ISIS PHARMACEUTICALS

ISIS-SMN$_{Rx}$ Investor Event

April 29, 2014

Introduction

Stan Crooke, M.D., Ph.D.

CEO and Chairman, Isis Pharmaceuticals

Forward Looking Language Statement

This presentation includes forward-looking statements regarding Isis' strategic alliance with Biogen Idec, and the discovery, development, activity, therapeutic and commercial potential and safety of ISIS-SMN_{Rx} and the discovery, development and therapeutic potential of an antisense drug for the treatment of spinal muscular atrophy. Any statement describing Isis' goals, expectations, financial or other projections, intentions or beliefs, including the commercial potential of KYNAMRO®, is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such drugs. Isis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Isis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' programs are described in additional detail in Isis' annual report on Form 10-K for the year ended December 31, 2013, which is on file with the SEC. Copies of this and other documents are available from the Company.

In this presentation, unless the context requires otherwise, "Isis," "Company," "we," "our," and "us" refers to Isis Pharmaceuticals and its subsidiaries.

Participants

Dr. Stan Crooke

CEO and Chairman
Isis Pharmaceuticals

Dr. Darryl De Vivo

Sidney Carter Professor of Neurology and Pediatrics, Department of Neurology, Columbia University Medical Center

Dr. Frank Bennett

SVP Research
Isis Pharmaceuticals

Dr. Claudia Chiriboga

Associate Professor of Clinical Neurology & Clinical Pediatrics, Columbia University Medical Center

Dr. Richard Finkel

Chief, Division of Neurology Department of Pediatrics, Nemours Children's Hospital

Dr. Kathie Bishop

VP Clinical Development
Isis Pharmaceuticals

Dr. Doug Williams

Executive Vice President, Research and Development
Biogen Idec

Purpose of Today's Meeting

- Summarize what we've learned to date as we initiate the Phase 3 program for ISIS-SMN$_{Rx}$
- Provide the opportunity to hear from key opinion leaders and investigators about the needs of SMA patients and their experience with ISIS-SMN$_{Rx}$
- Outline in more detail our Phase 3 plan

Agenda

- **Introduction:**
  - *Dr. Stan Crooke, CEO & Chairman, Isis Pharmaceuticals*
- **SMA Disease Overview and Patient Need for an Approved Therapy:**
  - *Dr. Darryl De Vivo, Sidney Carter Professor of Neurology and Pediatrics, Columbia University Medical Center*
- **ISIS-SMN$_{Rx}$ from Concept to Patient:**
  - *Dr. Frank Bennett, SVP Research, Isis Pharmaceuticals*
- **ISIS-SMN$_{Rx}$ Phase 2 SMA Children Data:**
  - *Dr. Claudia Chiriboga, Associate Professor of Clinical Neurology & Clinical Pediatrics, Columbia University Medical Center*
- **ISIS-SMN$_{Rx}$ Phase 2 SMA Infant Data:**
  - *Dr. Richard Finkel, Division Chief, Division of Neurology, Department of Pediatrics, Nemours*
- **ISIS-SMN$_{Rx}$ Development Plan & Upcoming Activities:**
  - *Dr. Kathie Bishop, VP Clinical Development, Isis Pharmaceuticals*
- **Closing Remarks:**
  - *Dr. Stan Crooke*
- **Q&A Panel**

ISIS-SMN$_{Rx}$: What Have We Learned? (1 of 2)

- **SMA is a severe unmet medical need that is recognized by all relevant groups, including regulatory agencies**
  - ISIS-SMN$_{Rx}$ has been granted Orphan Drug Status in U.S. and E.U. and Fast Track Designation in U.S.
- **ISIS-SMN$_{Rx}$ has been well tolerated to date**
  - Some patients have been treated for over 2 years
  - 44 doses in 15 infants and 138 doses in 54 children as of April 7
- **Magnitude of effect**
- **Effects observed to date have been consistent from:**
  - Mouse to human
  - Infant to children (Type 1 to Type 2/3)
  - Study to study

ISIS-SMN$_{Rx}$: What Have We Learned? (2 of 2)

- **ISIS-SMN$_{Rx}$ has shown both dose and time dependent effects on motor function**
- **Effects on multiple measures of activity observed**
- **PK/PD consistent with long half life and supportive of infrequent dosing**
- **Increases in SMN protein levels in CSF consistent with drug mechanism**
- **Additional advantages for program:**
  - The recent natural history study in infants provides context for evaluating efficacy
  - Solid relationships with regulatory agencies
  - Strong support by patient advocacy groups and KOLs
  - Seamless, effective working relationship between Biogen and Isis
  - Elegance of mechanism

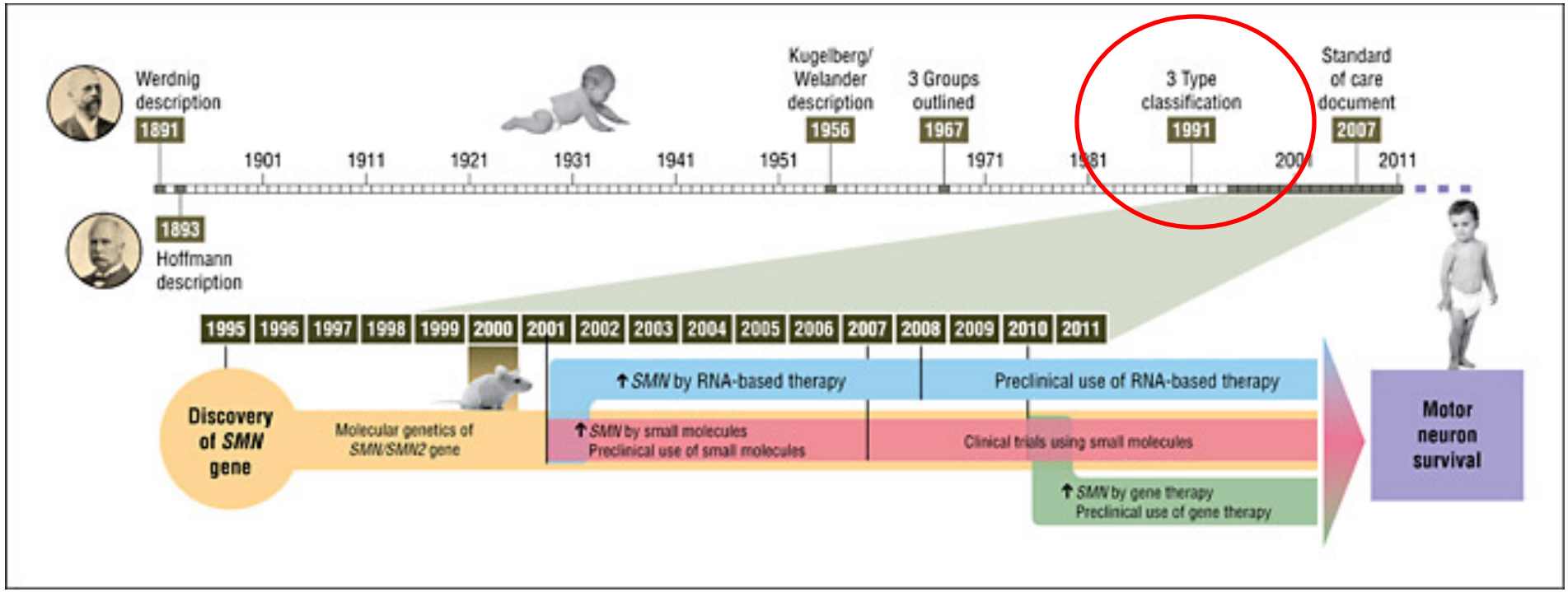
Disease Overview and Patient Need for an Approved Therapy

Darryl De Vivo, M.D.

Sidney Carter Professor of Neurology and Pediatrics, Columbia University Medical Center

SMA: 120 Years Later and on the Verge of a Cure?

Spinal Muscular Atrophy (SMA) Timeline

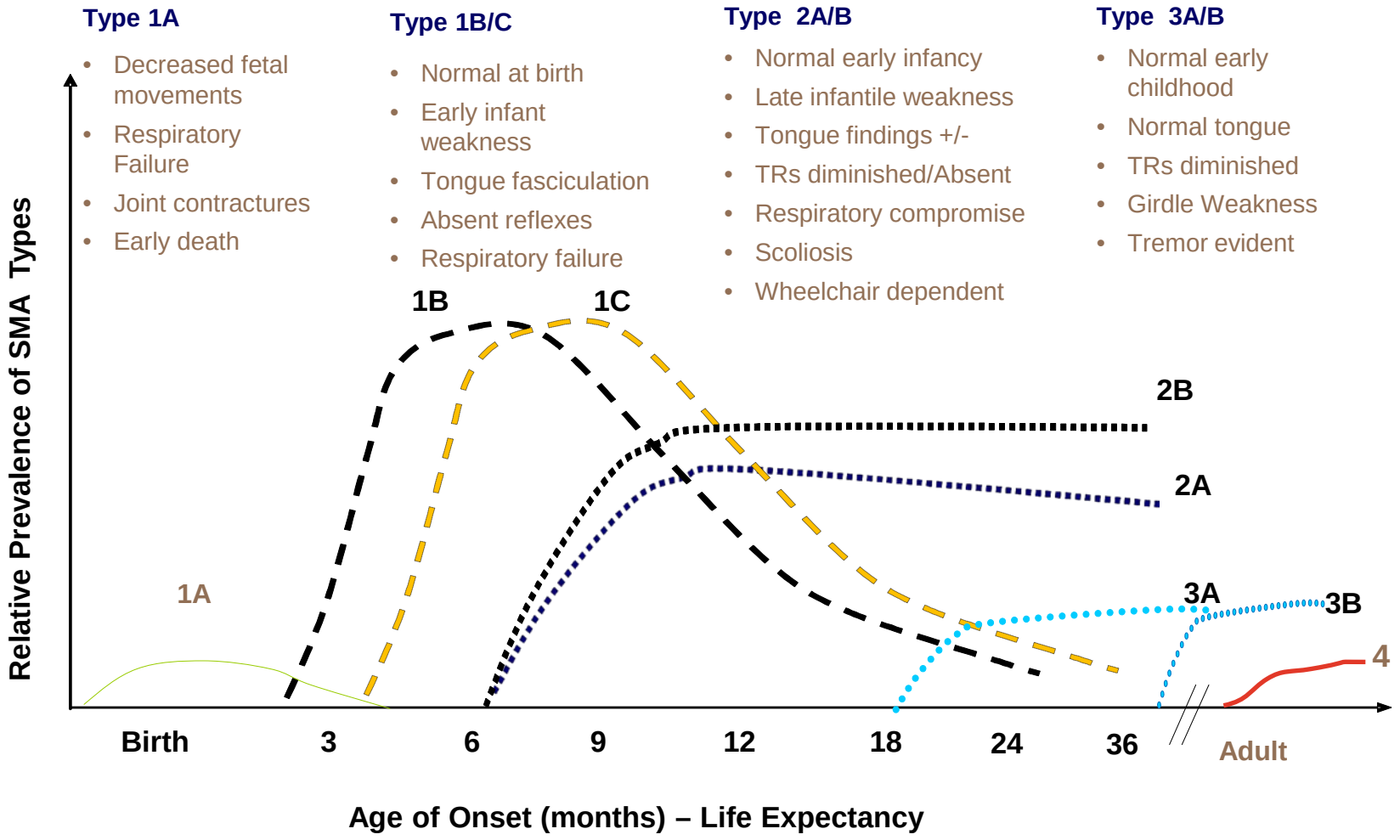


Kolb, S. J. et al. Arch Neurol 2011;68:979-984.

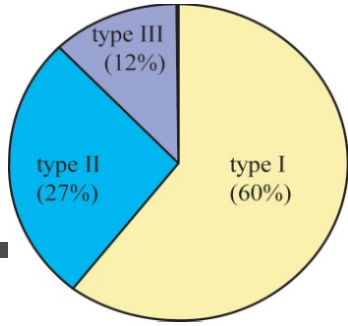
ARCHIVES OF NEUROLOGY

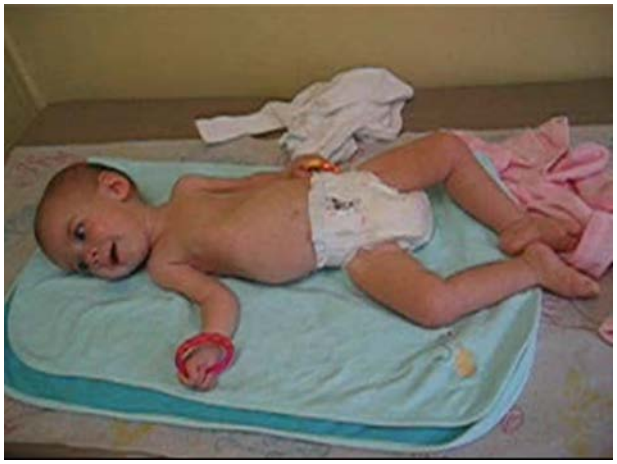
The SMA Clinical Spectrum:

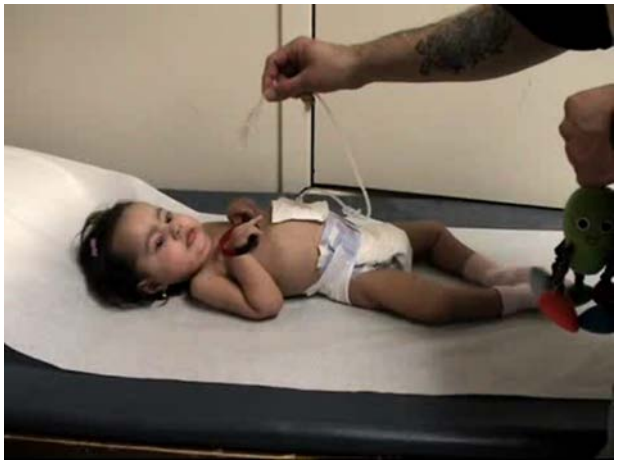
Disease spectrum is continuous from birth to adulthood

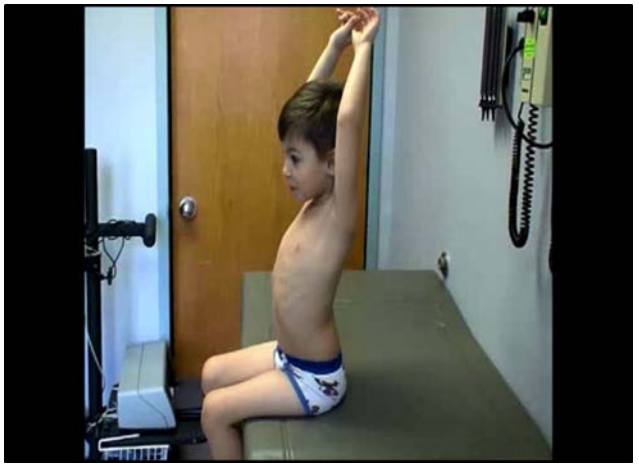


Broad Phenotypic Spectrum of SMA









SMA Type I

Severe form

Never sit

Limited life expectancy

Respiratory failure

Birth Prevalence 60%

SMA Type II

Intermediate form

Sitting or standing

Life expectancy shortened

Skeletal deformities

Birth Prevalence 27%

SMA Type III

Mild form

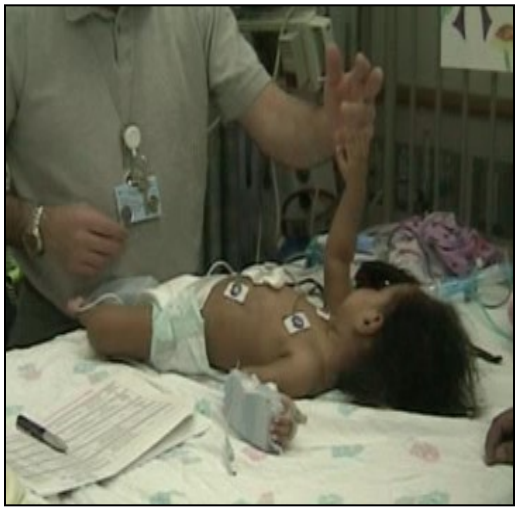
Walkers at some point

Life expectancy (nearly) normal

Proximal weakness prominent

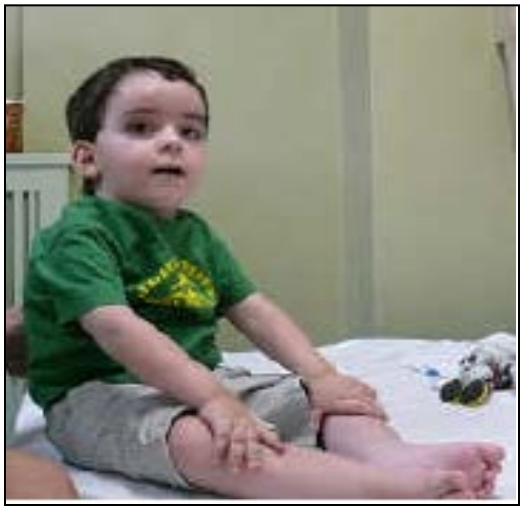
Birth Prevalence 12%

Key SMA Clinical Outcome Measures



SMA Type I

CHOP INTEND



SMA Type II

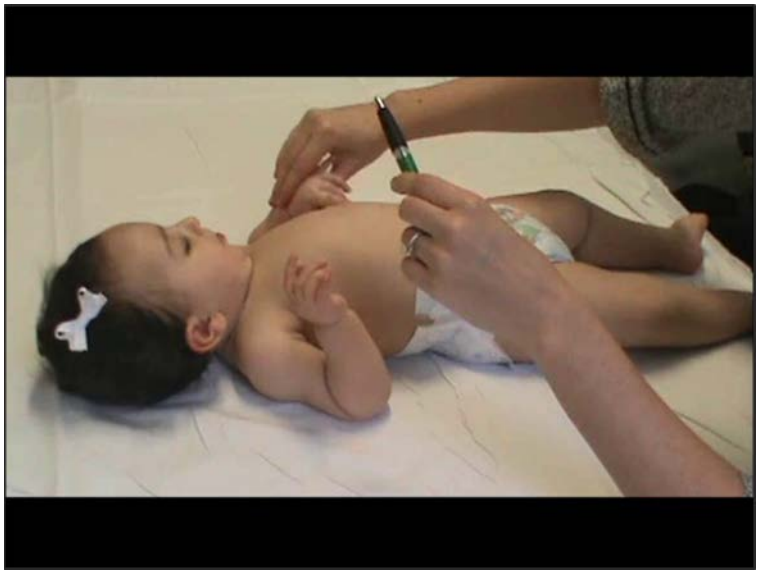
Hammersmith Expanded

SMA Type III

Hammersmith Expanded

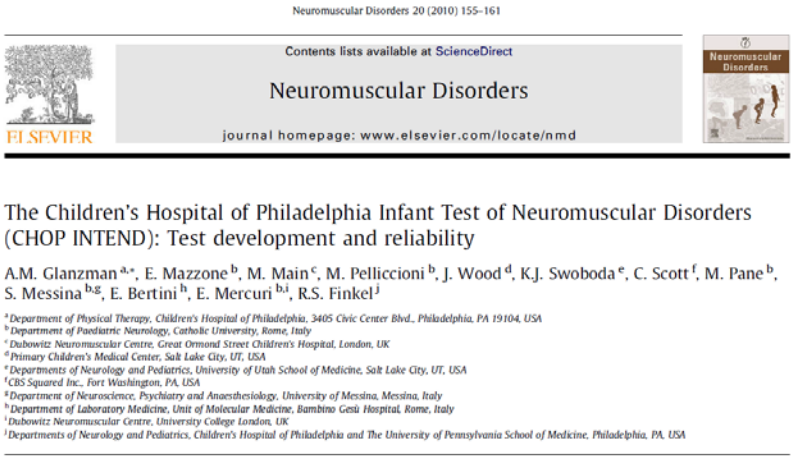
6 Minute Walk Test

Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)



- Structured to move from easiest to hardest (16 items)
- Does not include respiratory or feeding assessments
- Grading includes gravity eliminated (lower scores) to antigravity movements (higher scores)
- All items scores range from 0–4

CHOP INTEND for SMA Type 1



Neuromuscular Disorders 20 (2010) 155–161

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journal homepage: www.elsevier.com/locate/nmd

The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): Test development and reliability

A.M. Glanzman [a,*], E. Mazzone [b], M. Main [c], M. Pelliccioni [b], J. Wood [d], K.J. Swoboda [e], C. Scott [f], M. Pane [b], S. Messina [b,g], E. Bertini [h], E. Mercuri [b,i], R.S. Finkel [j]

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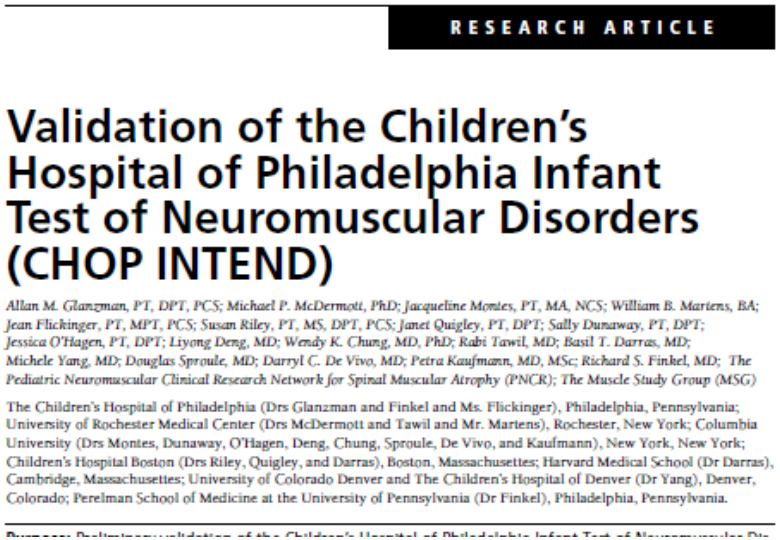


RESEARCH ARTICLE

Validation of the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)

Allan M. Glanzman, PT, DPT, PCS; Michael P. McDermott, PhD; Jacqueline Montes, PT, MA, NCS; William B. Martens, BA; Jean Flickinger, PT, MPT, PCS; Susan Riley, PT, MS, DPT, PCS; Janet Quigley, PT, DPT; Sally Dunaway, PT, DPT; Jessica O'Hagen, PT, DPT; Liyong Deng, MD; Wendy K. Chung, MD, PhD; Rabi Tawil, MD; Basil T. Darras, MD; Michele Yang, MD; Douglas Sproule, MD; Darryl C. De Vivo, MD; Petra Kaufmann, MD, MSc; Richard S. Finkel, MD; The Pediatric Neuromuscular Clinical Research Network for Spinal Muscular Atrophy (PNCR); The Muscle Study Group (MSG)

The Children's Hospital of Philadelphia (Drs Glanzman and Finkel and Ms. Flickinger), Philadelphia, Pennsylvania; University of Rochester Medical Center (Drs McDermott and Tawil and Mr. Martens), Rochester, New York; Columbia University (Drs Montes, Dunaway, O'Hagen, Deng, Chung, Sproule, De Vivo, and Kaufmann), New York, New York; Children's Hospital Boston (Drs Riley, Quigley, and Darras), Boston, Massachusettes; Harvard Medical School (Dr Darras), Cambridge, Massachusettes; University of Colorado Denver and The Children's Hospital of Denver (Dr Yang), Denver, Colorado; Perelman School of Medicine at the University of Pennsylvania (Dr Finkel), Philadelphia, Pennsylvania.

Intra-rater reliability (ICC = 0.96)

SMA infants (n = 9)

Inter-rater reliability (ICC = 0.98)

1 SMA video assessment / 4 raters

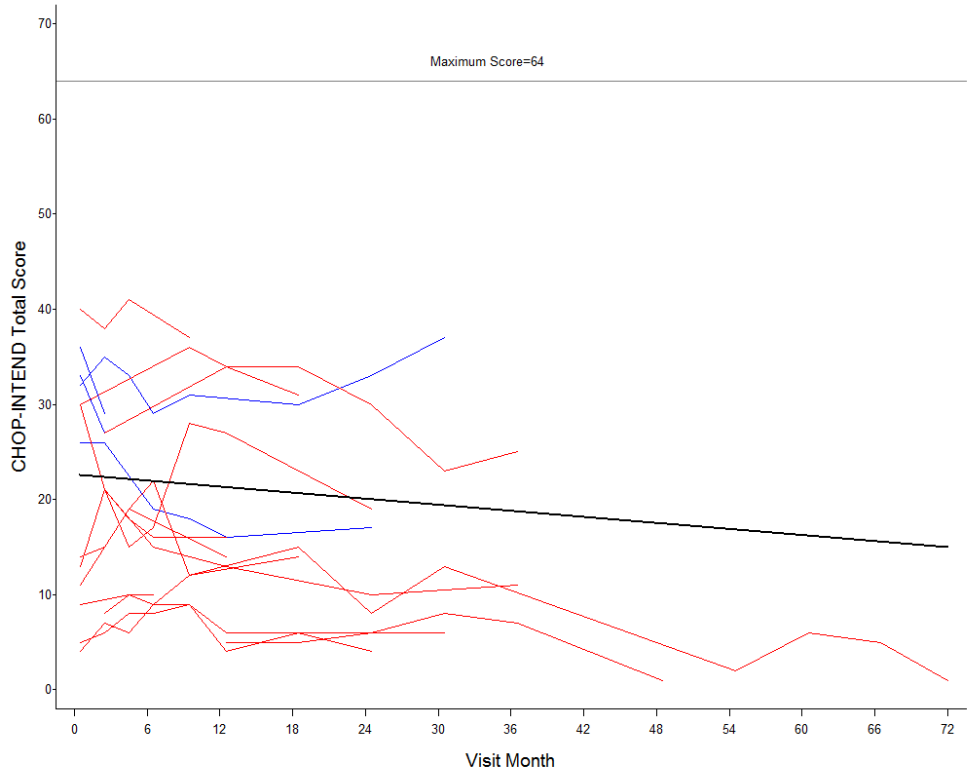
Inter-rater reliability (ICC = 0.93)

8 healthy infants and 5 raters

Associated with age, respiratory status, and SMN2 copy number

CHOP INTEND for SMA Type 1

- **Longitudinal Data**
  - Subjects enrolled within 3 months of symptom onset (“recent”)
  - Subjects enrolled more than 3 months after symptom onset (“chronic”)



N = 17
(4 recent,13 chronic)

Hammersmith Functional Motor Scale Expanded for SMA








Sitting	Rolling	Transitions/ Crawling	Standing	Transitions/ Kneeling	Squat/ Jump	Stairs

HFMSE ITEMS

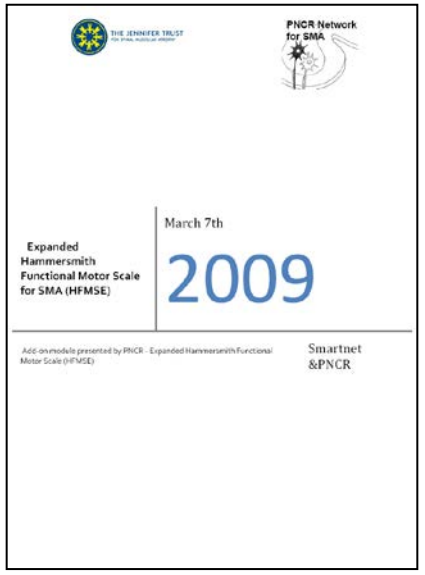
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33











Gross Motor Function for SMA Types 2 and 3

ELSEVIER

Neuromuscular Disorders 17 (2007) 693–697

www.elsevier.com/locate/nmd

An expanded version of the Hammersmith Functional Motor Scale for SMA II and III patients

Jessica M. O'Hagen [a,*,1], Allan M. Glanzman [b,1], Michael P. McDermott [d], Patricia A. Ryan [a], Jean Flickinger [b], Janet Quigley [d], Susan Riley [d], Erica Sanborn [d], Carrie Irvine [f], William B. Martens [f], Christine Annis [f], Rabi Tawil [f], Maryam Oskoui [a], Basil T. Darras [d,e], Richard S. Finkel [b,c], Darryl C. De Vivo [a]

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[b] *Children's Hospital of Philadelphia (Pediatrics [RSF] and Physical Therapy [AMG, JF])*
[c] *The University of Pennsylvania School of Medicine, Philadelphia, PA, USA*
[d] *Children's Hospital Boston, Boston, MA, USA*
[e] *Harvard Medical School, Boston, MA, USA*
[f] *University of Rochester Medical Center, Rochester, NY, USA*

Received 4 January 2007; received in revised form 20 April 2007; accepted 25 May 2007

- **HFMSE adds 13 clinically relevant items from the GMFM to include ambulant SMA and eliminate a ceiling effect**
- **Detailed manual with operational definitions and training videos**
- **Minimal patient burden requiring only standard equipment and taking less than 15 minutes on average**

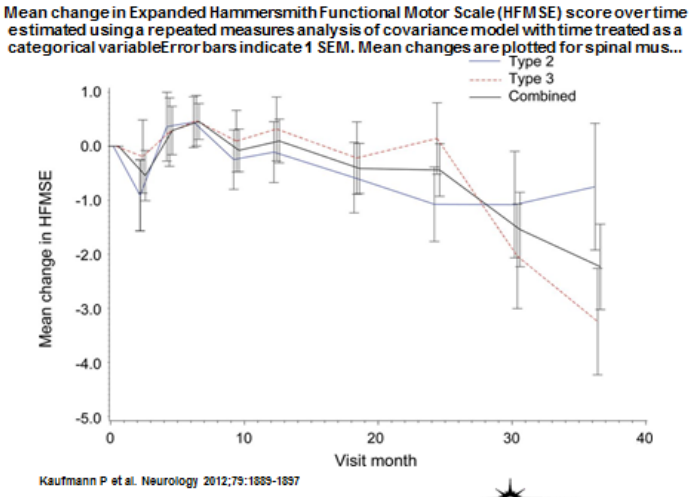
SMA shows slow functional declines when observation periods exceed 1 year.

Table 2 Estimated mean changes in motor and pulmonary function outcomes at 2 and 3 years obtained from mixed-effects models with linear and quadratic terms for time[a]

	2 Years			3 Years		
Variable	Mean	95% CI	p Value	Mean	95% CI	p Value
GMFM	−0.70	(−2.84, 1.44)	0.52	−4.39	(−8.38, −0.40)	0.03
HFMS	−0.34	(−1.26, 0.58)	0.46	−1.26	(−2.65, 0.12)	0.07
HFMSE	−0.54	(−1.45, 0.36)	0.24	−1.71	(−3.02, −0.39)	0.01
FVC (% predicted)	−3.14	(−6.01, −0.27)	0.03	−2.92	(−6.50, 0.66)	0.11

Abbreviations: CI = confidence interval; FVC = forced vital capacity; GMFM = Gross Motor Function Measure; HFMS = Hammersmith Functional Motor Scale (SMA 2 participants only); HFMSE = Expanded Hammersmith Functional Motor Scale.

[a] Mean changes, confidence intervals, and p values are obtained from a mixed-effects linear regression model that includes spinal muscular atrophy type as a covariate and linear and quadratic terms for time (continuous); see text for details.



Kaufmann P et al. Neurology 2012;79:1889-1897

AMERICAN ACADEMY OF NEUROLOGY

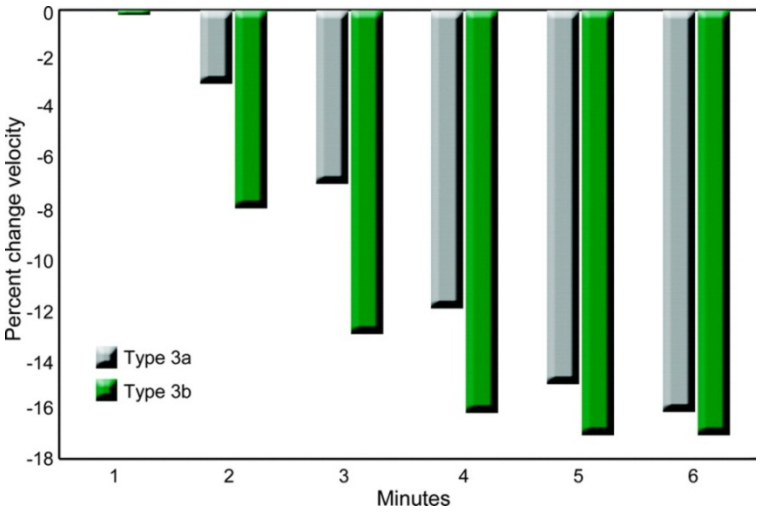
Six Minute Walk Test

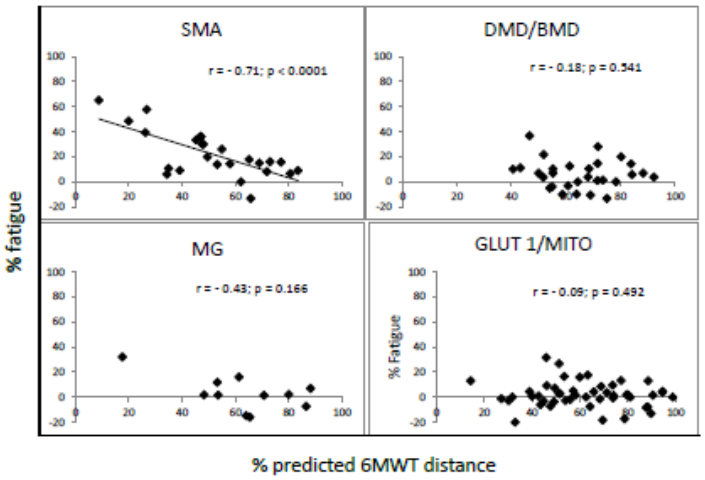
Neurology®

Six-Minute Walk Test demonstrates motor fatigue in spinal muscular atrophy

J. Montes, M. P. McDermott, W. B. Martens, et al.
Neurology 2010;74;833
DOI 10.1212/WNL.0b013e3181d3e308

- A test to measure the distance walked around a 25m course
- Objective, safe and easily administered evaluation of functional exercise capacity
- Used as the primary outcome in clinical trials in Duchenne Muscular Dystrophy
- Highly correlated with HFMSE and 10 meter walk/run in SMA
- Captures fatigue in SMA





Montes, J. et al. JCN 2013

Concept of Clinical Meaningfulness

- The minimal change that produces a functional benefit to the patient
- Clinical Meaningfulness is patient-specific as determined by their disease severity and individual needs
- Clinical Meaningfulness can be reflected in measurable change on an outcome measure

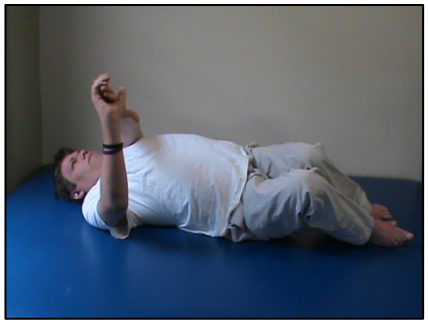
16 year old male, SMA type 2

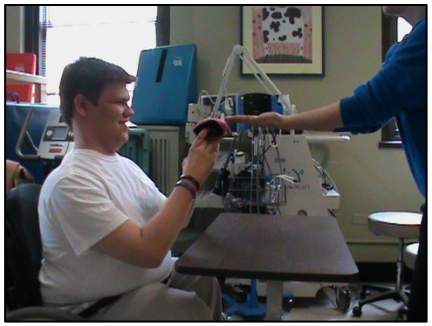
"Rolling and sitting up in bed"

HFMSE = 8/66

ULM = 15/18

"Reaching for items above my head"





HFMSE item 5 and 14
=
3 point change
would be meaningful to meet his goal

ULM item 6 and 7
=
3 point change
would be meaningful to meet his goal

2 year old male, SMA type 2

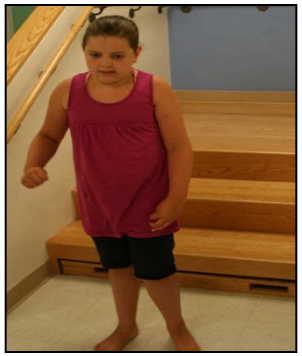
"Walk"

HFMSE = 30/66

ULM = 10/18

"Floor to stand transfers"

HFMSE item 20
=
2 point change
would be meaningful to meet his goal



HFMSE item 19 and 25
=
3 point change
would be meaningful to meet his goal

10 year old female, SMA type 3

"Climb stairs without assistance"

HFMSE = 58/66

6MWT = 304 meters

"Jump"

HFMSE item 32
=
2 point change
would be meaningful to meet his goal

HFMSE item 29
=
2 point change
would be meaningful to meet his goal

ISIS-SMN$_{Rx}$ from Concept to Patient

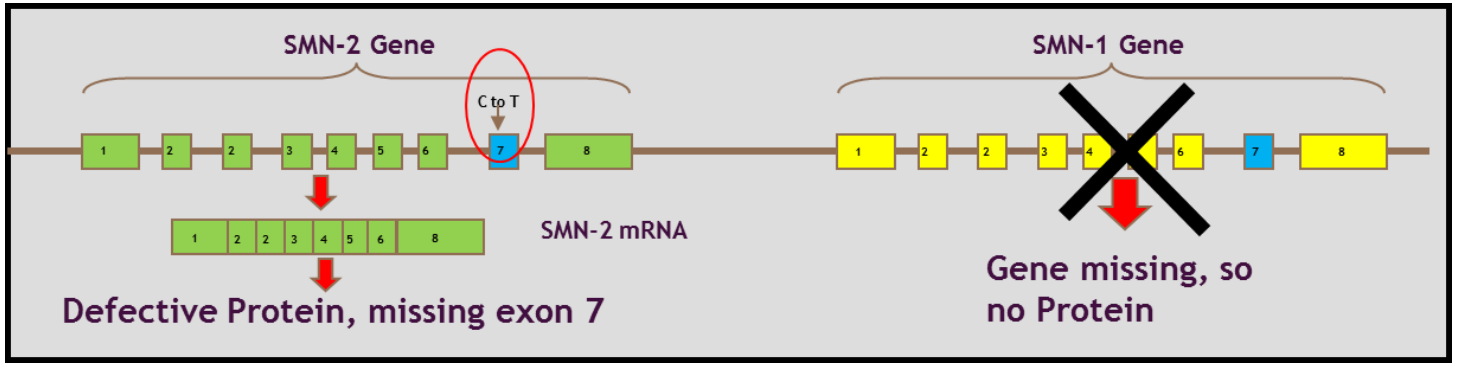
Frank Bennett, Ph.D.

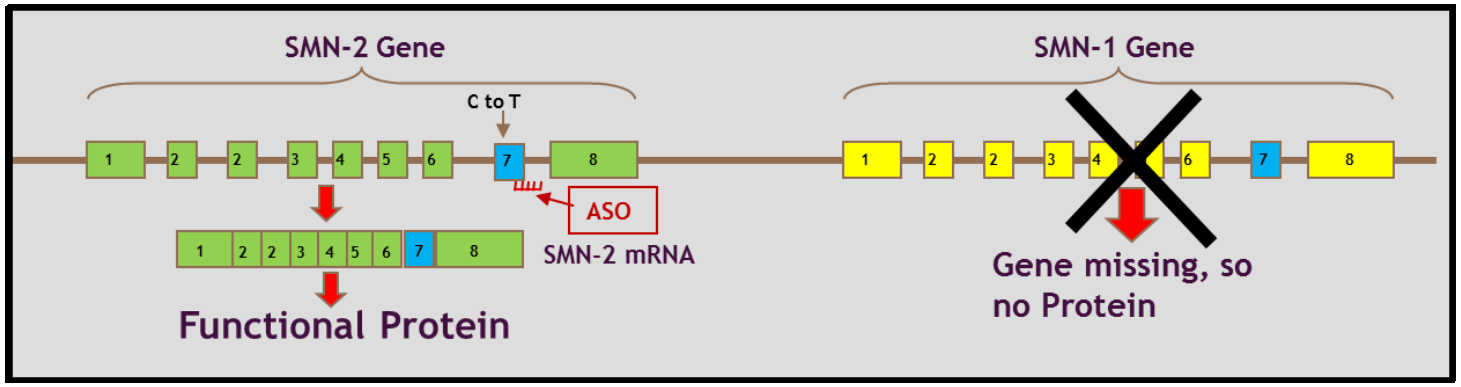
SVP Research, Isis Pharmaceuticals

ISIS-SMN$_{Rx}$ is Designed to Modulate RNA Processing to Positively Affect Disease

Cold Spring Harbor Laboratory

SMA Caused by Genetic Defects in the SMN1 Gene that Result in the Lack of Functional SMN Protein

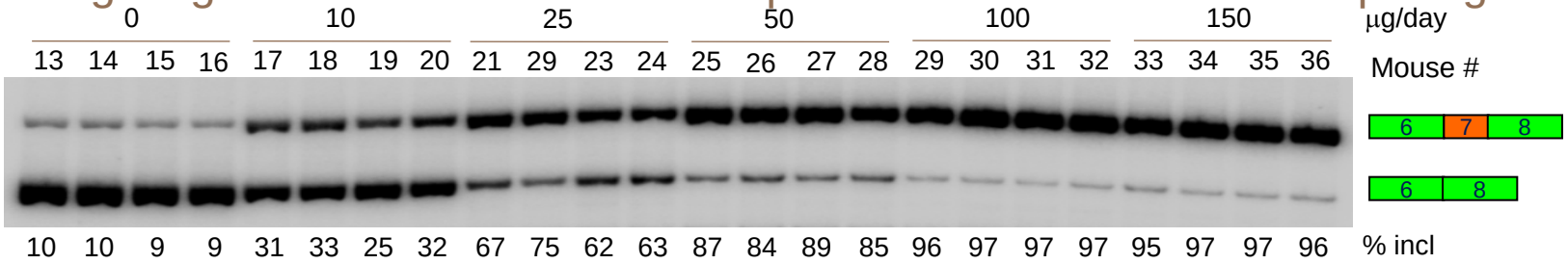




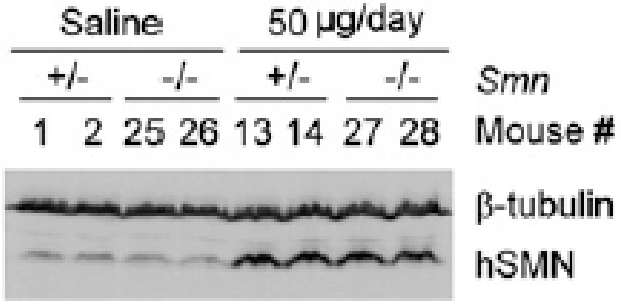
ISIS-SMN$_{Rx}$ Increases SMN2 Splicing, Increases Production of SMN Protein In Mouse Spinal Cord Tissue and CSF

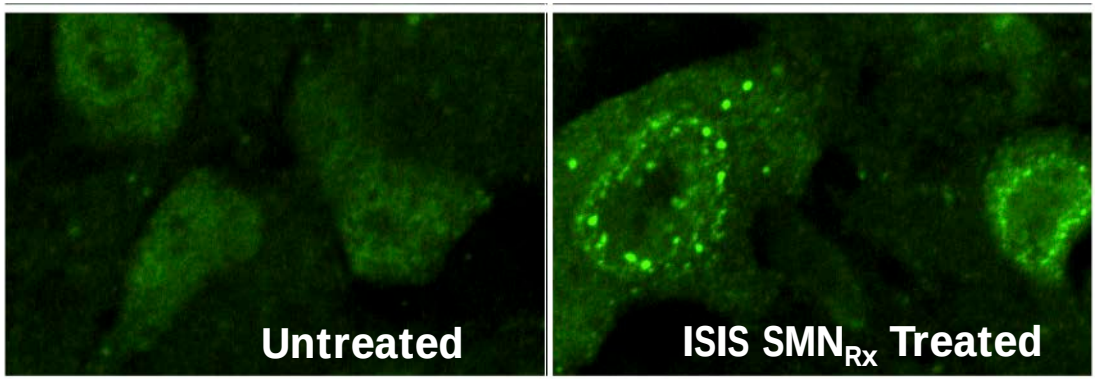
3.5 Fold Increase in Protein Achieved at >90% Corrected Splicing

SMN Targeting ASO Promotes a Dose Dependent Increase in SMN2 Splicing



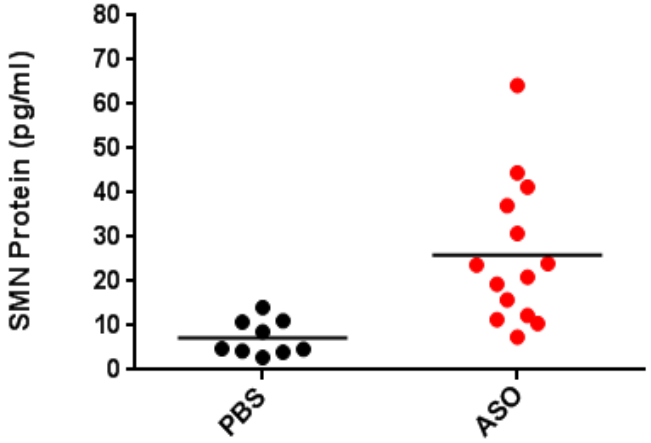
SMN Protein in Mouse Spinal Cord





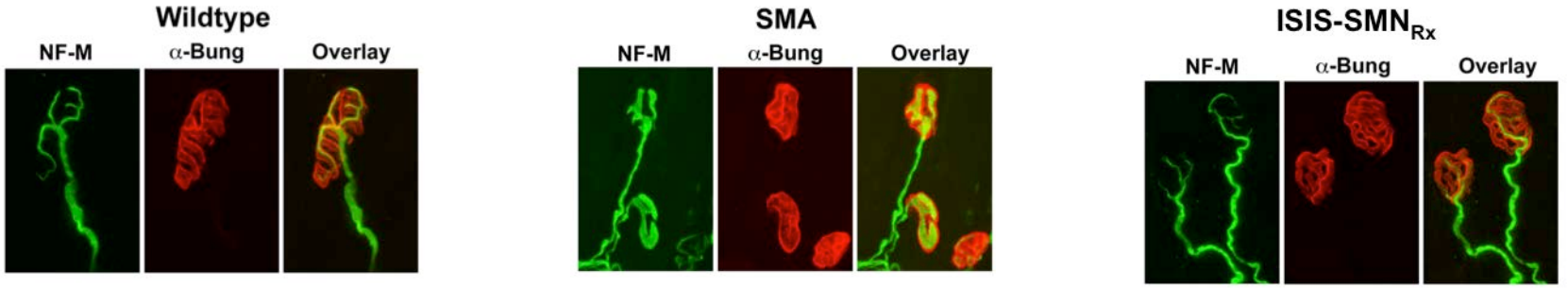
SMN Protein in CSF (Mean +/- SD)

3.5 fold Increase

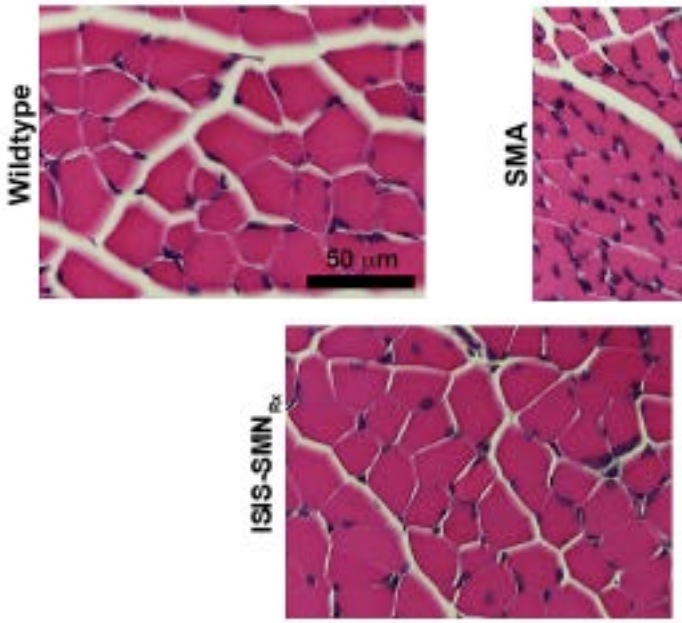


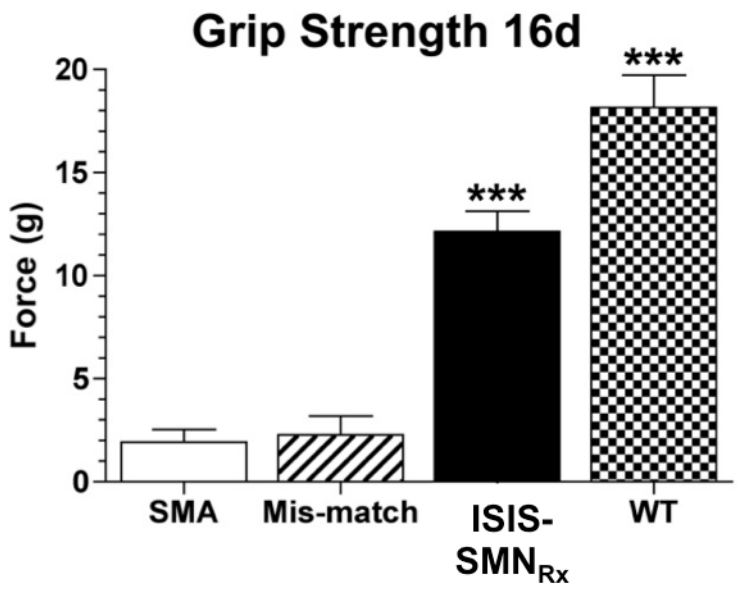
ISIS-SMN$_{Rx}$ Preserves Neuron and Muscle Function in a Mouse Model of SMA

ISIS-SMN$_{Rx}$ Treatment Preserves Neuromuscular Junctions



ISIS-SMN$_{Rx}$ Treatment Maintains Muscle Fiber Size and Muscle Strength

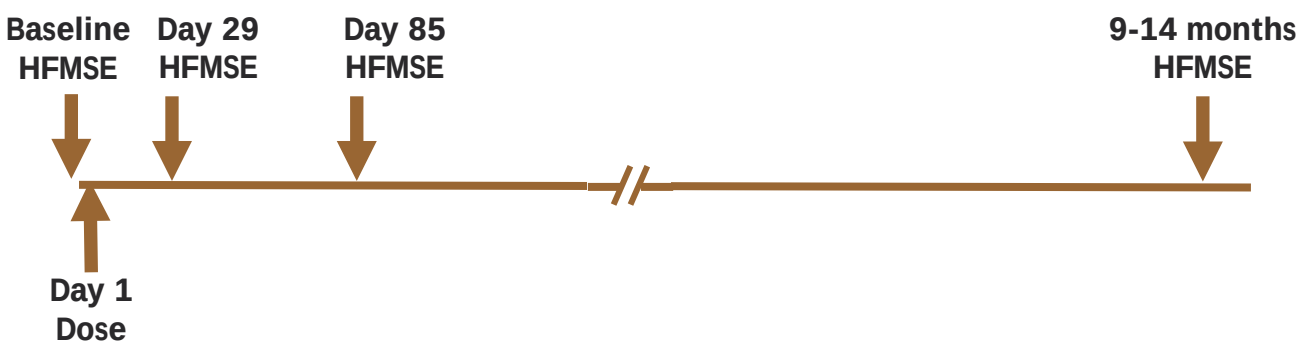




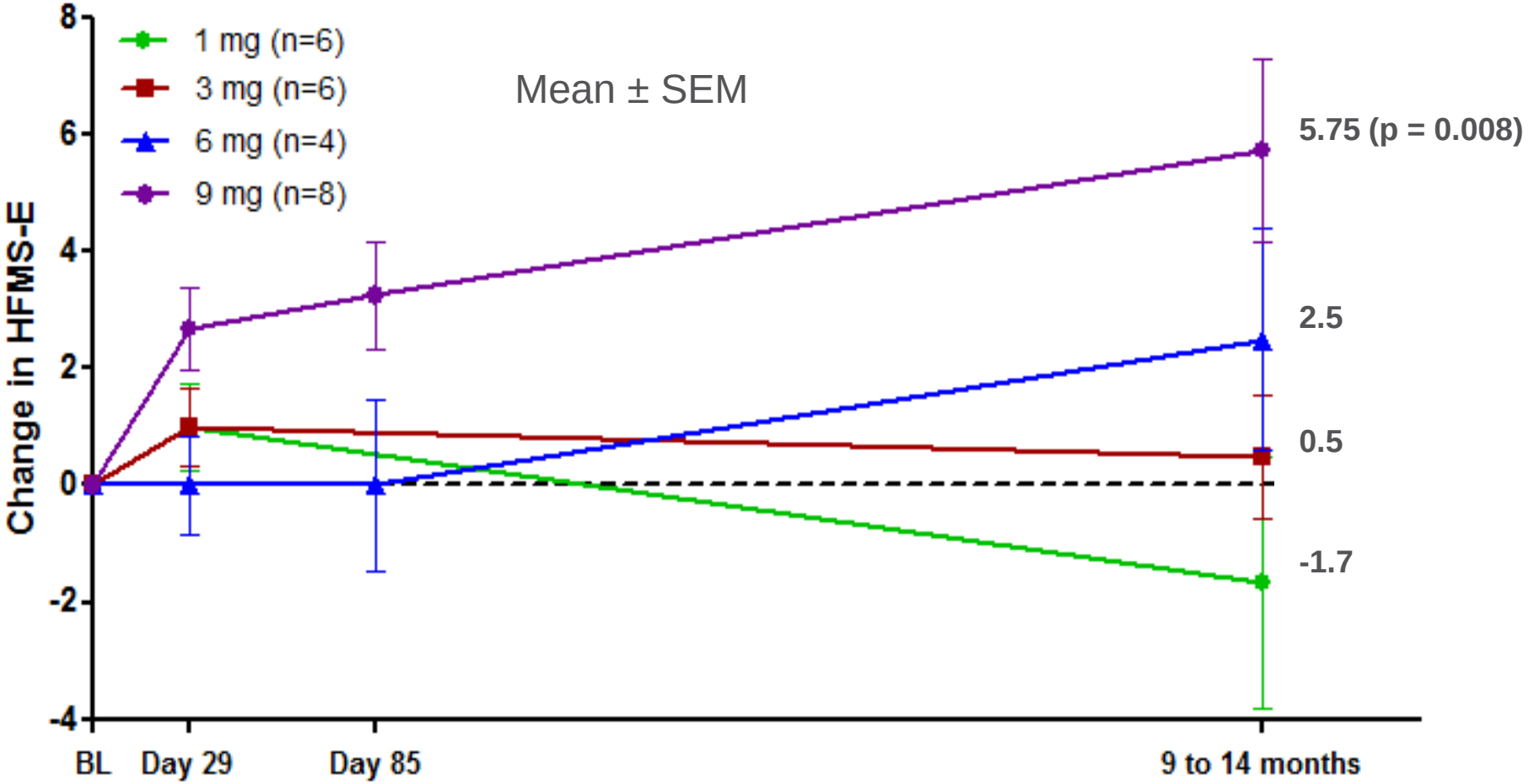
ISIS-SMN$_{Rx}$
Phase 1 Single-Dose Study in SMA Children (Completed)

- **Open-label, single-dose study to evaluate the safety and tolerability of ISIS-SMN$_{Rx}$ in SMA patients 2-14 years of age**
- **Summary of Observations:**
  - Intrathecal dosing of ISIS-SMN$_{Rx}$ was well tolerated
  - Feasibility of infrequent dosing demonstrated by prolonged effect
  - Increases in Hammersmith scores, a measure of muscle function, were observed in a number of children
- **Patients were eligible to re-enroll in a subsequent study 9-14 months post-dose**

Cohorts	Thru Day 85 (n)	9-14 mo (n)
1 mg	-	6
3 mg	-	6
6 mg	6	4
9 mg	10	8



Increases in Muscle Function Scores Observed in SMA Children Up to 14 Months After a Single Dose of ISIS-SMN$_{Rx}$



SMN Protein Increased >2 Fold in CSF of SMA Children After Single Doses of 9 mg of ISIS-SMN$_{Rx}$

- In multidose study, SMN protein increase of 115% (p=0.004, n=9) observed at 3 months
- In single dose study, SMN protein increase of 160% (p=0.09, n=6) observed at ~ 1 year

Long Half-life of ISIS-SMN$_{Rx}$ in the CNS Observed in the Single Dose Study Supports Infrequent Dosing

- 9-14 months after a single dose, ISIS-SMN$_{Rx}$ was detected in CSF
- These data confirm a long half-life in patients with SMA (approximately 4-6 month half-life)
- Provides for infrequent dosing

Dose	CSF Half-life
1 mg	132 days
3 mg	132 days
6 mg	159 days
9 mg	166 days

*CSF concentration in multi-dose study consistent with single-dose data

Conclusions and Lessons Learned from Phase 1

- Intrathecally delivered ISIS-SMN_{Rx} well tolerated
- Dose dependent increases in muscle function (Hammersmith) scores
- Continuing increases in muscle function scores up to 14 months after a single dose
- Increases in CSF SMN protein levels support biological mechanism
- Long half life of ISIS-SMN_{Rx} confirms feasibility of infrequent dosing
- Clinical profile of ISIS-SMN_{Rx} is consistent with preclinical findings and supports continued development

ISIS-SMN$_{Rx}$ Phase 2 SMA Children Data

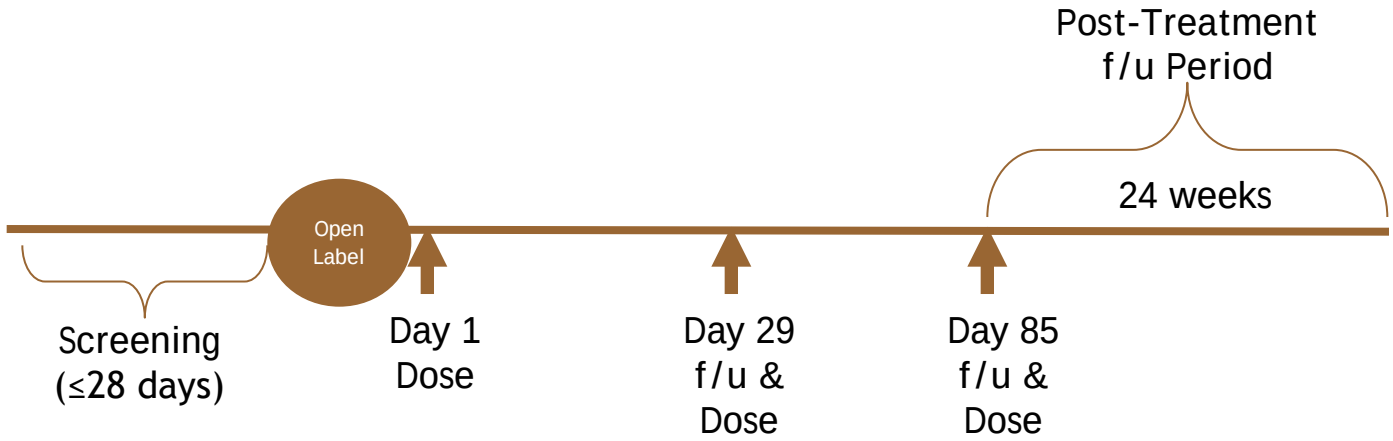
Claudia Chiriboga, M.D., M.P.H.

Associate Professor of Clinical Neurology
& Clinical Pediatrics,
Columbia University Medical Center

Phase 1b/2a Multiple-Ascending Dose, Open-Label Study in Medically Stable SMA Patients 2-15 Years of Age

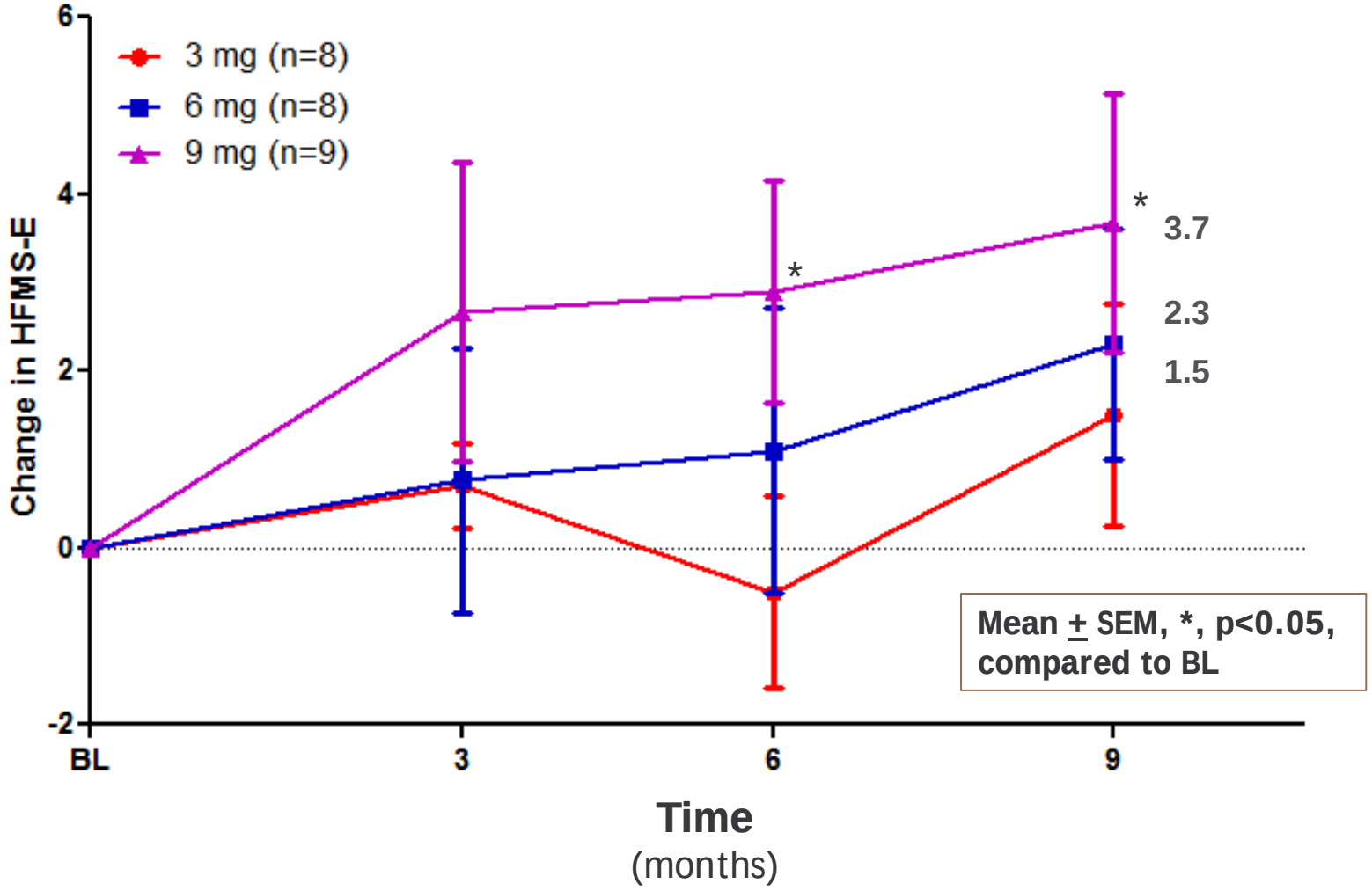
- **Objectives:**
  - Evaluate the safety and tolerability of multiple intrathecal doses of ISIS-SMNRx
  - Evaluate CSF, plasma PK, biomarkers and clinical outcomes related to SMA (including HMFSE)
- **Data Analysis:**
  - 3 mg, 6 mg, and 9 mg cohorts completed; 12 mg cohort currently ongoing

Cohort	Total Dose	n
3 mg	9 mg	8
6 mg	18 mg	8
9 mg	18 mg	9
12 mg	36 mg	8



SUBJECT DEMOGRAPHICS	N=25
SMA Type	Type 2 = 10; Type 3 = 15
Ambulatory/Non-ambulatory	9/16
Mean age (range)	7.5 years (2-15)
SMN2 Copy #	2 copies = 1; 3 copies = 20; 4 copies = 4

Dose and Time Dependent Increases in HFMSE Scores after Multiple Doses of ISIS-SMN$_{Rx}$



Preliminary Results in Additional Measurements of Motor Function Encouraging and Consistent with Increases Observed in Hammersmith Scores

- **Mean increase of 22.7 meters (SEM ±12.3) observed at 9 months in 6MWT in 9 ambulatory patients (mean baseline 230.8 m, ± SEM 31.4)**
- **Mean increase of 2.3 points (SEM ±0.9) observed at 9 months in the ULM test in 10 nonambulatory patients (mean baseline 10.5, SEM ±1.0)**

- **Six-Minute Walk Test (6MWT) available for SMA patients who are ambulatory**
  - Measures the distance an individual is able to walk over a total of six minutes on a hard, flat surface
- **Upper Limb Module (ULM) Test available for SMA patients who are nonambulatory**
  - 9 item scale with each item scored as 0, 1 or 2 (max score 18) that includes activities of daily living not typically included in measures of gross motor function (i.e., Hammersmith)

ISIS-SMN$_{Rx}$ Multiple Dose Study in Children with SMA Type II/III: Conclusions and Lessons Learned

- **ISIS-SMN$_{Rx}$ was well tolerated when given as multiple doses up to 9 mg - no safety or tolerability concerns were identified**
- **Treatment with ISIS-SMN$_{Rx}$ increased CSF SMN protein levels**
  - Observation supports biological mechanism and is consistent with clinical and preclinical data
- **Dose and time dependent increases in HFMSE scores observed**
- **Encouraging data for additional measures of muscle function (6 MWT, ULM) consistent with changes in HSMFE, although small numbers and open label study design limit interpretation**
- **Higher dose 12 mg Cohort is ongoing**

ISIS-SMN$_{Rx}$ Phase 2 SMA Infant Data

Richard Finkel, M.D.

Chief, Division of Neurology Department of Pediatrics, Nemours Children's Hospital Orlando

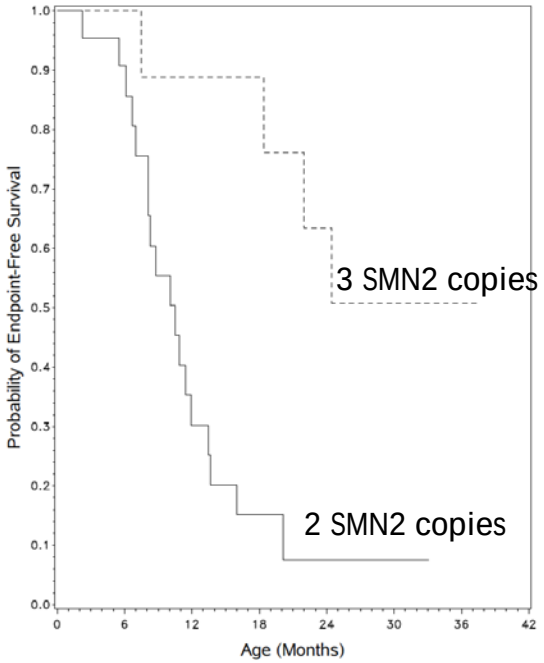
SMA Type 1: Observational Study by Finkel et al.

- **Objective: Characterize clinical features and course of SMA Type I**
- **Study Design**
  - 3 study sites in the US: Columbia University Medical Center (New York); University of Pennsylvania (Children's Hospital of Philadelphia); Harvard University (Boston Children's Hospital)
  - Primary Outcomes of Interest
    - Age at death
    - Age at reaching combined endpoint of either death or requiring at least 16 hours/day of ventilation support for at least 2 weeks in the absence of an acute reversible illness
  - Additional Outcomes
    - Motor function testing using CHOP-INTEND
    - Electrophysiological measurements (e.g., CMAP)
  - Patient Population
    - SMA Type I patients with homozygous deletion

Natural History of Infantile-onset Type 1 SMA (Finkel et at., under review)

Death/Permanent Ventilation

(≥16 hours/day ventilation continuously for >2 weeks, in the absence of an acute reversible illness)

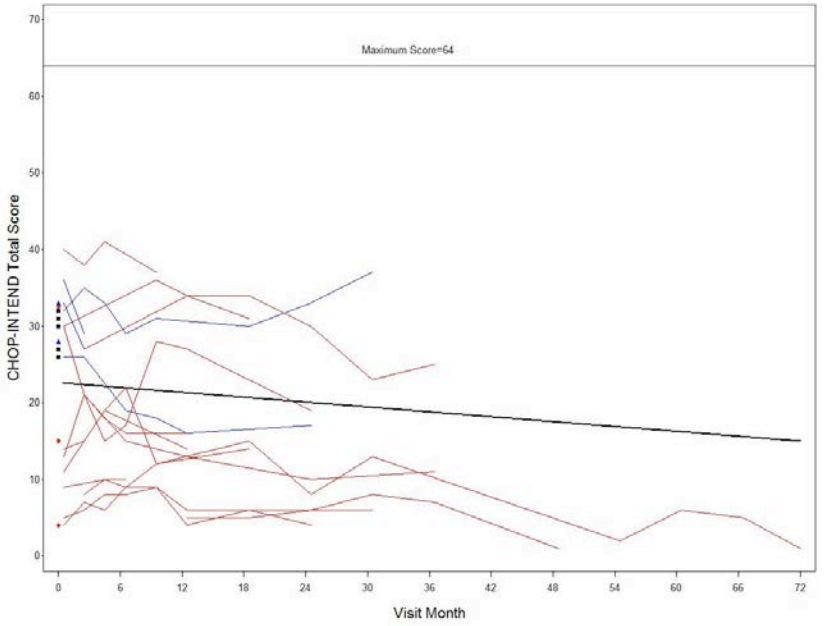


With 2 copies SMN2:

- **Median age at endpoint = 10.5 months**
- **At 18 months, 85% meet endpoint**

CHOP-INTEND

(SMA Infant Motor Function Test)



- **CHOP INTEND scores gradually decline, average decline = 1.27 points/year**

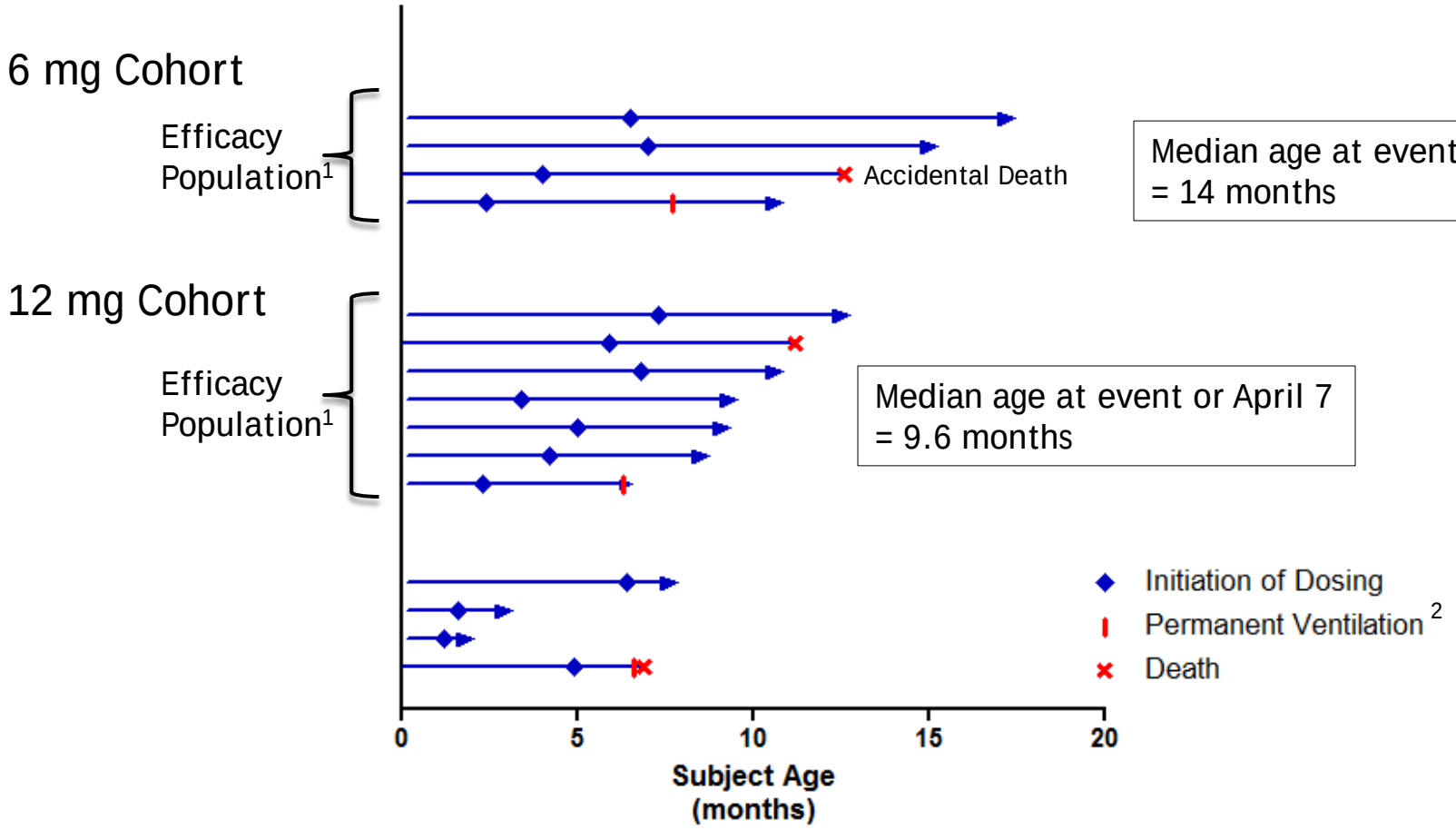
Phase 2 Open-Label Study of ISIS-SMN$_{Rx}$ in Patients with Infantile-onset (Type 1) Spinal Muscular Atrophy

- **Multiple doses given intrathecally as LP bolus injections in male and female infants with SMA ≤7 months of age who are not hypoxemic at screening**
  - Study conducted at 4 sites in North America
- **Primary endpoints:**
  - Safety and tolerability
  - CSF and plasma drug level pharmacokinetics
- **Clinical efficacy endpoints include clinical outcomes related to SMA (survival and ventilation; CHOP-Intend motor function; motor milestones; CMAP)**

Dose Cohort	n
6 mg equivalent	4
12 mg equivalent	11

SUBJECT DEMOGRAPHICS	6 mg Cohort (N=4)	12 mg Cohort (n=11)
Male: Female	3:1	6:5
Mean age at symptom onset (range)	7 weeks (4 to 10)	7 weeks (3 to 16)
Mean age at enrollment (range)	21 weeks (10 to 30)	18 weeks (5 to 30)
SMN2 Copy #	All 2 copies	2 copies=7; 3 copies=1; tbd=3

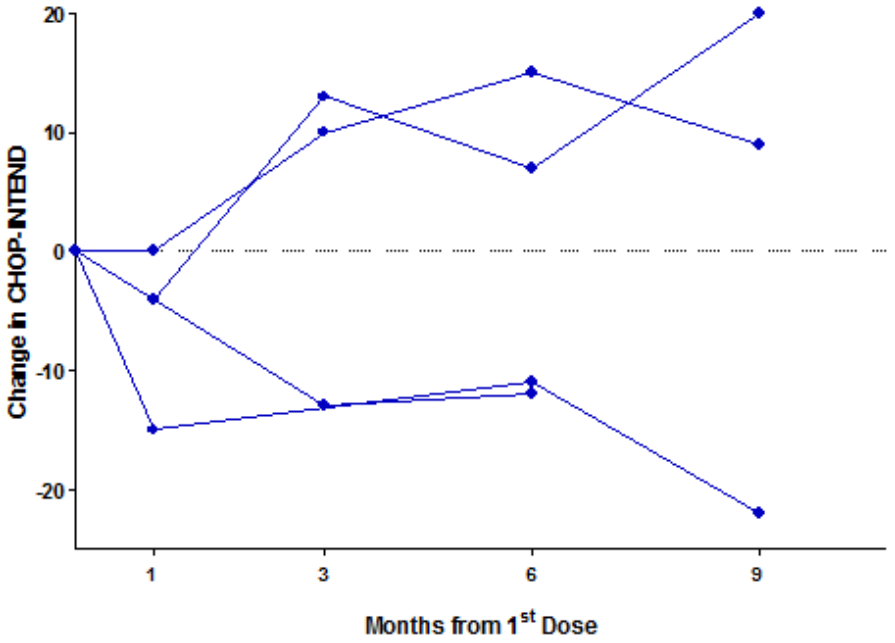
ISIS-SMN$_{Rx}$ Infant Phase 2 Study Subject Status
(as of April 7, 2014)



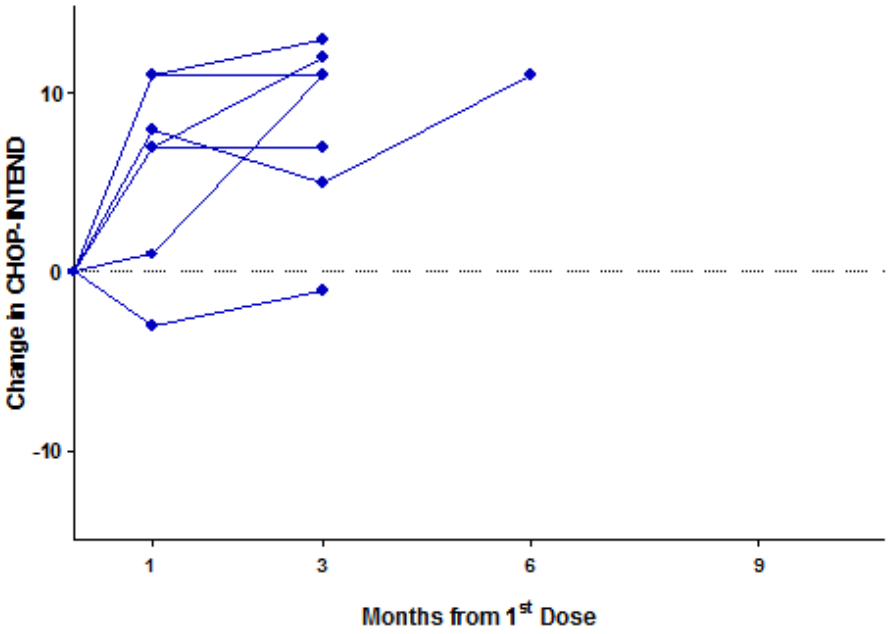
[1] Per protocol efficacy population = subjects who receive 3 initial loading doses and Day 92 evaluation
[2] ≥16 hours hours/day of ventilation continuously for >2 weeks, in the absence of an acute reversible illness

CHOP INTEND Infant Motor Function Test – Individual Subjects (Efficacy Population; Data Cut-off April 7)

6 mg Cohort



12 mg Cohort



- **Increases observed in the majority of subjects (≥5 point increase in 8/11 subjects; Mean change from baseline=5.4 points)**
- **At the 12 mg dose level significant increase observed at 3 Months:**
  - Mean change from baseline=8.3 points
  - 6/7 subjects with change ≥5 points

Additional Exploratory Endpoints (Efficacy Population; Data cut-off April 7, 2014)

- **Hammersmith Infant Neurological Exam Motor Milestones**
  - Incremental milestones achieved consistent with CHOP-INTEND score increases
    - (9/11 subjects exhibited improvements - 3/4 at 6 mg; 6/7 at 12 mg)

Achievement of New Motor Milestones Observed in Some Infants (Efficacy Population; Data cut-off April 7, 2014) at Last Non-dosing Visit

Blue—6 mg, Red—12 mg

Head control	Unable to maintain upright	Wobbles	All the time upright		
Sitting	Cannot sit	Sit with support at hips	Props	Stable sit	Pivots (rotates)
Voluntary grasp	No grasp	Uses whole hand	Index finger and thumb but immature grasp	Pincer grasp	
Ability to kick (in supine)	No kicking	Kicks horizontally; legs do not lift	Upward (vertically)	Touches leg	Touches toes
Rolling	No rolling	Rolling to side	Prone to supine	Supine to prone	
Crawling	Does not lift head	On elbow	On outstretched hand	Crawling flat on abdomen	On hands and knees
Standing	Does not support weight	Supports weight	Stands with support	Stands unaided	
Walking	No walking	Bouncing	Cruising (holding on)	Walking independently	

Achievement of New Motor Milestones Observed in Some Infants (Efficacy Population; Data cut-off April 7, 2014) at Last Non-dosing Visit

Blue—6 mg, Red—12 mg

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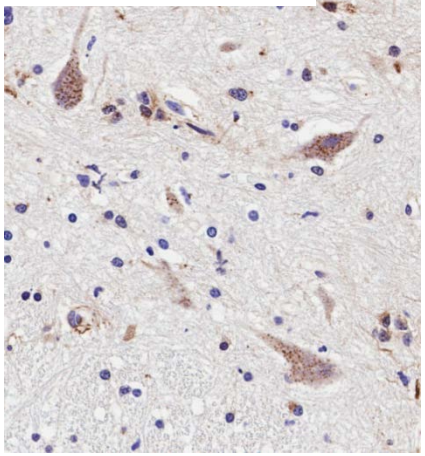
Standing	Does not support weight	Supports weight	Stands with support	Stands unaided	
Walking	No walking	Bouncing	Cruising (holding on)	Walking independently	

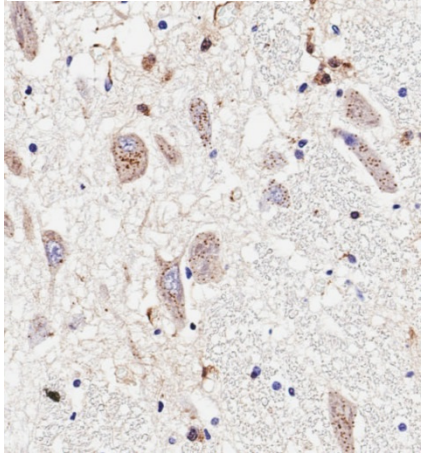
Confirmation of Drug in Spinal Cord and Brain

- **Autopsy material obtained from subject who received 3 doses of drug (12 mg equivalent on study days 1, 15, and 85, autopsy performed study day 163)**
- **Immunohistochemical staining confirms drug in all levels of spinal cord and in brain**

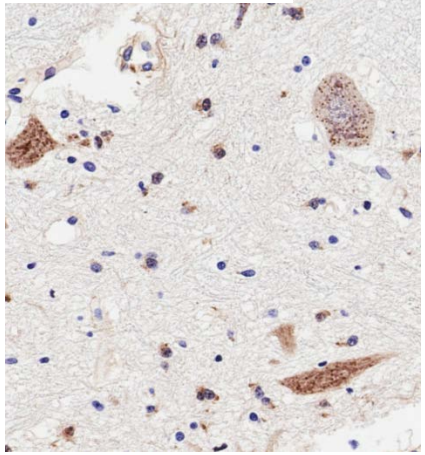
Lumbar Cord



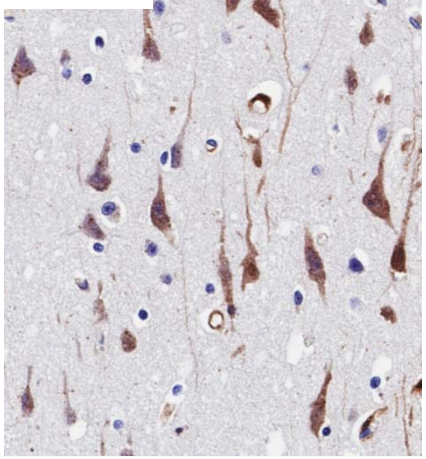
Thoracic Cord



Cervical Cord



Cortex



Conclusions and Lessons Learned from Phase 2 Multidose Study in SMA Infants

- **ISIS-SMN$_{Rx}$ intrathecal injection has been well tolerated up to 12 mg given as multiple doses over 9 months**
- **Confirmation of drug delivery to cells in spinal cord and brain**
- **Encouraging signs of efficacy observed in this open label study**
  - Increase in CHOP-INTEND motor function scores
  - Incremental achievement of Hammersmith Motor Milestones
  - Encouraging CMAP electrophysiology
- **Will continue to follow survival/time to permanent ventilation**
- **These data inform the design of a planned Phase 3 registration-enabling study in infants with SMA**
  - Given the severity of the disease in Type I patients, there is a need to treat as early and as aggressively as possible

ISIS-SMN$_{Rx}$ Development Plan & Upcoming Activities

Kathie Bishop, Ph.D.

VP Clinical Development, Isis Pharmaceuticals

ISIS-SMN$_{Rx}$ Development Plans

Two pivotal studies planned to start in 2014

- **Phase 3 Study in SMA Infants (Mid-year)**
- **Phase 3 Study in SMA Children (2H)**

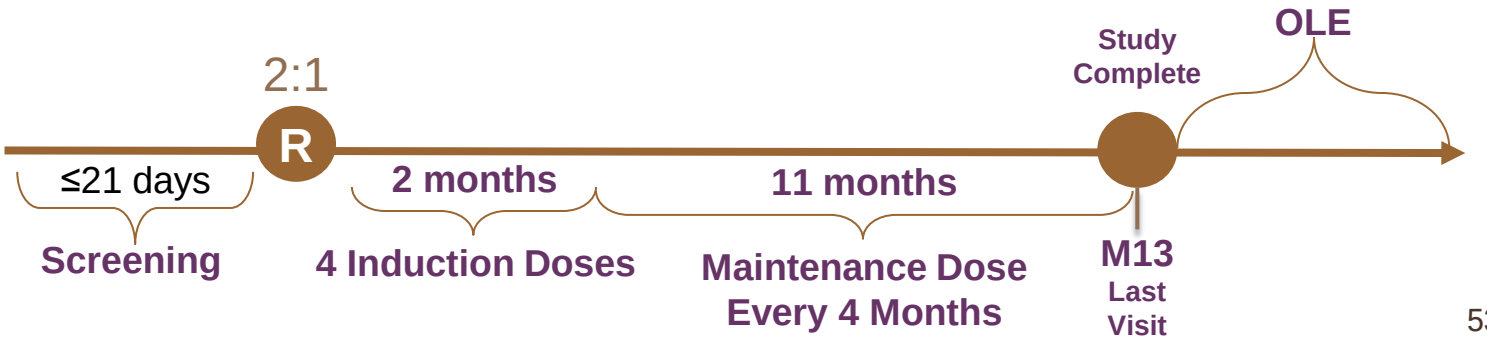
ISIS-SMN$_{Rx}$ Lessons Learned Supporting Phase 3 Design and Conduct

- **Data generated to date support selection of the 12mg dose for pivotal studies**
- **Long half-life of ISIS-SMN$_{Rx}$ in CNS support infrequent dosing**
  - Three month loading dose schedule followed by infrequent maintenance administration
- **The safety and tolerability profile of ISIS-SMN$_{Rx}$ observed to date supports early and aggressive treatment in the more severe SMA infant patients**
- **In SMA infants, data support time to death/permanent ventilation as primary endpoint with motor function (CHOP INTEND, motor milestones) as secondary endpoints**
- **In SMA children, data support change in Hammersmith motor function score as the primary endpoint in pivotal study**

ISIS-SMN$_{Rx}$ Phase 3 Study in SMA Infants

- **A Phase 3, Randomized, Double-blind, Sham-Procedure Controlled Study in Infants with SMA**
  - Global study in ~110 SMA infants ≤ 7 months old
  - Planned mid-year initiation; study start up activities in progress
  - 13 month study duration
    - All patients eligible to roll over to open label extension (OLE) study
- **Objectives**
  - Determine the efficacy and safety of ISIS-SMN$_{Rx}$
    - Primary efficacy endpoint is survival or permanent ventilation
    - Additional efficacy endpoints include CHOP INTEND and motor milestones

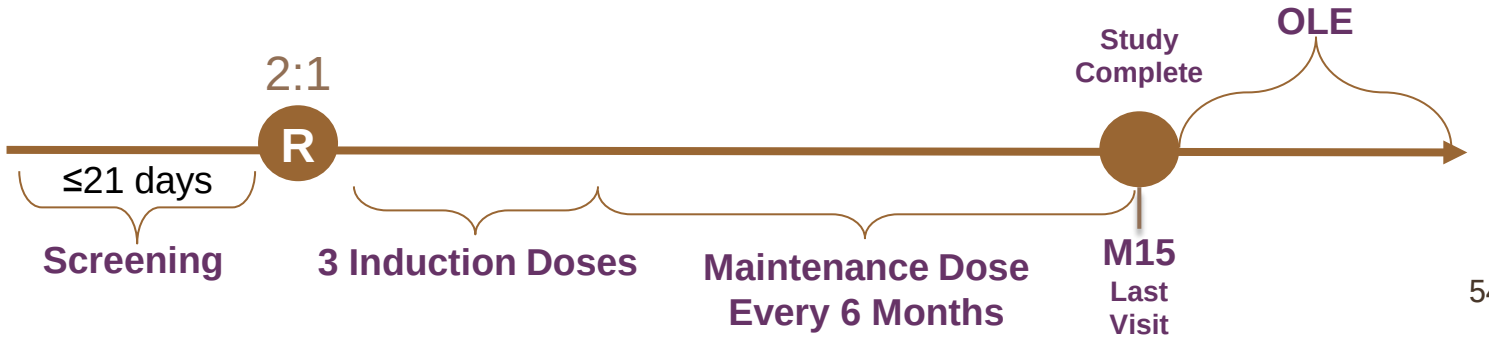
Cohorts
Sham
12 mg



ISIS-SMN$_{Rx}$ Phase 3 Study in SMA Children

- **A Phase 3, Randomized, Double-blind, Sham-Procedure Controlled Study in Children with SMA**
  - Global study in ~120 SMA children
  - Planned 2H 2014 initiation; more detail on study design will be provided later in year
  - 15 month study duration
  - All patients eligible to roll over to open label extension (OLE) study
- **Objectives:**
  - Determine the efficacy and safety of ISIS-SMN$_{Rx}$
    - Primary efficacy endpoint: change in Hammersmith motor function score

Cohorts
Sham
12 mg



Closing Remarks

Stan Crooke, M.D., Ph.D.
CEO and Chairman, Isis Pharmaceuticals

ISIS-SMN$_{Rx}$

Rapid Path to Market

- Initiation of Phase 3 study in infants with SMA planned for mid-year
- Initiation of Phase 3 study in children with SMA planned for 2H 2014

Concluding Remarks on ISIS-SMN$_{Rx}$ (1 of 2)

- **SMA is a severe unmet medical need that is recognized by all relevant groups, including regulatory agencies**
  - ISIS-SMN$_{Rx}$ has been granted Orphan Drug Status in U.S. and E.U. and Fast Track Designation in U.S.
- **ISIS-SMN$_{Rx}$ has been well tolerated to date**
  - Some patients have been treated for over 2 years
  - 44 doses in 15 infants and 138 doses in 54 children as of April 7
- **Magnitude of effect**
- **Effects observed to date have been consistent from:**
  - Mouse to human
  - Infant to children (Type 1 to Type 2/3)
  - Study to study

Concluding Remarks on ISIS-SMN$_{Rx}$ (2 of 2)

- **ISIS-SMN$_{Rx}$ has shown both dose and time dependent effects on motor function**
- **Effects on multiple measures of activity observed**
- **PK/PD consistent with long half life and supportive of infrequent dosing**
- **Increases in SMN protein levels in CSF consistent with drug mechanism**
- **Additional advantages for program:**
  - The recent natural history study in infants provides context for evaluating efficacy
  - Solid relationships with regulatory agencies
  - Strong support by patient advocacy groups and KOLs
  - Seamless, effective working relationship between Biogen and Isis
  - Elegance of mechanism

Thank You to Our Partners in this Endeavor

SMA Patients & Families

Strong Partnerships in Support of ISIS-SMN$_{Rx}$

Cold Spring Harbor Labs
Dr. Adrian Krainer
Dr. Yimin Hua

- **Partnered with** biogen idec®
  - **Global development & commercial capabilities**
  - **Biogen Idec has the option to license ISIS-SMN$_{Rx}$ upon completion of the first successful Phase 2/3 trial or the completion of two Phase 2/3 studies**

UMASS

Q&A

Dr. Stan Crooke

CEO and Chairman
Isis Pharmaceuticals

Dr. Darryl De Vivo

Sidney Carter Professor of Neurology and Pediatrics, Department of Neurology, Columbia University Medical Center

Dr. Frank Bennett

SVP Research
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