Designing the Ryplazim® (Plasminogen, Human-tvmh) Arm of the ATHN Transcends: Safety and Effectiveness in People with Plasminogen Deficiency

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Background

Plasminogen deficiency type 1 (PLGD-1) is a rare, inherited, systemic disorder with an estimated incidence of 1-2 per million population due to homozygous/compound heterozygous variants in *PLG*, the gene coding for plasminogen (PLG). Clinical manifestations of PLGD-1 result from inadequately lysed extravascular fibrin leading to accumulation of pseudomembranes accumulation of pseudomembranes on mucous membranes resulting in impaired organ function, morbidity, decreased quality of life (QoL), and, at times, mortality. In 2021, plasma-derived plasminogen, human-tvmh (Ryplazim®) received regulatory approval for treatment of people with PLGD-1 (PwPLGD-1).

Ryplazim® is purified from pooled human plasma sourced from US FDA and plasma collection centers. Ryplazim is a Glu-plasminogen concentrate (greater than 95% purity) which is the native circulating form of plasminogen in the blood. Ryplazim is available in a single-dose 50-mL vial containing plasminogen as a lyophilized powder for reconstitution with sterile water for injection. Ryplazim® is intended for intravenous (IV) administration as a replacement therapy for children and adults with PLGD-1.

Objectives

Primary Objective

To describe the real-world safety and effectiveness of plasminogen, human-tvmh (Ryplazim®) in PwPLGD-1.

Secondary Objectives

- To describe the real-world effectiveness of Ryplazim® for prophylaxis of lesions in PwPLGD-1
- To describe the real-world effectiveness of Ryplazim® for treatment of lesions in PwPLGD-1
- To describe the real-world effectiveness of Ryplazim® for perioperative management of minor and major surgical procedures in PwPLGD-1
- To describe the real-world effectiveness of Ryplazim® on clinical outcomes assessments including age-appropriate patient-reported outcomes (PROs) in PwPLGD-1
- To describe the real-world consumption of Ryplazim® for prevention and treatment of lesions in PwPLGD-1

Endpoints

Primary Endpoints

- Occurrence of any European Haemophilia Safety Surveillance (EUHASS) project endpoint:
  - Allergic or other acute events
  - Treatment-emergent side effects of therapy
  - Transfusion transmitted infection
  - Thrombosis/thromboembolism
  - Cardiovascular events
  - Malignancies
  - Neurologic events
  - Death
- Occurrence of any of the following adverse events of special interest (AESIs):
  - Injection site reactions
  - Hospitalizations
  - Pregnancy
  - Overdose
  - Bleeding from site of resolving or resolved lesion
  - Tissue sloughing requiring additional medical intervention
  - Elevations of D-dimer

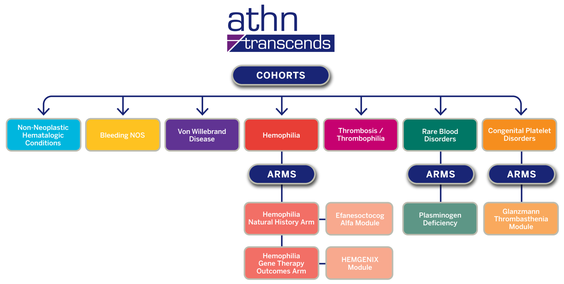
Secondary Endpoints

- To describe the effectiveness of Ryplazim® in treatment of lesions associated with PLGD-1
- To describe the effectiveness of Ryplazim® in prevention of lesions associated with PLGD-1
- To describe the effectiveness of Ryplazim® for perioperative management of minor and major surgical procedures in PwPLGD-1
- To describe the effectiveness of Ryplazim® on clinical outcomes assessments including age-appropriate PROs in PwPLGD-1
  - Patient and caregiver preferences for Ryplazim®
  - Treatment satisfaction
  - Pain, physical activity, and quality of life
- To describe consumption of Ryplazim® for the treatment and prevention of lesions associated with PLGD-1
  - Total annualized injection frequency per participant assessed by prescription and actual use
  - Total annualized Ryplazim® consumption per participant assessed by prescription and actual use in milligrams (mg)/kilograms (kg)
  - Investigator assessed adherence to recommended therapy

Study Design

This is an open-label, single arm, multicenter study evaluating the safety and effectiveness of plasminogen, human-tvmh (Ryplazim®) in PwPLGD-1 as an arm of the Rare Blood Disorders Cohort of ATHN Transcends (NCT04398628) (Figure 1). Following confirmation of eligibility, a participant can be treated either on-demand or prophylactically with Ryplazim®. Because we are collecting real-world data, concomitant use of other medications for the treatment of PLGD-1 will be allowed and recorded. The study will last for a total of 5 years. The study will end when at least 100 participants have attained 100 exposure days (EDs) to Ryplazim®. Surgery is allowed during the study.

Figure 1.



Study Population

Inclusion Criteria:

- Subject or legal guardian provided informed consent (as well as assent by participants with ages dictated by local Investigational Review Board [IRB] guidelines)
- Any person with a documented history of lesions and symptoms consistent with the diagnosis of PLGD-1
- A plasminogen activity ≤ 45%
- No history of hypersensitivity to Ryplazim® or to components of Ryplazim®
- No current or history of an inhibitor to Ryplazim®
- Currently using or planning on using Ryplazim®
- Those recently having received exogenous plasminogen (ocular or intravenous), such as laboratory grade plasminogen, fresh frozen plasma, or other plasma-derived plasminogen concentrate

Exclusion Criteria:

- Not meeting all inclusion criteria
- Enrollment in a concurrent clinical interventional drug study
- Intake of an Investigational Medicinal Product within 3 months prior to inclusion in this study
- Having a history of anaphylactic reactions to blood or blood products that may interfere with participation in the study
- Having a known hypersensitivity to Ryplazim® or to components of Ryplazim®
- Having a history of or current inhibitor to Ryplazim®
- Having a chronic or acute clinically significant condition that the investigator determines could interfere with the assessments in this study

Figure 2. Study Schematic

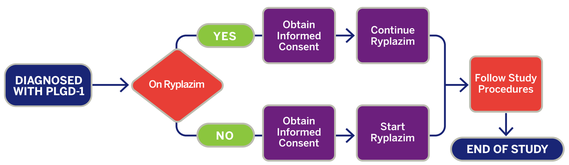


Table 1. Schedule of Events

EVENTS	ENROLLMENT/ BASELINE	QUARTERLY	ANNUAL	AD HOC	STUDY EXIT
Informed consent	X				
Medical history	X	X	X	X	X
Treatment plan	X	X	X	X	X
Review of log	X	X	X	X	X
Adverse events	X[5]	X	X	X	X
PATIENT-REPORTED OUTCOMES					
EQ-5D-5L[1]	X		X		X
PROMIS profile	X		X		X
LABORATORY TESTING					
Genotype[2]	Collected once at any visit				
ARB[3]	X	X	X	X	X
Plasminogen ADA[4]	X		X	X	X
Plasminogen recovery[5]	X			X	
D-dimer[5]	X		X	X	

[1] For participants 12 years of age and older
[2] Performed once
[3] ATHN Research Biorepository samples collected at baseline and any time plasminogen inhibitor is suspected
[4] If clinically available and clinically suspected
[5] Plasminogen activity levels obtained at time 0 and 30 minute after infusion
[5] Obtained at time of plasminogen recovery at 0 minutes and 30 minutes

Results

ATHN Transcends has received central IRB approval and is currently being rolled out across participating ATHN affiliates in the United States. Final approval of the Ryplazim® module is in process. Once approved, an ATHN Transcends study amendment will be submitted to the central IRB. Once central IRB approval is obtained, enrollment in the ATHN Transcends rare blood disorders cohort, Ryplazim® module can begin.

Conclusions

ATHN Transcends provides a real-world mechanism in which to collect safety, tolerability, and effectiveness data in people with rare blood disorders. The Ryplazim® module of ATHN Transcends will allow collection of Good Clinical Practice-grade data in this population.

Acknowledgements

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