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Hepatobiliary events in the fitusiran clinical development program with the revised AT-based dose regimen

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Disclosures for Steven W. Pipe

- Steven W. Pipe has received consultancy fees from for Apcintex, ASC Therapeutics, Bayer, BioMarin, CSL Behring, HEMA Biologics, Freeline, LFB, Metagenomi, Novo Nordisk, Pfizer, Precision Bioscience, Poseida Therapeutics, Roche/Genentech, Sanofi, Takeda, Spark Therapeutics and uniQure, and research funding from Siemens and Yewsavin and holds a membership on a Scientific advisory committee for GeneVentiv and Equilibra Bioscience.

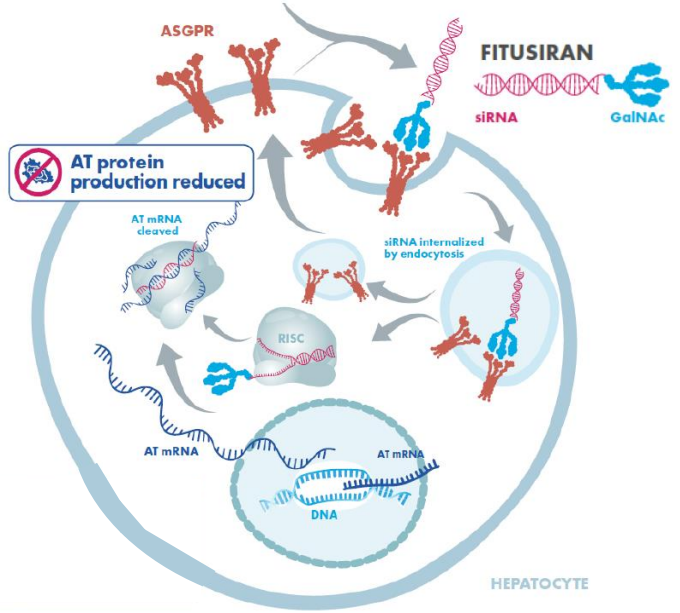
Fitusiran is an investigational medicine. Its safety and efficacy have not been established by any health authorities.

Fitusiran is a subcutaneous AT-lowering, liver-targeted siRNA therapeutic for people with hemophilia A or B, with or without inhibitors

Fitusiran has a first-in-class mechanism of action for hemophilia treatment, utilizing siRNA covalently linked to an ESC–GalNAc[a] ligand to facilitate liver uptake[1,2]

Fitusiran decreases liver production of antithrombin, a natural anticoagulant and the main endogenous inhibitor of thrombin which is essential for stable clot formation[1–3]

Fitusiran mechanism of action: delivery to the liver and reduction in AT levels by RNA interference



aESC–GalNAc: enhanced stabilization chemistry conjugate technology is a patent technology of Alnylam. ASGPR, asialoglycoprotein receptor; AT, antithrombin; DNA, deoxyribonucleic acid; ESC, enhanced stabilization chemistry; GalNAc, N-acetylgalactosamine; mRNA, messenger RNA; PwH, people with hemophilia; RISC, RNA-induced silencing complex; RNAi, RNA interference; siRNA, small interfering RNA.

1. Hu B, et al. J Gene Med 2019;21:e3097; 2. Pasi KJ, et al. N Engl J Med 2017;377:819–28; 3. Machin N and Ragni MV. J Blood Med. 2018;9:135–40.

Fitusiran has been studied in the largest pre-approval hemophilia cohort to date, with 373 participants exposed from 24 countries[a]

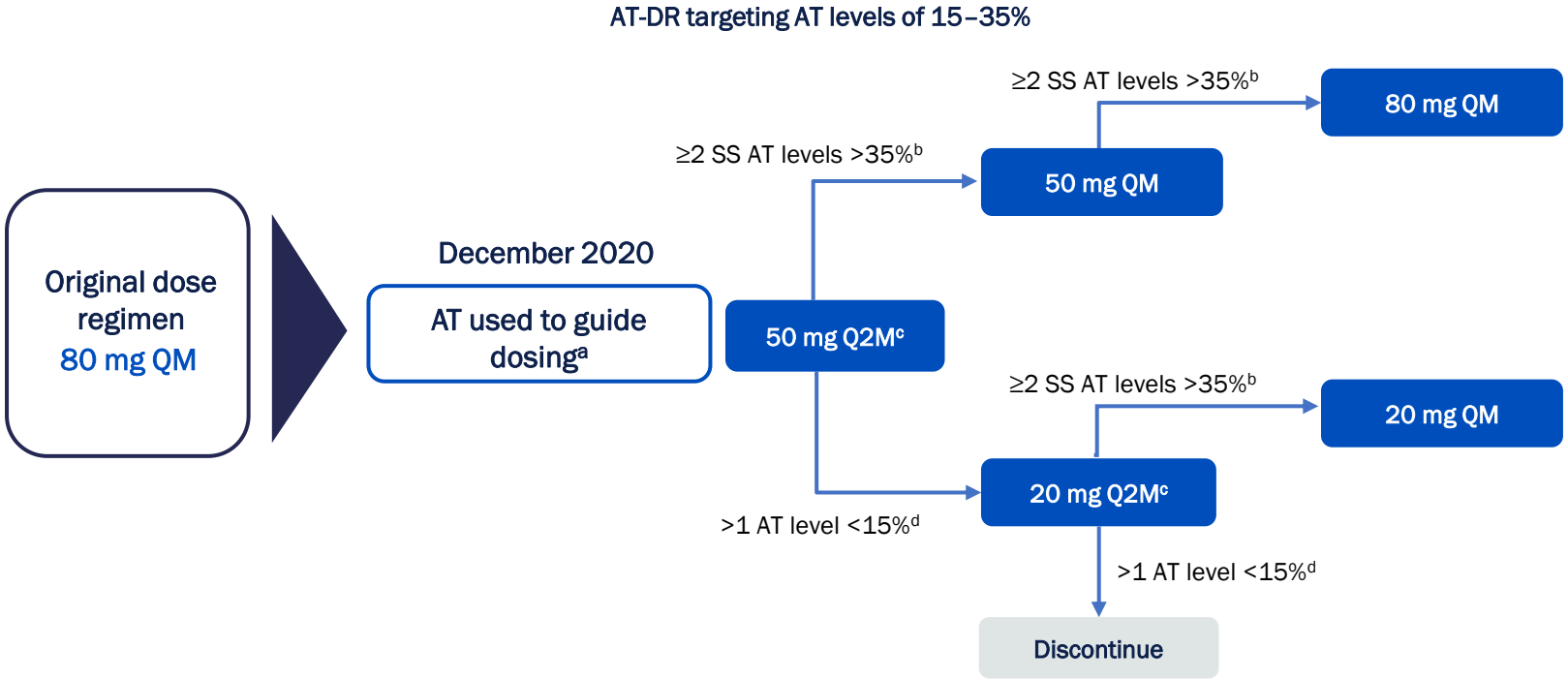
Completed Phase 3 trials
(original dose regimen)

	ATLAS-INH NCT03417102[1] (N=60)	ATLAS-A/B NCT03417245[2] (N=120)	ATLAS-PPX NCT03549871[3] (N=80)
Study population	PwHA/B aged ≥12 years, **with or without inhibitors**		
Intervention	**fitusiran 80 mg** PPX or **OD BPAs**	**fitusiran 80 mg** PPX or **OD CFCs**	**fitusiran 80 mg** PPX with prior **BPA/CFC PPX**
Efficacy	**Median AsBR, AjBR, and ABR of 0**		
Mean AT levels (SD)	**10.7%** (2.9)	**11.8%** (4.0)	**11.0%** (2.5)
Participants with hepatobiliary disorders, n (%)	**ALT/AST >3x ULN**: 10 (24.0%) **Cholecystitis and/or cholelithiasis:** 6 (14.6%)	**ALT/AST >3x ULN**: 15 (19.0%) **Cholecystitis and/or cholelithiasis:** 5 (6.3%)	**ALT/AST >3x ULN**: 17 (25.4%) **Cholecystitis and/or cholelithiasis:** 8 (11.9%)

[a]As of data cut-off date 19 November 2023. Data on PwHA/B, with or without inhibitors are from ongoing/completed unblinded/open-label studies: Phase 1, Phase 1/2 OLE, ATLAS-INH, ATLAS-A/B, ATLAS-PPX, ATLAS-OLE and ATLAS-PEDS. Participants in both Phase 1 and the extension study, and in both ATLAS-INH (or ATLAS-A/B or ATLAS-PPX) and the extension study, ATLAS-OLE, were counted only once. Information presented here is intended as a summary of these trials only – direct comparisons cannot be made between trials. ABR, annualized bleeding rate; AjBR, annualized joint bleeding rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AsBR, annualized spontaneous bleeding rate; AT, antithrombin; BPA, bypassing agent; CFC, clotting factor concentrate; OD, on-demand; PPX, prophylaxis; PwH, people with hemophilia; SD, standard deviation; ULN, upper limit of normal.

1. Young G, et al. Lancet 2023;401:1427–17; 2. Srivastava A, et al. Lancet Haematol 2023;10:e322–32; 3. Kenet G, et al. Blood 2024:blood.2023021864 (Epub ahead of print).

The revised AT-based dose regimen (AT-DR) was designed to enhance the benefit-risk profile of fitusiran



[a]Per protocol there is no requirement to measure AT levels monthly after a dose change unless it is a change from 50mg Q2M to 20mg Q2M in which case the measurements restart for a year; [b]Clinical criteria for dose escalation at AT activity levels <35% may also be considered; [c]Participants eligible for cohort - start of dosing after de-escalation from higher dose to occur only after centrally measured AT activity levels ≥22%. Participants receiving fitusiran at a dose of 20 mg Q2M who experience ≥1 AT level <15% (as per central laboratory) within a 12-month period must permanently discontinue fitusiran treatment; [d]Within 12-month period.
AT, antithrombin; AT-DR, AT-based dose regimen; QM, once monthly; Q2M, once every other month; SS, steady state. Young G, et al. Presented at EAHAD 2024. Oral presentation.

The ongoing Phase 3 ATLAS-OLE trial assesses the safety and efficacy of fitusiran prophylaxis with the AT-based dose regimen

	Completed Phase 3 trials (original dose regimen)			Ongoing Phase 3 trial
	ATLAS-INH NCT03417102[1] (N=60)	ATLAS-A/B NCT03417245[2] (N=120)	ATLAS-PPX NCT03549871[3] (N=80)	ATLAS-OLE NCT03754790[4] (N=227[a])
Study population	PwHA/B aged ≥12 years, **with or without inhibitors**			Participants who **completed a Phase 3 study**
Intervention	**fitusiran 80 mg** PPX or **OD BPAs**	**fitusiran 80 mg** PPX or **OD CFCs**	**fitusiran 80 mg** PPX with prior **BPA/CFC PPX**	fitusiran **AT-DR**
Efficacy	**Median AsBR, AjBR and ABR: 0**			Inhibitor / Without inhibitors / Overall **Median AsBR:** 1.9 / 1.9 / 1.9 **Median AjBR:** 1.9 / 2.1 / 1.9 **Median ABR:** 1.9 / 3.8 / 3.7
Mean AT levels (SD)	**10.7%** (2.9)	**11.8%** (4.0)	**11.0%** (2.5)	**23.5%** (4.6)
Participants with hepatobiliary disorders, n (%)	**ALT/AST >3x ULN:** 10 (24.0%) **Cholecystitis and/or cholelithiasis:** 6 (14.6%)	**ALT/AST >3x ULN:** 15 (19.0%) **Cholecystitis and/or cholelithiasis:** 5 (6.3%)	**ALT/AST >3x ULN:** 17 (25.4%) **Cholecystitis and/or cholelithiasis:** 8 (11.9%)	**ALT/AST >3x ULN:** 10 (3.5%) **Cholecystitis and/or cholelithiasis:** 10 (4.7%)

Information presented here is intended as a summary of these trials only – direct comparisons cannot be made between trials.
[a]Additionally, 54 de-novo participants from China were enrolled; interim ATLAS-OLE study results focus on participants who previously completed a Phase 3 study.
ABR, annualized bleeding rate; AjBR, annualized joint bleeding rate; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AsBR, annualized spontaneous bleeding rate; AT, antithrombin; AT-DR, antithrombin-based dose regimen; BPA, bypassing agent; CFC, clotting factor concentrate; OD, on-demand; PPX, prophylaxis; PwH, people with hemophilia; SD, standard deviation; ULN, upper limit of normal.
1. Young G, et al. Lancet. 2023;401:1427–37; 2. Srivastava A, et al. Lancet Haematol 2023;10:e322–32; 3. Kenet G, et al. Blood 2024:blood.2023021864 (Epub ahead of print); 4. Young G, et al. Presented at EAHAD 2024. Oral presentation.

The incidence of **ALT/AST elevations >3x ULN** was substantially reduced with the AT-DR

Integrated safety analysis of the original dose and the AT-based dose regimen included all study participants exposed to fitusiran across the clinical development program[a]

TEAESIs, n (%)	Original dose regimen (N=270)	AT-based dose regimen (N=286)
ALT/AST elevations > 3xULN		
Participants with any ALT/AST elevations >3xULN	56 (20.7)	10 (3.5)
Participants with any ALT elevations >3xULN	53 (19.6)	8 (2.8)
Participants with any AST elevations >3xULN	18 (6.7)	6 (2.1)
Exposure-adjusted incidence rate (per 100 participant years)	**18.25** →	**2.06**

With the AT-DR, there were no cases of severe liver toxicity or liver failure

With the AT-DR, two (2/14 [14%]) events of ALT or AST elevations >3xULN were classified as SAEs

- Assessed by the Investigator as related to study drug; no SAE had a fatal outcome or resulted in study drug discontinuation

[a]Phase 1 and 1/2 OLE: NCT02035605,[1] NCT02554773;[2] Phase 3: ATLAS-INH (NCT03417102),[3] ATLAS-A/B (NCT03417245),[4] ATLAS-PPX (NCT03549871)[5] and ATLAS-OLE (NCT03754790).[6]
ALT/AST elevations > 3xULN were identified by central lab. Excluding events reported during major surgery periods. Exposure adjusted incidence rate = # of participants with events/participant year of exposure *100 participant years.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; AT-DR, antithrombin-based dose regimen; SAE, serious adverse event; TEAESI, treatment-emergent adverse event of special interest; ULN, upper limit of normal.

1. ClinicalTrials.gov. NCT02035605. (Accessed May 2024); 2. ClinicalTrials.gov. NCT02554773. (Accessed May 2024); 3. ClinicalTrials.gov. NCT03417102. (Accessed May 2024); 4. ClinicalTrials.gov. NCT03417245. (Accessed May 2024); 5. ClinicalTrials.gov. NCT03549871. (Accessed May 2024); 6. ClinicalTrials.gov. NCT03754790. (Accessed May 2024).

Majority of ALT/AST elevations >3xULN with the AT-DR spontaneously resolved

Participants on revised AT-DR	Time to onset, median	Time to resolution, median
ALT >3xULN	211.5 days	87.5 days
AST >3xULN	185.5 days	49.0 days

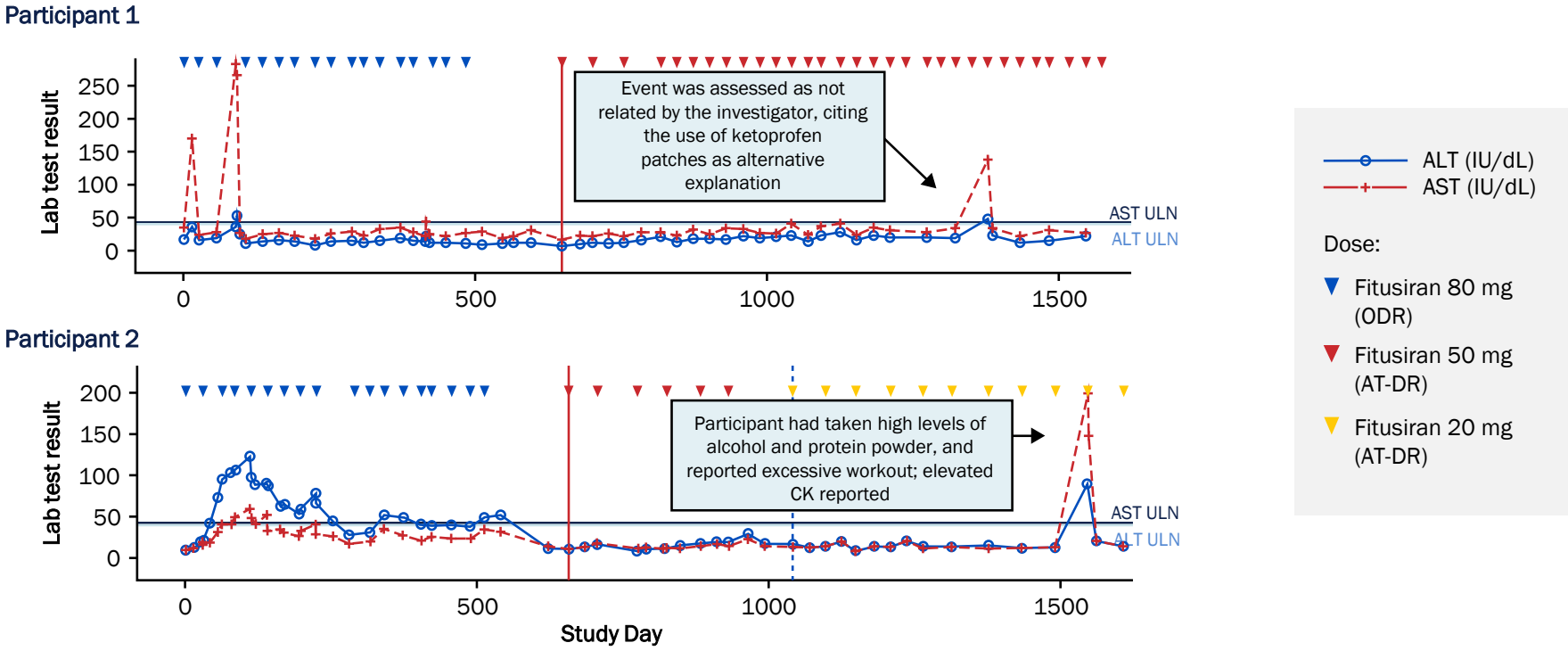
ALT/AST elevations >3xULN were **asymptomatic**, **transient** and resolved without any therapeutic intervention

- The majority (12/14 [86%]) of ALT/AST elevations >3xULN with the AT-DR were reported as **recovered/resolved** without dose change or interruption
- Recurrent ALT and AST >3xULN elevations occurred in 1 participant each[a] in the setting of repeated fitusiran exposure

In 1 participant fitusiran treatment was discontinued due to asymptomatic transaminase elevations[b]

[a]Among participants who experienced an ALT/AST elevation of >3×ULN while on the revised AT-DR; [b]At physician discretion; this event was considered related to fitusiran, was not serious, and the participant recovered from the event.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; AT-DR, revised antithrombin-based dose regimenULN, upper limit of normal.

Liver function trajectories demonstrate alternate etiologies and transient nature of ALT/AST elevations



Both participants met criteria of ALT/AST>3x ULN after dose resumption, had no HCV history/antibody and no inhibitors.
ALT, alanine transaminase; AST, aspartate aminotransferase; AT-DR, antithrombin-based dose regimen; CK, creatine kinase; HCV, hepatitis C virus; IU, international unit; ODR, original dose regimen.

The incidence of **cholecystitis/cholelithiasis** was substantially reduced with the AT-DR

Integrated safety analysis of the original dose and the AT-based dose regimen included all study participants exposed to fitusiran across the clinical development program[a]

TEAESIs, n (%)	Original dose regimen (N=270)	AT-based dose regimen (N=286)
Cholecystitis/cholelithiasis		
Participants with any cholecystitis/cholelithiasis	45 (16.7)	11 (3.8)
Exposure adjusted incidence rate (per 100 participant years)	**14.67** →	**2.26**

No participant discontinued fitusiran due to events of cholecystitis/cholelithiasis with the AT-DR

One participant with the AT-DR underwent cholecystectomy

A total of 3 (1.0%) participants with the AT-DR experienced a SAE of cholecystitis/cholelithiasis (cholecystitis [2 [0.7%] participants] and cholangitis [1 [0.3%] participant])

[a]Phase 1 and 1/2 OLE: NCT02035605,[1] NCT02554773;[2] Phase 3: ATLAS-INH (NCT03417102),[3] ATLAS-A/B (NCT03417245),[4] ATLAS-PPX (NCT03549871)[5] and ATLAS-OLE (NCT03754790).[6]
Excluding events reported during major surgery periods. Exposure adjusted incidence rate = # of participants with events/participant year of exposure *100 participant years.
AT, antithrombin; AT-DR, antithrombin-based dose regimen; SAE, serious adverse event; TEAESI, treatment-emergent adverse event of special interest.
1. ClinicalTrials.gov. NCT02035605. (Accessed May 2024); 2. ClinicalTrials.gov. NCT02554773. (Accessed May 2024); 3. ClinicalTrials.gov. NCT03417102. (Accessed May 2024); 4. ClinicalTrials.gov. NCT03417245. (Accessed May 2024); 5. ClinicalTrials.gov. NCT03549871. (Accessed May 2024); 6. ClinicalTrials.gov. NCT03754790. (Accessed May 2024).

Conclusions

- The AT-DR targeting AT activity levels of 15–35% enhanced the benefit-risk profile of fitusiran
- Fitusiran AT-DR prophylaxis led to reductions in ALT/AST elevations and cholecystitis/cholelithiasis events versus the original dose regimen despite substantially longer exposure on the AT-DR
- Transaminase elevations have been also observed during clinical trials with liver-targeted siRNA therapies evaluated for other conditions[1,2]
- ALT or AST elevations >3xULN with the AT-DR were asymptomatic and transient, and the majority were reported as recovered/resolved spontaneously
  - Median time to onset for ALT or AST elevations >3xULN was ~6 months
- The majority of events of cholecystitis/cholelithiasis resolved without clinical sequalae and participants continued dosing with fitusiran, and one participant underwent cholecystectomy

Fitusiran is an investigational medicine. Its safety and efficacy have not been established by any health authorities.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; AT, antithrombin; AT-DR, antithrombin-based dose regimen; siRNA, small interfering RNA; ULN, upper limit of normal.
1. Schmidt HH, et al. Am J Transplant. 2022;22(6):1646–1657; 2. Balwani M, et al. N Engl J Med. 2020;382(24):2289-2301.

Acknowledgments

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Fitusiran presentations at ISTH 2024:

Surgical experience in people with hemophilia A or B with and without inhibitors receiving fitusiran

Oral presentation by Alok Srivastava (Sunday June 23, 09:45–10:00)

Incidence of thrombotic events in the fitusiran clinical development program

Oral presentation by Guy Young (Monday June 24, 15:00–15:15)