Nusinersen: The Case for FDA Approval Now
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Families for Accelerated SMA Treatments—The FAST Movement

- We are an independent group of parents, individuals with SMA, and supporters organized in 2015 that believe clinical trial data released by Ionis Pharmaceuticals clearly shows there is an effective treatment for Spinal Muscular Atrophy (SMA) ready to save lives. This treatment is Nusinersen. We support continued research and clinical trials in SMA, but there are no longer compelling reasons to delay access to Nusinersen.

- We have a petition with more than 124,000 signatures as of December 19, 2015, calling on Congress and the FDA to expedite Nusinersen approval.

- We support the multiple research efforts investigating treatments and a SMA cure underway at universities and companies around the world. However, Nusinersen has completed the rigorous experimental and clinical trial process—Nusinersen is the first of future therapies. Because it is ready today for dying children, we call upon the FDA to open Nusinersen access to treat SMA, the #1 genetic killer of infants.

What is Spinal Muscular Atrophy (SMA)?

SMA is a rare genetic disease in which individuals are missing the primary gene that is responsible for creating a protein called Survival Motor Neuron (SMN). The primary gene is called SMN1 and, in humans, there is a back-up gene, called SMN2, but this gene has a defect that prevents it from producing fully-functional SMN protein. SMN protein is critical for the health and survival of nerve cells in the spinal cord responsible for neuromuscular growth and function. The lack of SMN causes skeletal muscles to progressively atrophy, leading to muscle death. The death of these muscles affects a person’s ability to move, swallow, and breathe. The amount of SMN a person produces determines the severity of their SMA disease. In the most severe form of SMA, Type 1, 50% of babies are not expected to live until their first birthday and 90% are not expected to live until their second birthday. SMA is the #1 genetic killer of children under 2 years old. For those who do survive with SMA Types 1, 2, 3, and 4, there are severe physical difficulties that they must face. Methods of modifying the back-up gene to allow it to create sufficient supplies of SMN to prevent motor neuron death are the focus of current research and clinical trials.

At this time, there are NO EXISTING TREATMENTS for SMA.

Every day two children are diagnosed with SMA.
Every day one child dies because of SMA.
Why should Nusinersen be available today?

“We are not blinded by hope in an experimental drug because it worked once or twice. We have supported this research and waited years for clinical trials to prove Nusinersen as safe and effective. The data shows that Nusinersen is working and in a disease that is progressive over time, that is a miracle. Now is the time to treat people with SMA.”

—Jennifer Peters, FAST Movement

- The FDA granted Nusinersen orphan drug designation because it would treat a rare disease that currently has no other option. Orphan drug designation provides financial incentives for rare disease drug development, such as clinical trial tax credits, user fee waivers, and eligibility for market exclusivity.

- Nusinersen was granted Fast Track Designation—a provision intended to encourage development of new drugs and biologics for the prevention and treatment of rare pediatric diseases.

- In 2011, the National Institutes of Health and the National Institute of Neurological Disorders and Stroke selected SMA as the #1 disease closest to treatment of more than 600 neurological disorders—we have reached this goal with Nusinersen.

- Nusinersen is an antisense drug Ionis Pharmaceuticals (formerly Isis Pharma) developed in collaboration with Dr. Adrian R. Krainer at Cold Spring Harbor Laboratory. Isis designed Nusinersen to treat people with SMA. SMA is a severe motor-neuron disease that kills more infants and young children than any other genetic disease. SMA occurs from a deletion or mutation of a gene responsible for producing a protein critical for normal cellular function. Nusinersen is designed to increase the production of this protein by modifying the splicing of a closely-related gene, thereby compensating for the underlying genetic defect.

- Ionis Pharmaceuticals states that the latest update on the infants enrolled in their mid-stage program for Nusinersen shows that toddlers with the most severe form of the disease have been getting progressively stronger and living longer while taking this drug.

- According to an analysis performed on May 15, 2015, Nusinersen led to continued and durable increase in measures of muscle function.

- Measures of muscle function at 9-month evaluation demonstrated a mean increase in score in scales for ambulatory patients and upper limb test for non-ambulatory patients measuring the clinical endpoints of the study. Nusinersen continues to show it is safe and effective in ongoing clinical trials.
"Based on the historical control we would expect infants to have an event [meaning ventilatory dependence or death] by 6 to 10 months old, 10 on the outside. What we've seen is extraordinarily more than we expected… They are living longer, achieving milestones that are simply unheard of. Five of the Type 1 patients are now able to sit unassisted. What we hoped to see [in this study] were good safety data. We never dreamt we'd see this."
- Stanley Crooke, M.D., PhD., CEO Ionis Pharmaceuticals

Ionis Pharmaceuticals has stated that they plan to file multiple applications, meaning they will only seek FDA approval for those fitting the patient criteria that have been tested in clinical trial. However, this would exclude the majority of the entire patient population, including older children and adults who have been living with the disease the longest. It is a miracle that these patients are even still living, so to seek approval excluding them from the opportunity to receive it, as though they are an unfortunate, expendable group of people, is wholly unacceptable. All people with SMA have the same missing genetic component that causes their disease. Obviously, dosing will vary based on age, weight, and progression of disease, but that can be sorted by physicians once Nusinersen is approved. Whenever Ionis applies for approval for Nusinersen, it is paramount that they seek approval of this amazing treatment for ALL patients, including those who have been fighting the disease the longest.

Because, statistically, many more children will die before Nusinersen is approved, we believe Ionis should offer Nusinersen for Expanded Access (Compassionate Use) for all those who are not enrolled in a clinical trial. Especially considering that Ionis has expressed no intention to offer a trial phase that will enroll those who have been living with the disease the longest, these facets of the patient population cannot be expected to wait any longer for approval. Even if the approval process were begun today, the length of time to submit paperwork would not pass without further loss of dozens of lives. Currently, Ionis has no Expanded Access Program and no expressed intention to apply for one.


Needham & Company analyst, Dr. Chad Messer, reiterated June 23, 2015, that "Isis recently presented updates from ongoing studies with Nusinersen. We remain impressed with the efficacy of these studies. Importantly, Nusinersen has corroborated survival improvements with meaningful functional improvements in infants and in children. Phase 3 studies are well underway but we reiterate our belief that the efficacy demonstrated so far by Nusinersen already exceeds what is necessary for approval in a deadly pediatric orphan indication."
• Carlsbad, CA, June 22, 2015 (PRNewswire) — In an update provided by Ionis Pharmaceuticals, Dr. Darryl De Vivo, Professor of Neurology and Pediatrics, Columbia University Medical Center and Nusinersen investigator said, "The natural course for children with untreated type II or type III SMA typically experience loss of muscle function that develops slowly and continually over time... a sustained increase of three or more points in Hammersmith Motor Function Scale Expanded scores [following treatment with Nusinersen] represents a significant departure from the natural course and is unusual for these children."

• C. Frank Bennett, Ph.D., senior vice president of research at Ionis Pharmaceuticals commented, "In these studies using multiple measurements of muscle and motor function changes, we observed encouraging results that were consistent with earlier results from our open-label Phase 2 study. Taken together, these data suggest that ISIS-SMN\textsubscript{Rx} [clinical name of Nusinersen] could provide benefit to patients with SMA beyond halting their disease progression."

• According to current information on clinicaltrials.gov, the open label, phase 3 trial, SHINE, isn’t expected to be completed until 2020.

**FAST Movement’s Intentions**

• We are actively engaging key U.S. Senators and Members of Congress, including the Senate Committee on Health, Education, Labor & Pensions (HELP) to step forward and ask the FDA to allow Nusinersen access today.

• We continue to ask the FDA to expedite approval of Nusinersen.

• We call upon Congress and the FDA to expedite Nusinersen clearance and to expedite any bureaucratic barriers such as global patent rights to Biogen to protect this research investment.

We followed the research leading to Nusinersen and more than a dozen other drug therapies under development. Years of research brought this miracle in biotechnology. We believe the research is clear—Nusinersen is effective and ready to save lives today.

• We continue to support ongoing SMA research in many different targets that may one day cure this disease. Until then, Nusinersen is proven to rescue strength and survival for thousands across the nation.

"Just compare videos of kids receiving Nusinerson to kids of comparable age and type of SMA, waiting for treatment. It doesn’t take a neurologist to see the dramatic difference between one boy standing and breathing independently and one in a wheelchair on a ventilator."

—Mary Bodzo, FAST Movement
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Comparative Cases Approved by the Food and Drug Administration

Introduction

The Food and Drug Administration (FDA) has specific administrative flexibility to grant special consideration to diseases that currently have no other treatment available and for which the patient population is either small or has a short life-expectancy. Nusineren is a drug therapy advanced to the level for access to patients with Spinal Muscular Atrophy (SMA). SMA is an example of a disease for which this flexibility must be used. SMA is the number one genetic killer of children, 1 in 6,000 live births are affected and patients rarely survive childhood.

In Quantum of Effectiveness Evidence in FDA’s Approval of Orphan Drugs, Frank Sasinowski¹, Chairman of the Board, National Organization for Rare Disorders states the FDA publicly has expressed sensitivity to applying this flexibility to new therapies for rare disorders. For example, in his testimony to the United States Senate on June 23, 2010, Dr. Jesse Goodman, FDA Chief Scientist and Deputy Commissioner for Science and Public Health, testifying on “the FDA’s Efforts on Rare and Neglected Diseases” stated the FDA is fully committed to applying the requisite flexibility in the development and review of products for rare diseases, while fulfilling its important responsibility to assure that the products are safe and effective for these highly vulnerable populations.

Set forth below are examples of drugs approved for treating rare diseases where the FDA’s flexibility and sensitivity to the obstacles of drug development for rare diseases brought forth a successful treatment. Many of the 357 approved orphan drugs were tested on limited numbers of patients, serving as a testament to the FDA’s commitment to these patients. This is possible when the best science is applied and when therapies are demonstrated effective.

This is a brief list of other FDA approved drugs following clinical trials that were far less rigorous than those currently conducted by Ionis Pharmaceuticals in partnership with Biogen Idec for Nusinersen. While the FDA has the ability to approve a drug, as in the following instances, after only one phase of trial, tested on a minimal patient population, and without requiring a control (placebo) arm of study, Ionis is now in open-label, post-phase 3, and continues to enroll more patients in ongoing phase 3 study arms, including a 1:2 placebo ratio group, and has further phase 3 and even phase 4 study arms planned.

While these diseases are certainly devastating for those affected and warranting of treatment, it is our position that, if the FDA employed the administrative flexibility granted to it specifically for these instances in the case of these diseases, some of which actually already have alternative approved treatments available, it is justifiable that the FDA utilize flexibility in the case of SMA.
Terms to Understand

Accelerated Approval - allows the FDA to approve products for serious or life-threatening diseases based on evidence that the product has an effect on an outcome that is reasonably likely to predict clinical benefit.

Breakthrough Therapy Designation - an FDA expedited drug development tool, which allows the FDA under Section 902 of the July 9, 2012 Food and Drug Administration Safety and Innovation Act, to grant priority review to drug candidates if preliminary clinical trials indicate that the therapy may offer substantial treatment advantages over existing options for patients with serious or life-threatening diseases.

Orphan Drug Designation - provides orphan status to drugs and biologics which are defined as those intended for the safe and effective treatment, diagnosis, or prevention of rare diseases/disorders that affect fewer than 200,000 people in the U.S., or that affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug. Orphan Drug Designation also provides incentives such as tax credits, user fee waivers, and eligibility for exclusivity to assist and encourage the development of drugs for rare diseases.

Priority Review Status - an expedited review granted by the FDA to the developer of a treatment for neglected diseases.

Approved Drugs

Kanuma: Approved December 8, 2015 as the first treatment for patients with a rare disease known as lysosomal acid lipase (LAL) deficiency, also known as Wolman disease and cholesteryl ester storage disease (CESD). Symptoms typically present between 2 and 4 months of life, and patients rarely are expected to live beyond one year. Treatment is provided via intravenous infusion once weekly in infants with rapidly progressive LAL deficiency presenting in the first six months of life, and once every other week in all other patients. The Center for Drug Evaluation and Research evaluated the safety and efficacy of Kanuma in an open-label, historically controlled trial in nine infants with rapidly progressive Wolman disease and in a double-blind, placebo-controlled trial in 66 pediatric and adult patients with CESD. In the trial in infants with Wolman disease, six of nine infants (67 percent) treated with Kanuma were alive at 12 months of age, whereas none of the 21 infants in the historical control group survived. In the trial in CESD patients, there was a statistically significant improvement in LDL-cholesterol levels and other disease-related parameters in those treated with Kanuma versus placebo after 20 weeks of treatment.

1 phase
Small patient population tested
Natural history data used as placebo in infant study
Vastly different patient types tested in one arm of study
Approved for ALL patients

See the FDA Press Announcement for the approval of Kanuma here.

Xuriden: Approved September 14, 2015 for patients with hereditary orotic aciduria, a rare metabolic disorder, which has been reported in approximately 20 patients worldwide. The safety and
effectiveness of Xuriden were evaluated in a single arm, 6-week, open-label trial in four patients with hereditary orotic aciduria, ranging in age from 3 to 19 years of age, and in a 6-month extension phase of the trial. The study assessed changes in the patients’ pre-specified hematologic parameters during the trial period. At both the 6-week and 6-month assessments, Xuriden treatment resulted in stability of the hematologic parameters in all four clinical trial patients. The safety and effectiveness of uridine replacement therapy were further supported by case reports from the published literature.

1 phase
No placebo arm
Small patient population tested
Approved

See the FDA Press Announcement regarding Xuriden's approval here.

Tagrisso: Lung cancer treatment approved November of 2015 as part of FDA’s Accelerated Access Program. The safety and efficacy of Tagrisso were demonstrated in two multicenter, single-arm studies involving a total of 411 patients with advanced EGFR T790M mutation-positive NSCLC whose disease worsened after treatment with an EGFR-blocking medication. In these two studies, 57% of patients in the first study and 61% of patients in the second study experienced a complete or partial reduction in their tumor size (known as objective response rate).

1 phase
No placebo arm
Approved

See the FDA Press Announcement regarding Tagrisso's approval here.

Palbociclib: Breast cancer treatment granted Breakthrough Therapy designation in April 2013. On February 3, 2015, the U.S. Food and Drug Administration granted accelerated approval to Palbociclib (IBRANCE, Pfizer, Inc.) for use in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease. Palbociclib was tested in a randomized, multicenter, open-label trial in 165 women, randomly allocated to receive either palbociclib plus letrozole or letrozole alone.

Overall response rate in patients with measurable disease (investigator assessment) was higher in the palbociclib plus letrozole compared to the letrozole alone arm, and the drug was approved, even though many patients (greater than 10%) experienced multiple side effects, some even exhibiting serious adverse reactions, such as pulmonary embolism.

1 phase
No placebo arm
Small patient population tested
Adverse effects reported
Approved

See the FDA Press Announcement regarding Palbociclib's approval here.
**Alecensa**: Approved December 2015 for the treatment of ALK-positive lung cancer. The safety and efficacy of Alecensa were studied in two single-arm clinical trials of patients with metastatic cancer whose disease was no longer controlled by treatment with an alternative drug. Study participants received Alecensa twice daily to measure the drug’s effect on their lung cancer tumors. In the first study, 38% of participants experienced a partial shrinkage of their tumors, an effect that lasted for an average of 7.5 months. In the second study, 44 percent of participants experienced a partial shrinkage of their tumors, lasting for an average of 11.2 months. The trials also examined Alecensa’s effect on individuals’ brain metastases, a common occurrence in this population. 61% of participants in the two trials who had measurable brain metastases experienced a complete or partial reduction in their brain tumors, lasting an average of 9.1 months.

Alecensa is not without associated side effects, some of which can be life-threatening. The FDA granted the Alecensa application breakthrough therapy designation, priority review status, and orphan drug designation.

2 phases
No placebo arm
Adverse effects reported
Approved

See the FDA Press Announcement regarding Alecensa's approval here.

**Cerezyme**: Enzyme-replacement therapy for sufferers of Gaucher's disease, approved with limited patient enrollment in 1994. The approval of Cerezyme was based on a Phase 3 study comparing the recombinant version to Ceredase (approved 1991), which involved 30 patients. The patients, who were split evenly between the two treatments, received repeated doses of the drugs over a period of six to nine months. The study found that fewer patients in the Cerezyme-treated arm had antibody reactions against the treatment than those who received Ceredase (16% versus 40%).

No placebo arm
Small patient population tested
Approved

See Press Announcement regarding the approval of Cerezyme here.

**Myozyme**: Enzyme therapy approved in April 2006 to treat the human enzyme acid deficiency in infants and children with Pompe disease. Approval of Myozyme was based on a pair of clinical trials, which enrolled a combined 39 patients with Pompe disease.

Study 1, 18 infant patients with results being measured against the historical baseline of the disease (natural history).

Study 2, 21 patients (3 months-3.5 years in age) with efficacy being measured purely by those remaining alive at the end of the study.

2 phases
No placebo arm (natural history data considered instead)
Small patient population tested
Approved

See Press Announcement for the approval of Myozyme here.

**Conclusion**

The FDA is responsible for protecting the public health by assuring the safety, efficacy and security of human... drugs... and advancing the public health by helping to speed innovations that make medicines more effective, safer, and more affordable. SMA patients and their families value the efforts of the FDA to ensure that any drug released will not only be effective, but also safe. FAST also appreciates that certain allowances are available to the FDA in the case of diseases just like SMA. There are no other options available to patients for the treatment of SMA and the life expectancy of the disease is so devastating that those living with this disease cannot wait another day for a treatment to be approved.

That being said, this is hardly an emotion-driven rush to judgment. The results of the patients enrolled in the Nusinersen trials by Ionis Pharmaceuticals have been nothing short of breathtaking-- far surpassing even the expected results of the researchers. To date, there have been no drug-related serious adverse events reported with Nusinersen. The natural history data of the disease is more than enough to warrant discontinuing any further placebo groups and it is our position that continuing to enroll patients to receive placebo is not only unnecessary, but unethical. Even so, placebo arms began in June 2014, which should be more than sufficient, especially when considered alongside the natural history multi-study data.

The FAST Movement is asking key U.S. Senators and Members of Congress, including the Senate Committee on Health, Education, Labor & Pensions (HELP) to step forward and ask the FDA to allow Nusinersen access today. We continue to ask the FDA to expedite approval of Nusinersen, and we call upon Congress and the FDA to expedite Nusinersen clearance and to expedite any bureaucratic barriers such as global patent rights to Ionis-Biogen to protect this research investment. We believe the research is clear—Nusinersen is safe, effective, and ready to save lives today.
References


Nusinersen reported results as of April 2015

All presentation slides provided by Ionis in regards to Nusinersen can be downloaded and viewed at:

The natural history of SMA Type 1 children is death or permanent ventilation at 6.1-10.5 months with a mean DECLINE in CHOP scores of 1.27 points per year

In infants treated with Nusinersen, there was a median change of 17 points in CHOP scores within 15 months

53% of treated infants scored 40 or more points on the CHOP scale, 40 is at the lower end of normal

80% event free survival of those treated with Nusinersen vs 18% event free survival in those untreated

August 2015 results showed a 22.7 mean change in CHOP scores, increased from 17 point change

ISIS-SMN
Rx has been well tolerated with no safety concerns to date
No drug-related SAEs; majority of SAEs were related to respiratory infections
Adverse Events (non-SAEs) mostly mild or moderate in severity
No potential Dose Limiting Toxicities reported No drug-related changes on neurological exams
No clinically significant changes in CSF safety labs
No change in safety profile with repeated injections