INNOVANCE Antithrombin Assay

Advanced Therapy in Hemophilia Care

Antithrombin testing during fitusiran treatment

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Clinical Brief

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Introduction

Hemophilia A and B are rare, inherited bleeding disorders caused by deficiencies in specific clotting factors essential for normal blood coagulation.

- **Hemophilia A is due to a deficiency of factor VIII.**
- **Hemophilia B results from a deficiency of factor IX.**

These conditions lead to prolonged bleeding episodes, spontaneous bleeding (often into joints and muscles), and an increased risk of complications from injuries or surgeries. Hemophilia predominantly affects males, as this is inherited in an X-linked recessive pattern, but women can also be affected.[1]

Traditional treatment involves regular intravenous infusions of the missing clotting factor to prevent or control bleeding. However, these treatments can be burdensome and costly, and some patients develop inhibitors (antibodies) that reduce the effectiveness of factor replacement therapy.

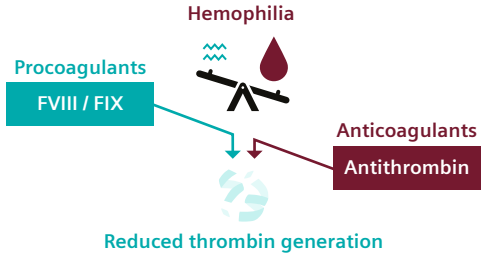
Hemophilia A and B are serious bleeding disorders that require lifelong management. Fitusiran offers a promising alternative that could transform care by improving efficacy, reducing treatment burden, and addressing limitations of current therapies.[2]

Fitusiran, a novel siRNA therapeutic of hemophilia A and B

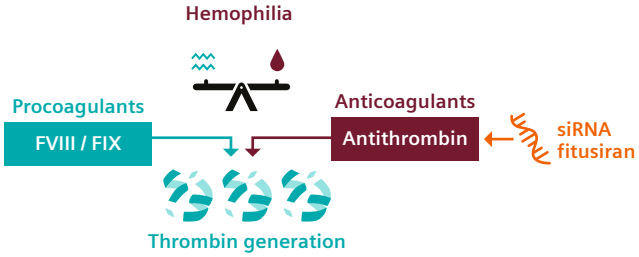
Fitusiran is a small interfering ribonucleic acid (siRNA) therapeutic that downregulates antithrombin (AT) synthesis to increase thrombin generation and rebalance hemostasis in people with hemophilia A or B, with or without factor VIII or IX inhibitors.[3] AT is a serine protease inhibitor (serpin) and the most important endogenous anticoagulant. Synthesized in the liver, AT can inhibit all procoagulant proteases of the coagulation cascade but targets primarily thrombin and factors Xa and IXa.[4]

Figure 1: Visualization of the effect of fitusiran in hemophilia A/B (simplified)[3]

Thrombin and antithrombin in hemostasis
In individuals with hemophilia A or B, the deficiency of FVIII or FIX results in insufficient thrombin generation



Thrombin-targeted therapeutic strategy with fitusiran
siRNA fitusiran targets and lowers antithrombin levels to restore sufficient thrombin generation



Simplified and adapted from: Young G, et al. RPTH 2023;7(4):100179. https://doi.org/10.1016/j.rpth.2023.100179

INNOVANCE Antithrombin assay for testing during fitusiran treatment

Achieving the correct therapeutic level of a medication is essential to ensure both safety and effectiveness in managing hemophilia. Maintaining the right therapeutic window is critical. The INNOVANCE Antithrombin assay can reliably quantify AT activity to ensure that it is within this window.

Treatment with fitusiran follows an AT-based dose regimen to target AT activity in the range of 15–35%.[5]

INNOVANCE Antithrombin assay can also be used for monitoring antithrombin substitution therapy.

Importance of antithrombin testing in the low range

Accuracy and precision of AT measurements in the low range are especially essential for fitusiran treatment but may not be achieved by all AT activity assays. Many AT activity assays are able to detect moderate to severe AT deficiency, but linearity, precision and reproducibility at, for example, 15% may not be sufficient.

Low-range results are crucial to directly support safe and effective dose adjustments and ensure consistent monitoring across different clinical settings. They are also vital for interpreting pharmacodynamic responses, guiding individualized treatment plans, and meeting regulatory expectations. In the context of fitusiran, low-range assay performance is not optional—it is central to patient safety and therapeutic success.

Antithrombin activity during fitusiran treatment

Fitusiran helps restore hemostasis by lowering antithrombin in individuals with hemophilia A or B, with or without inhibitors. The fitusiran AT-based dose regimen is individually adjusted based on AT activity levels:

- The dose can be increased or decreased to maintain AT activity at 15-35%.[5]
- This AT-based dose regimen has been tested in clinical trials using the INNOVANCE Antithrombin assay and supports a positive benefit-risk balance during fitusiran treatment.[5]

Proven performance along the low range

A global field study evaluated and compared eight commercially available AT activity assays used by 48 laboratories located across 16 countries worldwide.[6] AT activity assays employed were either based on factor Xa (FXa) from human or bovine sources or on thrombin (FIIa) from bovine sources. Depending on the AT activity assay, different systems were used for the testing. For AT assays from Siemens Healthineers and Stago, at least three different system types were used. The assays from Hyphen/Sysmex, Werfen and Technoclone were tested with one or two different system types.

The study assessed the accuracy as well as the intra- and inter-laboratory variability in measuring AT activity particularly around or below 30% of norm in plasma samples. In this range, which is highly relevant for the AT-based dosing regimen with fitusiran, the authors found a higher variation of results. As the AT activity level decreased, variability increased: Assays displayed up to 57.5% CV—but INNOVANCE Antithrombin assay displayed, e.g., 9.7% CV at 14% of norm and 18.8% CV at 9% of norm AT activity (Table 1). These values compared well with the results of the precision study across automated systems presented below in Table 2 and the results of a recent ECAT survey.[7]

Table 1: Variability (CV)* of antithrombin assay results in the low measuring range[6]

Assay name	INNOVANCE Antithrombin	BERICHROM Antithrombin III (A)	STA-STACHROM AT III	HEMOSIL Liquid Antithrombin	BIOPHEN AT anti-(h)-Xa (LRT)	BIOPHEN AT (LRT)
Participating laboratories	9	11	12	22	3	3
Sample†						
36% of norm	5.4%	6.9%	11.4%	11.1%	7.7%	6.2%
14% of norm	9.7%	22.4%	16.4%	n/a	18.6%	29.7%
9% of norm	18.8%	33.0%	n/a	n/a	50.1%	57.5%

**3x3 model employed. Assays with just one participating laboratory excluded. For sample at 14% activity, only 8 of 12 participating labs reported results for STA-STACHROM AT III assay. n/a: no results were reported by the participating labs due to issues with the assay setting.*
†Assigned value of the sample.

This global AT field study also demonstrated that different AT assays cannot be used interchangeably if consistent results are needed in the low measuring range because the recovery varied between 46.9 and 124.4% depending on the sample and assay. According to the study authors, AT assays from Werfen and Stago could not report results for samples at 14% activity (Werfen) and 9% activity (Stago and Werfen) due to assay limitations.[6]

In a recent ECAT survey, various AT activity assays evaluated an abnormal coagulation control plasma ranging between 30 and 63% AT activity depending on the assay. For this particular sample, a variance of 5.5% CV was observed with INNOVANCE Antithrombin assay across the participating laboratories, compared to 6.5–11.3% CV with other AT activity assays.[7]

In conclusion:

- The global AT field study reported a lower variability of results with INNOVANCE Antithrombin assay compared to different AT activity assays from various vendors. This observation was more pronounced with decreasing AT activity levels.[6]
- Similar results were observed in a recent ECAT survey.[7]

Evaluated across fitusiran patients and across systems

The INNOVANCE Antithrombin assay was used to measure the reduction of AT activity in adult and pediatric patients aged ≥12 years receiving fitusiran therapy through testing of more than 17,000 samples from more than 270 patients enrolled in the clinical trial program for fitusiran who have hemophilia A and B with or without inhibitory antibodies to FVIII or FIX.

Finally, a total of 213 patients followed an AT-based dose regimen with the target AT activity range of 15 to 35% in the ATLAS-OLE study[5] (Home | ClinicalTrials.gov Identifier NCT03754790).‡ A comprehensive summary of the clinical study is also available with the 510(k) summary.[8]

The INNOVANCE Antithrombin assay was used to measure AT activity at baseline (before starting treatment with fitusiran) as well as after fitusiran throughout the ATLAS-OLE study:

- The dose of fitusiran was adjusted based on AT activity levels, if needed, to target an AT activity range of 15 to 35%.
- Of the total AT-DR population, 199 patients started at the 50 mg dose every other month with dosing guided by the INNOVANCE Antithrombin assay.
- The ATLAS-OLE study confirmed the safety and efficacy of the AT-based dose regimen targeting an AT activity of 15–35% of norm.[5]

> In conclusion, the procedure including the AT testing with INNOVANCE Antithrombin assay was evaluated as safe and effective.

In all fitusiran clinical studies, AT testing was accomplished with the INNOVANCE Antithrombin assay on the BCS XP system. To demonstrate comparability of results across the different systems, the following data was established across the automated CN, CS, CA and BCS XP systems:

- Assay precision covered the target range for patients treated with fitusiran (15 to 35% AT activity; Table 2). For CN, CS and CA systems, it yielded 5.5% CV or less at the fitusiran critical decision point of 15% of norm.
- Limits of detection (LoD) and quantitation (LoQ) of 7.5% of norm or less, and the measuring range in combination with the precision results described above demonstrated that precise results are achievable even below the clinical decision threshold for patients treated with fitusiran (Table 3).
- Method comparison data demonstrate substantial equivalence of results across systems (Table 4).
- Interference to hemophilia-specific therapeutics at clinically relevant concentrations was tested and revealed no relevant impact on AT quantification by the assessed substances (Table 5).

Table 2: Precision data for the INNOVANCE Antithrombin assay, specific for each system

	Within-device/lab results (based on n=80)§									
	CN-3000/CN-6000[9]		CS-5100		CS-2500		CA-600 series		BCS XP	
Sample	Mean [% of norm]	CV	Mean [% of norm]	CV	Mean [% of norm]	CV	Mean [% of norm]	CV	Mean [% of norm]	CV
Control Plasma P	31.5	2.5%	30.2	2.3%	30.2	2.3%	29.1	6.9%	31.4	4.5%
Plasma pool 1	–	–	66.6	1.2%	66.6	1.2%	56.6	4.5%	61.7	3.5%
Plasma pool 2	40.9	1.9%	–	–	–	–	–	–	–	–
Plasma pool 3	17.5	5.2%	15.1	3.8%	14.8	5.5%	17.3	3.1%	15.7	9.7%
Plasma pool 4	–	–	10.3	5.5%	12.1	7.5%	12.3	SD:** 0.5	9.8	SD:** 1.6

‡For more details about QFITLIA drug labelling refer to Drugs@FDA.
§Following the model 20x2x2 (n=80). CA-660 and BCS XP: testing of plasma pool 3 and 4 was performed across 3 different lots with a final n=240.
***SD is provided as % of norm*

Table 3: LoQ/LoD and measuring range [% of norm] specific for each system

	CN-3000/CN-6000	CS-5100	CS-2500	CA-600 series	BCS XP
[% of norm]					
LoD	N/A	4.2	4.2	2.3	7.1
LoQ	5.8	6.0	6.0	7.6	7.3
Measuring range	5.8–150	6.0–150	6.0–150	7.6–140	7.32–150

Table 4: Method comparisons of INNOVANCE Antithrombin assay on BCS XP system vs. other systems

Y =	CN-3000/CN-6000			CS-5100	CS-2500	CA-600 series
X =	BCS XP	CS-2500	CA-660	BCS XP	BCS XP	BCS XP
Samples (n)	111	109	112	109	109	111
Slope	1.000	0.985	0.972	1.005	0.985	0.976
Intercept	0.500	0.038	1.666	1.249	0.704	2.120
r	0.998	0.999	0.999	0.997	0.997	0.997

r: Pearson correlation coefficient

Figure 2: Method comparison BCS XP system vs. CN-3000/6000 systems: Scatter plot including Passing-Bablok regression, AT activity [% of norm] (green dots: native samples, orange dots: spiked samples)

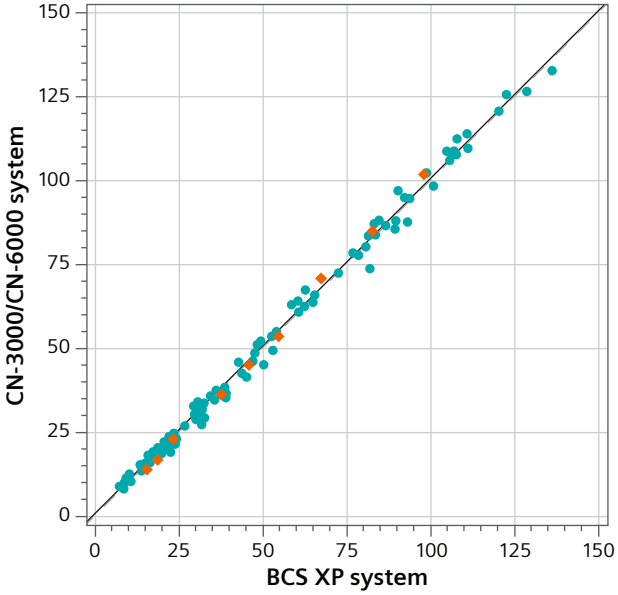


Table 5: Interference levels of INNOVANCE Antithrombin assay to certain therapeutics relevant for patients with hemophilia A or B.

Interferent	No interference up to...
Desmopressin	0.0144 µg/mL
Tranexamic acid	0.48 mg/mL
Recombinant Factor VIIa	2.16 µg/mL
Coagulation Factor VIII	0.96 IU/mL
Coagulation Factor IX	1.44 IU/mL
Activated prothrombin complex concentrate (aPCC)	2.4 IU/mL

More about INNOVANCE Antithrombin assay

INNOVANCE Antithrombin assay:

- Quantifies functionally active AT by means of automated chromogenic methods.
- Uses human factor Xa.
- Employs liquid, ready to use reagents.
- Is calibrated with Standard Human Plasma based on a WHO reference material.
- Aids in the diagnosis and monitoring of congenital or acquired AT deficiencies in patients at risk for or suspected to have AT deficiency
- Can be used to measure AT reduction in patients treated with fitusiran.
- Has demonstrated high sensitivity to multiple genetic mutations.
- Can be used for monitoring AT substitution therapy.

Conclusion

The INNOVANCE Antithrombin assay has proven to be a high performing tool for measuring AT activity in patients receiving fitusiran therapy for hemophilia A or B. Its consistent performance in the low AT activity range, in which therapeutic decisions are most critical, supports clinicians also in the low range between 15-35% AT activity.

Extensive clinical testing combined with method comparison data supports its use for fitusiran patients on a range of laboratory platforms. Since different AT activity assays can test the same sample differently, especially in the low range, monitoring of AT values should be accomplished using the same AT assay throughout.

With robust assay precision, suitable measuring interval, lack of interference, and high accuracy at clinically relevant levels, the INNOVANCE Antithrombin assay supports achieving better treatment outcomes and safety in patient care.

At Siemens Healthineers, we pioneer breakthroughs in healthcare. For everyone. Everywhere. Sustainably. As a leader in medical technology, we want to advance a world in which breakthroughs in healthcare create new possibilities with a minimal impact on our planet. By consistently bringing innovations to the market, we enable healthcare professionals to innovate personalized care, achieve operational excellence, and transform the system of care.

Our portfolio, spanning in vitro and in vivo diagnostics to image-guided therapy and cancer care, is crucial for clinical decision-making and treatment pathways. With the unique combination of our strengths in patient twinning,* precision therapy, as well as digital, data, and artificial intelligence (AI), we are well positioned to take on the greatest challenges in healthcare. We will continue to build on these strengths to help overcome the world's most threatening diseases, enable efficient operations, and expand access to care.

We are a team of more than 72,000 Healthineers in over 70 countries passionately pushing the boundaries of what is possible in healthcare to help improve the lives of people around the world.

*Personalization of diagnosis, therapy selection and monitoring, aftercare, and managing health.

CN-3000, CN-6000, CS-5100 and CS-2500 Systems refer to Automated Blood Coagulation Analyzer CN-3000, CN-6000, CS-5100 and CS-2500 respectively. CA-600 Systems refer to CA-660 and CA-620 Systems. CA-660 and CA-620 Systems refer to Automated Blood Coagulation Analyzer CA-660 and Automated Blood Coagulation Analyzer CA-620 respectively.

The products/features (mentioned herein) are not commercially available in all countries. Due to regulatory reasons, their future availability cannot be guaranteed. Please contact your local Siemens Healthineers organization for further details.

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Abbreviations:

AT	Antithrombin
CV	Coefficient of variation
LoD	Limit of detection
LoQ	Limit of quantitation
N	Number
SD	Standard deviation
siRNA	Small interfering ribonucleic acid

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