# Position on Expanded Access to Investigational Gene Therapies

## Background

Gene therapy is a new generation of treatment with the potential to offer meaningful improvements for patients. This new technology may address the underlying causes of disease but requires finding answers to new and challenging development and delivery questions.

Pfizer's ability to answer these questions relies on preserving the integrity of our clinical trials and following strict scientific and ethical standards designed to produce reliable results. Where possible, use of a gene therapy within a clinical trial is preferable because clinical trials are designed to answer safety and efficacy questions, generating the data needed for approval and eventual wider use by patients.

Patients seeking preapproval access to investigational treatments outside of a clinical trial often suffer from serious or immediately life-threatening diseases. Some patients may be willing to try an experimental drug or gene therapy for which regulatory approval has not been granted. These programs can be referred to by different names; two common ones are "expanded access" and "compassionate use". At Pfizer, we have a robust program that provides expanded access to investigational drugs under the following conditions: patients who are diagnosed with a serious or life-threatening disease, who have exhausted approved treatment options, and who are not eligible for clinical trials.[1] These core conditions remain when considering expanded access to gene therapies for diseases with high unmet need.

Gene therapy clinical trials look to answer a unique set of questions that are different from those addressed in other investigational drug trials, including understanding immune-related side effects at administration, the long-term safety and duration of treatment response, and the potential for loss of some or all treatment effects over time. In addition, because of the body's immune response, patients at this time may only be able to receive a single dose of gene therapy that has the potential to confer the desired degree and/or duration of benefit. Therefore, at least currently, as a gene therapy may be limited to a single administration in a patient's lifetime, it is particularly important that sufficient clinical trial data be generated to support the assessment that the potential benefit outweighs the potential risks of treatment.

At Pfizer, we are continually working towards finding mechanisms to provide timely and sustainable access to our gene therapies. When developing our expanded access policies, we look to balance patient needs with our ability to conduct clinical trials and to address the logistical and technical barriers of broader access. These considerations have led Pfizer to apply an additional level of review when developing our expanded access policy for gene therapies.

In developing our disease-specific policies, Pfizer has consulted with internal and external scientific and medical experts, our Bioethics Advisory Council, and importantly, members of rare disease and disease-specific patient advocacy communities. We are committed to the patient communities that may benefit from these breakthrough therapies and will continue to engage with stakeholders across the globe to incorporate their feedback as we review our policies in a timely and transparent manner.

[1] See Pfizer's Position on Expanded Access to Investigational Drugs.

## Hemophilia Gene Therapy Expanded Access Policy

Pfizer has a strong legacy of innovation in hemophilia with more than 40 completed hemophilia clinical trials. As a result of these efforts, thousands of hemophilia patients across the globe are being treated with our medicines.

Hemophilia is a family of genetic diseases that results in a deficiency of a protein required for normal blood clotting – clotting factor VIII (FVIII) in hemophilia A and clotting factor IX (FIX) in hemophilia B. Hemophilia A occurs in approximately 1 in 5,000 male births, while hemophilia B occurs in 1 in 25,000 male births.[2] Today, in countries with established healthcare systems, the availability of recombinant factor has reduced the reliance on plasma-derived clotting factor products and driven substantial change in hemophilia patient care, in some cases shifting the paradigm from on-demand to prophylaxis treatment.

While recent advances in available treatment options have greatly improved hemophilia management, there remains unmet need and we believe more can be done to advance the science and deliver these breakthrough therapies for the benefit of people living with hemophilia. We are working to develop and deliver transformational hemophilia therapies to patients, including gene therapies for hemophilia A and B. Pfizer's current hemophilia gene therapy approach provides a single-dose in-vivo delivery of recombinant adeno-associated virus (AAV) vectors to transfer a healthy copy of a gene into certain liver cells of a patient which allows for the production of functional factor protein.[3,4] The goal is to restore levels of factor protein in the blood, potentially enabling a patient to produce their own clotting factor without the need for routine supplemental clotting factor infusions.[5]

A decision to provide expanded access to our gene therapies, like investigational drugs, is based on the core conditions of addressing the unmet needs of patients diagnosed with a serious or life-threatening disease, who have exhausted all available treatment options, and where a clinical trial is not an option.

After careful review of these core conditions, Pfizer has decided not to provide expanded access to our hemophilia gene therapies at this time. This decision is based in part on the availability of multiple treatment options for both hemophilia A and B and a review of open clinical trials at Pfizer and elsewhere. We are focused on ensuring our research programs can meet regulatory requirements as quickly as possible to ensure broad patient access. We are committed to the hemophilia patient community and our goal is to ensure availability and access to this breakthrough therapy to as many eligible patients with hemophilia as possible.

[2] National Organization for Rare Disorders, Inc. rarediseases.org/rare-diseases/hemophilia-b. Accessed March 2023.
[3] Pfizer. Gene Therapy Fact Sheet. Pfizer.com. https://www.pfizer.com/science/innovation/gene-therapy/gene-therapy-promise. Accessed March 2023.
[4] Kattenhorn LM, et al. Adeno-Associated Virus Gene Therapy for Liver Disease. *Hum Gene Ther*. 2016;27:947–61.
[5] Centers for Disease Control and Prevention. Treatment of hemophilia. CDC.gov. https://www.cdc.gov/ncbddd/hemophilia/treatment.html. Accessed March 2023.

## Duchenne Muscular Dystrophy Gene Therapy Expanded Access Policy

Duchenne Muscular Dystrophy (DMD) is a serious genetic disorder primarily affecting boys, characterized by progressive loss of muscle tissue. Due to the progressive nature of the disease, impacting skeletal as well as cardiac and respiratory muscles, the need for disease-modifying therapies is urgent.

DMD is caused by mutations in the gene encoding dystrophin, a protein needed to stabilize the membrane of muscle cells. It is a rare genetic disease affecting approximately 1 in 3,500 to 5,000 live male births worldwide. Most people with DMD will die between 20 and 40 years of age due to cardiac failure and/or respiratory complications.[6] The substantial disease burden of DMD for patients, caregivers, and health care systems coupled with the lack of treatments targeting the underlying cause of disease results in a significant unmet need.

A decision to provide expanded access to our gene therapies, like investigational drugs, is based on the core conditions of addressing the unmet needs of patients diagnosed with a serious or life-threatening disease, who have exhausted all available treatment options, and where clinical trials are not an option.

Pfizer has conducted a review of these core conditions for providing expanded access to our DMD gene therapy. The severity of DMD, the limited number of treatment options that improve function and target the root cause of the disease, and the current number of clinical trials has led Pfizer to conduct an additional level of review and consideration.

As part of this review, we examined the current state of scientific and clinical research and explored key ethical concerns raised by experts.[7] We systematically reviewed each of these concerns in the context of our current developmental program, including understanding our capabilities to: balance expanded access with conducting clinical trials, determine whether potential benefits exceed potential risks, develop a fair allocation strategy, consider the possible implications of a potentially one-dose therapy, and ensure all logistical and technical needs are sustainably met. In parallel to these reviews, we also engaged in transparent conversations with the patient advocacy community and key stakeholders, discussing many of the ethical and logistical issues under review.

After careful consideration, and consistent with external guidance we received, Pfizer has decided not to provide expanded access to our DMD gene therapy at this time. We understand that there is a high unmet need and recognize that gene therapies for DMD have the potential to be transformative, changing the course of a disease and reducing the burden associated with current disease management. Given the significance of the concerns associated with providing expanded access in a safe, timely, and sustainable way, Pfizer has decided to focus on completing our clinical trials to ensure wider and faster patient access.

We also recognize that a potential breakthrough of this magnitude requires an equally transformative approach to ensure broad and accelerated access upon regulatory approval. We are committed to collaborating with global healthcare decision makers and patient communities to find novel ways to optimize patient access to these breakthroughs once approved.

[6] Duan, D., et al. 2021. Duchenne muscular dystrophy. *Nat Rev.* 7:13.
[7] Chapman, C.R., et al. 2019. What compassionate use means for gene therapies. *Nat. Biotechnol.* 37:352-55.