

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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Fitusiran

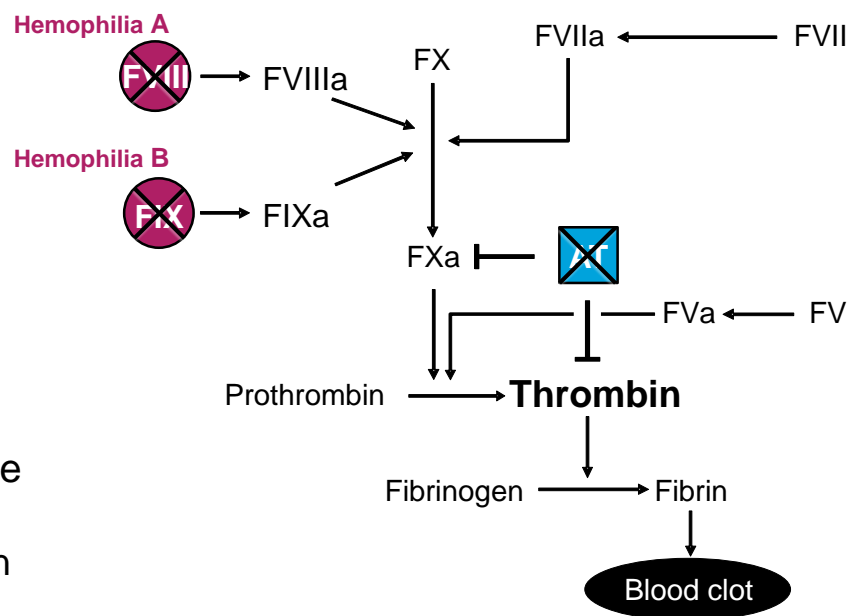
Investigational RNAi Therapeutic for Treatment of Hemophilia

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 hemophilia¹⁻⁴
 - Supported by pre-clinical data⁵ and emerging Phase 1 clinical results⁶



¹Kurnik K, et al. *Haematologica*. 92:982-985 (2007); ²Ettingshausen E, et al. *Thromb Haemost*. 85:218-220 (2001); ³Negrier C, et al. *Blood*. 81:690-695 (1993); ⁴Shetty S, et al. *Br J Haematol*. 138:541-544 (2007); ⁵Seghal A, et al. *Nat Med*. 21:492-497 (2015); ⁶Pasi 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

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 | 2 | 6 | 2 | 2 | 2 | 3 | 3 | 3 | 5 |
| Hemophilia B | 1 | 0 | 1 | 1 | 1 | 0 | 0 | 3 | 1 |
| Severe | 3 | 6 | 3 | 2 | 3 | 2 | 3 | 5 | 6 |
| Moderate | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 |
| Weight (kg), mean (SD) | 76 (10) | 80 (22) | 82 (8) | 85 (12) | 76 (16) | 76 (2) | 71 (12) | 74 (10) | 73 (17) |

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 $\geq 10\%$ 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

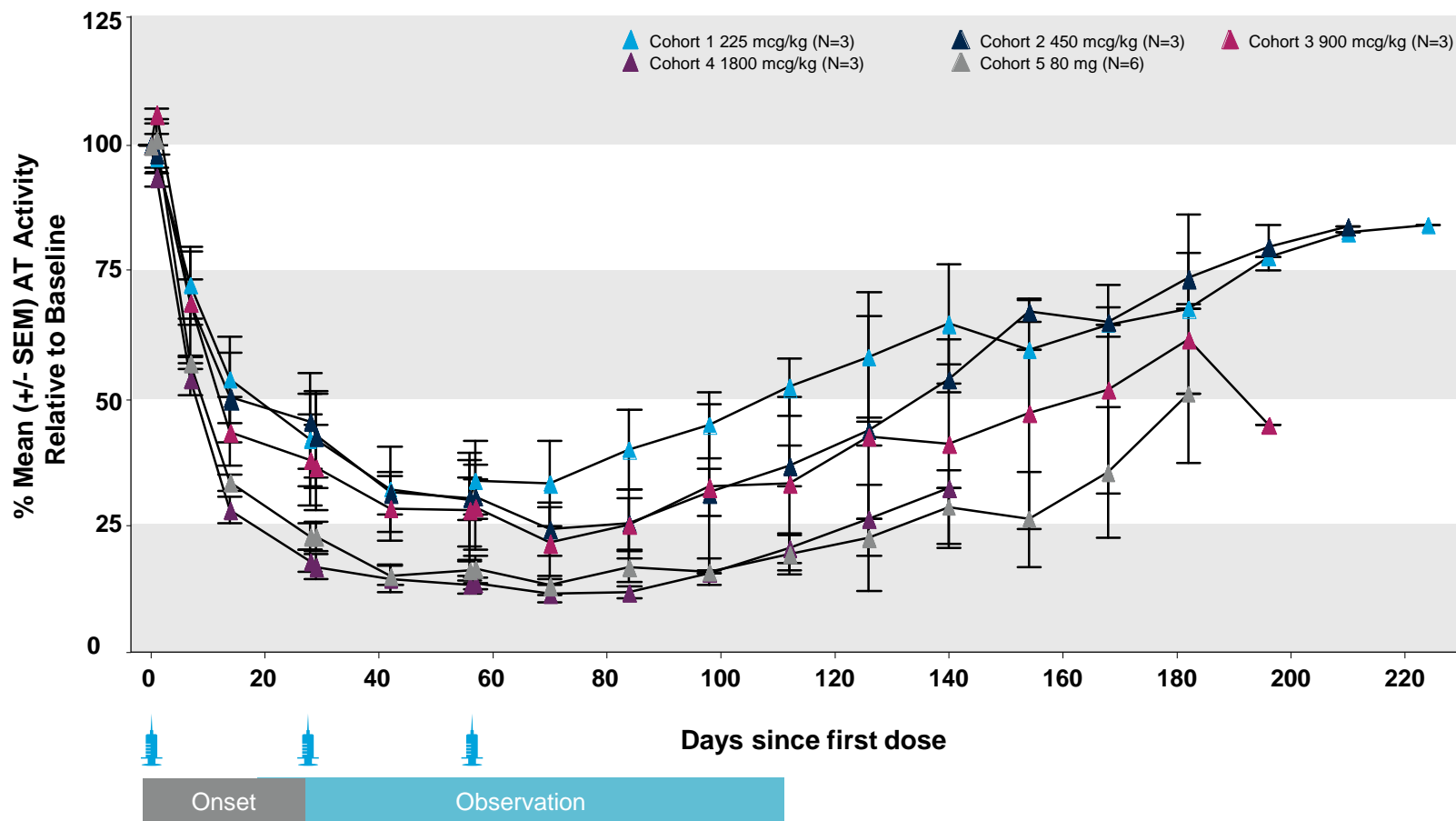
*Data transfer up to 11 July 2016

†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

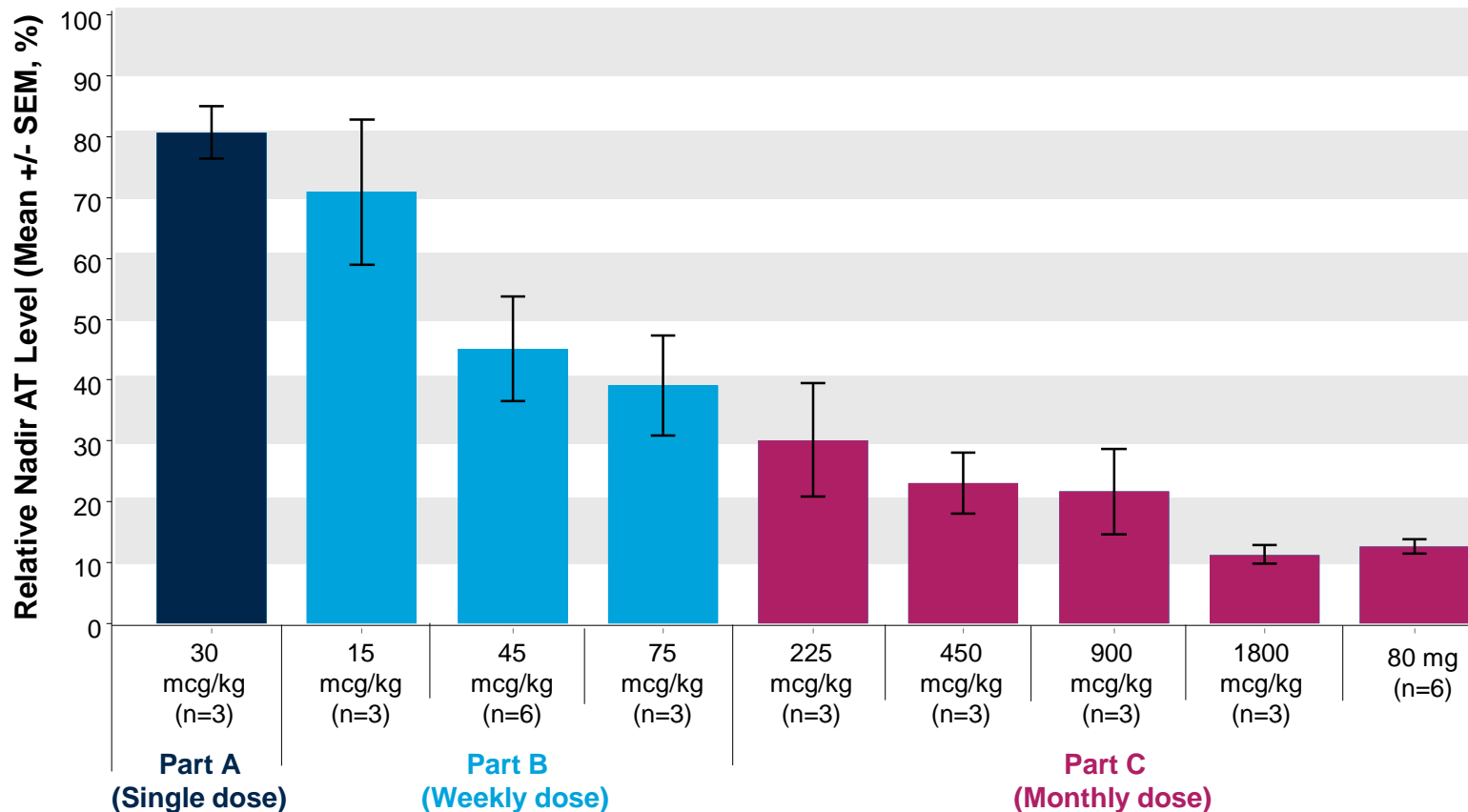


Interim Fitusiran Phase 1 Study Results*

AT Lowering, Parts A, B & C

Dose-dependent AT lowering

- Mean maximal AT lowering of $87 \pm 1\%$ at 80 mg fixed dose

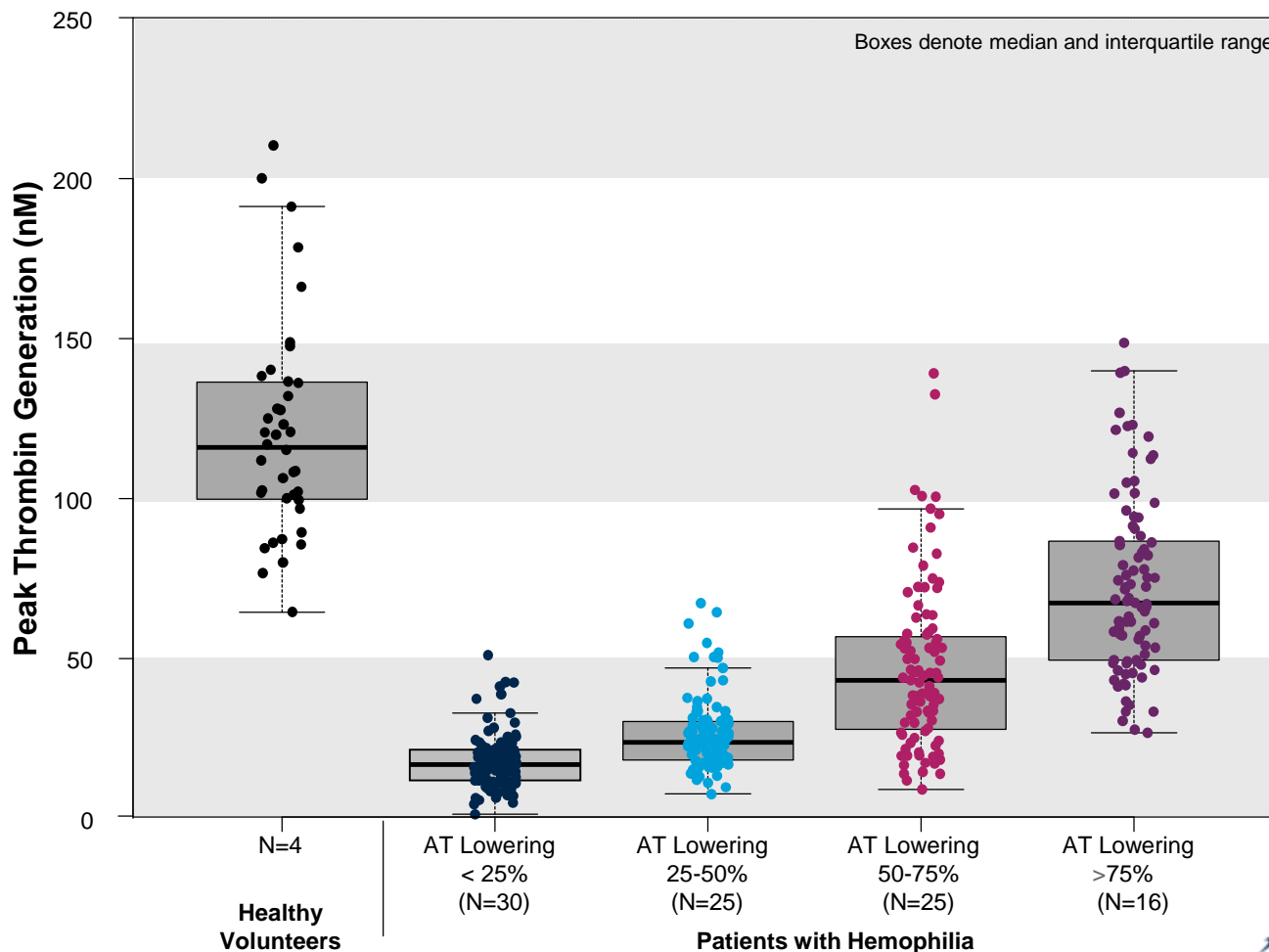


Interim Fitusiran Phase 1 Study Results*

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

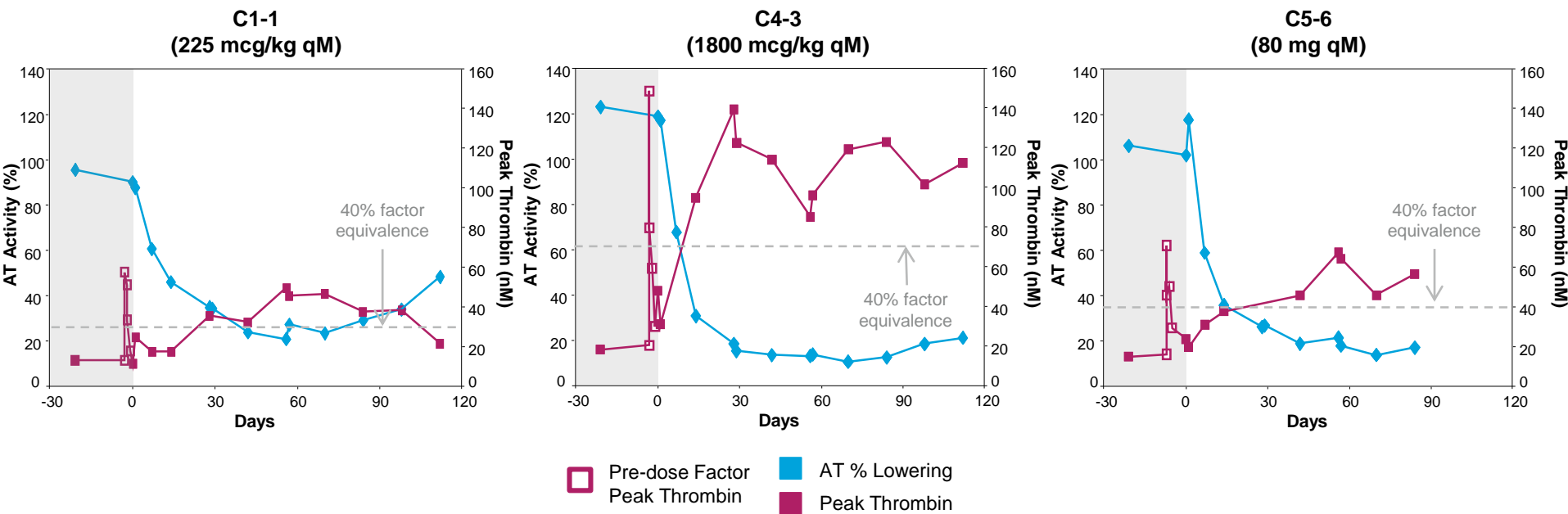
† %Change in Peak TG: $p < 0.001$ by Mann-Whitney test, when compared with AT3 lowering than <25% group

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

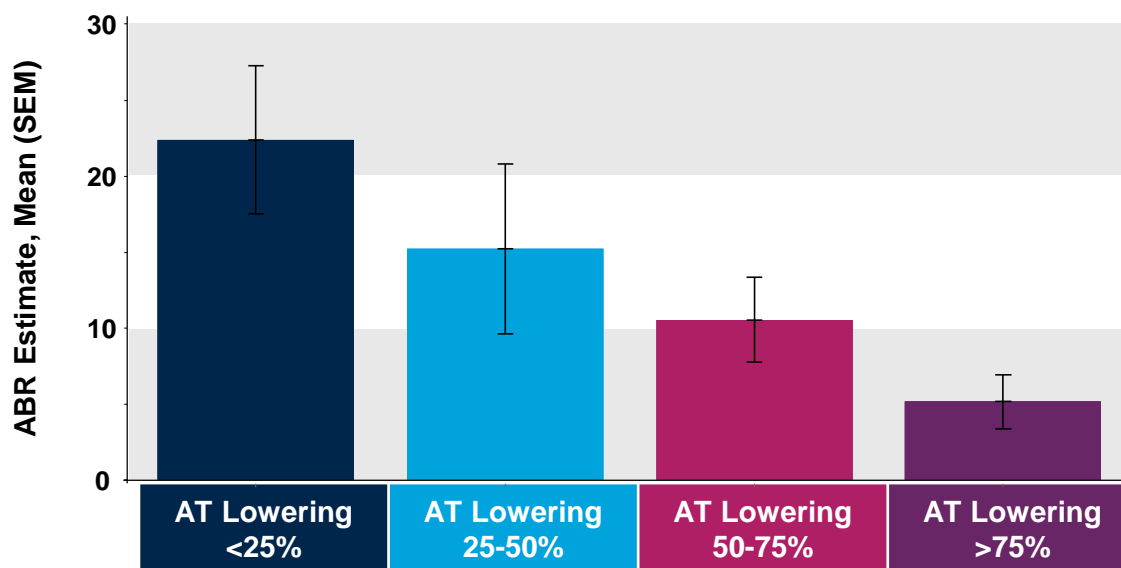


Interim Fitusiran Phase 1 Study Results*

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



| | | | | |
|--------------------------------------|--------|--------|--------|-------|
| 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

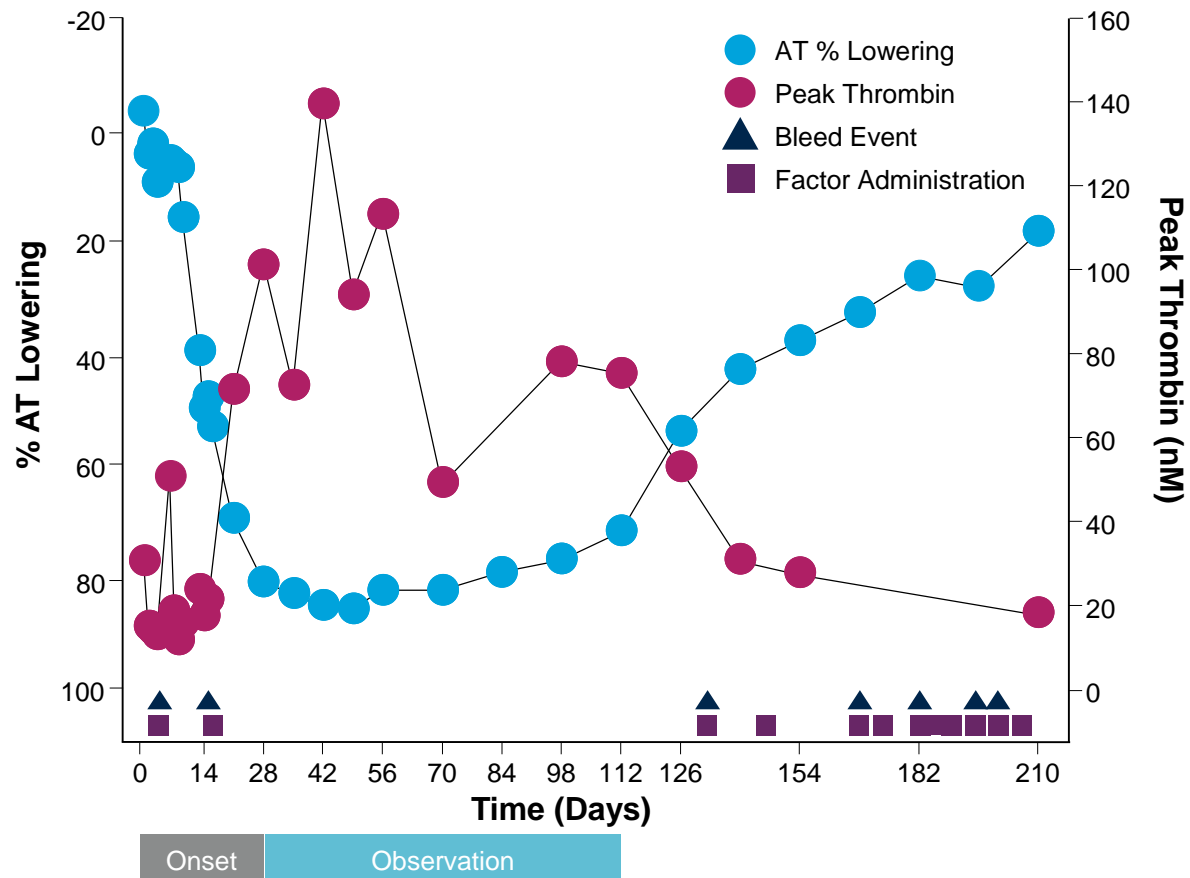
[†]Number of patients with time spent in quartile; [‡]For each patient, the ABR in each quartile is calculated by 365.24*(number of bleed events/number of days in quartile)

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)



*Data transfer: 30Jun2016

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

Plot updated on 11Aug2016 to reflect corrected peak thrombin values (reruns conducted on samples with assay errors)



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

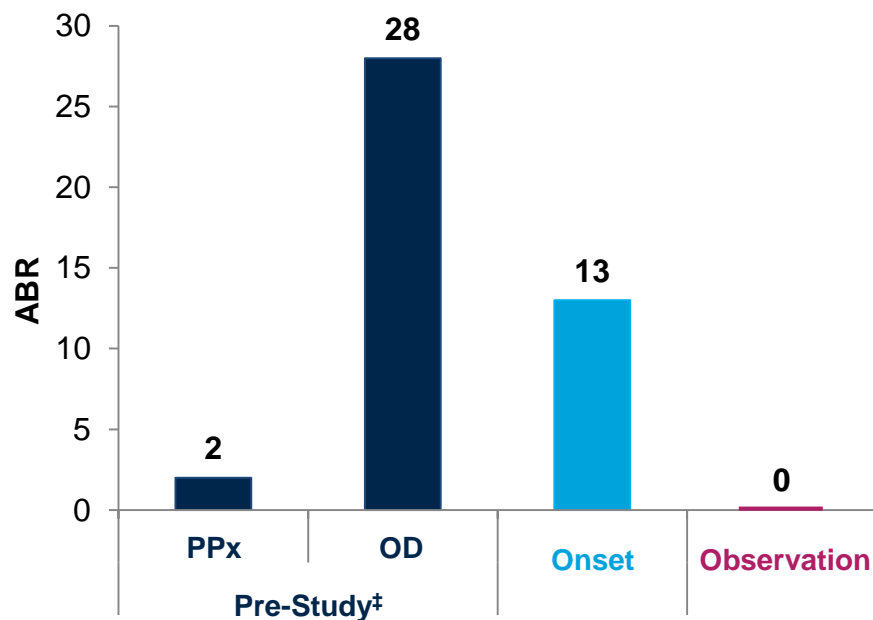
PPx: Prophylaxis, OD: On-Demand; ABR, annualized bleeding rate; AsBR, annualized spontaneous bleeding rate

†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

Interim Fitusiran Phase 1 Study Results*

Exploratory Analysis of Bleed Events, Part C†

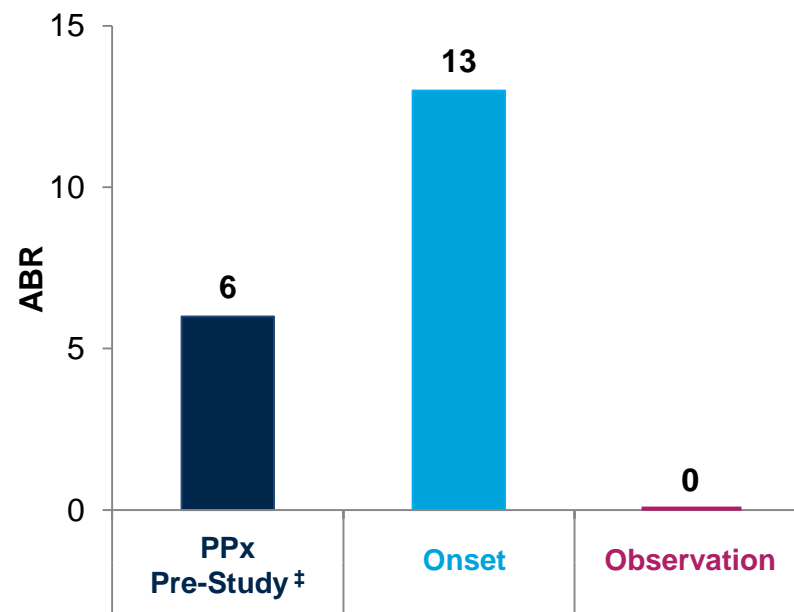
Summary of Median ABR (All Cohorts)



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

Summary of Median ABR (80 mg)



Part C, 80 mg dosing cohort[^]

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

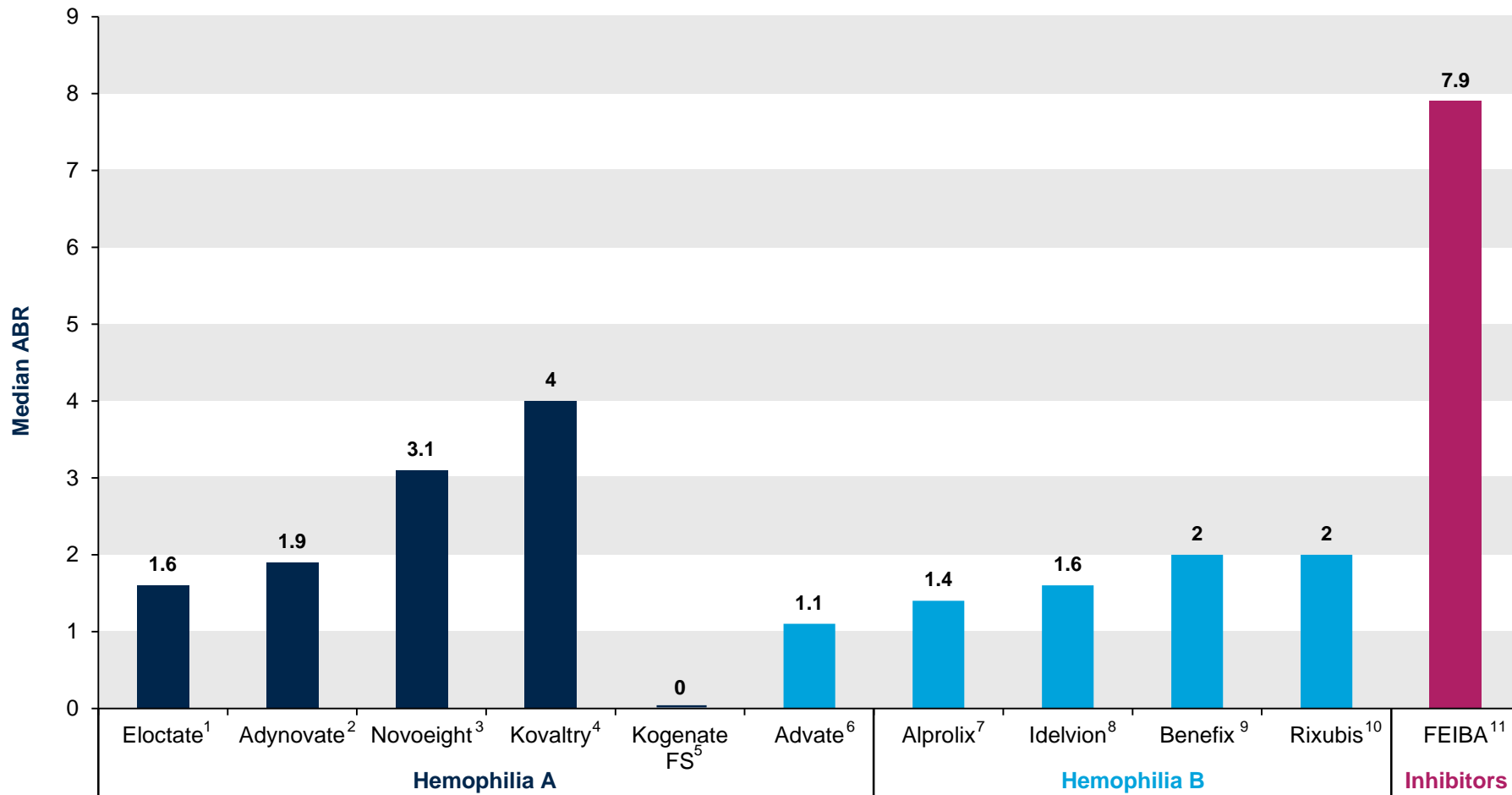
*Data transfer: 30Jun2016

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

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

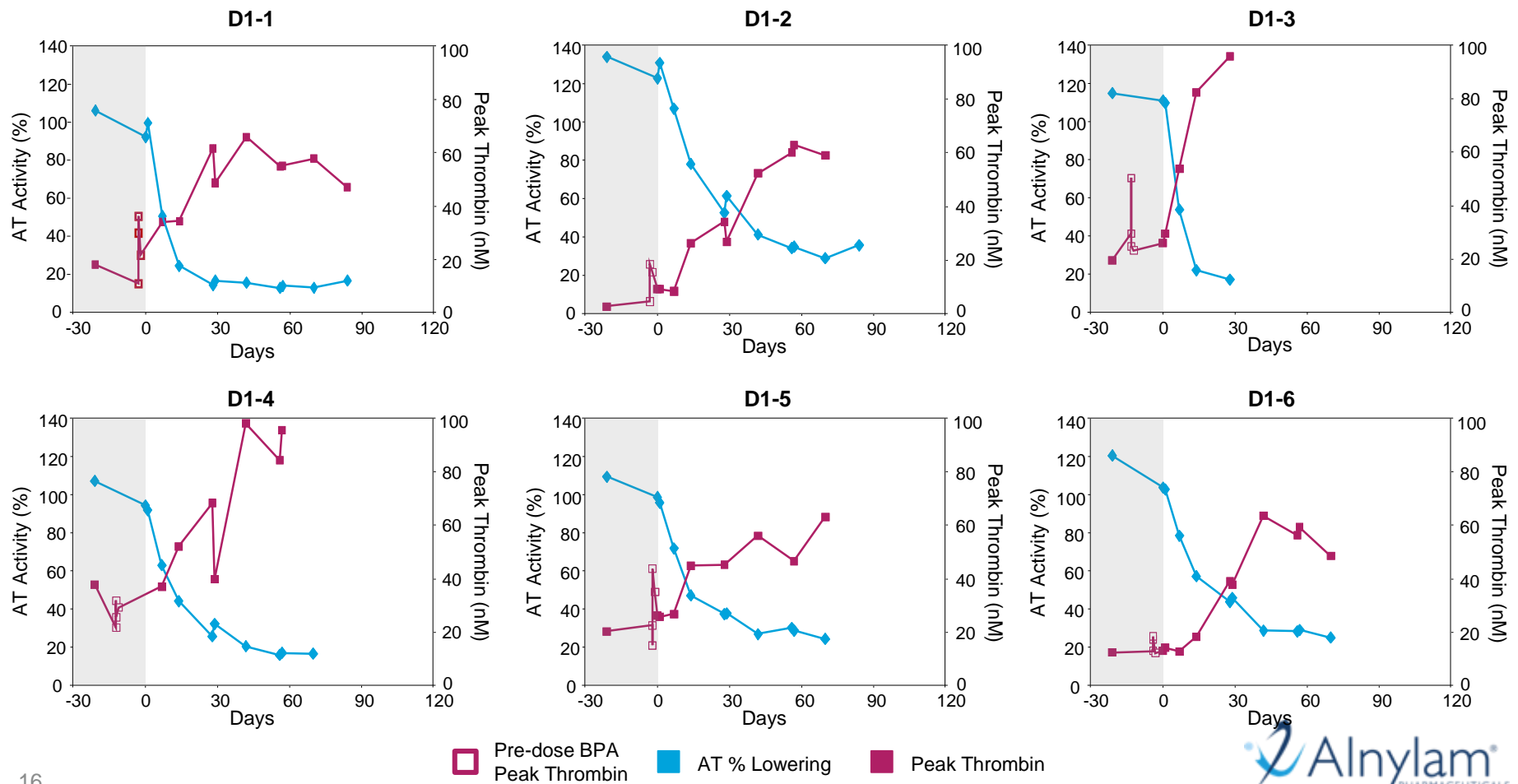
- First cohort (N=6) enrolled and dosed at fixed, low monthly dose of 50 mg
- Second cohort (N=6) enrolled and being dosed at fixed, monthly dose of 80 mg
 - Follow-up ongoing

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



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

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 $\geq 10\%$ 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

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

Acknowledgements

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

| Country | PI Name | Location |
|----------------|---------------------------|---|
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