

Medical Treatment of spinal muscular atrophy

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Spinal muscular atrophy

Spinal muscular atrophy

- Autosomal recessive inheritance
- Incidence : 1:6000~1:10,000 live births
- Carrier frequency : 1:35-1:50

- Degeneration of spinal cord motor neurons
 - Progressive muscular atrophy and weakness
 - Symmetric weakness proximal > distal, LE>UE
 - Respiratory complications leads to premature deaths

- No cure or effective treatment available

Spinal muscular atrophy

- The spectrum of SMA type 0, 1, 2, 3 and 4
 - Depends on the age of onset and the maximal achievable motor function
 - **SMA 0**
 - The most severe form beginning already in utero and death usually occurs within days to weeks after birth
 - **SMA 1**
 - Manifests within the first 6 months
 - **Non-sitters**
 - Begins as “floppy infants” and die within the first 2 years of life, mean survival ~7 months
 - Makes up 50-60% of all SMA cases
 - **SMA 2**
 - **Non-standers**
 - ~30% of newly diagnosed SMAs
 - **SMA 3**
 - Onset usually after 18 months
 - **Learn to walk** but often become wheelchair bound due to progressive nature of SMA
 - **SMA 4**
 - Rare (~1% of the disease population), age of onset after 30 years

Standard of Clinical Care

Basic principles

- *No curative treatment so far*
- No known therapies proven to alter the natural progression of muscle weakness
- Emphasis of care
 - Integrated, multidisciplinary team approach
 - Neurology, pulmonary medicine, orthopedics, GI, nutrition, oral care, physio/occupational therapies
 - Transition to adult care
 - *Anticipatory guidelines preventing or reducing secondary morbidities*

Basic principles

- Correct diagnosis, then give appropriate information to families
 - Diagnosis, prognosis, relevant organ systems affected
 - Future recurrence with pregnancy
 - Associated medical risk
 - Prophylactic immunization
 - Monitor nutrition and growth development
 - Family support and resources
 - Participation in research projects
 - Follow up determined on individual basis
 - Support medical team in the event of hospitalization
 - Mobility devices for independence : walkers, scooters and wheelchairs

Consensus Statement for Standard of Care in SMA

- Current Problems in the medical care of SMA
 - Wide clinical spectrum ranges from early infant death to normal adult life with only mild weakness
 - **Progressive nature** of the disease involving
 - Skeletal and respiratory muscle weakness
 - Gastrointestinal issues and associated under/overnutrition
 - Orthopedic issues progressing over time
 - Palliative care management
 - Genetic counseling for the patients and families

Clinical management of newly diagnosed SMA patients

- Family education and Counseling
 - Important d/t complexity of medical problems associated with the diagnosis of SMA
 - Inform multidisciplinary needs and regular follow up care
 - Explain disease process, pathogenesis, phenotype classification and expected prognosis
 - Inform online resources e.g. patient advocacy groups and clinical trials
- Genetic Topics
 - Autosomal recessive inheritance
 - Genetic testing for siblings and parents, and relatives of both sides of the families for recurrence risk in future pregnancy
 - Neonatal screening: controversial

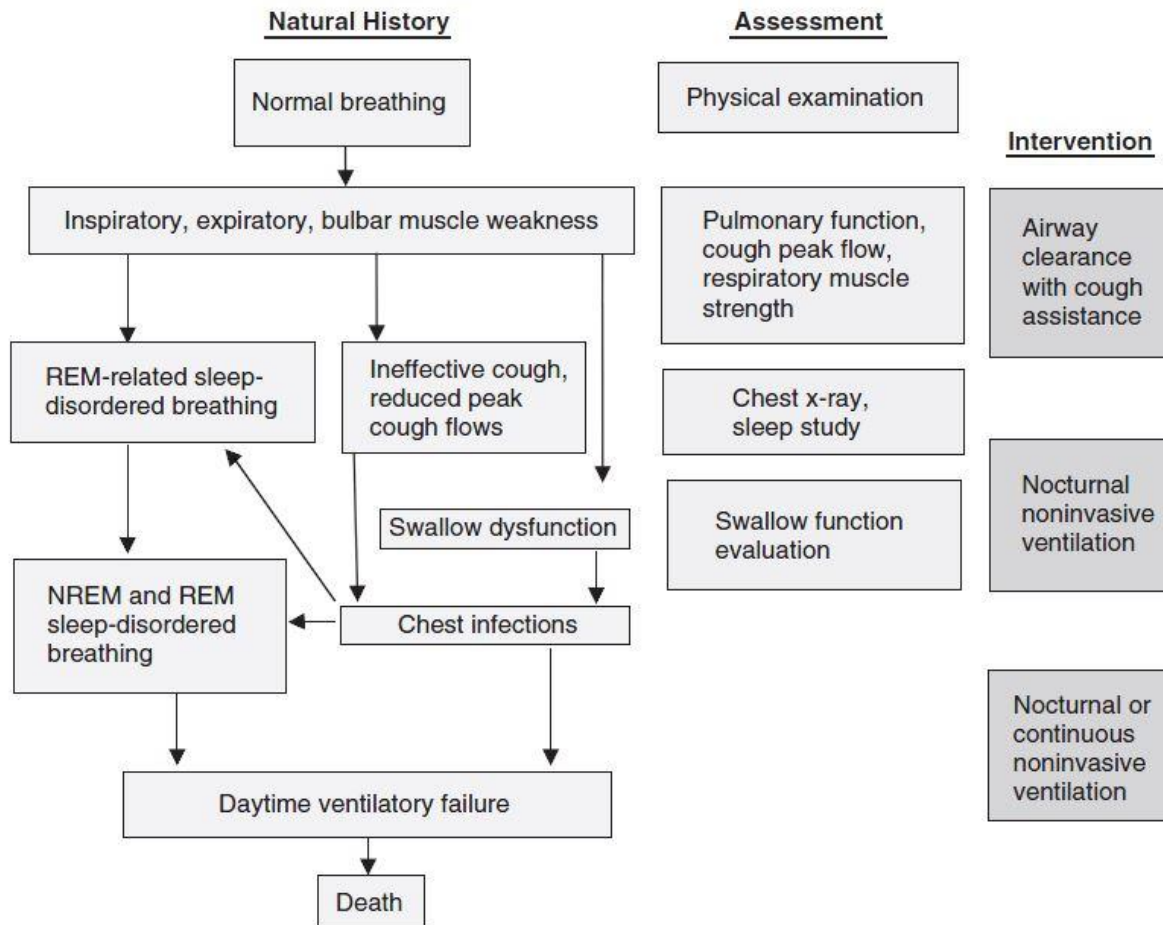
Pulmonary Care

- Key respiratory problems
 - Impaired cough resulting in poor clearance of lower airway secretions
 - Hypoventilation during sleep
 - Chest wall and lung underdevelopment
 - Recurrent infections that exacerbate muscle weakness

Pulmonary Care

- Pulmonary disease: major cause of morbidity and mortality
 - Combination of inspiratory and expiratory muscle weakness
 - Greater involvement of expiratory and intercostal muscles
 - Diaphragm relatively spared initially
 - Resultant bell-shaped chest c sternal depression
 - Even more compromised d/t scoliosis, swallowing dysfunction and reflux
 - Recurrent chest infection
 - nocturnal oxygen desaturation
 - nocturnal hypoventilation
 - daytime hypercarbia
 - daytime respiratory failure
 - No strong correlation between pulmonary functional score and need for mechanical ventilation (different from DMD!)

Pulmonary Care



Pulmonary Care

- Assessment frequency depends on the clinical status and rate of disease progression for each individual
- Regular evaluation every 3 to 6 months
- SMA 1
 - Cough effectiveness, breathing, gas exchange
 - Respiratory rate, work of breathing, paradoxical breathing, chest wall shape, skin color (cyanosis or pallor)
 - Respiratory muscle function tests
 - Peak cough flow, maximal inspiratory pressure, maximal expiratory pressure
 - Majority too young or too weak to perform PFT
 - Observation of cough ability may be useful
 - If $O_2 < 94\%$, airway clearance technique should be initiated
 - Overnight pulse oximetry: screen for nocturnal hypoxemia
 - EtCO₂, transcutaneous Co₂ and serum bicarbonate measures
 - Assess sleep-related hypoventilation
 - Insidious, and the patient may be clinically asymptomatic
 - Polysomnography/sleep study
 - Baseline and at least annual chest X-ray
 - Unsuspected atelectasis and aspiration pneumonia
 - **Survey the risk for dysphagia and aspiration**

Pulmonary Care

- SMA 2
 - P/Ex, evaluation for cough effectiveness
 - Pulmonary function tests
 - Maximal inspiratory pressure, maximal expiratory pressure, peak cough flow
 - Forced vital capacity
 - Scoliosis
 - Pulse oximetry
 - Sleep disordered breathing
 - [Routine swallow study not recommended unless clinically indicated](#)

Pulmonary Care

- Anticipatory respiratory care
 - Rapid access to specialty medical care providers
 - Daily management of airway clearance, secretion care and respiratory support (including NIV)
 - Nutrition and hydration
 - Low threshold to start antibiotics
 - Immunization for
 - Annual **influenza** vaccine, **pneumococcus** vaccine, **RSV** prophylaxis (palivizumab)
- Chronic Management
 - Airway clearance
 - Respiratory Support
 - Additional Management
 - Perioperative Care
 - At high risk of post anesthesia complication
 - Upper airway obstruction, hypoventilation, atelectasis
 - **Prolonged intubation, nosocomial infection, tracheostomy and even death**
 - **Postoperative pain should be actively managed**
 - **Respiratory status be optimized before surgery**

GI and Nutrition Care

- Key gastrointestinal problems
 - Feeding and swallowing problems
 - **Bulbar dysfunction universal** in SMA c severe weakness
 - May result in aspiration pneumonia
 - Gastrointestinal dysfunction
 - GE dysmotility, constipation, delayed gastric emptying, potentially life-threatening GE reflux
 - Growth and undernutrition/overnutrition
 - At risk for **undernutrition in SMA1**
 - At risk for **excessive weight gain in SMA 2 and 3**
 - Respiratory problem
 - Increased work of breathing may also result in increased energy expenditure

GI and Nutrition Care

- Feeding and Swallowing problems
 - Common in SMA 1 & 2
 - Prolonged mealtime, fatigue with oral feeding, choking or coughing during or after swallowing
 - Recurrent pneumonia
 - Difficulty in preoral phase c limited mouth opening and getting food to mouth for self-feeding
 - Difficulty in oral phase c weak bite force, reduced range of mandibular motion limiting mouth opening, increased fatigue of masticatory muscles
 - Biting and chewing issues
 - Prolonged mealtime and fatigue, insufficient intake
 - Poor coordination leads to penetration and aspiration of the airway

GI and Nutrition Care

- Evaluation of feeding and swallowing problems
 - Trained speech or occupational therapists
 - Videofluoroscopic swallow study
 - Effect of positioning and head control
 - Specific assessment required for laryngeal aspiration
 - Therapeutic strategies
 - **Adapted food texture and positioning**
 - **Gastrostomy tube feeding**
 - Optimal method when insufficient caloric intake or unsafe oral feeding is of concern
 - Consider Nissen fundoplication if reflux (+)
 - Laparoscopic procedure better for early postoperative extubation
 - Minimize amount of fasting preoperatively and to resume full nutritional support ASAP

GI and Nutrition Care

- Gastrointestinal dysfunction
 - Gastroesophageal reflux
 - Important determinant of mortality and morbidity
 - Can be associated c silent aspiration and pneumonia
 - “spitting up” or vomiting after meals, complaints of chest or abdominal discomfort, bad breath, obvious regurgitation of feeds
 - Some refuse feeds and risk for undernutrition
 - High-fat foods delay gastric emptying
 - Constipation, abdominal distension and bloating
 - Multifactorial in origin
 - Abnormal GI motility, ↓ dietary fiber, inadequate fluid intake, low muscle tone of the abdominal wall
 - Desaturation or respiratory distress may occur

GI and Nutrition Care

- Management
 - GE reflux
 - Acid neutralizers (Mg, Ca carbonate)
 - Acid secretion inhibitors
 - Histamine blockers, PPI (famotidine, ranitidine, omeprazole)
 - Short-term use reasonable
 - Delayed gastric emptying or diminished motility
 - Prokinetics (metaclopramide, erythromycin)
 - Probiotics (acidophilus, lactobacillus)
 - Gastrostomy tube feeding **DOES NOT ameliorate GE reflux**
 - Needs Nissen fundoplication

GI and Nutrition Care

- Growth and Undernutrition/Overnutrition problems
 - Growth failure common in SMA 1
 - Obesity in SMA 2 & 3
 - Pitfalls of being underweight
 - SMA kids have acceptable fat mass but low lean body mass
 - Underweight based on weight/height criteria not accurate
 - Decreased activity and lean body mass, reduced resting energy expenditure leads to risk of obesity
 - Regular follow up of growth charts especially growth velocity curve is important

GI and Nutrition Care

- Use of elemental formula – controversial
- Need for a reduced fat intake, in view of concern for mitochondrial fatty acid oxidation abnormality
- Need for protein supplementation in view of muscle wasting/atrophy
- Regular biochemical tests needed
- Determine body composition with DEXA (dual energy x-ray absorptiometry)
- Appropriate calcium and Vit D intake in view of osteoporosis and risk of fractures

Orthopedic care and Rehabilitation

- Key problems
 - Contractures throughout
 - Spinal deformity
 - Limited mobility and activities of daily living
 - Increased risk of pain
 - Osteopenia
 - Fractures

Palliative Care Issues

- Placing quality of life in conflict with duration of life, sometimes prolonging suffering rather than relieving the disease burden
- Always be mindful of potential conflict of therapeutic goals
- Open discussions and considerations ahead of
 - **Gastrostomy** tube placement
 - **Ventilatory support** before potential life-threatening respiratory insufficiency
 - Even end-of-life decisions

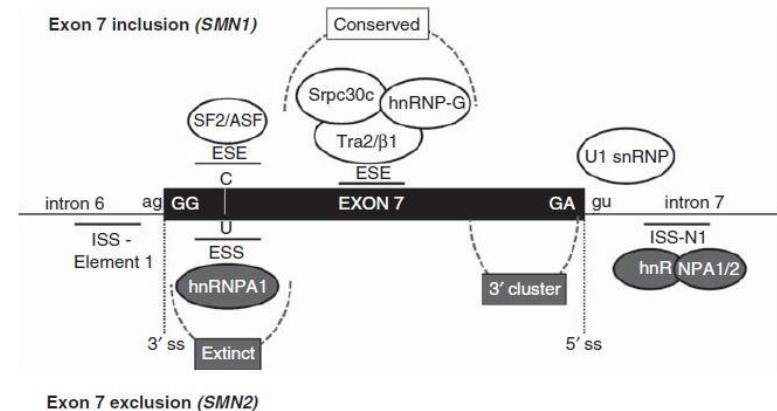
SMA Pathophysiology and Clinical Trials

Pathophysiology of SMA

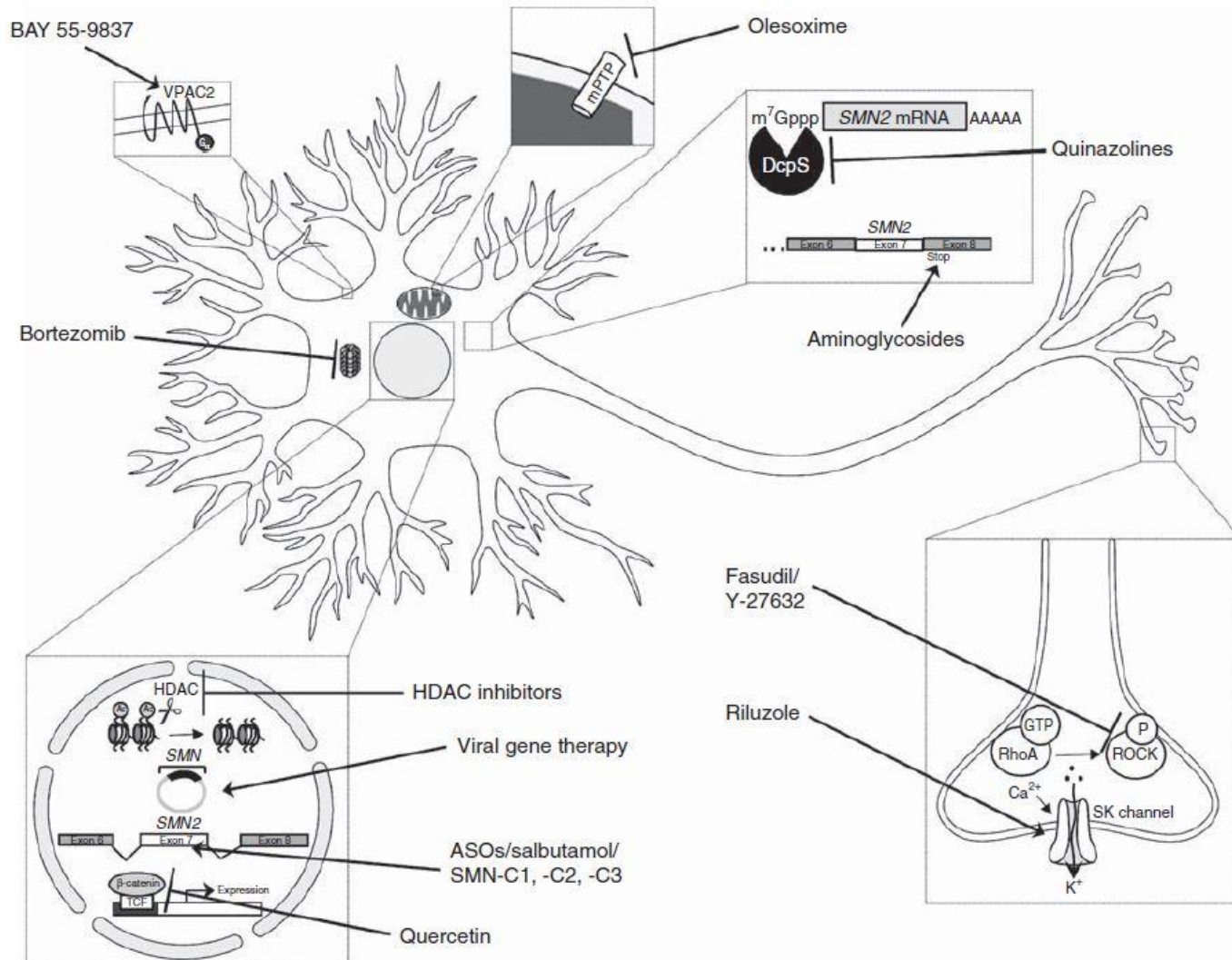
- Survival motor neuron (SMN) 1 and SMN 2 gene
 - Genetic and functional basis of SMA
 - All patients have homozygous functional absence of SMN1 gene on chromosome 5q13
 - Variety is mainly determined by **SMN2 gene**
 - Shares 99% homology with SMN1 gene
 - Produces **~10% correctly spliced full-length SMN protein** of SMN1 gene
 - Low level full length protein
 - Unstable but partially functional
 - Not enough to compensate effect of SMN1 deletion
 - Functional modifier
 - Main target gene for potential therapy

- SMA therapeutic strategies

- SMN1 replacement (gene therapy)
- **Splicing correction of SMN2**



Subcellular targets of SMA therapies



Spinal muscular atrophy

- Designing a reasonable clinical trials for SMA
 1. Enough number of HOMOGENOUS patients to be enrolled easily?
 - SMN2 copy numbers used as a stratification criterion
 - SMN2 copy numbers $\hat{=}$ motor function achieved
 - Still, heterogenous, not homogenous, **this is a SPECTRUM disorder** !!!!
 - Intensity of care profoundly affect survival, (maybe not b/o drugs)
 2. Relative power of the study
 3. **Reliable, valid and sensitive outcome measures** available
 - Numerous overlapping motor functional scales as endpoints
 - SMA1 : motor unit number estimation and compound muscle action potential may be better indicator of efficacy than survival
 4. Drug selection based on preclinical data may not be a reliable predictor of a therapeutic effect on REAL patients
 5. **Timing of the study**
 - Mouse studies showing neonatal treatment is fundamental for efficacy with limited therapeutic window
 - 1st few months of life as most critical time of denervation for SMA1 and 2
 - Timing of rescue in SMA1 different from SMA2 or 3 (but loads of clinical trials are based upon SMA 2 and 3)
 6. **Absence of specific biomarkers** for SMA

Overview of the compounds by therapeutic approaches – SMN independent drugs

Substance	Experimental approach		Clinical Trial			
	Cell culture	SMA mouse model	Phase I	Phase II	Phase III	Open-label trial
SMN independent drugs						
<i>Fasudil</i>		+				
<i>Y-27632</i>		+				
<i>PTEN-downregulation</i>	++	+				
<i>Quercetin</i>	++	++				
<i>Olesoxime (TRO19622)</i>	+++		+	+	+	
<i>Riluzole</i>	+++	+	+	?	?	
<i>Gabapentin</i>					o/+	
<i>Physical Training</i>					+	
<i>Somatropin</i>					o	

Overview of the compounds by therapeutic approaches – SMN dependent drugs

Substance	Experimental approach		Clinical Trial			
	Cell culture	SMA mouse	Phase I	Phase II	Phase III	Open-label trial
SMN dependent drugs						
<i>BAY 55-9837</i>	++	+				
<i>Aminoglycosides</i>	++	+				
<i>Bortezomib</i>	++	+				
<i>Viral Gene Therapy</i>	+++	+++				
<i>Quinazolines</i>	++	+				
<i>Salbutamol</i>	++					+
<i>HDACi (VPA)</i>	++	+	+	+		+
<i>HDACi (SAHA)</i>	++	+				
ISIS-SMN_{Rx}	+++	+++	++	++		
<i>Roche (small molecules)</i>	+++	+++				

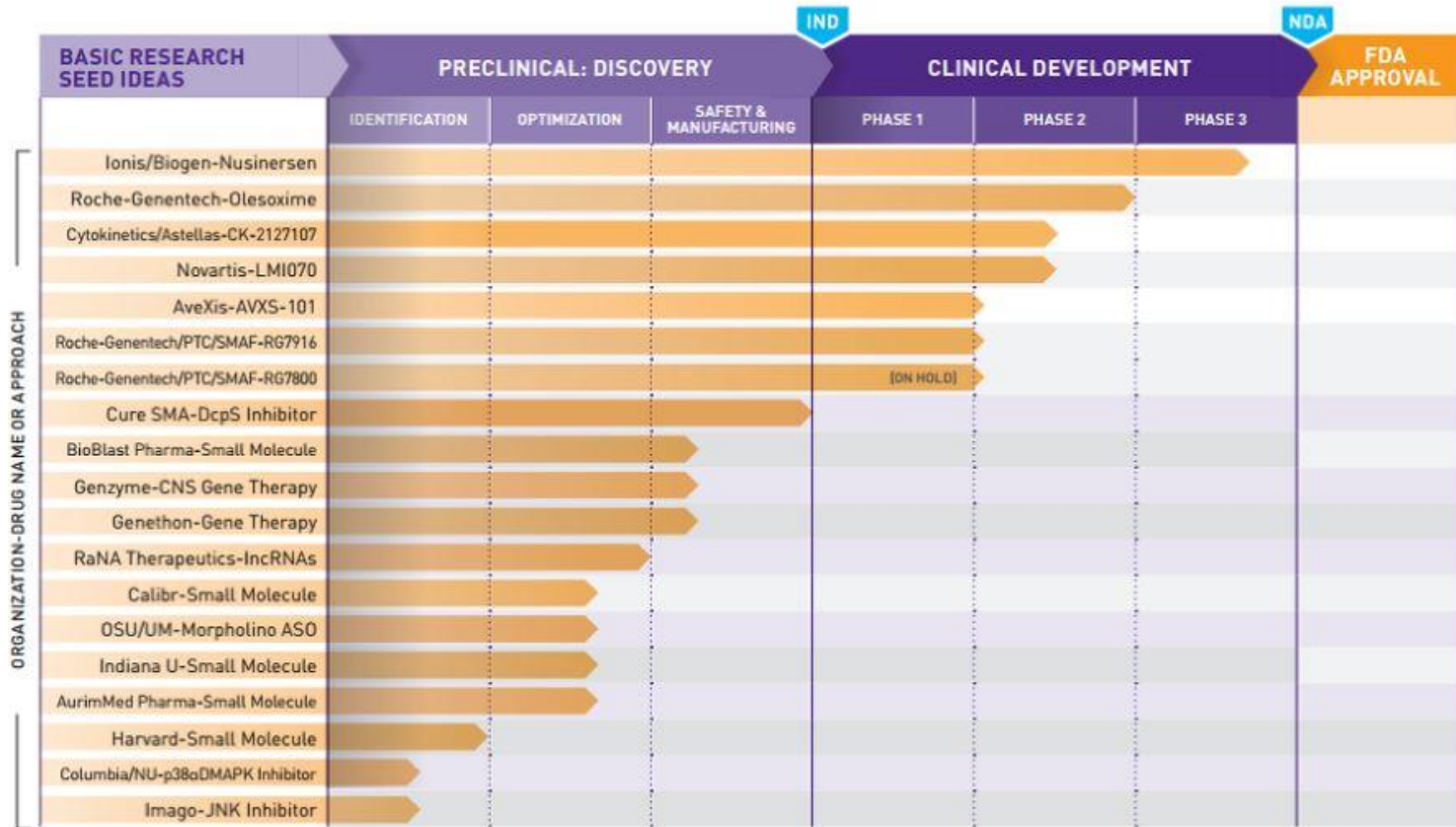
Completed trials

- Gabapentin
 - 2 placebo-controlled trials : negative
- Riluzole
 - Neuroprotective agent with modest benefit in ALS
 - Possible benefit in 7 SMA 1 patients → insufficient enrollment in open label study
- Albuterol
 - Anabolic properties and possible effect on SMN2
 - Open label study showed modest benefit in strength in 13 SMA 2/3 patients for 6 months
- Thyrotropin-releasing hormone
- Phenylbutyrate
- Acetyl-L-carnitine
- Creatinine
- Hydroxyurea
- Valproic acid + L-carnitine

Ongoing clinical trials in SMA

2016 SMA DRUG PIPELINE

This year, we are funding research with more breadth, depth, and diversity than ever before. This chart shows the drugs and therapies that are currently in the pipeline for SMA, including a few that are just steps away from potential FDA approval.



IND = Investigational New Drug

NDA = New Drug Application

Last updated: June 2016.



Motor Function Measure (MFM)

In practice...

Practically any disorder which is principally characterized by muscle weakness may be evaluated by the MFM.

Precise exercises with a rigorously defined initial position are executed by the patient with no external help, and are scored from 0 (failure to execute the movement) to 3 (normal).



- Quantitative scale
 - Measure functional motor ability of any NM disease
 - Specify symptoms and evolution of NM disease



The exercises (items) of the MFM-32 and the MFM-20 are classified into 3 dimensions:

- D1 Standing and transfers
- D2 Axial and proximal motor function
- D3 Distal motor function

A detailed and precise MFM User's Manual permits scoring of the motor capacities of each patient.

The utilization of the MFM in both ambulatory and non-ambulatory patients makes it possible to use the same follow-up tool throughout the life of the patient.

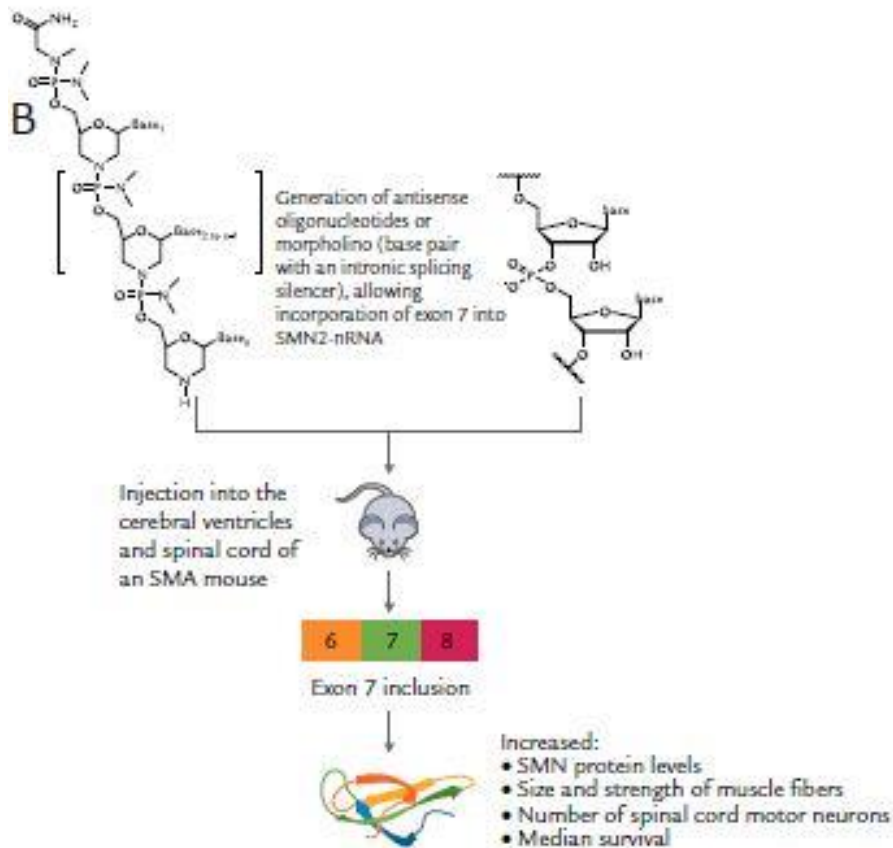
Hammersmith Functional Motor Scale (HFMS)

Test item 1: Plinth /chair sitting

Starting position	Sitting on edge of plinth or chair (feet unsupported) or on a plinth/floor (feet supported) Not in wheelchair. Back unsupported		
Instruction	Can you sit on the plinth/chair without using your hands for support for a count of 3?		
Scoring detail / Diagram			
Activity Plinth / chair sitting	2	1	0
	Able to sit using no hand support for a count of 3 or more	Needs one hand support to maintain balance for a count of 3	Needs two hand support to maintain balance Unable to sit
Photographs / Notes	 <p>Figure 1a Score 2 Subject able to sit without hand support for more than a count of 3. Arms need to be clear of floor and body for more than a count of 3. This degree of shoulder flexion is not required.</p>	 <p>Figure 1b Score 1 Subject able to maintain sitting with one hand support for a count of 3.</p>	 <p>Figure 1c Score 0 Subject unable to maintain independent sitting for a count of 3 without the use of both hands.</p>

- Functional scale to use
 - Assess gross motor abilities of nonambulant children with SMA
 - Monitor disease progression
 - Monitor gross motor abilities over time

Oligonucleotides Therapy for SMA: ISIS-SMN_{RX} (Nusinersen)



- SMA caused by
 - Loss of SMN1 gene
 - Resultant SMN protein level reduction
 - SMN2 gene
 - Additional production of low level full-length SMN protein
 - However, not sufficient to compensate d/t aberrant splicing lacking exon 7
 - Unstable but partially functional SMN protein
- ISIS-SMNRx
 - Antisense oligonucleotide for strong splice silencer for exon7 in SMN2
 - Promote inclusion of missing exon7 in SMN2
 - Production of full-length functional SMN protein
- Both phenotypic and pathologic benefit (when delivered centrally) + long half-life of >6 mo in CNS in mild and severe SMA mouse models

Oligonucleotides Therapy for SMA: ISIS-SMN_{RX} (Nusinersen)

- ISIS phase 1, open-label, safety, tolerability, dose range-finding study completed
 - CSF (LP) in patients with SMA (total n=28)
 - 11/2011-1/2013
 - Total 28 subjects with SMA completed
 - Documented SMN1 homozygous deletion + clinical signs of SMA + age 2-14 years + estimated life expectancy > 2 years
 - Exclusion : need for invasive or noninvasive ventilation for 24 hours period, gastric tube, s/p scoliosis surgery or scheduled surgery
 - 4 dose levels sequentially evaluated (each cohort 6 to 10 patients)
 - All received active drugs, no placebo
 - Results
 - Well-tolerated at all dose levels
 - No safety or tolerability issues
 - Lumbar puncture injection procedure feasible for children with SMA
 - CSF and plasma drug levels dose dependent and consistent with preclinical data
 - HFMS improvement at day 85, +3.1 points from baseline, 17.6% change observed in highest dosing group
 - Electrophysiology measures stable CMAP and increase in MUNE
 - Open-label study at 14 months
 - improvements in HFMS in 6 and 9 mg dosing group with single injection of drug
 - no decline observed

Oligonucleotides Therapy for SMA: ISIS-SMN_{RX} (Nusinersen)

- ISIS Phase II study
 - Safety, tolerability, pharmacokinetics of multiple doses with SMA1
 - <210 days when enrolled
 - Exclusion : major comorbidity, hypoxemia <96%
 - All received active drugs
 - Result
 - Well-tolerated without significant adverse effect
 - Statistically meaningful increase in HFMS score
 - SMN protein in CSF increased compared to baseline

ISIS (ASO) phase III

A Study to Assess the Efficacy and Safety of ISIS-SMN Rx in Infants With Spinal Muscular Atrophy

This study is not yet open for participant recruitment. (see [Contacts and Locations](#))

Verified July 2014 by Isis Pharmaceuticals

Sponsor:

Isis Pharmaceuticals

ClinicalTrials.gov Identifier:
NCT02193074

First received: July 14, 2014

Last updated: July 15, 2014

Last verified: July 2014

Primary Outcome Measures:

- Time to death or permanent ventilation [Time Frame: Up to 13 months] [Designated as primary outcome measure: Yes]

Secondary Outcome Measures:

- Change from baseline in CHOP INTEND [Time Frame: At 13 months] [Designated as primary outcome measure: No]
- Change from baseline in motor milestones [Time Frame: At 13 months] [Designated as primary outcome measure: No]
- Percent of subjects not requiring permanent ventilation [Time Frame: Up to 13 months] [Designated as primary outcome measure: No]
- Survival rate [Time Frame: Up to 13 months] [Designated as safety issue: No]
- Time to death or permanent ventilation in the subgroups of subjects below the study median [Designated as safety issue: No]
- Time to death or permanent ventilation in the subgroups of subjects above the study median [Designated as safety issue: No]

Estimated Enrollment: 111

Study Start Date: July 2014

Estimated Study Completion Date: July 2017

Estimated Primary Completion Date: June 2017 (Final data collection date for primary outcome measure)

▶ Eligibility

Ages Eligible for Study: up to 210 Days

Genders Eligible for Study: Both

Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

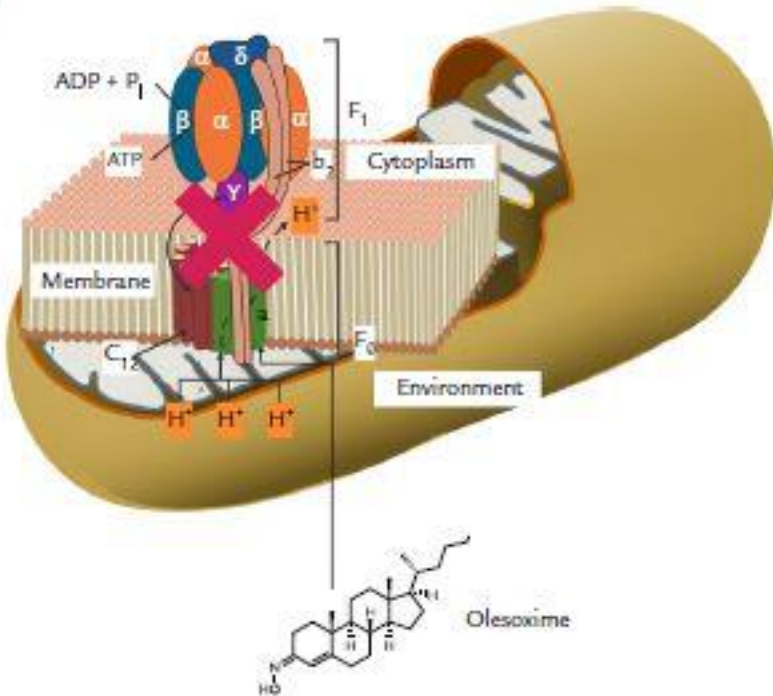
- Be 7 months (210 days) of age or younger at screening
- Be born (gestational age) between 37 and 42 weeks
- Be medically diagnosed with spinal muscular atrophy (SMA)
- Have SMN2 Copy # of 2
- Body weight equal to or greater than 3rd percentile for age using appropriate growth chart
- Be able to follow all study procedures
- Reside within 9 hours ground travel each way, for the duration of the study
- Meet additional study-related criteria

Oligonucleotides Therapy for SMA: ISIS-SMN_{RX} (Nusinersen)

- ENDEAR study
 - 13 months trial **~110 SMA1 patients**
 - Safety and efficacy of Nusinersen
 - 1' endpoint : ventilation-free survival
 - Increasingly clear that motor milestones measurement could be a useful indicator of nusinersen's potential efficacy
 - Currently under interim analysis for formal conclusion

Neuroprotection Strategy for SMA : Olesoxime (TRO19622)

A



- Olesoxime (TRO19622)
 - Small molecule with a cholesterol-like structure with strong neuroprotective properties
 - Effective in keeping motor neurons alive (in culture)
 - **Promotes function and survival of neurons** and other cell types under oxidative stress in vitro when interacting with the mitochondrial permeability transition pore

→ Results in **preserving mitochondrial integrity and function** in stressed cells!

Neuroprotection Strategy for SMA : Olesoxime (TRO19622)

- Trophos phase 2 randomized clinical trial
 - N=165 with SMA 2 and 3, non-ambulant, age 3-25 years
 - 22 centers in 7 European countries
 - Baseline MFM $\geq 15\%$ (D1+D2), HFMS ≥ 3
 - Age of onset ≤ 3 years
 - Oct 2010~late 2013

 - Randomization 2:1 to olesoxime vs. placebo
 - Olesoxime dosing 10 mg/kg/day, once a day, liquid suspension

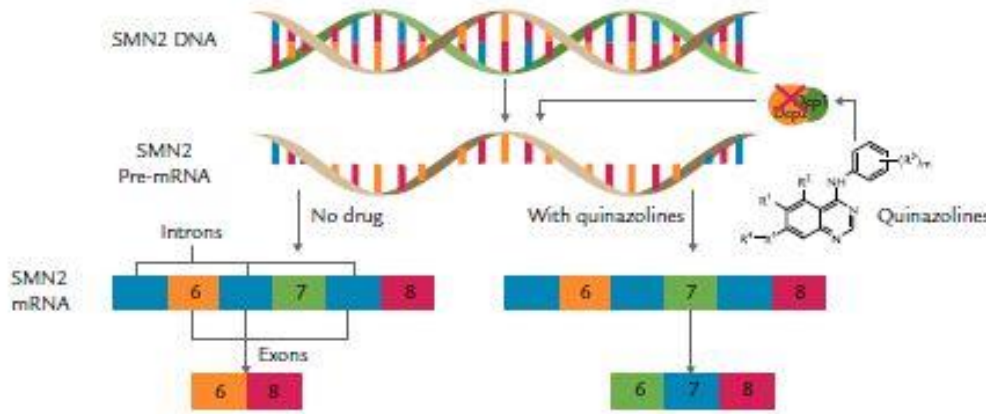
 - Clinical endpoints
 - 1' : MFM functional scale (D1+D2)
 - 2' : HFMS, EMG (CMAP and MUNE), measures of safety, tolerance, quality of life

 - Evaluation : clinic visit every 3 months, 1st summary at year 1, 2nd summary at year 2

Neuroprotection Strategy for SMA : Olesoxime (TRO19622)

- Result summary (2014/2015)
 - Able to maintain motor function over \geq 2yr
 - Treatment arm
 - Stable MFM D1+D2 score
 - Placebo arm
 - Mean loss of -1.9 points of MFM D1+D2 scores over \geq 2yr
 - In favor of treated arm with
 - Statistically significant effect on motor function ($p=0.038$)
 - Effect initially noted within 6 months of treatment
 - Similar positive trend with HFMS changes (48% olesoxime vs. 28% placebo, $p=0.015$)
 - Less frequent SMA complications, leading to a better well-being
 - Less frequent lower respiratory tract infection or spine surgery
 - Safety confirmed with no severe adverse event

Small molecules for SMA: Quinazolines



- Per preclinical mouse models..
 - Increase survival by 400% in severe SMA mice
 - Increase survival by 600% intermediate SMA mice
 - Increase physical ability, survival, body weight in all cohorts in mice
 - Ameliorates phenotype of SMA mice

- Quinazoline (RG3039)
 - Inhibits RNA decapping enzyme Dcp1 (involved in RNA turnover)
 - Results in \uparrow SMN2 expression

- Pfizer/Quinazoline phase 1 study
 - Human, double-blind, placebo-controlled, ascending single-dose + safety and pharmacokinetics in healthy volunteer (n=16)

Small molecules for SMA: Roche/RG7916

- RG7916
 - Splicing modifier of SMN2 gene
 - Resultant increased SMN protein
 - Roche [planning to start clinical trial enrollment for SMA 1 and 2/3 by the end of 2016](#)

Thank you for your
attention!