ALN-6400

An Investigational RNAi Therapeutic Targeting Plasminogen to Address Rare Bleeding Disorders

June 25, 2026

Alnylam Forward-Looking Statements

This presentation contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. All statements other than historical statements of fact regarding Alnylam's ability to achieve the goals in its "*Alnylam 2030*" strategy, including to achieve RNAi delivery to at least 10 tissue types and over 40 programs in the clinic by the end of 2030, and to deliver two or more new transformative medicines beyond TTR with blockbuster potential; Alnylam's ability to file 3-4 new INDs each year; the potential for the programs in Alnylam's pipeline, including ALN-6400, zilebesiran and ALN-HTT02, to represent the next wave of transformative medicines and to change the practice of medicine; the potential efficacy, treatment effect, safety and product profile of ALN-6400, including its potential to provide durable and safe bleeding protection across a range of bleeding disorders, to enable effective prophylaxis through infrequent subcutaneous administration, to be a first-in-class treatment for hereditary hemorrhagic telangiectasia (HHT), and to transform prophylaxis for patients with von Willebrand Disease (VWD); the potential for ALN-6400's mechanism not to increase thrombin generation or to be associated with increased thrombotic risk; the size and future growth of the patient populations with HHT and VWD, including estimated patient numbers globally and in the U.S., and the potential for diagnosis and treatment rates to increase as new treatments become available; the timing of initiation of, completion of enrollment in, or announcement of results from, Alnylam's clinical trials of ALN-6400, including the Phase 1 study in healthy volunteers and the InsigHHT (HHT) and HMBeacon (VWD) Phase 2 studies, as well as Alnylam's plans to advance ALN-6400 into Phase 3 development; and the potential for any of Alnylam's product candidates, including ALN-6400, to successfully complete clinical development, receive regulatory approval and launch commercially should be considered forward-looking statements.

Actual results and future plans may differ materially from those indicated by these forward-looking statements as a result of various important risks, uncertainties and other factors, including, without limitation, risks and uncertainties relating to: Alnylam's ability to successfully execute on its "*Alnylam 2030*" strategy; Alnylam's ability to successfully launch, market and sell Alnylam's approved products globally, including AMVUTTRA; Alnylam's ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of its product candidates; the pre-clinical and clinical results for Alnylam's product candidates; actions or advice of regulatory agencies and Alnylam's ability to obtain and maintain regulatory approval for its product candidates, as well as favorable pricing and reimbursement; delays, interruptions or failures in the manufacture and supply of Alnylam's marketed products or its product candidates; obtaining, maintaining and protecting intellectual property; Alnylam's ability to manage its growth and operating expenses through disciplined investment in operations; Alnylam's ability to maintain strategic business collaborations; Alnylam's dependence on third parties for the development and commercialization of certain products; the outcome of litigation and government investigations; the risk of future litigation and government investigations; and unexpected expenditures; as well as those risks and uncertainties more fully discussed in the "Risk Factors" filed with Alnylam's most recent periodic report (Quarterly Report on Form 10-Q or Annual Report on Form 10-K) filed with the SEC and in its other SEC filings. In addition, any forward-looking statements represent Alnylam's views only as of today and should not be relied upon as representing its views as of any subsequent date. Alnylam explicitly disclaims any obligation, except to the extent required by law, to update any forward-looking statements.

Introduction

Pushkal Garg, M.D.

Chief Research & Development Officer

Agenda

01	Introduction	**Pushkal Garg, M.D.** *Chief Research & Development Officer*
02	ALN-6400 Opportunity	**John Gansner, M.D., Ph.D.** *Executive Director, ALN-6400 Program Lead*
03	Physician Perspective	**Hanny Al-Samkari, M.D.** *Harvard Medical School* *Massachusetts General Hospital*
04	Clinical Plans and Progress	**Martina Slingsby, Ph.D.** *Senior Clinical Scientist,* *ALN-6400 Clinical Science Lead*
05	Q&A Session	

Pioneering a Generational Class of RNAi Medicines

- Silence *any* gene in genome
- Upstream of today's medicines
- Catalytic mechanism
- Highly potent
- Highly specific and reversible
- Infrequent administration

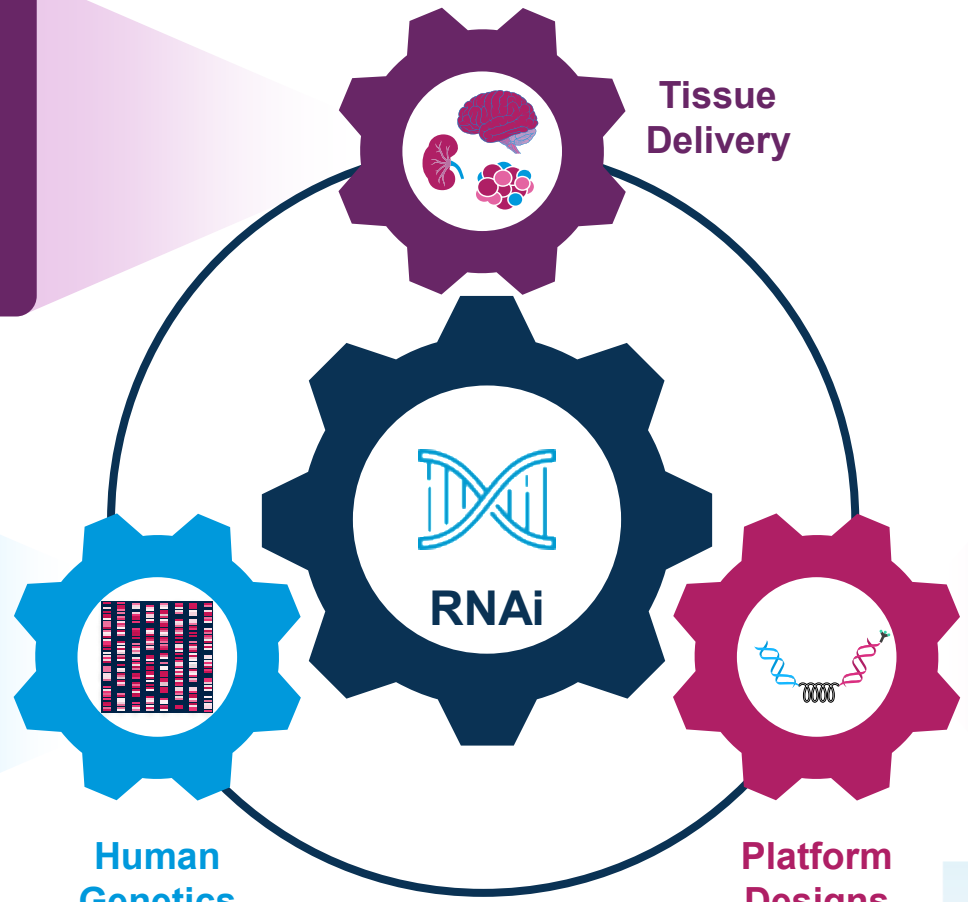
Building a Portfolio of RNAi Therapeutics with Transformational Patient Impact

Alnylam's Sustainable Innovation Engine

Modular Drug Discovery Platform to Catalyze Long-Term Growth

Expand into
10 TISSUES
by 2030

Access to
2 MILLION
lives through
genetics databases



Potency

Specificity

Durability

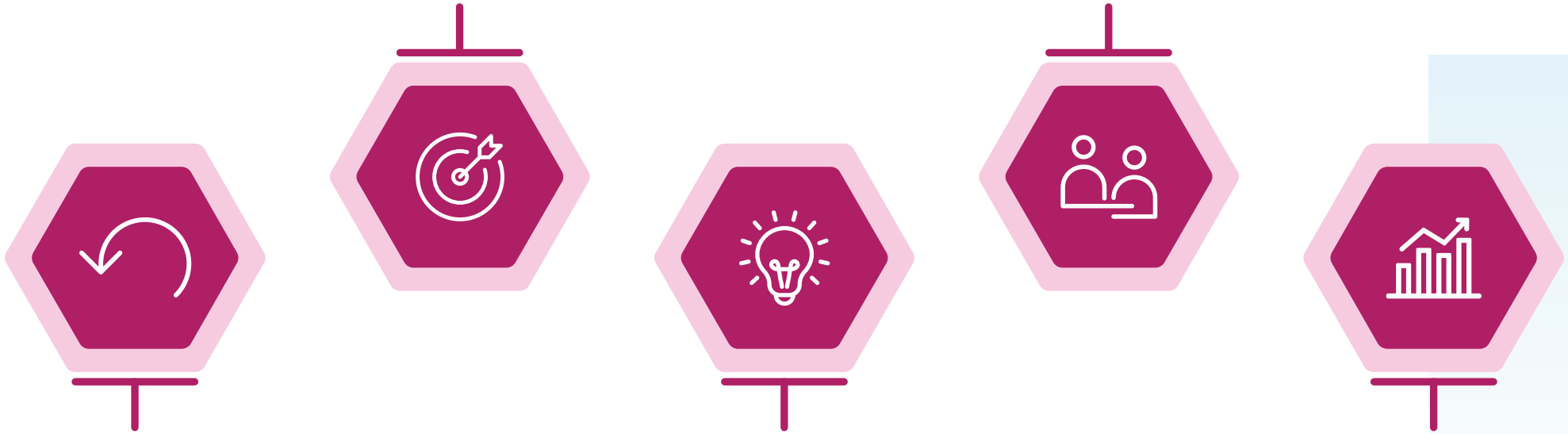
Reversibility

Multiplexing

Strategic Principles Driving a Differentiated Approach

Pursue high conviction targets
strong biologic rationale, informed by human genetics

Address diseases with high morbidity & mortality

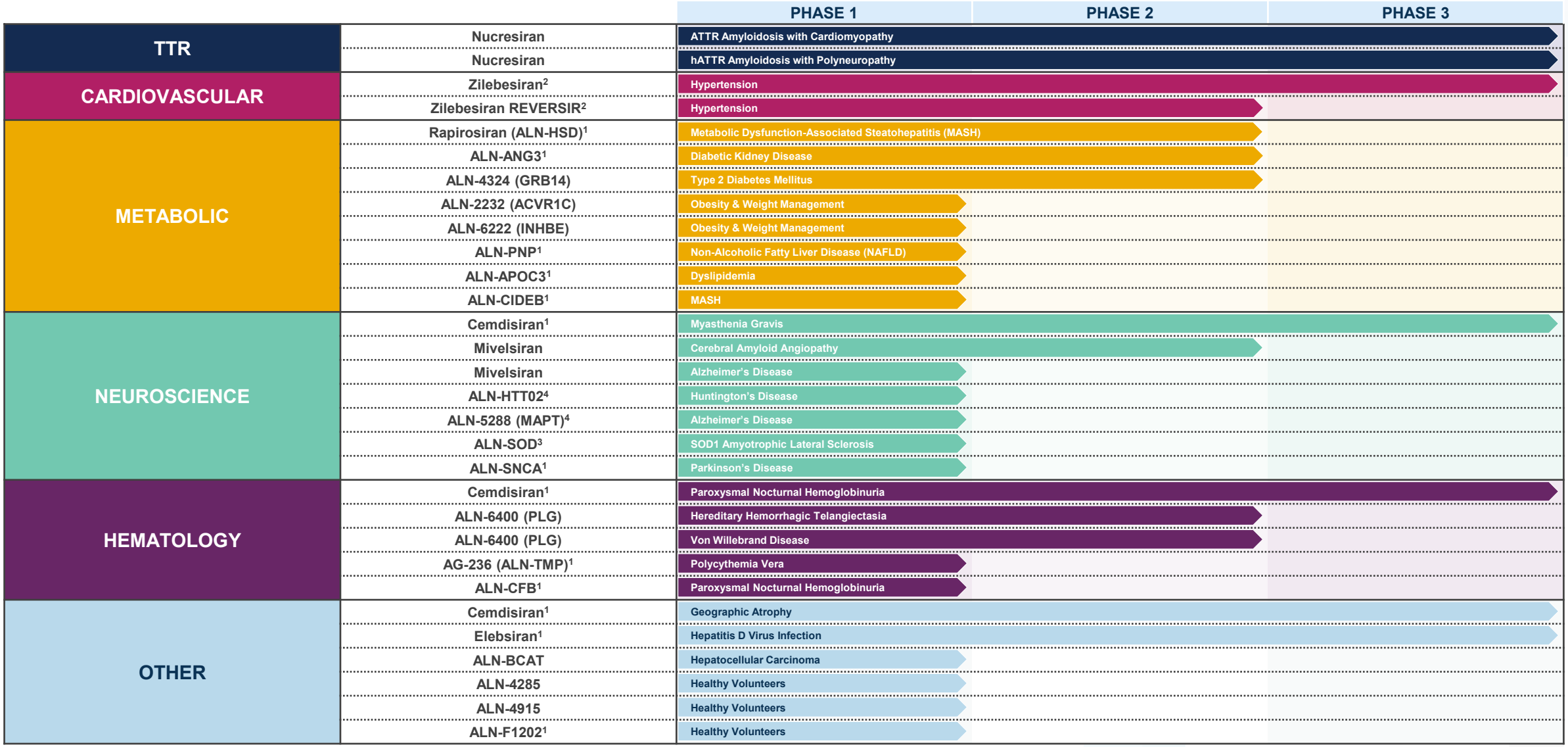


Potential to halt or reverse disease; best-in-class potential

Clear clinical proof-of-concept

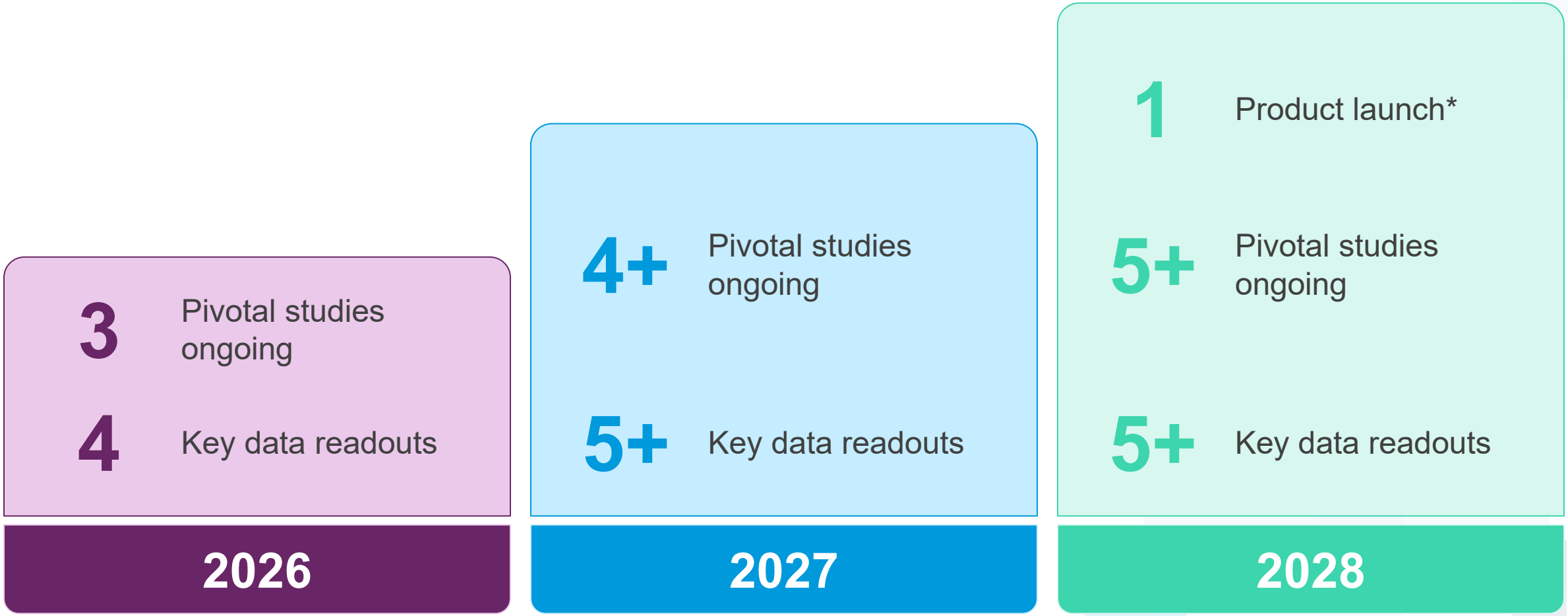
Encouraging market opportunity & access dynamics

Industry Leading Pipeline of RNAi Therapeutics



1 Out-licensed with milestones and/or royalties; 2 Partnered, Alnylam-led development with U.S. profit split and milestones/royalties ex-U.S.; 3 Partner-led with profit split; 4 Partnered, Alnylam-led with profit split

Expect Significant Clinical Milestones Over Next Two Years



** Assuming positive phase 3 data and regulatory approval*

Alnylam 2030 – Growth Through Sustainable Innovation

Delivering Therapies that Prevent, Halt, or Reverse Disease

Deliver 2+ new transformative medicines beyond TTR with blockbuster potential

Expand to 10 tissue types & >40 clinical programs

Invest ~30% of revenues in non-GAAP R&D, including select external innovation

Next Wave of Potential Transformative Medicines

HEMATOLOGY

ALN-6400

Targeting Plasminogen to Address Rare Bleeding Disorders

~5M people living with bleeding disorders globally[1]

Von Willebrand Disease
#1 most common inherited bleeding disorder[2]
Hereditary Hemorrhagic Telangiectasia
#2 most common inherited bleeding disorder[3]

Clinical PoM achieved in healthy volunteers

Phase 1 healthy volunteer data and Phase 2 HHT initial results in 2H26

CARDIOVASCULAR + METABOLIC

ZILEBESIRAN

Targeting Angiotensinogen to Achieve Continuous Control of Blood Pressure

>60M patients in 7 major markets with uncontrolled hypertension and high CV risk[4]

2 doses per year

Continuing enrollment in ZENITH Phase 3 CVOT; Launch expected ~2030[5]

NEUROSCIENCE

ALN-HTT02

Targeting Exon 1 of Huntington Gene to Reduce Progression of Huntington's Disease

>100K symptomatic HD patients globally[6]

>75% reductions in HTT[7]

Initial Phase 1 data expected 2H26

The safety and efficacy of ALN-6400, zilebesiran, and ALN-HTT02 have not been established or approved by the FDA, EMA or any other health authority. 1 Al-Samkari H et al. Standardization of Terminology, Definitions, and Outcome Criteria for Bleeding in Hereditary Hemorrhagic Telangiectasia: International Consensus Report. Am J Hematology 2025; Castaman G et al. Von Willebrand disease: classification and epidemiology. Haematologica 2026.; World Federation of Hemophilia Report on the Annual Global Survey 2024.; Komodo claims data. 2 https://www.bleeding.org/bleeding-disorders-a-z/types/von-willebrand-disease. 3 Zhang, et al. Blood (2023) 142 (Supplement 1): 28. doi: https://doi.org/10.1182/blood-2023-187772. 4 Internal estimate based on NCD-RisC, 2021; Nguyen T & Chow C, Lancet (2021); Muntner P et al., Hypertension (2020). 5 Launch assumes positive clinical trial results and regulatory approval. Zilebesiran is being co-developed and co-commercialized by Alnylam and Roche. 6 Internal estimate based on Medina A et al., Movement Disorders (2022); Ibanez K et al., Nature Medicine (2024). 7 Data in non-human primates. ALN-HTT02 is being developed in partnership with Regeneron Pharmaceuticals.

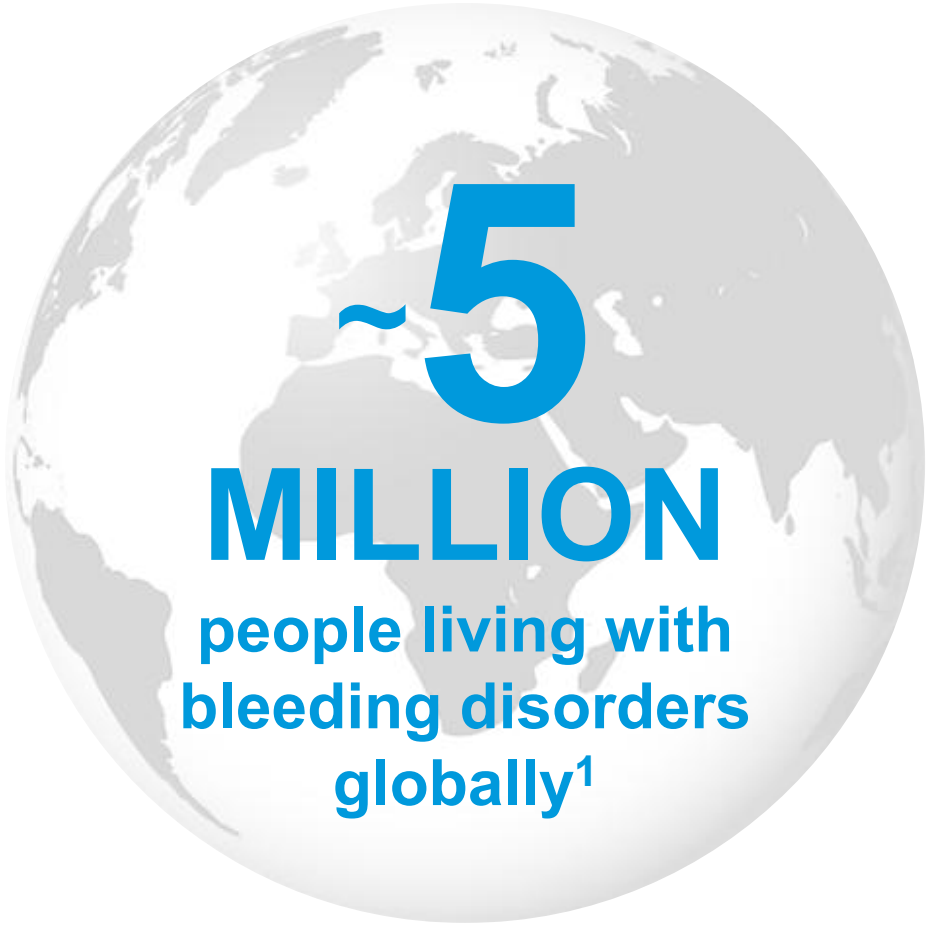
ALN-6400 Opportunity

John Gansner, M.D., Ph.D.

Executive Director, ALN-6400 Program Lead

Broad Opportunity Across Bleeding Disorders

High Disease Burden Underscores Unmet need for Therapies with Durable and Safe Bleeding Protection



~5 MILLION

people living with bleeding disorders globally[1]

Varying Disease Etiologies → **Common Bleeding Phenotype**

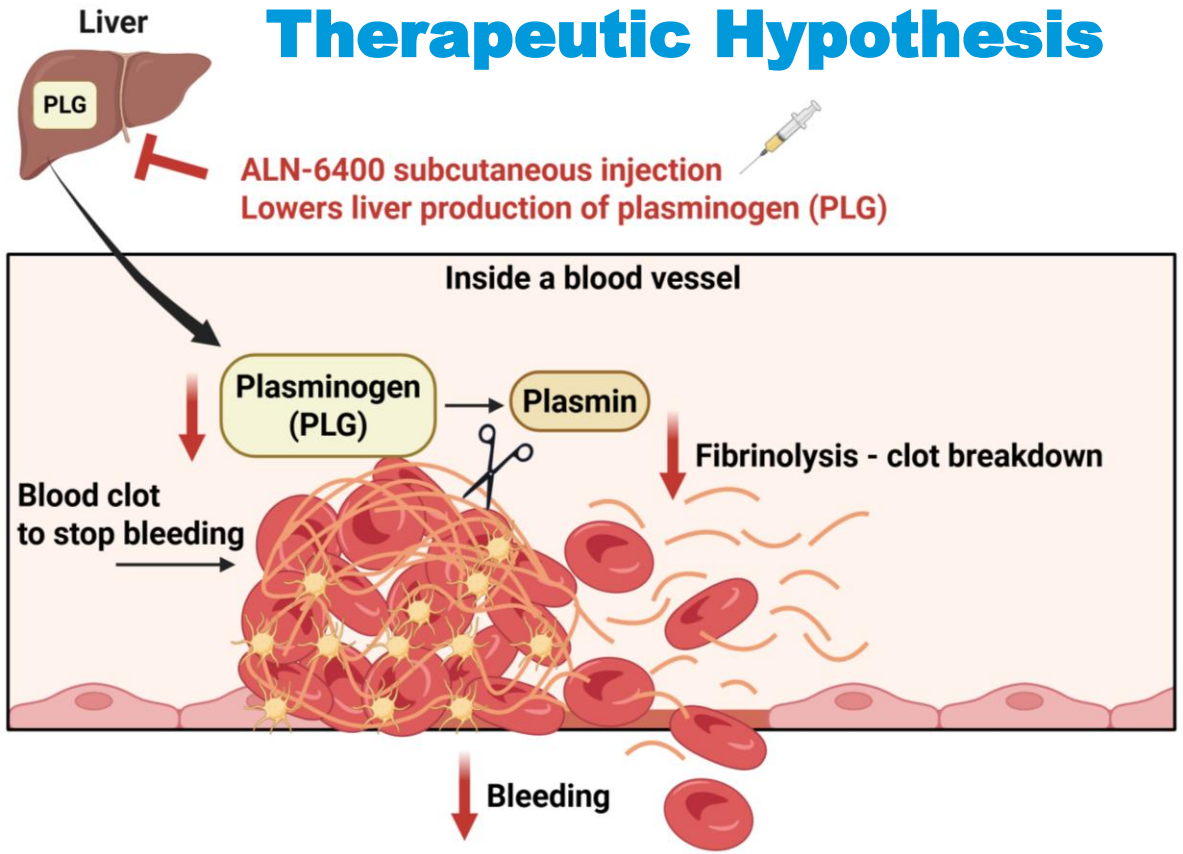
Disease burden associated with:

- Anemia, Iron Infusions, Blood Transfusions
- Procedures, Hospitalizations
- Social Stigma, Anxiety
- Limited or No Approved Treatments

1 Al-Samkari H et al. Standardization of Terminology, Definitions, and Outcome Criteria for Bleeding in Hereditary Hemorrhagic Telangiectasia: International Consensus Report. Am J Hematology 2025.; Castaman G et al. Von Willebrand disease: classification and epidemiology. Haematologica 2026. World Federation of Hemophilia Report on the Annual Global Survey 2024. Komodo claims data.

ALN-6400 Targets Liver-Expressed Plasminogen (PLG) to Prophylactically Reduce Bleeding

Therapeutic Hypothesis



Created with BioRender.com

Supporting Rationale

- Genetically and Preclinically Validated Target
- Mechanism Clinically De-Risked
- Not Expected to Increase Thrombotic Risk
- Infrequent subcutaneous administration to enable effective prophylaxis

Strong Evidence to Support PLG Knockdown to Reduce Bleeding

Genetic Evidence

Genetically-predicted lower levels of PLG protein are associated with[1]:

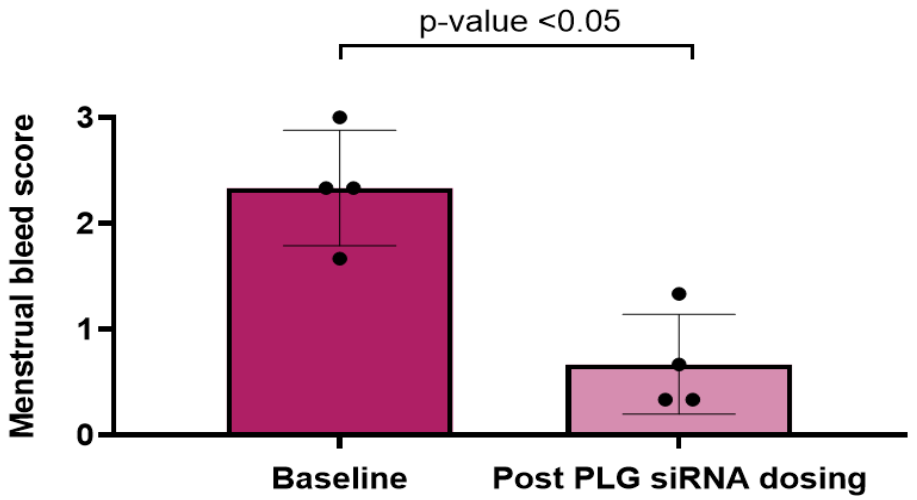
- **Reduced** GI bleeding
- **Reduced** nose bleeding
- **Reduced** heavy menstrual bleeding

biobank uk

Preclinical Data

PLG-siRNA reduces fibrinolysis and mucosal bleeding in Non-Human Primates[2]

Reduced Menstrual Bleeding



1 In house genetic analysis from UK Biobank; 2 In house preclinical data

ALN-6400 Not Expected to Increase Thrombotic Risk

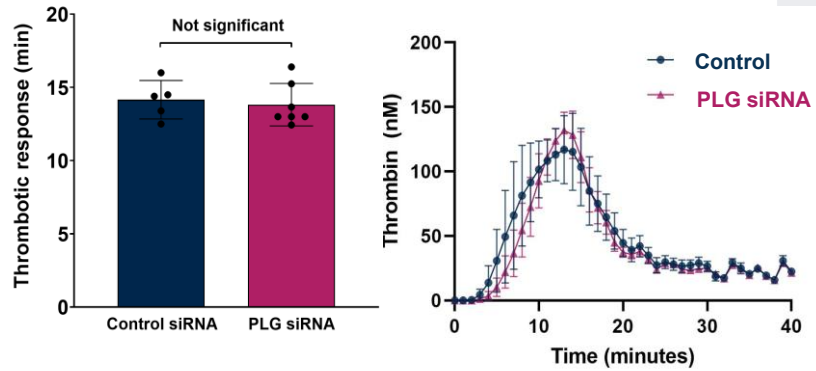
Genetic and Proteomic Data

Low PLG levels **not associated with increased risk** of arterial or venous thrombosis[1,2,3]

Natural History Data

107 patients with PLG deficiency had **no history of venous thrombosis**[3]

Pre-Clinical Data



Thrombotic response same as control[1]

Thrombin generation not altered[4]

with ~95-99% PLG knockdown[1,4]

1 Ivanciu L et al. Hepatic Plasminogen Lowering with RNA Interference for the Treatment of Bleeding Disorders is Unlikely to Pose Thrombotic Risk Based on UK Biobank Analyses and Mouse Models of Provoked Thrombosis. Presented at the European Hematology Association Conference; Milan, Italy 2025; 2 Krohn L et al. Low plasminogen levels are not associated with an increased risk of arterial thrombosis, accepted for ISTH Paris 2026; 3 Sang Y et al. Plasminogen activation and plasmin activity are not required to prevent venous thrombosis/thromboembolism. Blood 2025; 4 Cevasco C et al. Hepatic plasminogen lowering with a GalNAc-conjugated siRNA reduces plasmin generation and fibrinolysis but has no effect on thrombin generation in rats and mice. Presented at the American Society of Hematology Annual Meeting, US 2025.

Indications Prioritized Based on Unmet Need and Disease Burden – 2 Most Common Inherited Bleeding Disorders

1

Hereditary Hemorrhagic Telangiectasia (HHT)

~1.5M patients globally (1:5,000) [1]

No approved treatments

2

Von Willebrand Disease (VWD)

~1.5-3M patients with clinically significant disease globally (1:2,500-1:5,000) [2]

Current prophylactic treatments have high burden

1 Al-Samkari H et al. Standardization of Terminology, Definitions, and Outcome Criteria for Bleeding in Hereditary Hemorrhagic Telangiectasia: International Consensus Report. Am J Hematology 2025; 2 Castaman G et al. Von Willebrand disease: classification and epidemiology. Haematologica 2026. Komodo claims data.

Hereditary Hemorrhagic Telangiectasia (HHT)

Multi-System Bleeding Disorder with High Clinical Burden; No Approved Treatments

Abnormal blood vessels lead to **fragile**, high-flow connections that are prone to **rupture and bleeding**

*"…**nosebleed**…picture a **faucet of a sink on full**."*

*"…**severely anemic** and low on blood…"*

*"…**emergency room visits** to have blood transfusions…"*

95%
experience nosebleeds[1]

Nosebleeds can be

- *Frequent*
- *Severe*
- *Unpredictable*
- *Life-threatening*

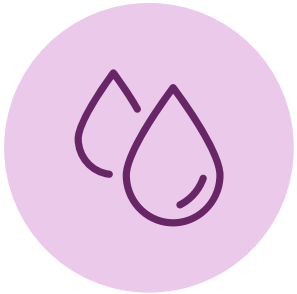
68%
are anemic or iron deficient[1]

30%
experience GI bleeding[1]

11%
hospitalized due to HHT at least 1x/year[2]

[1] *Al-Samkari H et al. Clinical Spectrum of Hereditary Hemorrhagic Telangiectasia: Data from the Comprehensive HHT Outcomes Registry of the US (CHORUS). Blood 2026;* [2] *Al-Samkari H et al. Characterizing the Healthcare Utilization and Costs of Hereditary Hemorrhagic Telangiectasia. Am J Hematol. 2025.*

ALN-6400: Potential First-in-Class Treatment for HHT Providing Durable and Safe Bleeding Control



Durable Bleeding Control

Long-acting mechanism expected to provide sustained bleeding protection with only four injections per year

Approved Tx → Increased Diagnosis

~35% patients with HHT diagnosed; expect to increase with disease education and awareness efforts

Von Willebrand Disease (VWD)

Limited/Burdensome Treatment Options Leave Clinical Gap

Deficient or defective VWF **disrupts platelet adhesion** and **stability of FVIII**, leading to **increased bleeding**

*"…**systemic challenges** and **repeated dismissal**, and it's exhausting."*

*"…**multiple treatments** that **didn't work**. I've since had a **hysterectomy**."*

*"I had to have a port placed because I **got stuck over 32 times one day** to get a treatment"*

>90% experience heavy menstrual bleeding[1]

>50% experience nosebleeds[1]

>40% report excessive bleeding after surgery[1]

GI bleeding is the most common cause of hospitalization[2]

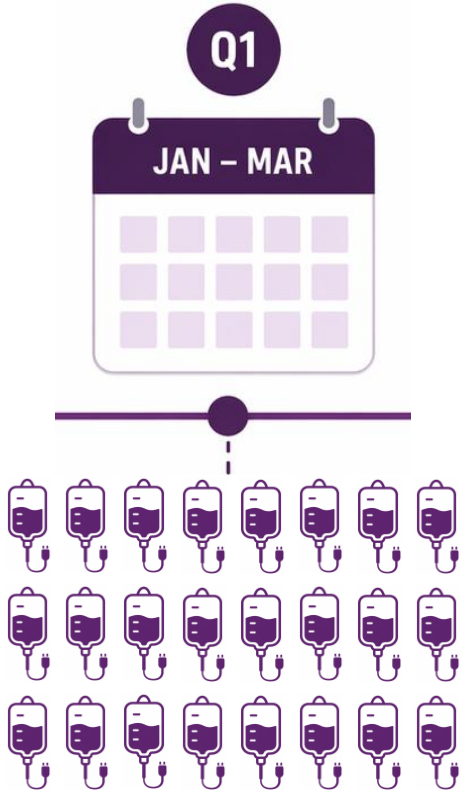
1 Reported in patients with VWD who menstruate; CDC; 2 Holm et al. Bleeding-related hospitalization in patients with von Willebrand disease and the impact of prophylaxis. Haemophilia 2018.

ALN-6400 Aims to Transform Prophylactic Treatment for Patients with VWD

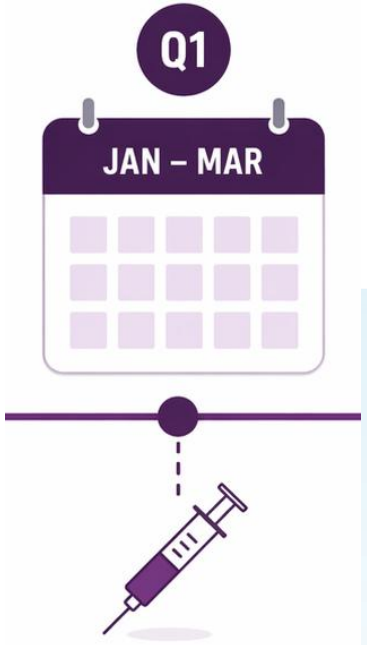
Targeting Durable Bleeding Protection Expected Across All VWD Types and Bleed Types

- ✓ Type 1 VWD
- ✓ Type 2 VWD
- ✓ Type 3 VWD

Simple, Quarterly Dosing Reduces Treatment Burden and is Expected to Increase Prophylaxis Use



Current SOC:
24-36 IV infusions



ALN-6400:
1 SC injection

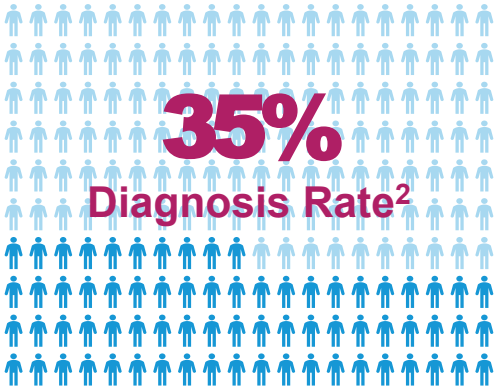
Two Unique and Sizeable Opportunities

HHT

No therapies available, Low diagnosis rates

~70K
U.S. patients

~1.5M
Globally

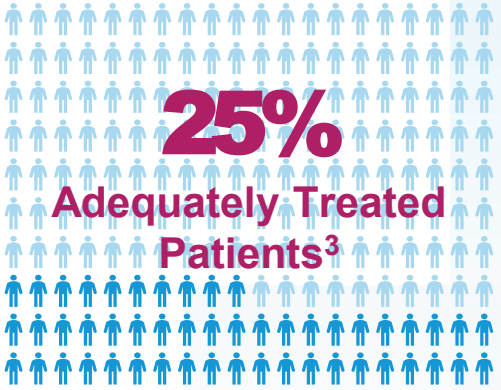


VWD

Low treatment rates due to high burden of current therapies[1]

~140K
U.S. patients Types 1-3

~3M
Globally



Potential Multi-Billion Dollar Opportunity

1 Weyand A et al. The first characterization of disease burden and healthcare resource utilization for the recent definition of severe von Willebrand disease using a large United States real-world dataset. Blood 2025.; 2 Al-Samkari H et al. Characterizing the Healthcare Utilization and Costs of Hereditary Hemorrhagic Telangiectasia. American Journal of Hematology 2025; 3 Castaman G et al. Von Willebrand disease: classification and epidemiology. Haematologica 2026. CDC Data and Statistics on von Willebrand Disease.

ALN-6400: Investigational Therapeutic with Differentiated Approach and Broad Impact Potential Across Bleeding Disorders

Targeting Durable Bleed Protection

Universal Hemostatic Agent

Not Expected to Increase Thrombotic Risk

Address primary clinical concern of hematologists

Reduced Treatment Burden

Expand prophylactic use to address unmet needs

A Teaching Affiliate
of Harvard Medical School

Hereditary Hemorrhagic Telangiectasia and Von Willebrand Disease

Hanny Al-Samkari, M.D.
Associate Professor of Medicine
Harvard Medical School

The Peggy S. Blitz Endowed Chair in Hematology/Oncology
Classical Hematologist and Clinical Investigator
Co-Director, HHT Center of Excellence
Massachusetts General Hospital

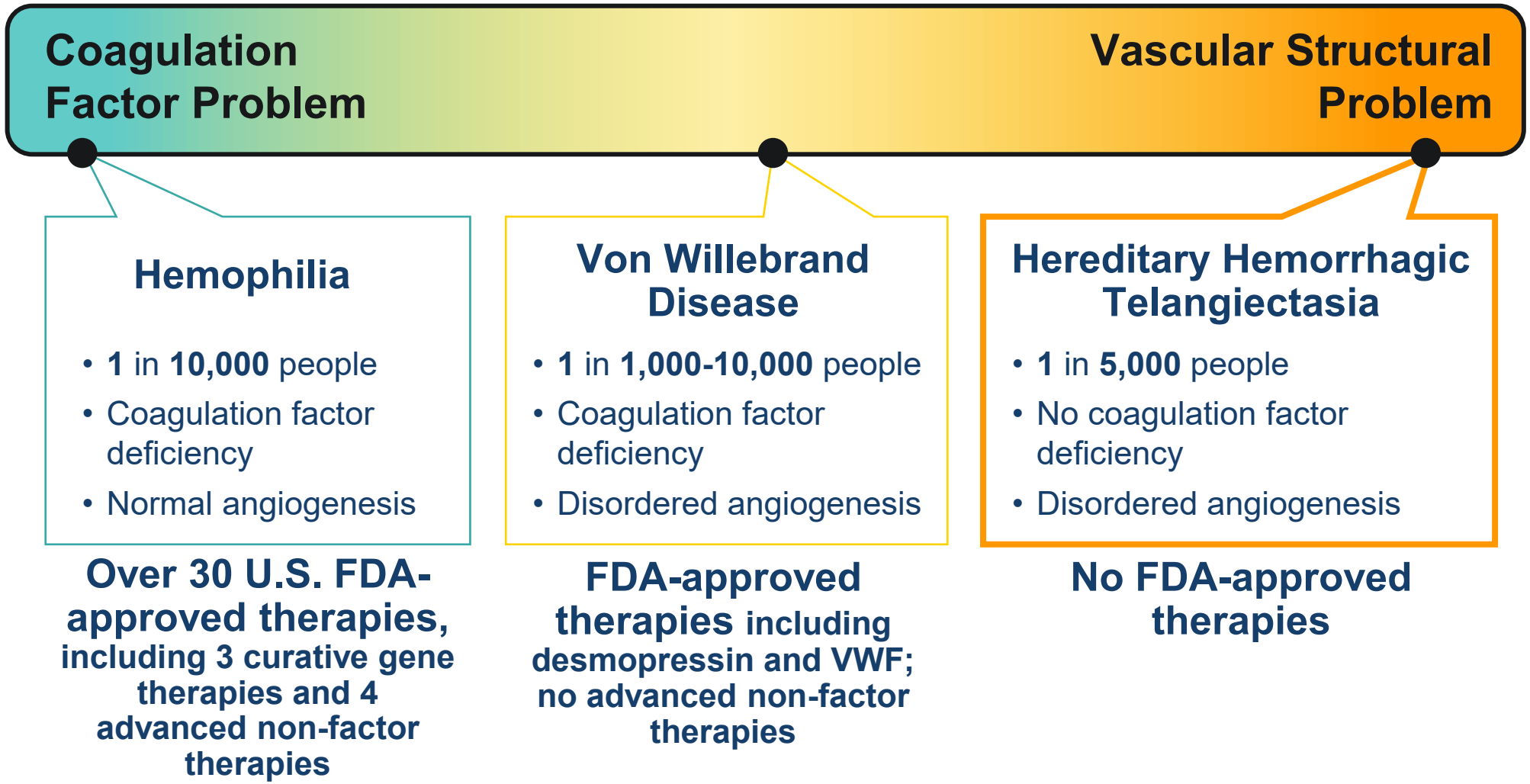
MASSACHUSETTS
GENERAL HOSPITAL

Disclosures

Universal Disclosures (financial):

- Consultancy (Agios, Amgen, Alnylam, Sobi, Sanofi, argenx, Pharmacosmos, Novartis, Alpine, Diagonal, Vaderis, Terremoto)
- Research Funding (Agios, Sobi, Amgen, Vaderis, Novartis, Alnylam, Atavistik)

The Spectrum of Inherited Bleeding Disorders



Platelet Problem

26 Castaman, G. Haematologica 2026, Konkle, B. Haemophilia 2021.

Agenda

Hereditary Hemorrhagic Telangiectasia

Von Willebrand Disease

Case: 41-Year-Old Man with HHT, Severe Epistaxis

- 41-year-old man with severe nosebleeds working in the biomedical field
- Diagnosed with HHT in his 20s, sent for regular nasal and intestinal cautery procedures that each worked for a couple of months but provoked worse nosebleeding as time went on
- Ultimately went on disability and career halted because of:
  - Unpredictable blood gushing from his face limiting him at work
  - Chronic anemia requiring regular intravenous iron
  - Constant ER visits for severe nosebleeds
  - Diagnosis of major depressive disorder from nosebleeding; started on antidepressant which worsened his bleeding (prescribing doctor did not recognize this as a side-effect of the antidepressant)
- “I am barely 40 but I feel like my life is nearly over. I just want to go back to work, and maybe one day be able to have a girlfriend.”

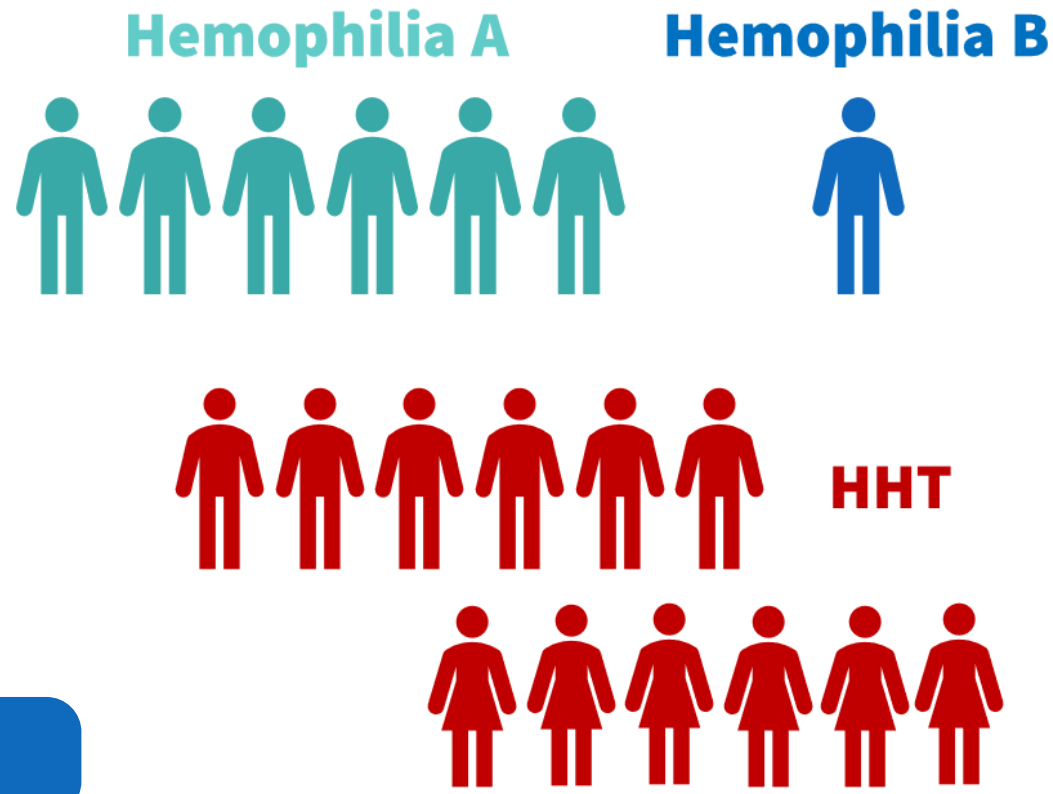
HHT is a Multisystem Hereditary Bleeding Disorder with Numerous Morbid and Potentially Fatal Manifestations

- Progressive, multisystem bleeding disorder due to abnormal vessel formation
  - Mucocutaneous telangiectasias → **chronic gastrointestinal hemorrhage** and **severe recurrent epistaxis**
  - Severe **iron deficiency anemia**, often **iron infusion and RBC transfusion-dependent**
  - Visceral arteriovenous malformations (AVMs) in **lung, liver, brain,** others
    - High output cardiac failure
    - Liver disease and cirrhosis
    - Pulmonary hypertension, pulmonary hemorrhage
    - Hemorrhagic stroke, TIA, epilepsy, sudden death
- Patients rank ***bleeding*** as most important clinical manifestation (by a wide margin)
  - AVMs and anemia tie for second
- ***No U.S. FDA or EMA-approved therapies to date***

Al-Samkari H., *Blood* 2021

HHT is the Second-Most-Common Inherited Bleeding Disorder

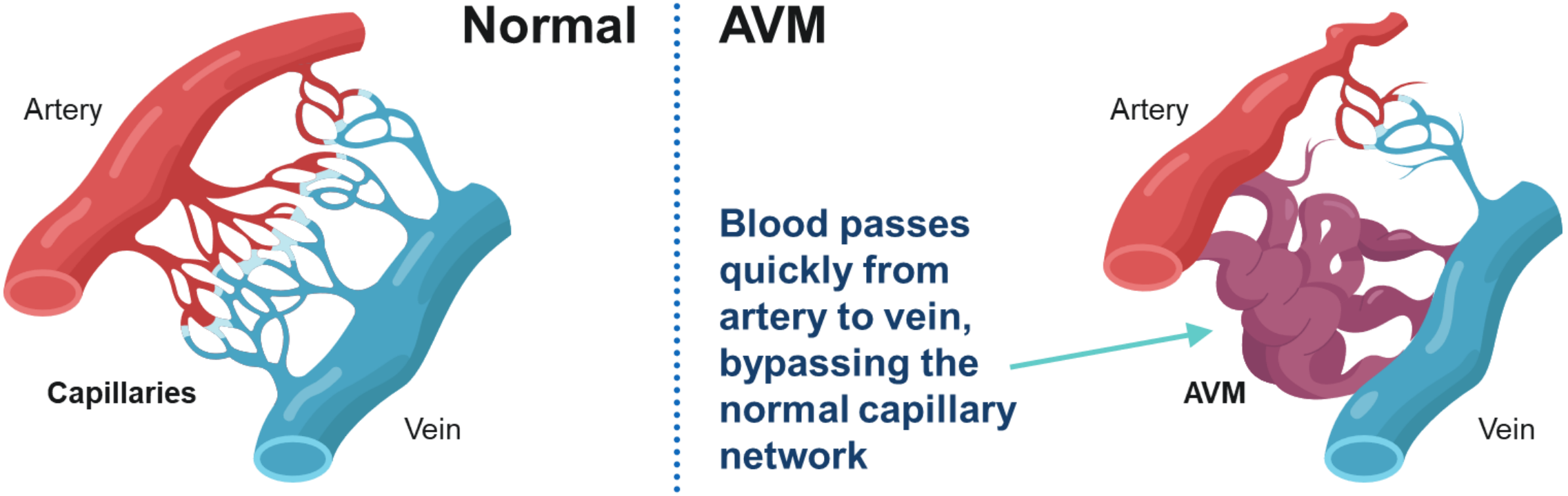
- **Autosomal dominant** inheritance
- Occurs in all sexes equally
- Most clinically significant and morbid inherited bleeding disorder of women
  - **More severe bleeding and visceral disease manifestations in women**
- Patients with HHT have **reduced overall survival** compared with healthy controls



HHT Affects 1.4 Million Worldwide

 Al-Samkari H., *Blood* 2021; Zhang et al., *Blood Advances* 2024

The Pathologic Lesion of HHT is the Arteriovenous Malformation

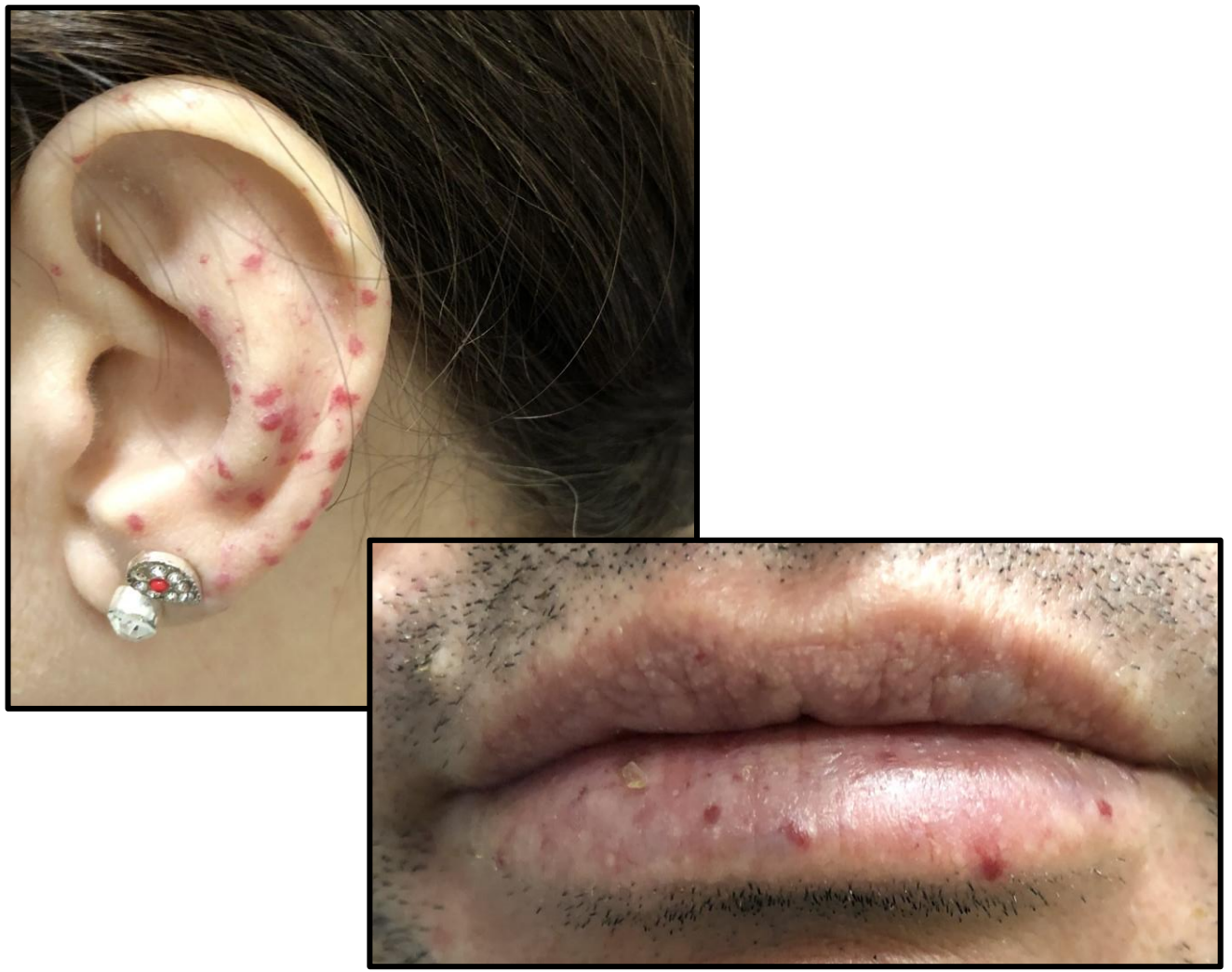


Telangiectasia is small AVM (<1 millimeter to few millimeters in diameter), usually occur in skin, GI mucosa, upper aerodigestive tract

AVMs are more than a few millimeters in diameter and most commonly occur in lung (>50%), liver (~70%) and brain (10-20%)

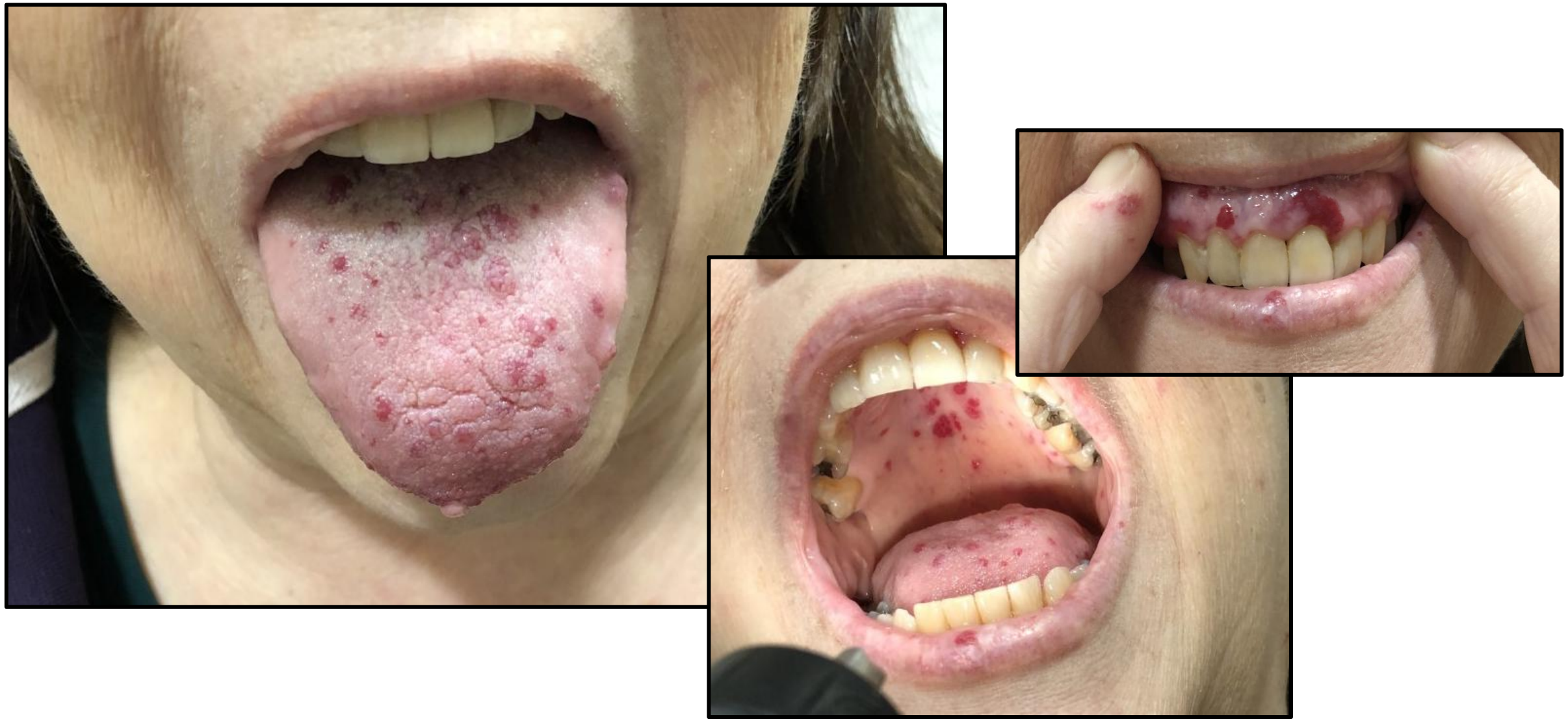
 Ferry AM, et al. *Am J Rhinol Allergy*. 2020; Viteri-Noel A, et al. *J Clin Med*. 2022; Droege F, et al. *Vasc Med*. 2018.

Mucocutaneous Telangiectasias: Skin



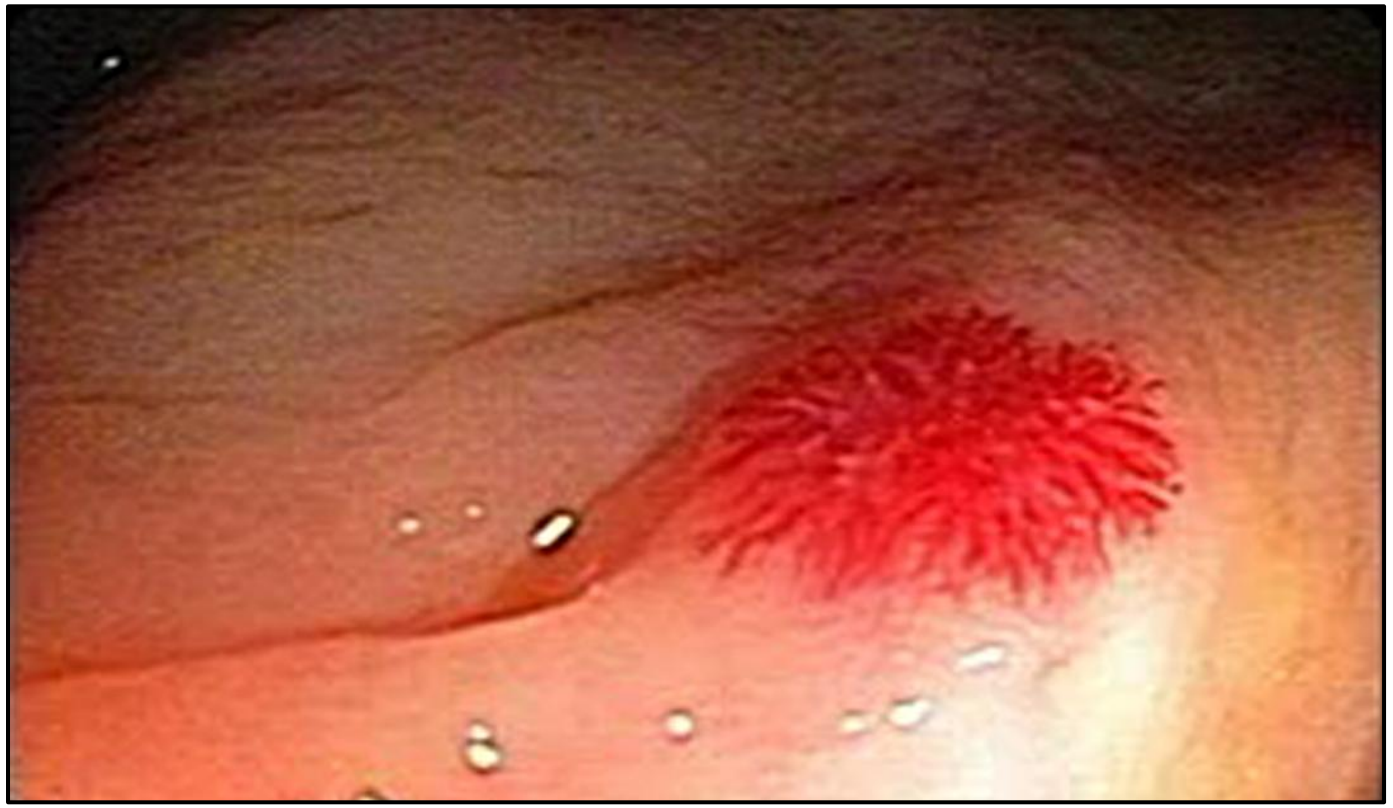
 Images from Hanny Al-Samkari, MD

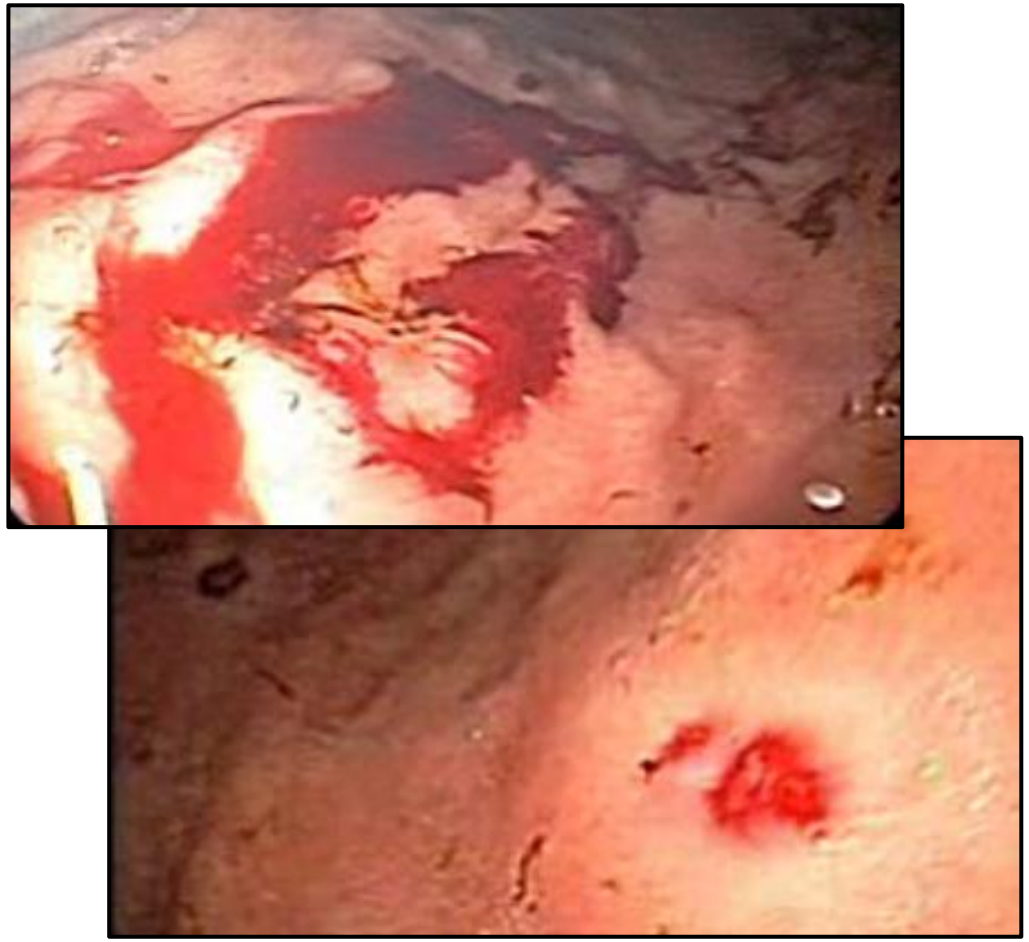
Mucocutaneous Telangiectasias: Oral Cavity



 Images from Hanny Al-Samkari, MD

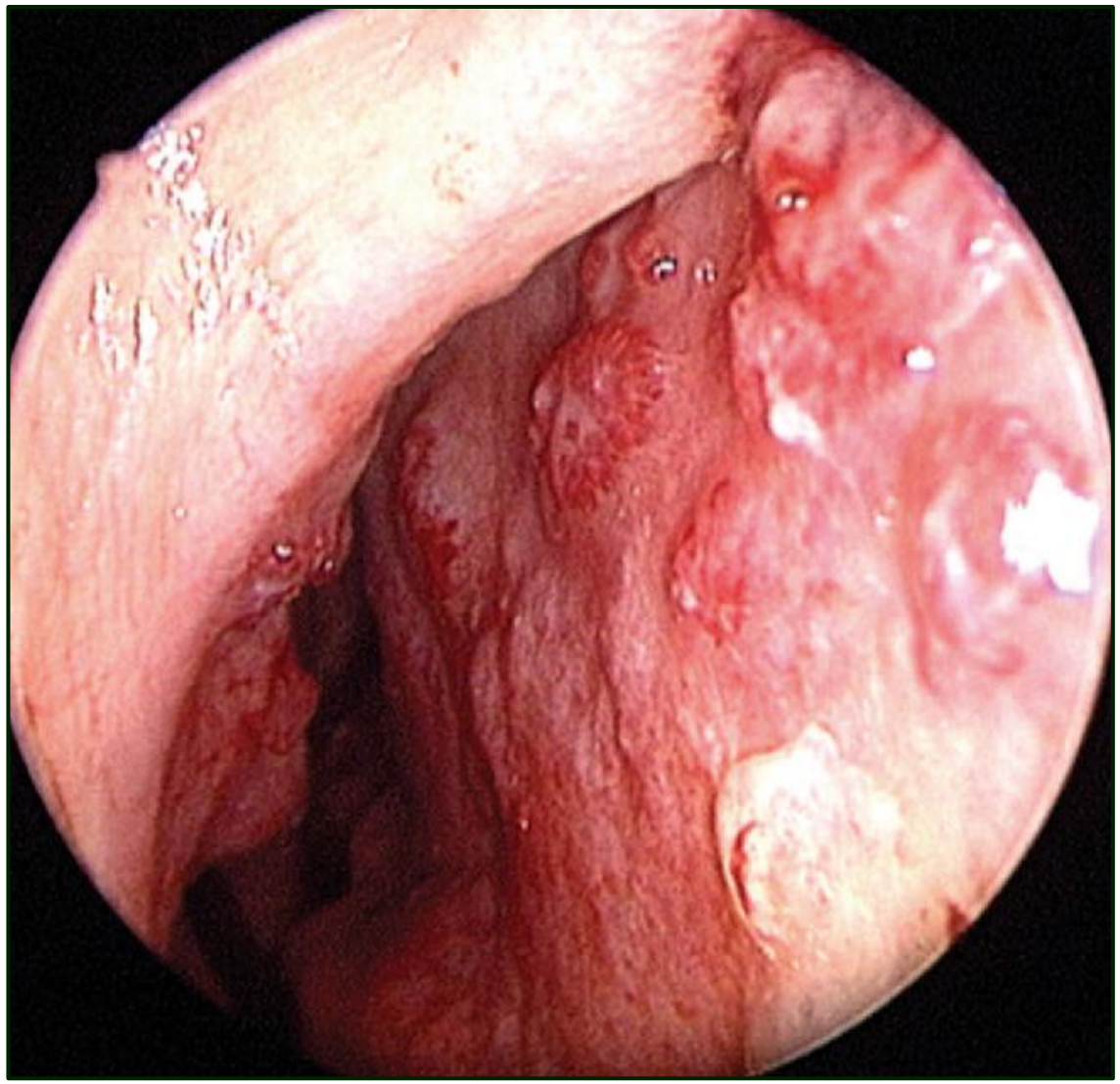
Mucocutaneous Telangiectasias: Gastrointestinal Tract

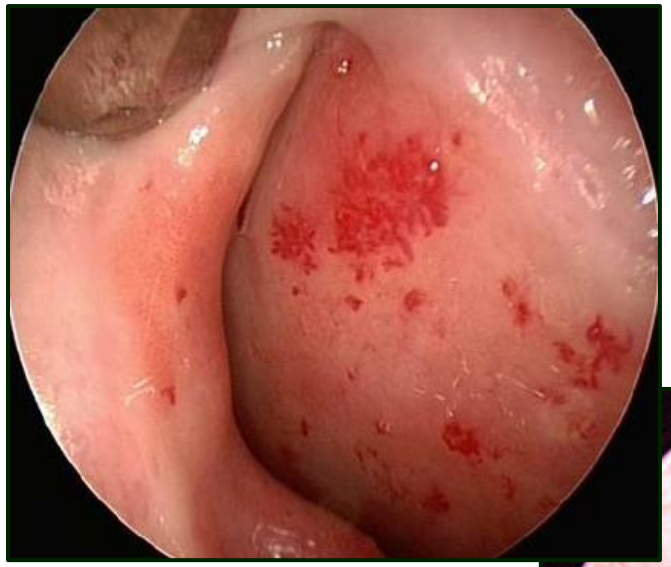


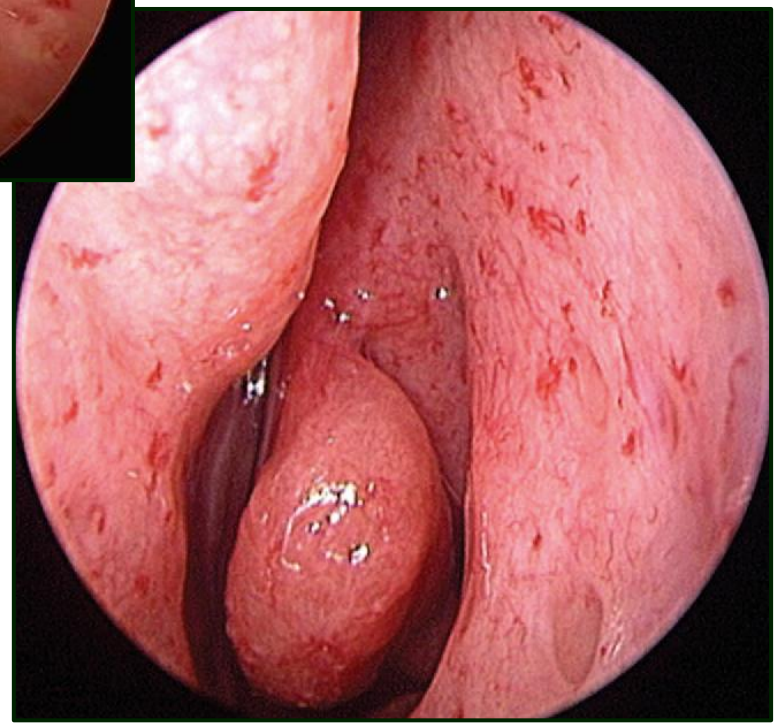


Images from https://gastrointestinalatlas.com/english/hereditary_hemorrhagic_telangi.html

Mucocutaneous Telangiectasias: Nasal Cavity

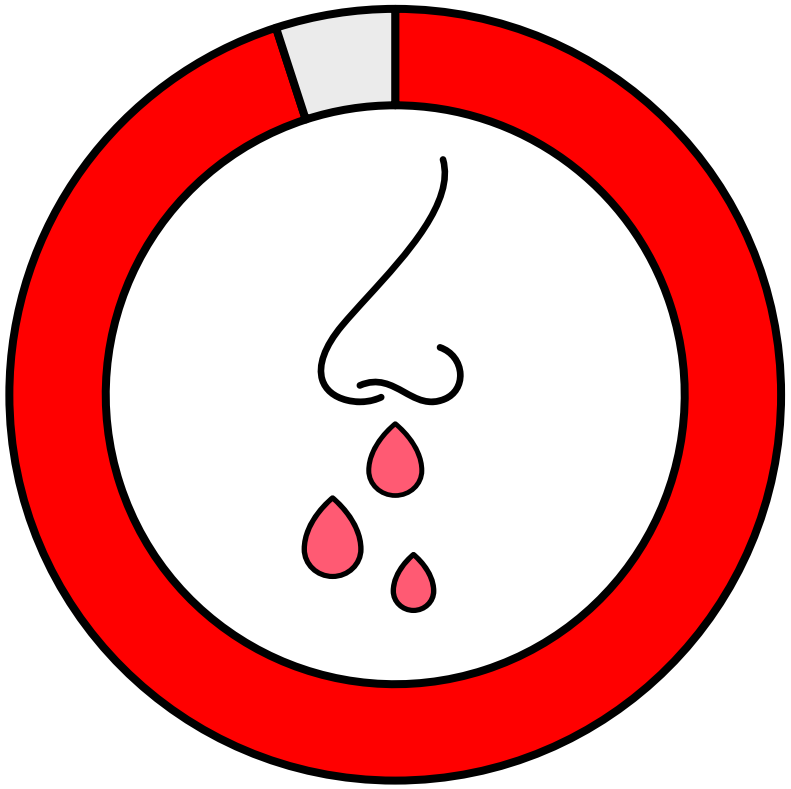






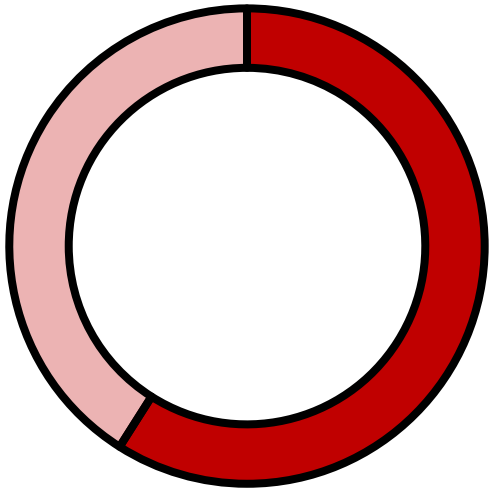
 Pagiella et al. *Amer J Rhinol Allergy* 2009, Folz et al. *Eur Arch Otorhinolaryngology* 2006

Incidence of Spontaneous, Recurrent Epistaxis



95%

Mild
41%

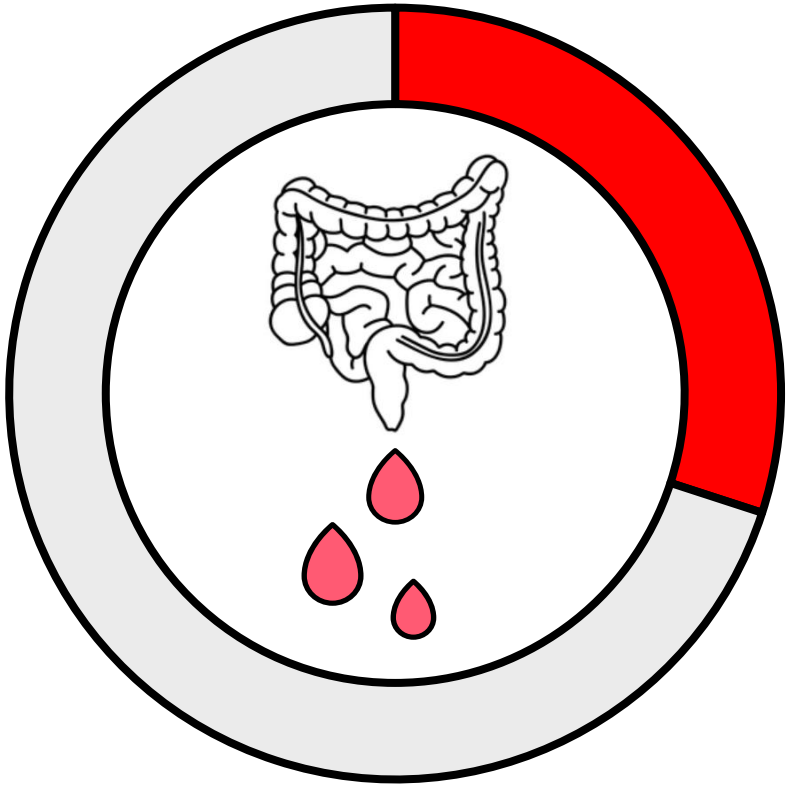


Mod-Severe
59%

Moderate-to-Severe Epistaxis:
(1) Epistaxis Severity Score>4.00,
(2) Systemic medical or surgical intervention, and/or
(3) intravenous iron and/or red cell transfusion to manage anemia

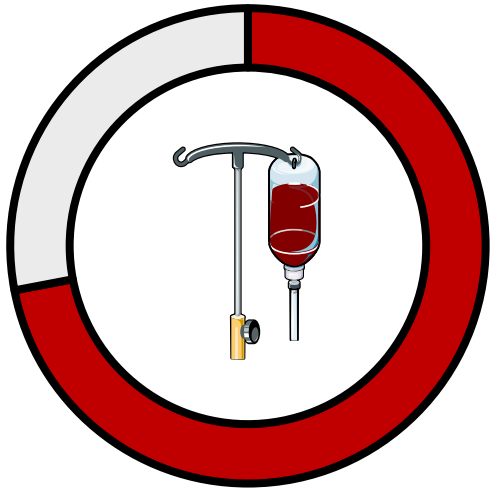
Al-Samkari et al., *Blood* 2026

Incidence of Chronic Gastrointestinal Bleeding



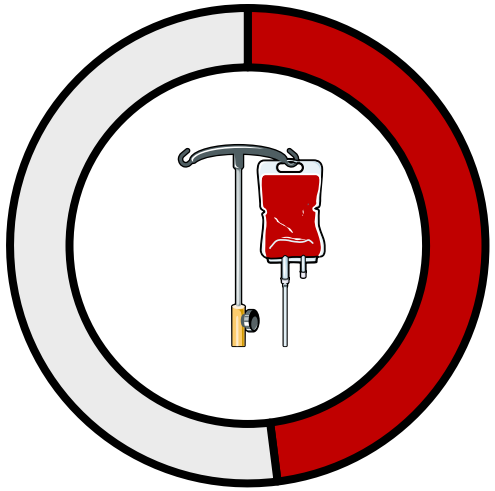
30%

(Upper Endoscopy only in 40%)



Patients with GI bleeding receiving IV iron

72%

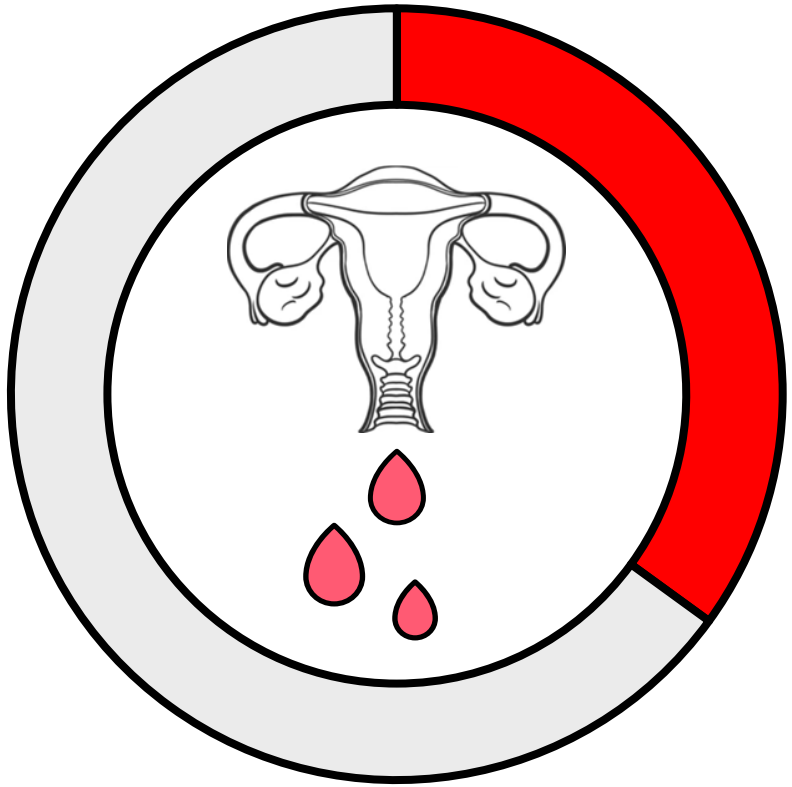


Patients with GI bleeding receiving RBC transfusion

48%

Al-Samkari et al., *Blood* 2026

Incidence of Heavy Menstrual Bleeding and Other Clinically-Significant Mucocutaneous Bleeding



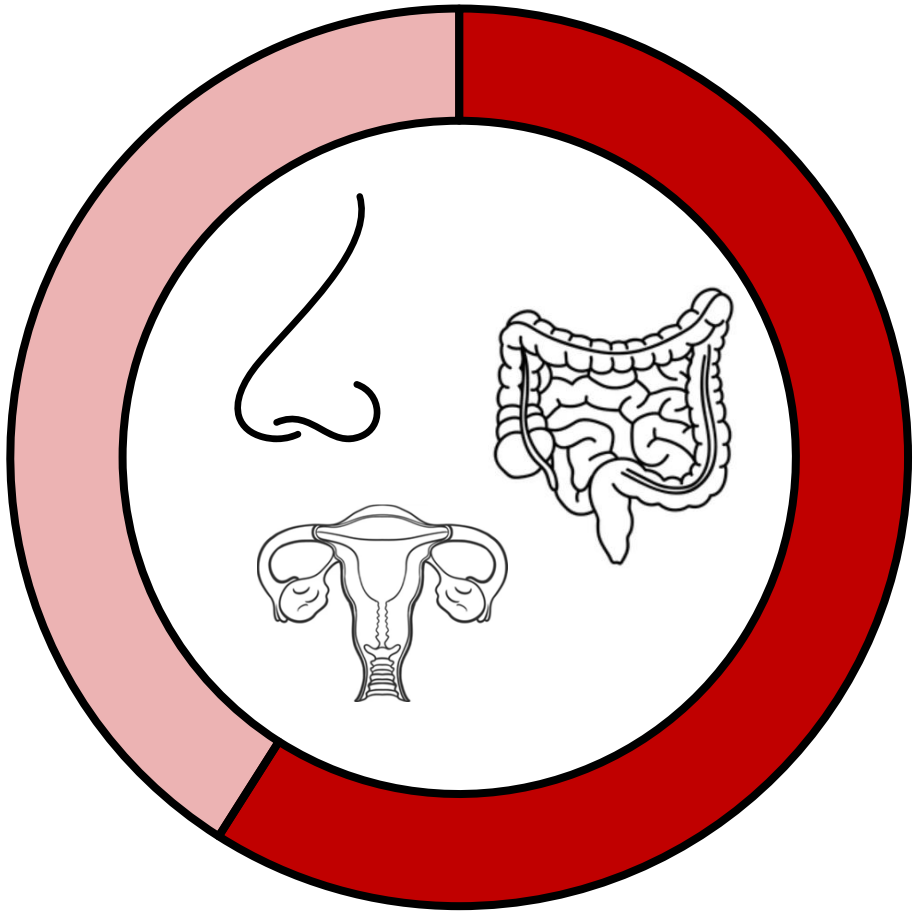
35%

41%

Al-Samkari et al., *Blood* 2026

Incidence of Moderate-to-Severe HHT-Associated Mucosal Bleeding

Mild 24%



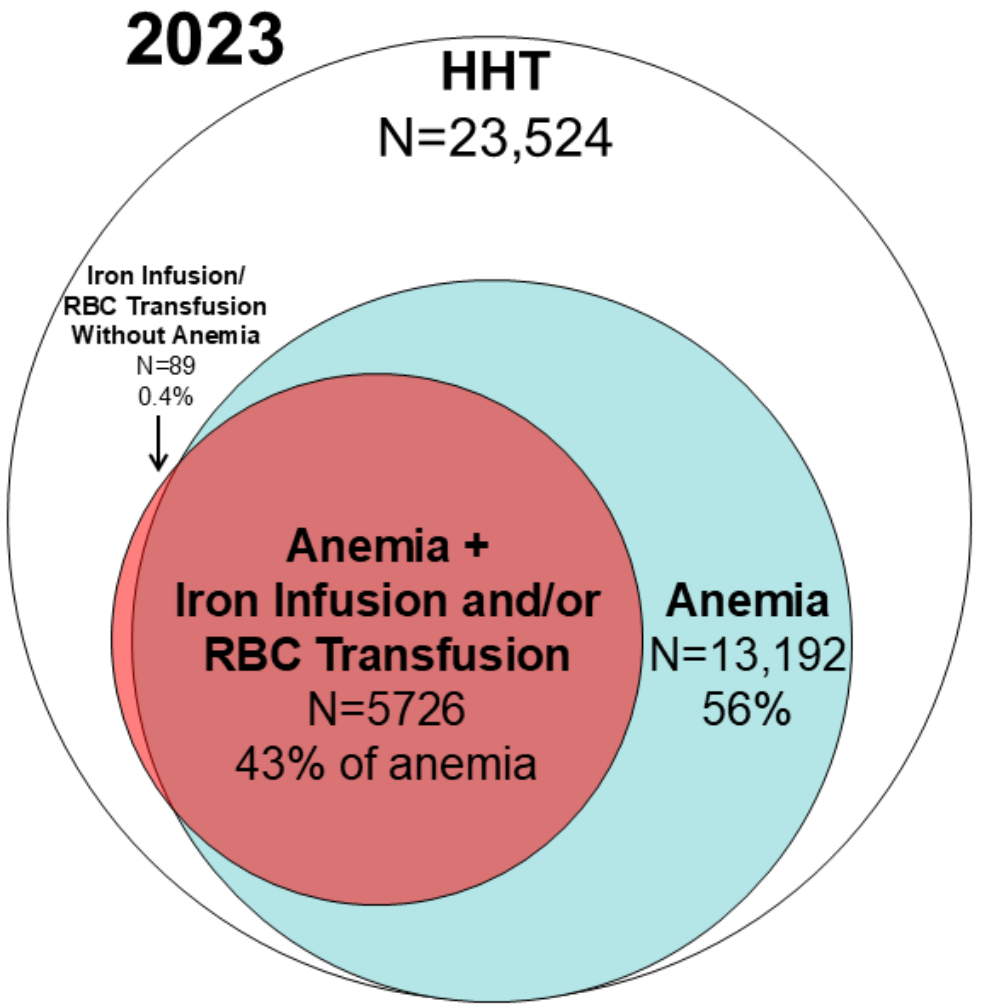
Mod-Severe 76%

Moderate-to-Severe HHT Mucosal Bleeding:
(1) Epistaxis Severity Score>4.00,
(2) Systemic medical or surgical intervention for epistaxis and/or GI bleeding,
(3) intravenous iron and/or red cell transfusion to manage anemia

Al-Samkari et al., *Blood* 2026

Iron Deficiency and Iron Deficiency Anemia is “the Norm” in HHT

	2023 N=23,524
Sex (% female)	61%
Age	
<18	7%
18-29	7%
30-49	18%
50-64	26%
≥65	41%
Insurance	
Medicare	40%
Commercial	48%
Medicaid	12%



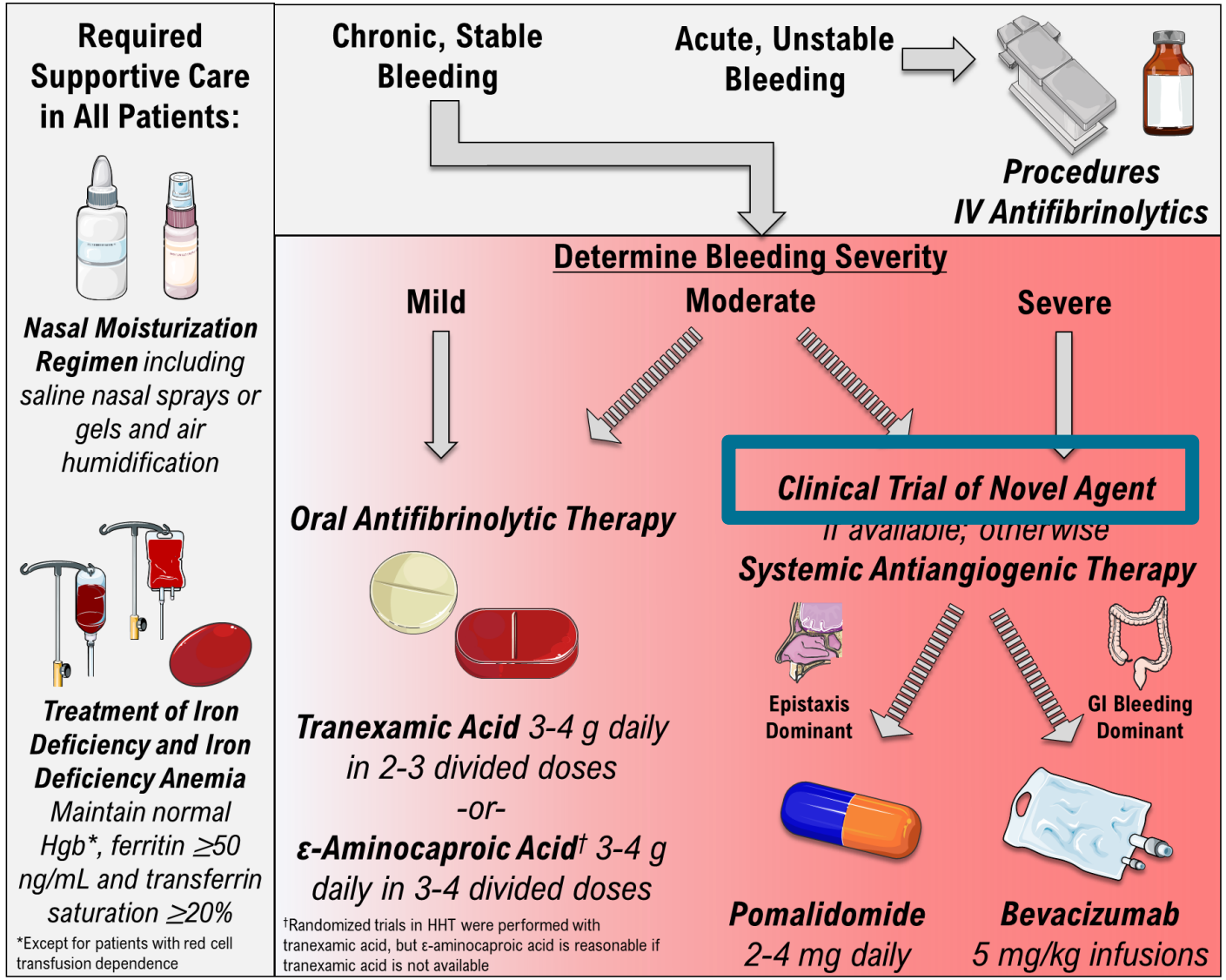
 Al-Samkari H. et al, *Am J Hematol* 2025

Bleeding Complications of HHT

- ***3 in 4*** people with HHT develop moderate-to-severe mucosal bleeding, including epistaxis, gastrointestinal, and/or heavy menstrual bleeding
- ***1 in 3*** menstrual-age women with HHT develop heavy menstrual bleeding
- ***7 in 10*** people with HHT develop iron deficiency and/or anemia
- ***1 in 4*** people with HHT develop severe enough anemia to merit RBC transfusion
- ***1 in 50*** people with HHT develop pulmonary hemorrhage
- ***1 in 30*** people with HHT develop intracranial hemorrhage

 Al-Samkari et al., *Blood* 2026

Standard of Care for Bleeding in HHT in 2026



 Hanny Al-Samkari, How I treat bleeding in hereditary hemorrhagic telangiectasia, Blood, 2024.

Agenda

Hereditary Hemorrhagic Telangiectasia

Von Willebrand Disease

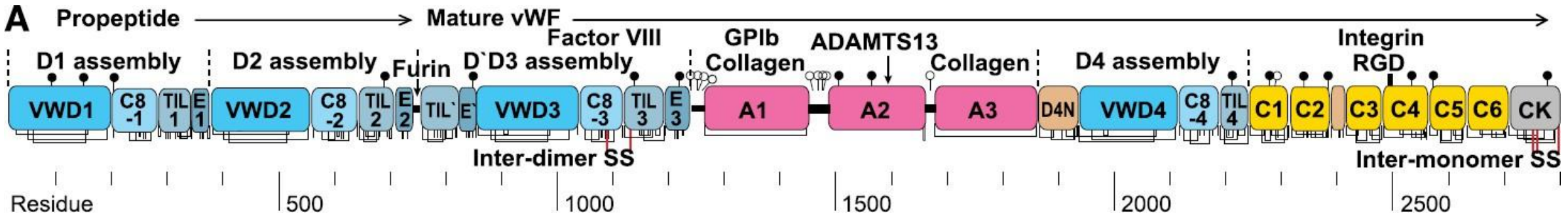
Case: 40-Year-Old Woman with Type 2B VWD Complicated by Chronic GI Bleeding

- Previously managed on 3x weekly IV pdVWF, but developed infusion fatigue; switched to twice-weekly rVWF, but this only treated HMB, not GI bleeding
- On endoscopy has numerous vascular malformations that intermittently bleed
- Put on octreotide, with minimal effect on GI bleeding
- Still missing infusions of rVWF due to job, single mother of 3 kids, infusion fatigue

pdVWF = plasma-derived VWF; rVWF = recombinant VWF

Von Willebrand Factor

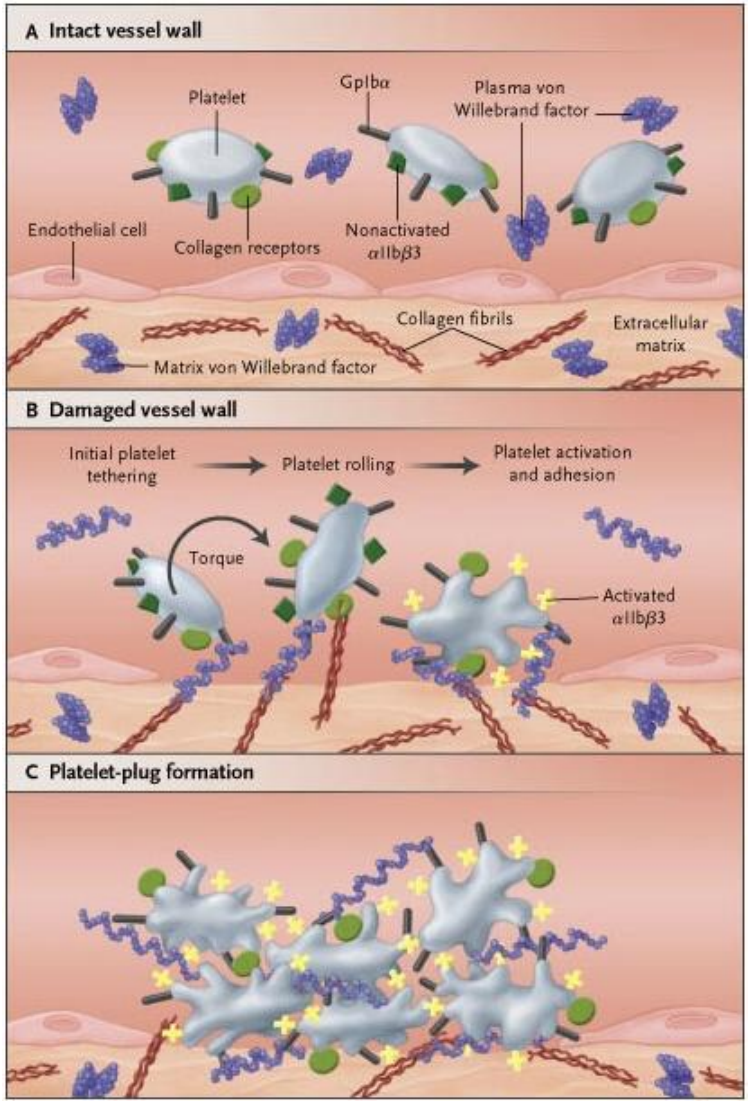
- A protein in the blood that helps form clots to stop bleeding
- Two (main) functions:
  - Facilitate platelet binding to subendothelial collagen (GPIb, GPIIb/IIIa), platelet-platelet interactions
  - Protect clotting factor VIII



BLOOD, 28 AUGUST 2014 • VOLUME 124, NUMBER 9

Von Willebrand Disease is a Common, Frequently Missed, Important Cause of Excessive Bleeding and Iron Deficiency

- Results in mucocutaneous bleeding due to insufficient VWF for normal platelet tethering and adhesion
- Results in impaired primary hemostasis and ability to form platelet plug, leading to mucocutaneous bleeding
- Also results in angiogenic dysregulation and formation of abnormal vascular lesions (usually GI tract) in minority of patients



 Mannucci PM., *NEJM* 2024

VWD is the Most Common Inherited Bleeding Disorder and Results in a Significant Burden of Mucocutaneous Bleeding

- **Heavy menstrual bleeding in women**
- Obstetric bleeding (labor, delivery, postpartum)
- Epistaxis
- Gingival bleeding
- Easy bruising
- Gastrointestinal bleeding
- Increased surgical bleeding
- Higher likelihood of more severe bleeding episodes after trauma
- Most severe cases (type 2N and type 3) can have hemarthrosis/musculoskeletal bleeding

Von Willebrand Disease

Table 5. Inheritance, Prevalence, and Bleeding Propensity in Patients Who Have VWD

Type	Inheritance	Prevalence	Bleeding Propensity
Type 1	Autosomal dominant	Up to 1%	Mild to moderate
Type 2A	Autosomal dominant (or recessive)	Uncommon	Variable—usually moderate
Type 2B	Autosomal dominant	Uncommon	Variable—usually moderate
Type 2M	Autosomal dominant (or recessive)	Uncommon	Variable—usually moderate
Type 2N	Autosomal recessive	Uncommon	Variable—usually moderate
Type 3 (Severe)	Autosomal recessive	Rare (1:250,000 to 1:1,000,000)	High (severe bleeding)

2007 National Heart, Lung, and Blood Institute (NHLBI) guideline on diagnosis, evaluation, and management of von Willebrand disease.

Current Treatments for VWD Leave a Conspicuous Gap

- Patients with mild type 1 and type 2 disease:
  - Desmopressin before most procedures
  - VWF-containing factor concentrate before major procedures
  - Antifibrinolytics PRN for a few days after dental procedures, certain surgeries
- Patients with moderate to severe type 1 and type 2, and patients with type 3 disease:
  - Type 3 patients go on pdVWF (2-3 times weekly) or rVWF (2 times weekly) intravenous infusions
  - The most severe type 1 and type 2 patients can also go on these treatments
  - They are challenging (as in patients with severe hemophilia) and patients want an easier, effective non-IV infusion option
  - Moderate patients are left with either regular factor infusion (which is too much) or oral antifibrinolytics (which is too little)—this is the gap that novel agents must fill

pdVWF = plasma-derived VWF; rVWF = recombinant VWF

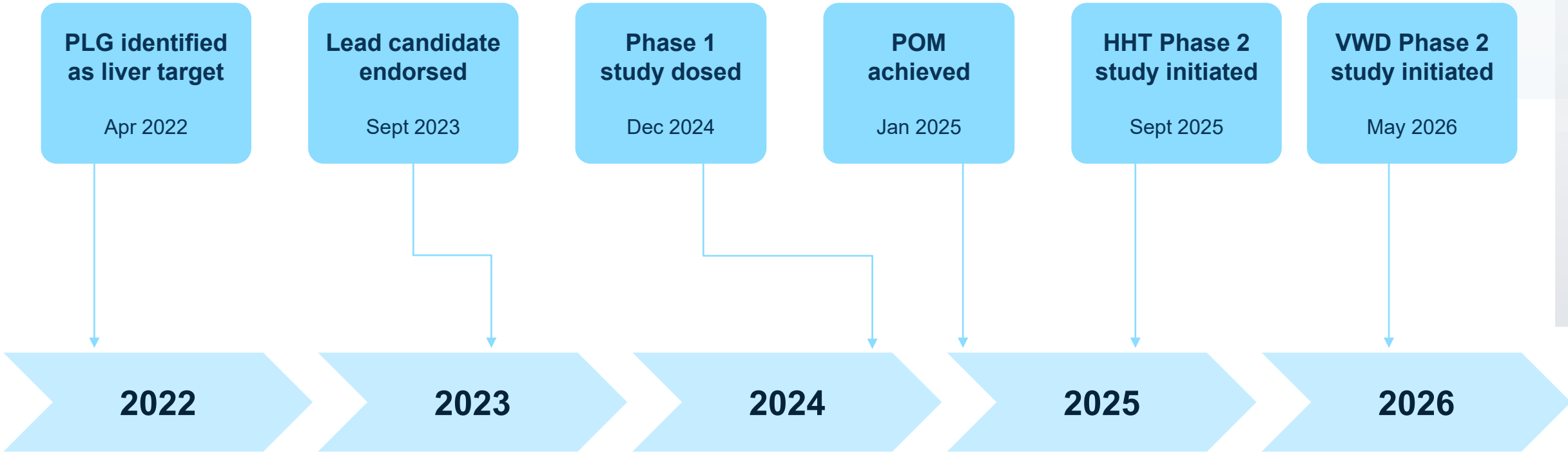
What Do Physicians and Patients Need?

- **Safe and effective** medications for moderate-to-severe mucocutaneous bleeding in HHT and VWD
- Ideally be **convenient** for patients
- It should have a **minimal or nil thromboembolic risk**
- Be a **prophylactic agent** administered **infrequently** rather than something on-demand
- It must **reduce epistaxis in HHT**, and must **reduce overall mucocutanous bleeding in HHT and VWD**
- Ideally it would reduce **burden of anemia** and **requirements for hematologic support** (particularly in HHT)
- It would improve patient **health-related quality of life**

ALN-6400 Clinical Plans & Progress

Martina Slingsby, Ph.D.
Senior Clinical Scientist, ALN-6400 Clinical Science Lead

From Idea to Proof of Mechanism in Under 3 Years



Disciplined execution & early progress support streamlined late-stage development

PLG, plasminogen; POM, proof of mechanism; HHT, hereditary hemorrhagic telangiectasia; VWD; Von Willebrand disease.

Phase 1 Study in Healthy Adult Volunteers

Double-Blind, Placebo-Controlled

Screening

tPA-ROTEM

TXA Benchmark Run-in & Washout
1000mg/dose,
5 doses over 2 days

All cohorts randomized 3:1 ALN-6400:placebo

ALN-6400 Dose Level 1 or placebo

ALN-6400 Dose Level 2 or placebo

ALN-6400 Dose Level 3 or placebo

ALN-6400 Dose Level 4 or placebo

N=32 (8/dose level)

Double-blind period | Safety/PD follow-up

Single SC injection

Baseline | Week 12 | Up to Week 36

Primary Objective

- Safety and tolerability

Secondary Objectives

- PK and PD

Included standard-of-care oral TXA dosing prior to SC ALN-6400/Placebo (all dose levels) to allow comparison of intra-individual antifibrinolytic response with ALN-6400 relative to TXA by tPA-ROTEM

Full Data to be Presented in H2

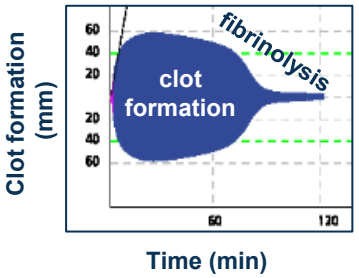
NCT06659640. PD, pharmacodynamics; PK, pharmacokinetics; PLG, plasminogen; SC, subcutaneous; TXA, tranexamic acid.

Clinical Proof of Mechanism – Inhibition of Fibrinolysis

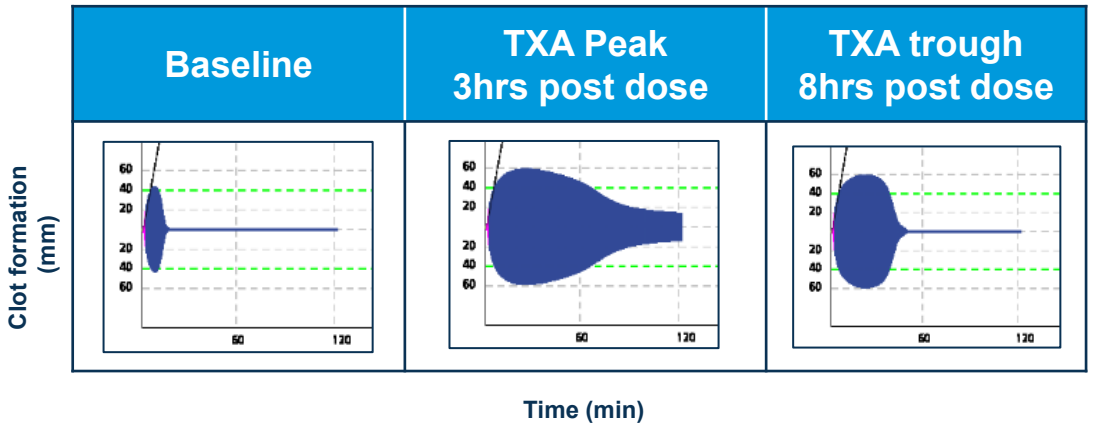
tPA-ROTEM traces from a healthy volunteer showing deep, sustained antifibrinolytic effect with ALN-6400

tPA-ROTEM

Blue trace shows whole blood clot formation and fibrinolysis over time

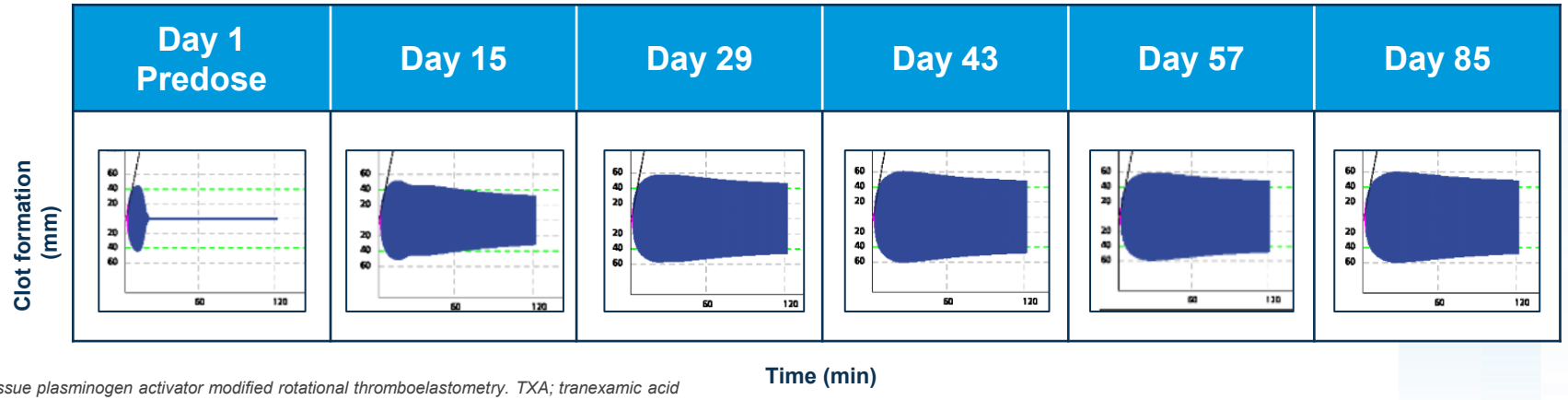


Healthy Volunteer dosed with oral TXA*



Clot breakdown (fibrinolysis) is reduced ***for hours***

Double-Blind Period | ALN-6400



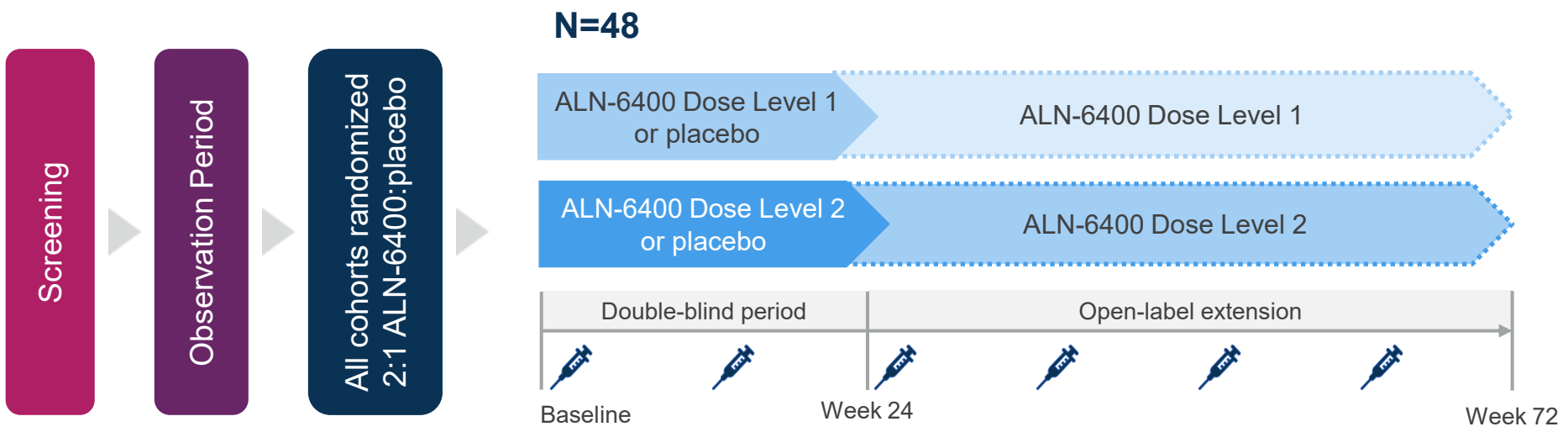
Clot breakdown is reduced ***for 85 days***

tPA-ROTEM; tissue plasminogen activator modified rotational thromboelastometry. TXA; tranexamic acid

*.*SOC dose of TXA given orally during the run-in phase of the study. Steady state of TXA reached after 5th dose. Traces show steady state TXA Peak and TXA trough.*

HHT Phase 2 Multinational Study

Patients with HHT with moderate to severe nosebleeds



Primary Objective

- Safety and tolerability

Secondary Objectives

- PD
- Efficacy

Goals:

- Evaluate safety and tolerability
- Determine Phase 3 dose and regimen
- Assess efficacy: reduction in nosebleeds

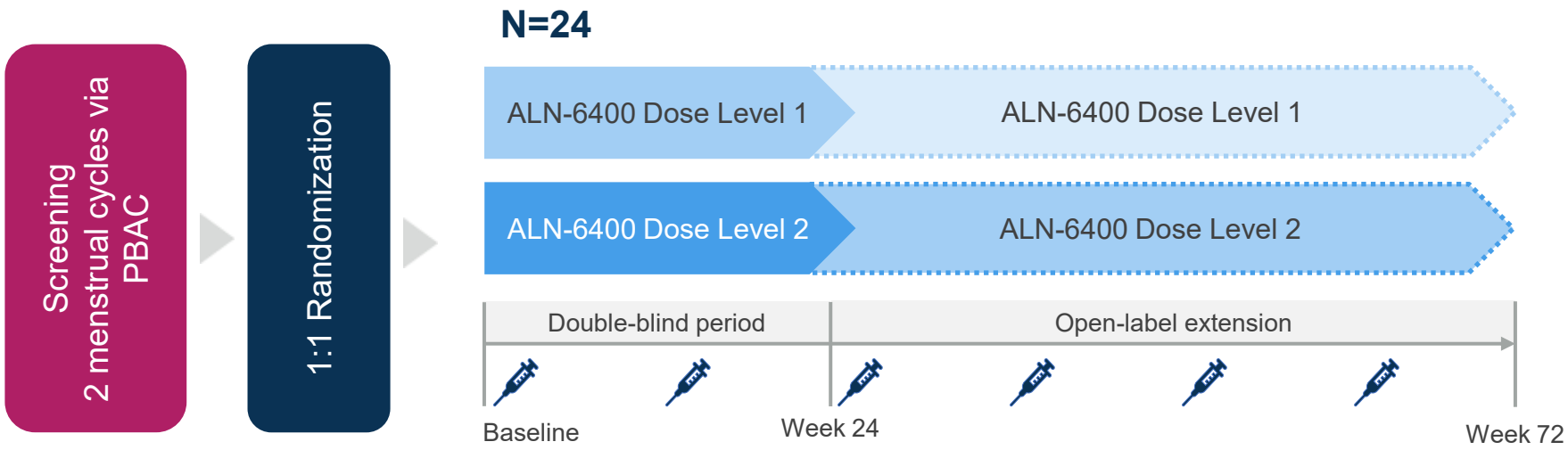
ENROLLING

Initial Results Expected in H2; Full P2 data and P3 start anticipated 2027

NCT06659640

VWD Phase 2 Multinational Study

Adult and adolescent female patients with VWD (all types) and heavy menstrual bleeding



Primary Objective

- Safety and tolerability

Secondary Objectives

- PD
- Efficacy

Goals:

- Evaluate safety and tolerability
- Determine Phase 3 dose and regimen
- Assess efficacy: reduction in menstrual bleeding and other bleeds

ENROLLING

Phase 3 planned in male and female patients (all VWD types); primary endpoint ABR
Anticipate P3 start 2027

NCT07575308; ABR; annualized bleeding rate; PBAC; Pictorial Blood Assessment Chart assessment of menstrual bleeding

ALN-6400: Investigational Therapeutic with Differentiated Approach and Broad Impact Potential Across Bleeding Disorders

Targeting Durable Bleed Protection

Universal Hemostatic Agent

Not Expected to Increase Thrombotic Risk

Address primary clinical concern of hematologists

Reduced Treatment Burden

Expand prophylactic use to address unmet needs

Austin, USA
Living with Hereditary Hemorrhagic Telangiectasia (HHT)

Q&A Session

RNAi Roundtable

ALN-6400: Targeting Plasminogen to Address Rare Bleeding Disorders

Upcoming RNAi Roundtables

RNAi 2026 ROUNDTABLES

Sept. 17

CARDIOVASCULAR + METABOLIC

ZILEBESIRAN

Potential to reduce the risk of cardiovascular events by providing continuous control of blood pressure

Oct. 26

NEUROSCIENCE

ALN-HTT02

Unique targeting strategy aiming to reduce progression of Huntington's disease


Silence disease
Amplify life™
Alnylam®