TWIST AROUND

A tale of intertwined lives in the MDA clinic in the golden age of evolving genetic therapies

Tom Reynolds, DO

Maine AAP Spring Conference

April 2022

1

Disclosures/CME

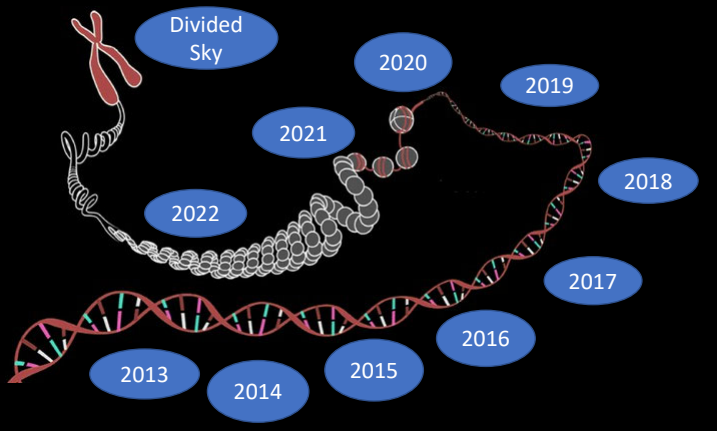
- No relevant financial relationships
- All patients and parents have given me permission to discuss their cases and use their images

2

Objectives

1) Community/Relationships
2) Take chances
3) Read the Book!
4) Share your experience

Outline



3

If life were easy and not so fast…I wouldn't think about the past…

- 2013
- The Denger Family
- Letter to Rich Peterson
- Physician Leadership Development Fellowship

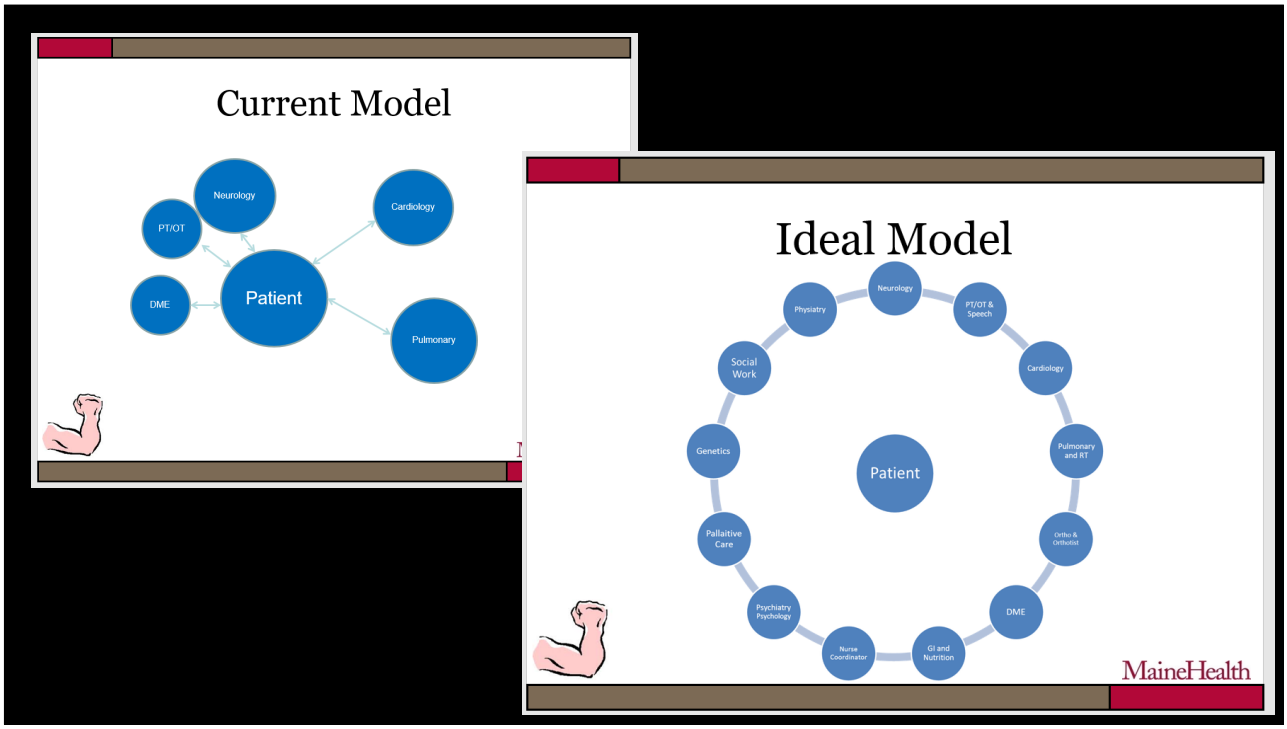
4

Just a few old guys who set the stage…

5

Community! Relationships!

6


Current Model
Neurology
PT/OT
Cardiology
DME
Patient
Pulmonary
Ideal Model
Neurology
Physiatry
PT/OT & Speech
Social Work
Cardiology
Genetics
Patient
Pulmonary and RT
Pallaitive Care
Ortho & Orthotist
Psychiatry Psychology
DME
Nurse Coordinator
GI and Nutrition
MaineHealth

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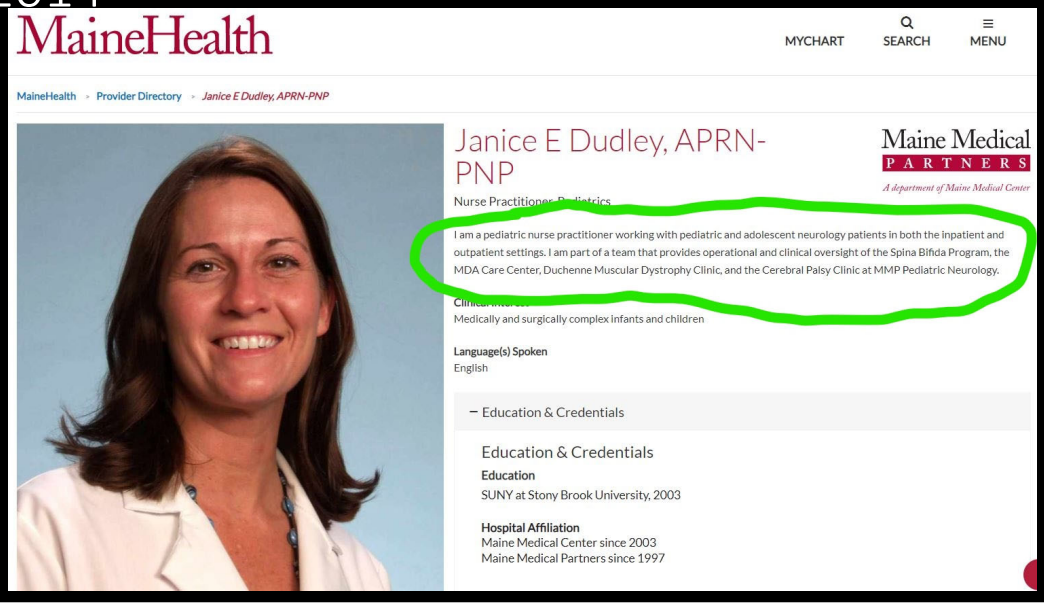
2014


MaineHealth
MYCHART
SEARCH
MENU
MaineHealth » Provider Directory » Janice E Dudley, APRN-PNP
Janice E Dudley, APRN-PNP
Maine Medical PARTNERS
A department of Maine Medical Center
Nurse Practitioner, Pediatrics
I am a pediatric nurse practitioner working with pediatric and adolescent neurology patients in both the inpatient and outpatient settings. I am part of a team that provides operational and clinical oversight of the Spina Bifida Program, the MDA Care Center, Duchenne Muscular Dystrophy Clinic, and the Cerebral Palsy Clinic at MMP Pediatric Neurology.
Medically and surgically complex infants and children
Language(s) Spoken
English
– Education & Credentials
Education & Credentials
Education
SUNY at Stony Brook University, 2003
Hospital Affiliation
Maine Medical Center since 2003
Maine Medical Partners since 1997

8

2015

- Caroline Chaloner
- Pediatric PT
- 5 different specialized neuromuscular evaluations

9

Duchenne

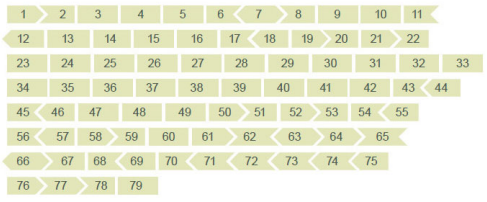
- X-linked genetic disorder
- Dystrophinopathy
- Chronic, progressive
  - Cardiopulmonary systems eventually affected
- Very elevated CK level
  - Molecular genetic testing -> Exon deletions, duplications
- Steroids to prolong ambulation
- Supportive therapy otherwise, life expectancy late 20's/early 30's
- Gene therapies now exist

10

Exon skipping therapy

Duchenne Deletion Tool

Parent Project Muscular Dystrophy



exon map of the dystrophin gene

If there is a missing piece within the dystrophin gene (deletion) or an extra piece (duplication), your body can have difficulty making dystrophin. The most common genetic mutation causing Duchenne is a deletion, where part of the gene is missing.

One approach that strives to address this lack of dystrophin is exon skipping, which tells the body to hide an exon next to the missing piece, so the whole section can be skipped over and the remaining exons can fit together. The intent is to allow the body to make a shorter form of the dystrophin protein. The tool below will help you to know whether your/your child's genetic mutation might benefit from an exon skipping therapy.

missing exon

skipped exon

WHAT IS THE DIFFERENCE BETWEEN IN-FRAME VS OUT-OF-FRAME ERRORS?

If you or your child have a deletion mutation, you have probably heard the terms **in-frame** and **out-of-frame**. Sometimes this is referred to as the **reading frame rule.**

In-Frame

A deletion is in-frame if the reading frame of the gene is preserved and not disrupted, so some dystrophin protein can be made. The protein may be shorter than normal, but it is still functional. In-frame deletions typically result in Becker muscular dystrophy, which usually has a more mild presentation (compared to Duchenne) because there is some dystrophin protein present in the cells.

Out-of-Frame

A deletion is out-of-frame if the reading frame is completely disrupted, so that no dystrophin protein can be made. Out-of-frame deletions typically result in Duchenne muscular dystrophy, which usually has a more severe presentation (compared to Becker) because there is no dystrophin protein present in the cells.

It is important to remember that this reading frame rule is not always perfect. There are some out-of-frame deletions that cause Becker, and some in-frame deletions that cause Duchenne. Sometimes a child's diagnosis will be "intermediate or unclear" until the child grows older and their progression can be observed. Please speak with your doctor or genetic counselor if you have questions.

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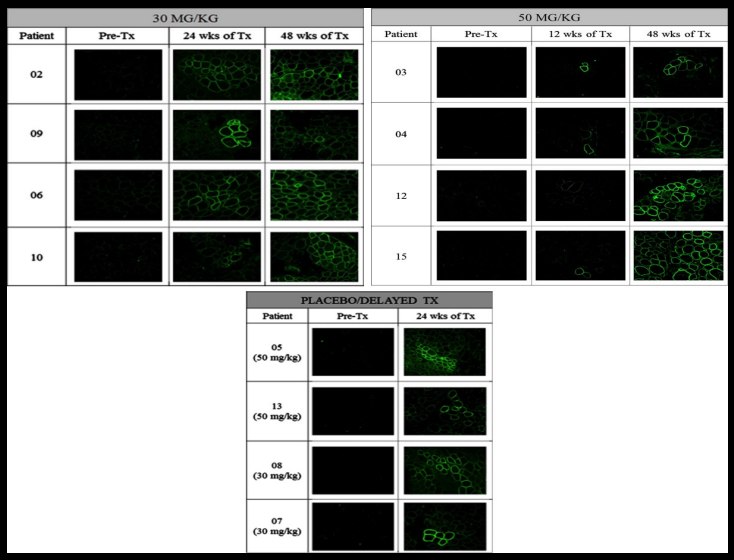
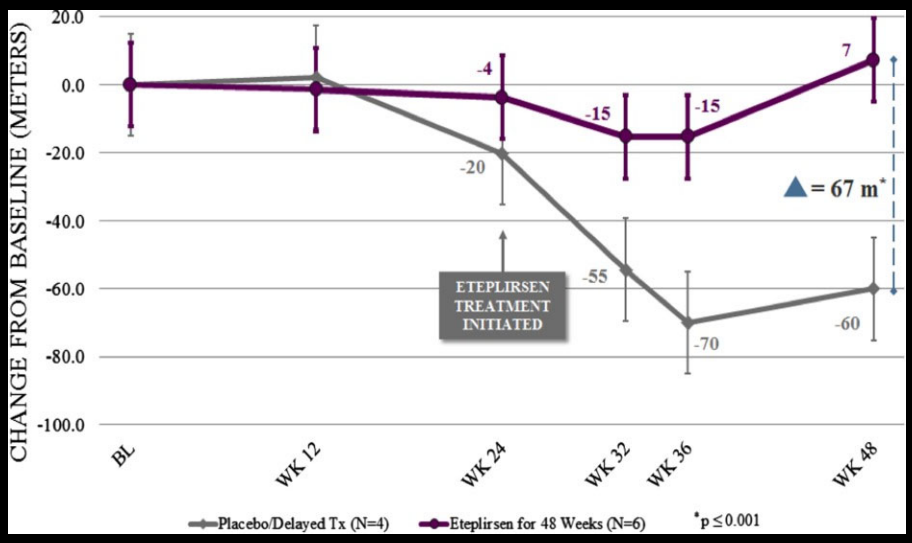
Eteplirsen for the treatment of Duchenne muscular dystrophy



Annals of Neurology, Volume: 74, Issue: 5, Pages: 637-647, First published: 01 August 2013, DOI: (10.1002/ana.23982)

12

Eteplirsen for the treatment of Duchenne muscular dystrophy



Annals of Neurology, Volume: 74, Issue: 5, Pages: 637-647, First published: 01 August 2013, DOI: (10.1002/ana.23982)

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VIEWPOINT

Approving a Problematic Muscular Dystrophy Drug
Implications for FDA Policy

Aaron S. Kesselheim, MD, JD, MPH
Program on Regulation, Therapeutics, and Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

Jerry Avorn, MD
Program on Regulation, Therapeutics, and Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

In September 2016, the US Food and Drug Administration (FDA) approved eteplirsen (Exondys 51), a new drug for Duchenne muscular dystrophy (DMD), overruling the recommendations of both its scientific staff and its external advisory committee. Duchenne muscular dystrophy is a progressive and usually fatal X-linked genetic disease caused by mutations in a gene that produces the protein dystrophin that helps stabilize muscle fibers. No disease-modifying treatments are available.

Eteplirsen was designed to offer a promising new therapeutic approach that would bypass a stop codon in a gene coding for dystrophin, allowing production of a truncated but functional version of the protein. In particular, eteplirsen targeted exon 51, the location of the stop codon in about 10% to 15% of patients with DMD (an estimated 2000-2500 cases in the United States). Despite this innovative mechanism, the development of eteplirsen was controversial, starting with its manufacturer-supported pivotal double-blind study, which involved only 12 patients: 8 were randomized to 2 different eteplirsendoses and 4 were randomized to placebo for 24 weeks. The latter were then switched to eteplirsen and all were to be followed for an additional 24 weeks. The sample size was substantially smaller than the study sample size in which a similar DMD drug, drisapersen, had been tested in 3 randomized trials that together enrolled 290 patients. The FDA declined to approve drisapersen in 2015 after these studies showed no clear benefit after 24 weeks in prespecified clinical end points, such as changes in a 6-minute walk test. Those trials also suggested the possibility of safety problems, including renal toxic effects and thrombocytopenia.

In the eteplirsen study, by contrast, the primary trial end point was a surrogate measure: an increase in the presence of dystrophin in muscle biopsy specimens. Several [illegible] provide clinical benefit. A more rigorous, fully blinded reanalysis of the immunohistochemical assay organized by the FDA cast further doubt on the initial results.[3]

The trial also assessed clinical progression. At 24 and 48 weeks, there was no consistent advantage in the 6-minute walk test capacity of patients who received eteplirsen compared with those initially given placebo. However, new post hoc calculations excluded 2 eteplirsen-treated patients who deteriorated quickly while receiving therapy; these analyses suggested a statistically significant advantage for the remaining treated patients. These more selective post hoc analyses were highlighted in the figure displaying this finding in the 2013 article[2] and in the manufacturer's press release announcing the success of the trial.[4] Subsequent evaluation of 6-minute walk test data over 3 to 3.5 years of open-label therapy appeared to be associated with slower rates of decline when compared with a historical cohort, but the problematic nature of historical controls complicated the interpretation.

Controversy over eteplirsen came into broader public view when the FDA convened an advisory committee in April 2016 to review these data. That hearing included more than a thousand public attendees and more than 4 hours of comments from patients, families, advocates, scientists, and legislators. The public presentations were frequently emotional, and nearly all of the presenters (51 of 52) favored drug approval. The advisory committee was generally unimpressed with the efficacy data, although the committee split its vote: 7 members found no evidence that eteplirsen was clinically effective in treating DMD (vs 3 in favor and 3 abstentions), and 7 members found that the drug did not produce dystrophin at a level likely to result in clinical benefit (vs 6 in favor).

After the meeting, the FDA delayed its decision and requested additional data, including Western blot as-

JAMA Published online October 24, 2016

One partial solution could be the adoption of novel regulatory models, such as limited approval with intensive collection of new clinical evidence, before a drug becomes universally available. As a further step, drugs that have not yet shown clinical outcome benefit could be made available at just the cost of production, or most profits could be kept in escrow, until adequate trials are completed.

Patients with DMD need better treatments, and drugs like eteplirsen might one day fill that role. For now, though, the drug has provided a worrisome model for the next generation of molecularly targeted therapies: demonstrate a slight difference in a laboratory test, activate the patient community, win approval, and charge high prices, while relying on limited regulatory follow-up.

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December 2016

- Patrick Denger
- My first prescription of a genetic therapy – eteplirsen!
- Lots of uncertainty
- Take Chances!

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Spinal Muscular Atrophy

- AR disorder, deletion or mutation of exon 7 of SMN1 gene on 5q
  - 95% of individuals have homozygous deletion
- Affected individuals have variable copy numbers of SMN2
  - SMN2 a paralog of SMN1, producing low but essential levels of SMN protein
  - The more copies, the milder the disease
- 1:54 carrier frequency
- Incidence of 1:10,000-11,000 births, prevalence of ~1-2:100,000
- Historically the leading monogenic cause of death in infancy

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Spinal Muscular Atrophy

- Type 1
  - < 6 months of life, most severe form
  - Accounts for 60% of cases
  - Generally 2 copies of SMN2
- Type 2
  - > 6 months of life, sit but never learn to walk
  - Accounts for 30% of cases
  - Generally 3 copies of SMN2
- Type 3 or 4
  - Accounts for remaining 10% of cases
  - Generally 4 or more copies of SMN2

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SMA Treatments – Nusinersen - 2017

- Anti-Sense Oligonucleotide (ASO)
  - Modifies pre-mRNA splicing to promote exon 7 inclusion in SMN2 mRNA transcripts
  - *SMN Up-Regulating Therapy*
  - More full length SMN protein produced
  - Intrathecal injection
    - 4 loading doses in first 60 days
    - One dose every 4 months thereafter

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ORIGINAL ARTICLE

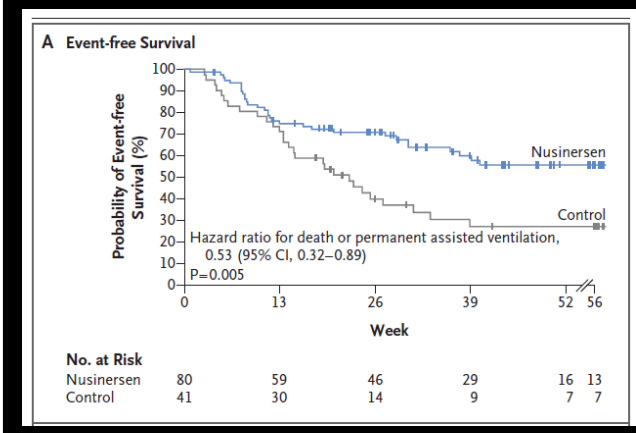
Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy

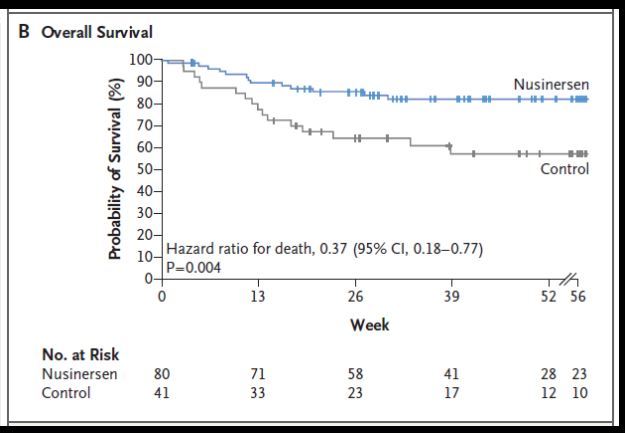
Richard S. Finkel, M.D., Eugenio Mercuri, M.D., Ph.D., Basil T. Darras, M.D., Anne M. Connolly, M.D., Nancy L. Kuntz, M.D., Janbernd Kirschner, M.D., Claudia A. Chiriboga, M.D., M.P.H., Kayoko Saito, M.D., Ph.D., Laurent Servais, M.D., Ph.D., Eduardo Tizzano, M.D., Ph.D., Haluk Topaloglu, M.D., Már Tulinius, M.D., Ph.D., et al., for the ENDEAR Study Group*

Article Figures/Media Metrics

20 References 871 Citing Articles Letters

November 2, 2017
N Engl J Med 2017; 377:1723-1732
DOI: 10.1056/NEJMoa1702752
Chinese Translation 中文翻译





19

Journal of Neuromuscular Diseases 5 (2018) 145–158 145
DOI 10.3233/JND-180304
IOS Press

Research Report

Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening

Table 1
Summary of motor milestone achievements of infants receiving nusinersen in ENDEAR versus NURTURE clinical trials

Milestone	Total number of infants achieving milestone, n/N (%)	
	ENDEAR[a] (Symptomatic patients; N = 73)	NURTURE[b] (Pre-symptomatic patients; N = 13)
Head control (full)	16/73 (22)	5/9 (55)
Sitting (independent: stable, pivot)	6/73 (8)	6/13 (46)
Standing (stands with support, unaided)	1/73 (1)	4/13 (31)
Walking (cruising, walking)	0/73 (0)	2/13 (15)

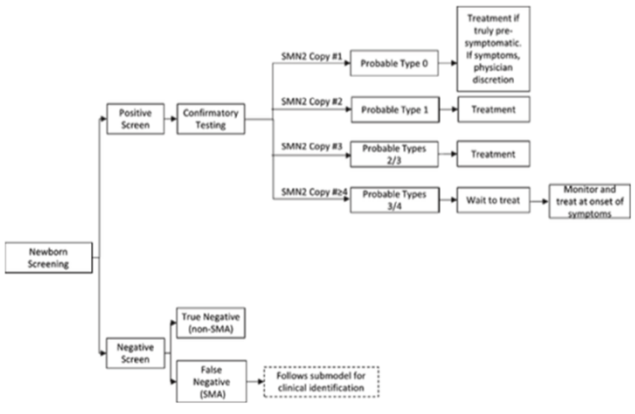


Fig. 1. SMA Newborn Screening Treatment Schematic for SMN-Up-Regulating Therapy. SMA=spinal muscular atrophy; SMN=survival motor neuron.

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November 2017

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LAKES REGION WEEKLY > Posted November 6, 2019 | Updated November 8, 2019

INCREASE FONT SIZE

Local filmmaker honors brother with movie

"Brothers," co-produced by Mike Norton and Reggie Groff, will be shown in Westbrook on Nov. 15.

BY JANE VAUGHAN LAKES REGION WEEKLY

Share

Family members say Michael and JT were inseparable. *Portland Press Herald file photo*

Lakes Region Weekly

alt="LRW"

BROWSE MORE LOCAL NEWS

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NAPLES NEWS
NEW GLOUCESTER NEWS
RAYMOND NEWS
STANDISH NEWS
WINDHAM NEWS

Did You Know?

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Maine Filmmaker Showcase: BROTHERS - MFA

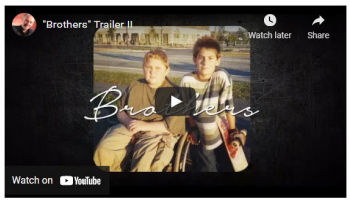
Maine Film Association

ABOUT MEMBERS EVENTS NEWS SIGN IN JOIN

MAINE FILMMAKER SHOWCASE

The Maine Film Association and Portland Media Center are proud to present the Maine Filmmaker Showcase, featuring the Maine-made film BROTHERS, followed by a talkback and Q&A with the film's director, Reggie Groff.

BROTHERS trailer:



ABOUT THE FILM:

This is a film about a family who have faced incredible adversity but continue to push forward. It centers around Mike, an artist and filmmaker, wheelchair bound with Muscular Dystrophy and only the use of two fingers, who is grappling with the recent loss of his brother and daily caregiver. Mike's younger brother, JT, the athletic, charismatic and once potential pro-skateboarder, took his own life after years of deepening schizophrenia. We learn what it takes to be a parent and a brother with overwhelming grief and yet we see how love and creativity give the family the strength to carry on.

24

2019 Follow-up

Medicine (Baltimore). 2019 Jun; 98(26): e15858. PMCID: PMC6617421
Published online 2019 Jun 28. doi: 10.1097/MD.0000000000015858 PMID: 31261494

Long-term treatment with eteplirsen in nonambulatory patients with Duchenne muscular dystrophy

Lindsay N. Alfano, PT, DPT, PCS,[a,*] Jay S. Charleston, PhD,[b] Anne M. Connolly, MD,[c,d] Linda Cripe, MD,[a] Cas Donoghue,[b] Robert Dracker, MD,[e] Johannes Dworzak,[b] Helen Eliopoulos, MD,[b] Diane E. Frank, PhD,[b] Sarah Lewis, HT, ASCP,[a] Karin Lucas, PhD,[b] Jessie Lynch, MS,[b] A. J. Milici, PhD,[f] Amy Flynt, PhD,[g] Emily Naughton,[b] Louise R. Rodino-Klapac, PhD,[a,h] Zarife Sahenk, MD, PhD,[a] Frederick J. Schnell, PhD,[b] G. David Young, DVM,[f] Jerry R. Mendell, MD,[a] and Linda P. Lowes, PT, PhD[a]

Original ambulation measurements

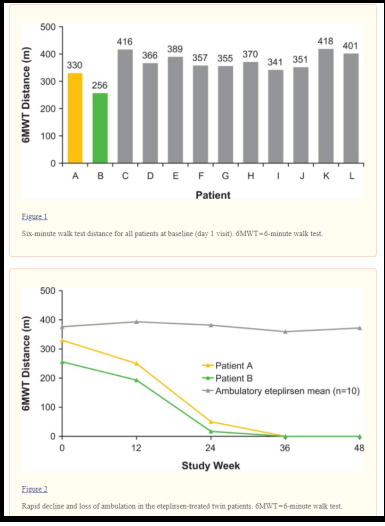


Figure 1

Six-minute walk test distance for all patients at baseline (day 1 visit). 6MWT=6-minute walk test.

Figure 2

Rapid decline and loss of ambulation in the eteplirsen-treated twin patients. 6MWT=6-minute walk test.

Cardiopulmonary measurements

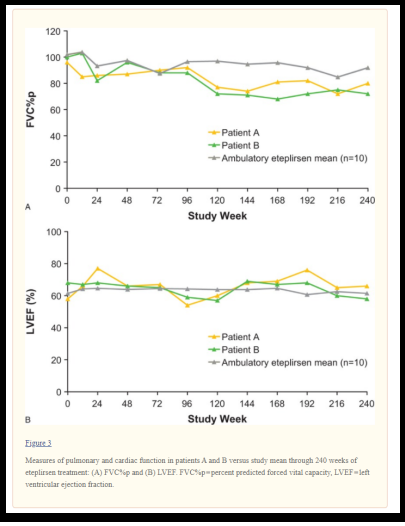


Figure 3

Measures of pulmonary and cardiac function in patients A and B versus study mean through 240 weeks of eteplirsen treatment: (A) FVC%p and (B) LVEF. FVC%p=percent predicted forced vital capacity; LVEF=left ventricular ejection fraction.

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Fall 2018

- Meet Ronan
- Outpatient diagnosis
- PICU
- MGH for zolgensma
- Followed by nusinersen

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OUR FACULTY

Kathryn J. Swoboda, MD

The Katherine B. Sims M.D. Endowed Chair in Neurogenetics

Director of the Neurogenetics Program at MGH/HMS

Pediatric Motor Disorders Research Program

Swoboda Publications

Swoboda Neurogenetics Profile

Dr. Swoboda received her medical degree at The Northwestern Feinberg School of Medicine. She completed her neurology residency at the Harvard Longwood Neurology Program at the Brigham and Women's Hospital, and additional subspecialty training in Clinical Genetics and Neuromuscular disease/ Neurophysiology at Boston Children's Hospital and the Lahey-Hitchcock Clinic. Dr. Swoboda's research and clinical activities are dedicated to the diagnosis and treatment of neurologic disorders, especially neuromuscular diseases, movement disorders, and neurodegenerative disorders with childhood-onset.

Questions | Projects | Answers

Questions being addressed in the lab

Do non-neural, systemic tissues contribute to Spinal Muscular Atrophy (SMA) pathology?

What clinical, genetic, and molecular tools can predict the age of onset, disease severity and course of pathogenesis for rare neurogenetic diseases?

What tissues, proteins, and molecular pathways can be targets of potential novel or co-adjuvant therapeutics for children and adults with neurogenetic diseases?

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FDA approves innovative gene therapy to treat pediatric patients with spinal muscular atrophy, a rare disease and leading genetic cause of infant mortality

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For Immediate Release: May 24, 2019

The U.S. Food and Drug Administration today approved Zolgensma (onasemnogene abeparvovec-xioi), the first gene therapy approved to treat children less than two years of age with spinal muscular atrophy (SMA), the most severe form of SMA and a leading genetic cause of infant mortality.

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Expanding exponentially, like some recursive virus....

- Zolgensma approved in 2019
- AAV-9 gene transfer
  - Using adeno associated virus as a vector to deliver genetic material
  - Does not integrate into the patient genome
  - Low immunogenicity
  - Delivery of a fully functional SMN gene into motor neurons
  - AAV-9 capsid shell crosses BBB
  - Contains human SMN transgene
  - Introduced as a self-complementary double stranded molecule
    - Enables rapid onset of transcription and protein synthesis
  - Continuous promoter

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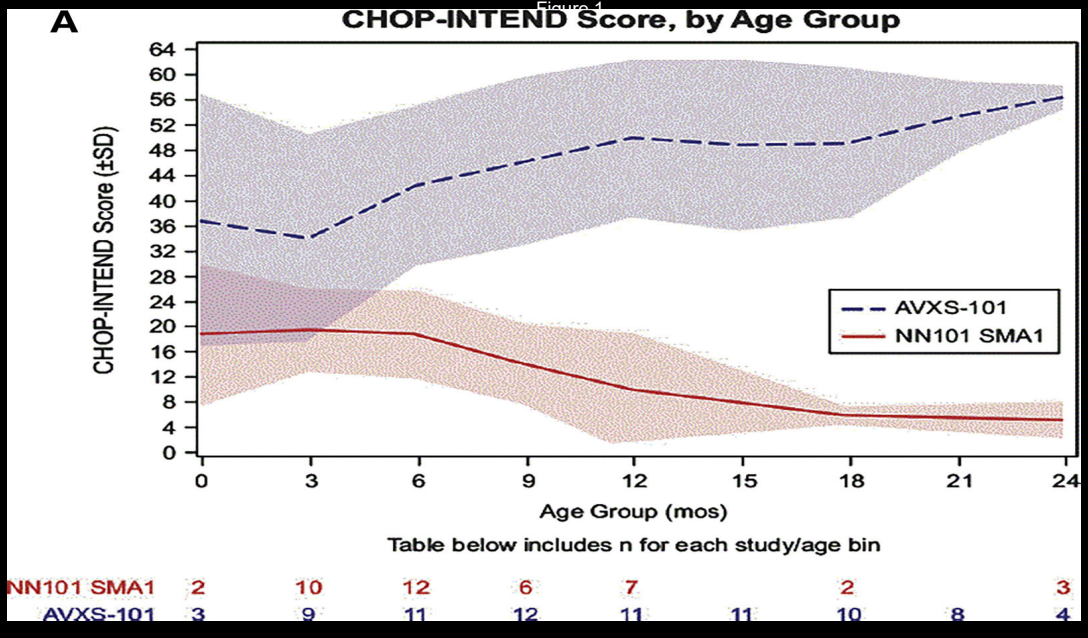

Figure 1

Cell PRESS
Molecular Therapy 2021 29464-488DOI: (10.1016/j.ymthe.2020.12.007)

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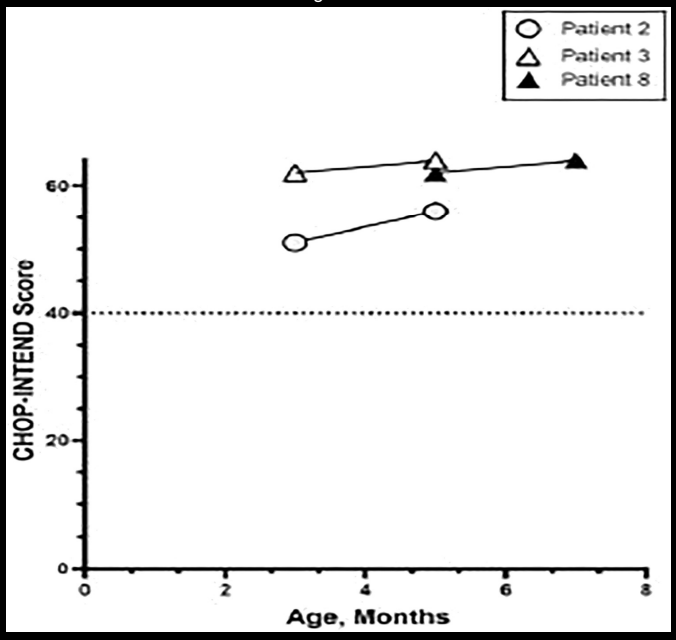
Figure 2



Molecular Therapy 2021 29464-488DOI: (10.1016/j.ymthe.2020.12.007)

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Ronan making gains!!

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2020 s/p zolgensma and ongoing nusinersen

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Risdiplam – 2020!

FDA NEWS RELEASE

FDA Approves Oral Treatment for Spinal Muscular Atrophy

Share | Tweet | Linkedin | Email | Print

For Immediate Release: August 07, 2020

The U.S. Food and Drug Administration today approved Evrysdi (risdiplam) to treat patients two months of age and older with spinal muscular atrophy (SMA), a rare and often fatal genetic disease affecting muscle strength and movement. This is the second drug and the first oral drug approved to treat this disease.

"Evrysdi is the first drug for this disease that can be taken orally, providing an important treatment option for patients with SMA, following the approval of the first treatment for this devastating disease less than four years ago," said Billy Dunn, M.D., director of the Office of Neuroscience in the FDA's Center for Drug Evaluation and Research.

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Risdiplam

- Modifies the splicing of *SMN2* mRNA to include exon 7
- Resulting in an increase in the concentration of the functional SMN protein
- Similar to nusinersen, *upregulates functional SMN protein*
- Only oral drug, given daily

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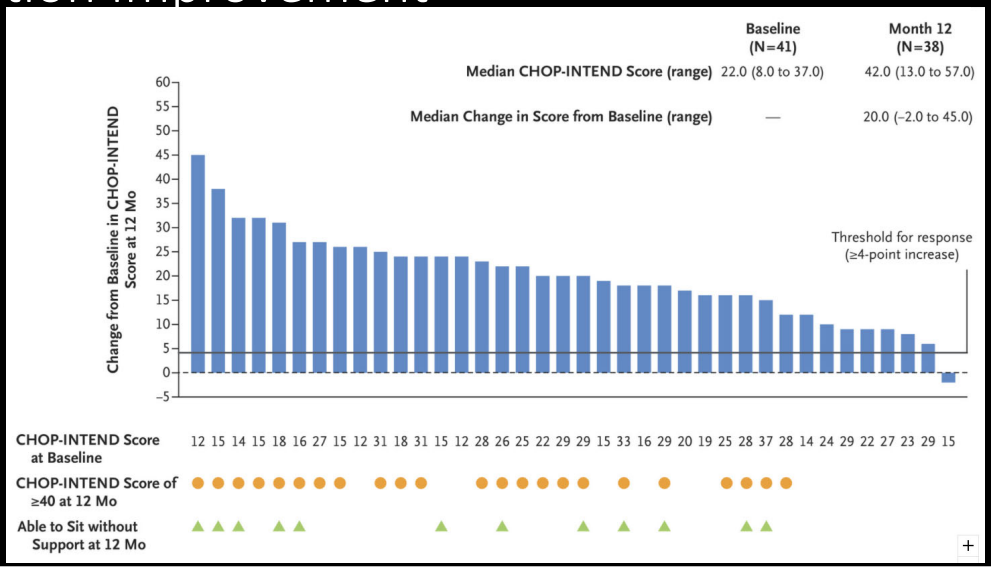
Risdiplam SMA 1 Motor Function Improvement

ORIGINAL ARTICLE

Risdiplam-Treated Infants with Type 1 Spinal Muscular Atrophy versus Historical Controls

Basil T. Darras, M.D., Riccardo Masson, M.D., Maria Mazurkiewicz-Bełdzińska, M.D., Kristy Rose, Ph.D., Hui Xiong, M.D., Edmar Zanoteli, M.D., Giovanni Baranello, M.D., Ph.D., Claudio Bruno, M.D., Ph.D., Dmitry Vlodavets, M.D., Yi Wang, M.D., Ph.D., Muna El-Khairi, Ph.D., Marianne Gerber, Ph.D., et al., for the FIREFISH Working Group*



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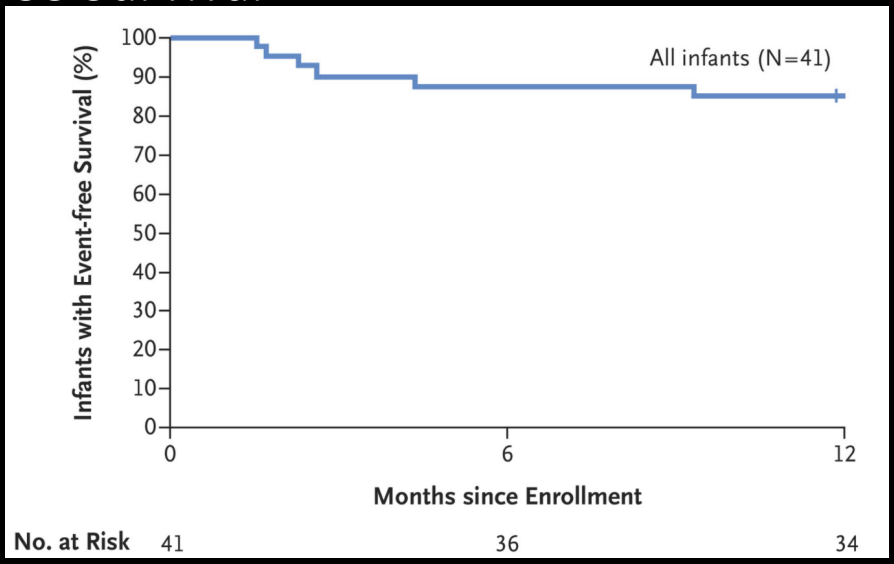
Risdiplam SMA1 Event Free Survival

ORIGINAL ARTICLE

Risdiplam-Treated Infants with Type 1 Spinal Muscular Atrophy versus Historical Controls

Basil T. Darras, M.D., Riccardo Masson, M.D., Maria Mazurkiewicz-Beldzińska, M.D., Kristy Rose, Ph.D., Hui Xiong, M.D., Edmar Zanoteli, M.D., Giovanni Baranello, M.D., Ph.D., Claudio Bruno, M.D., Ph.D., Dmitry Vlodavets, M.D., Yi Wang, M.D., Ph.D., Muna El-Khairi, Ph.D., Marianne Gerber, Ph.D., et al., for the FIREFISH Working Group*



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Safety and efficacy of once-daily risdiplam in type 2 and non-ambulant type 3 spinal muscular atrophy (SUNFISH part 2): a phase 3, double-blind, randomised, placebo-controlled trial

Eugenio Mercuri, Nicolas Deconinck, Elena S Mazzone, Andres Nascimento, Maryam Oskoui, Kayoko Saito, Carole Vuillerot, Giovanni Baranello, Odile Boespflug-Tanguy, Nathalie Goemans, Janbernd Kirschner, Anna Kostera-Pruszczyk, Laurent Servais, Marianne Gerber, Ksenija Gorni, Omar Khwaja, Heidemarie Kletzl, Renata S Scalco, Hannah Staunton, Wai Yin Yeung, Carmen Martin, Paulo Fontoura, John W Day, on behalf of the SUNFISH Study Group*

Lancet Neurol 2022; 21: 42–52
This online publication has been corrected. The corrected version first appeared at thelancet.com/neurology on January 19, 2022

Summary

Background Risdiplam is an oral small molecule approved for the treatment of patients with spinal muscular atrophy, with approval for use in patients with type 2 and type 3 spinal muscular atrophy granted on the basis of unpublished data. The drug modifies pre-mRNA splicing of the *SMN2* gene to increase production of functional SMN. We aimed to investigate the safety and efficacy of risdiplam in patients with type 2 or non-ambulant type 3 spinal muscular atrophy.

Overall baseline demographics were balanced between risdiplam and placebo/risdiplam groups

	Risdiplam (n=120)	Placebo/risdiplam* (n=60)	Total (N=180)
Age at screening, years, median (range)	9 (2–25)	9 (2–24)	9 (2–25)
Age group, years, n (%)			
2–5	37 (30.8)	18 (30.0)	55 (30.6)
6–11	39 (32.5)	18 (30.0)	57 (31.7)
12–17	30 (25.0)	16 (26.7)	46 (25.6)
18–25	14 (11.7)	8 (13.3)	22 (12.2)
Gender, n (%)			
Female	61 (50.8)	30 (50.0)	91 (50.6)
Male	59 (49.2)	30 (50.0)	89 (49.4)
SMA type, n (%)			
2	84 (70.0)	44 (73.3)	128 (71.1)
3	36 (30.0)	16 (26.7)	52 (28.9)
SMN2 copy number, n (%)			
2	3 (2.5)	1 (1.7)	4 (2.2)
3	107 (89.2)	51 (85.0)	158 (87.8)
4	10 (8.3)	8 (13.3)	18 (10)

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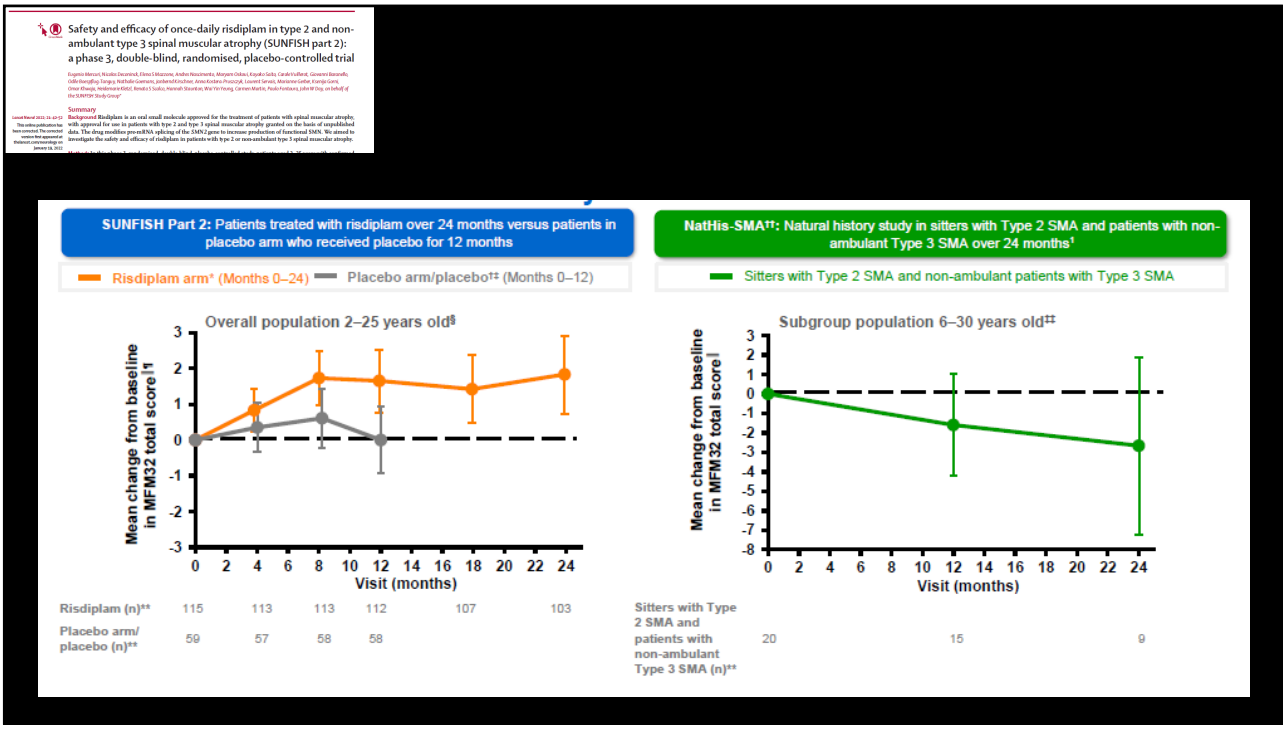

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April 2021 – Maine initiates Newborn Screen

- NBS assay:
  - PCR to detect presence of SMN1 in blood spot
  - Can identify SMN1 exon 7 deletions in all SMA patients while all unaffected patients showed presence of exon 7
  - Inexpensive, can be multiplexed to SCID assay
  - Pilots 100% PPV
  - Ongoing study of a 2nd PCR test to identify both homozygous and heterozygous SMN1 Exon 7 deletions and SMN2 copy number

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(+) Newborn Screen for SMA

Workflow for Administration of Zolgensma

Infant screens positive for SMA on state newborn screen → Dr. Wendy Smith and Dr. Reynolds notified

STEP 1: confirm genetic diagnosis of SMA (need to have biallelic mutations in SMN1 gene- Dr. Smith to coordinate SMN1 mutations and SMN2 copy numbers); schedule urgent visit with genetics and neurology

STEP 2: Order labs: liver function tests (AST, ALT, total bilirubin, prothrombin time), platelet count, troponin-I, and anti-AAV9 antibodies- neurology to order

- Patients in clinical trials had baseline anti-AAV9 antibody titers of < or = 1:50- safety and efficacy has not been established if this is not the case (may need to delay and retest or possibly start steroids earlier than 24 hours)

STEP 3: Complete Zolgensma prescription form and patient consent form

- Fax signed forms to OneGene Program at 1-855-951-4363

STEP 4 (*concurrent with STEP 5): Receive Zolgensma: ships frozen, needs to thaw in refrigerator for 12 hours or at room temperature for 4 hours

STEP 5 (*concurrent with STEP 4): Administer systemic corticosteroids 24 hours prior to infusion equivalent to oral prednisolone at 1mg/kg/day- ordered by neurology

STEP 6: Administer single dose IV infusion through venous catheter over 60 minutes. Flush line with saline upon completion.

STEP 7: Postmedicate with PO prednisolone 1mg/kg/day and continue x 30 days. Work with endocrine to determine weaning protocol (Toni Eimicke NP to be point person)

STEP 8: Monitor LFTS, platelets and troponin x 3m at regular intervals, wean steroids based on lab values, work with PCPs on vaccination plan

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What about >4 copies SMN???

Table 3
Summary of tests used to monitor patients with ≥4 SMN2 copies for whom treatment is not initiated immediately

Test or Outcome Measure	Level of Change/Results Which Would Prompt Initiation of Treatment	Appropriate Age of Patient for Test
EMG/nerve conduction	Any active or chronic neurogenic change	All
CMAP	Below normative values for an age-matched child	All
Myometry	Decrease in extent of muscle contraction	≥4 years
Physical Exam/Reflexes	Any of the following: loss of reflexes, failure to meet or regression in ability to perform motor milestones, proximal weakness, and weakness in trunk righting/de-rotation	All
CHOP INTEND	A failure to gain motor functions with age in keeping with normal development **or** a drop in total score from previous assessment	Infants
HINE	A failure to gain motor functions with age in keeping with normal development **or** a drop in total score from previous assessment	Infants
Hammersmith Functional Motor Scale – Expanded	A failure to gain motor functions with age in keeping with normal development **or** a drop in total score from previous assessment	≥2 years
6MWT	A failure to gain motor functions with age in keeping with normal development **or** a drop in total score from previous assessment	≥5 years
Bayley Scales of Infant and Toddler Development	A failure to gain motor functions with age in keeping with normal development **or** a drop in total score from previous assessment	Infants/Toddlers (Recommended 1 to 42 months)

CHOP INTEND = Children's Hospital of Philadelphia Infants Test of Neuromuscular Disorders; CMAP = compound muscle action potential; EMG = electromyograph; HINE = Hammersmith Infant Neurological Exam; *SMN2* = spinal motor neuron 2; 6MWT = six-minute walk test.

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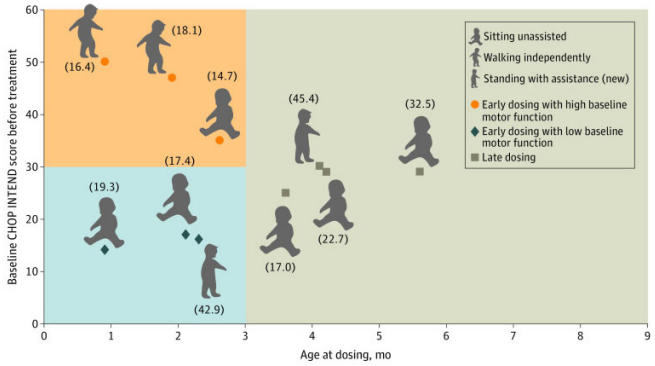
JAMA Neurol. 2021 Jul; 78(7): 1–8.
Published online 2021 May 17. doi: 10.1001/jamaneurol.2021.1272
PMCID: PMC8129901
PMID: 33999158

Five-Year Extension Results of the Phase 1 START Trial of Onasemnogene Abeparvovec in Spinal Muscular Atrophy

Jerry R. Mendell, MD,[✉ 1, 2, 3] Samiah A. Al-Zaidy, MD,[4] Kelly J. Lehman, MSN,[1] Markus McColly, BA,[1] Linda P. Lowes, PT, PhD,[1, 2] Lindsay N. Alfano, PT, DPT,[1] Natalie F. Reash, PT, DPT,[1] Megan A. Iammarino, PT, DPT,[1] Kathleen R. Church, MSW,[1] Aaron Kleyn, PhD,[5] Matthew N. Meriggioli, MD,[5] and Richard Shell, MD[2, 6]



Greatest Development Milestones Achieved During the START Long-term Follow-up Study

Milestones are shown for the 10 patients in the therapeutic-dose cohort who received dosing early and had low baseline motor function (blue quadrant), those who received dosing early and had high motor function (orange quadrant), and those who received dosing late (gray quadrant). Values in parentheses are the age at which the milestone was achieved (in months). Patients were grouped according to baseline motor function (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders scores <20 points [low] or ≥20 points [high]) and age at dosing (<3 months [early] or ≥3 months [late]).[2] This figure was adapted with author permission from Lowes LP et al.[15]

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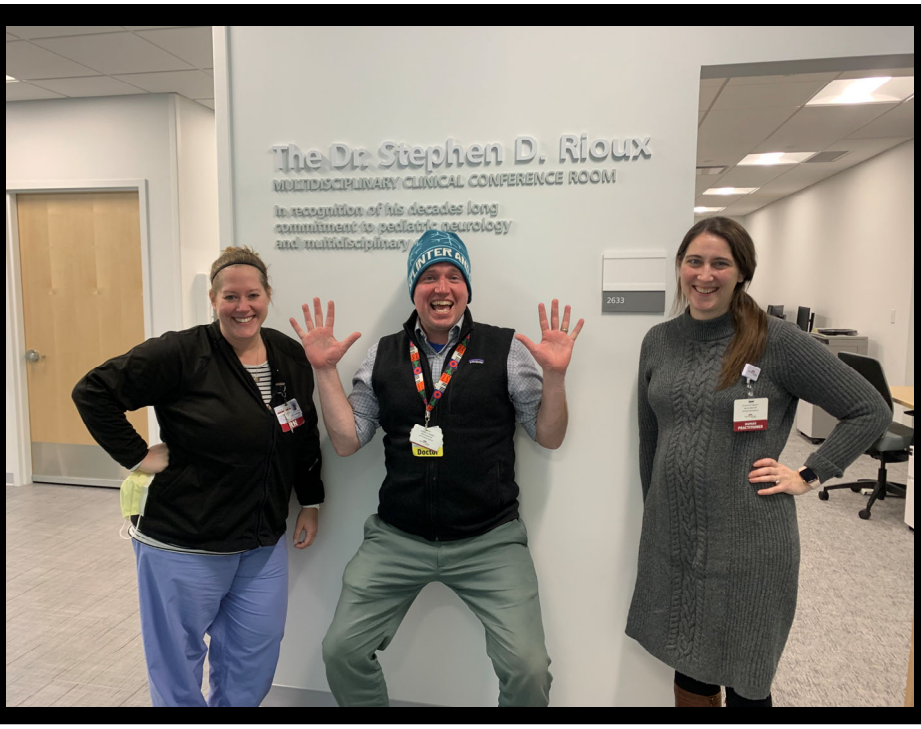

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Ronan 2021 after changing to risdiplam

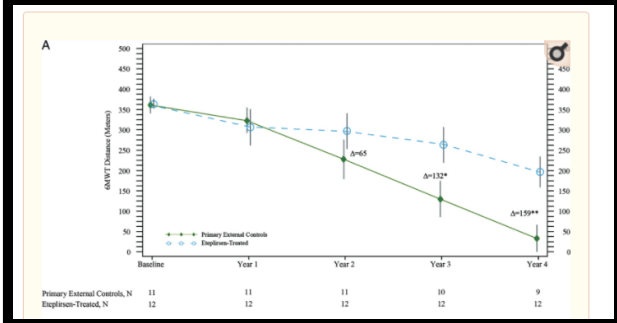
45

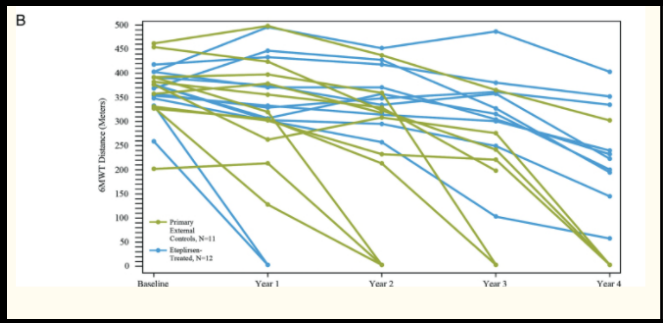
2021 Follow-up

J Neuromuscul Dis. 2021; 8(4): 469–479. PMCID: PMC8385516
Published online 2021 Jul 30. Prepublished online 2021 Feb 19. doi: 10.3233/JND-200548 PMID: 33523015

Comparison of Long-term Ambulatory Function in Patients with Duchenne Muscular Dystrophy Treated with Eteplirsen and Matched Natural History Controls

Jerry R. Mendell,[a,b] Navid Khan,[c] Nanshi Sha,[c] Helen Eliopoulos,[c] Craig M. McDonald,[d] Nathalie Goemans,[e] Eugenio Mercuri,[f,g,h] Linda P. Lowes,[a,b] Lindsay N. Alfano,[a,*] and on behalf of the Eteplirsen Study Group





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Sarepta and New Exon Skipping Therapies

FDA NEWS RELEASE

FDA Approves Targeted Treatment for Rare Duchenne Muscular Dystrophy Mutation

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For Immediate Release: February 25, 2021

Today, the U.S. Food and Drug Administration granted approval for Amondys 45 (casimersen) injection for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping (Exons are pieces of DNA that provide information for making proteins in a person's genome). The agency approved Amondys 45 based on an increase in dystrophin (a protein that helps keep muscle cells intact) production in skeletal muscle observed in patients treated with the therapy. This is the first FDA-approved targeted treatment for patients with this type of mutation. Approximately 8% of patients with DMD have a mutation that is amenable to exon 45 skipping.

7-44
12-44, 18-44, 44
46, 46-47, 46-48, 46-49
46-51, 46-53, 46-55, 46-57, 46-59
46-60, 46-67, 46-69
46-75, 46-78

This list contains documented as well as theoretical mutations potentially amenable to exon 45 skipping.
Not all deletions have been studied and this list may not be complete.

FDA NEWS RELEASE

FDA grants accelerated approval to first targeted treatment for rare Duchenne muscular dystrophy mutation

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For Immediate Release: December 12, 2019

The U.S. Food and Drug Administration today granted accelerated approval to Vyondys 53 (golodirsen) injection to treat Duchenne muscular dystrophy (DMD) patients who have a confirmed mutation of the dystrophin gene that is amenable to exon 53 skipping. It is estimated that about 8 percent of patients with DMD have this mutation.

3-52, 4-52, 5-52, 6-52, 9-52
10-52, 11-52, 13-52, 14-52, 15-52, 16-52, 17-52, 19-52
21-52, 23-52, 24-52, 25-52, 26-52, 27-52, 28-52, 29-52
30-52, 31-52, 32-52, 33-52, 34-52, 35-52, 36-52, 37-52, 38-52, 39-52
40-52, 41-52, 42-52, 43-52, 45-52, 47-52, 48-52, 49-52
50-52, 52, 54-58, 54-61, 54-63, 54-64, 54-66, 54-76, 54-77

This list contains documented as well as theoretical mutations potentially amenable to exon 53 skipping.
Not all deletions have been studied and this list may not be complete.

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But if you ever need the names of those you couldn't save….

OBITUARIES > Posted August 9, 2020 | Updated August 10, 2020

Obituary: Michael James Norton

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Michael James Norton

STANDISH – Michael James Norton, 33, also known as Michael HMC Norton, the Heavy Metal Cripple, was born April 18, 1987, in Portland, to Terrence and Suzan (Roberts) Norton.

He was born with bilateral club feet, for which he had to have casting and surgery. It wasn't until he was 4 years old, living in Germany, that we noticed he was having other difficulties. We found later that he had Duchenne Muscular Dystrophy. The doctors did not give us much encouragement, except that we would need counseling if we had problems along the way because Michael's life would be shortened. All we can say is that doctors do not have all the answers. Nobody should take away your hope, ever. Mike's life proved that. He lived until the age of 33, using a ventilator for five years.

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With your past and your future precisely divided….

- AAV therapy?
- Stem cell therapy?
- Good old prednisone?

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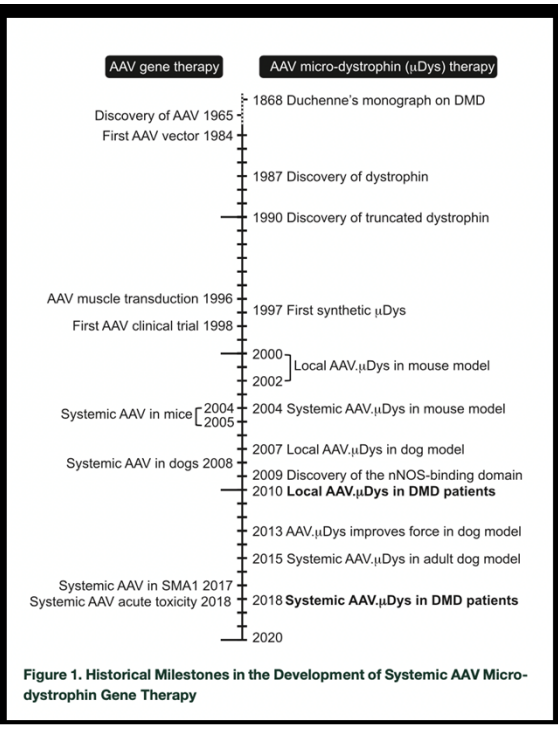

Figure 1. Historical Milestones in the Development of Systemic AAV Micro-dystrophin Gene Therapy

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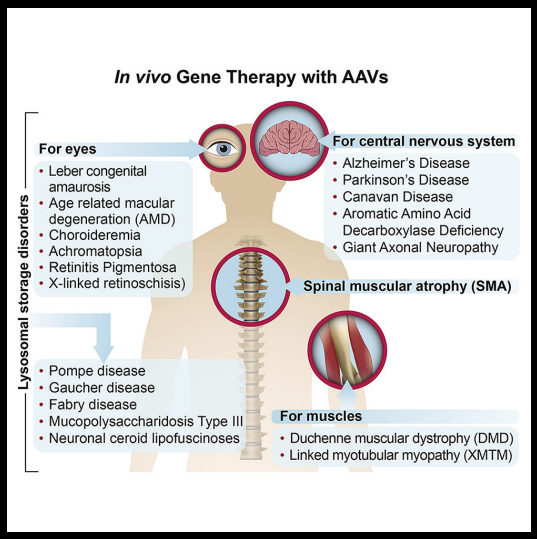

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3 active trials now!

- Micro-Dystrophin Clinical Trials
  - Using AAV to deliver miniaturized dystrophin gene
  - Based upon clinical observations of mild Becker patients who are missing very large portions of the DMD gene
  - Open label/safety muscle biopsy study show increased micro-dystrophin expression and clinical improvement

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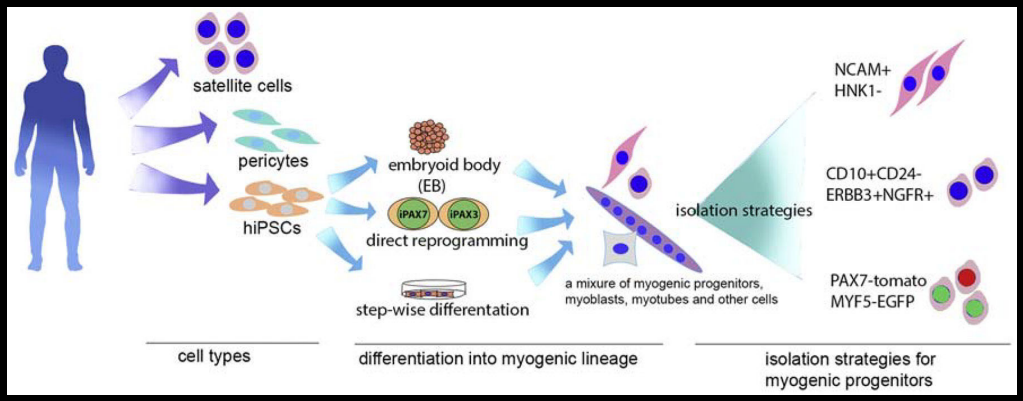
Exp Neurol. 2020 January ; 323: 113086. doi:10.1016/j.expneurol.2019.113086.

Stem cell-based therapies for Duchenne muscular dystrophy

Congshan Sun[1,3], **Carlo Serra**[1,3], **Gabsang Lee**[2], **Kathryn Wagner**[1,3]

[1]Departments of Neurology and Neuroscience, Johns Hopkins University School of Medicine, Baltimore, Maryland, 21205, USA.



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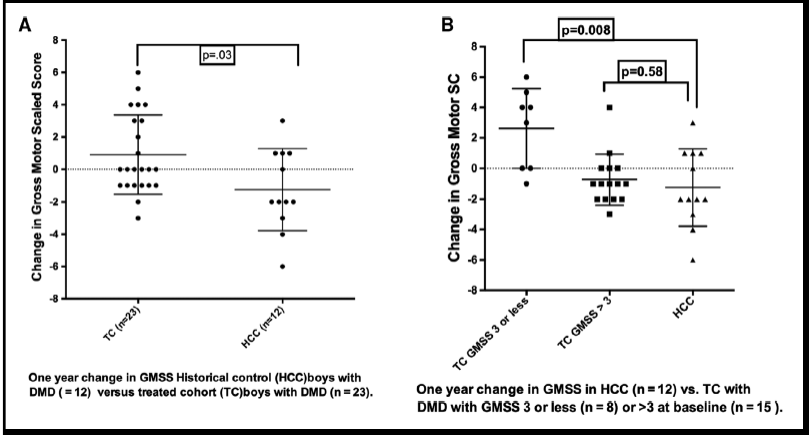
TWICE-WEEKLY GLUCOCORTICOSTEROIDS IN INFANTS AND YOUNG BOYS WITH DUCHENNE MUSCULAR DYSTROPHY

ANNE M. CONNOLLY, MD,[1,2] CRAIG M. ZAIDMAN, MD,[1,2] PAUL T. GOLUMBEK, MD, PhD,[1,2] MARY M. CRADOCK, PhD,[2] KEVIN M. FLANIGAN, MD,[3] NANCY L. KUNTZ, MD,[4] RICHARD S. FINKEL, MD,[5] CRAIG M. MCDONALD, MD,[6] SUSAN T. IANNACCONE, MD,[7] PALLAVI ANAND, MBBS,[1] CATHERINE A. SIENER, PT, MHS,[1] JULAINE M. FLORENCE, PT, DPT,[1] LINDA P. LOWES, PT, PhD,[3] LINDSAY N. ALFANO, PT, DPT, PCS,[3] LINDA B. JOHNSON, PT,[6] ALINA NICORICI, BS,[6] LESLIE L. NELSON, PT, PhD,[7] JERRY R. MENDELL, MD,[3] and FOR THE MDA DMD CLINICAL RESEARCH NETWORK



One year change in GMSS Historical control (HCC)boys with DMD (= 12) versus treated cohort (TC)boys with DMD (n = 23).

One year change in GMSS in HCC (n = 12) vs. TC with DMD with GMSS 3 or less (n = 8) or >3 at baseline (n = 15).

Current standard of care suggests early use of daily or twice-weekly corticosteroids for children starting before "substantial physical decline" without specifying an exact age.[15] Controlled studies have never been performed in children younger than 4 years. This work suggests a different approach for this very young population. An additional limitation is that this study was not dose finding, and therefore it is possible that a lower dose might be equally efficacious. Because the effect was most profound in the most delayed children, twice-weekly GC appears to provide a safe approach for early treatment as long as weight is carefully monitored.

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Summary of agents

- Duchenne:
- Current FDA approval:
  - Prednisone, deflazacort
  - 3 different exon skipping therapies accounting for ~29% of all mutations
- Future: AAV microdystrophin therapy, earlier intervention with twice weekly hormonal therapy

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Summary of agents

- SMA:
- Current FDA approval:
  - Nusinersen/Spiranza, mRNA splicing modifier to upregulate SMN production, intrathecal only every 4 months, approved for all SMA types
  - Risdiplam/Evrysdi, mRNA splicing modifier to upregulate SMN production, daily oral therapy, approved for all SMA types
  - Onasemnogene Abeparvovev/Zolgensma, AAV-9 therapy to deliver fully functional SMN gene into motor neurons

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Conclusions

- Community/Relationships!
- Take Chances!
- Read the book!
- Share your experience!
- Build it with your patients and your colleagues. You can't get it done on your own.
- Get inspired by your patients and families – its ok to be uncomfortable and the only one doing something
- The great and knowledgeable Icculus
- The good and the bad, we all learn from each other

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