WORLD FEDERATION OF HEMOPHILIA
FÉDÉRATION MONDIALE DE L'HÉMOPHILIE
FEDERACIÓN MUNDIAL DE HEMOFILIA

December 10, 2018

Dr. Scott Gottlieb
Commissioner
Food and Drug Administration
Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, RM. 1061
Rockville, MD 20852

Re: Docket No. FDA 2018-D-2238: Human Gene Therapy for Hemophilia; Draft Guidance for Industry

Dear Commissioner Gottlieb,

Thank you for the opportunity to comment on the Draft Guidance for Industry: Human Gene Therapy for Hemophilia. The World Federation of Hemophilia (WFH) is the not-for-profit global advocacy organization working to ensure that individuals affected by hemophilia and related inherited bleeding disorders have access to high quality medical care and services. Our work in 140 national member countries extends from the developed world to severely resource constrained countries, where the expected number of persons with hemophilia is more than 10 times the patients identified. WFH sincerely appreciates the FDA's interest in assisting sponsors developing safe and effective gene therapy products to treat hemophilia and is pleased to offer comments on this generally well written Draft Guidance on behalf of members in the United States and many other countries who rely upon FDA guidance documents. For many of our national members, gene therapy is a promising solution far beyond the goal of obtaining sufficient access to clotting factors for 70% of the world that have no treatment. Hemophilia is a lethal disease in these countries.

Hemophilia and Gene Therapy

FDA has reviewed and approved significant hemophilia treatment advances over the past 50 years, since the development of plasma-derived clotting factor concentrates. Morbidity and mortality have decreased dramatically, despite the loss of life due to hepatitis viruses and HIV. Unfortunately, morbidity and mortality related to bleeding do continue despite these advancements. For instance, prophylactics delays but do not entirely eliminate progressive joint disease due to the need for compliance with frequent repeated intravenous treatment and aiming for trough levels of 1%, which are inadequate to prevent all bleeding. Thus, the concept of curing these monogenic diseases (Hemophilia A and B) has captured the imagination of

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patients, their caregivers, and their healthcare providers since the genes were cloned in the early 1980s. Based on the clinical trial results reported to date, we appear to be closer to a treatment that will overcome the bleeding risks and their sequelae of present treatments. At the same time, safety remains paramount, especially given our history with iatrogenic delivery of viral pathogens in plasma derived concentrates, leading to widespread mortality.

Comments on the Guidance

Our comments on the Guidance follow by section:

IV. Considerations for Factor VIII/Factor IX Activity Measurements Assessed by Different Clinical Laboratory Assays

Circulating factor activity is directly and linearly correlated to the risk of bleeding, thus a reasonably accurate assay is required for the assessment of bleeding risk in participants of gene therapy clinical trials. The FDA identifies the discrepancy between one stage clotting and chromogenic assay factor activity measurements as being a challenge to both Factor IX Padua and Factor VIII gene therapy product development. The Agency encourages sponsors to "resolve" these discrepancies, particularly if they seek to use factor activity level as a surrogate endpoint. While we are aware of, and strongly encourage industry scientists, to pursue studies to better understand the biologic bases of this discrepancy, we don't believe the discrepancies warrant any delays in the clinical trial process and approval of gene therapy products for hemophilia. Clinicians have had to contend with Factor VIII one-stage/chromogenic assay discrepancies for decades. In some cases, this may be due to the patient's underlying *F8* mutation. It is also an accepted variable of the clinical monitoring of patients on replacement therapy and may be exacerbated by bioengineered factor VIII products (eg. B domain deletion, PEGylation). In some cases, these discrepancies may be overcome through product-specific standards or changes to labeled potency. However, in most clinical practice, the assay discrepancy has not been "resolved" and clinicians have still been able to incorporate these therapies into routine clinical care. Beyond a threshold of ~15%, differences in the two assays do not affect clinical management. Preferential use of the more conservative chromogenic assay or similar recommendations should permit reasonable monitoring in cases where it is required such as surgery. Consideration of gene therapy product field studies would allow recognition of assay discrepancies as a function of reagents, instruments, or individual lab practices, and provide guidance analogous to that offered for bioengineered clotting factors.

We should be aiming for FVIII and FIX circulating levels that eliminate bleeding. While the chromogenic assay may be more precise, even the one stage assay will give a reasonable picture of the situation at factor levels beyond the 15% threshold. We suggest considering all the natural history evidence showing that patients are at a progressively lower risk of bleeding as factor levels move toward normal. Mild severity patients with factor VIII activity of 15-20 IU/dl and above may not even be diagnosed due to absence of clinical manifestations. For patients

with pre-existing hemophilic arthropathy and it's attendant inflammatory state, aiming for levels closer to the normal range may be most appropriate.

VI. Considerations for Clinical Trials – A. Efficacy Endpoints

The FDA is proposing the use of Annualized Bleed Rates (ABR) as a primary endpoint for clinical effectiveness and factor activity level as a surrogate endpoint for accelerated approval. We do acknowledge that prevention of bleeds and their complications is the ultimate goal of hemophilia treatment. However, we are concerned that ABR is not an ideal primary end-point for efficient gene therapy clinical trials.

We would like to state the obvious. Hemophilia is a deficiency of a protein activity encoded by a single gene. Measuring levels of that protein in both natural history studies of different hemophilic severity levels and within interventional studies replacing the missing factor have established the correlation with bleeding and risk of bleeding in surgery, treatment of bleeding, and prophylaxis. Achieved factor activity level (i.e., restoration of inadequate clotting capacity) to treat bleeding was the single measure required for approval in the early era of hemophilia treatment. Bioequivalence was abandoned in more recent trials in favor of ABR for measuring clinical outcomes when the goal became proving the superiority of bioengineered clotting factors, or non-factor therapies to conventional clotting factors. With the currently available treatment for hemophilia, generally good ABR results are achieved if troughs remain above 1%. However, there are no troughs to measure in gene therapy, thus factor levels make sense as a primary endpoint, followed by ABR as one of several secondary endpoints. Meaningful and feasible trials should focus on factor activity levels, as indeed already suggested by draft FDA guidance for accelerated approval.

It is important to appreciate ABR has a major subjective component, lead to both false positive and false negative rates of joint bleeding due to the underlying arthropathy and inflammation. A patient's current joint disease status is largely based on his treatment history and has a large influence on occurrence and reporting of ABR. Moreover, ABR only captures clinically-recognized bleeding events; it does not capture subclinical bleeds[1] that regularly occur when factor activity level drops below a therapeutic level. ABR is an incomplete and imprecise measure, very relevant as a secondary endpoint to patients, but not as relevant as a primary endpoint in gene therapy clinical trials.

Finally, a multidisciplinary group of stakeholders completed a robust modified Delphi process[2] on outcome measures in hemophilia gene therapy clinical trials, designated CoreHEM. In addition to factor activity and ABR, a series of additional measures can inform on-and

[1] Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. N Engl J Med. 2007 Aug 9;357(6):535-44.
[2] Iorio A, Skinner MW, Clearfield E, et al. Core outcome set for gene therapy in haemophilia: Results of the coreHEM multistakeholder project. Haemophilia. 2018 Jul;24(4):e167-e172. doi: 10.1111/hae.13504. Epub 2018 May 20.

potentially distinguish between- existing treatments and gene therapy. These outcomes include frequency of bleeds; duration of expression [of clotting factor gene]; chronic pain; utilization of healthcare system (direct costs); and mental health status.

VI. Considerations for Clinical Trials – B. Study Design

WFH has comments on several of the study design recommendations included in the Guidance:

- Pre-administration considerations: The FDA recommends limiting gene therapy clinical trial participants to patients "who have not had dose adjustments to their prophylactic replacement therapy for at least 12 months." While we support that the FDA is seeking to have sponsors include well-controlled patients in trials, we are concerned that this requirement would preclude participation in a trial from any patient on Emicizumab or who is forced to switch clotting factor treatments by their insurance plan (i.e., from extended half-life to conventional product or vice versa). This would pose a barrier to clinical trial enrollment and create informed consent challenges for hemophilia treaters. We recommend deleting this language and consider stating for inclusion "well managed patients over the past 12 months."

- Post-administration considerations: Correlating factor activity and bleeding rates will be complex, since it requires understanding what else may have changed in a person's life (such as more or less physical activity, career changes, comorbidities that could increase a person's likelihood for bleeding) that could confound the analysis. People with hemophilia who receive gene therapy may be more active or take more "risks" than previously, perhaps prematurely before their joints/muscles have time to rehabilitate and strengthen. Post-administration bleeds must be carefully evaluated and understood and long term, multi-year monitoring of progressive joint damage should be carried out as part of post-marketing surveillance to understand a major benefit of gene therapy (elimination of subclinical bleeding).

VI. Considerations for Clinical Trials – E. Study Monitoring

We agree with the FDA that there must be ongoing monitoring of patients receiving gene therapy to monitor their safety and durability of response. WFH has comments on several of the recommendations that the FDA is proposing for short-term (first two years) and long-term (longer than 2 years) monitoring following gene therapy administration. In particular:

- Short-Term Monitoring: We understand the importance of frequent monitoring of factor activity and liver function. The frequency– once or twice weekly to monthly in the first year – is prohibitively burdensome for patients, some of whom may live a great distance away from their hemophilia treatment center. We would encourage sponsors and the FDA to define processes to allow patients to have fluids obtained in their home communities to substitute for at least some hospital visits. We remain concerned about the mild transaminase elevations, since they are incompletely explained and may

represent a low level of hepatotoxicity. We encourage further investigation by trial sponsors and others to understand the proximate source of the insult.

- Long-Term Monitoring: We do not believe that 5 years is a sufficient long-term horizon for monitoring for adverse events for non-integrating gene therapy nor 15 years for integrating gene therapy. We do not agree that AAV is "non-integrating." While integration rates are orders of magnitude less efficient than for integrating vectors, the sheer magnitude of vector dose will result in possibly a billion integrations or more per patient. We acknowledge the good safety record established to date in hemophilia gene therapy trials but have a concern about the unknown unknowns[3] and strongly recommend lifelong monitoring for patients who receive investigational and subsequently marketed gene therapy. The monitoring can be quite minimal, hence may not be a substitute for more intensive post-marketing surveillance but would give assurance that rare events are not occurring many years distant from the treatment. The major unknowns include long term hepatotoxicity and risk of hepatocellular carcinoma, but other unknowns may emerge from a registry. Moreover, we encourage FDA to support international harmonization of data collection given the small patient size globally. We encourage the FDA, as well as sponsors, researchers and hemophilia treaters to coordinate activities regarding a core data set for global surveillance of rare events. FDA should consider a registry as a post-marketing requirement. Otherwise, how will we know the long-term safety?

VI. Considerations for Clinical Trials – F. Patient Experience

We appreciate that FDA has affirmed its intention to focus on outcomes important to patients and is encouraging sponsors to gather and submit patient experience data in their submissions. CoreHEM, the international multi-stakeholder project to develop a core outcome set for clinical trials of gene therapy in hemophilia reflects patient perspectives on critical outcomes for inclusion in pivotal trials to allow more accurate assessments of the value of these therapies.

In addition, the National Hemophilia Foundation-McMaster treatment guidelines on care models for hemophilia specifically reviewed outcomes important to assessing care.[4] Outcomes such as bleeding and bleeding rate were considered important but judged not important enough to be included in the final list of patient-important outcomes.

Finally, on September 22, 2014 FDA held a Patient Focused Drug Development Initiative (PFDD) meeting on hemophilia and other bleeding disorders. These data were included in the Voice of

[3]Pierce GF, Iorio A. Past, present and future of haemophilia gene therapy: From vectors and transgenes to known and unknown outcomes. Haemophilia. 2018 May;24 Suppl 6:60-67. doi: 10.1111/hae.13489. Review.

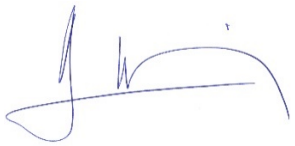
[4] Pai M, Key NS, Skinner M, et al. NHF-McMaster Guideline on Care Models for Haemophilia Management. Haemophilia. 2016 Jul;22 Suppl 3:6-16. doi: 10.1111/hae.13008.

the Patient report released by the Agency following the meeting.[5] The report emphasizes our patients' concerns about the pain, anxiety and depression they experience associated with their bleeding disorder. We encourage you to reference this report as you consider patient centered outcome measures for gene therapy.

Conclusion

Thank you for the opportunity to comment on this Draft Guidance for Industry. WFH appreciates the FDA's interest in facilitating research and ultimately approval of safe and effective gene therapy treatments for hemophilia. These treatments will not only change the natural history of hemophilia in the United States and other developed nations but will be the difference between life and death in the developing world, assuming they are demonstrated to be safe and effective. If we may be of further assistance, please contact Donna Coffin, Director of Research at WFH, dcoffin@wfh.org, or any of us.

Sincerely,



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[5] The Voice of the Patient: Hemophilia A, Hemophilia B, von Willebrand Disease and Other Heritable Bleeding Disorders (PDF - 396KB) Public Meeting 9/22/2014; Report Date: 5/2016. Accessed from https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm368342.htm 8 Dec 18