# ATHN Transcends: A Natural History Study of Non-Neoplastic Hematologic Disorders

Status: RECRUITING

## Eligibility Criteria

Sex: ALL
Age:
Healthy Volunteers: This study is NOT accepting healthy volunteers
Participants who meet the following inclusion criteria and none of the exclusion criteria are eligible for enrollment in one of the open disease-specific arms.

Inclusion Criteria:

1. Any age
2. Having a congenital or acquired blood disorder; or
3. Having a bleeding phenotype as indicated by an age adjusted abnormal ISTH Bleeding Assessment Tool score with an unknown diagnosis; or
4. Connective tissue disorder with bleeding tendency as indicated by an age adjusted abnormal ISTH Bleeding Assessment Tool score.
5. Eligible for a currently active disease-specific arm.
6. Concurrent enrollment in the ATHNdataset or current ATHNdataset participant.

Exclusion Criteria:

1. Does not qualify for inclusion in a currently activedisease-specific arm; participants may be eligible to enroll as future cohorts and arms are activated; 2. Unable to give informed consent or assent 3. Unwilling to perform study procedures

Cohort Participant Selection

Each participant is to be enrolled in the cohort for which they qualify as defined below.

Hemophilia Cohort

Inclusion Criteria:

Participants who meet any of the following inclusion criteria are eligible for enrollment into this cohort:

1. Factor VIII or factor IX activity <50%, without another explanation for low clotting factor other than congenital hemophilia or being a known carrier for congenital hemophilia; OR
2. Carrier for congenital hemophilia with a factor VIII >=50% or factor IX activity >=50% with or without a bleeding phenotype as indicated by an ISTH Bleeding Assessment Tool score of ≥4 for adult males, ≥6 for adult females, or ≥3 for children younger than 18 years OR
3. Known congenital hemophilia that have a factor level >50% after receiving vector, OR 4. Acquired hemophilia.

Exclusion Criteria:

None

Von Willebrand Disease Cohort

Inclusion Criteria:

Participants who meet the following inclusion criteria are eligible for enrollment into this cohort:

1. Meeting the definition of VWD or low VWF per most recent international guidelines

Exclusion Criteria:

None

Congenital Platelet Disorders Cohort

Inclusion Criteria:

Participants who meet the following inclusion criteria are eligible for enrollment into this cohort:

1. Abnormalities of platelet function a. Glanzmann thrombasthenia (GPIIb or GPIIIa) b. Bernard-Soulier syndrome (GPIbalpha, GPIbbeta, or GPIX)
2. Abnormalities of platelet granules
3. Abnormalities of platelet signal transduction
4. Abnormalities of platelet secretion
5. Collagen Receptor Defect
6. ADP Receptor Defect
7. Thromboxane Receptor Defect
8. Giant Platelet Disorder
9. Abnormalities in platelet aggregation testing due to another or unknown cause (not drug related)

Exclusion Criteria:

1. Platelet disorders secondary to medications or other substances

Rare Disorders Cohort

Inclusion Criteria:

Participants who meet the following inclusion criteria are eligible for enrollment into this cohort:

1. Have an established Rare Coagulation Disorder (RCD) diagnosis of one of the following:

1. PAI-1 deficiency
2. Factor I, II, V, VII, X, XI, XIII deficiencies
3. Combined FV and FVIII deficiency
4. Plasminogen deficiency
5. Decreased tissue plasminogen activator
6. Afibrinogenemia/hypofibrinogenemia/dysfibrinogenemia
7. Thrombotic Thrombocytopenia Purpura or Congenital Hemolytic Uremic Syndrome
8. Wiskott-Aldrich
9. Methylenetetrahydrofolate Reductase Deficiency

Exclusion Criteria:

None

Bleeding NOS Cohort

Inclusion Criteria:

Participants who meet the following inclusion criteria are eligible for enrollment into this cohort:

1. Have a bleeding phenotype as indicated by an ISTH Bleeding Assessment Tool score of ≥4 for adult males, ≥6 for adult females, or ≥3 for children younger than 18 years with an unknown diagnosis, OR
2. Connective tissue disorder with bleeding tendency as indicated by an ISTH Bleeding Assessment Tool score of ≥4 for adult males, ≥6 for adult females, or ≥3 for children younger than 18 years.

Exclusion Criteria:

None

Thrombosis/Thrombophilia Cohort

Inclusion Criteria

Participants who meet the following inclusion criteria are eligible for enrollment into this cohort:

1. Have a prior history of arterial or venous thrombosis. 2. Participants with a known congenital or acquired thrombophilia with or without thrombosis.

a. Common congenital thrombophilias: i. Protein C deficiency ii. Protein S deficiency iii. Antithrombin deficiency iv. Factor V Leiden v. Prothrombin gene mutation b. Rare genetic factors i. Hyperhomocysteinemia c. Indeterminate genetic factors i. Elevated factor VIII ii. Elevated factor IX iii. Elevated factor XI iv. Elevated lipoprotein (a) d. Acquired thrombophilias i. Lupus anticoagulant ii. Anti-cardiolipin antibodies/Beta2 glycoprotein antibodies iii. Antiphospholipid syndrome

Exclusion Criteria Acquired thrombophilia secondary to medications (birth control pills or hormone replacement therapy), overweight or obesity, smoking, cancer, pregnancy, surgery, injury, prolonged inactivity/bedrest, heart failure, inflammatory bowel disease, or kidney disease

Non-Neoplastic Hematologic Conditions Cohort

Inclusion Criteria

Participants who meet the following inclusion criteria are eligible for enrollment into this cohort:

1. Having any congenital or acquired non-neoplastic hematologic disorder not included in any other cohort

Exclusion Criteria None

Arm/Module Participant Selection

Previously Untreated Patients Arm

Inclusion Criteria:

1. Diagnosis of congenital hemophilia A (FVIII <40%) or hemophilia B (FIX <40% or below lower limit for age)
2. Age <18 years at time of enrollment
3. Parent or authorized guardian or legally authorized representative (LAR) can provide informed consent
4. Care established at one of the ATHN Transcends participating HTCs
5. Clotting Factor Concentrate (CFC) exposure, fresh frozen plasma (FFP), cryoprecipitate, and single donor platelets <3 exposure days (ED)

Exclusion Criteria

1. Concomitant diagnosis with another bleeding disorder

2. History of a confirmed, positive inhibitor

INHIBIT Module

Inclusion Criteria:

1. Diagnosis of severe factor VIII deficiency with baseline factor VIII level <1% 2. Initiating or plan to initiate prophylaxis with emicizumab or factor replacement 3. Factor concentrate exposure, Fresh Frozen Plasma (FFP), cryoprecipitate, and single donor platelets ≤3 EDs 4. ≤5 years of age

Exclusion Criteria

1. Concomitant diagnosis with bleeding disorder other than hemophilia A
2. Immune disorder
3. Previous history or presence of factor VIII inhibitor. A confirmed, positive inhibitor is defined as two consecutive positive inhibitor titers (≥ 0.6 BU) that result in changes in treatment recommendations.

Efanesoctocog alfa (ALTUVIIIO®) Module

Inclusion criteria:

1. 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 and authorization to use confidential health information in accordance with national and local participant privacy regulation.
2. People with severe HA with a baseline FVIII activity of less than 1%. (While inclusion for participation in ATHN Transcends lists <5% FVIII activity, this proposed module will limit enrollment to people with FVIII activity levels of <1%.) Other severities may be included per ATHN Transcends PI approval.
3. <18 years of age.
4. No history of a confirmed, positive FVIII inhibitor.
5. Sex assigned at birth of male, female, or intersex.
6. Participants should have no more than three (3) exposure days of blood products (fresh frozen plasma, cryoprecipitate, or platelets), no more than three (3) doses of any FVIII concentrate other than efanesoctocog alfa, and up to three (3) doses of efanesoctocog alfa prior to enrollment.
7. Site PI confirmed all inclusion criteria has been met.

Exclusion criteria:

1. Not meeting all the inclusion criteria; confirmed by site PI.
2. Any exposure to blood products or FVIII replacement products except as described in the inclusion criteria.
3. History of positive inhibitor testing.
4. History of hypersensitivity reactions associated with efanesoctocog alfa administration.
5. Other coagulation disorder(s) in addition to Hemophilia A.
6. Any concurrent clinically significant major disease such as cancer that, in the opinion of the investigator, would make the participant unsuitable for enrollment.
7. 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.
8. Enrollment in a concurrent clinical interventional drug study.
9. Intake of an Investigational Medicinal Product within three (3) months prior to inclusion in this study.
10. Inability to comply with study requirements.
11. Other, unspecified reasons that, in the investigator's opinion, make the participant unsuitable for enrollment.

Hemophilia Natural History Arm

Inclusion Criteria

1. Congenital or acquired hemophilia A or B of any severity with or without inhibitors receiving a current therapy, a non-factor product, or for whom use of a non-factor product is a possibility, OR
2. Females of any age, with confirmed congenital hemophilia A or B carrier status with genetic mutational analysis and any factor level.

Exclusion Criteria

1. Presence of any known bleeding disorder other than congenital hemophilia A or B
2. Presence of concurrent hemophilia and a second hemostatic defect (low von Willebrand Factor (vWF) without vWD diagnosis is not excluded)
3. Unable or unwilling to comply with the study arm protocol.

Nonacog beta pegol (Rebinyn®) Module

Inclusion Criteria:

1. Has provided signed written consent for the nonacog beta pegol (Rebinyn®)Module before any study-related activities.
2. Male participants, at any age with hemophilia B, naïve or minimally exposed (up to 3 EDs) to nonacog beta pegol treatment at time of study enrollment. Additional doses may be allowable per ATHN Transcends PI approval.
3. Decision to initiate continuous prophylaxis treatment with commercially available nonacog beta pegol has been made by the participant(s)/Legally Authorized Representative(s) (LAR(s)) and the treating physician before and independently from the decision to include the participant in this study.

Exclusion Criteria:

1. Previous participation in this study. Participation is defined as having given informed consent in this study.
2. Mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation, including a diagnosis or suspicion of attention deficit hyperactivity disorder (ADHD) or autism spectrum disorder (ASD) per the discretion of the Principal Investigator.
3. Known or suspected hypersensitivity to nonacog beta pegol or related products.
4. Clinical suspicion or presence of FIX inhibitor at time of inclusion.
5. Inability or unwillingness to undergo neurological assessment/structured developmental history.

Emicizumab (Hemlibra®) Module

Inclusion Criteria:

1. Participant currently treated with emicizumab (Hemlibra®)
2. Currently enrolled in the Hemophilia Natural History Arm of ATHN Transcends

Exclusion Criteria:

1. Unable or unwilling to comply with the protocol

Distress Module

Inclusion Criteria:

1. Congenital hemophilia A or B of any severity with or without inhibitors receiving a current therapy, a non-factor product, or for whom use of a non-factor product is a possibility
2. Age 18 years of age or older
3. English speaking

Exclusion Criteria:

1. Presence of any known bleeding disorder other than congenital hemophilia A or B;
2. Presence of concurrent hemophilia and a second hemostatic defect (low von Willebrand Factor (vWF) without vWD diagnosis is not excluded); and
3. Unable or unwilling to comply with the study arm protocol

Hemophilia Gene Therapy Outcomes Arm

Inclusion Criteria

1. Hemophilia A or B of any severity with or without inhibitors having received or will receive a hemophilia gene transfer product in the next 6 months.
2. Age 18 years and older.
3. Able to give informed consent.

Exclusion Criteria None

Etranacogene dezaparvovec (HEMGENIX®) Module

Inclusion Criteria:

Etranacogene dezaparvovec (HEMGENIX®) Cohort

1. Age 18 years of age or older
2. Treatment with commercial etranacogene dezaparvovec (HEMGENIX®)
3. Have provided signed written informed consent within 3 months before or within 6 months after etranacogene dezaparvovec (HEMGENIX®) treatment, or within 6 months of when the study is initiated at the treating site.

FIX Prophylaxis Cohort

1. Age 18 years of age or older
2. Treatment with FIX prophylaxis therapy
3. Has provided signed written consent at any time for ATHN Transcends Study

Exclusion Criteria, both cohorts:

1. Have been treated with etranacogene dezaparvovec in a clinical trial prior to commercial availability. These patients are still eligible for enrollment in the Gene Therapy Outcomes Arm, and their data may be collected for separate analysis.

Congenital Platelet Disorders Arm

Inclusion Criteria

1. Platelet adhesion defect
    1. Bernard Soulier syndrome (Defective GPIb-IX-V receptor, impaired adhesion to vWF)
    2. Velocardio-facial syndrome/DiGeorge syndrome (Defective GPIb-IX-V receptor)
    3. Platelet type vWD (Defective GPIb-IX-V, gain of function interaction between vWF-GP1bα)
2. Platelet aggregation defect
    1. Glanzmann thrombasthenia (Defective integrin αIIbβ3 (GPIIb/IIIa)
    2. Platelet aggregation defect, NOS
3. Agonist receptor defects

1. Epinephrine
2. ADP
3. Collagen
4. Thromboxane A2

4. Platelet signaling defects

1. Cyclooxygenase deficiency (PTGS1 mutation)
2. Phospholipase A2 deficiency
3. Thromboxane synthase deficiency (TBXAS1 mutation)
4. G protein activation defect (GNAS mutation)
5. Scott syndrome (defect in phosphatidyl serine translocation)

5. Platelet Granule disorders

1. Dense granule storage pool disorder

* Hermansky Pudlak syndrome
* Chediak Higashi syndrome
* Griscelli syndrome

1. Alpha granule storage pool disorder

* Grey platelet syndrome
* Arthrogryposis-Renal Dysfunction-Cholestasis (ARC) syndrome
* Quebec platelet disorder
* Paris-Trousseau syndrome

1. Combined alpha delta granule deficiency

1. Platelet cytoskeletal structure defects

2. Wiskott Aldrich syndrome

3. MYH9 associated disorders (myosin heavy chain)

* May Hegglin syndrome
* Fechtner syndrome
* Sebastian syndrome
* Epstein syndrome

1. Other mutations

* FLNA mutations (Filamin)
* DIAPH1 (Actin and microtubules)
* ACTN1 (alpha actinin)
* TPM4 (tropomyosin)
* TUBB1 (beta tubulin)

1. Other Congenital thrombocytopenias

1. Familial platelet disorders and predisposition to AML (RUNX1)
2. X linked thrombocytopenia with dyserythropoiesis (GATA1)
3. Congenital amegakaryocytic thrombocytopenia (MPL)

Exclusion Criteria

1. Diagnosis of von Willebrand Disease (Meeting the definition of vWD or low vWF per most recent international guidelines)
2. Diagnosis of Hemophilia A or Hemophilia B (Factor VIII or IX ≤ 40%)

Glanzmann Thrombasthenia (GT) Module

Inclusion Criteria

1. Participant has signed the informed consent/assent form
2. Participant has flow cytometry or aggregometry or genetics confirmed GT
3. Participant is willing to perform study procedures, including daily bleed tracking for 3 months and further if requested
4. Participants are 2 years or older at time of consent

Exclusion Criteria None

## Conditions & Interventions

Conditions:
Hematologic Disorder, Bleeding Disorder, Connective Tissue Disorder, Hemophilia, Thrombosis, Von Willebrand Diseases, Thrombophilia, Rare Bleeding Disorder, Platelet Disorder, Factor IX Deficiency, Factor VIII Deficiency, Thalassemia, Sickle Cell Disease

## More Information

Description:
In parallel with the growth of ATHN's clinical studies, the number of new therapies for all blood disorders is increasing significantly. Some of the recently FDA-approved therapies for congenital and acquired hematologic conditions have not yet demonstrated long-term safety and effectiveness beyond the pivotal trials that led to their approval. In addition, results from well controlled, pivotal studies often cannot be replicated once a therapy has been approved for general use.2,3,4,5 In 2019 alone, the FDA has issued approvals for 24 new therapies for congenital and acquired hematologic conditions.6 In addition, almost 10,000 new studies for hematologic diseases are currently registered on www.clinicaltrials.gov.7 With this increase in potential new therapies possible, it is imperative that clinicians and clinical researchers in the field of non-neoplastic hematology

this increase in potential new therapies possible, it is imperative that clinicians and clinical researchers in the field of non-neoplastic hematology have a uniform, secure, unbiased, and enduring method to collect long-term safety and efficacy data. As emphasized in a recently published review, accurate, uniform and quality national data collection is critical in clinical research, particularly for longitudinal cohort studies covering a lifetime of biologic risk.8

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