SUNFISH Part 1: Risdiplam (RG7916) treatment results in a sustained increase of SMN protein levels and improvement in motor function in patients with Type 2 or 3 SMA

E Mercuri[1*], G Baranello[2], J Kirschner[3], L Servais[4], N Goemans[5], MC Pera[1], J Buchbjerg[6], WY Yeung[7], H Kletzl[6], M Gerber[6], C Czech[6], Y Cleary[6], K Gorni[6] and O Khwaja[6]

1. Paediatric Neurology and Nemo Center, Catholic University and Fondazione Policlinico Gemelli, Rome, Italy; 2. Carlo Besta Neurological Research Institute Foundation, Developmental Neurology Unit, Milan, Italy; 3. Department of Neuropediatrics and Muscle Disorders, Medical Center-University of Freiburg, Freiburg, Germany; 4. Institute of Myology, Paris, France and Reference Center for Neuromuscular Disease, Centre Hospitalier Régional de La Citadelle, Liège, Belgium; 5. Neuromuscular Reference Centre, Department of Paediatrics and Child Neurology, University Hospitals Leuven, Leuven, Belgium; 6. Roche Pharmaceutical Research and Early Development, Roche Innovation Center Basel, Basel, Switzerland; 7. Roche Products Ltd, Welwyn Garden City, UK

*eugeniomaria.mercuri@policlinicogemelli.it

Background

- Spinal muscular atrophy (SMA) is a severe, progressive, inherited neuromuscular disease leading to loss of motor function and reduced life expectancy.[1,2]
- SMA is caused by reduced levels of the survival of motor neuron (SMN) protein due to deletions and/or mutations of the *SMN1* gene.[1,2]
  - A second SMN gene, *SMN2*, produces low levels of functional SMN protein.[3]
- Increasing preclinical evidence indicates that SMA is a multisystem disorder.[4]
  - Therapies that increase SMN protein levels systemically may have broader therapeutic benefit than those targeting motor neurons alone.
- Risdiplam (RG7916; RO7034067) is an orally administered, centrally and peripherally distributed small molecule that modulates *SMN2* pre-mRNA splicing to increase SMN protein levels.[5]

Study design

- SUNFISH (NCT02908685)[6] is a multicenter, two-part, operationally seamless, randomized, placebo-controlled, double-blind study.
  - Part 1: Dose finding (complete).
    - Risdiplam:placebo (2:1) for 12 weeks, followed by open-label extension at pivotal dose with the dose selected for Part 2.
  - Part 2: Efficacy and safety (enrollment complete).
    - Risdiplam:placebo (2:1) for 12 months, followed by a further 12 months on active treatment and then an open-label extension.
  - Inclusion criteria differ between Part 1 and Part 2.

		Inclusion/exclusion criteria*	
SUNFISH[6] Type 2 or 3 SMA 2–25 years old	Key inclusion criteria	**Part 1 (N=51)** • Type 2 or ambulatory and non-ambulatory Type 3 SMA. • Confirmed genetic diagnosis of SMA.‡	**Part 2 (N=168†)** • Type 2 or non-ambulatory Type 3 SMA. • Confirmed genetic diagnosis of SMA.‡ • Non-ambulant *(at screening).*
	Key exclusion criteria	• Previous participation in an *SMN2*-targeting study or gene therapy study. • Planned (within 18 months) or previous (<1 year prior) surgery for scoliosis or hip fixation.	

*See supplementary page and SUNFISH (NCT02908685)[6] for additional details on inclusion criteria; †Target enrollment; ‡5q-autosomal recessive SMA.

SUNFISH Part 1: Patient baseline characteristics

- Within this poster we present an efficacy analysis of the 35 SUNFISH Part 1 patients randomized to risdiplam for more than 12 months (total N=51).
  - Of these 35 patients, 14 received the dose selected for Part 2 from the beginning of the study and 21 patients received a lower dose initially.

	All patients (n=35)	Aged 2–11 (n=21)	Aged 12–24 (n=14)
Age at screening, years, median (range)	8 (2–24)	5 (2–11)	14 (12–24)
Gender, female/male, n (%)	22 (62.9) / 13 (37.1)	12 (57.1) / 9 (42.9)	10 (71.4) / 4 (28.6)
Risdiplam treatment duration, days, median (range)†	540 (287–677)	–	–
Type 2 SMA, n (%) **Type 3 SMA, n (%)**	26 (74.3) 9 (25.7)	16 (76.2) 5 (23.8)	10 (71.4) 4 (28.6)
Ambulatory, n (%) **Non-ambulatory, n (%)**	5 (14.3) 30 (85.7)	4 (19) 17 (81)	1 (7.1) 13 (92.9)
Patients with scoliosis, n (%)	22 (62.9)	11 (52.4)	11 (78.6)
Baseline median MFM32 total score (range)	(n=31)* 37.5 (10.4–81.3)	(n=17)* 37.5 (29.2–81.3)	(n=14) 38.54 (10.4–74.0)

Data cut-off: 6 July 2018. *Excludes four patients who performed the MFM20 assessment. †Data unavailable by age range. Includes one patient who dropped out of the study prior to Month 12 visit.

Considerations for SUNFISH patient population

- Patients enrolled in the SUNFISH trial have a wide age range (2–24 years; median age 8 years).
- SUNFISH Part 1 patients display a broad range of functional characteristics (weak non-ambulant to stronger ambulant).
- Five (14.3%) SUNFISH Part 1 patients had severe scoliosis on enrollment (i.e. possessed a spine curvature with a Cobb angle of >40 degrees).[7]

To date, risdiplam has been well tolerated at all doses

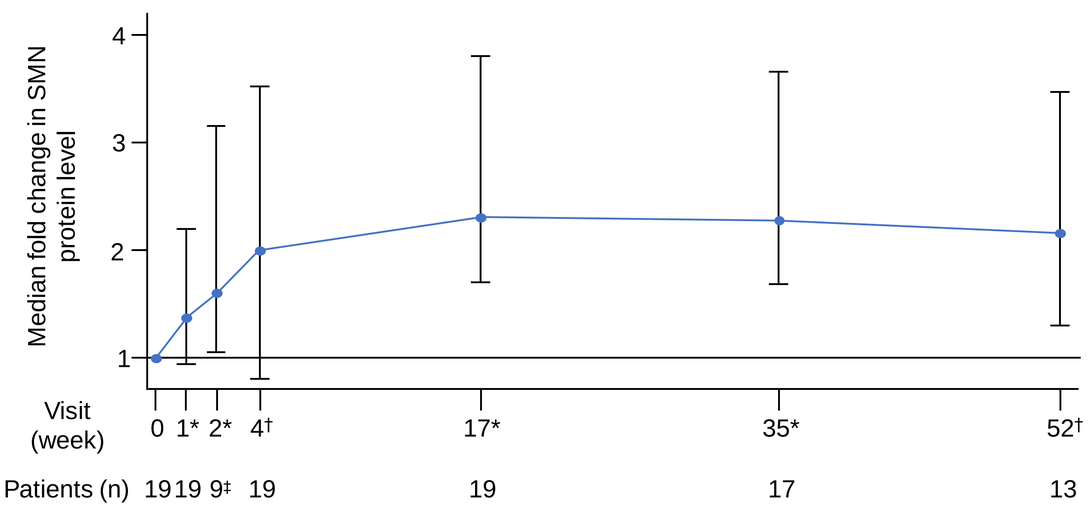
- After at least 1 year of treatment, risdiplam has been well tolerated.
- A review of currently available safety data did not show any clinically significant adverse findings compared with baseline.
- There have been no deaths or drug-related safety findings leading to withdrawal: *(Detailed AE information can be accessed in supplementary information via QR code*)
  - 46 patients (90.2%) had at least one AE; AEs were generally reflective of the underlying disease
  - 6 patients (11.8%) had at least one serious AE. All serious AEs were reported as unrelated to risdiplam and resolved
- No clinically significant ophthalmological findings have been observed in any patient receiving risdiplam to date.

Supplementary information

Please scan using your QR reader application to access the graphs and data presented in this poster. NB: there may be associated costs for downloading data. These costs may be high if you are using your smartphone abroad. Please check your mobile data tariff or contact your service provider for more details. Alternatively this can be accessed at: http://bit.ly/2D8foHo

Risdiplam treatment leads to sustained increases in SMN protein over 1 year of treatment

Patients who received the selected dose for SUNFISH Part 2



Data from patients who received the selected dose for SUNFISH Part 2; *Samples were taken pre-risdiplam dose. †Sample was taken 4 hours after receiving risdiplam. ‡Patients aged 12–25-years old only due to limitations on the volume of blood that could be obtained from the 2–11 years old population; Error bars represent minimum–maximum values. Data cut-off: 6 July 2018.

Risdiplam treatment leads to stabilization or improvements in motor function in patients with Type 2 or 3 SMA

Endpoint : (At 12 months of treatment)	>12 months Treatment		
MFM	**All patients (n=30)***	**Aged 2–11 (n=17)**	**Aged 12–24 (n=13)**
Total MFM change from baseline, mean (SD)	2.47 (4.17)	3.31 (4.5)	1.36 (3.57)
Total MFM change from baseline, median (range)	3.13 (-7.3–11.5)	4.17 (-6.3–11.5)	2.08 (-7.3–5.2)
Proportion of patients who achieve improvement (i.e., a change from baseline in MFM score ≥3), % (n)	63.3 (19/30)	76.5 (13/17)	46.2 (6/13)

*Excludes four patients who performed the MFM20 assessment (only patients who performed the full MFM32 assessment are included in the analysis) and one patient who had dropped out of the study prior to the Month 12 visit. Data cut-off: 6th July 2018.

- 63.3 (19/30) patients with SMA across all ages achieved improvement in MFM32 score from baseline of ≥3 after 12 months of risdiplam treatment.
  - This was further divided into 13/17 (76.5%) in the 2–11 year age group and 6/13 (46.2%) in the 12–24 year age group.

SUNFISH Part 1 conclusions

- To date, risdiplam has been well tolerated at all doses assessed
- MFM results indicate an improvement over 12 months compared with natural history, despite a broad range of patient age and functional characteristics
- A sustained >2-fold increase in median SMN protein versus baseline was seen after 12 months of treatment with risdiplam
- 63.3% of all patients achieved improvement of ≥3 in MFM32 following 12 months treatment with risdiplam
- Greater increases in MFM32 scores were observed in the 2–11 year age group (76.5% of patients achieving improvements in MFM32 >3) compared with the 12–24 year age group (46.2%)

Abbreviations

AE, adverse event; MFM, Motor Function Measure; SD, standard deviation; SMA, spinal muscular atrophy; SMN, survival of motor neuron.

Acknowledgments

We would like to thank the patients and their families who participated in this study, as well as the investigators and trial staff involved in the SUNFISH study. We thank Anna-Katharina Wiegers and Johann Karl of the Roche Biomarker Team for their contributions to this study. We thank Dr. Riccardo Masson of the Carlo Besta Neurological Research Institute Foundation, Developmental Neurology Unit, Milan, Italy for his support of this study. We would also like to thank our collaborators at PTC Therapeutics and the SMA Foundation. The study was sponsored by F. Hoffmann-La Roche AG, Basel, Switzerland. Writing and editorial assistance was provided by Lindsey Weedon, of MediTech Media, UK, in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

References

1. Mercuri E, et al. *Lancet Neurol*. 2012; 11:443–452;
2. Lefebvre S, et al. *Cell.* 1995; 80:155–165;
3. Lorson CL, et al. *PNAS*. 1999; 96:6307–6311;
4. Hamilton G and Gillingwater TH. *Trends Mol Med.* 2013; 19:40–50;
5. Ratni H, et al. *J Med Chem.* 2018. 61:6501–6517;
6. ClinicalTrials.gov. NCT02908685 (Accessed July 2018);.
7. Mercuri E, et al. *N Engl J Med.* 2018; 378: 625–635.

Presented at the 23rd International Annual Congress of the World Muscle Society, Mendoza, Argentina, October 2–6, 2018

SUPPLEMENTARY INFORMATION – the content below was not in the poster presented at WMS 2018 but is available via a QR code

SUNFISH Part 1: Risdiplam (RG7916) treatment results in a sustained increase of SMN protein levels and improvement in motor function in patients with Type 2 or 3 SMA

E Mercuri[1], G Baranello[2], J Kirschner[3], L Servais[4], N Goemans[5], MC Pera[1], J Buchbjerg[6], WY Yeung[7], H Kletzl[6], M Gerber[6], C Czech[6], Y Cleary[6], K Gorni[6] and O Khwaja[6]

1. Paediatric Neurology and Nemo Center, Catholic University and Fondazione Policlinico Gemelli, Rome, Italy; 2. Carlo Besta Neurological Research Institute Foundation, Developmental Neurology Unit, Milan, Italy; 3. Department of Neuropediatrics and Muscle Disorders, Medical Center-University of Freiburg, Freiburg, Germany; 4. Institute of Myology, Paris, France and Reference Center for Neuromuscular Disease, Centre Hospitalier Régional de La Citadelle, Liège, Belgium; 5. Neuromuscular Reference Centre, Department of Paediatrics and Child Neurology, University Hospitals Leuven, Leuven, Belgium; 6. Roche Pharmaceutical Research and Early Development, Roche Innovation Center Basel, Basel, Switzerland; 7. Roche Products Ltd, Welwyn Garden City, UK

No patients have died or left the study due to drug-related adverse events

		Total patients (N=51)
Patients with at least one AE, n (%)		46 (90.2)
AEs reported in ≥5 patients with SMA, n (number of events)	Pyrexia	17
	Cough	15
	Vomiting	14
	Nasopharyngitis	9
	Oropharyngeal pain	9
	Upper respiratory tract inflammation	8
	Upper respiratory tract infection	8
	Rash	7
	Headache	7
	Pain in extremities	6
	Pharyngitis	6
	Respiratory tract infection	6
	Abdominal pain	6
	Bronchitis	5
	Influenza	5
Total Serious AEs, N		11
Patients with at least one serious AE, n (%)		6 (11.8)
Serious AEs*, n (number of events)	Atrial fibrillation	1
	Chronic respiratory failure	1
	Gastroenteritis	1
	Femur fracture	1
	Nausea	2
	Pneumonia	1
	Upper respiratory tract infection	2
	Vomiting	2
Study interruptions due to serious AEs, n (number of patients)		2
Discontinuations due to drug-related AEs, n		0

Data cut-off: 6 July 2018.

SUNFISH: Detailed inclusion criteria

	Part 1 (N=51)	Part 2 (N=168*)
Detailed inclusion criteria	• Type 2 or ambulatory and non-ambulatory Type 3 SMA. • Confirmed genetic diagnosis of SMA† including: a. genetic confirmation of homozygous deletion or heterozygosity predictive of the loss of function of the *SMN1* gene. b. clinical symptoms attributable to Type 2 or Type 3 SMA.	• Type 2 or non-ambulatory Type 3 SMA. • Confirmed genetic diagnosis of SMA.† • Non-ambulant *(at screening):* a. RULM entry item A (Brooke score) ≥ 2 (i.e. Can raise one or two hands to mouth, but unable to raise a 200g weight to mouth). b. ability to sit independently (i.e. Scores ≥1 on Item 9 of the MFM32 "with support of one or both upper limbs, maintains the seated position for 5 seconds).

*Target enrollment; †5q-autosomal recessive SMA.

SUNFISH: Expanded details of MFM score

Endpoint : (At 12 months of treatment)	>12 months Treatment		
MFM	**All patients (n=30)***	**Aged 2–11 (n=17)**	**Aged 12–24 (n=13)**
Total MFM change from baseline, mean (SD)	2.47 (4.17)	3.31 (4.5)	1.36 (3.57)
Total MFM change from baseline, median (range)	3.13 (-7.3–11.5)	4.17 (-6.3–11.5)	2.08 (-7.3–5.2)
Proportion of patients who achieve improvement (i.e., a change from baseline in MFM score), % (n)			
≥1	70 (21/30)	76.5 (13/17)	61.5 (8/13)
≥3	63.3 (19/30)	76.5 (13/17)	46.2 (6/13)

*Excludes four patients who performed the MFM20 assessment (only patients who performed the full MFM32 assessment are included in the analysis) and one patient who had dropped out of the study prior to the Month 12 visit. Data cut-off: 6th July 2018.

Abbreviations

AE, adverse event; MFM, Motor Function Measure; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy; SMN, survival of motor neuron.

Supplementary page

(This page provides additional online content and will not be available at the poster stand. Attendees will be able to view and download this page by scanning the QR code on the main poster)