Fitusiran, an Investigational RNAi Therapeutic Targeting Antithrombin for the Treatment of Hemophilia: Results from Phase 1 and Phase 2 Extension Studies in Patients without Inhibitors

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Fitusiran

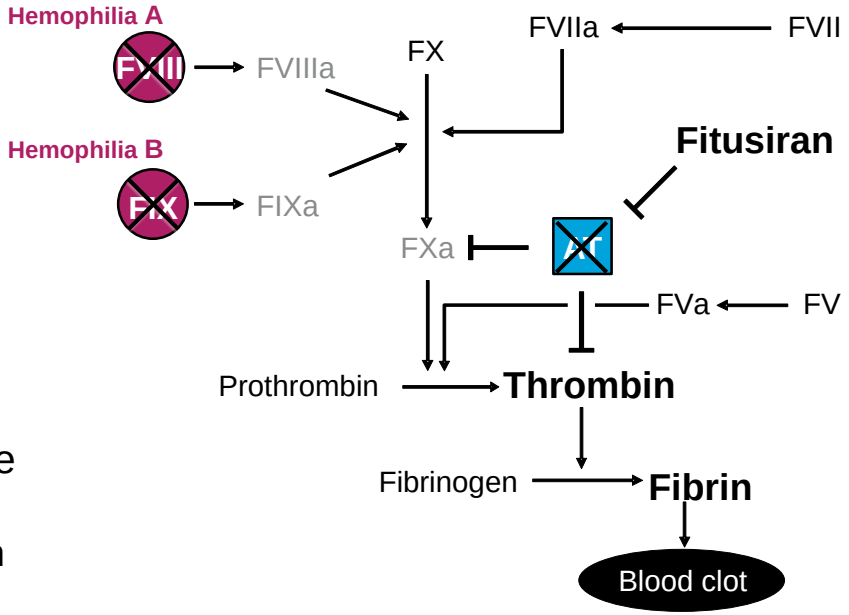
Investigational RNAi Therapeutic for Treatment of Hemophilia

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

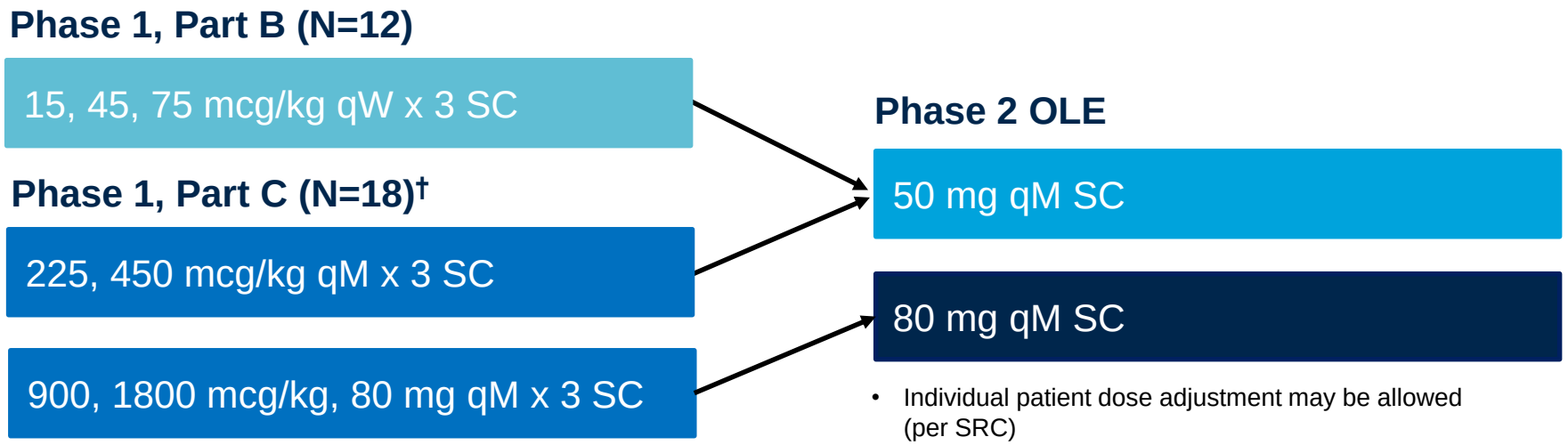
- Hemophilia A and B are bleeding disorders characterized by ineffective clot formation due to insufficient thrombin generation
- Fitusiran is designed to lower AT, with goal of promoting sufficient thrombin generation to restore hemostasis and prevent bleeding
  - Observation of ameliorated bleeding 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[6,7]



[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. 2015, 126:551*; [7]Pasi KJ, et al. *Haemophilia.* 2016, 22(Suppl 4)

Fitusiran Phase 2 OLE Study Design
Patients with Hemophilia without Inhibitors

Patients previously dosed in Phase 1* study eligible to roll over onto Phase 2 Open-Label Extension (OLE)^ study



- As of data cut-off of 06Oct2016, 16 patients from Phase 1, Parts B & C have transitioned to Phase 2 OLE
  - Days between doses in Phase 1 and Phase 2 OLE ranged from 30 (no interruption in dosing) to 461

OLE, open-label extension; qW, weekly; qM, monthly; SC, subcutaneous
*ClinicalTrials.gov Identifier:NCT02035605; Pasi KJ, et al. *Haemophilia.* 2016, 22(Suppl 4)
^ClinicalTrials.gov Identifier: NCT02554773
†5 patients participating in Part C previously participated in Part B

Interim Fitusiran Phase 2 OLE Study Results*

Demographics/Baseline Characteristics in Patients without Inhibitors

	50 mg N=8	80 mg N=8
Age, years; mean (range)	35 (19-61)	41 (24-58)
Weight, kg; mean (range)	80 (65-94)	74 (58-80)
Hemophilia A Hemophilia B	6 2	7 1
Severe Moderate	7 1	6 2
Medical history of hepatitis C	6	6

*Data cut-off 06Oct2016

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Interim Fitusiran Phase 2 OLE Study Results*
Safety/Tolerability† in Patients without Inhibitors

Fitusiran generally well tolerated with up to 14 months continuous administration at 50-80 mg qM

- No discontinuations due to AEs or drug-related SAEs
- No thromboembolic events
- All AEs mild or moderate in severity
  - Non-laboratory AEs reported in ≥2 patients: 4/16 (25%) injection site reactions (ISRs) and vomiting 2/16 (13%)
  - ISRs all mild; mostly pain and/or erythema at injection site
- ALT increases >3x ULN were observed in 3 patients
  - All asymptomatic, with no concurrent elevations of bilirubin >2x ULN
  - All patients had medical history of HCV
  - With currently available follow-up, 2 patients with declining ALT through continued dosing
- No laboratory evidence of pathologic clot formation (changes in D-dimer, platelet count, fibrinogen, and/or PT/INR)
- No clinically significant changes in other laboratory parameters
- No instances of anti-drug antibody (ADA) formation
- All bleed events successfully managed with replacement factor
- Safety profile generally consistent with observations in Phase 1 study[1]

*Data cut-off 06Oct2016;
AE, adverse events; SAE, serious adverse events
†Adverse event grouping based on MedDRA-coded terms, excluding bleed events
1. Pasi KJ, et al. *Haemophilia.* 2016, 22(Suppl 4)

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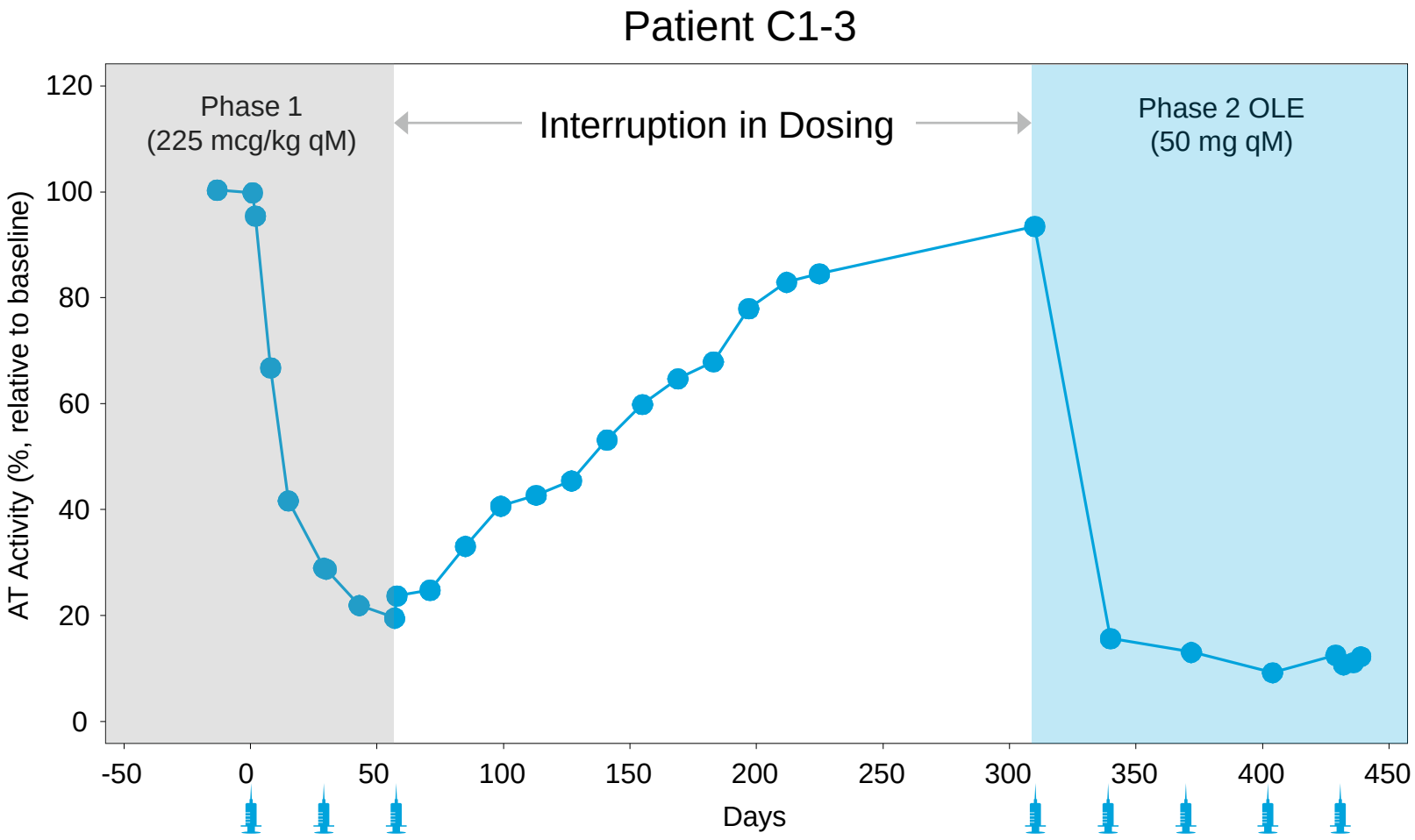
Illustration of Reversibility of AT Lowering

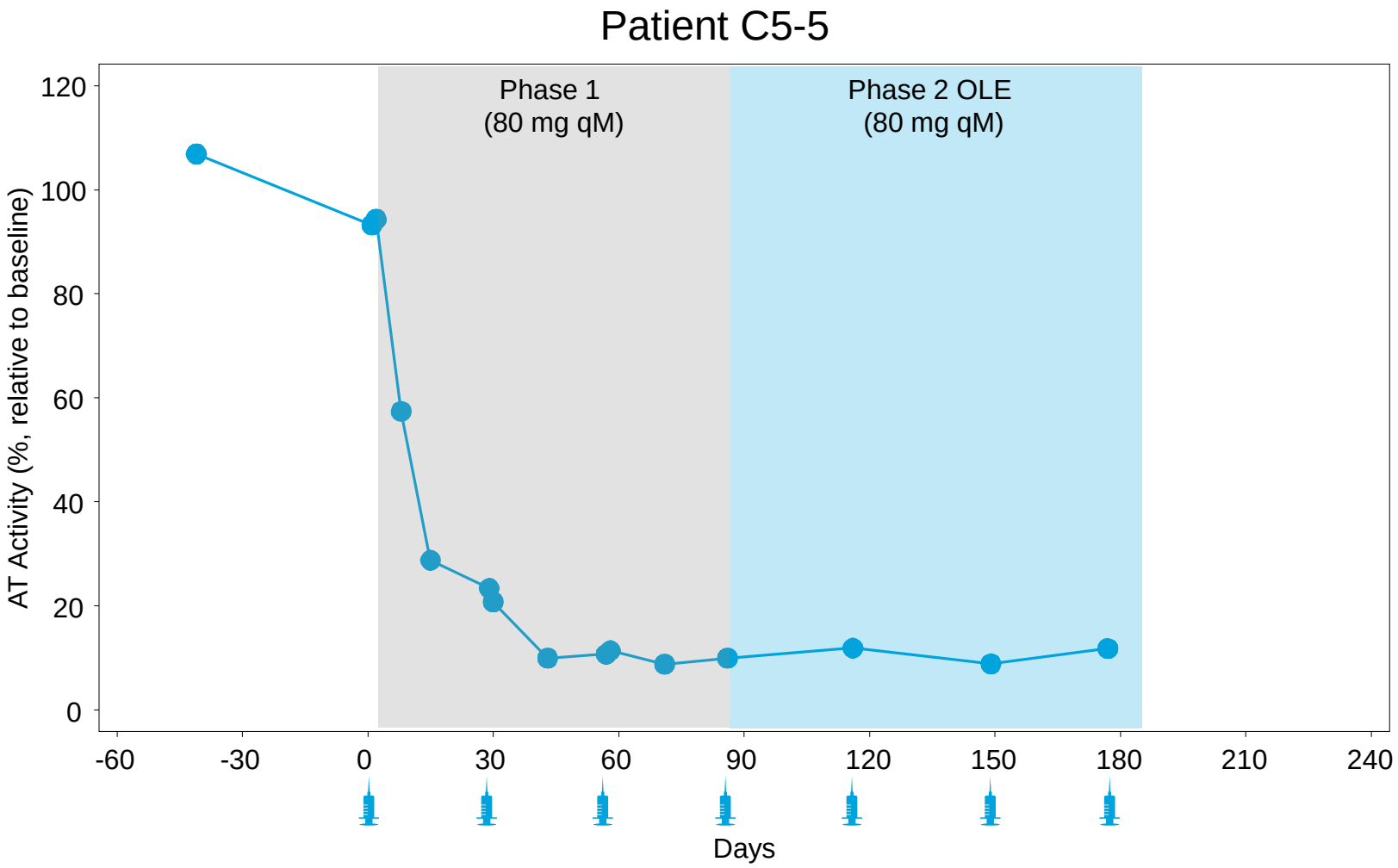
Interruption in Dosing Phase 1 to Phase 2 OLE



*Data cut-off 06Oct2016
OLE, open-label extension

Illustration of Consistency of AT Lowering

Continuous Dosing Phase 1 to Phase 2 OLE

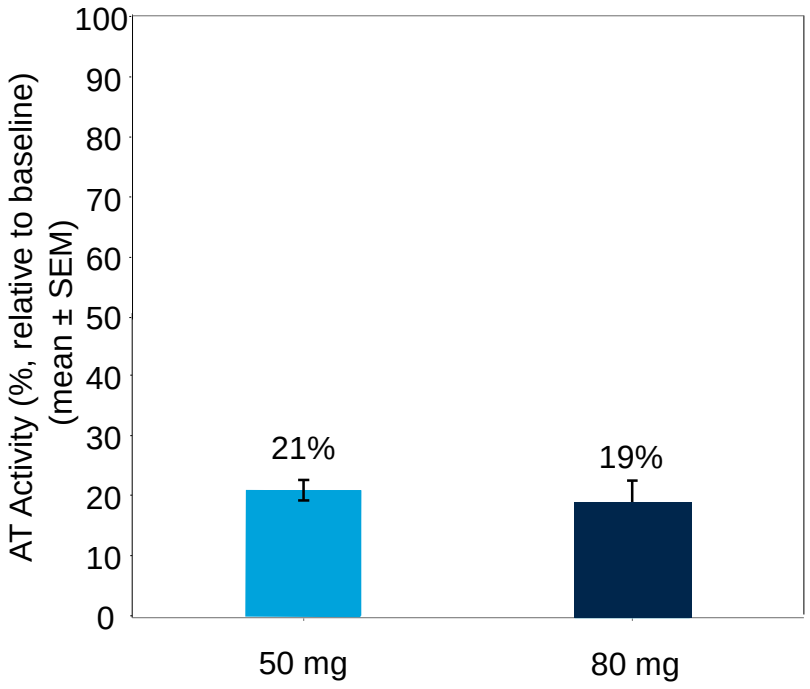


*Data cut-off 06Oct2016
OLE, open-label extension

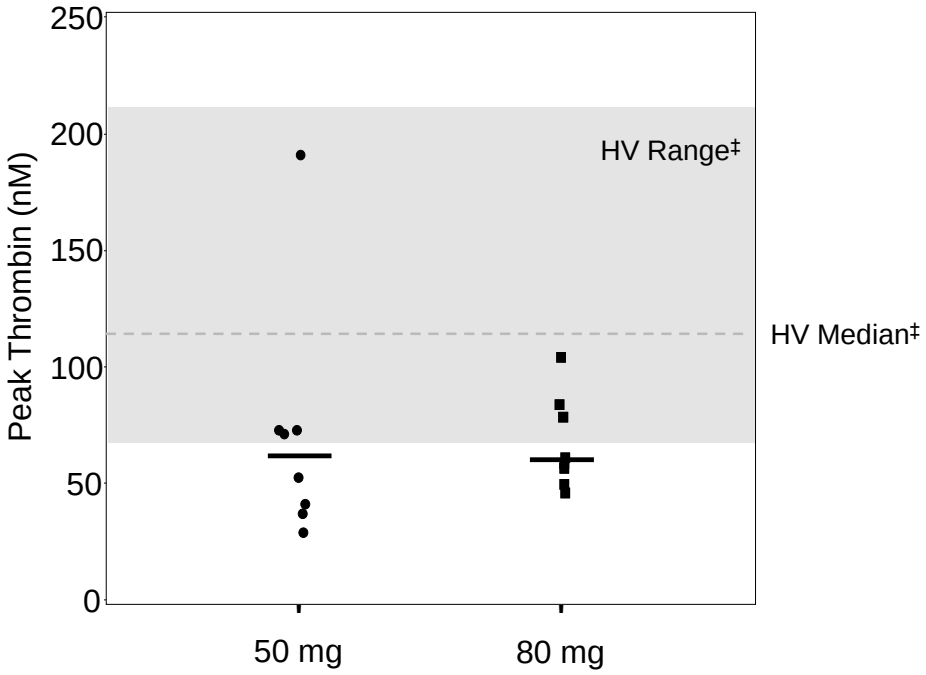
Interim Fitusiran Phase 2 OLE Study Results*

AT Level and Thrombin Generation in Patients without Inhibitors†

AT Levels



Thrombin Generation



*Data cut-off 06Oct2016
OLE, open-label extension; AT, antithrombin; SEM, standard error of the mean; HV, Healthy Volunteer
†Based on last available measurement; ‡Healthy volunteers with AT lowering <25% (Pasi KJ, et al. *Haemophilia.* 2016, 22(Suppl 4))

Interim Fitusiran Phase 2 OLE Study Results*

Exploratory Analysis of Bleed Events† in Patients without Inhibitors

Patient	Prior Tx	Pre-study ABR‡	Phase 1 Dose	Current Dose (qM)	Observation Period				
					Days	All Bleeds, n	ABR	Spontaneous Bleeds, n	AsBR
B2-4	OD	26	45 mcg/kg qW	50 mg	162	4	**9.0**	2	**4.5**
B2-5	OD	22	45 mcg/kg qW	50 mg	162	0	**0**	0	**0**
B3-1	PPx	4	75 mcg/kg qW	50 mg	63	0	**0**	0	**0**
B3-3	PPx	4	75 mcg/kg qW	50 mg	167	0	**0**	0	**0**
C1-1	PPx	2	225 mcg/kg qM	50 mg	335	4	**4.4**	3	**3.3**
C1-2	PPx	0	225 mcg/kg qM	50 mg	189	1	**2.0**	0	**0**
C1-3	PPx	0	225 mcg/kg qM	50 mg	148	2	**4.9**	0	**0**
C2-2	OD	38	450 mcg/kg qM	50 mg	174	0	**0**	0	**0**
C3-1^	PPx	0	900 mcg/kg qM	80 mg	373	0	**0**	0	**0**
C3-2	OD	20	900 mcg/kg qM	80 mg	133	13	**35.7**	0	**0**
C3-3	OD	32	900 mcg/kg qM	80 mg	162	0	**0**	0	**0**
C4-1^	PPx	0	1800 mcg/kg qM	80 mg	329	0	**0**	0	**0**
C4-2	OD	24	1800 mcg/kg qM	80 mg	169	0	**0**	0	**0**
C4-3	PPx	0	1800 mcg/kg qM	80 mg	170	1	**2.1**	1	**2.1**
C5-5^	PPx	6	80 mg qM	80 mg	261	3	**4.2**	1	**1.4**
C5-6^	PPx	0	80 mg qM	80 mg	224	2	**3.3**	1	**1.6**

*Data cut-off 06Oct2016

OLE, open-label extension; qW, weekly; qM, monthly; ABR, annualized bleeding rate; AsBR, annualized spontaneous bleeding rate

†Post hoc analysis of treated bleed events during observation period (Day 29 to last study visit or last dose+56 days, whichever is earlier); ‡Pre-study ABR derived from medical records; ^Patients C3-1, C4-1, C5-5, and C5-6 had no treatment interruption and therefore continuous observation period from Phase 1

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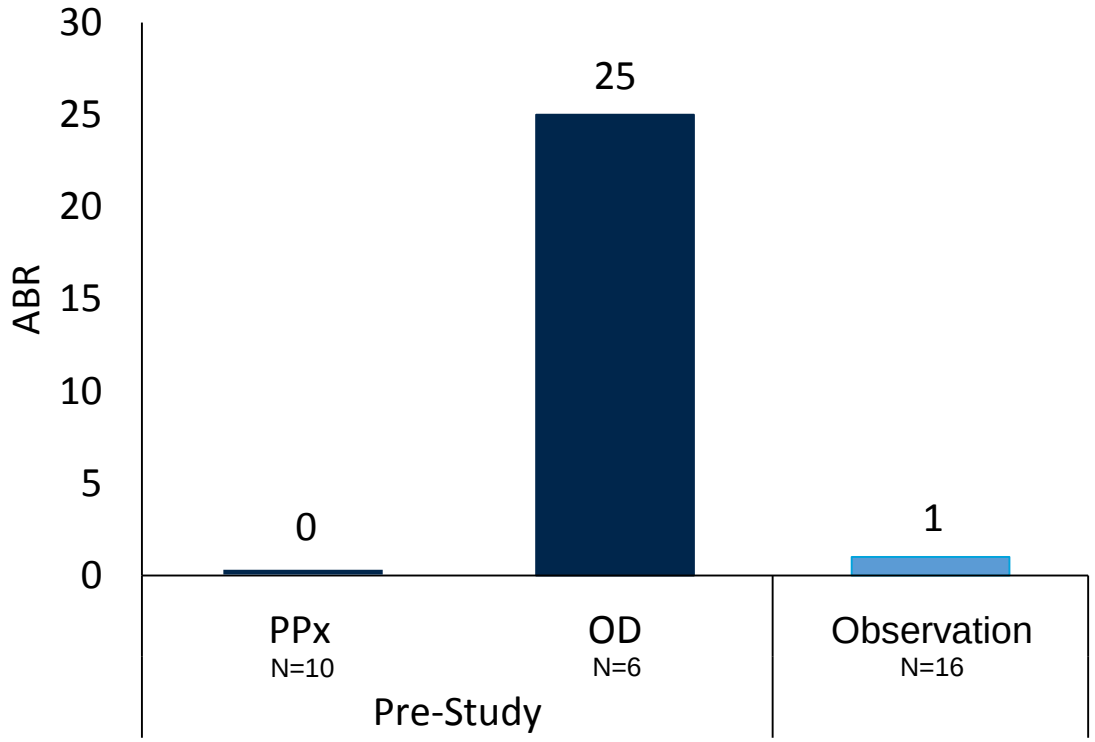
Interim Fitusiran Phase 2 OLE Study Results*

Summary of Median ABRs in Patients without Inhibitors



- Median ABR, Observation period = 1
  - Patients reporting no bleeds: 8/16 (50%)
  - Patients reporting no spontaneous bleeds (AsBR = 0): 11/16 (69%)
- Median duration in observation period = 170 days (5.7 months)

*Data cut-off 06Oct2016

PPx, prophylaxis; OD, on demand; ABR, annualized bleeding rate; AsBR, annualized spontaneous bleeding rate

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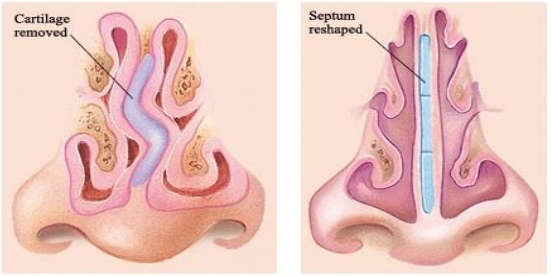
Initial Surgical Case Experience on Fitusiran
Elective Septoplasty



Patient

- C1-3, severe hemophilia A
- Dose level: 50 mg
- Last available AT level prior to procedure: 13% relative to baseline

Procedure

- Factor utilization: investigator reports cumulative periprocedural utilization of recombinant factor VIII as 20% of that typically used
- Investigator reported* hemostatic efficacy ratings based on ISTH score[1]
  - Intraoperative: Excellent
  - 24 h post-operative: Excellent
  - 7 days post-operative: Excellent
- Safety
  - No AEs reported in this patient during procedure or 64 days of subsequent continued follow up

*Per investigator's retrospective report

1. Khorsand N, et al. *J Thromb Haemost.* 14:211–4 (2016)

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Interim Fitusiran Phase 2 OLE Study Results*
Summary and Next Steps

Fitusiran generally well tolerated in hemophilia A and B patients without inhibitors
- No SAEs related to study drug; no thromboembolic events
- All AEs were mild or moderate in severity; ISRs most common AE, all mild

Transition from Phase 1 to Phase 2 OLE demonstrates key attributes of fitusiran pharmacology, including reversibility and clamped AT lowering

Evidence of clinical activity
- Once-monthly subcutaneous dosing at 50 mg and 80 mg achieves dose-dependent AT lowering of ~80% and thrombin generation levels approaching the lower end of normal range
- Exploratory post-hoc analysis of bleeding events demonstrates median ABR = 1 and median AsBR = 0
  - 8/16 (50%) patients bleed-free and 11/16 (69%) patients experiencing zero spontaneous bleeds

First surgical case experience on fitusiran
- Elective septoplasty successfully performed in severe hemophilia A patient without inhibitors
- Reduced factor utilization reported by investigator

Plan to advance fitusiran to pivotal studies in early 2017

*Data cut-off 06Oct2016
SAE: serious adverse events; AE, adverse events; ISR, injection site reactions; AT, anti-thrombin; ABR, annual bleed rate; OLE, open-label extension

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Acknowledgements

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