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

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25 July 2016 | WFH | Orlando, FL

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Fitusiran

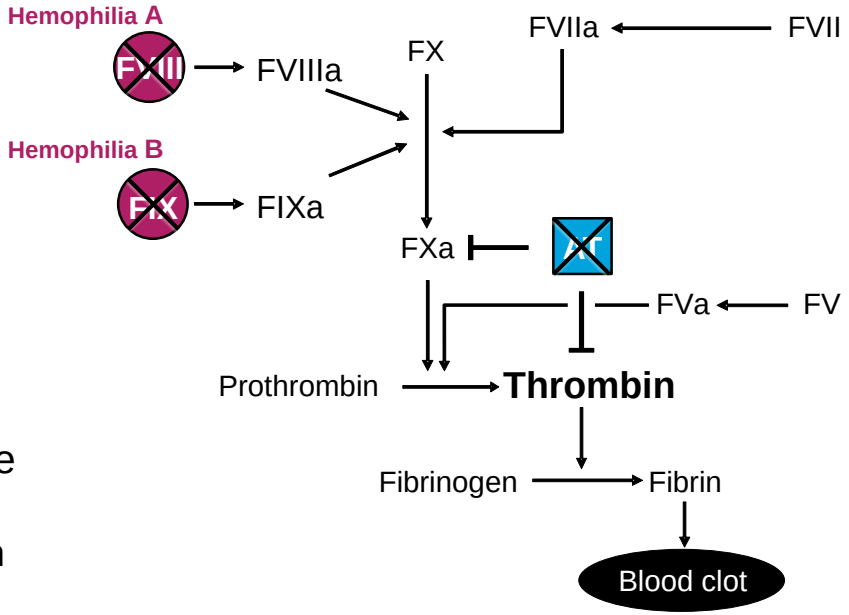
Investigational RNAi Therapeutic for Treatment of Hemophilia

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]



[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 J, et al. *ASH.* (2016)

Fitusiran Phase 1 Study

Dose-Escalation Study in Four Parts

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

- 30 mcg/kg x 1 SC, N=4 ✓

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 ✓

Part C: 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 ✓
- 80 mg qM x 3 SC, N=6 ✓

Part D: MAD – Monthly dosing | **Open-label, Patients with Hemophilia A or B with inhibitors**

- 50 mg qM x 3 SC, N=6
- 80 mg qM x 3 SC, N=6

Ongoing

†5 patients participating in Part C previously participated in Part B
qW, weekly; qM, monthly; SC, subcutaneous

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Interim Fitusiran Phase 1 Study Results*

Demographics & Baseline Characteristics, Parts B, C & D

	Part B Subcutaneous Weekly × 3			Part C Subcutaneous Monthly × 3					Part D Subcutaneous 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	80 mg N=6	50 mg N=6
Age, mean (SD)	28 (9)	42 (14)	40 (4)	37 (21)	37 (15)	38 (16)	46 (12)	32 (12)	33 (7)
Hemophilia A Hemophilia B	2 1	6 0	2 1	2 1	2 1	3 0	3 0	3 3	5 1
Severe Moderate	3 0	6 0	3 0	2 1	3 0	2 1	3 0	5 1	6 0
Weight (kg), mean (SD)	76 (10)	80 (22)	82 (8)	85 (12)	76 (16)	76 (2)	71 (12)	74 (10)	73 (17)

*Data transfer: 30Jun2016

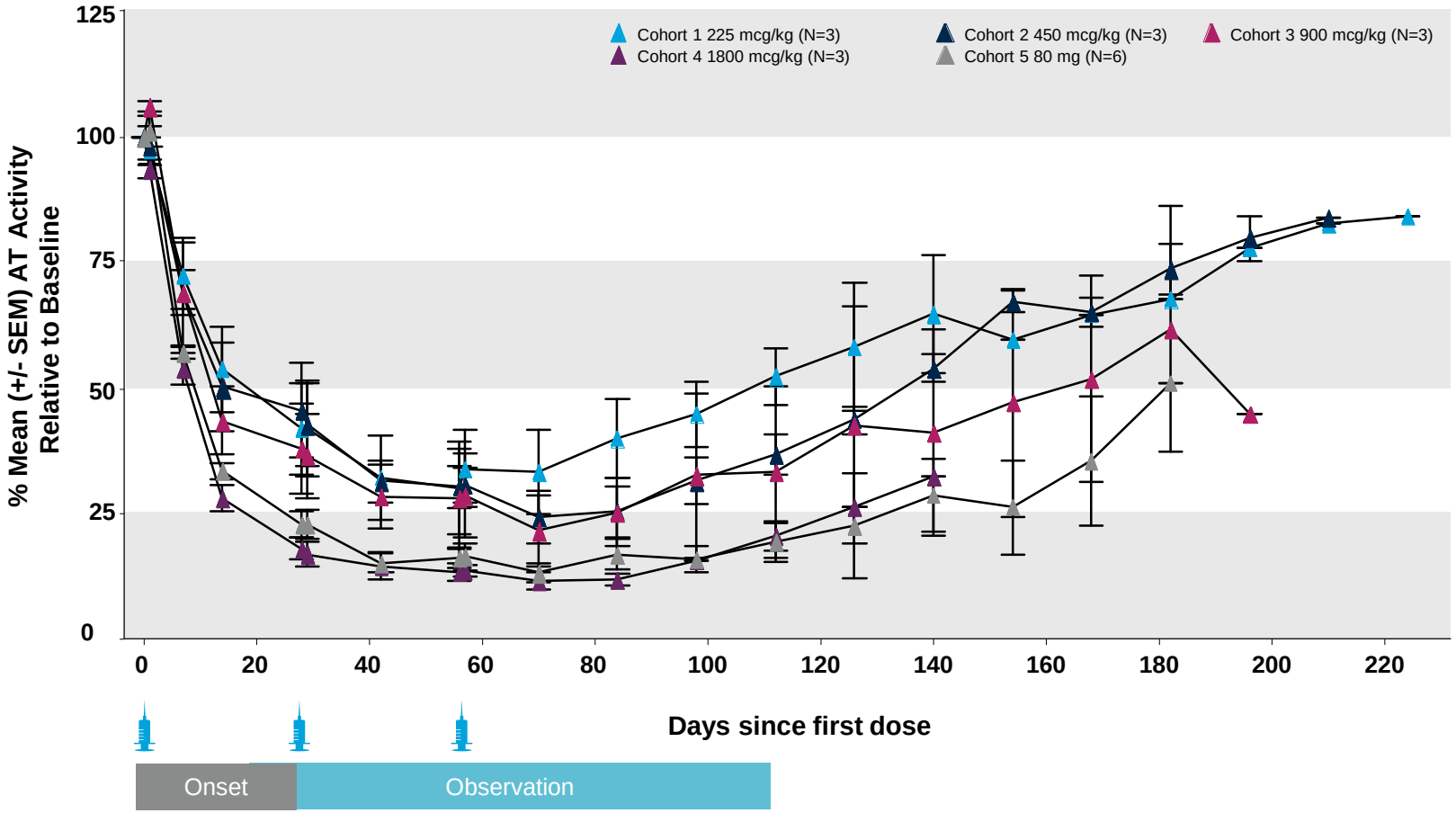
Interim Fitusiran Phase 1 Study Results*
Safety/Tolerability†, Parts B, C, & D

- No SAEs related to study drug
- Majority of AEs mild or moderate in severity
  - AEs (excluding ISRs) in ≥10% of patients
    - Upper respiratory tract infection (10%), arthralgia (10%)
- 11 (35%) patients reported drug-related ISRs, all mild
  - Mostly pain and/or erythema at injection site
- One patient discontinued due to AE of non-cardiac chest pain; considered severe and possibly related
  - Associated with transient elevations of ALT (10x ULN), AST (8x ULN), CRP and D-dimer; no increase in total bilirubin
  - Extensive evaluation unremarkable; VTE excluded by serial CT angiograms and liver and lower extremity ultrasound
  - This event resolved with symptomatic management, including antacids and analgesics
- No thromboembolic events or laboratory evidence of pathologic clot formation (D-dimer, platelet count, fibrinogen, and/or PT/INR)
- With exception of case noted above, no other clinically significant drug-related changes in laboratory parameters
- No instances of anti-drug antibody (ADA) formation
- Bleed events successfully managed with infusion of standard replacement factor or bypass agents

*Data transfer up to 11July2016
†Adverse event grouping based on MedDRA-coded terms, excluding bleed events

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

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

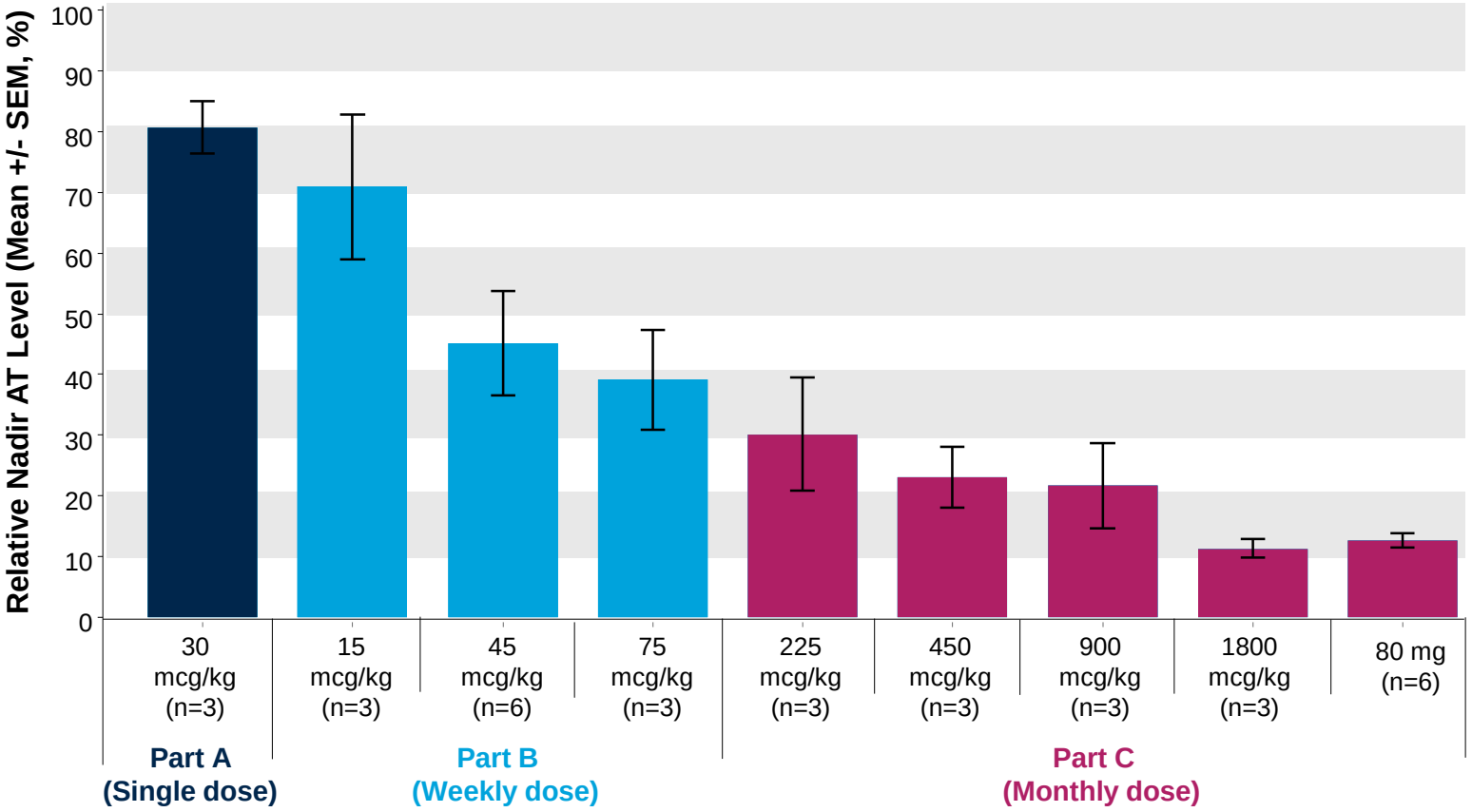


*Data transfer: 30Jun2016

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

Dose-dependent AT lowering

- Mean maximal AT lowering of 87 ± 1% at 80 mg fixed dose

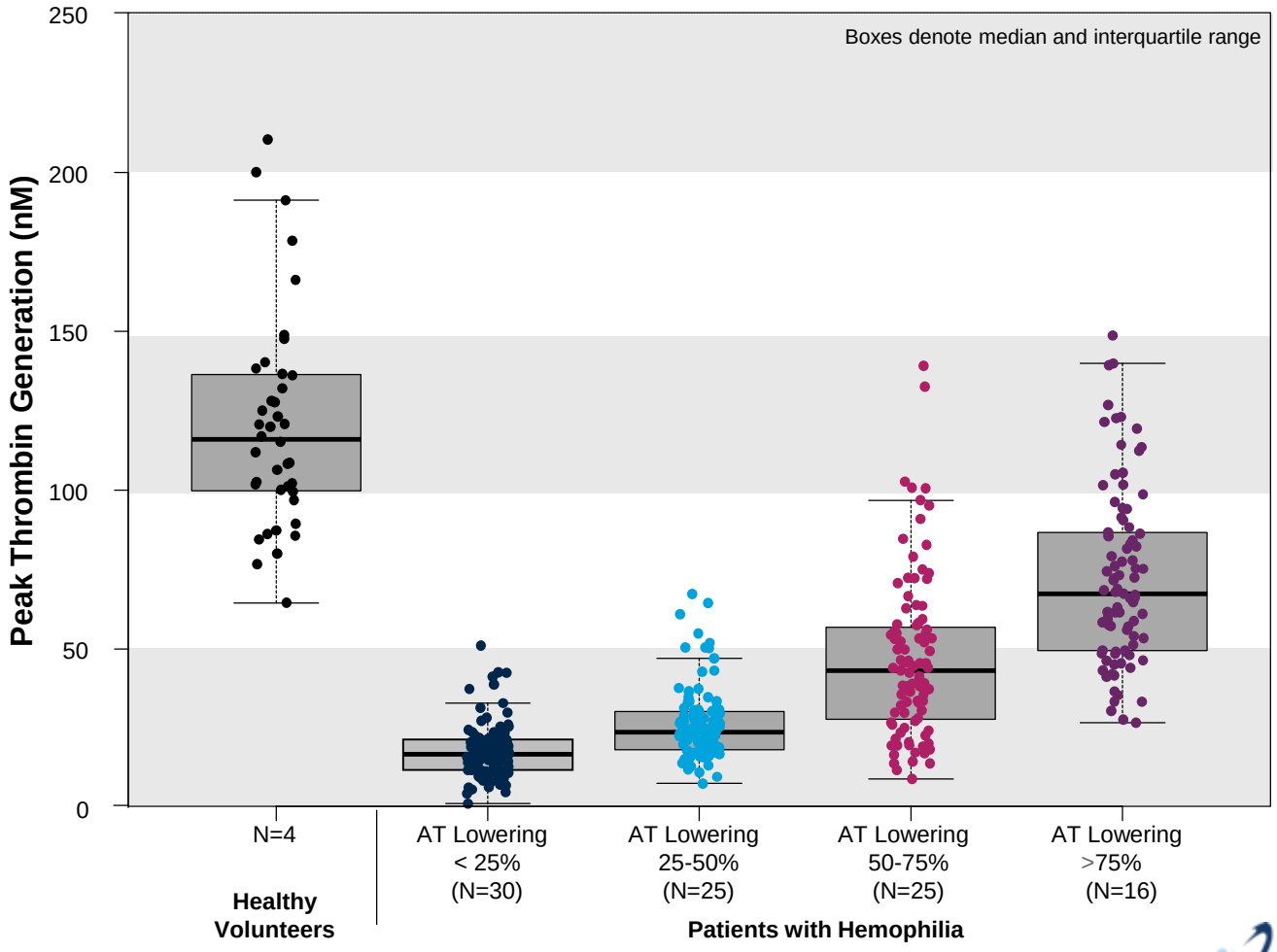


*Data transfer: 30Jun2016

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

Post hoc analysis of thrombin generation by AT lowering quartiles

- Mean thrombin generation increase of 289% relative to baseline at AT lowering >75% ($p<0.001^{\dagger}$)



*Data transfer: 30Jun2016

†%Change in Peak TG: p<0.001 by Mann-Whitney test, when compared with AT3 lowering than <25% group

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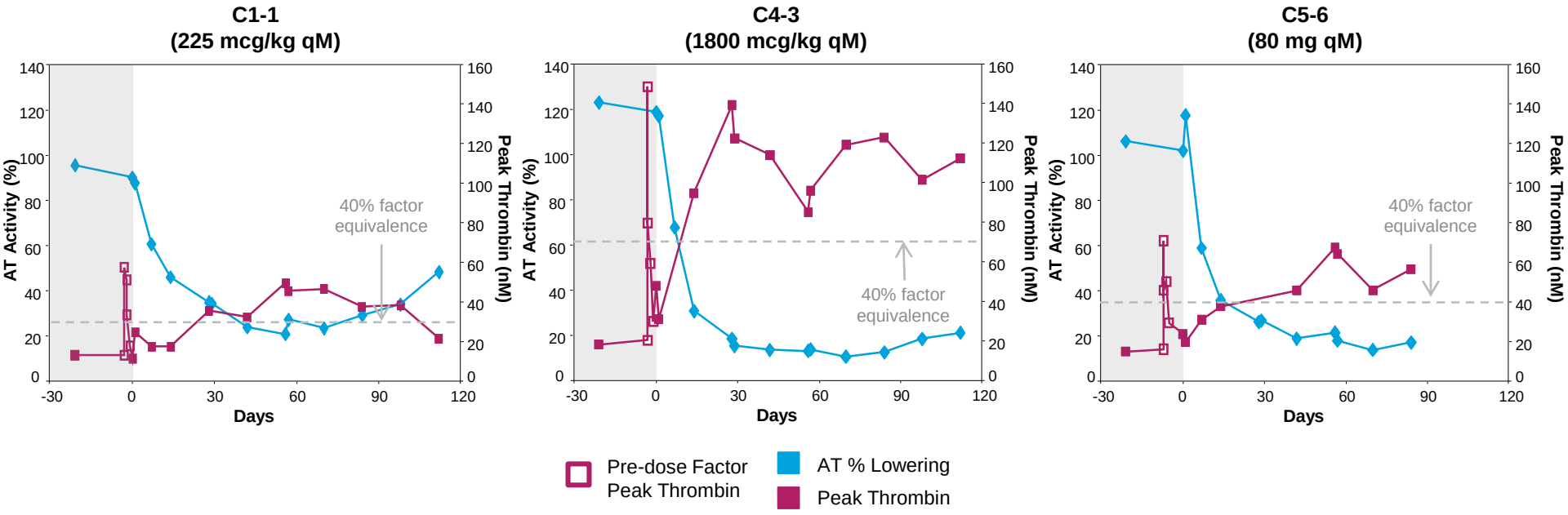
Interim Fitusiran Phase 1 Study Results*
Exploratory Analysis of Factor Equivalence

Fitusiran achieved peak thrombin generation values equivalent to >40% Factor VIII

- 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 >40% FVIII

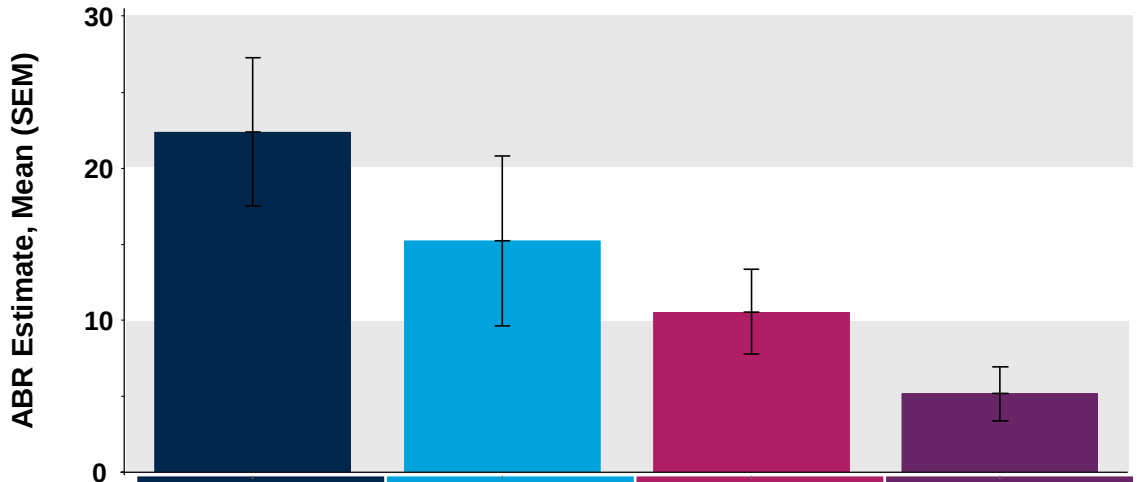


*Data transfer: 30Jun2016

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

Post hoc analysis of bleed events by AT lowering quartiles

- Includes more than 1100 cumulative days with AT lowering >75% in 16 patients



	AT Lowering <25%	AT Lowering 25-50%	AT Lowering 50-75%	AT Lowering >75%
Patients†	30	27	25	16
Cumulative Days	733	1119	1203	1128
Cumulative Bleeds	47	40	36	11
ABR‡, Mean (SEM)**	22 ± 5	15 ± 6	11 ± 3	5 ± 2
ABR, Median	10	0	6	1

**P-value < 0.05

*Data transfer: 30Jun2016
ABR, annualized bleeding rate; SEM, standard error of the mean
†Number of patients with time spent in quartile; ‡For each patient, the ABR in each quartile is calculated by 365.24*(number of bleed events/number of days in quartile)

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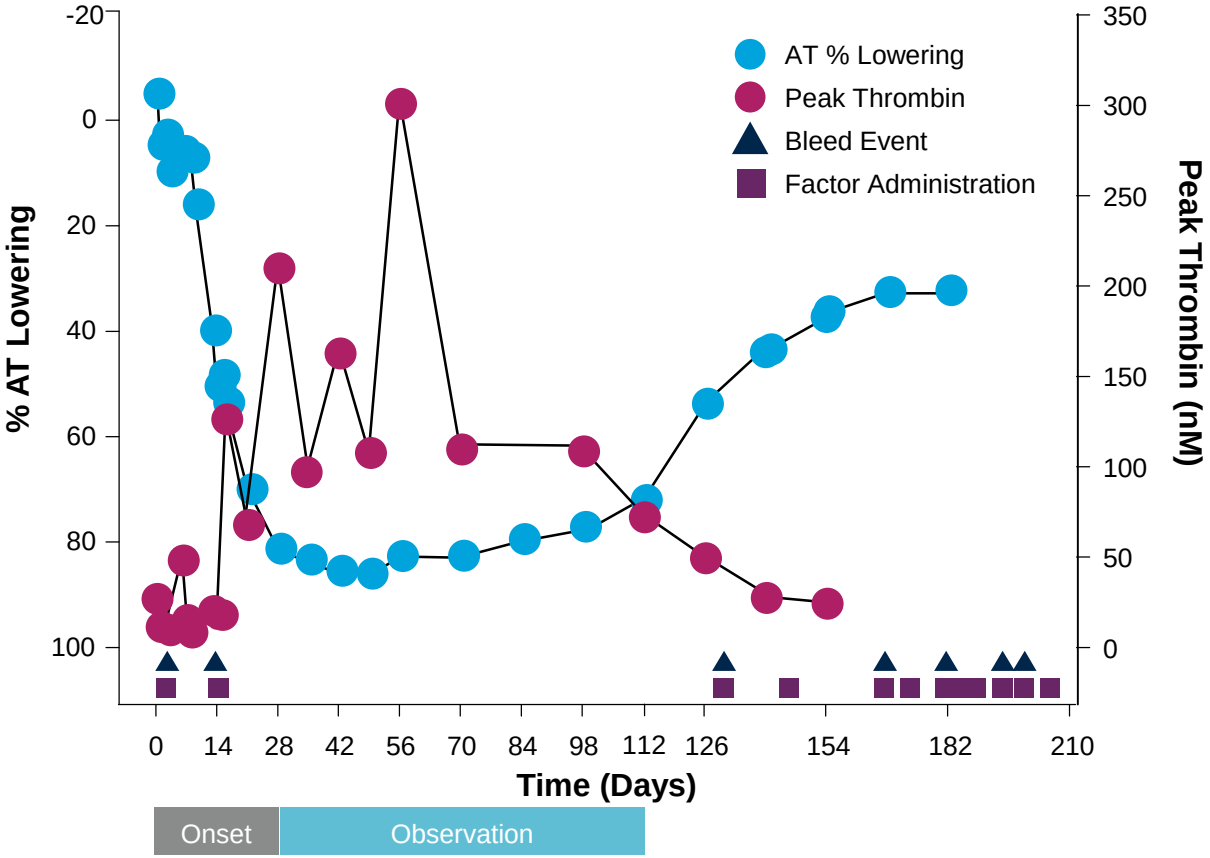
Interim Fitusiran Phase 1 Study Results*
Exploratory Analysis of Bleed Events

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)



*Patient has severe hemophilia A and has a self-reported ABR of 22; enrolled in Part B (45 mcg/kg dose cohort)
Sorensen, ISTH, June 2015

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Interim Fitusiran Phase 1 Study Results*

Exploratory Analysis of Bleed Events, Part C†

Dose	Patient	Prior Tx	Pre-study ABR‡	Onset ABR	Observation Period			
					All Bleeds, n	ABR	Spontaneous Bleeds, n	AsBR
225 mcg/kg	C1-1	PPx	2	13	1	**4**	1	**4**
	C1-2	PPx	0	0	1	**4**	0	**0**
	C1-3	PPx	0	50	4	**17**	0	**0**
450 mcg/kg	C2-1	PPx	4	25	4	**17**	3	**13**
	C2-2	OD	38	13	0	**0**	0	**0**
	C2-3	PPx	4	0	1	**4**	0	**0**
900 mcg/kg	C3-1	PPx	0	0	0	**0**	0	**0**
	C3-2	OD	20	25	3	**13**	0	**0**
	C3-3	OD	32	25	0	**0**	0	**0**
1800 mcg/kg	C4-1	PPx	0	25	0	**0**	0	**0**
	C4-2	OD	24	0	0	**0**	0	**0**
	C4-3	PPx	0	25	0	**0**	0	**0**
80 mg^	C5-1	PPx	12	13	2	**9**	1	**4**
	C5-2	PPx	16	0	0	**0**	0	**0**
	C5-3	PPx	6	13	2	**9**	0	**0**
	C5-5	PPx	6	13	0	**0**	0	**0**
	C5-6	PPx	0	13	0	**0**	0	**0**

*Data transfer: 30Jun2016
PPx: Prophylaxis, OD: On-Demand; ABR, annualized bleeding rate; AsBR, annualized spontaneous bleeding rate
†Post hoc analysis of treated bleed events during Onset (Day 0-28) and Observation periods (Day 29 to last study visit or last dose+56 days, whichever is earlier; ‡Pre-study ABR derived from medical records; ^Patient C5-4 withdrawn, excluded from analysis

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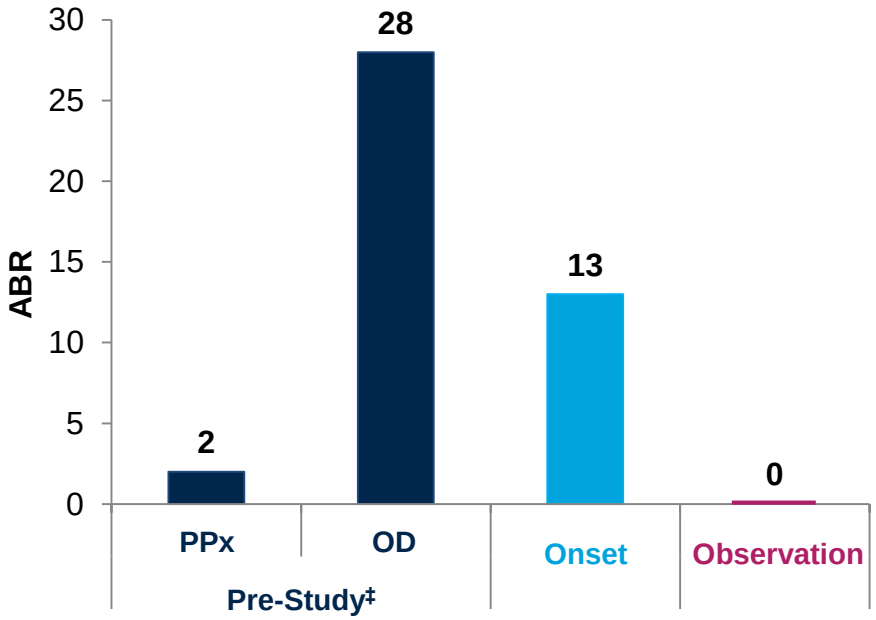
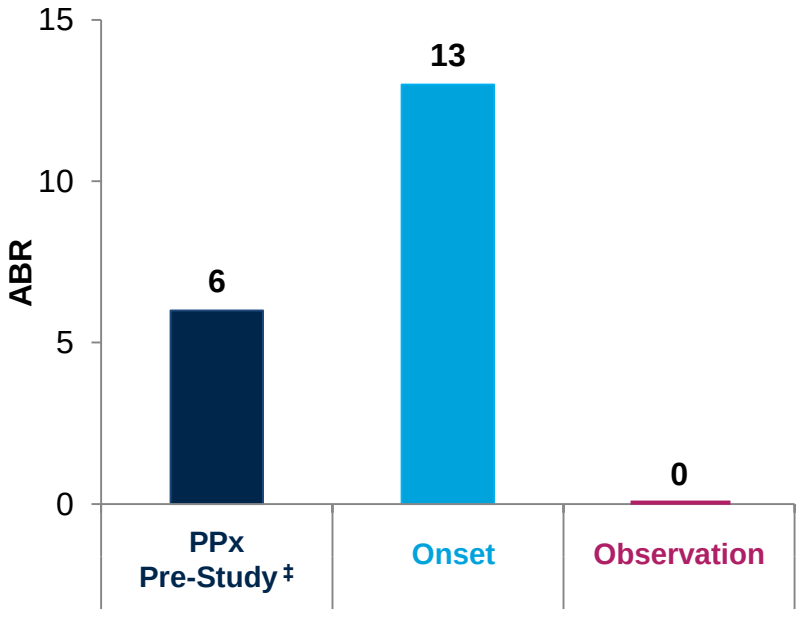
Interim Fitusiran Phase 1 Study Results*
Exploratory Analysis of Bleed Events, Part C†

Summary of Median ABR (All Cohorts)



Summary of Median ABR (80 mg)



All Part C patients^

- Median ABR, Pre-study period: 2 (PPx); 28 (OD)
- Median ABR, Observation period: 0
  - 53% of patients report no bleeds
  - 82% of patients report no spontaneous bleeds

Part C, 80 mg dosing cohort ^

- Median ABR, Pre-Study (all PPx patients): 6
- Median ABR, Observation period: 0

*Data transfer: 30Jun2016
PPx: Prophylaxis, OD: On-Demand; ABR, annualized bleeding rate;
†Post hoc analysis of treated bleed events during Onset (Day 0-28) and Observation periods (Day 29 to last study visit or last dose+56 days, whichever is earlier; ‡Pre-study ABR derived from medical records; ^Patient C5-4 withdrawn, excluded from analysis

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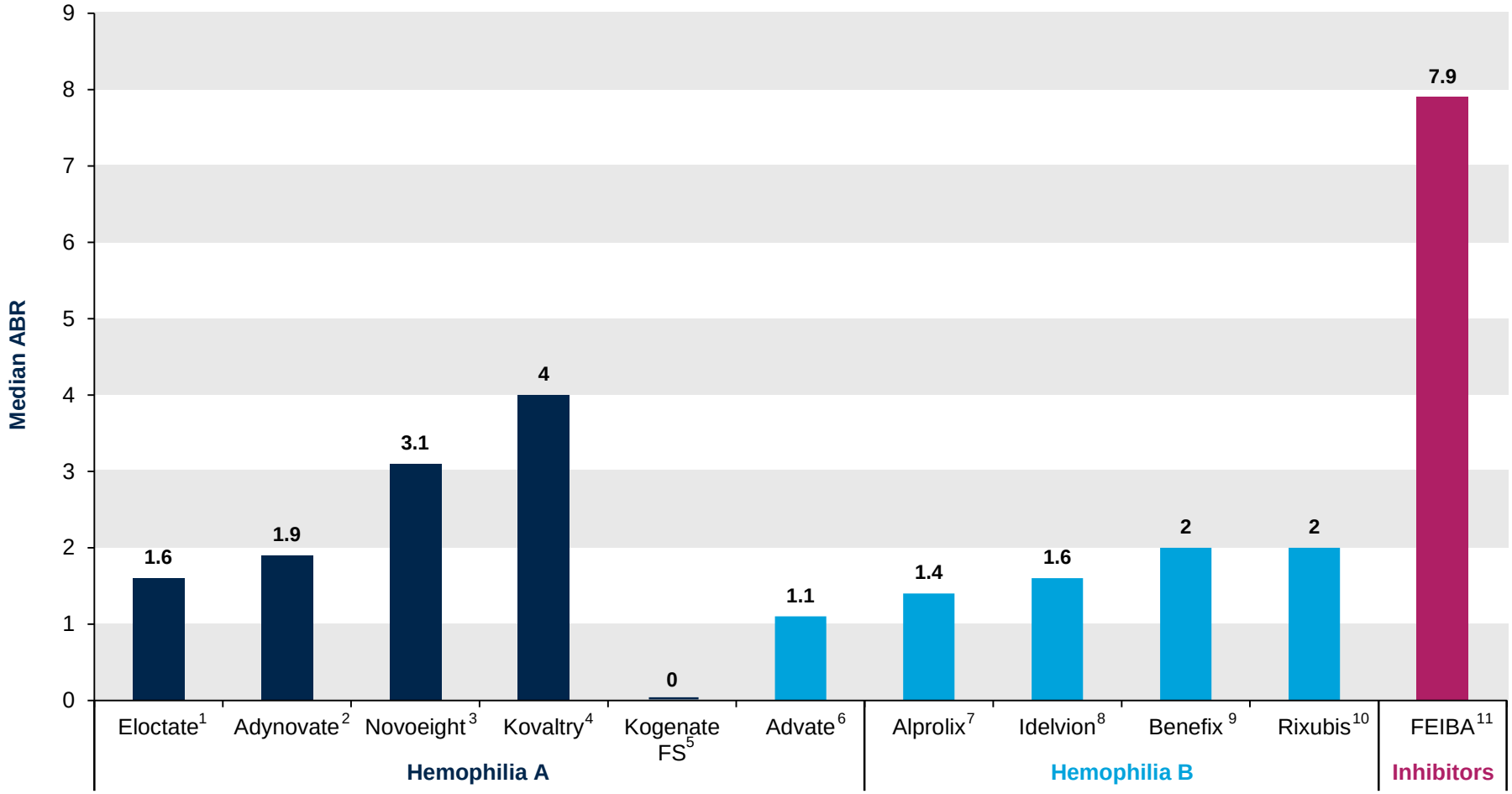
ABR Results in Select Prospective Studies*

Median ABRs for Prophylaxis Therapy



**The above graph does not reflect data from head-to-head studies; direct comparisons can not be made*

1. Mahlangu J, et al. *Blood*. 123:317-25 (2014); 2. Konkle BA, et al. *Blood*. 26:1078-85 (2015); 3. Lentz SR, et al. *Haemophilia*.19:691-7 (2013); 4. Kovaltry®[package insert]. Whippany, NJ: Bayer; 2016; 5. Manco-Johnson MJ, et al. *J Thromb Hemost*. 12:119-122 (2013); 6. Valentino LA, et al. *J Thromb Hemost*. 10:359-67 (2012); 7. Powell JS, et al. *N Engl J Med*.;369:2313-23 (2013); 8. Santagostino E, et al. *Blood*. 127:1761-9 (2016); 9. Kavakli K, et al. *Haemophilia.* DOI: 10.1111/hae.12878 (2016); 10. Windyga J, et al. *Haemophilia*. 20:15-24 (2014); 11. Antunes SV, et al. *Haemophilia* . 20: 65–72 (2014).

Fitusiran Phase 1 Study
Inhibitor Patients, Part D

Study population

- Hemophilia A and Hemophilia B patients with inhibitors, utilizing bypassing agents (BPAs) for bleed management

Exploratory pre-dose evaluation of response to BPAs

- BPA administered prior to fitusiran dosing to explore peak thrombin response to patient's standard BPA
  - Plasma collected at -1, 2, 6, and 24 hours post BPA administration, and samples analyzed for thrombin generation

Fitusiran dose cohorts

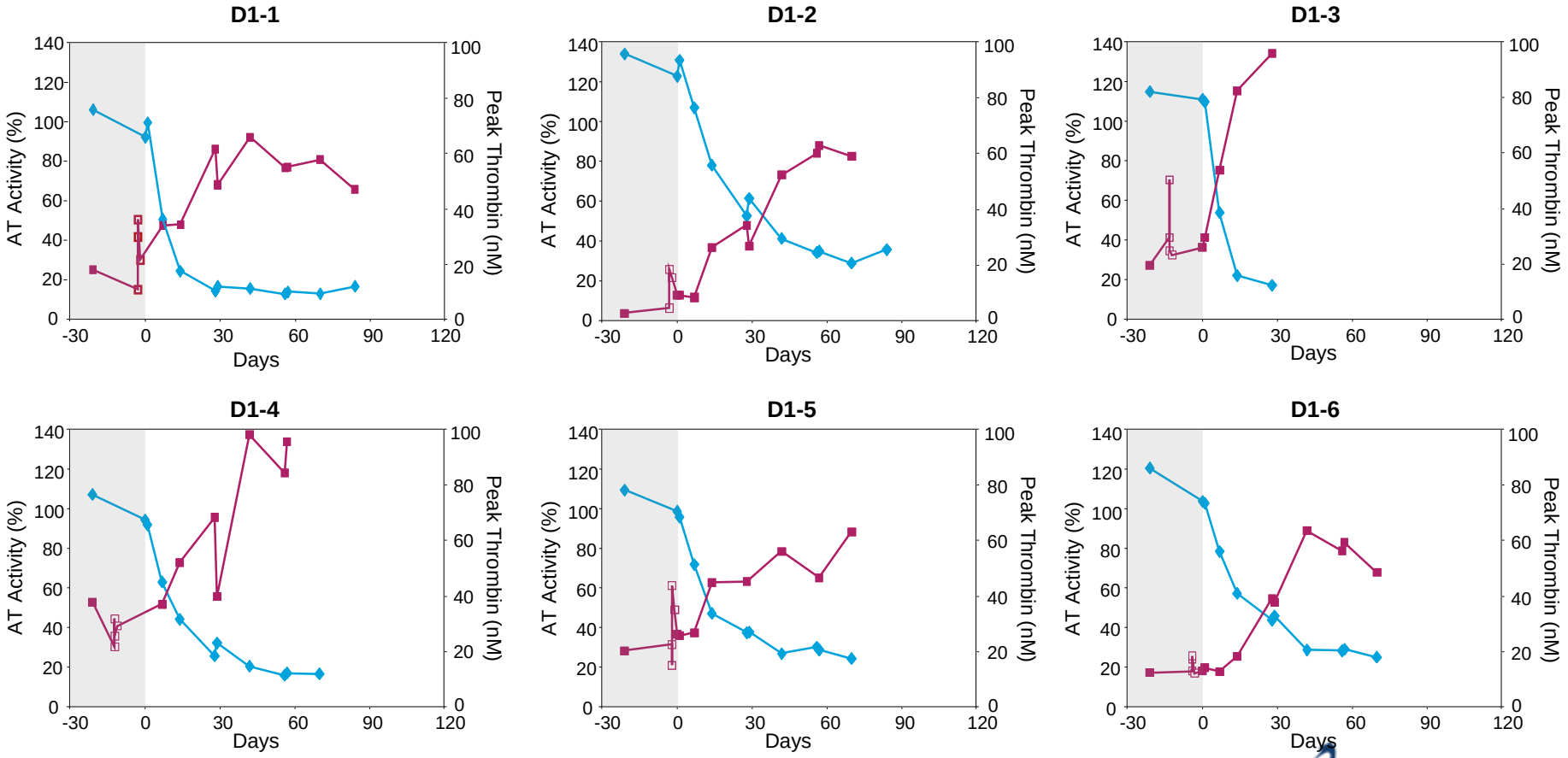
- First cohort (N=6) enrolled and dosed at fixed, low monthly dose of 50 mg
- Second cohort (N=6) enrolled and being dosed at fixed, monthly dose of 80 mg
  - Follow-up ongoing

Interim Fitusiran Phase 1 Study Results*

AT, Peak Thrombin, Part D (Cohort 1, 50 mg)

Initial AT lowering and thrombin generation results in patients with inhibitors

- Comparable AT lowering and thrombin generation as observed with similar doses in non-inhibitor patients
- Thrombin generation with fitusiran consistently exceeds transient levels achieved with BPA administration



*Data transfer: 11July2016

Interim Fitusiran Phase 1 Study Results*

Exploratory Analysis of Bleed Events, Part D (Cohort 1, 50 mg)†

Dose	Patient	Hemophilia	Prior Tx	Prescribed BPA	Pre-study ABR‡	Onset ABR	Observation Period		
							Days in Obs Period	Bleeds, n	ABR
50 mg	D1-1	HA w/ inh	OD	aPCC	40	13	57	0	0
	D1-2	HB w/ inh	OD	rFVIIa/aPCC	26	13	55	2	13
	D1-3	HA w/ inh	OD	rFVIIa	0	0	0**	N/A	N/A
	D1-4	HA w/ inh	OD	aPCC	52	38	56	4	26
	D1-5	HA w/ inh	OD	PCC	80	38	55	6	40
	D1-6	HA w/ inh	OD	rFVIIa	16	13	57	0	0

- Data suggest partial effect at 50 mg (49-100% reduction in Pre-study ABR)
- Further follow-up ongoing to explore safety and bleed efficacy with longer-term dosing; all eligible patients (reaching Day 84) have rolled over to extension study
- Second cohort dosed at 80 mg; follow-up ongoing

*Data transfer: 11Jul2016
w/ inh, with inhibitors; PPx, Prophylaxis; OD, On-Demand; ABR, annualized bleeding rate
**As of data transfer date, patient does not have sufficient follow up in Observation period
†Post hoc analysis of treated bleed events during Onset (Day 0-28) and Observation periods (Day 29 to last study visit or last dose+56 days, whichever is earlier); ‡Pre-study ABR derived from medical records

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Fitusiran Phase 1 Study*
Summary of Interim Results

Fitusiran generally well tolerated in hemophilia A and B patients with and without inhibitors

- No SAEs related to study drug; no thromboembolic events
- AEs (excluding ISRs) in ≥10% of patients: upper respiratory tract infection (10%) and arthralgia (10%); majority mild or moderate in severity
- 11 (35%) patients reported mild drug-related ISRs
  - Mostly pain and/or erythema at the injection site
- 1 discontinuation due to AE; event resolved in this patient with symptomatic management

Evidence of clinical activity and potential correction of hemophilia phenotype in non-inhibitor patients

- Dose-dependent AT lowering and thrombin generation increase achieved, with once-monthly subcutaneous dose regimen; fixed 80 mg dose provides consistent AT lowering >75%
- In exploratory post-hoc analysis in monthly dose cohorts, fitusiran achieved median ABR = 0, with 53% patients bleed-free and 82% patients experiencing zero spontaneous bleeds

Encouraging early data in inhibitor patients

- AT lowering and thrombin generation increase consistent with non-inhibitor patients
  - Thrombin generation increases consistently exceed those achieved transiently with BPA administration
- Exploratory post-hoc analysis shows 49-100% reduction of bleeds at initial 50 mg dose
- Second cohort (N=6) now fully enrolled at 80 mg

*Data transfer: up to 11Jul2016

Fitusiran
Next Steps

21 patients now enrolled in open-label extension (OLE) study, including inhibitor patients

- To date, patients have received up to 13 monthly doses of fitusiran

Additional data expected to be shared in late 2016

- Including updated results from Part D inhibitor patients and initial results from OLE study

Plan to advance to pivotal studies in early 2017

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Thank you to the Healthy Volunteers, Patients and Investigators who participated in this Phase 1 Study

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	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
	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
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United States	Margaret Ragni	Pittsburgh - Hemophilia Center of Western Pennsylvania

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