MDA Clinical & Scientific Conference 2022

Virtual IR event

Basel, 16 March 2022
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Welcome

Bruno Eschli |  Head of Investor Relations
Agenda

Welcome
Bruno Eschli, Head of Investor Relations

Neuromuscular franchise strategy
Samir Megateli, Global Franchise Head, Neuromuscular Diseases, Global Product Strategy

Key Data at MDA 2022
• Evrysdi - clinical update including 3-Year data for SUNFISH in type 2/3 SMA
• Delandistrogene moxeparvovec (SRP-9001) in DMD clinical update
Paulo Fontoura, Global Head of Neuroscience, Immunology, Ophthalmology, Infectious and Rare Diseases
Clinical Development

Q&A
Neuroscience portfolio differentiated on targets and technologies

Ph III studies in Alzheimer’s to read out in Q4 2022

**Ph I (5 NMEs)**
- RG6091
  - UBE3A LNA
  - Angelman syndrome
- RG7637
  - undisclosed
- RG6182
  - undisclosed
- RG6289
  - undisclosed
  - Alzheimer’s disease
- RG6035
  - brain shuttle
  - CD20
  - MS

**Ph II (9 NMEs)**
- RG7935
  - prasinezumab
  - Parkinson’s disease
- RG6100
  - semorinemab
  - Alzheimer’s disease
- UCB 0107
  - bepranemab
  - Alzheimer’s disease
- RG6102
  - brain shuttle gantenerumab
  - Alzheimer’s disease
- RG7412
  - crenezumab
  - Alzheimer’s disease
- RG7916 +
- RG6237
  - Evrysdi +
  - GYM329
  - SMA type 2/3
- NME
  - N/D
  - FSHD
- RG7906
  - ralmitaront
  - Schizophrenia
- RG7816
  - GABA_A α5 PAM
  - Autism spectrum disorder

**Ph III (3 NMEs, 1AI)**
- RG1450
  - gantenerumab
  - Alzheimer’s disease
- RG6356
  - delandistrogene moxeparovec
  - DMD
- RG6168
  - Ensyrng
  - gMG
- RG7845
  - fenebrutinib
  - MS

**Launched (3)**
- RG1594
  - Ocrevus
  - MS
- RG6168
  - Ensyrng
  - NMOSD
- RG7916
  - Evrysdi
  - SMA type 1/2/3

NME=new molecular entity; AI=additional indication; NMOSD=neuromyelitis optica spectrum disorders; DMD=Duchenne muscular dystrophy; gMG=generalised myasthenia gravis; MS=Multiple sclerosis; SMA=spinal muscular atrophy; OLE=open label extension; FSHD= Facioscapulohumeral muscular dystrophy; Risdiplam is developed in collaboration with PTC therapeutics and the SMA Foundation. 1. Phase II/III currently in Phase II start up.
# Gene & cell therapy at Roche

**Developing novel platforms in Neuroscience, Oncology and Ophthalmology**

<table>
<thead>
<tr>
<th>Gene therapy</th>
<th>Antisense RNA</th>
<th>Neoantigen vaccines</th>
<th>Personalized T cells</th>
<th>Stem cell therapy</th>
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<tr>
<td>AVV Adeno associated virus</td>
<td>Factor B ASO</td>
<td>iNeST platform: mRNA-LPX Liposome</td>
<td>Patient’s neo-antigens for anti-tumour immune response</td>
<td>OpRegen Epithelium cell replacement therapy</td>
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<tr>
<td>• Luxturna ✅</td>
<td>• HBV siRNA</td>
<td>mRNA</td>
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<td>• SPK-8011 (hem A)</td>
<td>• PDL1 LNA</td>
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<td>• SPK-8016 (hem A inhibitors)</td>
<td>• UBE3A LNA (Angelman syndrome)</td>
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<td>• SPK-3006</td>
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<td>• SRP-9001 (DMD)</td>
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<td>• 6 preclinical assets (Spark)</td>
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</table>
Gene therapy platform development on-going
Our approach driven by safety, predictability, efficacy and durability

Variety of naturally occurring and now engineered AAV capsids

AAV vectors have different tissue tropism

Vector payload optimisation including gene regulation

Advanced delivery methods
- less invasive
- targeted distribution
- lowest effective dose
- Optimal immunomodulatory regimens

Manufacturing: One Batch – several patients, e.g. gene therapies, RNA therapies

Mingozzi and High Blood 2013; LSC&D=late stage customisation & distribution
### 2022: Key late-stage newsflow* and upcoming IR events

<table>
<thead>
<tr>
<th>Compound</th>
<th>Indication</th>
<th>Milestone</th>
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<tbody>
<tr>
<td>Vaubysmo</td>
<td>nAMD/DME</td>
<td>US/EU approval</td>
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<tr>
<td>Susvimo</td>
<td>nAMD</td>
<td>EU approval</td>
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<tr>
<td>mosunetuzumab</td>
<td>3L+ FL</td>
<td>US/EU approval</td>
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<tr>
<td>Tecentriq</td>
<td>Adjuvant NSCLC</td>
<td>EU approval</td>
</tr>
<tr>
<td>Hemlibra</td>
<td>Mild to moderate hemophilia A</td>
<td>EU approval</td>
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<tr>
<td>Polivy + R-CHP</td>
<td>1L DLBCL</td>
<td>EU/US approval</td>
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<tr>
<td>glofisnab</td>
<td>3L+ DLBCL</td>
<td>Ph Ib NP30179</td>
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<td>Tecentriq + tiragolumab + chemo</td>
<td>1L ES-SCLC</td>
<td>Ph III SKYSCRAPER-02</td>
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<td>Tecentriq + chemo</td>
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<td>Ph III IMvolve010</td>
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<td>Ph III SKYSCRAPER-01</td>
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<td>giredestrant</td>
<td>2/3L HR+ mBC</td>
<td>Ph II acelERA</td>
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<td>Tecentriq + chemo</td>
<td>Adjuvant HCC</td>
<td>Ph III IMbrane050</td>
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<td>Vencixta + dexamethasone</td>
<td>t(11;14) MM</td>
<td>Ph III CANOVA</td>
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<tr>
<td>Tecentriq + chemo</td>
<td>Neoadjuvant NSCLC</td>
<td>Ph III IMPower030</td>
</tr>
<tr>
<td>Tecentriq + tiragolumab + chemo</td>
<td>1L esophageal cancer</td>
<td>Ph III SKYSCRAPER-08</td>
</tr>
<tr>
<td>Alecensa</td>
<td>Adjuvant ALK+ NSCLC</td>
<td>Ph III ALINA</td>
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<tr>
<td>gantenerumab</td>
<td>Alzheimer’s disease</td>
<td>Ph III GRADUATE 1/2</td>
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<tr>
<td>Susvimo</td>
<td>DME</td>
<td>Ph III PAGODA</td>
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<tr>
<td>Susvino</td>
<td>DR</td>
<td>Ph III PAVILION</td>
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### Phase III / pivotal readouts

<table>
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<td>DR</td>
<td>Ph III PAVILION</td>
</tr>
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### Virtual events

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
<th>Time</th>
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<tbody>
<tr>
<td>Virtual event Angiogenesis</td>
<td>Monday, 14 February</td>
<td>16:30 to 17:45 CEST</td>
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<tr>
<td>Virtual event MDA</td>
<td>Wednesday, 16 March</td>
<td>16:30 to 17:30 CEST</td>
</tr>
<tr>
<td>Roche ESG Day Access to Healthcare</td>
<td>Monday, 16 May</td>
<td>TBC</td>
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<tr>
<td>Virtual/live event ASCO</td>
<td>June</td>
<td>TBC</td>
</tr>
<tr>
<td>Roche Pharma Day</td>
<td>Monday, 12 September</td>
<td>TBC</td>
</tr>
</tbody>
</table>

* Outcome studies are event-driven: timelines may change
Neuromuscular franchise strategy

Samir Megateli | Global Franchise Head, Neuromuscular Diseases
Global Product Strategy
Neuromuscular Franchise at Roche

Together, we envision a future of unlimited potential for the NMD community by translating science into meaningful outcomes

BUILD the foundation to transform the future of neuromuscular diseases

LEAD the next wave of breakthrough innovation in neuromuscular field

EXPAND impact by advancing care across the patient journey in multiple neuromuscular diseases

Our key building blocks to achieve our vision

- Accelerate pipeline and expand portfolio of molecules and integrated solutions
- Partner with NMD community to shape ecosystem and sustainability
- Leverage One Roche NMD network and capabilities
## Our expanding Roche Neuromuscular portfolio

*Utilising a range of technology platforms and biological approaches*

<table>
<thead>
<tr>
<th>Early Stage</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Launched</th>
</tr>
</thead>
<tbody>
<tr>
<td>NME 3 projects</td>
<td>RG7916 + RG6237</td>
<td>RG6168</td>
<td>RG7916</td>
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<tr>
<td>N/D</td>
<td>RG6107</td>
<td>Satralizumab</td>
<td>Evrysdi</td>
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<tr>
<td>NME</td>
<td>FSHD²</td>
<td>Crovalimab</td>
<td>N/D</td>
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<tr>
<td>N/D</td>
<td></td>
<td>delandistogene moxeparvoce</td>
<td>DMD</td>
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</table>

**Small molecule**

**Antibody**

**Gene therapy**

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1. Phase II/III currently in Phase II start up; 2. Proof of concept study; N/D = not disclosed; NME=new molecular entity; DMD=Duchenne muscular dystrophy; gMG=generalised myasthenia gravis; SMA=spinal muscular atrophy; FSHD=Facioscapulohumeral muscular dystrophy
Evrysdi: Meaningful evidence generated across a broad program

Long term efficacy and safety data demonstrating sustained increase in motor function

Overview of the risdiplam development program

- Spanning Types 1, 2, & 3 SMA; both naive and pre-treated
- Newborns to 60 years old
- Including real-world spectrum of SMA – severe scoliosis, joint contractures, low baseline motor scale scores, etc.
- Long-term efficacy data from the pivotal SUNFISH study at 3 years confirm increases in motor function after one year of treatment with Evrysdi are sustained at three years

* Estimated 2020 prevalence in US and EUs
Evrysdi is well-positioned and making significant progress to becoming the most prescribed SMA therapy globally

Evrysdi in SMA

- Clinically meaningful efficacy sustained over the long-term
  3 year data in a broad and heterogeneous population (SUNFISH)

- >5,000 patients treated to date
  In clinical trials, CUP/PAA and in the commercial setting

- Preserves swallowing & feeding ability
  Bulbar function is highly important to patients and treating physicians

- Well-tolerated
  No treatment-related AEs discontinuations in trials

- Consistent increase in SMN protein
  Throughout the CNS and in peripheral tissues

- At-home administration
  Low burden on patients, caregivers and the health care system
SMA franchise: Evrysdi with strong US and EU launches

Most prescribed treatment in the US with >20% share; Germany with ~30% share

**Launch update**

- >5,000 patients treated worldwide (commercial, clinical trials, compassionate use), approved in 75 countries
- US: Ongoing growth in 2022 driven by switches and naive patient starts: ⅔ of total patients on Evrysdi from switches
- EU: Strong launches in early launch countries
- US/EU: Filed for label extension (<2 months old) based on RAINBOWFISH
  - Priority review granted in US

**Outlook 2022**

- Continued growth from geographical expansion and market share gains
- Ph II/III (MANATEE) Evrysdi + anti-myostatin in SMA to start in the coming weeks

CHFm YoY CER growth
Duchenne muscular dystrophy (DMD)
A rare, fatal neuromuscular genetic disease

An inherited muscle-wasting disorder associated with progressive muscle loss caused by mutations in the dystrophin gene

Currently, there are limited treatment options, all with low efficacy and many with significant side effects

Onset
early toddler years

Loss of ambulation
early teens

Death
early adulthood

Estimated incidence worldwide: 1 in ~3,500-5,000 live male births\(^2-3\)

Delandistrogene moxeparvovec (SRP-9001)

Designed to deliver the micro-dystrophin transgene directly to the muscle tissue for the targeted expression of functional micro-dystrophin protein

AAV, adeno-associated virus; DNA, deoxyribonucleic acid; rAAV, recombinant adeno-associated virus; RNA, ribonucleic acid.

Key components of delandistrogene moxeparvovec

The transgene has been developed with some of the most important parts of dystrophin

<table>
<thead>
<tr>
<th>Full length Dystrophin</th>
<th>Sarepta/Roche Micro-dystrophin(^{1,7})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extracellular matrix</td>
<td>Sarcolemma</td>
</tr>
<tr>
<td>Sarcolemma</td>
<td>Cytoplasm</td>
</tr>
<tr>
<td>F-actin</td>
<td>Microlattices</td>
</tr>
</tbody>
</table>

AAVrh74
- Muscle tropic capsid intended to target heart and skeletal muscle cells
- Low level of pre-existing immunity\(^{3}\)

PROMOTER MHCK7
Muscle-specific promoter α-MHC intended to enhance muscle-specific activity\(^{1,2}\)

Comprehensive development program of delandistogene moxeparvovec

**Study 101**
- 4 patients
- Ages 4-7, ambulatory
- Open-Label
- NCT03375164
- Goals included safety, proof-of-concept
- Enrolment completed
- One-year results published in *JAMA Neurology*
- Positive 2-year and 3-year functional data

**Study 102**
- 41 patients
- Ages 4-7, ambulatory
- Placebo-Controlled
- NCT03769116
- Goals included safety, function
- Enrolment completed
- 5-year 3-part study
- Part 1 (48 weeks) complete
- Part 2 Ongoing

**Study 103**
- 38 patients
- Ages 3+ ambulatory and non-ambulatory
- Open-Label
- NCT04626674
- Goals include expression and safety
- Enrolment completed
- No mutation exclusion, except for patients below 4 years

**Study 10**
- 41 patients
- Ages 4-7, ambulatory
- Placebo-Controlled
- NCT03769116

**Study 301**
- 120 patients
- Ages 4-7, ambulatory
- Double-blind, placebo-controlled
- NCT05096221
- Pivotal Phase III study
- Primary endpoint: NSAA
- Excludes mutations 1 to 17
- Planned FPI 2022, EU study population

**Study 302**
- 20 patients
- Ages 0-4
- Open label
- Safety (primary) and Expression (secondary)
- Excludes mutations 1 to 17
- Planned FPI 2022

**Study 303**
- 3:1 non-ambulatory/ambulatory patients in at least 80 patients
- Double-blind, placebo-controlled
- No upper age restrictions for non-ambulatory
- Ambulatory: 8-18
- Primary endpoint: PUL
- Excludes mutations 1 to 17
- Planned FPI 2022

**ENDEAVOR**

**EMBARK**

**ENVOL**

**ENVISION**
Key Data at MDA 2022

Paulo Fontoura MD, PhD |
Global Head of Neuroscience, Immunology, Ophthalmology, Infectious and Rare Diseases Clinical Development
Evrysdi - clinical update from MDA 2022
Sunfish: A randomized, placebo-controlled, double-blind study with broad inclusion criteria and a large dataset

- **Age 2–25 years**
- **Type 2/non-ambulant Type 3 SMA**
- **Ability to sit independently**
- **Scoliosis and surgery for scoliosis or hip fixation accepted**

**Primary endpoint:**
- Change from baseline in MFM32 total score at Month 12

**Exploratory efficacy analyses:**
- Change from baseline in MFM32 total score at Month 36
- Percentage of patients who achieve stabilization or improvement (≥0) or a change of ≥3 from baseline in MFM32 total score at Month 36
- Change from baseline in RULM total score at Month 36
- Change from baseline in HFMSE total score at Month 36
- Change from baseline in SMAIS patient and caregiver upper limb total score at Month 36

**Safety:**
- Most common AEs and SAEs from baseline to Month 36
- Rate of AEs and SAEs per 100PY over 36 months

*Non-ambulant is defined as not having the ability to walk unassisted for ≥10m. †RULM entry item A (Brooke score) ≥2; ability to sit independently (≥1 on item 9 of the MFM32). ‡Except in the 1 year preceding screening or planned within the next 18 months.

A total of 5% (9/180) of patients discontinued from SUNFISH Part 2 over 36 months

- Patients in the placebo arm received placebo for 12 months followed by risdiplam treatment for 24 months.
- †Two patients in the risdiplam arm switched to nusinersen (SPINRAZA®) treatment.
- ‡This patient withdrew from the study to start nusinersen treatment.


Day et al MDA 2022 abstract 73
The increase in MFM32 total score was maintained between months 12 & 36 in the risdiplam arm; an overall decline was seen in natural history.

**SUNFISH Part 2**
Overall population 2–25 years old*

<table>
<thead>
<tr>
<th>Visit (months)</th>
<th>Risdiplam (n)†</th>
<th>Placebo (n)†</th>
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</thead>
<tbody>
<tr>
<td>6</td>
<td>115</td>
<td>59</td>
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<tr>
<td>12</td>
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<td>18</td>
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<td>24</td>
<td>107</td>
<td>84</td>
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<tr>
<td>30</td>
<td>103</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>93</td>
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</table>

*31% (55/180) of the SUNFISH intent-to-treat population were 2–5 years old at baseline. †-95% CI. ‡Baseline is the last measurement prior to the first dose of risdiplam or placebo. ¶Data cut-off: 6 Sep 2021. Data cut-off: 6 Sep 2019. Patients in the placebo arm received placebo for 12 months followed by risdiplam treatment for 24 months. Risdiplam period not shown in this graph. Number of patients with valid results = number of patients with an available total score (result) at respective time points. Intent-to-treat patients. **The NatHis-SMA study (NCT02391831) included nine study sites in Europe and 81 patients aged 2–30 years with Types 2 and 3 SMA. Patients aged 2–5 years old in the NatHis-SMA study were assessed using the MFM20 and were therefore not included in the data shown. ††The full 95% CIs have not been included in this graph as the y-axis has been shortened to allow an accurate comparison with SUNFISH results.

AIM, Association Institut de Myology; CI, confidence interval; MFM, Motor Function Measure; MFM20, 20-item MFM; MFM32, 32-item MFM; NatHis, natural history; SMA, spinal muscular atrophy.1. Roche data on file; courtesy of AIM. Day et al MDA 2022 abstract.
The percentage of patients who had improved or stabilized in MFM32 total score from baseline was similar between Months 12 and 36.


The percentage of patients was calculated by using the number of valid total scores at corresponding visits as a denominator.

A score of ≥3 shows a marked improvement and a score of ≥0 shows stabilization or improvement.

CI, confidence interval; MFM32, 32-item Motor Function Measure.
The increase in RULM and HFMSE total scores from baseline was sustained between Months 12 and 36 in the risdiplam arm

Without treatment, patients with Types 2 and 3 SMA show a decline in RULM and HFMSE scores over time1,2

<table>
<thead>
<tr>
<th>RULM Overall population 2–25 years old</th>
<th>HFMSE Overall population 2–25 years old</th>
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<tbody>
<tr>
<td>Mean change from baseline in RULM total score*</td>
<td>Mean change from baseline in HFMSE total score*</td>
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<tr>
<td>Visit (months)</td>
<td>Visit (months)</td>
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<td>30</td>
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<td>36</td>
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<tr>
<td>placebo (n)</td>
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Day et al MDA 2022 abstract 73
Patients and caregivers reported stabilization or continuous improvements in the SMAIS-ULM total score change from baseline with risdiplam treatment over 36 months.

*Data cut-off: 6 Sep 2021. †Data cut-off: 6 Sep 2019. Patients in the placebo arm received placebo for 12 months followed by risdiplam treatment for 24 months. Risdiplam period not shown in this graph. ‡+/- 95% CI. Baseline is the last measurement prior to the first dose of risdiplam or placebo. §Number of patients with valid results = number of patients with an available total score (result) at respective time points. Intent-to-treat patients. CI, confidence interval; SMA, spinal muscular atrophy; SMAIS, SMA Independence Scale; SMAIS-ULM, SMAIS Upper Limb Measure.

Day et al MDA 2022 abstract 73
SUNFISH Parts 1 and 2: The observed AE profile over 36 months was reflective of underlying disease

<table>
<thead>
<tr>
<th>SUNFISH Part 1 (N=51)</th>
<th>Number of AEs per 100PY (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total PY at risk</td>
<td>214.5</td>
</tr>
<tr>
<td>AEs reported at a rate of ≥15 per 100PY</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>57.4 (47.7–68.4)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>36.4 (28.8–45.4)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>28.9 (22.2–37.1)</td>
</tr>
<tr>
<td>Cough</td>
<td>20.1 (14.5–27.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18.2 (12.9–24.9)</td>
</tr>
<tr>
<td>Dysmenorrhea</td>
<td>16.3 (11.4–22.7)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>15.9 (11.0–22.2)</td>
</tr>
<tr>
<td>SAEs reported at a rate of ≥0.9 per 100PY</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2.3 (0.8–5.4)</td>
</tr>
<tr>
<td>Femur fracture</td>
<td>0.9 (0.1–3.4)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>0.9 (0.1–3.4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.9 (0.1–3.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SUNFISH Part 2 (N=179)*</th>
<th>Number of AEs per 100PY (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total PY at risk</td>
<td>495.8</td>
</tr>
<tr>
<td>AEs reported at a rate of ≥11 per 100PY</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>46.4 (40.6–52.8)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>24.8 (20.6–29.6)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>22.4 (18.4–27.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18.8 (15.1–23.0)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>18.4 (14.8–22.5)</td>
</tr>
<tr>
<td>Cough</td>
<td>11.7 (8.9–15.1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11.3 (8.5–15.1)</td>
</tr>
<tr>
<td>SAEs reported at a rate of ≥0.8 per 100PY</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5.2 (3.4–7.7)</td>
</tr>
<tr>
<td>Gastritis</td>
<td>1.0 (0.3–2.4)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>0.8 (0.2–2.1)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>0.8 (0.2–2.1)</td>
</tr>
</tbody>
</table>

*Includes 120 patients in the risdiplam arm who have been treated with risdiplam for 36 months and 59 patients from the placebo arm who were switched to the risdiplam arm after 12 months and have been treated with risdiplam for 24 months. One patient randomized to placebo was withdrawn prior to receiving any risdiplam dose. Data cut-off: 6 Sep 2021. AE, adverse event; CI, confidence interval; PY, patient years; SAE, serious AE

There have been no treatment-related AEs leading to withdrawal or treatment discontinuation

Ophthalmologic monitoring has not shown any evidence in humans of the retinal findings seen in preclinical monkey studies

Hematologic parameters have remained stable over time and no drug-induced skin findings have been observed

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SUNFISH Parts 1 and 2: The overall rate of AEs per 100PY decreased over 36 months*

*Includes 51 patients from Part 1 and 179 patients from the risdiplam and placebo/risdiplam arms in Part 2 (one patient randomized to placebo was withdrawn prior to receiving any risdiplam dose). †+/- 95% CI.

AE, adverse event; CI, confidence interval; PY, patient years; SAE, serious AE. Data cut-off: 6 Sep 2021

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SUNFISH Part 2: 24-month efficacy of risdiplam compared with external control comparators

NatHis-SMA: A prospective and longitudinal natural history study of patients with Types 2 and 3 SMA

81 Patients aged 2–30 years

• 53 patients with Type 2 SMA
• 9 patients were non-ambulant with Type 3 SMA*
• 19 patients were ambulant with Type 3 SMA*

Olesoxime Phase 2 trial in patients with Type 2 or non-ambulant Type 3 SMA9,10

57 Patients randomized to placebo aged 3–25 years

• 39 patients with Type 2 SMA
• 18 patients with Type 3 SMA

*Rambulant is defined as being able to walk ≥10m without human or technical help (assessed by investigator).

Increases in MFM total score at Month 12 were observed in patients treated with risdiplam. Increases were sustained over 24 months, in contrast to a progressive decline in the untreated external comparator

Risdiplam administration over 24 months led to improvement or stabilization in motor function at 12 and 24 months

*Weighted analysis. For Month 12 results, patients with baseline and Month 12 results were included in the analysis. For Month 24 analysis, patients with baseline and Month 24 results are included in the analysis. Based on change from adjusted baseline. †n=sum of weights. SUNFISH data cut-off: 30 Sep 2020
Servais et al MDA 2022
The increase in motor function observed during the first year was sustained in the third year after long-term treatment with risdiplam (as measured by changes in MFM32, HFMSE and RULM).

Continuous improvement or stabilization in the level of help needed for activities of daily living was reported using the SMAIS-ULM.

In SUNFISH Parts 1 and 2, AEs and SAEs were reflective of underlying disease. No treatment-related AEs led to withdrawal from the study.

In SUNFISH Parts 1 and 2, the overall rate of AEs decreased over 36 months. A trend towards lower SAE rates was observed in the third year of treatment.

The gains observed with risdiplam treatment at Month 12 were maintained at Month 36.

These results are an important milestone confirming longer-term efficacy and safety of risdiplam in a broad, heterogeneous population of individuals with Type 2 and non-ambulant Type 3 SMA.
RAINBOWFISH: A multicenter, open-label, single-arm study of risdiplam in infants with genetically diagnosed, presymptomatic SMA

Primary endpoint (n≥5):
- Proportion of infants who are sitting without support for ≥5 seconds at Month 12 (BSID-III Gross Motor Scale, Item 22)

Secondary endpoints (all infants; n=261):
- Development of clinically manifested SMA
- Survival and permanent ventilation
- Achievement of motor milestones as defined by the HINE-2 and BSID-III
- CHOP-INTEND total score
- Growth measures
- Ability to swallow and feed orally
- CMAP amplitude
- PK/PD
- Safety

*The primary efficacy population includes infants with two copies of the SMN2 gene and CMAP amplitude ≥1.5 mV at baseline. *Final patient number. As of 22 February 2022, worldwide recruitment for RAINBOWFISH is complete.
RAINBOWFISH: Preliminary efficacy in risdiplam-treated infants with presymptomatic SMA

Seven infants have been treated with risdiplam for ≥12 months

**4 infants have 2 SMN2 copies**
- Most infants with 2 SMN2 copies treated for >12 months (n=4) achieved near-maximum CHOP-INTEND scores, and most achieved motor milestones within WHO windows for healthy children

**3 infants have >2 SMN2 copies**
- All infants with >2 SMN2 copies treated for >12 months (n=3) achieved the maximum CHOP-INTEND score, and most achieved motor milestones within WHO windows for healthy children

WHO, World Health Organisation
Finkel et al MDA 2022 abstract 76
RAINBOWFISH: Preliminary safety in risdiplam-treated infants with presymptomatic SMA

No SAEs were reported in infants with presymptomatic SMA treated with risdiplam

<table>
<thead>
<tr>
<th>Most common AEs, n (%) (reported in ≥3 infants)*</th>
<th>2 SMN2 copies (n=7)</th>
<th>&gt;2 SMN2 copies (n=11)</th>
<th>Total risdiplam (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teething</td>
<td>2 (29)</td>
<td>4 (36)</td>
<td>6 (33)</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>1 (14)</td>
<td>4 (36)</td>
<td>5 (28)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>0</td>
<td>5 (45)</td>
<td>5 (28)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>4 (36)</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Viral infection</td>
<td>2 (29)</td>
<td>2 (18)</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (14)</td>
<td>3 (27)</td>
<td>4 (22)</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (29)</td>
<td>1 (9)</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Cough</td>
<td>0</td>
<td>3 (27)</td>
<td>3 (17)</td>
</tr>
<tr>
<td>Eczema</td>
<td>1 (14)</td>
<td>2 (18)</td>
<td>3 (17)</td>
</tr>
</tbody>
</table>

• AEs were more reflective of the age of the infants rather than the underlying SMA.
• Two related AEs were reported in two infants
  — skin discoloration (reported in one infant).
• As of the data cut-off,† related AEs had resolved or were resolving with ongoing risdiplam treatment.
• Pneumonia had not been reported in any infants.

• Preclinical safety findings were not observed in any infants in RAINBOWFISH:

*Since the previous data cut-off (20 Feb 2021), one SAE of gastroenteritis norovirus was reclassified as an AE, and two AEs that were previously classified as related AEs (increased alanine aminotransferase and increased aspartate aminotransferase [both reported in one infant]) were deleted.
†Additional AEs that were reported in ≥2 infants were accidental overdose, conjunctivitis, gastroenteritis, papule, rhinitis and rhinorrhea. *Data cut-off: 1 Jul 2021. Multiple occurrences of the same AE in an individual are counted only once. Includes AEs with onset from first dose of study drug up to the cut-off date.
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Rainbowfish: Key conclusions from MDA 2022

- RAINBOWFISH will help to determine the dose of risdiplam for infants <2 months of age
- US/EU: Filed for label extension (<2 months old) based on RAINBOWFISH
  - Priority review granted in US

No SAEs were reported in presymptomatic infants treated with risdiplam for up to 22.8 months. No risdiplam-associated ophthalmologic findings were observed.

Most of the infants treated with risdiplam for ≥12 months reached near-maximum CHOP-INTEND scores by 4–5 months of age and achieved motor milestones within the WHO windows for healthy children.

All seven infants treated for ≥12 months achieved sitting without support by Month 12.

All seven infants who had received risdiplam for ≥12 months maintained the ability to swallow solid food and were able to feed exclusively by mouth.

SAE, Serious adverse event
Delandistrogene moxeparvovec (SRP-9001) in DMD clinical update from MDA 2022
## Comprehensive development program of delandistrogene moxeparvovec

<table>
<thead>
<tr>
<th>Study 101</th>
<th>Study 102</th>
<th>Study 103</th>
<th>Study 301</th>
<th>Study 302</th>
<th>Study 303</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4 patients</strong>&lt;br&gt;Ages 4-7, ambulatory&lt;br&gt;Open-Label&lt;br&gt;NCT03375164</td>
<td><strong>41 patients</strong>&lt;br&gt;Ages 4-7, ambulatory&lt;br&gt;Placebo-Controlled&lt;br&gt;NCT03769116</td>
<td><strong>38 patients</strong>&lt;br&gt;Ages 3+ ambulatory and non-ambulatory&lt;br&gt;Open-Label&lt;br&gt;NCT04626674</td>
<td><strong>120 patients</strong>&lt;br&gt;Ages 4-7, ambulatory&lt;br&gt;Double-blind, placebo-controlled&lt;br&gt;NCT05096221</td>
<td><strong>20 patients</strong>&lt;br&gt;Ages 0-4&lt;br&gt;Open label</td>
<td><strong>3:1 non-ambulatory/ambulatory patients in at least 80 patients</strong>&lt;br&gt;Double-blind, placebo-controlled</td>
</tr>
</tbody>
</table>

- **Goals included safety, proof-of-concept**
- **Enrolment completed**
- One-year results published in JAMA Neurology
- Positive 2-year and 3-year functional data
- **Goals included safety, function**
- **Enrolment completed**
- 5-year 3-part study
- Part 1 (48 weeks) complete
- Part 2 Ongoing
- **Goals include expression and safety**
- **Enrolment completed**
- No mutation exclusion, except for patients below 4 years
- **Pivotal Phase III study**
- **Primary endpoint: NSAA**
- **Excludes mutations 1 to 17, 45**
- Safety (primary) and Expression (secondary)
- **Excludes mutations 1 to 17**
- Planned FPI 2022, EU study population
- **No upper age restrictions for non-ambulatory**
- Ambulatory: 8-18
- Primary endpoint: PUL
- Excludes mutations 1 to 17
- Planned FPI 2022
EMBARK phase III study of delandistrogene moxeparvovec
Ambulatory boys with DMD, aged ≥4 to <8 years

EMBARK (NCT05096221) is a placebo-controlled study assessing the safety and efficacy of commercially representative delandistrogene moxeparvovec material in a larger DMD patient population.

Key inclusion criteria

- Ambulatory and aged ≥4 to <8 years at randomization
- Definitive diagnosis of DMD based on documented clinical findings and prior genetic testing
- Confirmed DMD mutation within exons 18—44 or 46—79
- Participants with mutations between or including exons 1–17 or mutations fully contained within exon 45 (inclusive) are not eligible
- In-frame deletions, in-frame duplications, and variants of uncertain significance are not eligible

Primary endpoint

- Change in NSAA total score from baseline to Week 52 in part 1

Secondary endpoints

- Number of skills gained or improved at Week 52 as measured by the NSAA*
- Quantity of micro-dystrophin protein expression at Wk 12 as measured by western blot of biopsied muscle tissue*
- Change from baseline to Wk 52 in timed function tests: time to rise from the floor, 100MWR, time to ascend 4 steps, and 10MWR*
- Change in SV95C from baseline to Week 52 as measured by Syde®, a wearable device*
- Change in PROMIS score per domain (mobility and upper extremity function) from baseline over 52 weeks*
- Incidence of treatment-emergent AEs, SAEs and AEs of special interest; clinically significant changes in vital signs, physical examination findings, safety laboratory assessments, ECGs and ECHOs
EMBARK study design

**Randomization (N=120)**

Part 1: 52 weeks*

- Single IV infusion: delandistrogene moxeparvovec
  - Muscle biopsy at Week 12§
  - NSAA at Week 52

- Single IV infusion: placebo
  - Muscle biopsy at Week 12§
  - NSAA at Week 52

Part 2: 52 weeks†

- Single IV infusion: placebo
  - Muscle biopsy at Week 52
  - NSAA at Week 104

- Single IV infusion: delandistrogene moxeparvovec
  - Muscle biopsy at Week 64§
  - NSAA at Week 104

Part 1 patients will be randomized to treated or placebo (1:1) and stratified according to age and NSAA.

Primary endpoint: Change in NSAA total score from baseline to Week 52 in Part 1.

*Double-blind, placebo-controlled. †Patients, caregivers, Investigators, and site staff remain blinded. §Only a subset of patients will receive a muscle biopsy for expression assessments.

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**OLE Study 305**

Up to 5 years*
Doing now what patients need next
Additional Slides from congress for reference
In SUNFISH Part 1, the increase in MFM32 total score change from baseline was maintained between Months 12 and 36 in patients treated with risdiplam.

### Baseline demographics* SUNFISH Part 1 intent-to-treat population (N=51)

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>2–25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at screening, years, median (range)</td>
<td>7 (2–24)</td>
</tr>
<tr>
<td>Gender, female/male, n (%)</td>
<td>27 (53)/24 (47)</td>
</tr>
<tr>
<td>Type 2 SMA, n (%)</td>
<td>37 (73)</td>
</tr>
<tr>
<td>Type 3 SMA, n (%)</td>
<td>14 (27)</td>
</tr>
<tr>
<td>Motor function at baseline†</td>
<td></td>
</tr>
<tr>
<td>Walkers, n (%)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Sitters, n (%)</td>
<td>33 (65)</td>
</tr>
<tr>
<td>Non-sitters, n (%)</td>
<td>11 (21)</td>
</tr>
<tr>
<td>Scoliosis, n (%)</td>
<td>29 (57)</td>
</tr>
<tr>
<td>Baseline MFM32 total score, mean (SD)</td>
<td>42.9 (15.0)</td>
</tr>
</tbody>
</table>

*Data cut-off: 28 June 2019. †Non-sitters are defined as scoring 0 on item 9 of the MFM32 while sitters scored ≥1 on item 9 of the MFM32 but did not qualify as ambulant. Ambulant patients are defined as walkers. ‡Excludes seven patients who performed the MFM20 assessment at baseline. §Data cut-off: 6 Sep 2021. ¶Number of patients with valid results = number of patients with an available total score (result) at respective time points. Intent-to-treat patients. MFM, Motor Function Measure; MFM20, 20-item MFM; MFM32, 32-item MFM; SD, standard deviation; SMA, spinal muscular atrophy.