Critical Juncture in the Development of Hemophilia Therapies

A Statement and Call-to-Action from the

International Society on Thrombosis and Haemostasis (ISTH)
European Association for Haemophilia and Allied Disorders (EAHAD)
World Federation of Hemophilia (WFH)

for the importance of continued research into and development of effective and safe hemophilia treatments

Hemophilia is a serious medical condition characterized by severe and potentially life-threatening bleeding tendencies requiring lifelong treatment. For decades, therapeutic interventions were predominantly limited to the intravenous administration of plasma-derived and recombinant clotting factor concentrates, establishing replacement therapy as the standard of care.

The past decade has witnessed significant advancements in the hemophilia therapeutic landscape, progressing to genetically engineered and chemically modified concentrates, FVIIIa mimetics, and rebalancing agents. These innovations enable less frequent and alternative administration routes, including subcutaneous application.

These expanded therapeutic options have significantly improved clinical outcomes, with the promise that also individuals with moderate and mild phenotypes, women with hemophilia, and patients with related bleeding disorders will benefit.

Despite advances, significant challenges persist as patients maintaining regular prophylaxis still experience breakthrough bleeding and subclinical micro-haemorrhages that contribute to joint deterioration. At the same time, treatment individualization remains burdensome due to patient-specific factors including bleeding phenotypes, activity profiles and, importantly, product availability.

Accessibility disparities create significant barriers to optimal care delivery—even many countries that could afford treatments continue to lack access to the full range of therapeutic options, while notably, two-thirds of the worldwide hemophilia population has no access to treatment at all.

These persistent challenges highlight the necessity for ongoing research, education, optimisation of existing treatment modalities and, importantly, continued and accelerated

therapeutic innovation to achieve comprehensive bleeding prevention and joint integrity preservation.

After 35 years of preclinical and clinical development, three adeno-associated virus (AAV) vector-based gene therapies for hemophilia received regulatory approval between 2022 and 2024: ROCTAVIAN for hemophilia A and both HEMGENIX and BEQVEZ for hemophilia B, marking historic milestones in treatment innovation for this previously incurable genetic disorder.
These important advancements demonstrate the important promise of gene therapies as a valuable addition to the range of hemophilia treatment options, offering the potential reduced treatment burdens and long-term benefits for eligible patients, contributing to a significant improvement in their quality of life.

However, recent developments have highlighted notable challenges and concerning developments in the progress of gene therapies for hemophilia. These include high-profile discontinuations and/or limitations to gene therapy commercialization. At the same time, a late-stage termination of a clinical trial for a hemophilia A gene therapy and the dissolution of a collaborative development agreement for another hemophilia A gene therapy program further decimated the pipeline for hemophilia gene therapies.

Currently, from a dozen that tried, only two pharmaceutical companies remain active with approved hemophilia gene therapy products and one of these companies has significantly restricted its market presence to only three high-income countries, while halting other clinical development initiatives.

While legitimate safety and efficacy concerns are important reasons to halt development programs, statements and reports citing low interest from both people with hemophilia and healthcare providers are misleading and can lastingly and negatively impact the interest, investment, research in and clinical development of innovative and life-saving therapies.

When companies cease development due to commercial uncertainty or perceived disinterest, the resulting effect on the clinical development of innovative therapies can be significant and long-lasting. Indeed, it is only through a shared commitment and collaboration between the various stakeholders that we have seen the progress that has led to life-saving treatments.

Therefore and more so than ever, scientific-medical societies, such as the International Society on Thrombosis and Haemostasis (ISTH), European Association for Haemophilia and Allied Disorders (EAHAD) and advocacy organizations, such as the World Federation of Hemophilia (WFH), explicitly welcome and in fact strongly encourage effective and safe gene therapies, as well as other novel therapies for hemophilia, such as FVIII mimetics and rebalancing agents, as important treatment options to meet the needs of hemophilia patients around the word.

It is important to note that the low uptake is also significantly related to the delayed development of appropriate reimbursement models that must account for both the long-term elevation of factor levels and potential complications associated with diminished expression and reduced protection over time. These confounders, including the unknown

long-term outcomes are part of the overall benefit-risk equation not only for patients, their caregivers, and healthcare providers, but for reimbursement agencies as well.

Furthermore, the lack of globally harmonized regulatory strategies, as well as unduly burdensome, lengthy and costly clinical development and drug approval processes create additional barriers and disincentivize critical and sustained investments in innovation.

In light of the recent highly concerning number of clinical development and commercial withdrawals of gene therapies, EAHAD, ISTH, and WFH issue a critical Call-to-Action to all stakeholders—industry, regulators, payors, funders, researchers, clinicians, and patients—not only to ensure the potential of gene therapy as an important treatment option but to provide and support continuous advancement of other innovative hemophilia treatments as well as, importantly, the optimization of, and access to, existing therapies. We urgently call upon all stakeholders to intensify collaborative approaches to reduce burdens and barriers, overcome challenges, foster innovation, and guarantee that effective and safe therapeutic options remain and become both transformative and accessible for patients worldwide.

In addition to ISTH, EAHAD and WFH, this statement is endorsed by the following organizations:

American Society of Gene & Cell Therapy
Asian-Pacific Society on Thrombosis and Hemostasis
Association for Haemophilia and Allied Disorders-Asia Pacific
European Haemophilia Consortium
European Society for Gene and Cell Therapy
Grupo Collectivo Latinoamericano de Hemostasis y Trombosis
National Bleeding Disorders Foundation