2019 Annual SMA Conference

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Funding a Comprehensive Research Program: Over $80 Million in Total Research Funding

- **Basic research** to understand disease biology
- **Drug discovery** to make practical new therapies
- **Clinical and regulatory** to efficiently approve new drugs
- **Care research** to improve patient care and quality of life
- **Researcher meeting** to share and promote progress

_The Cure SMA funding model is based on independent and expert review by our SAB, TAC, and MAC._

_Over $5M invested in care and research in both FY19 and FY20._
Two Approved Drugs
Six Drugs in Clinical Trials
Strategic Goals in Research

• Build a comprehensive clinical care network and data registry to enable an optimal SMA standard of care

• Redefine the SMA disease classification
  – Clinical data registry
  – Patient reported data project

• Enable drug development through the industry collaboration

• Fund basic and translational research leading to combination therapies
Therapeutic Strategies – SMN Dependent

- **SMN2 promoter activation**
  - SMN2 gene will be “on” more generating more SMN protein
- **Gene Therapy**
  - Replace the missing SMN1 gene via a viral vector
  - Ex. Zolgensma (Avexis)
- **SMN2 splicing modulation**
  - Redirect splicing of SMN2 to make more full-length transcripts
  - Antisense Oligonucleotides (ASOs) or small molecules
  - Ex. Spinraza (Biogen)
  - Ex. Risdiplam (Roche-Genentech)
  - Ex. Branaplam (Novartis)
Therapeutic Strategies – SMN Independent

- **Neuroprotection**
  - Protect against neuronal injury or degradation

- **Muscle enhancement**
  - Prevention or restoration of loss of motor function
  - Ex. CK2127107 (Cytokinetics)
  - Ex. SRK-015 (Scholar Rock)

- **Combinations of the above**
US Trials Currently Recruiting

• A Study of Risdiplam RO7034067 in Adult and Pediatric Participants with Spinal Muscular Atrophy (Clinicaltrials.gov Identifier: NCT03032172)
  – Also Known By: JEWELFISH
  – General Criteria: Children, teens and adults age 6 months -60 years who have previously been exposed to an SMN2-targeting therapy or a gene therapy (washout period applies).
  – Phase: Phase 2, open-label with sites in New York City and Palo Alto, California

• A Study of Risdiplam in Infants With Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy (Clinicaltrials.gov Identifier: NCT03779334)
  – Also Known By: RAINBOWFISH
  – General Criteria: Infants up to age 6 weeks
  – Open label with site in New York and Orlando, Florida

• Study of Intrathecal Administration of AVXS-101 for Spinal Muscular Atrophy (Clinicaltrials.gov Identifier: NCT03381729)
  – Also known as STRONG
  – Highest dose cohort 3
  – ≥6 months to 60 months of age; 3 copies of SMN2; symptoms < 12 months
  – Sit independently and not standing or walking independently
  – Phase1 : 27 subjects at 11 sites in the US
US Trials Currently Recruiting

- Phase 2 Study of SRK-015 in Patients With Type 2 or Type 3 Spinal Muscular Atrophy known as TOPAZ ((Clinicaltrials.gov Identifier: NCT03921528))

- Phase 2 trial to evaluate safety and efficacy in 55 Type 2 and 3 patients for 12 months
  - Cohorts 1: Patients with ambulatory Type 3, ages 5 to 21 years as monotherapy or in conjunction with an approved SMN upregulator therapy
  - Cohort 2: Patients with Type 2 or Non-Ambulatory Type 3, ages 5 to 21 years and who are already receiving treatment with an approved SMN upregulator.
  - Cohort 3: Patients with Type 2, ages ≥2 years old and and initiated treatment with an approved SMN upregulator before five years of age
- If receiving the SMN upregulator therapy spinraza, must have completed the loading regimen and initiated maintenance dosing with at least 4 weeks after the first maintenance dose having elapsed prior to screening and plan to remain on duration for study.
  - Current sites in New York and California
Strategic Goal: Facilitate SMA Drug Development with Industry Collaboration

- 7 companies co-funding and shaping projects
  - Regulatory Interactions
    - Patient Focused Drug Development Meeting with FDA in April 2017
    - Risk / Benefit Survey for SMA
    - Patient Reported Outcome Measure Development
    - Economic Burden of Disease Study
  - Increasing clinical trial site capacity
    - Identifying and training up to 20 new trial sites
  - Education of HCP & patients to reduce diagnosis time
    - Educational campaign with professional societies (AAP, AAN, CNS, NORD, CNF)
    - Concerned Parent and HCP website called SMARTMOES
  - Patient Reported Data Project
    - Annual Community Survey
    - New contacts data reports
  - Registry Discussion Group
Motor delays or missed milestones can signal serious conditions like SMA (spinal muscular atrophy). There is new hope, but it’s important to act swiftly and make SMArt Moves.

MICROSITE
Landing Page – Home Page

- User friendly
- Helpful tools
- Hopeful messaging
- Special hub for Healthcare Professionals

SmartMoves.CureSMA.org
Strategic Goal: Patient Experience in Cure SMA Database

- **7,900 individuals with SMA**
  - 15,000 family members and 185,000 supporters
- **3,717 new contacts since July 2009**
  - Over 350 newly diagnosed annually
  - Type, incidence, prevalence, burden of disease, geography, diagnostic journey, median survival
  - Care packages, informational packets, and scholarships for conference
- **Real time changes: annual survey**
- **Supports research recruitment efforts**
  - 15 requests per year
- **Supports clinical trial recruitment efforts**
  - 1,100 patients into 15 clinical trials
- **Shared with industry, payers, & regulators**

![Type distribution chart]

- Type 0: 4%
- Type I: 7%
- Type II: 0%
- Type III: 42%
- Type IV: 30%
- Unknown: 17%
Representative Data: Average Age of Diagnosis

- **Type I**
  - Median: 4 months **
  - Range: (-8* - 127 months)

- **Type II**
  - Median: 17 months
  - Range: (-9* - 520 months)

- **Type III**
  - Median: 4.2 years
  - Range: (0-76 years)

- **Type IV**
  - Median: 43 years
  - Range: (2 - 82.3 years)

**Expect to see reduction in future years with NBS.**

*Diagnosed prenatally*
Representative Data

Number of Deaths by 100 affected individuals in database, by month and year

Out of Pocket SMA-related Expenses

**Statistically Significant difference between the two time periods

2017 Community survey sub-analysis (n=207) of event group vs. non-event group (death or requiring > 16 hours of ventilation)

- Age at diagnosis: Event at 5.7 months vs. Non-event at 6.1 months
- BiPAP use: Event at 27.7% versus Non-event at 72.3% (p<0.0001)
- Participation in clinical trial: Event at 26.3% versus Non-event at 73.3% (p=0.001)
Representative Data: Sitting in SMA Type I

AAN presentation on Shine extension study in infantile SMA shows ongoing gains in motor milestones: shows 51% (26/51) sitting without support.

*2017 & 2018: Question was what was the maximum motor function you have ever achieved. Assumed able to sit without support if any of the following choices were picked: maintain seated position unsupported, crawl 4 point, stand with support, cruise along furniture, stand without support; 2019: Question was choose all the motor functions you have ever been able to achieve.
Strategic Goal: Combination Therapies and Multiple Drug Options

- 113 Basic Research Grants for $14M since 2004
- 14 Preclinical Drug Projects for $21M since 2000
- Novel target ID and combinations for maximally effective treatments for all SMA types and stages
  - Identify non-SMN drug targets
  - Test combinations with SMN up-regulating drugs
  - Optimized SMN enhancing therapies: next in class drugs
- All RFPs in basic & drug research now geared to these goals
Combinations

SMN2 splicing modifier approach
- Antisense oligonucleotides molecules
- Oral small molecules
  (Oral [systemic] and/or intrathecal delivery; increased expression of full-length SMN2 transcript)

SMN independent pharmacological approach
- Neuroprotectors/
  Neurotransmission enhancers / Myoactivators

Nutrition
Rehabilitation
Physiotherapy
Respiratory care
Orthopedic Surgery

Gene replacement
- Intrathecal or systemic
  SMN1 gene transfer/
  Stem cell therapy?

From Tizzano and Finkel, 2017.
SMN Protein: Where, When, How?

- SMN is in all cell types, so why motor neurons?
- What other cells need targeted by drugs?
- When is SMN needed (development or degeneration)?
- What does SMN protein do? What are its targets?
- New targets less validated and may result in more early failures.

How the pipeline has grown:

- Total programs
- Active programs
- Programs in clinical trials
- Approved drugs

Number of companies investing in SMA drug programs:

- 2000: 0
- 2005: 5
- 2010: 10
- 2015: 15
- 2019: 15
Data Needed for Combination Therapies: Combinations Must be Chosen Carefully

- **General**
  - Are they safe when used together?
  - Is there additive clinical benefit?
  - Does that benefit outweigh the risk of using together?
  - Does one drug reduce efficacy or availability of the other?
  - Can they readily be co-administered?

- **Combining Two SMN Enhancers**
  - Are SMN levels increased together over either drug alone?
  - Do they work by different biological mechanisms?
  - Do they target different cells?
  - Do they provide longer duration of effect together?
  - If not yes to one, utility of the particular combination is unlikely.
  - Readouts in trials with two combination therapies more challenging.
Summary of Our Research Goals

• Different mechanisms or routes of admin for SMN drugs
• Basic research leading to novel targets beyond SMN
• Drug combinations with different mechanisms of action
• Increased clinical trial capacity
• Understanding patient experience through data
• Regulatory education and sharing patient data
• HCP and general awareness to reduce diagnostic delay
Thank you!