Promising Genetic Engineering Therapies for Dravet Syndrome

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Dravet syndrome (DS) is a genetic disorder that is a form of early-onset epilepsy. DS is most commonly caused by a mutation in the SCN1A gene which results in haploinsufficiency in the Nav1.1 sodium channel. DS occurs in roughly 0.0064% of the population. Because of its relatively low prevalence rates, few long-term treatments have been explored, primarily due to clinical trial sample size and lack of funding. Current treatments include the ketogenic diet (KD), common anti-epilepsy medication (though most DS patients are resistant to their effects), vagus nerve stimulation (VNS) and deep brain stimulation (DBS). While researchers are exploring genetic engineering options for DS, all but Encoded Therapeutics' investigational new drug (IND), ETX-101 and Stoke Therapeutics' IND, STK-001 are in the early stages of preclinical development. ETX-101 delivers a regulatory gene, called an engineered transcription factor (eTF), to GABAergic inhibitory interneurons in order to increase expression of the SCN1A gene. STK-001 prevents non-productive exon inclusion of SCN1A and increases the synthesis of productive mRNA by delivering antisense oligonucleotides (ASOs) into the cells. These gene therapies target the root cause of DS but stop the progression of the disease. ETX-101 and STK-001 could revolutionize the treatment of DS; however, these drugs will not reverse the damage that the disease has already caused. Both gene therapies will likely be extremely expensive and will not be available for several years. As we look at the enormous potential of these therapies, it is important to keep their limitations in mind.

Keywords: Dravet syndrome (DS); ETX-101; STK-001; SCN1A; Nav1.1; Severe Myoclonic Epilepsy of Infancy (SMEI)

Introduction

DS, otherwise known as Severe Myoclonic Epilepsy of Infancy (SMEI), is a rare form of early-onset genetic epilepsy[1]. DS affects 0.0064% of the population, with prevalence rates of 1 in 15,000 to 1 in 40,000 people[1]. Over 80% of DS cases are caused by a de-novo mutation (most commonly a truncating or missense mutation and less commonly an intronic splice site change, duplication, or whole-exon deletion) in one allele of the SCN1A gene located on chromosome 2q24[1,2]. SCN1A encodes for the sodium voltage-gated channel alpha subunit 1, called Nav1.1, which transports sodium ions in and out of the neurons, creating an electrical current and thereby allowing the brain to function[3]. Mutations in the SCN1A gene result in haploinsufficiency, meaning that only 50% of healthy Nav1.1 sodium channels are expressed[4]. While DS may also be caused by de-novo variants in the SCN1B, GABRG2, GABRA1, STXBP1, HCN1, CHD2, or PCDH19 genes, 5% of cases are inherited in an autosomal dominant fashion[2].

There are many symptoms associated with DS, the most common being long-lasting seizures (convulsive, myoclonic, obtundation status, absence, tonic and focal seizures)[1]. Patients with DS also frequently experience motor system dysfunctions, cognitive impairments and psychiatric disturbances[1]. The first seizure episode, most likely focal or tonic, usually occurs between 5 to 8 months of age[1]. DS evolves with age, beginning with seizures during infancy, which evolve into neurodevelopmental delays in childhood and then severe neurological disabilities throughout adulthood[1]. In addition, patients with DS are subject to increased mortality[1,2]. The most common deaths are caused by sudden unexpected death in epilepsy (SUDEP) and status epilepticus[1]. Even though 85% of children with DS survive into adulthood, 10%-20% of people affected by DS die within the first 10 years of life[1]. However, the misdiagnosis of DS is common because it resembles many epileptic diseases and, in order to receive an accurate diagnosis of DS, one must be clinically diagnosed through imaging, electroencephalogram (EGG) or genetic testing.

Due to the rarity of the disorder and the scarcity of widespread funding support, DS research has been considered less of a pressing issue than some other diseases that affect a greater percentage of the population. The lack of research has resulted in few treatment options for the disorder. A KD, which is a high fat, low carbohydrate, and sufficient protein diet, is often used as a first course of treatment for seizures caused by DS[1]. Even though studies have shown that a KD reduced seizures by 50% in 40% of cases in the first 3 months, it is by no means a cure for DS and a limited treatment option for many[1,5]. The reason a KD is effective at reducing seizures is still largely unknown; however, it is based on the hypothesis that a KD increases the metabolism

of fats which increases acetoacetate levels in the brain (the main molecule that reduces seizures in mice models)[1]. Some antiepileptic drugs such as valproate, topiramate, stiripentol and fenfluramine have proved effective at reducing seizures in patients with DS even though DS patients are resistant to most antiepileptic drugs[1,2]. These drugs, however, cost thousands of dollars annually and do not provide a cure for DS. Surgical therapies, including DBS and VNS, are often used as last resort treatments for DS[1,6]. In order to perform DBS small holes are drilled into the skull and electrodes are implanted into brain tissue to decrease seizure frequency[6]. For VNS a stimulator is placed into the neck to inhibit excess electrical activity[1]. These surgical therapy treatments do provide some seizure relief for DS but they are not the permanent solution to the disorder, which is why in recent years scientists have begun exploring gene therapies as cures for DS. Gene editing technologies have great potential to be used on DS because following the modification of the one allele on the SCN1A gene the gene would restore normal expression levels of wild type (WT) Nav1.1, completely halting seizures and the progression of the disease.

Advancement in Genetic Engineering for DS

Researchers have made advancements on a variety of genetic engineering-based treatments for DS, however, most of them are still in the preclinical development phases and are not yet being tested on humans. In light of this, only treatments that are in the later phases of their clinical trials will be discussed. The preclinical progress being made on Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) therapy and transfer ribonucleic acid (tRNA) when used as a therapy for DS will be surveyed briefly.

There are many challenges when it comes to the eventual use of CRISPR for DS. The main obstacle is that the large size of the SCN1A gene exceeds the packaging capacity of the adeno-associated virus (AAV), which is used as a gene transfer tool[3,7]. Other difficulties may arise with the use of CRISPR because of the extremely unstable nature of the SCN1A gene and the broad spectrum of mutations across the entire genome within the patient population[8]. However, scientists have begun developing a dead version of the CRISPR associated protein 9 (Cas9), dCas9, which loses its ability to cleave DNA and functions by utilizing a single guide RNA (sgRNA) to direct it to a site on the genome[3]. sgRNA and dCas9 form a ribonucleoprotein, which can then bind to specific molecules in order to increase gene expression[9]. It is hopeful that by targeting dCas9 to specific regulatory regions of the SCN1A gene it could improve neuronal communication and limit seizure activity[3]. When this technology will become available to the public is unclear, as the clinical trials are yet to be approved.

Similarly to dCas9 scientists hope to use tRNA to increase SCN1A expression using 3 different strategies[3]. Approach 1 targets nonsense mutations which tell the DNA code to prematurely stop making the Nav1.1 protein[3]. The tRNA will ignore these stop signals allowing the Nav1.1 to be properly translated[3]. Approach 2 uses tRNA to help stabilize the SCN1A mRNA so that it can be used to generate more copies of Nav1.1[3,4]. Approach 3 uses an mRNA-amplifier to increase expression of the mRNA for the WT Nav1.1[3]. The first two approaches require only a one-time treatment as they will be delivered in AAV vectors to cells in the brain[3]. All preclinical experiments have been completed but these therapies have still not been approved for clinical trials on humans[3].

This article will focus on the recent developments in the two genetic therapies for DS that could potentially be widely available for humans in the near future. EXT-101 and STK-001.

ETX-101

In recent years Encoded Therapeutics' IND, ETX101, has received Food and Drug Administration (FDA) approval to begin clinical trials for Phase 1/2 of the 2-part dose study in the United States and Australia[10]. ETX101 was also granted Orphan Drug Designation (ODD) and Rare Pediatric Disease Designation (RPDD) by the FDA in July of 2020 for the treatment of DS[10]. The ODD and RPDD programs provide financial incentive for the drug development of rare diseases[11]. These programs exist since the treatments for rare diseases are often discontinued because of the lack of financial motivation[11].

As previously discussed, the most direct approach to treat DS would be to deliver a replacement SCN1A WT gene for integration into the genome[4]. However, since the gene, which consists of 6030 nucleotide base pairs, is too large it cannot be delivered inside of an AAV vector[4]. To work around this, ETX101 evades the need to deliver the intact gene to increase transcription of SCN1A for expression of Nav1.1 sodium channel[4]. ETX101 is envisioned to be a one-time treatment of a single dose that will be delivered to the central nervous system (CNS) via an intracerebroventricular (ICV) infusion[4]. The hope is that ETX101 will be a disease modifying treatment for both seizure and non-seizure related symptoms[10].

ETX-101 delivers DNA carrying the code for a regulatory gene, called an eTF, to the neurons, inside of the empty shell of the AAV vector[4,12]. The AAV vector is able to transport the DNA because it is smaller than the SCN1A gene[4,12]. Once inside of the neuron, the DNA carrying the eTF will exist in a circular strand (called an episome), completely separate from the patient's DNA[4,12]. The eTF binds to the promoter region ahead of the SCN1A gene, upregulating the transcription of the WT Nav1.1 gene, therefore increasing the expression of healthy sodium channels[4,12]. ETX101 targets a subset of cells, called GABAergic inhibitory interneurons, which, when functioning properly, help limit electrical activity in the brain[4,13]. It is delivered to the CNS through ICV in a single dose, using

AAV9 which carries the genetic information for the eTF transcription factor that increases SCN1A expression to neurons. ETX-101 is delivered through ICV so that it can target the CNS more effectively and successfully[4]. The GABAergic inhibitory interneurons are particularly impacted by SCN1A haploinsufficiency, leading to increased electrical activity in the brain and seizures[4,13]. ETX-101 counters this haploinsufficiency by increasing the expression of SCN1A. The vector in this therapy contains a genetic sequence for the GAD1 gene, which is expressed only in GABAergic interneurons; because of this, the therapy is only delivered to that specific subset of neurons[14].

Before clinical trials are approved for any drug, the drug must first go through preclinical testing. Preclinical studies for ETX101 were concluded and published in 2022[14]. Encoded Therapeutics used the scn1a+/- mouse model and the Scn1a+/R1407X mouse model to test the safety and efficacy of their IND[14]. They compared their model to models that represented the effectiveness of antiseizure medications used for DS such as clobazam, topiramate and stiripentol[14]. The mouse models received injections of ETX101 through an ICV infusion[14]. The results of the preclinical testing were an increase in SCN1A gene activity and significant increase in Nav1.1 expression in GABAergic inhibitory interneurons[14]. In addition, the mice showed a 68% reduction in the average number of daily seizures and a reduction in the severity of the seizures. In the other 32% seizures did not decrease[14]. The mice also experienced less temperature induced seizures, an extremely common seizure trigger in DS[1,14]. This reduction in seizures confirms the relationship between Nav1.1 expression with clinical outcomes, and the correlation between upregulation with seizure reduction. Most importantly, 100% of mouse models survived 90 days post treatment (in comparison to the 50% survival of placebo treatment group) and long-term survival benefit was sustained for around 470 days post treatment[14]. Though promising results, mouse models fail to show a comparable representation of other classical DS symptoms, such as behavioral issues or milestone delay. Still due to the success in the preclinical trials, EXT101 attracted attention and gained approval to begin clinical trials on humans. ETX101 has since received $135 Million in Series D financing to support the first clinical trials[15]. The funds will go towards a natural history study to further understand the progression of DS, in addition to financing the first-in-human trials[15].

The primary aim of the ETX101 clinical trial will be to assess the safety, tolerability, preliminary efficacy and dosage quantity in patients with DS[4]. In the US Phase 1/2 is called ENDEAVOR, whereas in Australia Phase 1/2 is called WAYFINDER[4,16]. Part 1 of ENDEAVOR is expected to begin within the first half of 2024[17]. There will be an estimated total of 22 participants in ENDEAVOR between the ages of 6 months to 36 months of age[17,18]. Part 1 of ENDEAVOR includes an open-label, dose escalation study where 2 different dose levels of ETX101 are administered to 4 patients[17,18]. Part 2 consists of a randomized, double-blind, sham delayed-treatment control, dose selection study that will be given to 18 patients divided into 3 cohorts[17]. The success of ENDEAVOR will be based on many factors such as: participants experiencing treatment related adverse effects (AEs), serious adverse events, related AEs, AEs with a severity grade ≥ 3 and AEs resulting in the discontinuation of the study. In addition to the measurement of AEs with a fatal outcome, the percentage of change in monthly countable seizure frequency, and the proportion of patients with $\geq 90\%$ reduction in monthly countable seizures[18]. The primary completion of ENDEAVOR is estimated for the beginning of 2027 and the study completion is estimated for early in 2031[18]. WAYFINDER also is expected to begin within the first half of 2024[18]. There will be an estimated enrollment of 4 participants between the ages of 36 to ¡84 months (3 to ¡7 years) of age[17,19]. Part 1 will follow an open label, dose-escalation design where Cohort X will consist of 2 participants and will evaluate ETX101 dose level 1 while Cohort Y will consist of the other 2 participants and will evaluate ETX101 dose level 2[19]. The plan for Part 2 of WAYFINDER is still unspecified. The success of WAYFINDER will be based on the same outcomes as those of ENDEAVOR. The primary completion and the study completion of WAYFINDER are both estimated for the end of 2029[19]. Phase 2 of both ENDEAVOR and WAYFINDER will be planned following the demonstration of safety of Phase 1[4].

STK-001

Stoke Therapeutics has recently developed a new investigational medicine, called STK-001, for the treatment of DS[20]. Thus far, STK-001 has received FDA approval and has been granted ODD and RPDD by the FDA[21]. STK-001 is part of Stoke Therapeutics' Targeted Augmentation of Nuclear Gene Output (TANGO) technology which targets diseases that cause haploinsufficiency and belongs to a class of therapeutics called ASOs[22]. ASOs are small pieces of genetic material that have the ability to interact with RNA[22]. They play a key role in allowing this therapy to function. STK-001 is intended to be a multiple dose gene therapy[22].

Similar to ETX101, the aim of STK-001 is to upregulate expression of Nav1.1 protein produced by the WT version of the SCN1A gene[22]. As many already know, DNA is copied into pre-messenger RNA (pre-mRNA) which is made up of exons and introns. Exons carry the code to create a protein; whereas, introns do not[20]. Because introns do not carry that code, they are removed during the splicing process so as to produce mRNA, which is then translated into protein[20]. However, at times, exons that contain premature stop codons are included in the mRNA[20]. This leads to a non-productive mRNA that is then degraded by the cell and does not become protein[20]. Only productive mRNA from functional copies of the gene will result in the creation of

protein[20]. In normal cells, unaffected by DS, both productive and non-productive mRNA is produced from the SCN1A gene[20]. STK-001 is delivered via intrathecal (IT) injections directly into the spinal canal which is surrounded by cerebrospinal fluid (CSF)[23]. It has been tested with both IT injections and ICV, but ultimately IT injections were chosen over ICV[24]. STK-001 functions because the ASOs bind to the SCN1A pre-mRNA and prevent non-productive exon inclusion[20]. STK-001 reduces the synthesis of non-productive mRNA, and therefore increases the synthesis of the productive mRNA[20]. The SCN1A mRNA is then translated, leading to significantly more Nav1.1 sodium channel[20]. Scientists hope that STK-001 will restore Nav1.1 protein levels to near normal in patients suffering from DS[20].

Preclinical studies concluded and Stoke Therapeutics published the preclinical data in August of 2020[25]. STK-001 was tested on DS mouse models in order to evaluate the safety and success of the therapy[25,26]. The SCN1A+/- mouse model and the Scn1atm1Kea mouse model were used to test the therapy[8]. The DS mice were treated with a single dose of STK-001, 2 days postnatal. 97% of the mice survived until Day 90, in contrast to the 23% that were given the placebo treatment[26]. Overall, after receiving STK-001, the mice demonstrated an increase in SCN1A expression, an increase in SCN1A mRNA and Nav1.1 expression, decreased SUDEP, reductions in seizure frequency and significant improvements in survival[25,26]. This reduction in seizures in STK-001 clinical trials confirms the relationship between Nav1.1 expression with the disease pathology. It also demonstrates the correlation between upregulation with seizure reduction. Though information on seizure frequency and ataxia can be observed in mouse models, these models provide little input on the therapies effects on other symptoms, such as milestone delays and behavioral issues. Upcoming clinical trials will shed light on this, as well as the role of Nav1.1 expression in these processes. These extremely promising preclinical results also lead to STK-001's approval for clinical trials on humans[26].

There are currently 4 studies of STK-001 throughout the US and the UK[27]. These participants received at least 1 dose of STK-001 between 10mg to 70mg[26]. The US studies are called MONARCH and SWALLOWTAIL[27,28]. MONARCH has been completed and was a Phase1/2a open-label study of single and multiple ascending doses of STK-001 in patients with DS, ages 2 to 18 years[27–29]. The aim of this study was to assess the tolerability and safety of STK-001[27]. In addition, MONARCH hoped to determine the exposure in CSF, pharmacokinetics in plasma and percentage change in convulsive seizure frequency[28]. Participants received 30mg to 45mg doses of STK-001 every 4 months[27]. This study was measured based on a variety of outcomes, such as: safety and tolerability of STK-001, pharmacokinetic parameters, prevalence of STK-001 in CSF, measurement of seizure frequency, change in caregiver global impression of change scale, change in clinician-assessed global impression of change scale and measurement of quality of life[29]. The MONARCH study began in 2020, with the primary completion in December of 2023 and the study completion in April of 2024[29]. Following the completion of MONARCH, patients, if eligible, had the option to continue their treatment in SWALLOWTAIL[28]. SWALLOWTAIL is an open-label extension (OLE) study, consisting of 60 participants, designed to evaluate the long-term tolerability of repeated doses of STK-001 and the long-term effects of STK-001 on seizure frequency, behavior, cognition and quality of life[28,30]. The effectiveness of SWALLOWTAIL is primarily measured based on the safety of multiple doses of STK-001[30]. The SWALLOWTAIL study began in 2021 and is currently ongoing. The estimated date of completion is set for the beginning of 2027[30].

The studies of STK-001 in the UK are called ADMIRAL and LONGWING[27]. ADMIRAL is extremely similar to MONARCH, the US study, in regards to the structure of the study and the aim of the study. The only difference is that ADMIRAL accepts participants from 2 to ¡18 years of age[27]. The total number of participants between the ADMIRAL and the MONARCH trials was 81[27]. Similar to MONARCH, ADMIRAL has been completed[27]. After the completion of ADMIRAL, eligible patients had the option to continue their treatment in LONGWING[27,31]. The setup of the LONGWING study is identical to SWALLOWTAIL, the study being conducted in the US[27]. The LONGWING study is ongoing. It was initiated in October of 2021 and the study completion is estimated for November of 2027[31].

Upon the completion of the MONARCH/ADMIRAL studies and the analysis of the interim results from SWALLOWTAIL/LONGWING, Stoke Therapeutics released their initial findings on STK-001. STK-001 was generally well-tolerated in both the Phase 1/2a and the OLEs[27,28]. In the Phase 1/2a studies, patients who received an initial dose of 70mg of STK-001 experienced a 43% reduction in convulsive seizure frequency 3 months post treatment and 57% reduction in seizure frequency at 6 months post treatment[27,28]. Patients who were given 2-3 doses of STK-001 at 70mg experienced a 85% convulsive seizure reduction at 3 months post treatment and a 74% seizure reduction at 6 months post treatment[27,28]. People who took part in the SWALLOWTAIL study underwent a sustained reduction in convulsive seizure frequency and improvements in measures of cognition, behavior and overall condition of the patients[27,28]. The data for the LONGWING study is currently unavailable. Based on the data collected from the Phase 1/2a studies and the OLEs, scientists determined that the ideal dosing regimen consists of 2-3 loading doses of 70mg of STK-001, followed by maintenance dosing of 45mg[21]. In March of 2024 the FDA approved this dosing of STK-001 for the treatment of DS[27].

Overall, the results of STK-001 have been extremely promising, but the risks also must be considered. In Phase 1/2a, 30% of patients experienced a treatment emergent adverse event (TEAE)[28]. The most common TEAEs were elevations in CSF

protein levels and procedural vomiting[28]. In addition, 22% of patients experienced a treatment emergent serious adverse event (TESAE)[28]. However, all but 1 TESAEs were found to be unrelated to STK-001[28]. After the conclusion of the Phase 1/2a studies 92% of patients entered the OLE studies and 84% remained in the OLE studies[28]. The extremely high rates of re-enrollment despite the adverse events demonstrates the success of the drug and the benefit of long-term seizure relief. Participants in the OLEs did experience a greater incidence of CSF protein elevation[28]. In total, 1 participant decided to leave the trials because of elevated CSF protein levels but 6 months after withdrawing from the trials, the levels had resolved[27].

In the future, there will be a global program for Phase 3 assessment of STK-001 before it becomes available to the public[27]. Phase 3 will be a controlled study with an anticipated design of multiple loading doses of STK-001 of 70mg then maintenance doses of 45mg[27]. Phase 3 is currently in the process of development in the US, Europe and Japan[27]. If the Phase 3 trial mimics the positive results of the Phase 1 and Phase 2 trails, STK-001 is on track to become the first gene specific disease modifying technology[28].

Concerns/Limitations

The findings of the clinical trials of ETX-101 and STK-001 are significant because there is no current gene therapy clinically approved for DS by the FDA. The preliminary results of these trials show promise for both new drugs in comparison to the current available treatments. For the most part, ETX-101 and STK-001 are still in the early stages of clinical development. Although significant progress has been made, more research is required to determine the safety of these drugs before they receive FDA approval.

As the gene therapies distinctly target neurons, the risk of off-target effects in other cell types are low. The gene therapies have attempted to address the SCN1A mutation as it is the most common mutation to cause DS by a large margin. However, the clinical trials of both ETX-101 and STK-001 are still in extremely early stages. Therefore, there is little information about the long-term effects of the gene therapies or potential off-target effects. It is unlikely patients will need additional doses of the therapy of the gene therapies as GABAergic inhibitory interneurons do not divide. The risks and long-term safety considerations have yet to be reported.

Because of the research and clinical trials that have yet to take place, it is likely that it will be many more years until ETX-101 and STK-001 are put on the market and available for general use. This timeline will provide a challenge for people who require an immediate effective treatment for DS. The aim of both ETX-101 and STK-001 to halt the rapid progression of the disease, rather than reverse its effects. ETX-101 targets GABAergic inhibitory interneurons with the goal of increasing endogenous SCN1A expression. DS symptoms should decrease once the SCN1A expression is restored, however increased expression of SCN1A will not repair previous neurological system trauma, if present. STK-001 also increases the expression of SCN1A, but by delivering ASOs to the cells. Therefore, since damage cannot be reversed simply by increasing the expression of SCN1A in the future, neither gene therapy can reverse damage that has already occurred. Because of this it is likely that these therapies will benefit the future generation of DS children and teenagers, not the current generation.

In addition, cost is another possible limitation of ETX-101 and STK-001. Right now, there is no released information predicting the cost of either therapy. Despite this, those hoping to use these medications in the future should be aware of the high cost of gene therapies, as the price of ETX-101 and STK-001 will likely be similar. Non-CRISPR gene therapies range in cost from $450,000 to $2 million per treatment, excluding Hemgenix (used to treat to adults with severe or moderately severe hemophilia B) which costs around $3.5 million and Zolgensma (used to treat spinal muscular atrophy) which costs around $2.1 million for one-time treatments[32–34]. CRISPR gene therapies cost about $2.2 million per treatment [N]. The extremely high price of these gene editing technologies makes them only available to society's most advantaged, excluding the vast majority of the population. As gene therapies become more readily available in the coming years, there is a chance prices will decrease, though this is not a certainty. Furthermore, as previously mentioned, both ETX-101 and STK-001 target the root cause of DS, signifying that the goal of these therapies is to stop the progression of the disease. Nevertheless, stopping the advancement of DS does not mean that these medications will reverse the cognitive decline caused by the frequent seizures that DS patients experience. In all the clinical trials for ETX-101 and STK-001 the success of the therapy is primarily determined by the safety of the medication and the percentage reduction in seizures[18,29,30]. The secondary measures of success are the cognitive and behavioral improvements of the participants[18,29,30]. More research must be dedicated to reversing the cognitive decline caused by DS and not only preventing the physical symptoms. Even though gene therapy will certainly be a more effective treatment for DS than any of the previous treatments, it might not cure the long-term effect of this disease.

As ETX-101 and STK-001 both target SCN1A expression, and are not able to reverse damage that has already occurred, the patient populations for both gene therapies will likely be very similar. Although they utilize different delivery systems and treatment regimes, at the preclinical level ETX-101 and STK-001 treat DS with roughly the same efficiency. After completion of clinical trials, ETX-101 and STK-001 can be adequately compared and utilized to ensure the best outcome for the patient. The patient populations of both will most likely consider the cost of gene therapy, how it is administered, and treatment regime.

ETX-101	STK-001
Delivers an eTF to GABAergic inhibitory interneurons	Delivers ASOs into cells
Increases expression of SCN1A	Prevents non-productive exon inclusion of SCN1A
Delivered via ICV	Increases synthesis of productive mRNA
Single dose treatment	Delivered via IT injections
	Multiple dose treatment

Table 1 Comparison between ETX-101 and STK-001 therapies

The biggest consideration in picking between these two gene therapies will presumably be the dosing regime.

Conclusion

DS, a severe form of pediatric epilepsy affecting 0.0064% of the population, currently does not have a cure [1]. While there are many therapies that are still in the early phases of development, ETX-101 created by Encoded Therapeutics and STK-001 by Stoke Therapeutics are the furthest along. ETX-101 selectively upregulates the expression of the SCN1A gene in GABAergic inhibitory interneurons by delivering a regulatory gene called an eTF[4,12]. STK-001 delivers ASOs into the cells in order to prevent non-productive exon inclusion and to increase the synthesis of productive mRNA[20]. The aim of these treatments is to decrease the frequency of seizures and halt the progression of the disease, not reverse the damage that has already been done to the mind and body of someone affected by DS. It is hopeful that ETX-101 and STK-001 will be available on the market within the next decade, though at an extremely high anticipated price. ETX-101 and STK-001 are not cures for DS; however, they are revolutionary advancements from the moderately ineffective treatments currently available for DS. These therapies hold enormous potential, not only for DS but also for the eventual treatment of other genetic diseases.

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Abbreviation	Full Name
DS	Dravet Syndrome
SMEI	Severe Myoclonic Epilepsy of Infancy
AAV9	Adeno-associated virus 9
IND	Investigational new drug
AEs	Adverse effects
KD	Ketogenic diet
OLE	Open-label extension
TESAE	Treatment emergent serious adverse event
ICV	Intracerebroventricular
IT	Intrathecal
CNS	Central nervous system
CSF	Cerebrospinal fluid
FDA	Food and Drug Administration
ASOs	Antisense oligonucleotides
TANGO	Targeted Augmentation of Nuclear Gene Output
eTF	Engineered transcription factor
ODD	Orphan Drug Designation
RPDD	Rare Pediatric Disease Designation
sgRNA	Single guide RNA
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
tRNA	Transfer ribonucleic acid
SUDEP	Sudden unexpected death in epilepsy
EGG	Electroencephalogram
VNS	Vagus nerve stimulation
DBS	Deep brain stimulation
WT	Wild type

Table 2 List of abbreviations and their full forms

References

1 A. Anwar, S. Saleem, U. Patel, K. Arumaithurai and P. Malik, *Dravet Syndrome*, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6713249/.

2 E. Chilcott, J. Díaz, C. Bertram, M. Berti and R. Karda, *Genetic therapeutic advancements for Dravet Syndrome*, https://doi.org/10.1016/j.yebeh.2022.108741.

3 M. Meskis, *Gene therapy for Dravet syndrome - Dravet Syndrome Foundation. Dravet Syndrome Foundation*, https://dravetfoundation.org/dsf-funded-research/gene-therapy-for-dravet-syndrome/.

4 V. Hood and PhD, *Encoded Therapeutics begins enrolling first in-human trials for ETX101, a potential one-time*, https://dravetfoundation.org/encoded-therapeutics-begins-enrolling-first-in-human-trials-for-etx101-a-potential-one-time-disease-modifying-gene-regulation-therapy-for-scn1a-dravet-syndrome/.

5 E. Neal, H. Chaffe, R. Schwartz, M. Lawson, N. Edwards, G. Fitzsimmons,

A. Whitney and J. Cross, *The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial*, https://doi.org/10.1016/s1474-4422(08)70092-9.

6 *Deep brain stimulation - Mayo Clinic*, https://www.mayoclinic.org/tests-procedures/deep-brain-stimulation/about/pac-20384562.

7 W. Yu and Z. Wu, *Use of AAV Vectors for CRISPR-Mediated In Vivo Genome Editing in the Retina*, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6730636/.

8 E. Chilcott, J. Díaz, C. Bertram, M. Berti and R. Karda, *Genetic therapeutic advancements for Dravet Syndrome*, https://doi.org/10.1016/j.yebeh.2022.108741.

9 K. Ishikawa, S. Soejima, F. Masuda and S. Saitoh, *Implementation of dCas9-mediated CRISPRi in the fission yeast Schizosaccharomyces pombe*, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8137136/#:~:text=dCas9.

10 I. Mph, *FDA clears IND for gene therapy candidate ETX101 in Dravet syndrome*, https://www.neurologylive.com/view/fda-clears-ind-gene-therapy-candidate-etx101-dravet-syndrome.

11 *Rare Diseases at FDA*, https://www.fda.gov/patients/rare-diseases-fda#:~:text=An.

12 *ETX101 for Dravet syndrome*, https://encoded.com/programs/etx101-for-dravet-syndrome/, n.d.). Encoded Therapeutics, Inc.

13 V. Hood and PhD, *Preclinical development of a gene therapy for Dravet syndrome - Dravet Syndrome Foundation. Dravet Syndrome Foundation*, https://dravetfoundation.org/preclinical-development-of-a-gene-therapy-for-dravet-syndrome/.

14 A. Tanenhaus, T. Stowe, A. Young, J. McLaughlin, R. Aeran, I. Lin, J. Li, R. Hosur, M. Chen, J. Leedy, T. Chou, S. Pillay, M. Vila, J. Kearney, M. Moorhead, A. Belle and S. Tagliatela, *Cell-Selective Adeno-Associated Virus-Mediated SCN1A gene regulation therapy rescues mortality and seizure phenotypes in a Dravet syndrome mouse model and is well tolerated in nonhuman primates*, https://doi.org/10.1089/hum.2022.037.

15 *Encoded Therapeutics announces $135 million Series D financing to support first clinical trials in SCN1A+ Dravet Syndrome and advance preclinical pipeline of gene therapies for debilitating neurological disorders*, https://encoded.com/press-releases/encoded-therapeutics-announces-135-million-series-d-financing-to-support-first-clinical-trials-in-scn1a-dravet-syndrome-and-advance-preclinical-pipeline-of-gene-therapies-for-debilitating-neurologic/, n.d.). Encoded Therapeutics, Inc.

16 K. Habet and M.D., *A variety of SCN1A-Targeted therapies show promise in treating Dravet syndrome*, https://www.rarediseaseadvisor.com/features/scn1a-targeted-therapies-show-promise-treatment-dravet-syndrome/.

17 N. Stansfield, *Encoded Therapeutics' Dravet Syndrome Gene therapy ETX101 cleared for separate clinical trials in the US and Australia*, https://www.cgtlive.com/view/encoded-therapeutics-dravet-syndrome-gene-therapy-etx101-cleared-separate-clinical-trials-us-australia.

18 ClinicalTrialsgov, https://clinicaltrials.gov/study/NCT05419492.

19 https://clinicaltrials.gov/study/NCT06112275?cond=Dravet, ClinicalTrials.gov. (n.d.-b).

20 S. Therapeutics, *TANGO - Stoke Therapeutics*, https://www.stoketherapeutics.com/scientific-platform/tango/.

21 *Stoke Therapeutics Announces Landmark New Data That Support the Potential for STK-001 to be the First Disease-Modifying Medicine for the Treatment of Patients with Dravet Syndrome - Stoke Therapeutics*, https://investor.stoketherapeutics.com/news-releases/news-release-details/stoke-therapeutics-announces-landmark-new-data-support-potential.

22 V. Hood and PhD, *Updates on STK-001: A Possible Disease-Modifying Therapy for Dravet Syndrome - Dravet Syndrome Foundation. Dravet Syndrome Foundation*, https://dravetfoundation.org/updates-on-stk-001-a-possible-disease-modifying-therapy-for-dravet-syndrome/.

23 L. Shapiro, *STK-001 led to reductions in seizures, trial data shows*, https://dravetsyndromenews.com/news/stk-001-reductions-seizures-trial-data-shows/#:~:text=STK.

24 L. Isom and K. Knupp, *Dravet Syndrome: Novel Approaches for the Most Common Genetic Epilepsy*, https://pmc.ncbi.nlm.nih.gov/articles/PMC8608987/.

25 Z. Han, C. Chen, A. Christiansen, S. Ji, Q. Lin, C. Anumonwo, C. Liu, S. Leiser, N. Meena, I. Aznarez, G. Liau and L. Isom, *Antisense oligonucleotides increase Scn1a expression and reduce seizures and SUDEP incidence in a mouse model of Dravet syndrome*.

26 *Stoke Therapeutics Announces Publication of Preclinical Data on STK-001 in the Journal Science Translational Medicine that Demonstrate Significant Improvements in Survival and Reductions in Seizure Frequency in a Dravet Syndrome Mouse Model*, https://investor.stoketherapeutics.com/news-releases/news-release-details/stoke-therapeutics-announces-publication-preclinical-data-stk, Stoke Therapeutics.

27 V. Hood and PhD, *Updates on STK-001: A Possible Disease-Modifying Therapy for Dravet Syndrome - Dravet Syndrome Foundation. Dravet Syndrome Foundation*, https://dravetfoundation.org/updates-on-stk-001-a-possible-disease-modifying-therapy-for-dravet-syndrome/.

28 *Stoke Therapeutics Announces Landmark New Data That Support the Potential for STK-001 to be the First Disease-Modifying Medicine for the Treatment of Patients with Dravet Syndrome - Stoke Therapeutics*, https://investor.stoketherapeutics.com/news-releases/news-release-details/stoke-therapeutics-announces-landmark-new-data-support-potential, n.d.-b). Stoke Therapeutics.

29 https://clinicaltrials.gov/study/NCT04442295?cond=Dravet, ClinicalTrials.gov. (n.d.-c).

30 https://clinicaltrials.gov/study/NCT04740476?cond=Dravet, ClinicalTrials.gov. (n.d.-d).

31 I.S.R.C.T.N., https://www.isrctn.com/ISRCTN12811235.

32 https://www.ema.europa.eu/en/medicines/human/EPAR/hemgenix#:~:text=Hemgenix, HemGenix — European Medicines Agency (EMA). (n.d.). European Medicines Agency (EMA).

33 A. Subica, *CRISPR in Public Health: The health equity Implications and Role of Community in Gene-Editing Research and Applications*, https://doi.org/10.2105/ajph.2023.307315.

34 https://www.ema.europa.eu/en/medicines/human/EPAR/zolgensma#:~:text=information, Zolgensma — European Medicines Agency (EMA). (n.d.). European Medicines Agency (EMA).

