Designing the Efanesoctocog Alfa Module of ATHN Transcends: Safety, Tolerability, and Effectiveness in Previously Untreated Patients with Hemophilia A

Lynn Malec[1], Courtney Thornburg[2], Shannon Carpenter[3], Carrie O'Neill[4], Michael Recht[4,5]

[1] Versiti Blood Center of Wisconsin, [2] Rady Children's Hospital – San Diego, UC San Diego School of Medicine, [3] Children's Mercy Hospital, Kansas City, [4] American Thrombosis and Hemostasis Network, [5] Yale University School of Medicine

Background

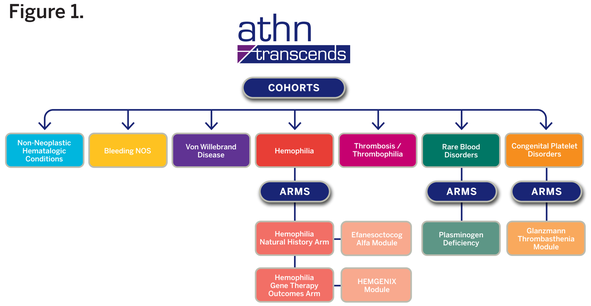
Hemophilia A (HA) is an x-linked bleeding disorder caused by variations and/or deletions in the F8 gene resulting in a deficiency of coagulation factor VIII (FVIII) activity. Treatment focuses on either the replacement of FVIII with the intravenous (IV) administration of FVIII-containing coagulation products to promote clotting or the administration of FVIII mimetics.

Efanesoctocog alfa (Altuviiio®, rFVIIIFc-VWF-XTEN) is a novel recombinant FVIII breaking the von Willebrand factor-imposed FVIII half-life ceiling. Composed of a single recombinant FVIII molecule, efanesoctocog alfa incorporates three additional components contributing to an increased half-life: an Fc domain, the D'D3 domain of von Willebrand factor, and XTEN® polypeptides. Recently, efanesoctocog alfa has received regulatory approval in the U.S. in all adults and children with congenital HA for routine prophylaxis to reduce the frequency of bleeding episodes, on-demand treatment and control of bleeding episodes, and perioperative management of bleeding.

Methods

This is an open-label, single arm, multicenter study evaluating the safety and effectiveness of efanesoctocog alfa in PUPs with HA as a module of the hemophilia natural history arm of the hemophilia cohort of ATHN Transcends (NCT04398628) (Figure 1). Following confirmation of eligibility, a participant can be treated either efanesoctocog alfa on-demand or prophylactically. Concomitant use of emicizumab for prophylaxis will be allowed, though the total number of participants using emicizumab will be limited. The number of participants treated with the combination of emicizumab with efanesoctocog alfa will be no more than 33% of the total number of participants enrolled in the study. The study will last for a total of 7 years. The study will end when at least 50 participants have attained 50 EDs. Immune tolerance induction with efanesoctocog alfa is allowed during the study for those participants developing a positive inhibitor.

Figure 1.



Objectives

The primary objective is to describe the safety and tolerability of efanesoctocog alfa in PUPs with HA without a history of inhibitors.

The secondary objectives of our study include (within this population):

- To describe the effectiveness of efanesoctocog alfa as prophylaxis of bleeding treatment episodes
- To describe the effectiveness of efanesoctocog alfa as on-demand treatment in bleeding episodes
- To describe the effectiveness of efanesoctocog alfa for perioperative management of minor and major surgical procedures
- To describe the effectiveness of efanesoctocog alfa on clinical outcomes assessments including age-appropriate patient-reported outcomes
- To describe the consumption of efanesoctocog alfa for the prevention and treatment of bleeding episodes

Inclusion Criteria

To be eligible to participate in this study, potential participants must meet the following eligibility criteria at the time of screening:

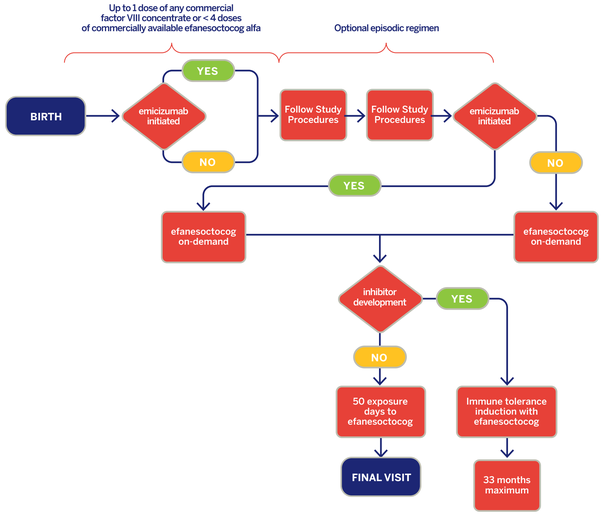
- Ability of the potential participant's legally authorized representative (e.g., their parent or legal guardian) to understand the purpose and risks of the study and provide signed and dated informed consent
- People with severe HA with a baseline FVIII activity of less than 1% documented in the medical record
- No history of FVIII inhibitor
- Sex at birth of male, female, or intersex
- Potential participants may be exposed to unfractionated blood components, one dose of FVIII concentrate other than efanesoctocog alfa and up to three doses of efanesoctocog alfa prior to enrollment
- Potential participants who have a history of bleeding will be eligible for participation if they meet all other inclusion criteria
- While inclusion for ATHN Transcends lists <5% FVIII activity, this module will limit enrollment to people with a FVIII activity level of < 1%

Exclusion Criteria

Potential participants will be excluded from the study if any of the following exclusion criteria exist:

- Not meeting all the inclusion criteria
- Any exposure to blood components or FVIII replacement products except as described in the inclusion criteria
- History of positive inhibitor testing
- History of hypersensitivity reactions associated with efanesoctocog alfa administration
- Other coagulation disorders(s) in addition to HA
- Any concurrent clinically significant major disease that, in the opinion of the investigator, would make the participant unsuitable for enrollment

Figure 2.



- Concurrent systemic treatment with chemotherapy and/or other immunosuppressant medications. Use of corticosteroids for the treatment of asthma or management of acute allergic or otherwise life-threatening episodes is allowed except for systemic corticosteroid treatment given to children daily or on an alternate day schedule at > 2 mg/kg/day of prednisone or its equivalent or > 20 mg/day if the duration is longer than 14 days
- Enrollment in a concurrent clinical interventional study
- Intake of an Investigational Medicinal Product within three months prior to inclusion in this study
- Inability to comply with study requirements
- Other, unspecified reasons that, in the opinion of the investigator, make the participant unsuitable for enrollment.

Inhibitor Development

Participants who develop high titer inhibitors and choose to attempt immune tolerance induction utilizing efanesoctocog alfa may remain in the study. Participants with low titer inhibitors will be eligible for immune tolerance induction if the Investigator determines that bleeding is no longer adequately controlled despite increased efanesoctocog alfa doses or if bypassing agents are required to treat bleeding in a participant with a positive low titer inhibitor.

The timing of immune tolerance induction initiation in patients with a peak inhibitor titer of >10 BU/mL, including patients who experience serious or life-threatening bleeding or have frequent mild to moderate bleeding, will be based on the investigator's clinical judgement.

If an investigator chooses to have the participant temporarily suspend treatment with efanesoctocog alfa, and delay the start of immune tolerance induction, the participant should continue to participate in interim visits every 12 ± 2 weeks.

Table 1. Schedule of Events

Non-inhibitor participants

EVENTS	ENROLLMENT/ BASELINE	QUARTERLY	ANNUAL	AD HOC	STUDY EXIT
Informed consent	x				
Medical/hematologic history	x				x
Pertinent medical events	x	x	x	x	x
Treatment plan	x	x	x	x	x
ISTH BAT	x				
PBAC	x	x	x		x
GOAL–Hêm	Optional	Optional	Optional	Optional	Optional
Review of bleed and infusion logs	x	x	x	x	x
Adverse events	x	x	x	x	x
PATIENT-REPORTED OUTCOMES					
EQ-5D-5L	x		x		x
Age-appropriate PROMIS profile	x		x		x
GAR					
Age-appropriate CATCH					
LABORATORY TESTING					
Inhibitor testing (Versiti) ,	x	x	x	x	x
Genetic testing	Collected once at any visit				
ATHN Research Biorepository	x	x	x	x	x

Table 2. Schedule of Events Inhibitor Participants

Inhibitor participants

INHIBITOR STATUS	FVIII INHIBITOR TITER	FVIII INCREMENTAL RECOVERY	FVIII HALF-LIFE
Confirmed positive FVIII inhibitor titer	Week 2 after confirmed positive Week 4 after confirmed positive Every 4 weeks through month 33		
Confirmed negative FVIII inhibitor titer	Every 4 weeks through end of study	Every 4 weeks until ≥ 66% expected	
Negative inhibitor titer and normal incremental recovery	Every 4 weeks through end of study	Every 4 weeks through end of study	Every 12 weeks through normalization or 33 months
Negative inhibitor titer and normal incremental recovery and normal half-life	Every 3 months through end of study	Every 3 months through end of study	12 months after immune tolerance induction success

Results

ATHN Transcends has received central IRB approval and is currently being rolled out across participating ATHN affiliates in the U.S.. Enrollment in the efa module can begin as soon as a site opens ATHN Transcends to enrollment.

Conclusion

As the FDA no longer requires PUP safety studies for approval, ATHN Transcends provides a real-world mechanism in which to collect safety, tolerability, and effectiveness data in the PUP population. The efanesoctocog alfa module of ATHN Transcends will allow collection of Good Clinical Practice-grade data in the PUP population.