
Roche

MDA Clinical & Scientific Conference 2022

Virtual IR event

Basel, 16 March 2022

This presentation contains certain forward-looking statements. These forward-looking statements may be identified by words such as ‘believes’, ‘expects’, ‘anticipates’, ‘projects’, ‘intends’, ‘should’, ‘seeks’, ‘estimates’, ‘future’ or similar expressions or by discussion of, among other things, strategy, goals, plans or intentions. Various factors may cause actual results to differ materially in the future from those reflected in forward-looking statements contained in this presentation, among others:

1 pricing and product initiatives of competitors;
2 legislative and regulatory developments and economic conditions;
3 delay or inability in obtaining regulatory approvals or bringing products to market;
4 fluctuations in currency exchange rates and general financial market conditions;
5 uncertainties in the discovery, development or marketing of new products or new uses of existing products, including without limitation negative results of clinical trials or research projects, unexpected side-effects of pipeline or marketed products;
6 increased government pricing pressures;
7 interruptions in production;
8 loss of or inability to obtain adequate protection for intellectual property rights;
9 litigation;
10 loss of key executives or other employees; and
11 adverse publicity and news coverage.

Any statements regarding earnings per share growth is not a profit forecast and should not be interpreted to mean that Roche’s earnings or earnings per share for this year or any subsequent period will necessarily match or exceed the historical published earnings or earnings per share of Roche.

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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
RG6035	**brain shuttle CD20** MS

Ph II (9 NMEs)

RG7935	**prasinezumab** Parkinson's
RG6100	**semorinemab** Alzheimer's
UCB 0107	**bepranemab** Alzheimer's
RG6102	**brain shuttle gantenerumab** Alzheimer's
RG7412	**crenezumab** Alzheimer's
RG7916+ RG6237	**Evrysdi + GYM329** [1] SMA type2/3 RD
NME	**N/D** FSHD
RG7906	**ralmitaront** Schizophrenia
RG7816	**GABA$_A$ α5 PAM** Autism spectrum disorder

Ph III (3 NMEs, 1AI)

RG1450	**gantenerumab** Alzheimer's
RG6356	**delandistrogene moxeparvovec** DMD RD
RG6168	**Enspryng** gMG RD
RG7845	**fenebrutinib** MS

Launched (3)

RG1594	**Ocrevus** MS	✓
RG6168	**Enspryng** NMOSD RD	✓
RG7916	**Evrysdi** SMA type 1/2/3 RD	✓

Small molecule
Antibody
Gene therapy
Brain shuttle
Locked nucleic acid

Neuro-immunologic disorders
Neuro-degenerative disorders
Neuro-developmental disorders
Neuro-muscular disorders
Psychiatric disorders
FDA approval
RD = Rare disease

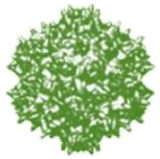
NME=new molecular entity; AI=additional indication; NMOSD=neuromyelitis optica spectrum disorders; DMD=Duchenne muscular dystrophy; gMG=generalised myasthenia gravis; MS=Multiple sclerosis; SMA=spinal muscular atrophy; OLE=open label extension; FSHD= Facioscapulohumeral muscular dystrophy; Risdiplam 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 Opthamology

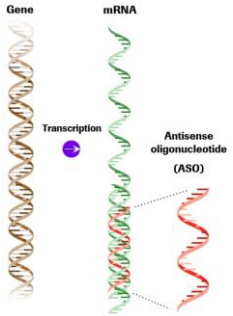
Gene therapy

AVV
Adeno associated virus



- Luxturna ✔
- SPK-8011 (hem A)
- SPK-8016 (hem A inhibitors)
- SPK-3006
- SRP-9001 (DMD)
- 6 preclinical assets (Spark)

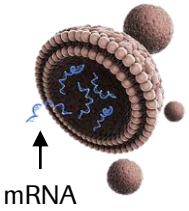
Antisense RNA



- Factor B ASO
- HBV siRNA
- PDL1 LNA
- UBE3A LNA (Angelman syndrome)

Neoantigen vaccines

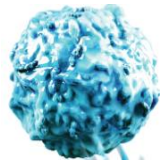
iNeST platform:
mRNA-LPX Liposome



Patient's neo-antigens for anti-tumour immune response

Personalized T cells

Activated T cell with neoantigen specificity

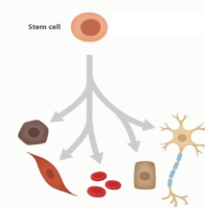


- programmed T cells

Patient's neo-antigens for anti-tumour immune response

Stem cell therapy

Epithelium cell replacement therapy

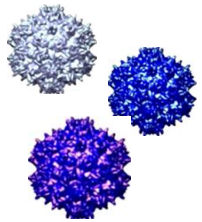


- OpRegen

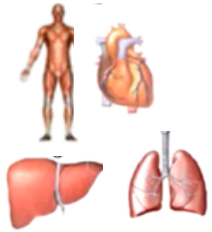
SAREPTA THERAPEUTICS · Adaptimmune · Adaptive · IONIS · BIONTECH · DYNO THERAPEUTICS · SQZBIOTECH · cevec · LINEAGE CELL THERAPEUTICS · nykode · ShapeTX · Dicerna

Gene therapy platform development on-going

Our approach driven by safety, predictability, efficacy and durability

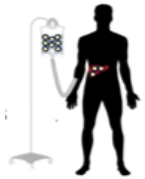


Variety of naturally occurring and now engineered AAV capsids



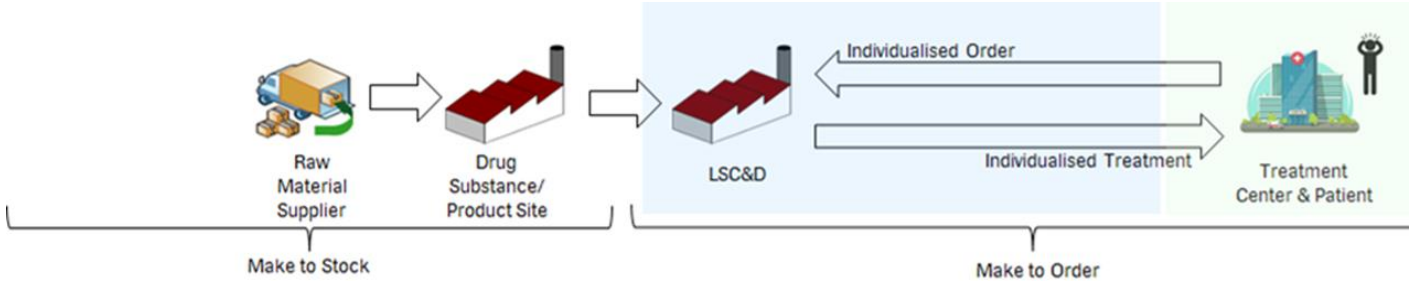
AAV vectors have different tissue tropism

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

	Compound	Indication	Milestone
Regulatory	Vabysmo	nAMD/DME	US/EU approval ✓
	Susvimo	nAMD	EU approval
	mosunetuzumab	3L+ FL	US/EU approval
	Tecentriq	Adjuvant NSCLC	EU approval
	Hemlibra	Mild to moderate hemophilia A	EU approval
	Polivy + R-CHP	1L DLBCL	EU/US approval
Phase III / pivotal readouts	glofitamab	3L+ DLBCL	Ph Ib NP30179
	Tecentriq + tiragolumab + chemo	1L ES-SCLC	Ph III SKYSCRAPER-02
	Tecentriq + chemo	Adjuvant SCCHN	Ph III IMvoke010
	Tecentriq + tiragolumab	1L PDL1+ NSCLC	Ph III SKYSCRAPER-01
	Tecentriq	Adjuvant RCC	Ph III IMmotion010
	giredestrant	2/3L HR+ mBC	Ph II acelERA
	Tecentriq + chemo	Adjuvant HCC	Ph III IMbrave050
	Venclexta + dexamethasone	t(11;14) MM	Ph III CANOVA
	Tecentriq + chemo	Neoadjuvant NSCLC	Ph III IMpower030
	Tecentriq + tiragolumab + chemo	1L esophageal cancer	Ph III SKYSCRAPER-08
	Alecensa	Adjuvant ALK+ NSCLC	Ph III ALINA
	gantenerumab	Alzheimer's disease	Ph III GRADUATE 1/2
	Susvimo	DME	Ph III PAGODA
	Susvimo	DR	Ph III PAVILION

Virtual event	*Virtual event*	*Roche ESG Day*	*Virtual/live event*	*Roche Pharma Day*
Angiogenesis	*MDA*	*Access to Healthcare*	*ASCO*	
Monday, 14 February	***Wednesday, 16 March***	***Monday, 16 May***	***June***	***Monday, 12 September***
16:30 to 17:45 CEST	**16:30 to 17:30 CEST**		***TBC***	***TBC***
✓	✓			

* 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

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

LEAD the next wave of breakthrough innovation in neuromuscular field

BUILD the foundation to transform the future of 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

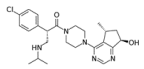
Utilising a range of technology platforms and biological approaches

Early Stage	
NME	3 projects

Phase II	
RG7916 + RG6237	Evrysdi + GYM329 [1] SMA type2/3
NME	N/D FSHD[2]

Phase III	
RG6168	Satralizumab gMG
RG6107	Crovalimab N/D
RG6356	delandistrogene moxeparvovec DMD

Launched	
RG7916	Evrysdi SMA



Small molecule

Antibody

Gene therapy

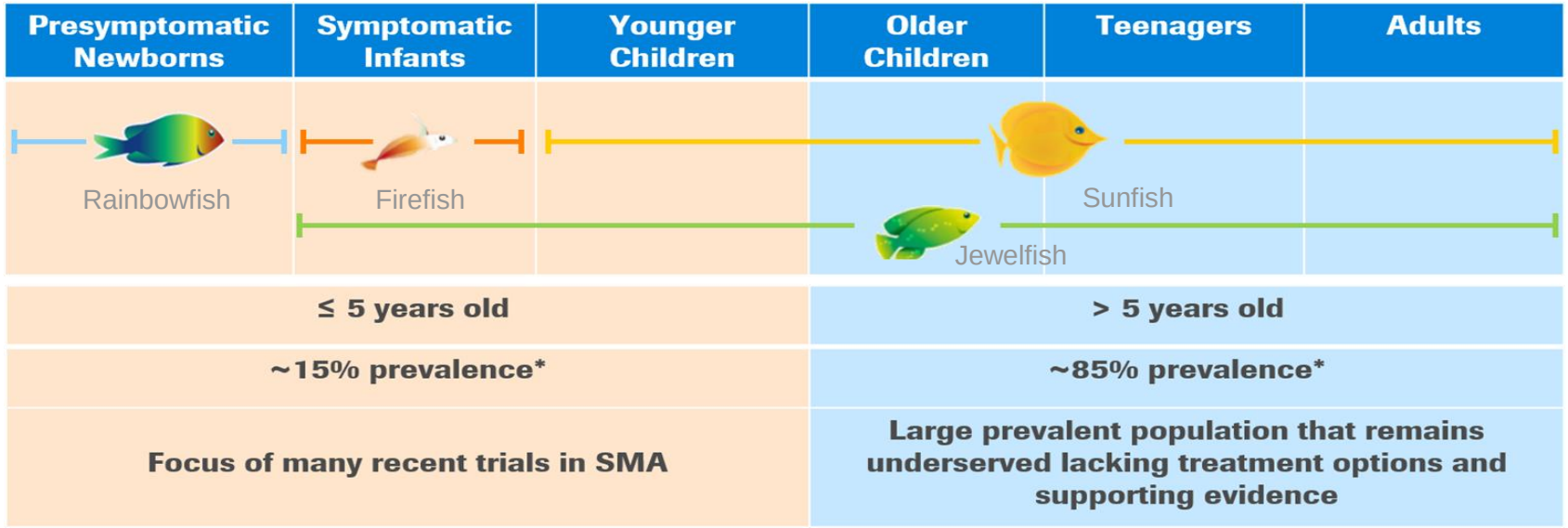
1. Phase II/III currently in Phase II start up; 2. Proof of concept study; N/D = not disclosed; NME=new molecular entity; DMD=Duchenne muscular dystrophy; gMG=generalised myasthenia gravis; SMA=spinal muscular atrophy; FSHD= Facioscapulohumeral muscular dystrophy

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 EU5

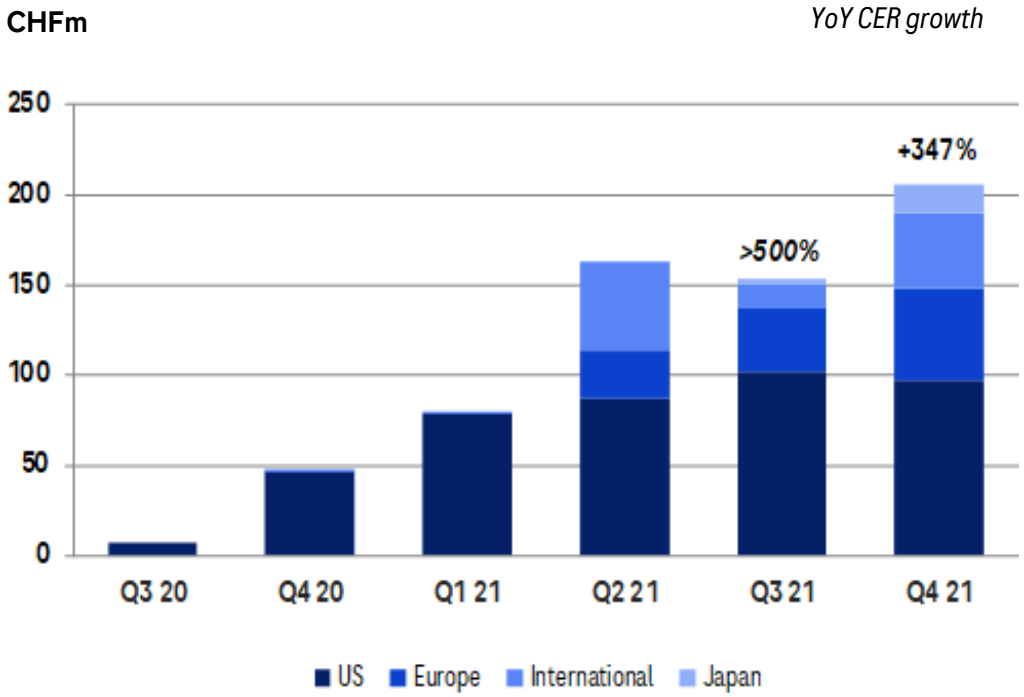
Evrysdi is well-positioned and making significant progress to becoming the most prescribed SMA therapy globally

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

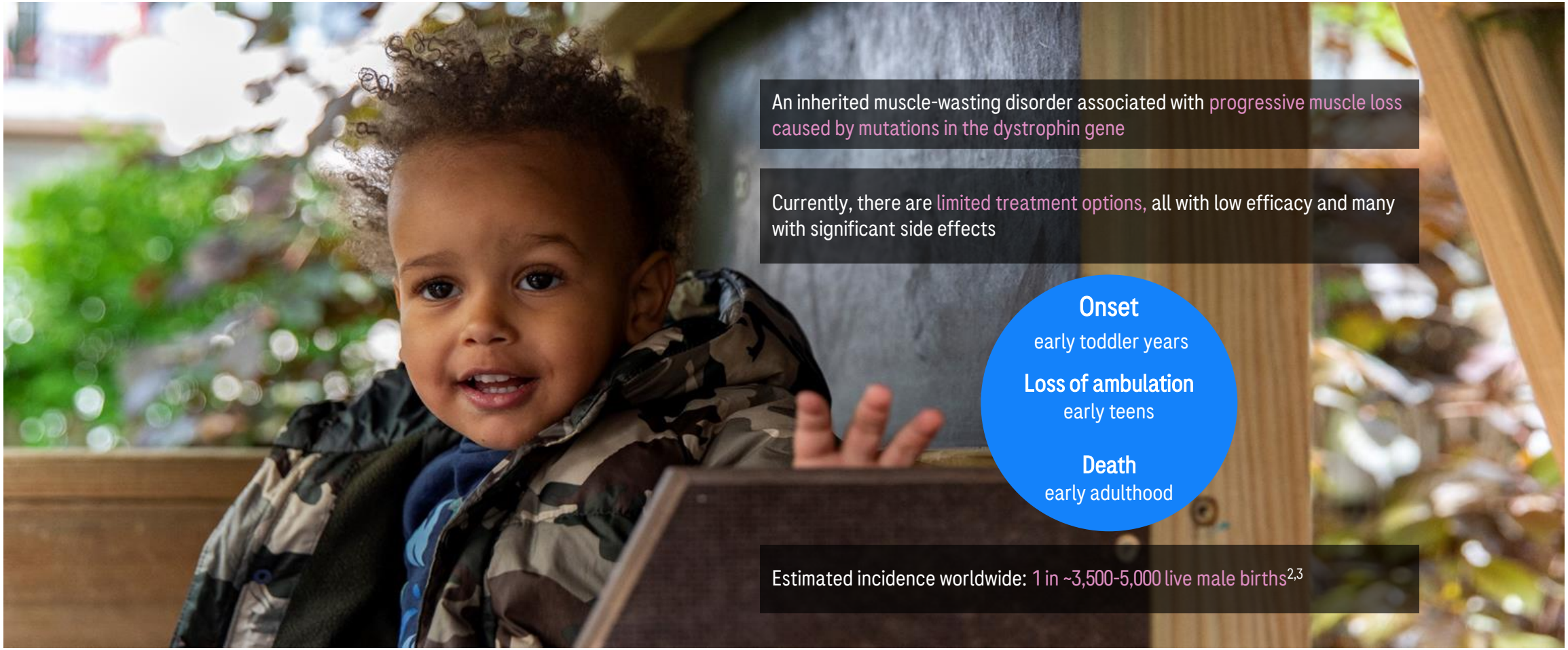
- >5,000 patients treated worldwide (commercial, clinical trials, compassionate use), approved in 75 countries
- US: Ongoing growth in 2022 driven by switches and naive patient starts: ⅔ of total patients on Evrysdi from switches
- EU: Strong launches in early launch countries
- US/EU: Filed for label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

Duchenne muscular dystrophy (DMD)

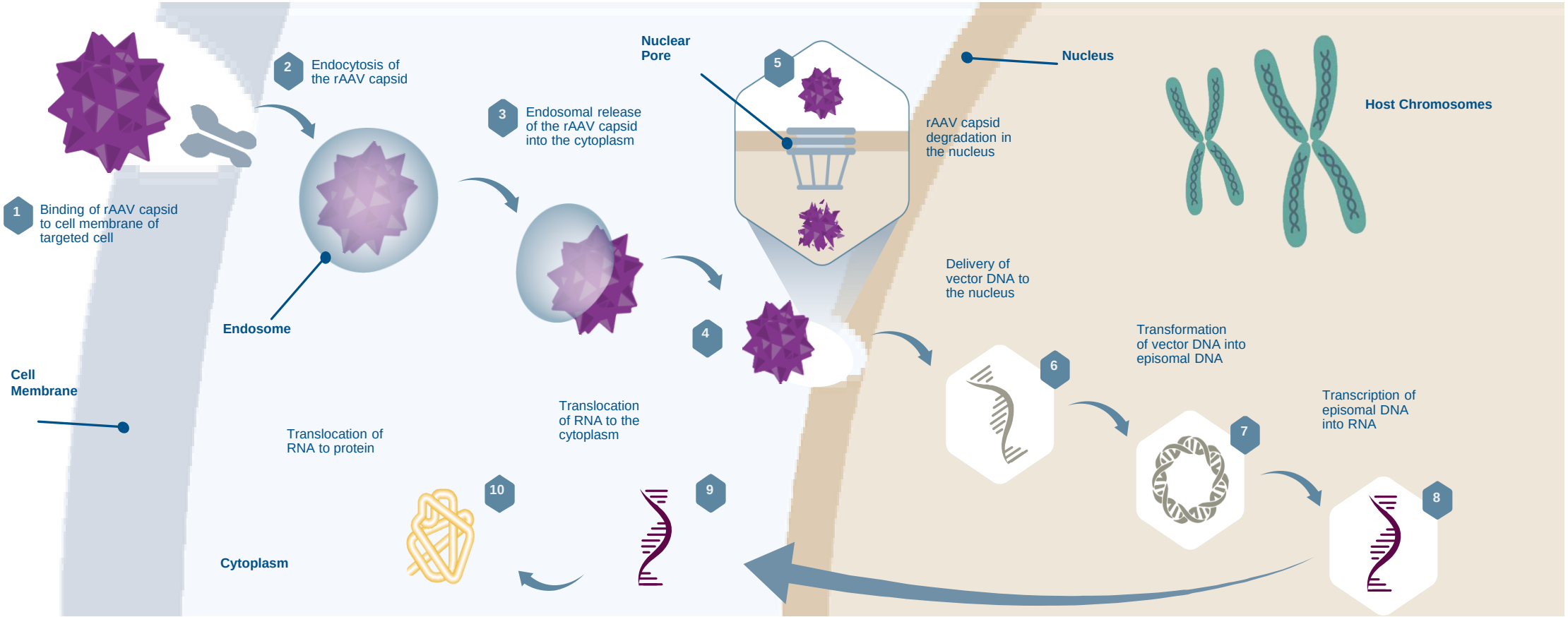
A rare, fatal neuromuscular genetic disease



1. Ciafaloni E, et al. J Pediatr Rehabil Med 2016;9:5–11, 2. Mendell JR, et al. Muscle Nerve. 2013;48:21–6; 3. Mendell JR, et al. Ann Neurol 2012;71:304–13.

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

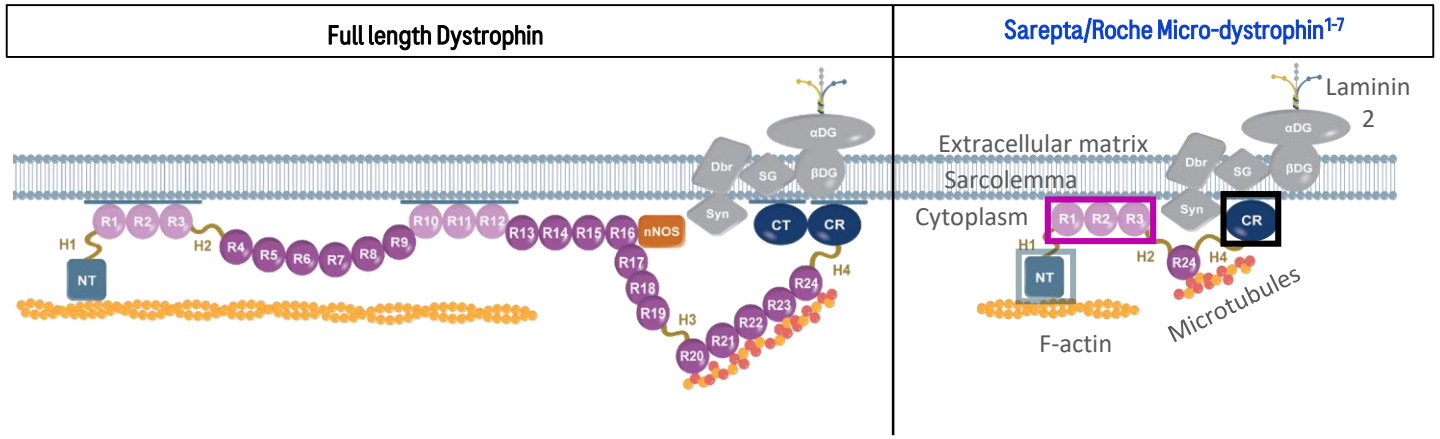


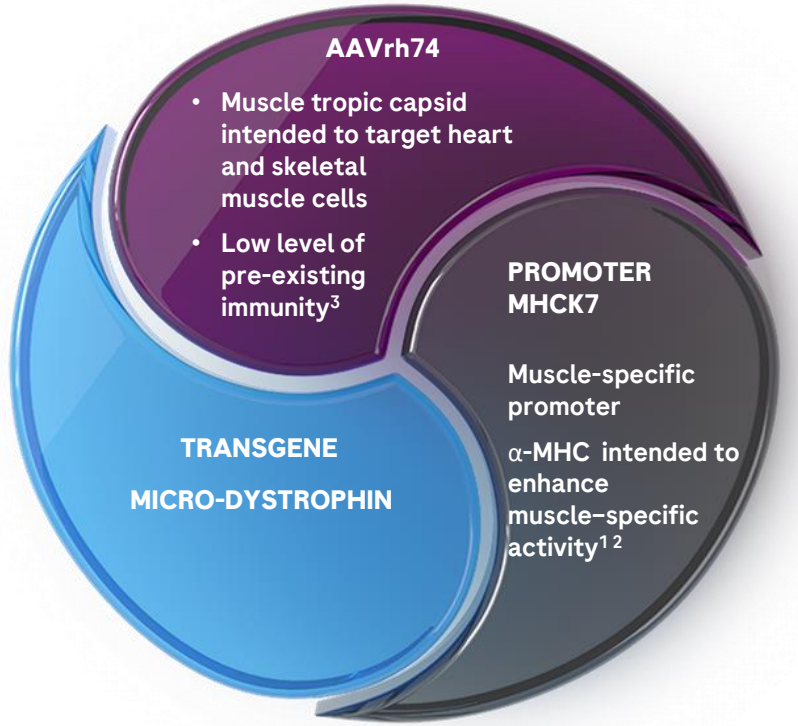
AAV, adeno-associated virus; DNA, deoxyribonucleic acid; rAAV, recombinant adeno-associated virus; RNA, ribonucleic acid.

1. Bartlett JS, et al. J Virol 2000;74:2777–85. 2. Kelich JM, et al. Mol Ther Methods Clin Dev 2015;2:15047.

Key components of delandistrogene moxeparvovec

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





1. Gao QQ. Compr Physiol. 2015;5(3):1223-1239. 2. Harper SQ. Nat Med. 2002;8(3):253-261. 3. Nelson DM. Hum Mol Genet. 2018;27(12):2090-2100. 4. Fairclough RJ. Nat Rev Genet. 2013;14(6):373-378. 5. Aartsma-Rus A. Muscle Nerve. 2006;34(2):134-144. 6. Zhao J. Hum Mol Genet. 2016;25(17):3647-3653. 7. Asher DR. Expert Opin Biol Ther. 2020;20(3):263-274. 8. England SB. Nature. 1990;343(6254):180-182. 9. Wells DJ. Hum Mol Genet. 1995;4(8):1245-1250.

Comprehensive development program of delandistrogene moxeparvovec

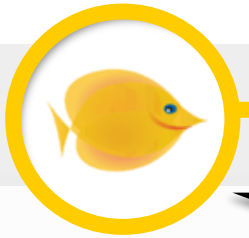
		ENDEAVOR	EMBARK	ENVOL	ENVISION
Study 101 *4 patients* *Ages 4-7, ambulatory* Open-Label NCT03375164	**Study 102** *41 patients* *Ages 4-7, ambulatory* Placebo-Controlled NCT03769116	**Study 103** *38 patients* *Ages 3+ ambulatory and non-ambulatory* *Open-Label* *NCT04626674*	**Study 301** *120 patients* *Ages 4-7, ambulatory* *Double-blind, placebo-controlled* *NCT05096221*	**Study 302** *20 patients* *Ages 0-4* *Open label*	**Study 303** 3:1 non-ambulatory/ambulatory patients in at least 80 patients Double-blind, placebo-controlled
• *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*

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



Part 2[1]

Month 12 | Month 24 | Month 36

Risdiplam:placebo 2:1 → Risdiplam → Extension

N=180

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

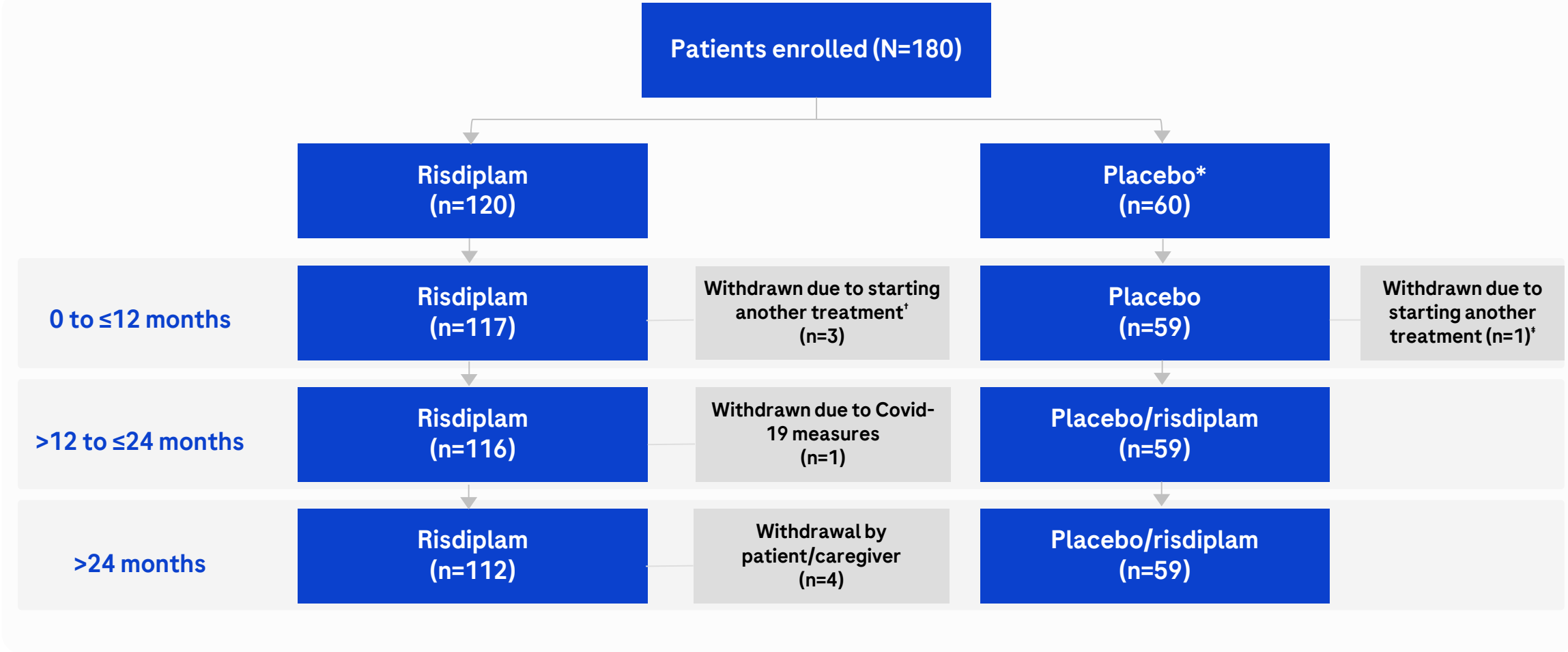
*Non-ambulant is defined as not having the ability to walk unassisted for ≥10m. [†]RULM entry item A (Brooke score) ≥2; ability to sit independently (≥1 on item 9 of the MFM32). [‡]Except in the 1 year preceding screening or planned within the next 18 months.

AE, adverse event; HFMSE, Hammersmith Functional Motor Score – Expanded; MFM32, 32-item Motor Function Measure; PY, patient years; RULM, Revised Upper Limb Module; SAE, serious AE; SMA, spinal muscular atrophy; SMAIS, SMA Independence Scale. 1. ClinicalTrials.gov. NCT02908685 (Accessed January 2022).

Day et al MDA 2022 abstract 73

SMA FOUNDATION and PTC THERAPEUTICS

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

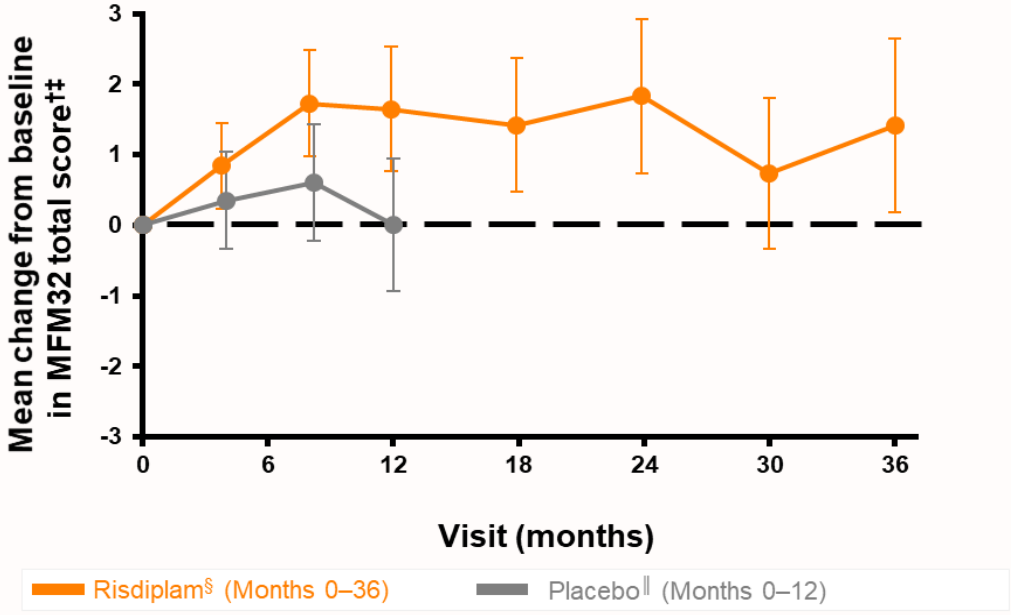


*Patients in the placebo arm received placebo for 12 months followed by risdiplam treatment for 24 months. †Two patients in the risdiplam arm switched to nusinersen (SPINRAZA®) treatment. ‡This patient withdrew from the study to start nusinersen treatment. Data cut-off: 6 Sep 2021.

Day et al MDA 2022 abstract 73

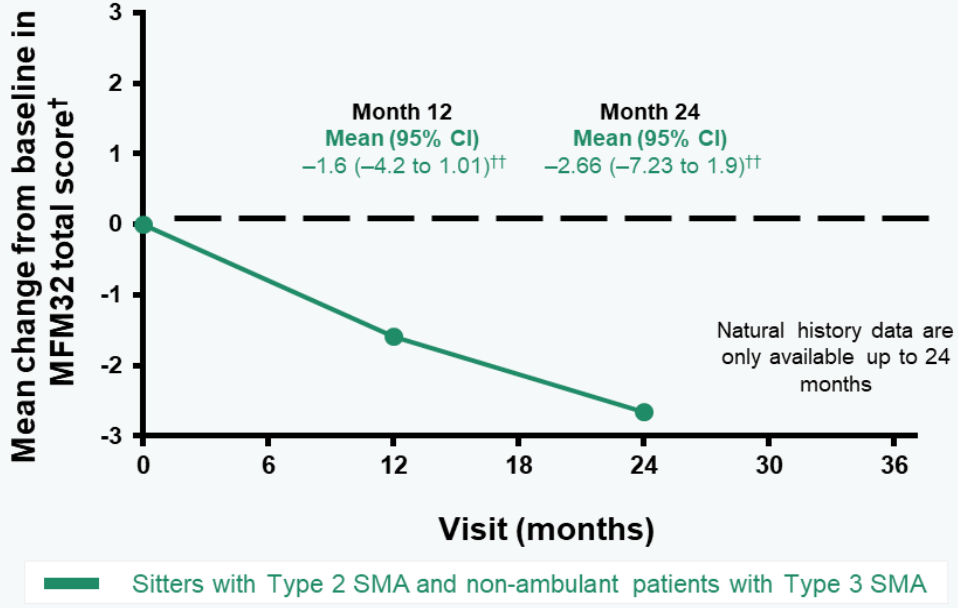
The increase in MFM32 total score was maintained between months 12 & 36 in the risdiplam arm; an overall decline was seen in natural history

SUNFISH Part 2
Overall population 2–25 years old*



Risdiplam (n)¶	115	112	113	112	107	103	84	93
Placebo (n)¶	59	57	58	58				

NatHis-SMA[1]
Subgroup population 6–30 years old**



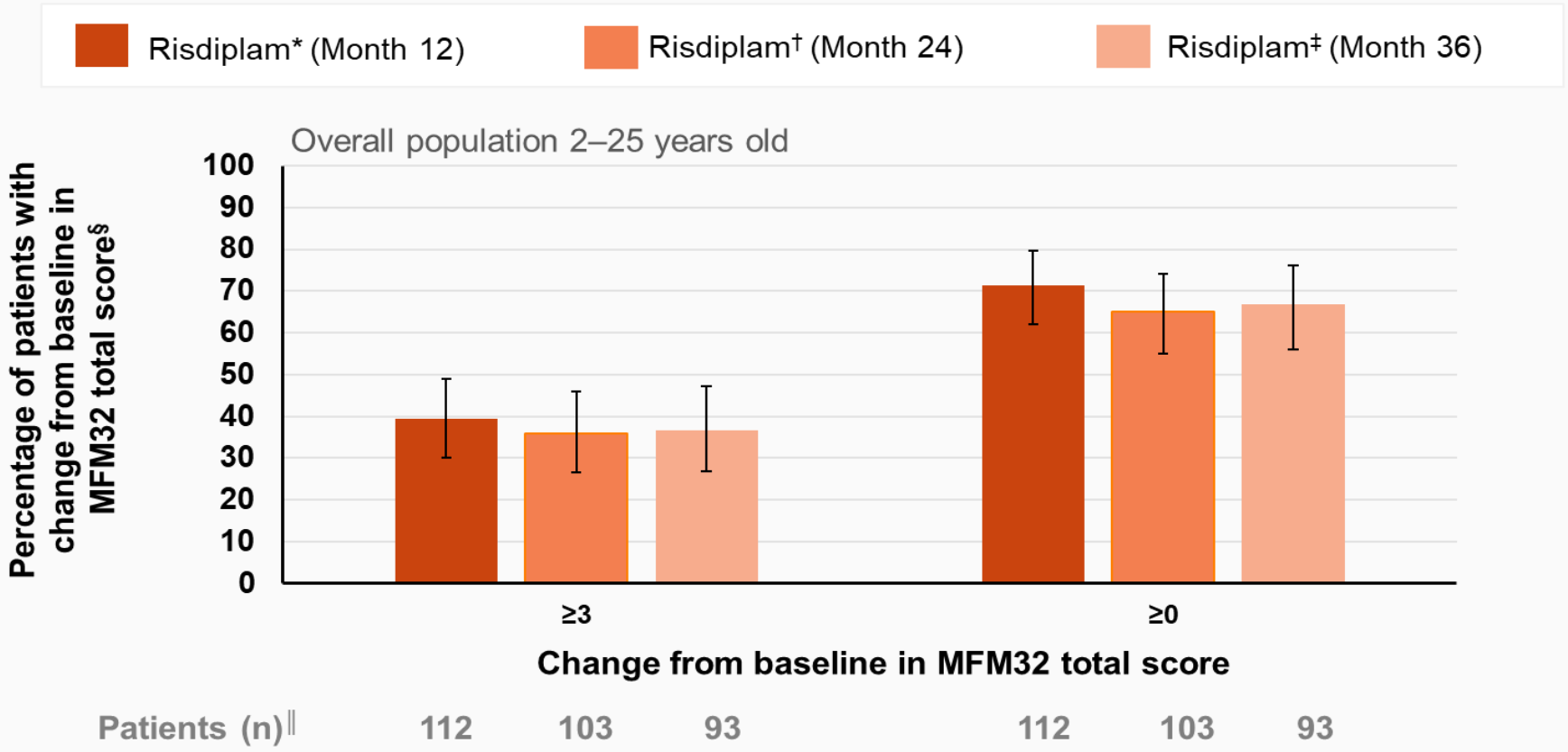
Patients (n)¶	20	15	9

*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 73

SMA FOUNDATION and PTC THERAPEUTICS

The percentage of patients who had improved or stabilized in MFM32 total score from baseline was similar between Months 12 and 36



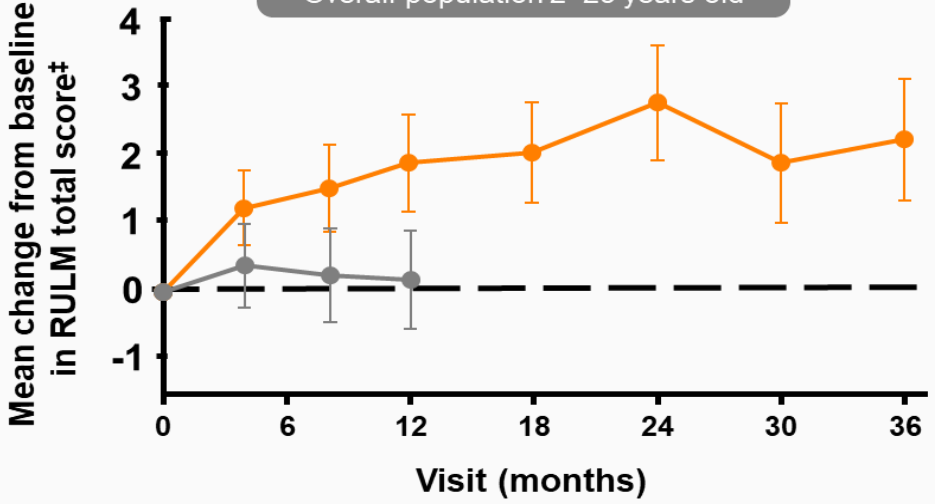
*Data cut-off: 6 Sep 2019. †Data cut-off: 30 Sep 2020. ‡Data cut-off: 6 Sep 2021. §+/- 95% CI. ‖Number of patients with valid results = number of patients with an available total score (result) at respective time points. Intent-to-treat patients.
The percentage of patients is calculated by using the 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.
Day et al MDA 2022 abstract 73

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 time[1,2]

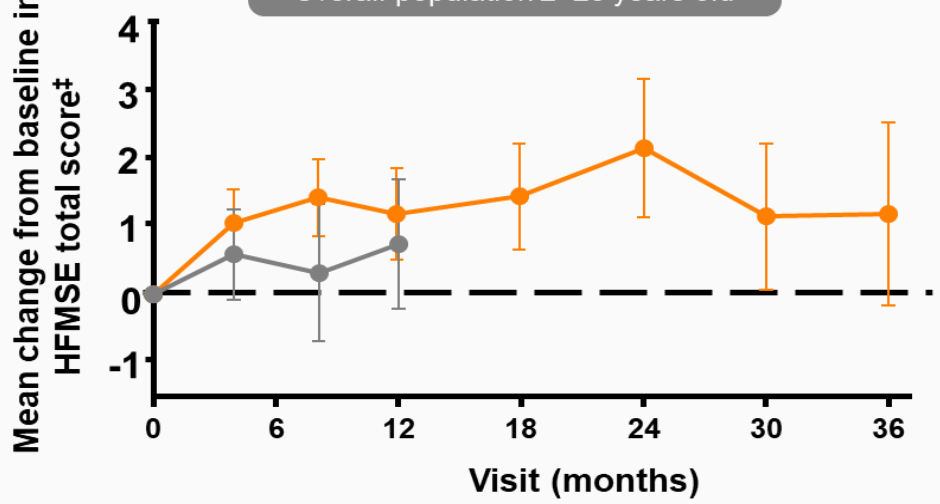
Risdiplam* (Months 0–36) **Placebo†** (Months 0–12)

RULM
Overall population 2–25 years old



Risdiplam (n)§	119	118	117	116	108	105	89	101
Placebo arm/ placebo (n)§	58	57	56	56				

HFMSE
Overall population 2–25 years old



Risdiplam (n)§	120	119	119	117	109	106	89	98
Placebo arm/ placebo (n)§	60	60	58	58				

*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; HFMSE, Hammersmith Functional Motor Scale – Expanded; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy.

1. Pera MC, et al. Muscle Nerve. 2019; 59:426–430; 2. Kaufmann P, et al. Neurology. 2012; 79:1889–1897.
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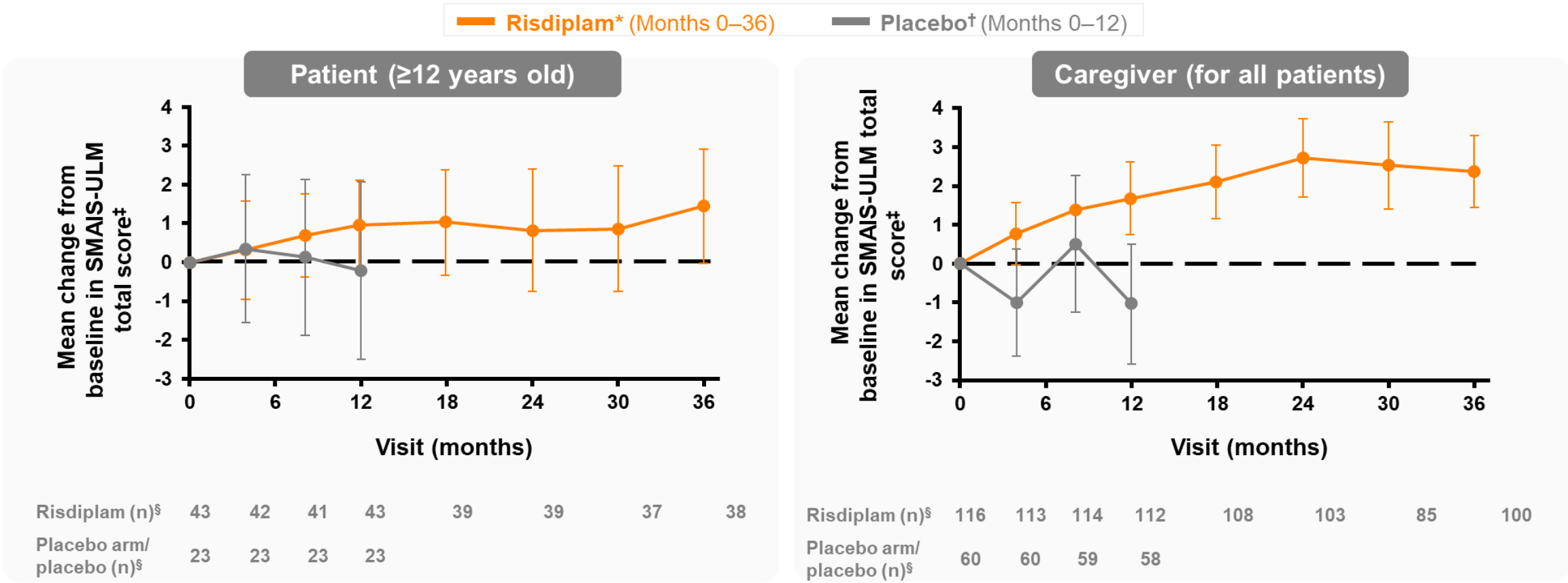
SMA FOUNDATION and PTC THERAPEUTICS

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

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SUNFISH Parts 1 and 2: The observed AE profile over 36 months was reflective of underlying disease

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

SUNFISH Part 2 (N=179)*		Number of AEs per 100PY (95% CI)
Total PY at risk		495.8
AEs reported at a rate of ≥11 per 100PY	Headache	46.4 (40.6–52.8)
	Upper respiratory tract infection	24.8 (20.6–29.6)
	Nasopharyngitis	22.4 (18.4–27.0)
	Vomiting	18.8 (15.1–23.0)
	Pyrexia	18.4 (14.8–22.5)
	Cough	11.7 (8.9–15.1)
	Diarrhea	11.3 (8.5–14.7)
SAEs reported at a rate of ≥0.8 per 100PY	Pneumonia	5.2 (3.4–7.7)
	Gastritis	1.0 (0.3–2.4)
	Pyrexia	0.8 (0.2–2.1)
	Upper respiratory tract infection	0.8 (0.2–2.1)

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

*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

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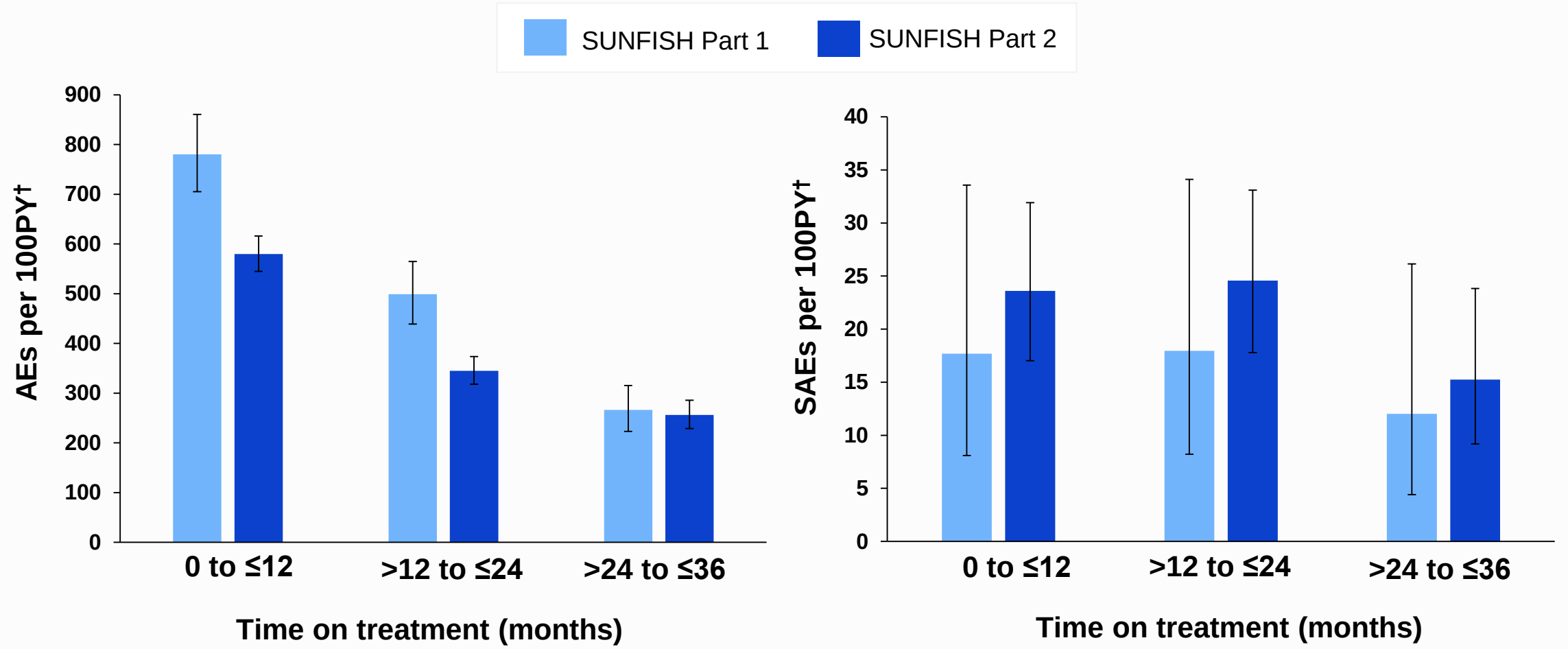
SUNFISH Parts 1 and 2: The overall rate of AEs per 100PY decreased over 36 months*



*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 SMA[9,10]

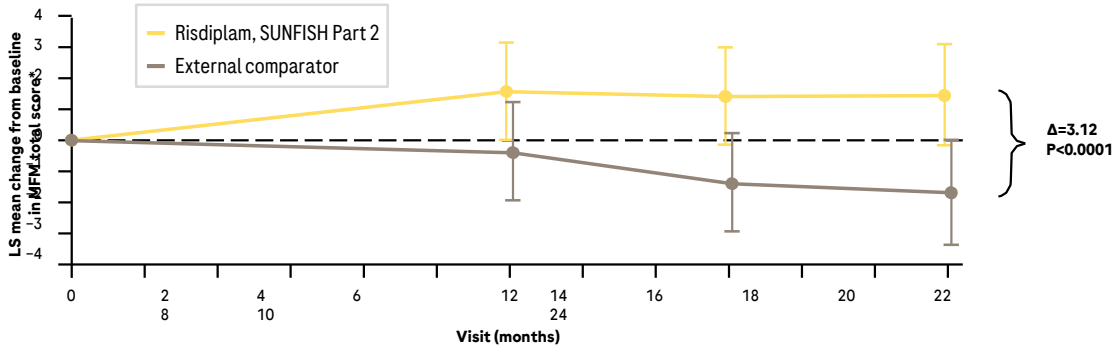
57

Patients randomized to placebo aged 3 – 25 years

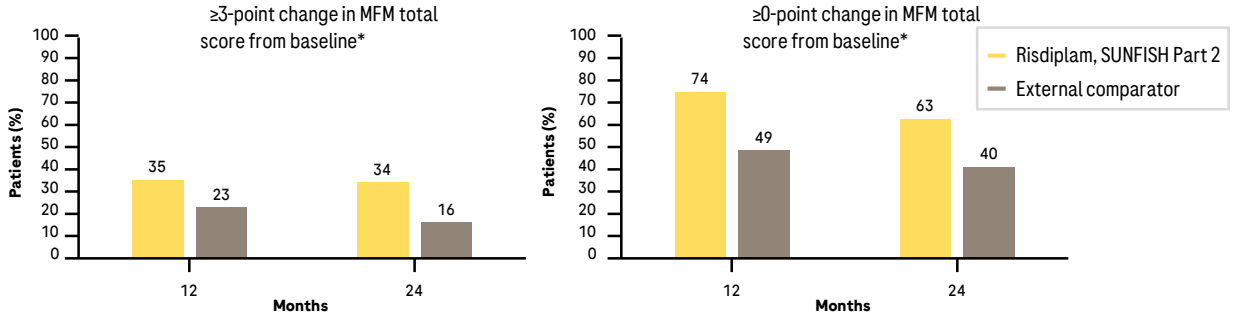
- 39 patients with Type 2 SMA
- 18 patients with Type 3 SMA

*Ambulant 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

Sunfish: Key conclusions from 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

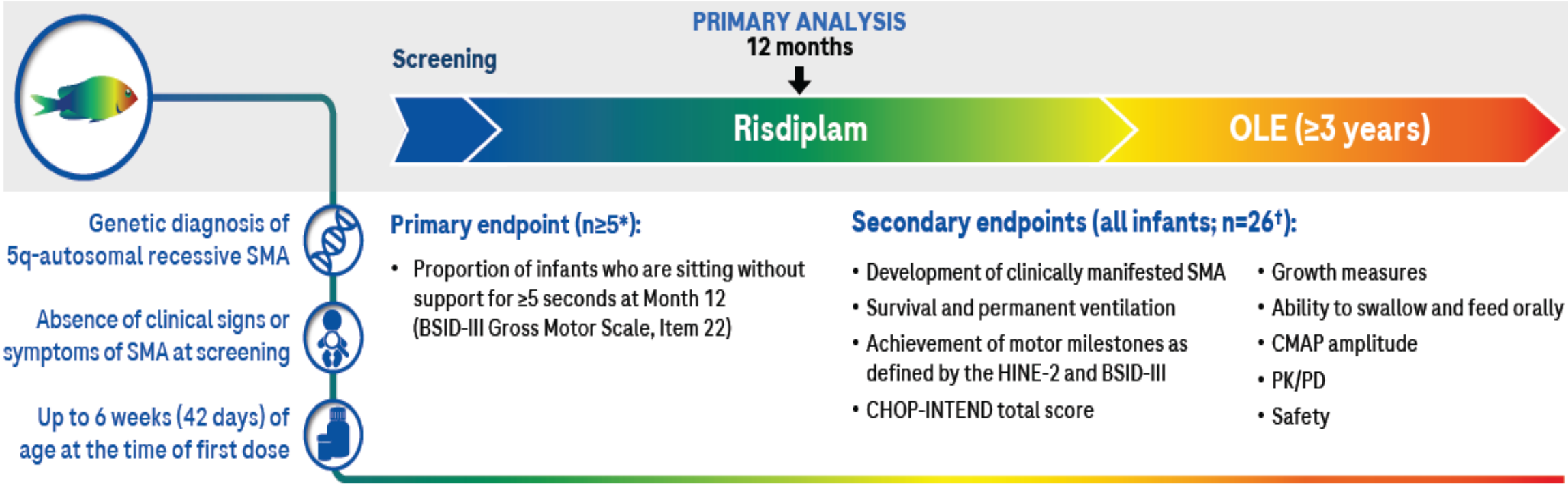
In SUNFISH Parts 1 and 2, the overall rate of AEs decreased over 36 months. A trend towards lower SAE rates was observed in the third year of treatment

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

AE, adverse event; HFMSE, Hammersmith Functional Motor Scale – Expanded; MFM32, 32-item Motor Function Measure; RULM, Revised Upper Limb Module; SAE, serious AE; SMA, spinal muscular atrophy; SMAIS, SMA Independence Scale

RAINBOWFISH: A multicenter, open-label, single-arm study of risdiplam in infants with genetically diagnosed, presymptomatic SMA

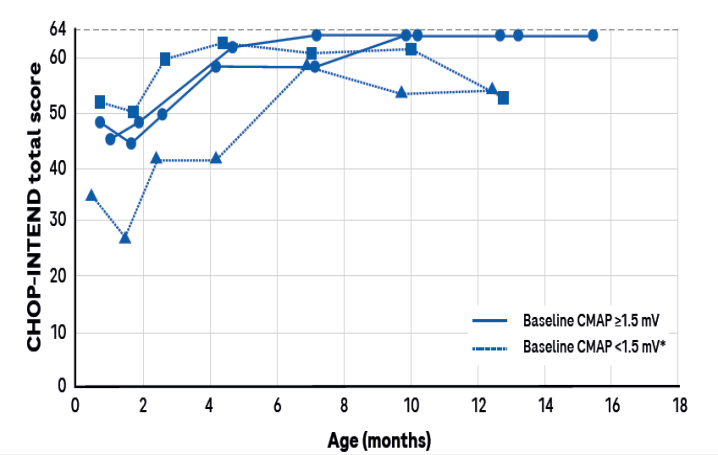


*The primary efficacy population includes infants with two copies of the *SMN2* gene and CMAP amplitude ≥1.5 mV at baseline. †Final patient number. As of 22 February 2022, worldwide recruitment for RAINBOWFISH is complete.

Finkel et al MDA 2022 abstract 76

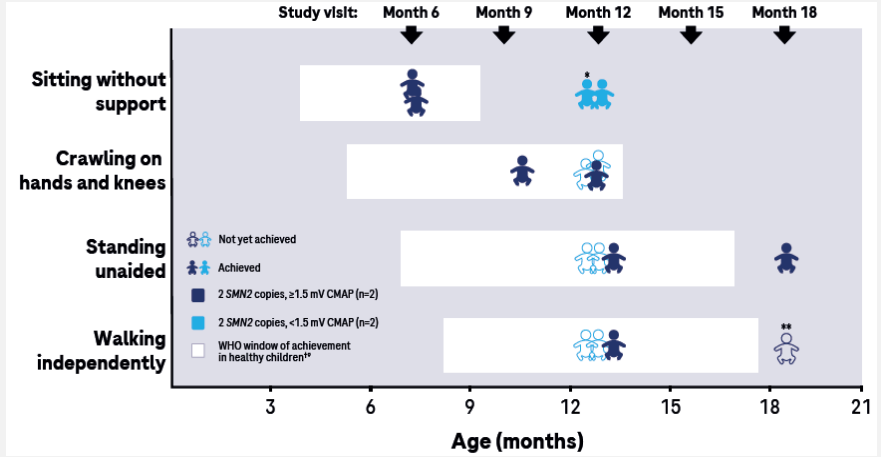
RAINBOWFISH: Preliminary efficacy in risdiplam-treated infants with presymptomatic SMA

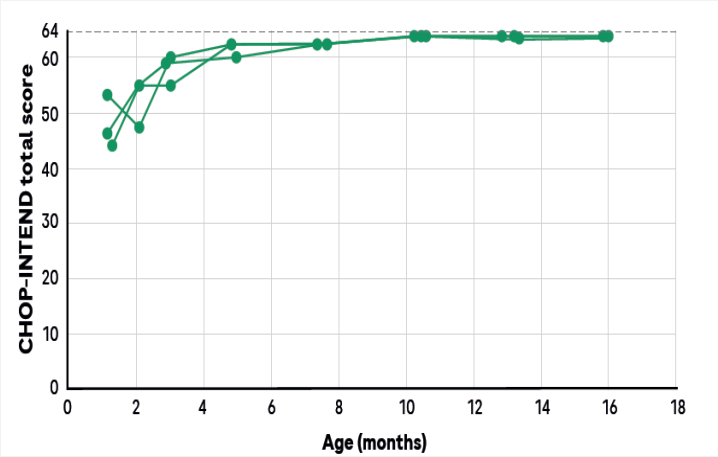
Seven infants have been treated with risdiplam for ≥12 months



4 infants have 2 *SMN2* copies

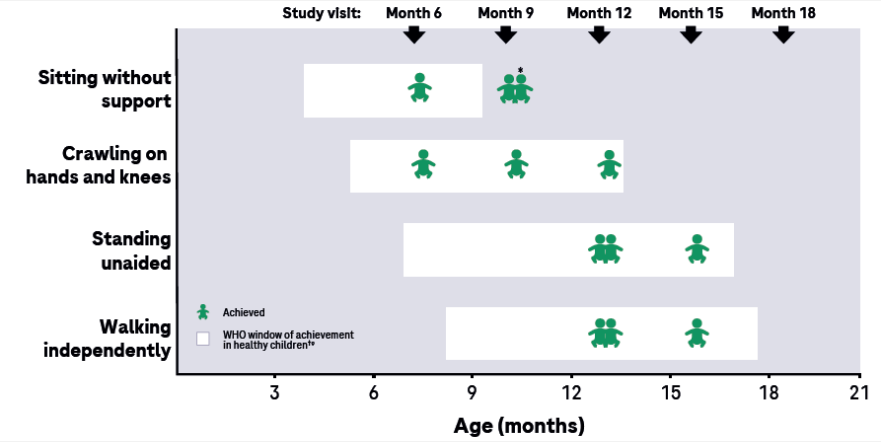
- Most infants with 2 SMN2 copies treated for >12 months (n=4) achieved near-maximum CHOP-INTEND scores, and most achieved motor milestones within WHO windows for healthy children





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



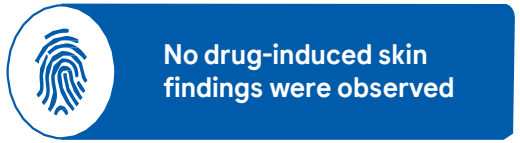
WHO,World Health Organisation
Finkel et al MDA 2022 abstract 76

RAINBOWFISH: Preliminary safety in risdiplam-treated infants with presymptomatic SMA

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

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

- AEs were more reflective of the age of the infants rather than the underlying SMA.
- Two related AEs were reported in two infants
- Diarrhoea (reported in one infant)
  - 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.
Finkel et al MDA 2022 abstract 76

Rainbowfish: Key conclusions from MDA 2022

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

- **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**

SAE, Serious adverse event

Delandistrogene moxeparvovec (SRP-9001) in DMD clinical update from MDA 2022

Comprehensive development program of delandistrogene moxeparvovec

ENDEAVOR

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*

EMBARK

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, 45*

ENVOL

Study 302

20 patients

Ages 0-4

Open label

- *Safety (primary) and Expression (secondary)*
- *Excludes mutations 1 to 17*
- *Planned FPI 2022, EU study population*

ENVISION

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*

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

* Part 1

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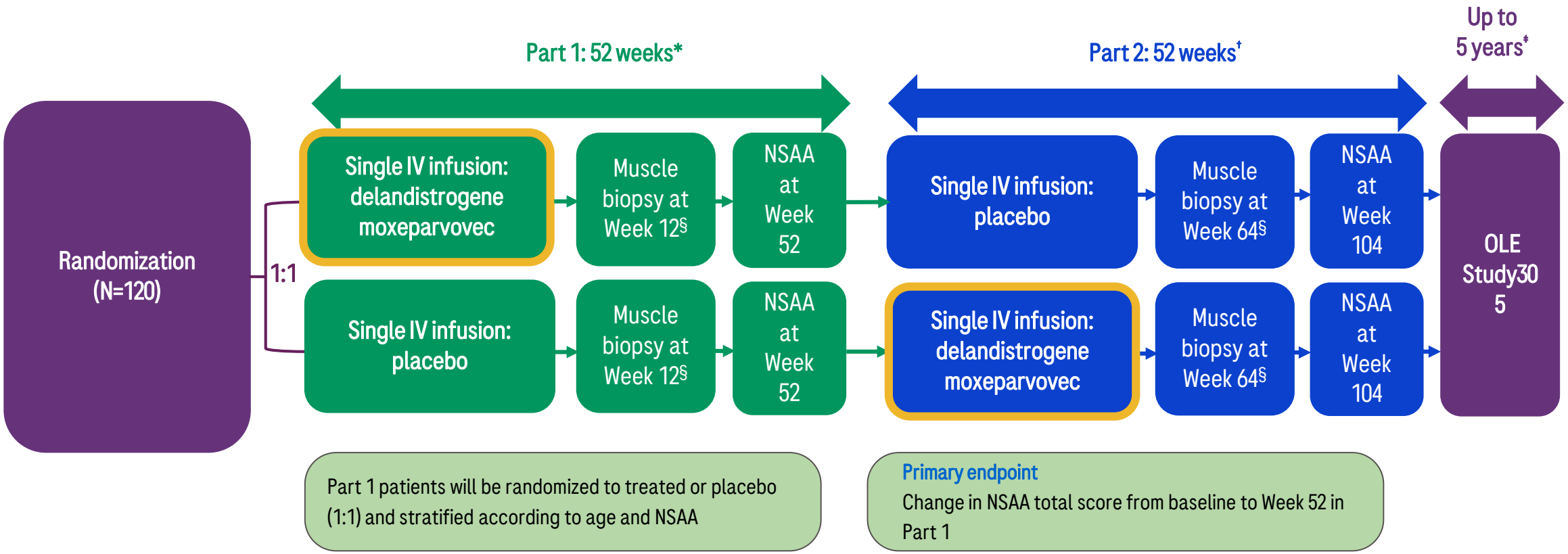
EMBARK study design



*Double-blind, placebo-controlled. †Patients, caregivers, Investigators, and site staff remain blinded. ‡Separate, planned open-label study (Study 305) of up to 5 years post-delandistrogene moxeparvovec infusion. §Only a subset of patients will receive a muscle biopsy for expression assessments

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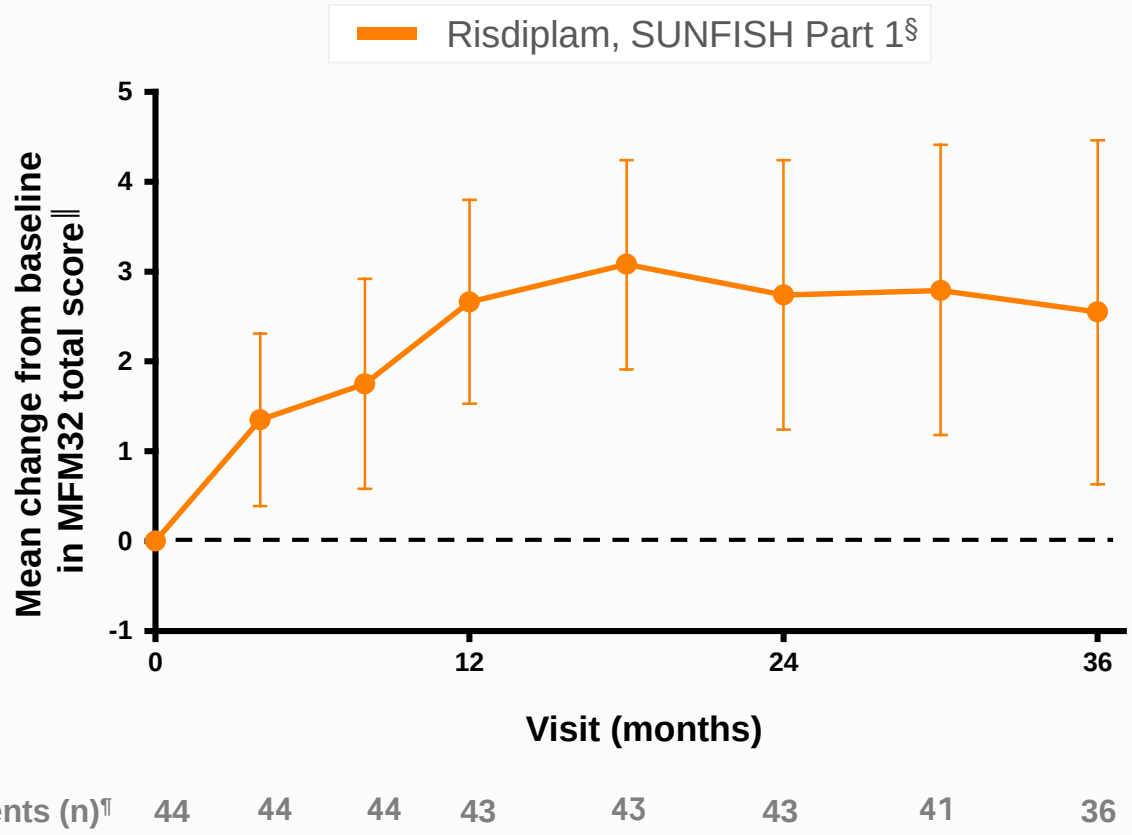
Doing now what patients need next

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)
Age range (years)	**2–25**
Age at screening, years, median (range)	7 (2–24)
Gender, female/male, n (%)	27 (53)/24 (47)
Type 2 SMA, n (%) Type 3 SMA, n (%)	37 (73) 14 (27)
Motor function at baseline† Walkers, n (%) Sitters, n (%) Non-sitters, n (%)	 7 (14) 33 (65) 11 (21)
Scoliosis, n (%)	29 (57)
Baseline MFM32 total score, mean (SD)	(n=44)‡ 42.9 (15.0)



*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. ‖+/- 95% CI. ¶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.