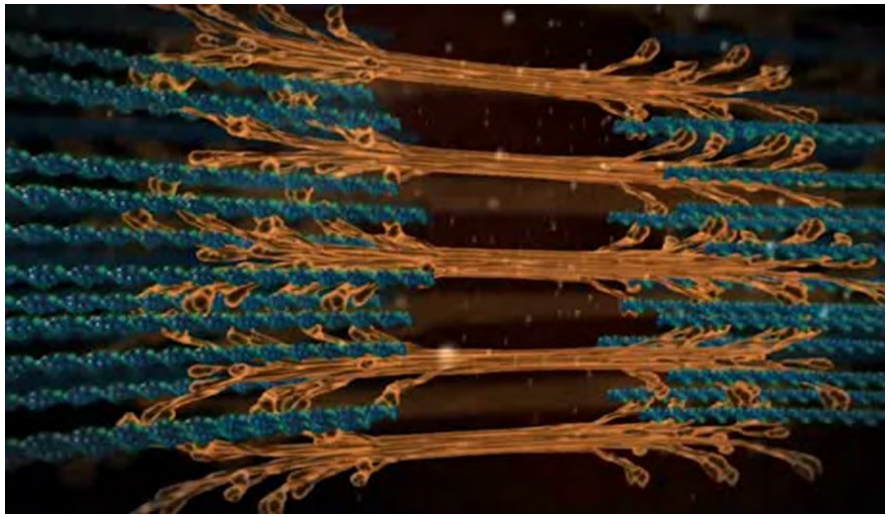
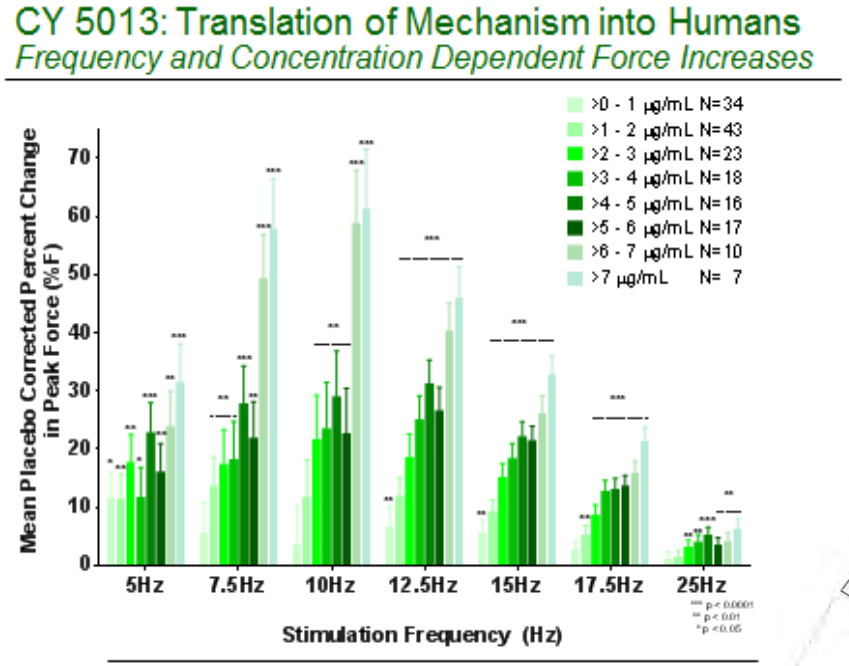
Panel II: SMA Drugs in Development

- **Jinsy Andrews MD,** Director of Clinical Research and Development, Cytokinetics
- **Thomas Blaettler MD**, Global Clinical Development Team Leader, F. Hoffmann-La Roche
- **Jerry R. Mendell MD,** Director, Center for Gene Therapy, Research Institute, Nationwide Children's Hospital
- **Irene Gerlach PhD,** Project Team Leader Rare Diseases, F. Hoffmann-La Roche
- **Wildon Farwell MD, MPH,** Medical Director, Neurology Early Clinical Development, Biogen
- **Eugene Schneider MD**, Executive Director, Clinical Development, Isis Pharmaceuticals
- **Emilie Voltz PhD,** Clinical Trials Leader, Neurosciences, Novartis Institutes for Biomedical Research

cure SMA

Jinsy Andrews MD on CK-2127107, a fast skeletal troponin activator, for the potential treatment of Spinal Muscular Atrophy (SMA)





- Five Phase I healthy volunteer studies completed
- Well-tolerated in healthy volunteers at single doses up to 4000 mg
- Exposures were generally dose proportional up to 4000 mg
- Increased the response of muscle to neuronal input with increasing dose and plasma concentration
- By directly increasing skeletal muscle function, CK-2127107 may enhance physical performance in patients with neuromuscular diseases including spinal muscular atrophy (SMA); this possibility warrants a Phase 2 study in patients with SMA.

Olesoxime Update from Roche: Thomas Blaettler, MD

WE ARE COMMITTED TO PEOPLE LIVING WITH SMA

1 What Is Olesoxime?

- An investigational medicine
- Studied in a double-blind, clinical trial in type II and non-walking type III SMA patients aged 3-25
- Given orally as a liquid

2 Where Are We Today?

- Advancing regulatory and development process needs

3 We Have A Path Forward

Since acquiring olesoxime in March 2015, we have taken immediate actions toward:

- Working with regulatory authorities on steps forward
- Establishing large-scale manufacturing process

4 Our Highest Priority: Provide Olesoxime to SMA Patients

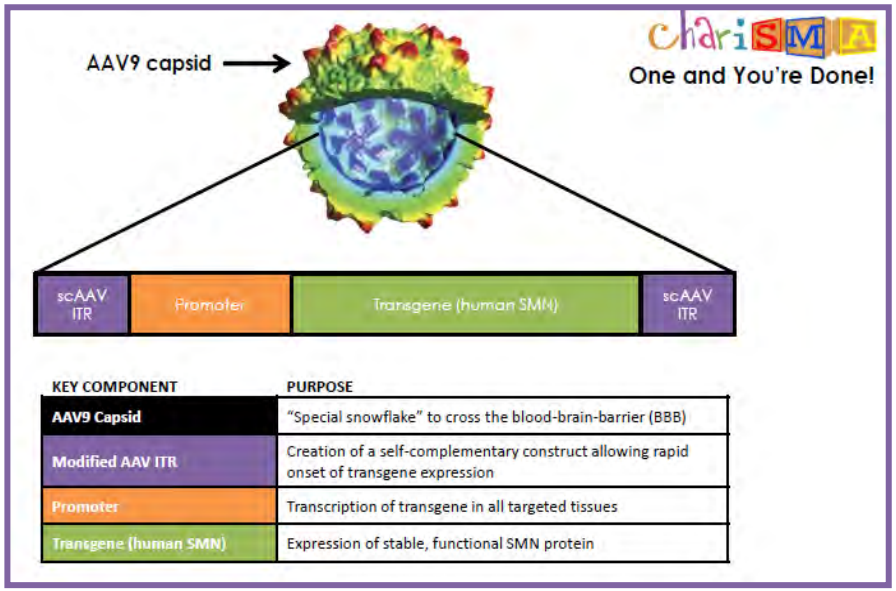
Pending discussions with health authorities, country regulations/laws, and drug availability:

- Open-label study in the EU, hopefully late 2015
- 2017: Regulatory submission in the US & EU

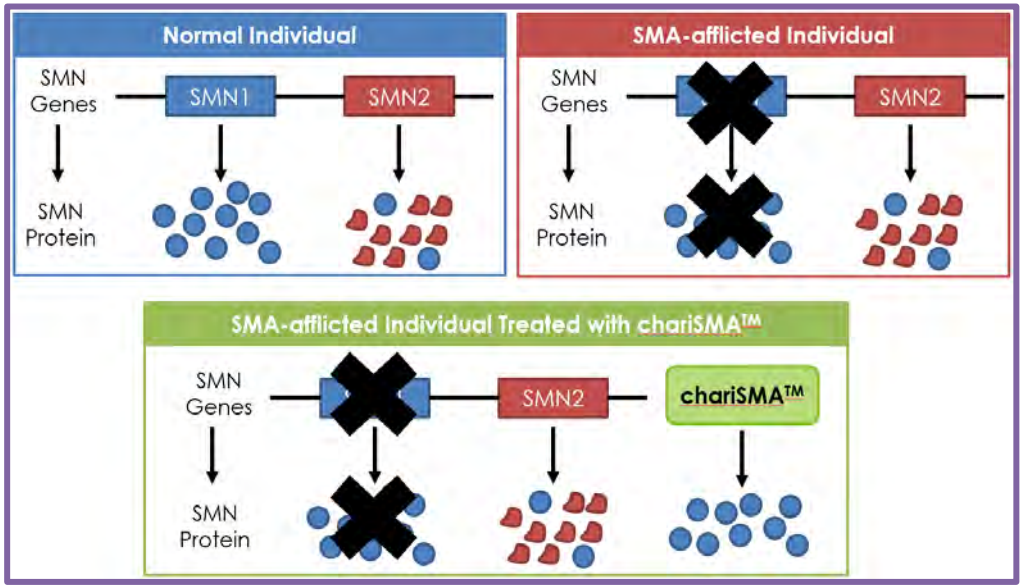
Nationwide Children's
When your child needs a hospital, everything matters.℠

avexis

The Ohio State University
College of Medicine



KEY COMPONENT	PURPOSE
AAV9 Capsid	"Special snowflake" to cross the blood-brain-barrier (BBB)
Modified AAV ITR	Creation of a self-complementary construct allowing rapid onset of transgene expression
Promoter	Transcription of transgene in all targeted tissues
Transgene (human SMN)	Expression of stable, functional SMN protein



- A **virus** is used to deliver a functional copy of the **SMN gene** to patients
- **Normal SMN protein** is made in **motor neurons** and other cells
- Preclinical **efficacy** and **safety** studies enabled an IND

- A **Phase 1/2 trial** is ongoing at Nationwide Children's Hospital
- **Preliminary results** are being reviewed
- All patients **tolerated the treatment**
- A second trial using **intrathecal delivery** is planned

Thank you!!

the Sophia's Cure foundation
Miracles do happen. Let's make one.

cure SMA

fightsma

Avery's Race to CURE SMA

National Institute of Neurological Disorders and Stroke

Irene Gerlach PhD on RG7800: WE ARE COMMITTED TO PEOPLE LIVING WITH SMA

1 RG7800

- An investigational molecule
- Oral SMN2 splicing modifier being studied for spinal muscular atrophy
- Development in collaboration with PTC Therapeutics and the SMA Foundation

2 SMA mouse model

SMN2 mRNA splicing modification

(*Naryshkin et al 2014, Science*)

3 Healthy volunteers – single dose study

- Study has explored
  - ❑ Safety & tolerability
  - ❑ Pharmacokinetics
  - ❑ SMN2 splicing (mechanism of action)

4 First Patient Trial (Moonfish) – Type 1-3 SMA

- Is exploring
  - ❑ Safety & tolerability
  - ❑ Pharmacokinetics
  - ❑ Effects on SMN2 mRNA & SMN protein
- Status: First cohort dosed - clinical hold due to new animal finding

IMPROVING PATIENT LIVES BY TREATING DISEASE…

through targeting **RNA**

Eugene Schneider, MD, Vice President, Clinical Development

Isis Pharmaceuticals

Wildon Farwell, MD, Neurology Medical Director

Biogen

IMPROVING PATIENT LIVES BY TREATING DISEASE…

through targeting **RNA**

ISIS PHARMACEUTICALS Biogen

ISIS-SMN$_{Rx}$ Studies Currently Enrolling

endear

ENDEAR (Isis study): Infant Onset SMA Registration Trial

- First patient dosed in August 2014
- Eligible patients may continue in open label extension
- Data planned 2016/2017

cherish

CHERISH (Isis study): Childhood Onset SMA Registration Trial

- First patient dosed in November 2014
- Eligible patients may continue in open label extension study
- Data planned 2016/2017

nurture

NURTURE (Biogen study) : Phase 2 study in pre-symptomatic newborns that are genetically predisposed to the disease

- Study is designed to evaluate the efficacy of the drug (whether early treatment with ISIS-SMN$_{Rx}$, before the signs of the disease are evident, could delay or prevent the development of the disease and its symptoms) and to further investigate the safety and tolerability of ISIS-SMN$_{Rx}$.
- First patient dosed in May 2015

embrace

EMBRACE (Biogen study): Phase 2 study in patients with infantile or childhood-onset SMA

- Study is designed to evaluate the safety and exploratory efficacy of the drug in a small subset of patients with infantile or childhood-onset SMA who do not meet the age and other criteria of the ongoing Phase 3 studies ENDEAR & CHERISH

LMI070 clinical study (NCT02268552)

Lawrence Charnas & Emilie Voltz on behalf of the SMA Team
Novartis Institutes for Biomedical Research

- **What are the objectives?** Safety and tolerability of LMI070
- **Why LMI070?** increase the amount of functional SMN protein and prevent motor neuron loss in Type I SMA
- **How?** Oral administration of LMI070, Open label study, no Placebo arm
  - An increase in the dose of LMI070 and continuation of LMI070 treatment beyond the initial 13 week study may be possible when safety is demonstrated
- **Who can participate?** Infants diagnosed with SMA Type I between 1 and 7 months with 2 SMN2 copies
- **Where is the trial?** Currently open in Europe