Novel therapeutic approaches in SMA

Francesco Muntoni
Chiara Bettolo
Mariacristina Scoto
Francesco Muntoni: disclosures

**Spinal Muscular Atrophy**
- PI of Trophos / Roche Olesoxime SMA study  (2013-14; 2016-)
- PI of Ionis / Biogen antisense study (2015-17)
- Avexis AAV Gene therapy: anticipated in 2018

**Duchenne**
- CI of three antisense trials with Sarepta Therapeutics (1 SAB meeting)
- PI of three Prosensa sponsored studies
- PI of two PTC124 sponsored trials (2 SAB meetings)
- CI of Summit Phase I and II studies on utrophin upregulation (1 SAB meeting)

**Others**
- Member of Pfizer Rare Disease SAB since 2014
- SAB meetings for Roche; Biogen; Avexis
Topic discussed

- Therapeutic approaches
  - Dealing with the primary consequences: increasing SMN protein levels
  - Dealing with secondary consequences: improving muscle health and function
SMA Therapeutics: A Comparative Overview of Drugs Approved and in Development

Sponsored By:

August 8, 2017
Targets for Therapeutic Intervention in SMA

- **Decrease in SMN protein due to SMN1 gene deletion or mutation**
  - **Strategy**
    - Provide functional SMN1 gene
  - **Mechanism**
    - Gene replacement using a viral vector to deliver SMN1 gene to cells
  - **Therapy**
    - AVXS-101
  - **Strategy**
    - Increase SMN mRNA and protein from SMN2 gene
  - **Mechanism**
    - Modify SMN2 mRNA splicing to increase amount of functional SMN protein
  - **Therapy**
    - SPINRAZA, RG7916, branaplam

- **Loss of motor neurons**
  - **Strategy**
    - Prevent motor neuron death
  - **Mechanism**
    - Maintain mitochondria integrity in neurons
  - **Therapy**
    - olesoxime

- **Muscle weakness/atrophy**
  - **Strategy**
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    - Fast skeletal muscle troponin activator amplifies muscle response to nerve
  - **Therapy**
    - CK-2127107

**INCREASES SMN PROTEIN**

**SMN INDEPENDENT**
<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Increases SMN</th>
<th>SMN Independent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strategy</td>
<td>SMN Gene Replacement</td>
<td>Neuroprotectant</td>
</tr>
<tr>
<td>Drug Type</td>
<td>Gene Therapy</td>
<td>ASO</td>
</tr>
<tr>
<td>Delivery Method</td>
<td>IV</td>
<td>Intrathecal</td>
</tr>
<tr>
<td>Dosing</td>
<td>One Time</td>
<td>4 Loading Doses Then Once Every 4 Months</td>
</tr>
<tr>
<td>Body Distribution</td>
<td>Systemic</td>
<td>CNS Only</td>
</tr>
<tr>
<td>Current Target Population</td>
<td>Type I</td>
<td>Approved All Types</td>
</tr>
</tbody>
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INCREASES SMN PROTEIN

SMN INDEPENDENT
Dealing with secondary consequences of SMN deficiency: mitochondrial dysfunction

Safety and efficacy of olesoxime in patients with type 2 or non-ambulatory type 3 spinal muscular atrophy: a randomised, double-blind, placebo-controlled phase 2 trial

Enrico Bertini, Eric Dessau, Eugenio Mecarii, Francesco Muntoni, Janae Schneider, Carol Reid, Anna Lusiakowski, Giacomo P Comi, Jean-Marie Courtet, Jean-Louis Abitbul, Bruno Scherer, Patricia Sanwald Ducray, Jeppe Buchberg, Eduard Viana, Willem van der Pol, Carole Vuillerot, Thomas Blaettler, Paula Fontoura, for the Olesoxime SMA Phase 2 Study Investigators*

*Tropeos and now Roche sponsored clinical trials
Primary outcome measure: Motor Function Measure
Secondary: Hammersmith Functional Motor Score

Trophos and now Roche sponsored clinical trials
Oleos: ongoing open label extension study

Figure 1. MFM D1 + D2 change from baseline in the Phase 2 study to the first visit in OLEOS

Figure 2. Change from OLEOS baseline (MFM D1 + D2 scores) after 12 months’ 10 mg/kg olesoxime open-label treatment

Roche sponsored clinical trials
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**INCREASES SMN PROTEIN**
- **SMN INDEPENDENT**
CK-2127107, an Activator of the Fast Skeletal Muscle Troponin Complex

By slowing down the calcium release from troponin C, the sarcomere is sensitize to Calcium and fast skeletal muscle contractility is increased.


**Patient Population (CY 5021)**

- Patients 12 years of age and older
- Genetically confirmed spinal muscular atrophy Types II, III, or IV
- 72 patients equally divided between ambulatory and non-ambulatory status

**Outcome Measures (CY 5021)**

<table>
<thead>
<tr>
<th>Respiratory</th>
<th>Motor Evaluation</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forced Vital Capacity</td>
<td>Hand held dynamometry</td>
<td>Safety Monitoring</td>
</tr>
<tr>
<td>Maximum Inspiratory Pressure</td>
<td>Revised upper limb module (RULM)</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>Maximum Expiratory Pressure</td>
<td>Hammersmith Functional Motor Score (HFMS-E)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Timed Up and Go (TUG)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Six-minute walk test (6MWT)</td>
<td></td>
</tr>
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Manipulating SMN2 gene splicing

Small molecules
Antisense oligonucleotides

Low SMN protein levels
Normal SMN protein levels
Small molecules to modify splicing of SMN2

SMN2 splicing modifiers improve motor function and longevity in mice with spinal muscular atrophy

Roche & PTC Therapeutics
# Neuroscience development programs

## Spinal muscular atrophy

<table>
<thead>
<tr>
<th>Molecule</th>
<th>SMN2 splicing modifier (2) (RG7918)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Spinal muscular atrophy</td>
</tr>
<tr>
<td>Phase/study</td>
<td>Phase II FIREFISH</td>
</tr>
<tr>
<td># of patients</td>
<td>N=48</td>
</tr>
</tbody>
</table>
| Design | Open-label study in infants with type 1 spinal muscular atrophy  
  - **Part 1** (dose-finding): At least 4 weeks  
  - **Part 2** (confirmatory): 24 months |  
  - Open-label single arm study in adolescents and adults (12–60 yrs) with spinal muscular atrophy type 2/3 previously treated with SMN2 targeting therapy. |
| Primary endpoint | Safety, tolerability, PK, PD and efficacy | Safety, tolerability and PK |
| Status | FPI Q4 2018 | FPI Q1 2017 |
| Collaborator | PTC Therapeutics, SMA Foundation |

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Roche & PTC Therapeutics
Small molecules to modify splicing of SMN2

Novartis sponsored clinical trial
An open-label multi-part first-in-human study of oral LMI070 in infants with Type 1 spinal muscular atrophy

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

- a) 13 patients treated with LMI070; longest to date is ~14 months
- b) No Maximum Tolerated Dose (MTD) has been reached; Adverse Events (AE) have generally been mild and LMI070 has been well tolerated
- c) New target organs identified only in a chronic dog toxicology study
- d) Patients remain on study with dose modification and additional safety measures
- e) Excluding 2 pulmonary deaths, no patients have withdrawn from treatment
- f) Increases in CHOP INTEND and maintenance of independent feeding/ventilation are seen
- g) Recruitment temporarily paused
- h) Novartis is continuing the study of LMI070 as a treatment in Type 1 SMA
Intrathecal ASO Drug Delivery to the CNS

- Antisense oligonucleotides (ASOs) do not cross an intact BBB
- Intrathecal drug administration: precedence for IT drug delivery with anesthetics, pain medications, and chemotherapeutics
- ASOs distribute broadly into spinal cord and specific brain tissues following intrathecal delivery
- ASOs can have long half-lives (several months) in CNS tissue, with even longer duration of action, so enables infrequent dosing
# Nusinersen Clinical Program Overview

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Study Name Logo</th>
<th>Protocol Title</th>
<th>Population Characteristics</th>
<th>SMN2 Copy</th>
<th>Study Design &amp; Treatment Period</th>
</tr>
</thead>
</table>
| ISIS 396443-C53b | ENDEAR | A Phase 3, Randomized, Double-blind, Sham-Procedures Controlled Study to Assess the Clinical Efficacy and Safety of ISIS 396443 Administered Intrathecally in Patients with Infantile-onset Spinal Muscular Atrophy | • Symptomatic  
• ≤7 months of age at time of screening  
• Onset of signs and symptoms ≤6 months | 2 | • Global  
• Randomized, double-blind, sham-procedure controlled  
• 13 months |
| ISIS 396443-C54 | CHERISH | A Phase 3, Randomized, Double-blind, Sham-Procedures Controlled Study to Assess the Clinical Efficacy and Safety of ISIS 396443 Administered Intrathecally in Patients with Later-onset Spinal Muscular Atrophy | • Symptomatic  
• Age 2-12 years at time of screening  
• Onset of signs and symptoms >6 months  
• Can sit, but has never walked | Any | • Global  
• Randomized, double-blind, sham-procedure controlled  
• 15 months |
| 2325M201 | NURe | A Phase 2, Open-Label Study to Assess the Efficacy, Safety, Tolerability and Pharmacokinetics of Multiple Doses of ISIS 396443 Delivered Intrathecally to Subjects with Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy | • Presymptomatic  
• ≤6 weeks of age at time of first dose | 2 or 3 | • Global  
• Open label  
• 2 years |
| 2325M202 | EMBRACE | A Phase 2, Randomized, Double-blind, Sham-Procedures Controlled Study to Assess the Safety and Tolerability and Explore the Efficacy of ISIS 396443 administered Intrathecally in Subjects with Spinal Muscular Atrophy who are not Eligible to Participate in the Clinical Studies ISIS 396443-C53B or ISIS 396443-C54 | • Symptomatic  
• Symptom onset >6 months (age 6-18 months)  
• Symptom onset ≤6 months (2 copies: age >7 months; 3 copies: no upper age limit) | 2 or 3 | • US, UK, & Germany  
• Randomized, double-blind, sham-procedure controlled  
• 12 months |
| ISIS 396443-C511 | SHINE | An Open-label Extension Study for Patients with Spinal Muscular Atrophy who Previously Participated in Investigational Studies of ISIS 396443 | • Previously participated in ENDEAR and CHERISH | Any | • Global  
• Open label with sham control blinded loading period (lead-in)  
• 2 years |

**Ionis/ Biogen sponsored clinical trials**
ENDEAR Study Design and Baseline Characteristics

Key Eligibility Criteria
- Genetic diagnosis of SMA
- 2 copies of the SMN2 gene
- Onset of SMA symptoms at age ≤6 months
- Age ≤7 months with no hypoxemia at screening

Dosing schedule:
- Randomization a
  - Double-blind treatment period
  - Pre-specified interim efficacy analysis D183 onwards: ~80 participants b
  - Nusinersen 12-mg scaled equivalent dose (n=80)
  - 2:1 randomization; 13 months of treatment and follow-up
  - Sham procedure control (n=41)

Sham procedure control (n=41)
- Loading dose
- Maintenance dose
- Study participants transferred to SHINE open-label extension c

Baseline Disease Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sham procedure control</th>
<th>Nusinersen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range) age at first dose, d</td>
<td>205 (30, 262)</td>
<td>165 (52, 242)</td>
</tr>
<tr>
<td>Median (range) age at SMA diagnosis, wk</td>
<td>20.0 (2, 30)</td>
<td>11.0 (0, 29)</td>
</tr>
<tr>
<td>SMA symptoms, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotonia</td>
<td>41 (100)</td>
<td>80 (100)</td>
</tr>
<tr>
<td>Paradoxical breathing</td>
<td>27 (66)</td>
<td>71 (89)</td>
</tr>
<tr>
<td>Pneumonia or respiratory symptoms</td>
<td>9 (22)</td>
<td>28 (35)</td>
</tr>
<tr>
<td>Swallowing or feeding difficulties</td>
<td>12 (29)</td>
<td>41 (51)</td>
</tr>
<tr>
<td>Participants requiring ventilation support, n (%)</td>
<td>6 (15)</td>
<td>21 (26)</td>
</tr>
</tbody>
</table>

aRandomization was stratified by disease duration during screening (age at screening minus age at symptom onset): ≤12 vs. >12 weeks. bInterim efficacy analysis was conducted on 15 June 2016, once ~80 participants had the opportunity to be assessed at the Day 183 visit. cAll infants completing the end of study visit for ENDEAR had the opportunity to enrol in SHINE. ClinicalTrials.gov, NCT02193074.
Motor performance

Highly clinically and statistically significant percentage of motor milestone responders

Infants on nusinersen achieved motor milestones unexpected for individuals with Type I SMA
Respiratory function and survival

Significantly prolonged event-free survival\textsuperscript{a} in nusinersen-treated infants (HR, 0.53; \( P=0.0046 \))

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Sham procedure control</th>
<th>Nusinersen</th>
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<tbody>
<tr>
<td>Death or permanent ventilation, n (%)</td>
<td>28 (68%)</td>
<td>31 (39%)</td>
</tr>
<tr>
<td>Alive and no permanent ventilation, n (%)</td>
<td>13 (32%)</td>
<td>49 (61%)</td>
</tr>
</tbody>
</table>

Graph showing the probability of ventilation-free survival over time (weeks) for Sham procedure control and Nusinersen groups.

Median time to death or permanent ventilation:
Nusinersen: not reached
Sham procedure control: 22.8 weeks

Sham procedure control: 41 30 14 9 7 7
Nusinersen: 80 59 40 29 16 13
Figure S8A. Kaplan-Meier Plot of Time to Death or Permanent Ventilation in the Subgroup of Infants below the Median Disease Duration at Screening.
**Figure S6B.** Kaplan-Meier Plot of Time to Death or Permanent Ventilation in the Subgroup of Infants above the Median Disease Duration at Screening.
Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy

E. Mercuri, B.T. Darras, C.A. Chiriboga, J.W. Day, C. Campbell, A.M. Connelly,
S.T. Iannaccone, J. Kirschner, N.L. Kuntz, K. Saito, P.B. Shieh, M. Tulinius,
E.S. Mazzone, J. Montes, K.M. Bishop, Q. Yang, R. Foster, S. Gheuens,
C.F. Bennett, W. Farwell, E. Schneider, D.C. De Vivo, and R.S. Finkel,
for the CHERISH Study Group*
The use of Nusinersen in the "real world": the UK and Ireland experience with the expanded access program (EAP)

16 specialised centres in UK and Ireland; between March 2017 - October 2017, 63 patients (25 males, 38 females)

Baseline age 14.5 months (range 1 month to 9.5 years);

23 children received at least five injections.
Mean CHOP-intend score at baseline 25/64 (range 5- 52), and 36/64 (range 9- 51) at the 5th injection.

Most patients improved the CHOP-intend total score (1-17 points); few remained stable, while only one dropped from 52 at baseline to 46 at the 5th injection due to limited mobility secondary to a bone fracture, but scored 58 after the 4th injection.

HINE-2 scores available in 16 patients at baseline and at 5th injection; an improvement of at least 2 points was observed in 8 patients with no cases of motor regression.

At baseline 33/63 patients were receiving non-invasive ventilation (NIV), fourteen of them for >16 hours/day; none had tracheostomy. In 5 patients a reduction of the hours on NIV was noted; four additional patients needed to start NIV while on treatment.
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AAV gene therapy

- A single intravenous injection
- Targets both the central nervous system and the peripheral system
- Early efficacy data encouraging

- Presence of pre-existing immunity
- Longevity of effect?
- Liver subclinical adverse events, requiring transient immunosuppression
- Hurdle of re-administration
AAV9 for SMA gene therapy

Jerry Mendell (Columbus, Ohio) is pursuing AAV gene therapy in infants with SMA I

Single IV injection

Two doses used:
A. Cohort 1: $6.7 \times 10^{13}$ vg/kg
B. Cohort 2: $2.0 \times 10^{14}$ vg/kg

Avexis sponsored clinical trial
COHORT 1 (n=3)
Baseline Age (months): 5.9 [median], 6.3 [mean]
Current Age (months): 30.8 [median], 30.4 [mean]
Mean CHOP INTEND Increase: 7.7 points

Infants with SMA type 1 older than 6 months of age do not score >40 (Finkel et al. 2014)

AVXS-101: CHOP-INTEND Motor Function Scores

Dashed lines for individual patients denote missed or partial CHOP-INTEND assessments
AVXS-101: CHOP-INTEND Motor Function Scores

**COHORT 2 (n=12)**
- Baseline Age (months): 3.1 [median], 3.4 [mean]
- Current Age (months): 20.2 [median], 20.7 [mean]
- Mean CHOP INTEND Increase: 24.7 points

**Rapid Response in Cohort 2**
- CHOP INTEND Increase at Month 1: 9.8 [mean]
- CHOP INTEND Increase at Month 3: 15.4 [mean]

**Early intervention and dose appear to affect response**

**Dashed lines for individual patients denote missed or partial CHOP-INTEND assessments**
Next step for Avexis

• Continue to demonstrate safety of this viral gene therapy approach

• Extend this single centre study to multiple centres

• 2 studies planned, one in the US and one in Europe, including the UK, targeting type 1 SMA

• In the more distant future, studies targeting also milder forms of SMA likely planned
Concluding remarks

Incredibly dynamic times for SMA therapeutic developments
Size of response to intervention especially in early treated SMA1 took many investigators by surprise

Timing of intervention plays a significant role
Size of effect in advanced and chronic forms limited
Evolution of treated patients and possible emergence of novel phenotypes/ complications necessary
Role for combinatorial therapies in the future