Real-World Use of Recombinant Factor IX Fusion Protein in Previously Untreated Patients with Congenital Hemophilia B from the ATHN 8 Study

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Background

- Previously untreated patients (PUPs) are particularly at risk of developing neutralizing inhibitors, particularly within the first 20 exposure days (EDs). Inhibitors reduce the efficacy of factor replacement to prevent and treat bleeds[1,2]
- In a previous study, recombinant factor IX fusion protein (rIX-FP) was shown to be safe and efficacious in preventing bleeding episodes among 12 PUPs with hemophilia B (NCT02053792)[3,4]
  - PUPs had a mean age of 1.3 years and received rIX-FP prophylaxis for a mean of 68.3 EDs[3]
  - One of the 12 participants, an 11-year-old male with deletion of exons 7 and 8 of the FIX gene, developed a FIX inhibitor[3]
- The ability to accurately predict who is at the highest risk for inhibitor development remains a challenge
  - Severe disease and large gene mutations, such as deletions, are known risk factors for inhibitor development[1,5]
  - However, some risk factors for inhibitor development are still unknown or not well understood[1]
- To address this knowledge gap, the American Thrombosis and Hemostasis Network (ATHN) 8 study (ATHN 8; NCT03818529) was conducted to determine the percentage of PUPs with confirmed inhibitors within the first 50 EDs and evaluate the variables contributing to inhibitor development[6]

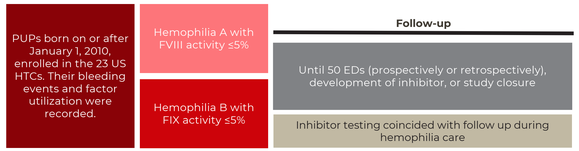
Objective

- **To evaluate inhibitor development in PUPs with congenital hemophilia B who received rIX-FP in the real-world setting in the ATHN 8 study**

Methods

- The ATHN 8 study was a multicenter cohort study at 23 hemophilia treatment centers (HTCs) in PUPs with moderate to severe congenital hemophilia A or B (**Figure 1**)
- Participants were followed (prospectively and retrospectively) during their first 50 EDs to clotting factor replacement
- All study procedures and follow-up were timed to coincide with scheduled hemophilia care when possible
- For this substudy, data were collected for a subset of PUPs from ATHN 8 with hemophilia B who were born between January 2010 and September 2021 and received rIX-FP at any time
  - Data collection was done from October 2018 to December 2021
- Participants were enrolled at ATHN-affiliated sites until 50 clotting factor EDs, development of a confirmed neutralizing inhibitor, or study closure
  - Per protocol, confirmed inhibitors are defined as 2 consecutive positive inhibitor titers (>0.3 Nijmegen Bethesda Units [BU] for hemophilia B) on different blood samples
- Summary statistics of demographics, clinical and diagnostic data, and therapeutic management were done for all participants

Figure 1: ATHN 8 study design



Primary endpoint:
- Inhibitor development (>0.5 and >0.3 Nijmegen BU for hemophilia A and B, respectively)

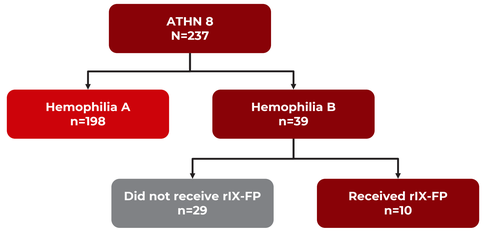
Secondary endpoints:
- Risk factors associated with inhibitor development
- Enrollment percentage
- Age of diagnosis and first exposure to factor treatment
- EDs prior to inhibitor development
- Bleeding complications within the first 50 EDs
- Factor replacement dosing within the first 50 EDs
- Incidence of transient inhibitor development (not confirmed on a consecutive repeat testing)
- SAEs during first 50 EDs

ATHN, American Thrombosis and Hemostasis Network; BU, Bethesda Units; ED, exposure day; FIX, factor IX; FVIII, factor VIII; HTC, hemophilia treatment center; PUP, previously untreated patient; SAE, serious adverse event.

Results

- The study enrolled 10 PUPs with moderate-to-severe hemophilia B who received rIX-FP (**Figure 2**)

Figure 2: PUPs with hemophilia B given rIX-FP enrolled in ATHN 8 study



ATHN 8, American Thrombosis and Hemostasis Network 8 Study; PUP, previously untreated patients; rIX-FP, recombinant factor IX fusion protein.

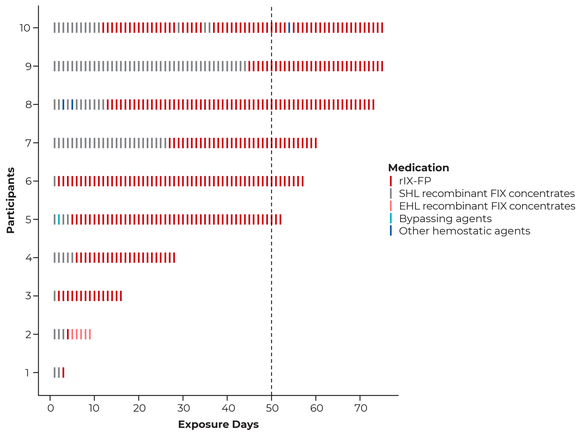
- Baseline characteristics are reported in **Table 1**
  - Most participants (80%) had severe hemophilia
  - Six participants (60%) were <1 month old at the time of their first bleed

Table 1: Baseline characteristics

Characteristics	N=10
Birth year, n (%)	
January 1, 2010, to December 31, 2015	5 (50)
After December 31, 2015	5 (50)
Hemophilia severity, n (%)	
Moderate	2 (20)
Severe	8 (80)
Age at first bleed, n (%)	
<1 month	6 (60)
1 month to <1 year	2 (20)
1 year to 10 years	2 (20)
Age at first treatment	
<1 month	3 (30)
1 month to <1 year	5 (50)
1 year to 10 years	2 (20)

- 70% (7/10) of participants had more than 20 EDs (**Figure 3**)
  - Of these, 6 participants had at least 50 EDs
  - Mean FIX EDs was 45 days (**Table 2**)

Figure 3: Exposure days



EHL, extended half-life; FIX, factor IX; rIX-FP, recombinant factor IX fusion protein; SHL, standard half-life.

Table 2: FIX treatment

Characteristics	N=10
FIX exposure days	
Mean (SD)	45 (28)
Median (Q1–Q3)	54 (19–70)
Treatment class prior to study exit, n (%)	
Other EHL recombinant FIX concentrates	1 (10)
rIX-FP	9 (90)
On prophylaxis, n (%)	8 (80)

EHL, extended half-life; FIX, factor IX; rIX-FP, recombinant factor IX fusion protein; Q1, first quartile; Q3, third quartile; SD, standard deviation.

- In the entire ATHN 8 study, 3 of 39 participants with hemophilia B developed inhibitors within the first 50 EDs
  - One of the risk factors identified for inhibitor development for all PUPs was factor exposure at <1 month of age
- In this subset analysis, no participants developed an inhibitor during the study

Among these 10 participants, **none** developed an inhibitor during the study

Conclusions

- **As data in PUPs are still limited, it is important to survey and illustrate information when available**
- **In this subanalysis of PUPs with hemophilia B who received rIX-FP none developed inhibitors**
  - **This included seven participants with more than 20 EDs, of whom six had more than 50 EDs**
- **The data presented in this real-world analysis are consistent with those seen in the clinical trial**

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