Interim Analysis of Safety and Efficacy in the Phase 2 Open-Label Extension Study of Fitusiran in Subjects With Hemophilia A or B, With or Without Inhibitors

K. John Pasi,[1] Claude Négrier,[2] Steven W. Pipe,[3] Margaret V. Ragni,[4] Toshko Lissitchkov,[5] Pencho Georgiev,[6] Vasily Mamonov,[7] Qifeng Yu,[8] Ievgeniia Uzun,[9] Shauna Andersson,[8] Baisong Mei[8]

[1]Royal London Haemophilia Centre, Barts and the London School of Medicine and Dentistry, London, United Kingdom; [2]Hôpital Cardiologique Louis Pradel, Lyon, France; [3]University of Michigan, Ann Arbor, MI, United States; [4]University of Pittsburgh and Hemophilia Center of Western Pennsylvania, Pittsburgh, PA, United States; [5]Clinical Department of Specialized Hospital for Active Treatment of Haematological Diseases, Sofia, Bulgaria; [6]University Multiprofile Hospital for Active Treatment "Sveti Georgi" and Medical University of Plovdiv, Plovdiv, Bulgaria; [7]National Research Center for Hematology, Moscow, Russia; [8]Sanofi, Cambridge, MA, United States; [9]Sanofi, Bridgewater, NJ, United States

June 19, 2020

Disclosures for K. John Pasi, MBChB, PhD, FRCP, FRCPath, FRCPCH

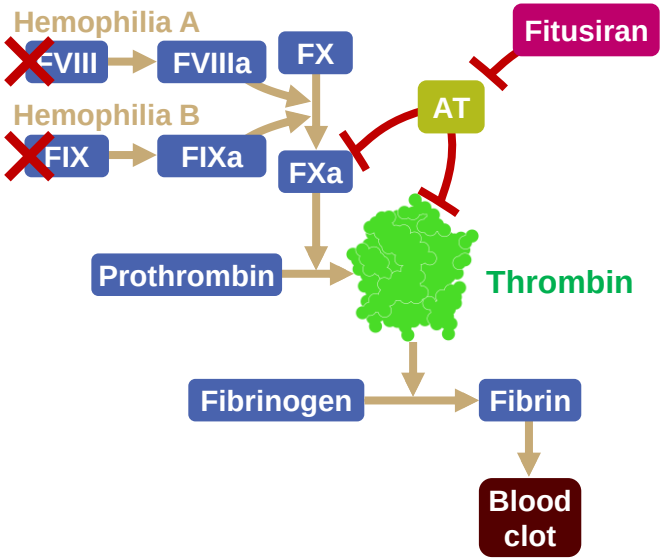
Conflict	Disclosure – if conflict of interest exists
Shareholder	
Grant/Research Support	
Consultant	**Scientific Advisory Board: ApcinteX, BioMarin, Biotest, Catalyst Bio, Roche, Sanofi, Sobi**
Employee	
Paid Instructor	
Speaker Bureau	**Bayer, BioMarin, Novo Nordisk, Octapharma, Pfizer, Sanofi Genzyme, Shire, Sobi**

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

Fitusiran: A Novel Investigational RNAi Therapeutic for Treating Hemophilia[1]

- Therapeutic hypothesis of antithrombin (AT) lowering
  - Hemophilia A and B are caused by an imbalance in hemostasis due to FVIII and FIX deficiency, respectively, resulting in insufficient thrombin generation (TG)[2]
  - Fitusiran is designed to lower AT levels, with the goal of improving hemostasis and TG[3]
  - Milder bleeding phenotypes are observed in people with hemophilia who have co-inherited thrombophilic markers, such as AT deficiency[4-6]
  - Preclinical data[7] and clinical studies[8-10] provide support for this hypothesis

Site of action of fitusiran in the coagulation cascade[1,11]

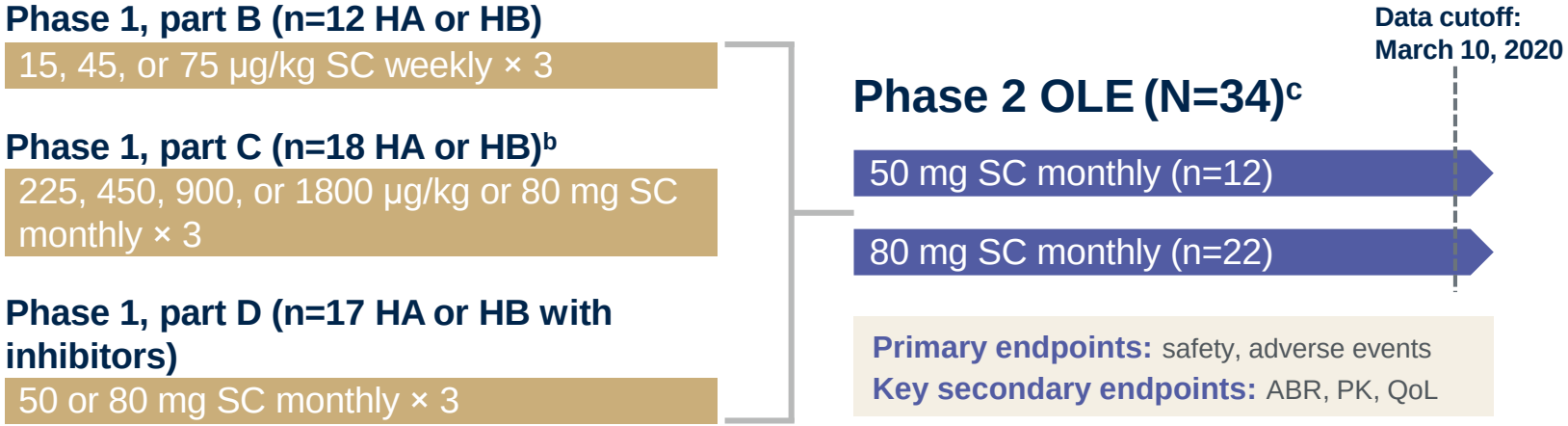


F, factor; RNAi, RNA interference. "a" indicates the activated form of a factor.

1. Machin N, Ragni MV. *J Blood Med.* 2018;9:135-140. **2.** Negrier C, et al. *Blood Rev.* 2019;38:100582. **3.** Sanofi Genzyme. ALN-AT3SC-002 Clinical Study Protocol. May 31, 2018. **4.** Kurnik K, et al. *Haematologica.* 2007;92:982-985. **5.** Ettingshausen CE, et al. *Thromb Haemost.* 2001;85:218-220. **6.** Shetty S, et al. *Br J Haematol.* 2007;138:541-544. **7.** Sehgal A, et al. *Nat Med.* 2015;21:492-497. **8.** Pasi KJ, et al. *Blood.* 2016;128:1397. **9.** Ragni MV, et al. *Blood.* 2016;128:2572. **10.** Pasi KJ, et al. *N Engl J Med.* 2017;377:819-828. **11.** Alnylam Pharmaceuticals. Investigator's Brochure: Fitusiran (ALN-AT3SC). 5th ed. 2017.

Fitusiran Phase 2 OLE: Study Design and Subject Disposition

Subjects with moderate or severe hemophilia A or B who tolerated fitusiran in phase 1 were eligible to continue into the phase 2 OLE[a]



The phase 2 OLE study was designed to evaluate the long-term efficacy and safety of fitusiran in subjects with moderate or severe hemophilia A or B, with or without inhibitors, who had participated in a previous study of fitusiran

[a]ClinicalTrials.gov identifiers: phase 1, NCT02035605; phase 2 OLE, NCT02554773. [b]A total of 5 subjects in part C previously participated in part B. [c]A total of 3 subjects started phase 2 OLE at their original phase 1 dose; later they were converted to 50 mg or 80 mg.
ABR, annualized bleed rate; HA, hemophilia A; HB, hemophilia B; OLE, open-label extension; PK, pharmacokinetics; QoL, quality of life; SC, subcutaneous.
Sanofi Genzyme. Data on file.

Fitusiran Phase 2 OLE: Subject Demographics and Exposure

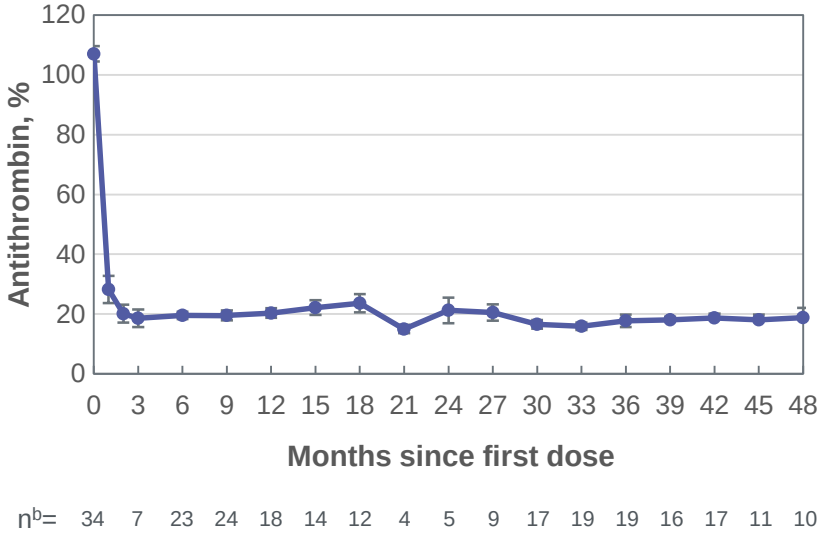
Characteristics	All subjects (N=34)		All subjects (N=34)		Overall (N=34)
	HA (n=27)	HB (n=7)	Inh (n=15)	Non-inh (n=19)	
Age, mean (range), y	36.4 (19-61)	31.4 (22-45)	32.1 (21-41)	37.9 (19-61)	35.4 (19-61)
Weight, mean (range), kg	75.0 (52-108)	76.3 (58-93)	75.3 (52-108)	75.2 (58-94)	75.2 (52-108)
50-mg dose, No. (%) 80-mg dose, No. (%)	9 (33) 18 (67)	3 (43) 4 (57)	2 (13) 13 (87)	10 (53) 9 (47)	12 (35) 22 (65)
Severe disease, No. (%) Moderate disease, No. (%)	26 (96) 1 (4)	5 (71) 2 (29)	15 (100) 0	16 (84) 3 (16)	31 (91) 3 (9)
History of hepatitis C, No. (%)	23 (85)	3 (43)	11 (73)	15 (79)	26 (77)
Exposure, median (range), d[a]	32 (3-57)	38 (22-47)	32 (3-43)	38 (9-57)	32 (3-57)

Maximum of 4.7 years (median 2.6 years) of fitusiran dosing

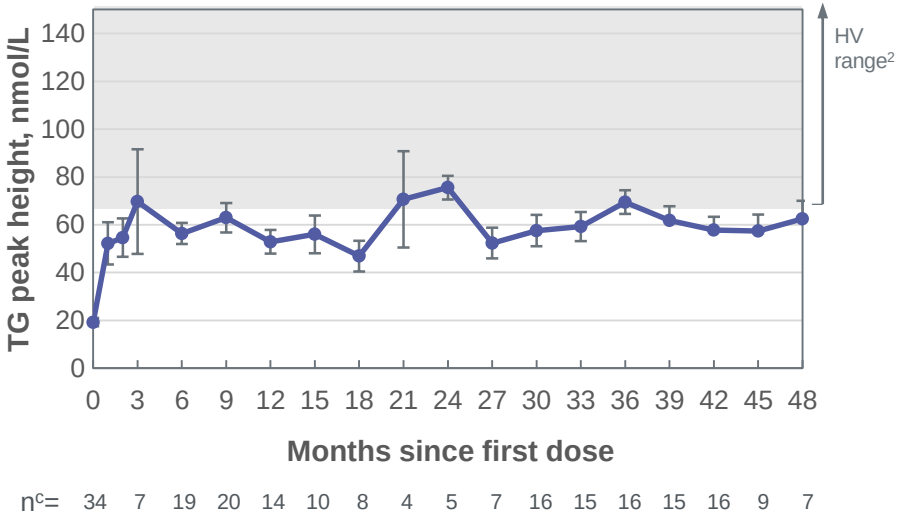
Data cutoff: March 10, 2020.
[a]Duration of treatment exposure = date of last dose of extension study – date of first dose of parent study – dose hold period in extension study – gap between parent study and extension study.
HA, hemophilia A; HB, hemophilia B; inh, with inhibitors; non-inh, without inhibitors; OLE, open-label extension.
Sanofi Genzyme. Data on file.

Fitusiran Phase 2 OLE Interim Results: AT Levels

AT lowering with monthly fitusiran[1,a]



TG with monthly fitusiran[1,a]



Data cutoff: March 10, 2020.

[a]Data indicate mean AT or mean TG peak height ± SE. Month 0 indicates baseline values.[b]n=7 for month 1 and month 2. [c]n=5 for months 1 and n=6 for month 2.

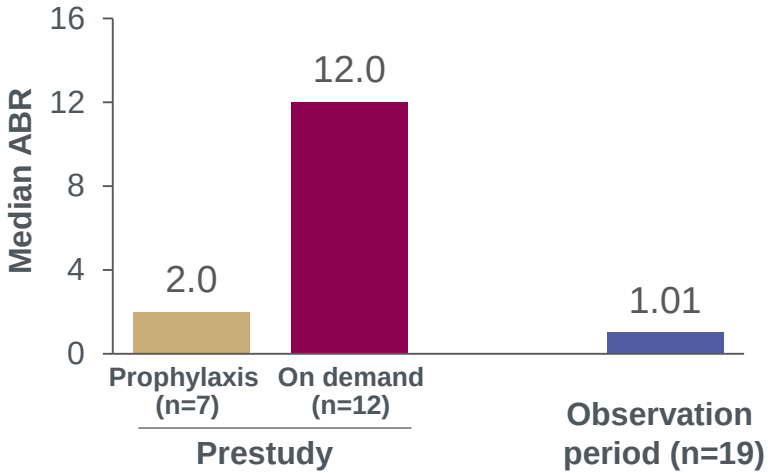
AT, antithrombin; HV, healthy volunteer; OLE, open-label extension; TG, thrombin generation.

1. Sanofi Genzyme. Data on file. **2**. Pasi KJ, et al. *N Engl J Med.* 2017;377:819-828.

Fitusiran Phase 2 OLE Interim Results: Exploratory Analysis of Bleeding Events

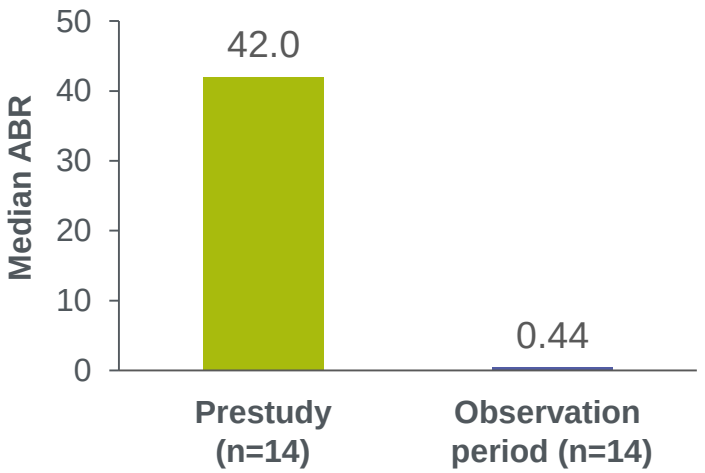
Overall median ABR of 0.84 during the observation period

ABR in subjects without inhibitors



Median duration in observation period:
36 months (range: 5-45 months)

ABR in subjects with inhibitors



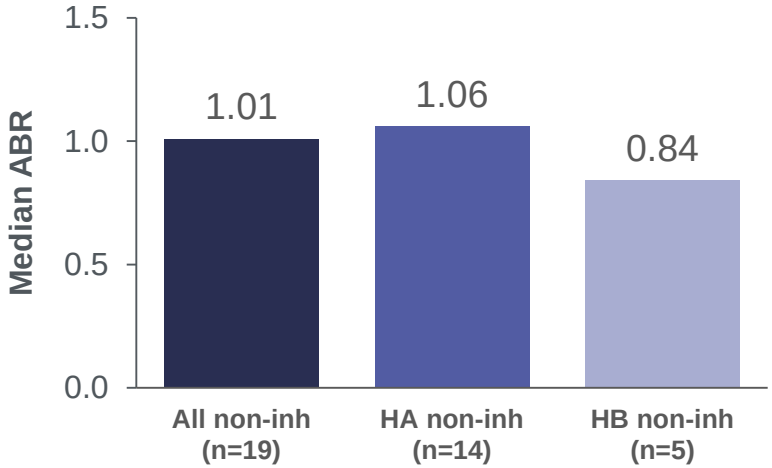
Median duration in observation period:
28 months (range: 7-36 months)

Data cutoff: March 10, 2020.
ABR and duration represent pooled data from phase 1 and phase 2 OLE studies. Phase 1 data are included if gap between studies was ≤56 days. Only subjects with 28 days of follow-up during the observation period are included in this analysis. Clinical hold period (last dose before hold + 29 days, first dose after hold + 28 days) is excluded.
ABR, annualized bleed rate; OLE, open-label extension.
Sanofi Genzyme. Data on file.

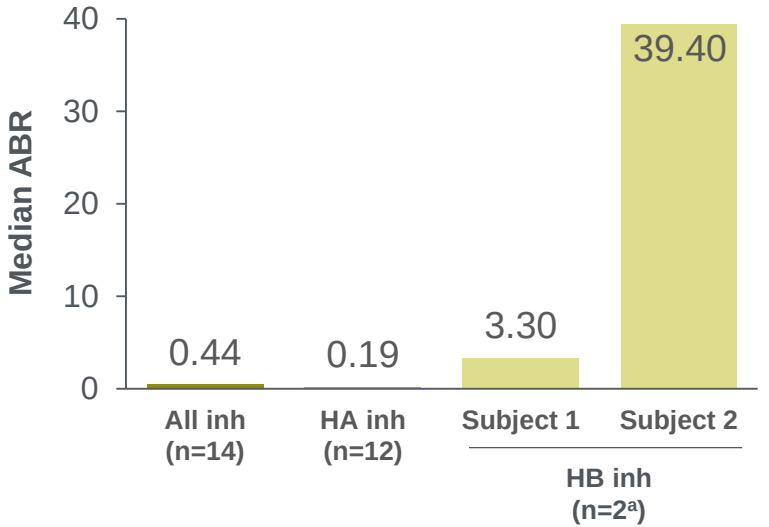
Fitusiran Phase 2 OLE Interim Results: Exploratory Analysis of All Bleeding Events by Subject Subgroup

Overall median ABR of 0.84 during the observation period

ABR in subjects without inhibitors



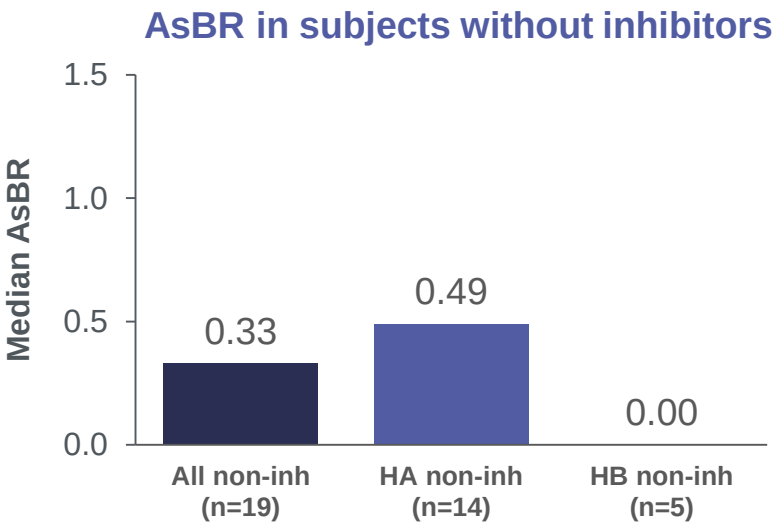
ABR in subjects with inhibitors

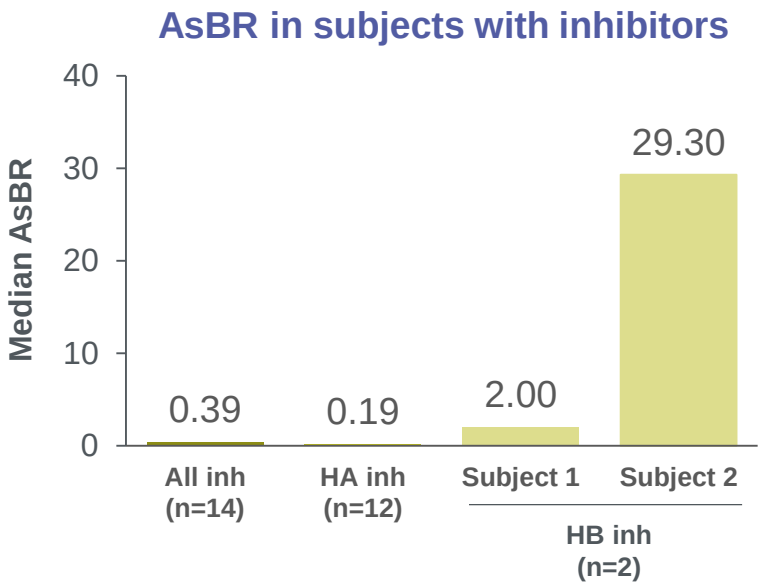


Data cutoff: March 10, 2020.
ABR and duration represent pooled data from phase 1 and phase 2 OLE studies. Phase 1 data are included if gap between studies was ≤56 days. Only subjects with 28 days of follow-up during the observation period are included in this analysis. Clinical hold period (last dose before hold + 29 days, first dose after hold + 28 days) is excluded.
[a]The prestudy ABR values for subject 1 and subject 2 were 26 and 54, respectively.
ABR, annualized bleed rate; HA, hemophilia A; HB, hemophilia B; inh, with inhibitors; non-inh, without inhibitors; OLE, open-label extension.
Sanofi Genzyme. Data on file.

Fitusiran Phase 2 OLE Interim Results: Exploratory Analysis of Spontaneous Bleeding Events by Subject Subgroup

Overall median AsBR of 0.38 during the observation period

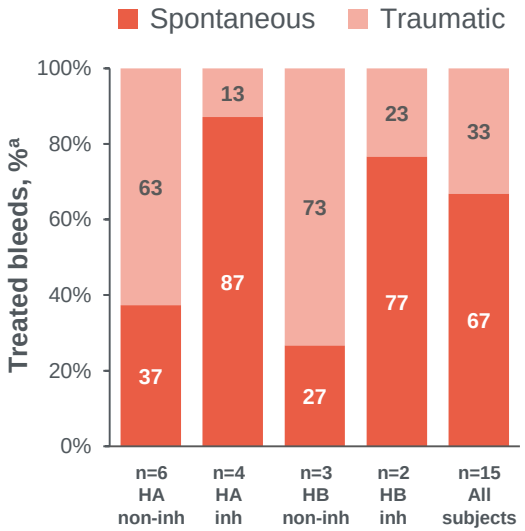




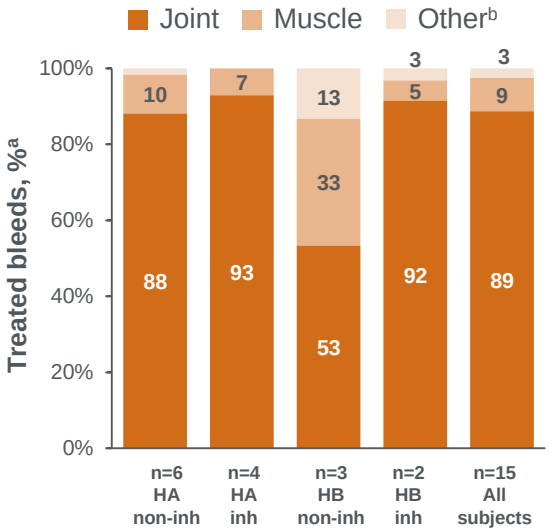
Data cutoff: March 10, 2020.
ABR and AsBR represent pooled data from phase 1 and phase 2 OLE studies. Phase 1 data are included if gap between studies was ≤56 days. Only subjects with 28 days of follow-up during the observation period are included in this analysis. Clinical hold period (last dose before hold + 29 days, first dose after hold + 28 days) is excluded.
ABR, annualized bleed rate; AsBR, annualized spontaneous bleeding rate; HA, hemophilia A; HB, hemophilia B; inh, with inhibitors; non-inh, without inhibitors; OLE, open-label extension.
Sanofi Genzyme. Data on file.

Fitusiran Phase 2 OLE Interim Results: Post Hoc Analysis of Treated Bleeds

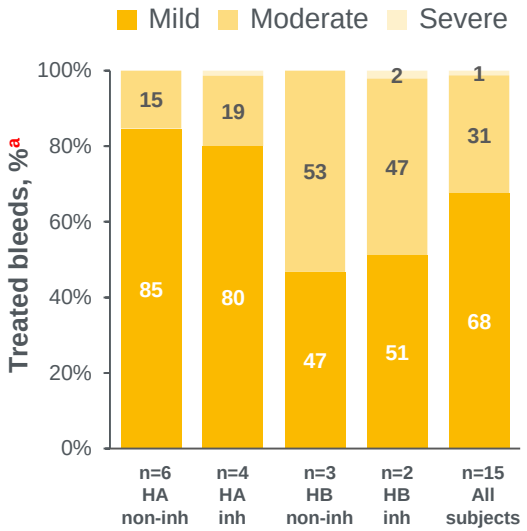
Bleed Causality



Bleed Location



Bleed Severity



	HA non-inh (n=6)	HA inh (n=4)	HB non-inh (n=3)	HB inh (n=2)	All subjects (N=15)
Treated bleeds, No.[a]	59	70	15	94	238

Data cutoff: March 10, 2020.
[a]Treated bleeds that started after fitusiran resumption and antithrombin <60%.[b]Includes internal bleeds.
HA, hemophilia A; HB, hemophilia B; inh, with inhibitors; non-inh, without inhibitors; OLE, open-label extension.
Sanofi Genzyme. Data on file.

Fitusiran Phase 2 OLE Interim Results: Overview of Safety and Tolerability

AEs, n (%)	All subjects (N=34)
At least 1 AE	33 (97)
At least 1 SAE	13 (38)
Leading to discontinuation	4 (12)
Antidrug antibody formation	0
Most common AEs, n (%)[a]	
ALT increased	10 (29)
Headache	9 (27)
Injection-site erythema	7 (21)
Nasopharyngitis	7 (21)
Upper respiratory tract infection	6 (18)
Diarrhea	6 (18)
Arthralgia	6 (18)
Back pain	6 (18)

- Of the reported SAEs, 4 were considered related to study drug
  - Atrial thrombosis in 1 subject
  - Seizures in 1 subject with a history of seizure disorder (CT and MRI negative for bleed and thrombosis)
  - Asymptomatic ALT and AST elevations in 1 subject with chronic HCV infection; led to discontinuation
  - Fatal CVST in 1 subject
- As of March 10, 2020, no thrombotic events had occurred in any subjects who were compliant with the bleed management guidelines since their implementation in December 2017

Data cutoff: March 10, 2020.
[a]Occurring in ≥15% of subjects overall.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, computed tomography; CVST, cerebral venous sinus thrombosis; HCV, hepatitis C virus; MRI, magnetic resonance imaging; OLE, open-label extension; SAE, serious adverse event.
Sanofi Genzyme. Data on file.

Fitusiran Phase 2 OLE Interim Results: Conclusions

- Fitusiran is an investigational RNAi therapeutic that shows potential for the prophylactic treatment of people with hemophilia A or B, with or without inhibitors
- Monthly subcutaneous dosing with fitusiran demonstrated a durable therapeutic effect, including sustained AT lowering, increased TG, and low overall (median 0.84) and spontaneous ABRs (median 0.38)
- Most bleeds were located in joints and were mild in severity across all subject groups
- Long-term exposure to fitusiran in the phase 2 OLE study reveals a safety profile that is supportive of continued evaluation in phase 3 studies
- The safety and efficacy of fitusiran is being evaluated in the ongoing global phase 3 ATLAS program[a]

[a]ATLAS trials: NCT03417245, NCT03417102, NCT03549871, NCT03754790, NCT03974113.
ABR, annualized bleed rate; AT, antithrombin; OLE, open-label extension; RNAi, RNA interference; TG, thrombin generation.

Acknowledgments

Thank you to the subjects, investigators, and study staff who participated in these studies

Country	Principal investigator	Institution
United Kingdom	Savita Rangarajan	North Hampshire Haemophilia Centre
	Sarah Mangles	North Hampshire Haemophilia Centre
	Catherine Bagot	Glasgow Royal Infirmary Department of Haematology
	Steve Austin	St. George's Healthcare NHS Trust Haemophilia Centre
	David Bevan	Centre for Haemostasis and Thrombosis, Guy's and St. Thomas' NHS Foundation Trust
	Pratima Chowdary	Royal Free Hospital Haemophilia Centre and Thrombosis Unit
	Tim Mant	Quintiles Drug Research Unit
	K. John Pasi	Royal London Haemophilia Centre
	Charles Hay	Manchester Royal Infirmary
	Desmond Creagh	Royal Cornwall Hospital
Bulgaria	Pencho Georgiev	University Multiprofile Hospital for Active Treatment "Sveti Georgi"
	Toshko Lissitchkov	Clinic Specialized Hospital for Active Treatment of Haematological Diseases Sofia
	Liana Gercheva-Kyuchukova	Clinical Hematology Clinic, Multiprofile Hospital for Active Treatment "Sveta Marina"
Switzerland	Inga Hegemann	Universitätsspital Zürich, Klinik für Hämatologie
	Brigitte Brand-Staufer	Universitätsspital Zürich, Klinik für Hämatologie
Russia	Vasily Mamonov	National Research Center for Hematology, Moscow
	Margarita Timofeeva	Kirov Research Institute of Hematology and Blood Transfusion
United States	Margaret V. Ragni	Hemophilia Center of Western Pennsylvania
	Steven W. Pipe	University of Michigan, Ann Arbor

- Study funding provided by Sanofi Genzyme
- Editorial assistance provided by Lindsay Tannenholz, PhD, and Sarah Qamar, PhD (Chameleon Communications International, with funding by Sanofi Genzyme)