Pathway Development Consortium

Draft Framework for AAV Gene Therapy Development

A Pathway Development Consortium White Paper[1]

Executive Summary

Adeno-associated virus (AAV) gene therapy has attracted significant attention in the field. Many AAV gene therapy products are being developed for serious or life-threatening diseases or conditions that are rare, have an unmet medical need, and will require an extended period of time to measure the intended clinical benefit.

Accelerated approval is an important regulatory tool for AAV gene therapy developers, as the use of this pathway can help expedite the availability of these products to patients. A key determination for use of this pathway is the identification of a surrogate endpoint reasonably likely to predict clinical benefit. In the case of AAV gene therapy, many diseases being pursued for treatment have a well-understood disease pathophysiology. Therefore, mechanistic evidence can be an important contributor to the determination that a biomarker can be used as a surrogate endpoint that is reasonably likely to predict clinical benefit. A two-step approach can be used to support the determination of a biomarker as reasonably likely to predict clinical benefit for AAV gene therapy: first, to demonstrate the presence of the measurable biomarker (e.g., a protein), and second, to connect this measurement to potential clinical benefit by relying on the totality of evidence.

Overview of AAV Gene Therapy

The U.S. Food and Drug Administration (FDA) defines "human gene therapy" as treatment seeking "to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use,"[2] and it can work by several mechanisms:

- replacing a disease-causing gene with a healthy copy of the gene;
- inactivating a disease-causing gene that is not functioning properly; or
- introducing a new or modified gene into the body to help treat a disease.

Transfer of genetic material is commonly achieved by utilizing viral vectors that use their own biological capacities – modified to remove their ability to cause infectious disease – to enter the cell and deposit the genetic material. Adeno-associated viruses (AAVs) are the basis of several recently approved gene therapies[3] and have "attracted a significant amount of attention . . . in clinical-stage experimental therapeutic strategies. [Their] ability to generate recombinant AAV particles lacking any viral genes and containing DNA sequences of interest for various therapeutic applications has thus far proven to be one of the safest strategies for gene therapies."[4] Indeed, a proven record of non-pathogenicity is one of main reasons AAV usage has risen so significantly.[5]

While gene therapy (GT) trials target a wide array of disease types – including hematological, ophthalmologic, musculoskeletal, neurological, metabolic, and oncological diseases – it is important to highlight the focus on rare diseases in GT: as of 2020, among the ongoing GT programs in the US, 59% were intended to treat rare diseases.[6] In addition, many of these diseases are often considered serious or life-threatening and have outstanding unmet medical need, many with few or no therapeutic options for patients.

One of main challenges encumbering wider application of AAV gene therapy is the immune response to the gene delivery vectors themselves and to the products of foreign transgenes. Although some AAV gene therapies have had great success and there have been a large number of clinical trials with AAVs, at one time as many as 50% of patients were excluded from treatment owing to pre-existing immunity to the viral capsids.[7] Other challenges include enhancing gene transfer or editing efficiency to levels essential for treatment of many target diseases as well as overcoming hurdles in the manufacturing and regulatory spaces.[8]

Another challenge to AAV gene therapy is that demonstrating long-term improvement may often take an extended period of time depending on the target disease's natural history profile, the heterogeneity of its progression among the affected population, and the rarity of the disease. Additionally, even once gene expression is achieved, there may be a significant duration before physical signs and symptoms of improvement and/or disease stabilization can be detected.

Despite these challenges, AAV gene therapy continues to hold much promise for rare diseases, as "more than 80 percent of rare diseases have a known monogenic (single-gene) cause."[9]

Overview of Accelerated Approval

Broadly speaking, FDA grants approvals to drugs[10] that have demonstrated substantial evidence of effectiveness and have been determined to be safe for its intended use. Whereas traditional approval relies on "clinical endpoints that reflect patient benefits (i.e., how patients feel, function, or survive) or validated surrogate endpoints (i.e., those that have been shown to predict a specific clinical benefit),"[11] accelerated approval relies on demonstrated effects on either:

- "a clinical endpoint that can be measured earlier than irreversible morbidity or mortality [(IMM)], that is reasonably likely to predict an effect on [IMM] or other clinical benefit"[12] (i.e., an intermediate clinical endpoint),[13] or
- "a surrogate endpoint that is reasonably likely to predict a clinical benefit but where there are not sufficient data to show that it is a validated surrogate endpoint."[14]

The use of the accelerated approval pathway is reserved for "a product for a serious or life-threatening disease or condition . . .taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments."[15] FDA's accelerated

approval regulations further stipulate that accelerated approval is available *only* for drugs that provide a meaningful therapeutic benefit over existing treatments.[16] FDA implemented the accelerated approval regulations because of the importance of "mak[ing] drugs that provide meaningful improvement over existing therapies for serious illnesses widely available . . . at the earliest time consistent with the law."[17]

As stated in the FDA regulations in 21 CFR part 312, Subpart E, FDA has committed to facilitating and expediting the availability of new therapies to patients with serious conditions, especially when there are no satisfactory alternative therapies, while preserving appropriate standards for safety and effectiveness. The Subpart E regulations specifically recognize that patients and physicians "are generally willing to accept greater risks or side effects from products that treat life-threatening and severely-debilitating illnesses,"[18] than they would for less serious diseases. Building upon the commitment expressed in the Subpart E regulations, the accelerated approval pathway was described and implemented via regulations by FDA in 1992,[19] and in 2012 Congress formally added the pathway into the law.[20]

Although the accelerated approval pathway is intended to expedite treatments for patients, it remains critically important that developers and regulators continue to assess the potential safety concerns associated with any such treatments. All FDA approvals, including accelerated approvals, are based on a benefit/risk assessment. One of the key distinctions between traditional and accelerated approvals in this regard, however, is that, as FDA has explained, "[r]eliance on a surrogate endpoint almost always introduces some uncertainty into the risk/benefit assessment, because clinical benefit is not measured directly and the quantitative relation of the effect on the surrogate to the clinical effect is rarely known."[21]

Specifically with respect to rare diseases, the FDA has additionally explained that "[t]he goal of safety evaluation during drug development is to characterize the drug's safety profile in a reasonable number of patients over a reasonable duration of time, consistent with the intended use of the drug."[22] For rare diseases, however, "reasonable" requires "consideration of feasibility challenges posed by the limited number of patients with the disease."[23] It is particularly important to highlight FDA's acknowledgment that "what is a feasible and sufficient safety assessment is a matter of scientific and regulatory judgment based on the particular challenges posed by each drug and disease, including patients' tolerance for risk in the setting of unmet medical need."[24]

FDA has also issued a guidance document about Long Term Follow-Up After Administration of Human Gene Therapy Products[25] that specifically focuses on "delayed adverse events," in contrast to more immediate adverse events that are discussed elsewhere. As the guidance states, "[n]ot all GT products will require LTFU observations."[26] Importantly, just as FDA has determined that it may approve certain products using accelerated approval despite some uncertainty regarding meaningful clinical efficacy, this guidance makes clear that some uncertainty regarding delayed adverse events should not necessarily impede licensure, noting that "the recommended LTFU . . . will often not elapse for all subjects who received an investigational GT product in the pre-marketing program before the product is licensed."[27]

It is important to recognize that an approval granted to a human drug or biologic under the accelerated approval pathway is not a lesser or partial approval compared to traditional approval. FDA has stated explicitly that "[d]rugs granted accelerated approval must meet the same statutory standards for safety and effectiveness as those granted traditional approval."[28] As such, any products approved under accelerated approval "will have met the requisite standards for safety and effectiveness under the [law] and, thus, will have full approval."[29]

As described above, the primary difference between accelerated approval and traditional approval is that the former permits the approval to be based on a surrogate or intermediate clinical endpoint that is reasonably likely to predict clinical benefit in cases of a serious or life-threatening disease or condition which might otherwise require a much longer timeframe to collect the data that would be required for a traditional approval.

The phrase "reasonably likely to predict clinical benefit" is of critical importance in understanding accelerated approval. The FDA has articulated that "[d]etermining whether an endpoint is reasonably likely to predict clinical benefit is a matter of judgment that will depend on the biological plausibility of the relationship between the disease, the endpoint, and the desired effect and the empirical evidence to support that relationship."[30] As sponsors seek to develop products for serious or life-threatening illnesses, it is important to understand that under the accelerated approval pathway, surrogate endpoints need not be validated. Indeed, the FDA has stated that "products used to treat serious or life-threatening illnesses, for which approval is based on a surrogate endpoint that is recognized as validated by definitive studies [and therefore, meets a higher threshold bar than 'reasonably likely to predict clinical benefit'], will be considered for approval under the traditional process rather than under accelerated approval."[31]

All drug products granted accelerated approval are subject to certain requirements, which may include postmarketing confirmatory trials to verify and describe clinical benefit[32] as well as submission of all promotional materials intended for dissemination or publication[33]. FDA generally expects confirmatory trials to be underway at the time of accelerated approval.[34] The requirement for any confirmatory study to demonstrate clinical benefit "will not be more stringent than those that would normally be required for marketing approval."[35] The law and regulations alike provide for expedited withdrawal of approval if an applicant fails to conduct a required postmarketing study with due diligence, the postmarketing study fails to verify the predicted clinical benefit, or other evidence demonstrates the product is not safe or effective under the conditions of use.[36] Withdrawal of an accelerated approval may be initiated by the Agency[37] or by the applicant.[38] Indeed, the integrity of the accelerated approval program rests on the assurances of prompt withdrawal from the market if clinical benefit is not confirmed, so it is important that applicants embrace this responsibility and request withdrawal of the accelerated approval when they become aware that the postmarketing study has failed to verify the predicted clinical benefit or when the applicant becomes aware of other evidence demonstrating the product is not safe or effective under the approved conditions of use. When considering gene therapy, it is important to note that Congress has provided greater explicit flexibility

about how some regenerative medicine products, in contrast to other types of products, can meet the requirement for accelerated approval and also address postapproval requirements. Regenerative medicine products, including gene therapy treatments, may be designated as Regenerative Medicine Advanced Therapies (RMATs) if they are "intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition" and "preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such a disease or condition."[39] Products designated as RMATs may be eligible for accelerated approval based on:

- Previously agreed-upon "surrogate or intermediate endpoints reasonably likely to predict long-term clinical benefit; or
- Reliance upon data obtained from a meaningful number of sites, including through expansion to additional sites, as appropriate."[40]

When such products are granted accelerated approval, their applicants may meet postapproval requirements by "postapproval monitoring of all patients treated with such therapy prior to approval of the therapy," among other methods, such as the use of real world evidence, not explicitly available to other products.[41] This explicit legal flexibility regarding postapproval requirements can thus serve to provide greater information regarding both sides of the benefit-risk determination for accelerated approval for certain gene therapies to resolve uncertainty in the original determination, while still maintaining the other provisions of the accelerated approval pathway.

Accelerated approval is most often used in settings in which the disease course is long and an extended time-frame would otherwise be necessary to measure the intended clinical benefit of the drug on outcomes like long-term morbidity or survival.[42] For example, accelerated approval proved vital in the setting of HIV where surrogate markers of CD4 cell counts and HIV viral load served well for predicting long term effect on survival or morbidity, allowing for the earlier approval of lifesaving products for a population with significant unmet medical need.[43] While early approvals used CD4 cell count, a biomarker at the time that had uncertainty related to the drug's ability to delay clinical progression,[44] its use led to the rapid availability of more effective therapies and the development of better surrogate endpoints for evaluation of HIV treatments.[45]

Accelerated Approval as a Framework for AAV Gene Therapy Development

Accelerated approval is an important regulatory tool for AAV gene therapy developers. Many AAV gene therapy products are being developed for serious or life-threatening diseases or conditions that are rare, have an unmet medical need, and will require an extended period of time to measure the intended clinical benefit. The use of the accelerated approval pathway can help expedite the availability of these products to patients. To help facilitate the application of the accelerated approval pathway, this paper proposes a framework that considers the different categories of AAV gene therapies that target underlying monogenetic changes that cause diseases. Based on these categories, generalized approaches can be clarified around the evidence needed to support a potential

surrogate endpoint as reasonably likely to predict clinical benefit and supportive data that can contribute to the finding of substantial evidence of effectiveness.

When applying the framework, a key determination for use of the accelerated approval pathway is the identification of a surrogate endpoint reasonably likely to predict clinical benefit. As noted earlier, this determination is a matter of judgement. However, a consistent approach to guide this determination will facilitate compiling the needed data to make these therapies available to patients as soon as possible. In the case of AAV gene therapy, many diseases being pursued for treatment have a well-understood disease pathophysiology. Therefore, just like mechanistic evidence can be supportive in demonstrating substantial evidence of effectiveness, it can also be an important contributor to the determination that a biomarker can be used as a surrogate endpoint that is reasonably likely to predict clinical benefit. For example, as noted in FDA's 2019 Draft Guidance on Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, this is the case with an "enzyme replacement therapy, where a single adequate and well controlled clinical investigation that demonstrates the therapy's efficacy is supported by evidence that the condition is caused by the enzyme deficiency and by earlier results that show the therapy increases enzyme activity to biologically active levels at the appropriate site and/or reduces disease-specific substrates."[46] In other words, the first step of identifying a surrogate endpoint that is reasonably likely to predict clinical benefit is clinical data demonstrating that the protein is present in the intended cells or tissues after administration and can be reliably measured.

Once these data are available, the next step to determining if a surrogate endpoint is reasonably likely to predict clinical benefit is to establish that how a patient feels, functions, or survives can reasonably likely be improved by this protein expression. This key link can be established through leveraging data known about the AAV gene therapy to model how AAV gene therapy administration can achieve the needed levels (relying on preclinical data, including in vitro and animal data, and clinical data, when available) and demonstrating correlation in humans when clinical data are not available. When available, understanding of minimum acceptable levels of the protein may come from data from natural history and/or clinical management of the disease. Using this two step approach - demonstrating the presence of measurable protein and connecting this measurement to potential clinical benefit by relying on the totality of evidence – one can support the determination of a biomarker as reasonably likely to predict clinical benefit for AAV gene therapy. Further clinical data on clinical benefit can ultimately provide the needed support to validate a reasonably likely surrogate endpoint to enable its use for traditional approval.

In addition to the data that support the determination of a surrogate endpoint as reasonably likely to predict clinical benefit, there are other data that can be included in a biologics license application (BLA) to further support its approval and demonstration of substantial evidence of effectiveness. This can include objective measures on other endpoints that in and of themselves are not necessarily clinical benefit.

Table 1: Category Descriptions

Category	Cellular/Non-Enzymatic (i.e., Structural)	Cellular/Enzymatic	Non-Cellular/Non-Enzymatic	Non-cellular/Enzymatic
Defining disease modifying protein function	• Protein complexes that are integral membrane proteins (permanently attached to the membrane). • Protein complexes/cytolinkers that work to link intracellular cytoskeleton network to transmembrane components (transmembrane connection from intracellular to extracellular matrix). • Protein complexes that play critical roles in cell structure and function. • Cytoskeleton complex, interlinking protein filaments present in the cytoplasm of cells including microfilaments, intermediate filaments, and microtubules.	• Enzymes that are intracellular proteins localized within membrane-enclosed organelles or membrane-bound vesicles. • Proteins that are involved with lysosomal, ubiquitin-proteolytic enzyme, caspase and DNA replication pathways.	• Proteins that are actively transported out of the cell, can be endocrine or exocrine. • Secretory proteins that are synthesized in the endoplasmic reticulum that contain a signal sequence. • Secretory proteins including many hormones, enzymes, toxins, and antimicrobial peptides. Other disease modifying protein function: • Coagulation factors that are a group of related proteins that are essential for the formation of blood clots. • Protease inhibitors belonging to the serpin superfamily with main function to inhibit the complement system to prevent spontaneous activation.	

Table 2: Example Set One

Category	Cellular/Non-Enzymatic (i.e., Structural)	Cellular/Enzymatic	Non-Cellular/Non-Enzymatic	Non-cellular/Enzymatic
Disease Example	**Duchenne Muscular Dystrophy (DMD)**	**Lysosomal Storage Diseases (LSDs)**	**Hemophilia (or very similar, von Willebrand Disease)**	**Phenylketonuria (PKU)**
Pathophysiology	DMD gene mutations result in alterations of the structure or function of dystrophin or prevention of any functional dystrophin from being produced. Thus, muscle cells become damaged due to lack of dystrophin as repeated muscle contraction and relaxation lead to damaged fibers that weaken and die over time. This results in progressive muscle weakness, including cardiac dysfunction.[47] The dystrophin complex strengthens the plasma membrane of striated muscle cells. Dystrophin is a protein that links the intracellular cytoskeleton network to the transmembrane components of the dystrophin-glycoprotein complex.[48]	LSDs represent a relatively large group of over 40 metabolic disorders. Most LSDs are caused by the deficient activity of a single lysosomal enzyme leading to a significant decrease (<10% normal levels) or a complete absence in the activity of a soluble lysosomal enzyme.[49] Without this activity, macromolecules such as glycosaminoglycans (GAGs) that are normally degraded by the enzyme build up to high levels leading to lysosomal distention in specific tissues, causing the pathophysiology of the respective LSD.[50] Therefore, as lysosomal enzymes are ubiquitously expressed, the absence of activity of a single enzyme can affect multiple organ systems and result in a broad spectrum of clinical signs and symptoms.[51] Although lysosomal enzymes are intracellular proteins localized within membrane-bound vesicles, a small proportion of the mature enzymes are secreted from the cell. The secreted enzymes can be endocytosed and targeted to the lysosome by plasma membrane proteins. This secretion, initially referred to as "cross-correction," forms the basis for most therapeutic approaches that have been developed for LSDs. For gene therapy, cells that are corrected can secrete the transfected lysosomal enzyme, which can then be taken up by neighboring cells. In addition, gene therapy can express superphysiologic amounts of enzyme in a target organ, such as the liver, muscle, and lung, that can be excreted and travel to effected tissues though the blood.[52]	Factor VIII is an essential blood-clotting protein, a glycoprotein procofactor also known as anti-hemophilic factor.[53] Factor VIII is encoded by the F8 gene and defects in this gene results in hemophilia A.[54] Factor VIII is produced mainly in liver sinusoidal cells.[55] After an injury that damages blood vessels occurs, this protein, which had been circulating in the bloodstream in an inactive form bound to another molecule called von Willebrand Factor, is activated and separates from von Willebrand Factor. The active protein interacts with another coagulation factor called Factor IX that sets off a chain of additional chemical reactions that form a blood clot.[56] Mutations in F9 gene cause insufficient levels of Factor IX, which cause hemophilia B.[57]	PKU is a rare inherited disorder that causes an amino acid called phenylalanine (Phe) to build up in the body. PKU is caused by a defect in the gene that helps create the enzyme needed to break down Phe called phenylalanine hydroxylase (PAH), where in the most severe form of the disorder the enzyme is missing or severely reduced, causing severe brain damage.[58]
AAV gene therapy	Restore function by delivering vector expressing microdystrophin cDNA.	The general principle of treatment for LSDs has been lowering the excessive amount of stored substrate, which can be achieved by enhanced substrate degradation or by reduced substrate production.[59] Gene therapy can deliver the missing enzyme to enhance substrate degradation. Restore function by delivering vector expressing cDNA of missing/defective enzyme. This leads to functional enzyme made which in turns degrades the substrate.	Restore function by delivering vector expressing Factor VIII cDNA or Factor IX cDNA, for hemophilia A and B, respectively.	Normalize blood Phe concentration by delivering vector expressing PAH cDNA.
Biomarker to detect/measure proof of concept/activity	The gene therapy product itself, microdystrophin protein.	The downstream targeted substrate, for example, GAGs.	The gene therapy product itself, Factor VIII protein, Factor IX protein.	Normalized plasma Phe levels.
Assay for biomarker	Muscle biopsy to detect/measure microdystrophin directly in tissue.	GAGs are complex carbohydrates that are expressed in large quantities and throughout both the cell surface and in the extracellular matrix.[60] Not possible/accessible to biopsy brain, lung, heart, liver, spleen, kidney, joint, and bone tissues. GAGs are also secreted into the circulatory system, urine, and cerebrospinal fluid (CSF), and thus have been widely evaluated as a biomarker of primary storage.[61] Assays have been developed to measure total or partial GAG levels in blood, urine, CSF.[62] This is reflective of the total burden of disease and levels would be expected to change in response to interventions known to be specific for the condition.[63] With regards to enzyme levels, studies in both Pompe disease and metachromatic leukodystrophy have shown that the most severe infantile-onset forms of the disease correlate with <1% enzyme activity, and that adult-onset forms correlate with <10%–15% of normal enzyme activity. This has been seen with other LSDs, including Fabry disease, Niemann–Pick disease, and Gaucher's disease.[64] These results suggest that if gene therapy is able to produce even a relatively small amount of a respective LSD enzyme, it may have a large clinical impact upon the course of the disease.	Circulating protein, measure in plasma. It has been established that in patients with severe hemophilia A, a moderate restoration of the Factor VIII levels in a patient's plasma can stop disease symptoms.[65]	Plasma. It has been established that plasma concentration of Phe should be kept at a safe level of ≤300 μmol/L (5 mg/dL).[66]
Other objective markers to measure as totality of evidence	Serum creatine kinase and other clinical outcome assessments such as imaging (MRI/MRS).	Liver and/or spleen volumes if systemic. Leukocyte SGSH enzyme activity level, brain volume if intrathecal.	Inflammatory markers such as interleukins.	Dietary protein intake from intact food.

Table 3: Example Set Two

Category	Cellular/Non-Enzymatic (i.e., Structural)	Cellular/Enzymatic	Non-Cellular/Non-Enzymatic	Non-cellular/Enzymatic
Disease Example	**Giant Axonal Neuropathy (GAN)**	**SOD-1 Associated Familial Amyotrophic Lateral Sclerosis (ALS)**	**Alpha 1-Antitrypsin Deficiency**	**Maple Syrup Urine Disease (MSUD)**
Pathophysiology	GAN is caused by loss-of-function mutations in the GAN gene. This gene encodes the gigaxonin protein that plays a critical role in the organization and degradation of intermediate filaments (IFs)[67] and performs a significant role in the integrity of the cytoskeletal structure by binding with a microtubule-associated protein.[68] Patients with GAN exhibit massively enlarged axons filled with randomly arrayed, densely bundled IFs.[69] GAN is characterized by generalized impaired function by many classes of IF proteins that are disorganized in multiple cell types including Schwann cells, perineurial cells, endothelial cells, neurons, astrocytes, muscle fibers, and fibroblasts.[70] Children with GAN first experience gait abnormalities, sensory loss, and clumsiness related to muscle weakness and ataxia, which, over time, will further degrade until there is a total loss of ambulation, weakened upper extremity function, dysarthria and dysphagia, and eventually death from respiratory failure.[71]	ALS is a progressive neurodegenerative disease resulting from motoneuron loss.[72] Ten percent of ALS can be classified as familial, with ~70% of familial cases explained by known gene mutations.[73] The first ALS-associated gene, superoxide dismutase-1 (SOD1), accounts for up to 20% of familial ALS and 2-7% of sporadic ALS cases.[74] It is believed that mutations in SOD1 may cause ALS via toxic gain of function that results from buildup of misfolded SOD1 protein which in turn reduces nuclear protection from the active enzyme (loss of function in the nuclei).[75] The genetic mutations destabilize the protein and data suggest that the familial form of ALS should be considered a protein misfolding disorder resulting in a non-native toxic oligomeric conformation that is generated in the mutant protein(s). This protein misfolding leads to protein accumulation, possibly followed by axonal transport alterations, mitochondrial and/or proteasome dysfunctions. Ultimately, this can cause overproduction of reactive oxygen species and caspase activation.[76]	Mutations in the SERPINA1 gene causes Alpha-1 deficiency.[77] This gene is essential for making a protein called alpha-1 antitrypsin (AAT), a serine protease inhibitor (serpin).[78] Serpins are a superfamily of proteins with shared structural features that act as protease inhibitors and are distinguished by their unusual mechanism of action, which is a suicide substrate-like inhibitory mechanism, in which they irreversibly inhibit their target serine proteinase by undergoing a large metastable conformational change to disrupt its active site.[79] The AAT protein is mainly produced by the liver and its main function is to protect the lungs from inflammation. When AAT is abnormal and not released from the liver at the normal rate, it results in low levels of AAT in the blood, leading to a build-up of AAT in the liver. This can cause liver disease and lung disease.[80]	MSUD is a rare genetic metabolic disorder characterized by high levels of the three branched-chain amino acids (BCAAs) leucine, isoleucine and valine and their ketoacid derivatives. MSUD is primarily caused when a mutated form of the BCKDHA, BCKDHB, or DBT gene is inherited from both parents.[81] Together these genes produce proteins that work together to form the enzyme complex known as branched-chain α-keto acid dehydrogenase complex (BCKDC) which in turn is critical to break down the three BCAA amino acids leucine, isoleucine and valine.[82] As a result of the genetic mutation, the enzyme complex is either missing or defective, and this in turn leads to the toxic build-up of the three BCAA amino acids and their by-products.[83] High levels of these substances are toxic, causing damage to skeletal muscle and the brain.[84] There are several forms of MSUD. The most common is the classic or infantile form. Clinical features of the classic form of MSUD start in the neonatal period and include poor feeding, irritability, extra sleepiness, and muscle spasms. Left untreated, respiratory failure can occur. Symptoms of other forms of MSUD may manifest only in adolescence or adulthood.[85]
AAV gene therapy	Restore function by delivering vector expressing gigaxonin cDNA.	Restore function by delivering micro ribonucleic acid (miRNA) vector construct to suppress activity of SOD1 gene to slow or reverse progression.	Restore function by delivering vector expressing AAT cDNA.	Restore function by delivering vector expressing BCKDHA, BCKDHB or DBT cDNA.
Biomarker to detect/measure proof of concept/activity	Neuropathology such as neurofilament levels/IF structure. The pathological hallmark of GAN is a variable number of giant axons filled with neurofilament in the nerve biopsy associated with axonal loss and demyelination.[86]	Silencing of SOD-1 as measured by reduction in protein levels.	The gene therapy product itself, AAT protein.	Reduction of BCAAs in blood and urine.
Assay for biomarker	Nerve biopsies analyzed for neuropathology.	Biopsy.	AAT is produced mainly in the liver, reaching the lung by diffusion from the circulation,[87] measure in plasma.	Measure in plasma and urine.
Other objective markers to measure as totality of evidence	The gene therapy product itself, gigaxonin protein and/or CSF for inflammatory markers.	Preservation of neuromuscular junction, number of axons and nerves.	Inflammatory markers.	Levels of leucine, isoleucine and valine.

Appendix

FDA has provided the following definitions and explanations to clarify the qualifying criteria described above for accelerated approval. (Brief descriptions are included here however, more fulsome explanations and examples are also included in FDA's 2014 Guidance on Expedited Programs for Serious Conditions.)

Term(s)	Definition/Explanation
Serious Disease or Condition[88]	For the purposes of the accelerated approval program, FDA has clarified it applies this definition in interpreting serious disease or condition[89]: a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.[90]
Life-Threatening Disease or Condition	For the purposes of accelerated approval, FDA applies the same definition of life-threatening disease or condition as set forth at 21 CFR 312.81(a)[91], namely: "(1) Diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted; and (2) Diseases or conditions with potentially fatal outcomes, where the end point of clinical trial analysis is survival."
Surrogate Endpoint	"For purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure, that is thought to predict clinical benefit, but is not itself a measure of clinical benefit."[92]
Clinical Benefit	"A clinical benefit is a positive therapeutic effect that is clinically meaningful in the context of a given disease. The clinical benefit must be weighed against a treatment's risks to determine whether there is an overall benefit for patients (i.e., a positive benefit-risk profile)."[93]
Clinical Endpoint	"A clinical endpoint is a characteristic or variable that directly measures a therapeutic effect of a drug––an effect on how a patient feels (e.g., symptom relief), functions (e.g., improved mobility), or survives."[94]
Intermediate Clinical Endpoint	"For purposes of accelerated approval, an intermediate clinical endpoint is a measurement of a therapeutic effect that can be measured earlier than an effect on IMM [(irreversible morbidity or mortality)] and is considered reasonably likely to predict the drug's effect on IMM or other clinical benefit."[95]
Available Therapy or Treatment	"FDA generally considers *available therapy* as a therapy that: • Is approved or licensed in the United States for the same indication being considered for the new drug and • Is relevant to current U.S. standard of care (SOC) for the indication"[96] Importantly, a "drug would not be considered available therapy if the drug is granted accelerated approval based on a surrogate endpoint or an intermediate clinical endpoint and clinical benefit has not been verified by postapproval studies."[97]

[1] This white paper was drafted by co-founding members REGENXBIO and Solid Biosciences.
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[10] For the purposes of this document, unless otherwise specified, all references to drugs or drug products include both human drugs and human biological drug products regulated by the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA).
[11] FDA Draft Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, at 2. December 2019. Available at: https://www.fda.gov/media/133660/download.
[12] 21 U.S.C. § 356(c)(1)(A); 21 CFR 314.510 and 21 CFR 601.41.
[13] FDA Guidance for Industry: Expedited Programs for Serious Conditions –Drugs and Biologics, at 2. May 2014. Available at: https://www.fda.gov/media/86377/download.
[14] FDA Draft Guidance for Industry: Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, at 2. December 2019. Available at: https://www.fda.gov/media/133660/download. See 21 U.S.C. § 356(c)(1)(A); 21 CFR 314.510 and 21 CFR 601.41; and Food and Drug Administration, Final Rule, New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval (57 FR 58942, December 11, 1992).
[15] 21 U.S.C. § 356(c)(1)(A).
[16] 21 CFR 314.500 and 601.40. FDA Guidance for Industry: Expedited Programs for Serious Conditions –Drugs and Biologics, at 16. May 2014. Available at: https://www.fda.gov/media/86377/download.
[17] Food and Drug Administration, Final Rule, New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval (57 FR 58942, December 11, 1992) at 58943.
[18] 21 CFR 312.80.
[19] First proposed in April of 1992 (published in the Federal Register on April 15, 1992 at 57 FR 13234), the final accelerated approval regulations (located at 21 CFR part 314, subpart H and 21 CFR part 601, subpart E) were issued in December of 1992 (published in the Federal Register on December 11, 1992 at 57 FR 58942) and went into effect in January of 1993.

[20] Specifically, section 506(c) of the Federal Food, Drug, and Cosmetic Act (codified at 21 U.S.C. § 356(c)) was amended by Congress through section 901 of the Food and Drug Administration Safety and Innovation Act (FDASIA) (Public Law 112-144, 2012).
[21] Food and Drug Administration, Final Rule, New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval (57 FR 58942, December 11, 1992) at 58944.
[22] FDA Draft Guidance for Industry: Rare Diseases: Common Issues in Drug Development, at 15. January 2019. Available at: https://www.fda.gov/media/119757/download.
[23] *Id.* at 15.
[24] *Id.* at 15.
[25] FDA Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products. January 2020. Available at: https://www.fda.gov/media/113768/download.
[26] *Id.* at 1.
[27] *Id.* at 26.
[28] FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics, at 19. May 2014. Available at: https://www.fda.gov/media/86377/download. See also, Food and Drug Administration, Final Rule, New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval (57 FR 58942, December 11, 1992) at 58944 where FDA asserted that approval under the accelerated approval pathway requires "that the effect shown be, in the judgment of the agency, clinically meaningful, and of such importance as to outweigh the risks of treatment. This judgment does not represent either a 'lower standard' or one inconsistent with [the Food, Drug, and Cosmetic Act], but rather an assessment about whether different types of data show that the same statutory standard has been met."
[2929] Food and Drug Administration, Final Rule, New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval (57 FR 58942, December 11, 1992) at 58942, citing 21 CFR 314.510, 314.520, 601.41, and 601.42.
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[34] 21 CFR 314.510 and 21 CFR 601.41; Food and Drug Administration, Final Rule, New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval (57 FR 58942, December 11, 1992) at 58942.
[35] Food and Drug Administration, Final Rule, New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval (57 FR 58942, December 11, 1992) at 58942, 58948.
[36] 21 U.S.C. § 356(c)(3); 21 CFR 314.530 and 21 CFR 601.43.
[37] 21 U.S.C. § 356(c)(3); 21 CFR 314.530 and 21 CFR 601.43.
[38] 21 CFR 314.150(d) and 601.5(a). The 2014 FDA Guidance for Industry: Expedited Programs for Serious Conditions –Drugs and Biologics explicitly notes "An applicant may also request the Agency to withdraw approval of an application approved under accelerated approval" citing 21 CFR 314.150(d) and 601.5(a). FDA Guidance for Industry: Expedited Programs for Serious Conditions –Drugs and Biologics, at 24. May 2014. Available at: https://www.fda.gov/media/86377/download.
[39] 21 U.S.C. § 356(g)(2).
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[42] Food and Drug Administration, Final Rule, New Drug, Antibiotic, and Biological Drug Product Regulations; Accelerated Approval (57 FR 58942, December 11, 1992) at 58942; FDA Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics, at 15-16. May 2014. Available at: https://www.fda.gov/media/86377/download; Beaver JA, Pazdur R. "Dangling" accelerated approvals in oncology. N Engl J Med. 2021 May 6;384(18)e68. doi: 10.1056/NEJMp2104846. PMID: 33882220. Available at https://www.nejm.org/doi/10.1056/NEJMp2104846; FDA web page on Development & Approval Process: Drugs, available at https://www.fda.gov/drugs/development-approval-process-drugs.
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