Nomination and Prioritization Workgroup Report: Spinal Muscular Atrophy (SMA)

ADVISORY COMMITTEE ON HERITABLE DISORDERS
IN NEWBORNS AND CHILDREN
MAY 11 – 12, 2017

PRESENTED BY DR. BETH TARINI, MD
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UNIVERSITY OF IOWA STEAD FAMILY CHILDREN'S HOSPITAL

Nomination of Spinal Muscular Atrophy (SMA)

NOMINATOR:

Cure SMA

CO-SPONSORING ORGANIZATIONS:

Muscular Dystrophy Association

SMA NBS Working Group

Spinal Muscular Atrophy (SMA) - Overview

- Muscle weakness and atrophy resulting from progressive degeneration and loss of anterior horn cells in the spinal cord and the brain stem
- Onset ranges from birth to adolescence/young adulthood
- Clinical features span a continuum without clear delineation of subtypes

SMA overview (cont.)

SMA Type	Alternate Name	Age at Onset	Maximum muscular activity achieved	Life Expectancy
SMA Type 0	Congenital	Prenatal	None	Rarely survive past 6 months
SMA Type I	Severe infantile acute; Werdnig-Hoffman disease	Birth to six months	Never sit without support, problems sucking, swallowing	Median = 24 months
SMA Type II	Infantile chronic	Six to twelve months	Sit independently, lose this ability by mid-teens	70% alive at age 25
SMA Type III	Juvenile, Wohlfart-Kugelberg-Welander disease	After 18 months	Walk independently, lose this ability with time	Normal
SMA Type IV	Adult-onset	20-30 years	Mild to moderate muscle weakness; Typically only proximal muscles are affected (upper arms, legs)	Normal

Genetics and Epidemiology of SMA

- Autosomal recessive inheritance, variable phenotypic expression
- Incidence estimated at 1 in 10,000 live births
- Carrier frequency of 1/40 – 1/60
- *SMN1* exon 7 is absent in the majority of patients independent of the severity of SMA
- *SMN2* copy number modifies the severity of disease

Prior et al [2011]

Genetics and Epidemiology of SMA

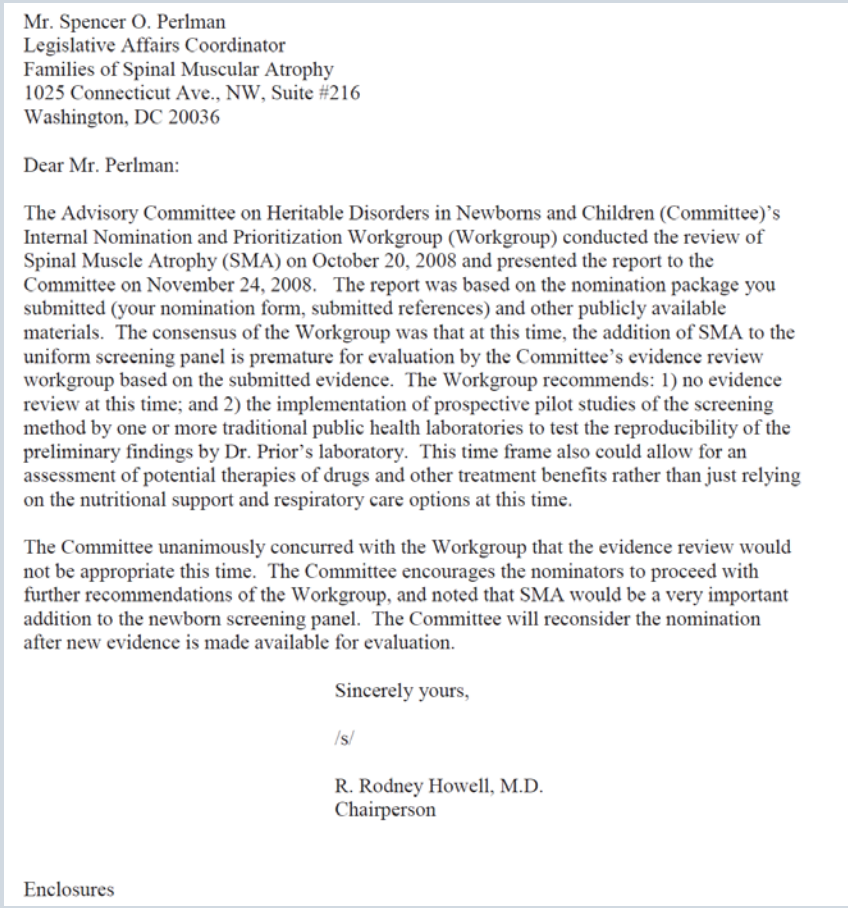
SMA Type	Alternate Name	Number of SMN2 copies
SMA Type I	Severe infantile acute; Werdnig-Hoffman disease	2
SMA Type II	Infantile chronic	3-4
SMA Type III	Juvenile, Wohlfart-Kugelberg-Welander disease	3-4
SMA Type IV	Adult-onset	4-8

Phan [2015]

2008 ACHDNC N&P Workgroup Review and Committee Decision

"The consensus of the Workgroup was that at this time, the addition of SMA to the uniform screening panel is premature for evaluation by the Committee's evidence review workgroup based on the submitted evidence."

"The Workgroup recommends: 1) no evidence review at this time; and 2) the implementation of prospective pilot studies of the screening method by one or more traditional public health laboratories"



Mr. Spencer O. Perlman
Legislative Affairs Coordinator
Families of Spinal Muscular Atrophy
1025 Connecticut Ave., NW, Suite #216
Washington, DC 20036

Dear Mr. Perlman:

The Advisory Committee on Heritable Disorders in Newborns and Children (Committee)'s Internal Nomination and Prioritization Workgroup (Workgroup) conducted the review of Spinal Muscle Atrophy (SMA) on October 20, 2008 and presented the report to the Committee on November 24, 2008. The report was based on the nomination package you submitted (your nomination form, submitted references) and other publicly available materials. The consensus of the Workgroup was that at this time, the addition of SMA to the uniform screening panel is premature for evaluation by the Committee's evidence review workgroup based on the submitted evidence. The Workgroup recommends: 1) no evidence review at this time; and 2) the implementation of prospective pilot studies of the screening method by one or more traditional public health laboratories to test the reproducibility of the preliminary findings by Dr. Prior's laboratory. This time frame also could allow for an assessment of potential therapies of drugs and other treatment benefits rather than just relying on the nutritional support and respiratory care options at this time.

The Committee unanimously concurred with the Workgroup that the evidence review would not be appropriate this time. The Committee encourages the nominators to proceed with further recommendations of the Workgroup, and noted that SMA would be a very important addition to the newborn screening panel. The Committee will reconsider the nomination after new evidence is made available for evaluation.

Sincerely yours,

/s/

R. Rodney Howell, M.D.
Chairperson

Enclosures

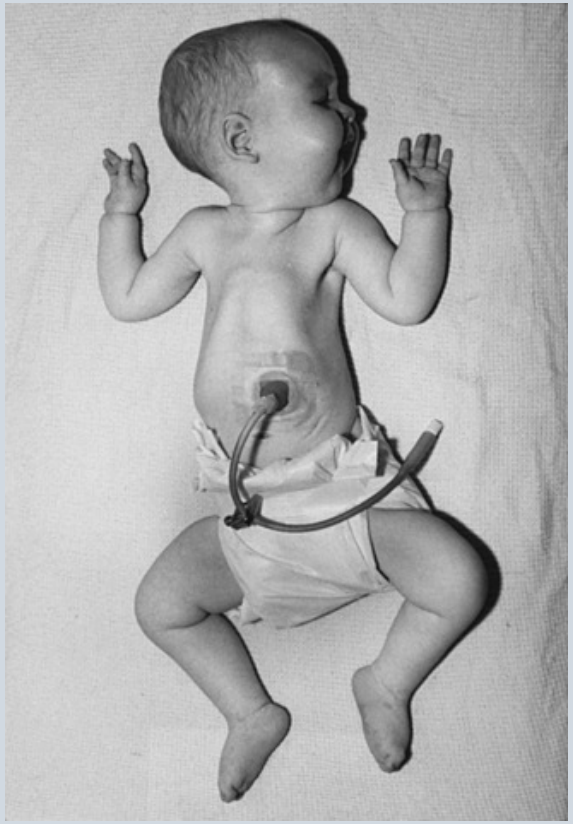
https://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/nominatecondition/workgroup.html

Key Questions

- Is the condition medically serious?
- Is the case definition and the spectrum of the disorder well described, to help predict the phenotypic range of those children who will be identified based on population-based screening?
- Are there prospective pilot data (U.S. and/or international) from population-based assessment available for this disorder?
- Does the screening test have established analytic validation?
- Are the characteristics of the screening test(s) reasonable for the newborn screening system (among other aspects, a low rate of false negatives)?
- Are those who are most likely to benefit from treatment identifiable (especially if the treatment is onerous or risky)?
- Is there a widely available and CLIA and/or FDA approved confirmatory test/diagnostic process?
- Are there defined treatment protocols, FDA approved drugs (if applicable) and treatment available?

Is the condition medically serious?

YES



http://clinicalgate.com/anterior-horn-cell-and-cranial-motor-neuron-disease/

http://curesma.ca/sma_type2.htm

Is the case definition and the spectrum of the disorder well described, to help predict the phenotypic range of those children who will be identified based on population-based screening?

- Continuum of clinical features correlating loosely to genotype
  - The type designations are based on the highest achieved functional milestone, not genotype
  - SMN2 is predictive but not determinative of SMA clinical severity
- Type III and IV, less severe, late-onset forms

Are there prospective pilot data (U.S. and/or international) from population-based assessment available for this disorder?

Taiwan NBS SMA Pilot Study

- Detect the SMN1 deletion
  - Real-time PCR TaqMan® single nucleotide polymorphism (SNP) genotyping assay on a StepOnePlus™ RT-PCR 96-well System (Applied Biosystems)
  - Second Tier - digital droplet PCR (ddPCR) to exclude false positives, and to detect SMN2 copy number

New York SMA Pilot Study

- Detect the SMN1 deletion
  - Custom TaqMan real-time polymerase chain reaction (PCR) assay on a real-time PCR platform such as an ABI 7900 or QuantStudio ™ 12K Flex Real-Time PCR System (ThermoFisher ™ Scientific)
  - Second Tier – targeted sequencing for infants positive for SMN1 deletion, custom TaqMan assay/ddPCR to detect SMN2 copy number

Assay in Development - PerkinElmer Five-Plex qPCR

- Real-time PCR assay targeting SMN1 and SMN2 SNPs in exon 7 using dual-labeled lock nucleic acid Taqman® probes using a 96-well or 384-well format on a ThermoFisher ™ QuantStudio 5 or a QuantStudio ™ DX real time PCR platform.
- No second tier necessary

Does the screening test have established analytic validation?

Taiwan:

- Project submitted for peer review publication
- All positive cases have been validated by 2 other methods
- Nov. 2014 - Sept. 2016: Infants screened = 120,267, PPV = 100%, FPR = 0%
- Infants Screen Positive = 15 by primary test, 7 by 2nd tier, incidence = 1 in 17,181
- Carriers NOT detected

New York:

- All positive cases have been confirmed by an outside diagnostic laboratory
- Jan. 2016 – Dec. 2016: Infants screened = 3,269, PPV = 100%, FPR = 0%
- Infants Screen Positive = 1 by both primary and 2nd tier testing
- Carriers ARE detected and reported

Are the characteristics of the screening test(s) reasonable for the newborn screening system (among other aspects, a low rate of false negatives)?

- Specificity for the detection of SMN1 is 100%
- Both screening pilots have a 5% false negative rate; neither will detect compound heterozygous cases
- The pilot NBS programs have not reported any false negatives to date

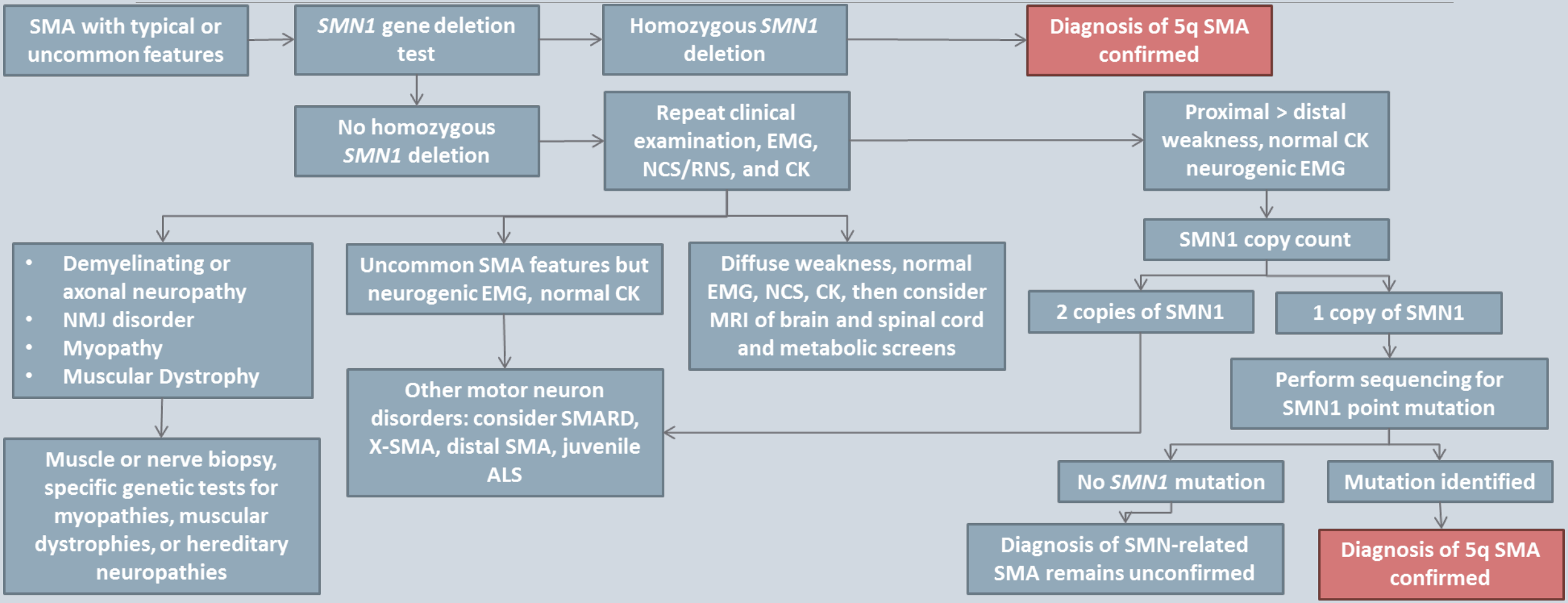
Are those who are most likely to benefit from treatment identifiable (especially if the treatment is onerous or risky)?

Severe SMA mice models show that induction of SMN expression in the early postnatal period substantially improves survival, whereas later induction is less effective

Presymptomatic or early symptomatic restoration of SMN (during NMJ maturation) will likely produce the best response to therapy

Farrar et al [2017]

Is there a widely available and CLIA and/or FDA approved confirmatory test/diagnostic process?



Wang et al [2007]

Confirmatory test/diagnostic process (cont.)

SMN deletion testing and SMN2 copy number determination analysis takes 5 to 8 days.

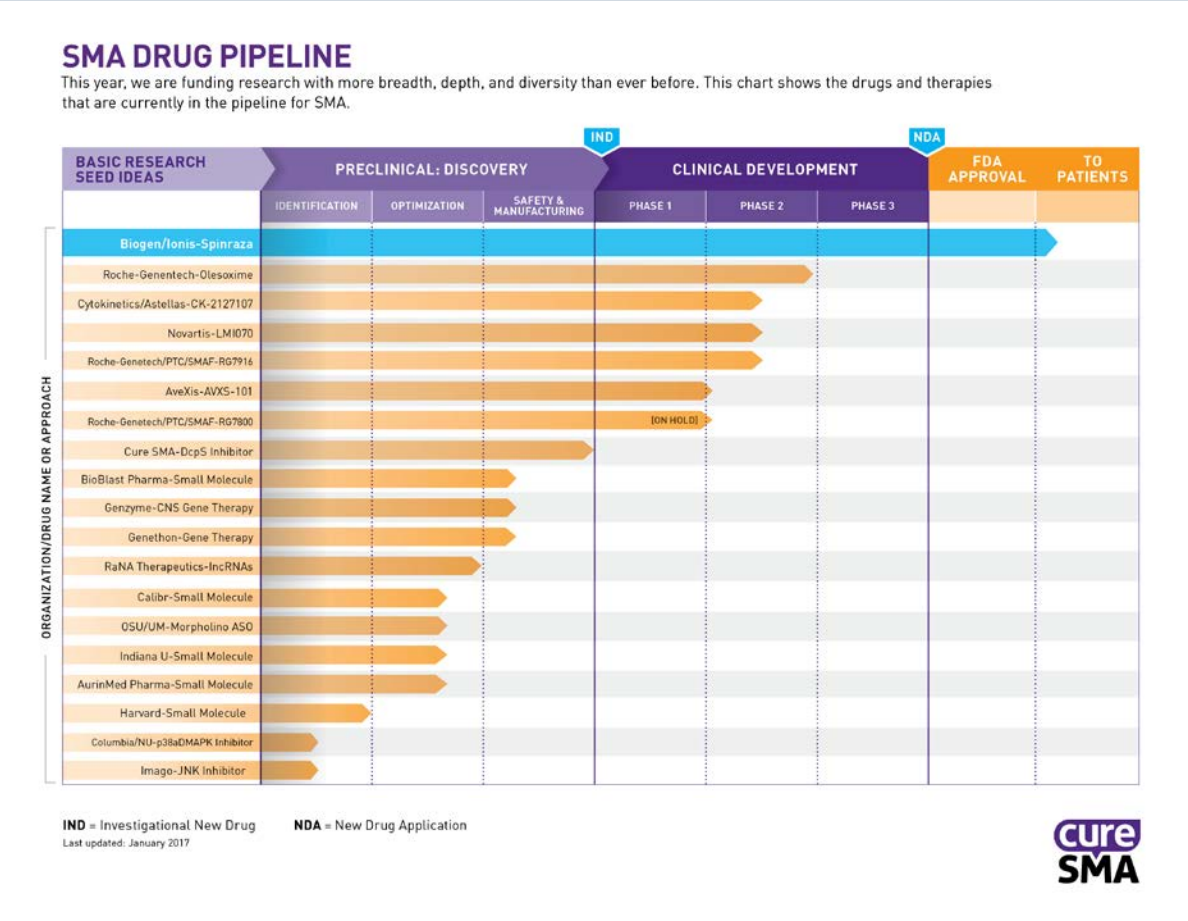
Test is available at CLIA certified labs throughout the United States.

Are there defined treatment protocols, FDA approved drugs (if applicable) and treatment available?

- Pulmonary care
- Gastrointestinal and Nutritional care
- Orthopedic and Rehabilitation care
- Palliative care

Wang et al [2007]

Are there defined treatment protocols, FDA approved drugs (if applicable) and treatment available?



http://www.curesma.org/research/latest-advances/

Are there defined treatment protocols, FDA approved drugs (if applicable) and treatment available?

FDA News Release

FDA approves first drug for spinal muscular atrophy

New therapy addresses unmet medical need for rare disease

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For Immediate Release

December 23, 2016

Release

The U.S. Food and Drug Administration today approved Spinraza (nusinersen), the first drug approved to treat children and adults with spinal muscular atrophy (SMA), a rare and often fatal genetic disease affecting muscle strength and movement. Spinraza is an injection administered into the fluid surrounding the spinal cord.

https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm534611.htm

http://media.biogen.com/press-release/neurodegenerative-diseases/us-fda-approves-biogens-spinraza-nusinersen-first-treatment

FDA approved drugs (cont.)

Spinraza® (Nusinersen):

- Administered through intrathecal injection
- The wholesale acquisition cost for the first year of treatment is $750,000; and $375,000 in subsequent years

https://www.nytimes.com/2016/12/30/business/spinraza-price.html?_r=0

FDA approved drugs (cont.)

ENDEAR Study

- Phase 3, randomized, double-blind, sham procedure controlled study
- Genetic diagnosis of SMA, 2 copies of *SMN2*, onset of symptoms at age ≤6 mos. and age ≤7 mos.

NURTURE Study

- Phase 2, open-label, single arm study
- Genetic diagnosis of 5q SMA, 2 or 3 copies of *SMN2*, presymptomatic infants, age ≤6 weeks

Kuntz et al [2017]; De Vivo et al [2017]

Final Results - Phase 3 ENDEAR

Nusinersen n=80, Control n=41

Nusinersen Treatment Group vs. Sham Control

- Clinically and statistically significant percentage of motor milestone responders (more HINE categories with improvement than worsening), greater improvement in total motor milestone score, and achievement of motor milestones unexpected for infants with SMA Type I
  - Continued improvement over course of the study
- Prolonged event-free survival (time to death or permanent ventilation), and overall survival
  - Risk of permanent ventilation was 34% lower in Nusinersen-treated infants
- No adverse events considered related to treatment

Kuntz et al [2017]

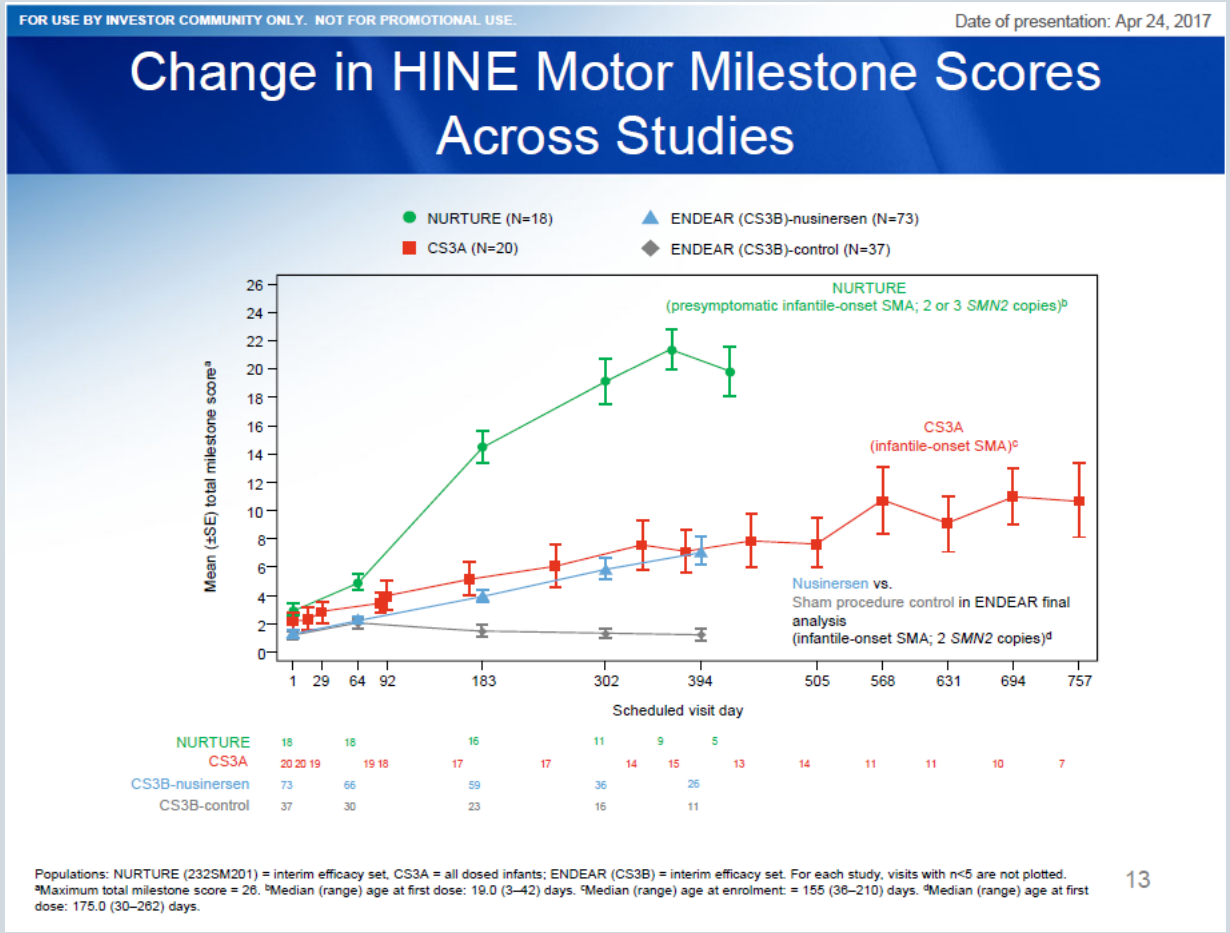
Interim Results - Phase 2 NURTURE

Nusinersen n=20

- Data cut-off: October 31, 2016, median (range) enrollment of 317.5 (2-524) days
- All infants alive and none required respiratory intervention
- Continued beneficial effects of Nusinersen, most infants achieving motor milestones consistent with normal development
  - Some enrollees achieving standing unaided, independent walking
- Well tolerated / no specific safety concerns

De Vivo et al [2017]

FDA approved drugs (cont.)



ENDEAR Study

- Nusinersen-treated infants: clinically and statistically greater percentage of motor milestones, statistically significant increases in event-free and overall survival (vs. sham procedure control)

NURTURE Study

- All infants alive without requiring chronic respiratory support, most infants achieving motor milestones generally consistent with normal development and not with SMA Type 1 or 2

Kuntz et al [2017]; De Vivo et al [2017]

Are there defined treatment protocols, FDA approved drugs (if applicable) and treatment available?

There is no formal consensus on when to treat SMA patients who are diagnosed pre-symptomatically.

Which pre-symptomatically identified infants should be treated as soon as possible with SMN up-regulating therapy?

For those whom you would NOT recommend immediate treatment, what should be done (follow up frequency, monitoring/tests, threshold for treatment)?

Nomination and Prioritization Workgroup Recommendation

MOVE SPINAL MUSCULAR ATROPHY FORWARD TO FULL EVIDENCE REVIEW

N & P Workgroup cont.

Considerations for evidence review:

- No recommendations or guidelines for specific SMA types management strategies
- Burden associated with carrier identification
- Addressing the 5% compound heterozygous cases

References

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Phan HC, Taylor JL, Hannon H, Howell R. Newborn screening for spinal muscular atrophy: Anticipating an imminent need. *Semin Perinatol*. 2015;39(3):217-29.

Farrar MA, Park SB, Vucic S, et al. Emerging Therapies and Challenges in Spinal Muscular Atrophy. *Ann Neurol*. 2017;81:355-368.

Wang CH, Finkel RS, Bertini ES, et al. Consensus Statement for Standard of Care in Spinal Muscular Atrophy. *Journal of Child Neurology*. 2007;22(8):1027-1049.

Kuntz N, Finkel RS, Mercuri E, et al. Final Results of the Phase 3 ENDEAR Study Assessing the Efficacy and Safety of Nusinersen in Infants With Spinal Muscular Atrophy (SMA). Presentation, American Academy of Neurology 69th Annual Meeting, Boston, MA, April, 2017.

De Vivo DC, Wuh-Liang H, Reyna SP, et al. Interim Efficacy and Safety Results from the Phase 2 NURTURE Study Evaluating Nusinersen in Presymptomatic Infants with Spinal Muscular Atrophy. Presentation, American Academy of Neurology 69th Annual Meeting, Boston, MA, April, 2017.