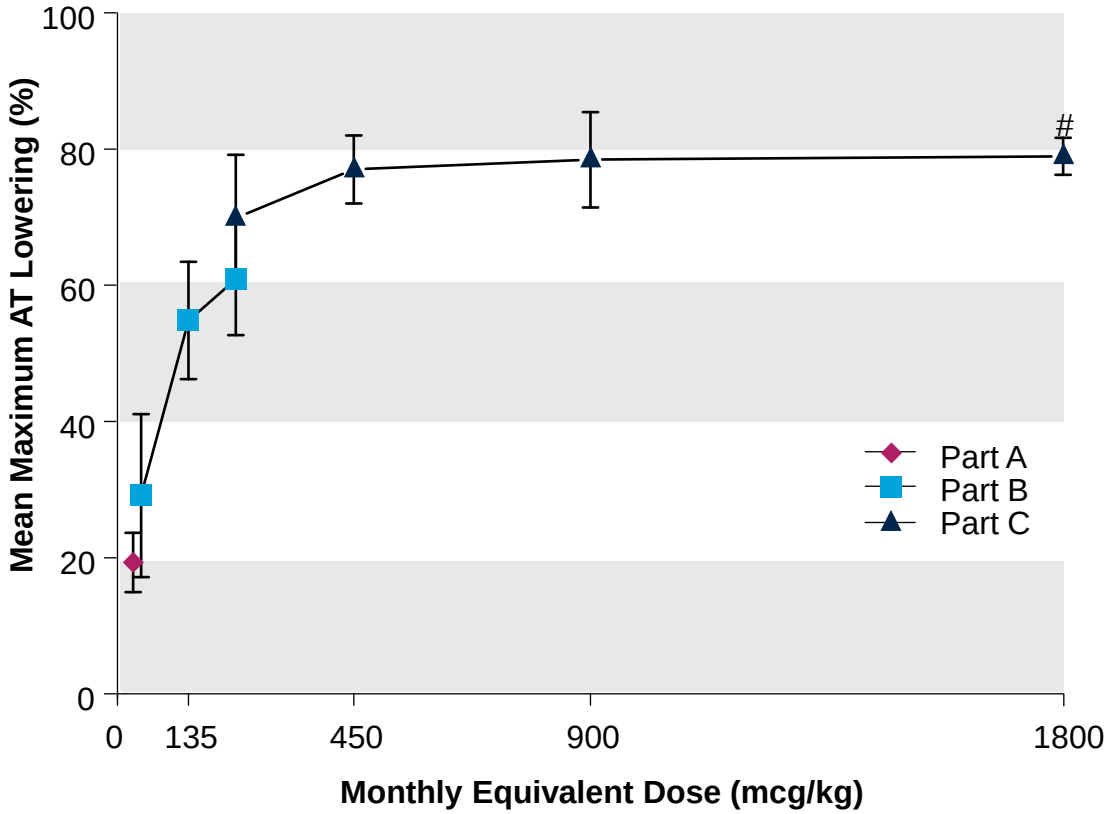


	Mean Max AT Lowering ± SEM	Max AT Lowering
225 mcg/kg (N=3)	70 ± 9%	80%
450 mcg/kg (N=3)	77 ± 5%	85%
900 mcg/kg (N=3)	78 ± 7%	88%
1800 mcg/kg (N=3)	79 ± 3%	84%

*Data as of 12 November 2015

Interim Fitusiran Phase 1 Study Results*
AT Lowering, Parts A, B & C

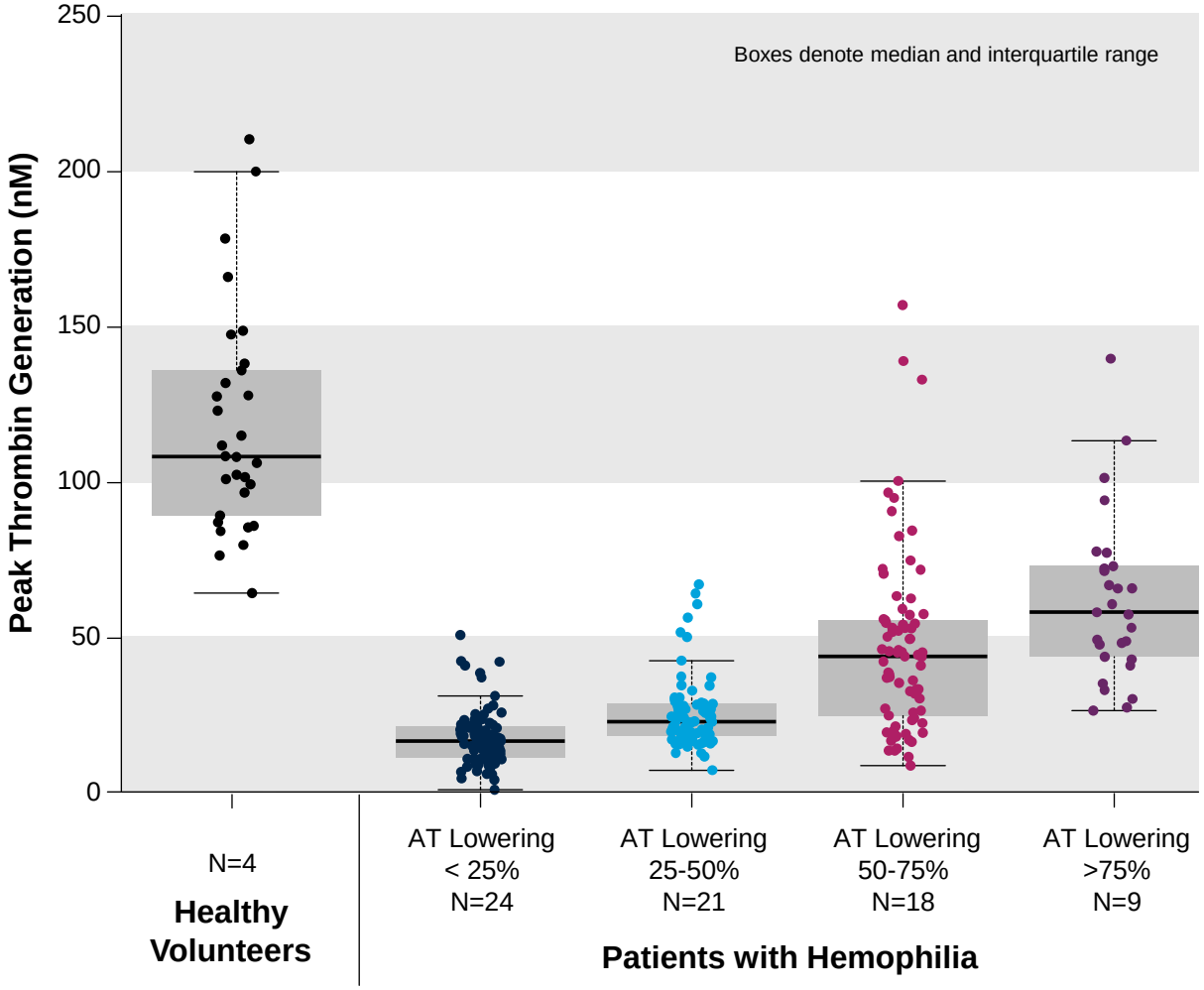
Mean maximum AT lowering by monthly equivalent dose



*Data as of 12 November 2015
#Single dose only (1 of 3)

Interim Fitusiran Phase 1 Study Results*
Thrombin Generation, Part B & C

Post hoc analysis of thrombin generation by AT lowering quartiles



	Peak Thrombin Generation, nM (Mean ± SD)	% Increase in Peak Thrombin Generation (Mean ± SD)
AT Lowering <25%	18 ± 9	20 ± 72%
AT Lowering 25-50%	26 ± 12	48 ± 61%
AT Lowering 50-75%	47 ± 29	218 ± 272%
AT Lowering >75%	62 ± 27**	285 ± 165%**

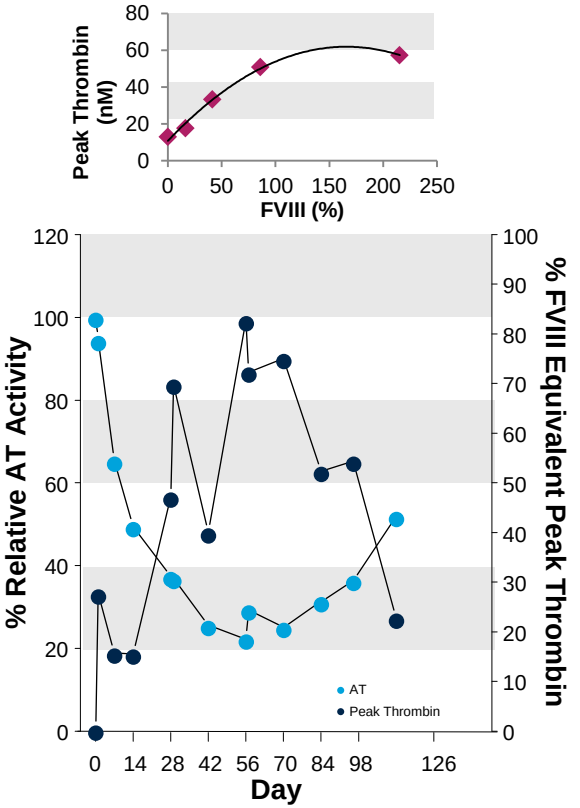
**p < 0.001, compared with AT lowering less than 25%

*Data as of 12 November 2015; reruns conducted on samples with analytical errors

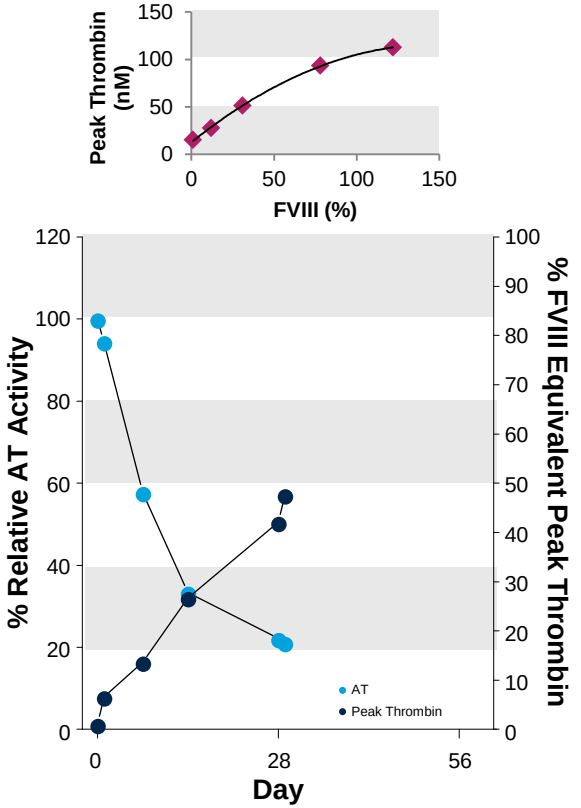
Interim Fitusiran Phase 1 Study Results*
Exploratory Analysis of Factor Equivalence

- Pre-dose factor administration used to establish individualized factor-peak thrombin relationship (in all 3 patients with pre-dose factor data)
  - Plasma collected at -0.5, 1, 2, 8, 24, and 48 hours post factor administration
  - Samples analyzed for FVIII level and thrombin generation
- Peak thrombin achieved post fitusiran dose compared to peak thrombin achieved with FVIII

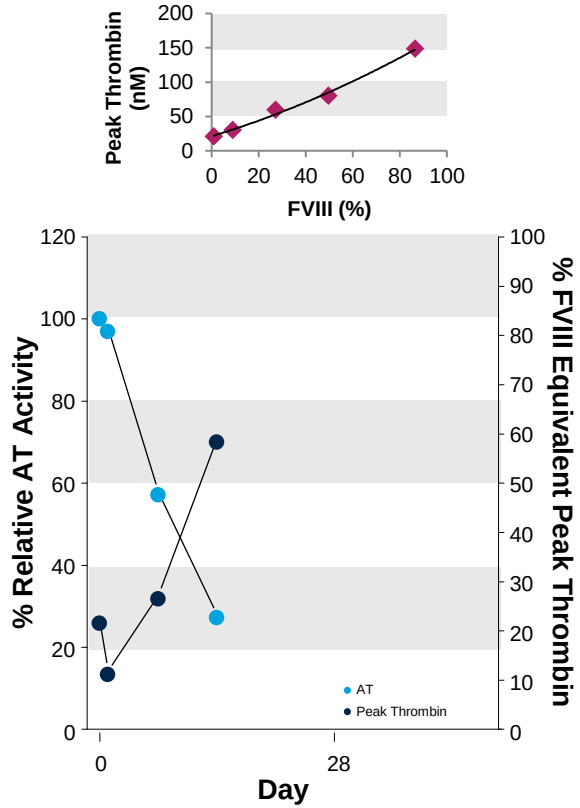
C1-1 (225 mcg/kg qM)



C4-2 (1800 mcg/kg qM)



C4-3 (1800 mcg/kg qM)

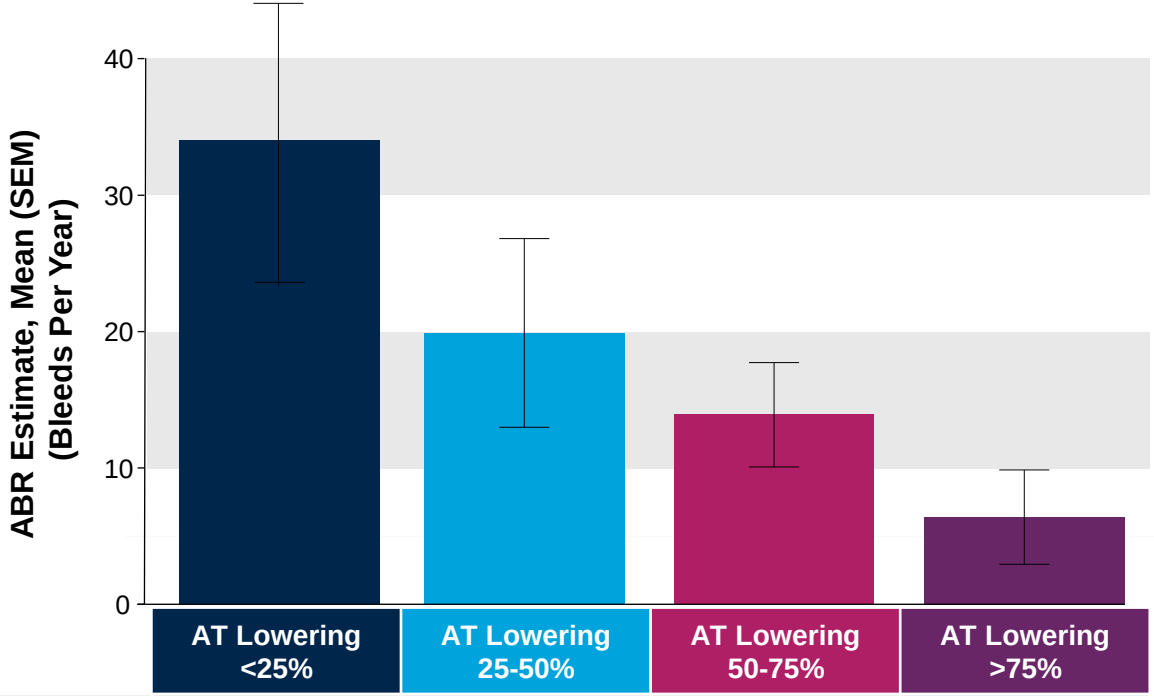


Achieved peak thrombin generation values equivalent to >40% factor VIII

*Data as of 12 November 2015

Interim Fitusiran Phase 1 Study Results*
Exploratory Analysis of Bleed Events, Parts B & C

Post hoc analysis of bleed events by AT lowering quartiles



	AT Lowering <25%	AT Lowering 25-50%	AT Lowering 50-75%	AT Lowering >75%
Patients†	24	21	18	9
Cumulative Days	602	838	862	304
Cumulative Bleeds	43	34	35	3
ABR‡, Mean (SEM)	34 ± 10	20 ± 7	14 ± 4	6 ± 3
ABR, Median	13	11	10	0

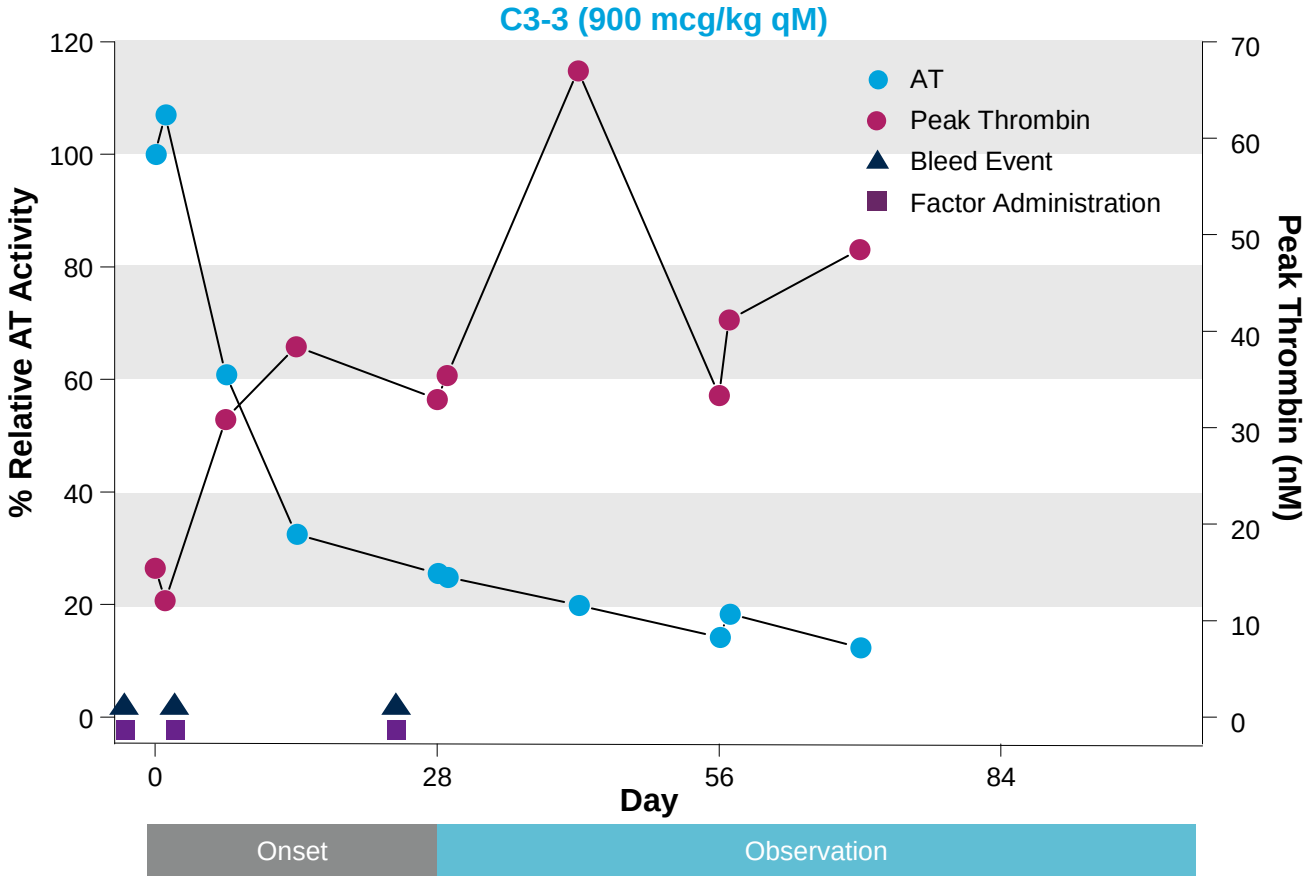
**p<0.05

**Data as of 12 November 2015*
†Number of patients with time spent in quartile
‡For each subject, the ABR in each quartile is calculated by 365.24(number of bleed events/number of days in quartile); .*
***Based on negative binomial regression model*

Interim Fitusiran Phase 1 Study Results*
Exploratory Analysis of Bleed Events, Part C

Post hoc analysis of bleed events during Onset and Observation periods

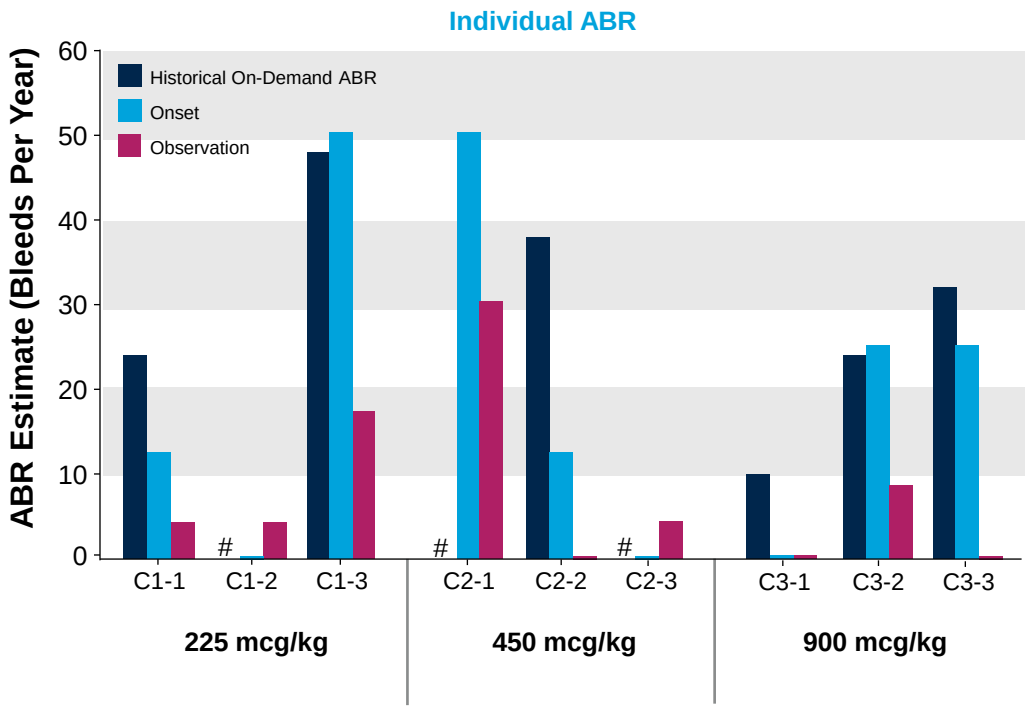
- Prospectively collected bleed events during Onset (Day 0-28) and Observation periods (Day 29 to last available, to maximum of Day 112)

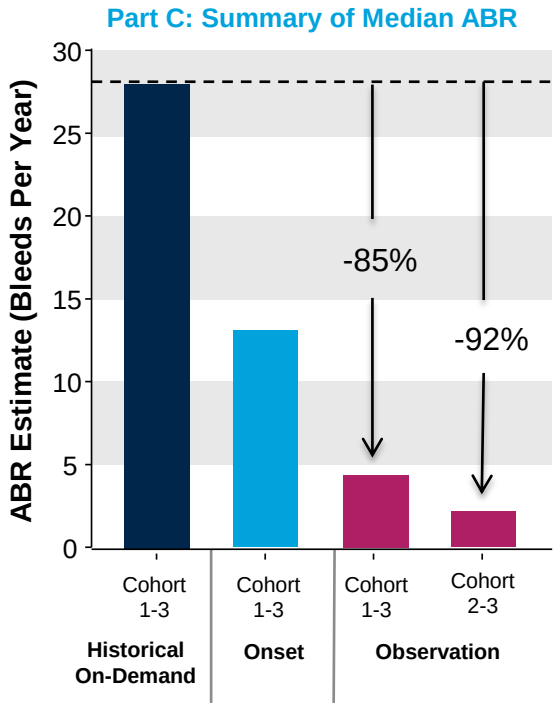


*Data as of 12 November 2015

Interim Fitusiran Phase 1 Study Results*
Exploratory Analysis of Bleed Events, Part C†

Post hoc analysis of bleed events by individual and Part C median





- Available Median Part C (Cohorts 1-3) Observation Period ABR = 4.3 (85% reduction relative to median Historical On-Demand ABR)
- Median Cohort 2 & 3 Observation Period ABR = 2.2 (92% reduction relative to median Historical On-Demand ABR)

**Data as of 12 November 2015*
†Observation Period data for Cohort 4 (1800 mcg/kg) not yet available
#Historical On-Demand ABR value not available; excluded from summary median ABR calculation

Fitusiran Phase 1 Study*
Summary

- Fitusiran generally well tolerated in hemophilia A and B patients with both weekly and monthly SC dose regimens (N=24)
  - No SAEs related to study drug and no discontinuations
  - Total of 3 drug-related AEs; all mild (2 injection site reactions, 1 headache)
  - No clinically significant increases in D-dimer
  - No instances of ADA formation
- Initial evidence for clinical activity and potential correction of hemophilia phenotype
  - Up to 88% AT lowering achieved, with once-monthly subcutaneous dose regimen
  - At highest AT lowering quartile (>75% AT lowering), achieved increase in mean peak thrombin to 62 ± 27 nM (within the range of values observed in healthy volunteers)
  - Sub-study in 3 patients demonstrated increase in thrombin generation to levels consistent to that attained with >40% factor VIII
  - Reduced bleeding tendency observed with increasing levels of AT lowering; mean estimated ABR at highest AT lowering quartile of 6 ± 3 (median = 0)
  - In exploratory post-hoc analysis of ABR in monthly dose cohorts, observed significant decrease in median ABR relative to median historical on-demand ABR
    - 85% reduction in all evaluable cohorts (225-900 mcg/kg)
    - 92% reduction in highest two evaluable cohorts (450 and 900 mcg/kg)
- Plan to advance to pivotal study in mid-2016

**Data as of 12 November 2015*

Acknowledgements

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Country	PI Name	Location
United Kingdom	Steve Austin	London – St. George's Healthcare NHS Trust Haemophilia Centre
	David Bevan	London – The Centre for Haemostasis and Thrombosis Guy's and St. Thomas' Hospital
	Desmond Creagh	Truro – Royal Cornwall Hospital
	Charles Hay	Manchester – Manchester Royal Infirmary
	Tim Mant	London – Quintiles Drug Research Unit
	John Pasi	London – The Royal London Haemophilia Centre
	Savita Rangarajan	Basingstoke – North Hampshire Haemophilia Centre
	Pratima Chowdary	London – Royal Free Hospital Haemophilia Centre and Thrombosis Unit
	Rashid Kazmi	Southampton - University Hospital Southampton NHS Foundation Trust
	Catherine Bagot	Glasgow - Glasgow Royal Infirmary Department of Haematology
Bulgaria	Pencho Georgiev	Plovdiv – University Multiprofile Hospital for Active Treatment "Sveti Georgi'
	Toshko Lissitchkov	Sofia - Department of Chemotherapy, Haemotherapy and Hereditary Blood Diseases at Clinical Hematology Clinic Specialized Hospital for Active Treatment of Haematological Diseases
	Liana Gercheva-Kyuchukova	Varna - Clinical Hematology Clinic, Multiprofile Hospital for Active Treatment "Sveta Marina"
Switzerland	Brigitte Brand-Staufer	Zurich – Universitatsspital Zurich, Klinik fur Hamatologie
	Thomas Lehmann	St. Gallen – St. Gallen Cantonal Hospital
Russia	Vasily Mamonov	Moscow – Hematology Research Center of the Russian Academy of Medical Sciences
	Tatiana Andreeva	St. Petersburg - City Outpatient Clinic #37
	Margarita Timofeeva	Kirov - Kirov Research Institute of Hematology and Blood Transfusion
United States	Margaret Ragni	Pittsburgh - Hemophilia Center of Western Pennsylvania

Thank You