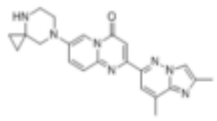
TreatSMA
Treat Spinal Muscular Atrophy

Roche have posted an update on the ongoing study programme for risidiplam.

## Risdiplam in SMA type 1/2/3



- Oral, systemically available SMN2 splicing modifier
- Durably increases SMN protein throughout the CNS and in peripheral tissues
- Excellent efficacy

- Positive Ph III (SUNFISH part 2) data in type 2 & 3 SMA ages 2 to 25 years presented in Q1
- Positive Ph III (FIREFISH part 2) in type 1 SMA presented at virtual event on 28 April
- US launch for types 1/2/3 expected in 2020;
  Priority review granted, PDUFA date set for August 24

**Risdiplam:FIREFISH part 2 -efficacy and safety in infants with type 1 SMA**

**Prof. Laurent Servais, MDUK Oxford Neuromuscular Center, Department of Paediatrics, University of Oxford, UK**

# FIREFISH Part 2: Efficacy and safety of risdiplam (RG7916) in infants with Type 1 spinal muscular atrophy (SMA)

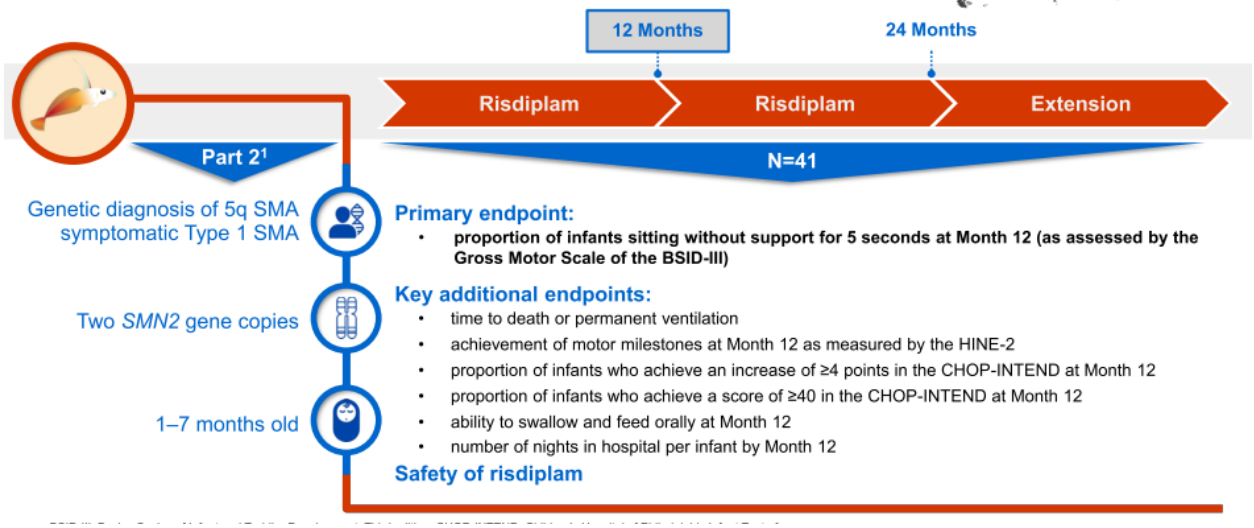
Laurent Servais,[1–3*] Giovanni Baranello,[4,5] Riccardo Masson,[4] Maria Mazurkiewicz-Bełdzińska,[6] Kristy Rose,[7] Dmitry Vlodavets,[8] Hui Xiong,[9] Edmar Zanoteli,[10] Muna El-Khairi,[11] Sabine Fuerst-Recktenwald,[12] Marianne Gerber,[13] Ksenija Gorni,[14] Heidemarie Kletzl,[15] Renata Scalco,[12] Basil T. Darras[16] on behalf of the FIREFISH Working Group

[1]Division of Child Neurology, Centre de Références des Maladies Neuromusculaires, Department of Pediatrics, University Hospital Liège & University of Liège, Belgium; [2]MDUK Oxford Neuromuscular Center, Department of Paediatrics, University of Oxford, Oxford, UK; [3]I-Motion - Hôpital Armand Trousseau, Paris, France; [4]Developmental Neurology Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; [5]The Dubowitz Neuromuscular Centre, NIHR Great Ormond Street Hospital Biomedical Research Centre, Great Ormond Street Institute of Child Health University College London, & Great Ormond Street Hospital Trust , London, UK;(current); [6]Department of Developmental Neurology, Medical University of Gdańsk, Gdańsk, Poland; [7]Paediatric Gait Analysis Service of New South Wales, The Children's Hospital at Westmead, Sydney, Australia; [8]Russian Children Neuromuscular Center, Veltischev Clinical Pediatric Research Institute of Pirogov Russian National Research Medical University, Moscow, Russia; [9]Department of Pediatrics, Peking University First Hospital, Beijing, China; [10]Department of Neurology, Hospital das Clínicas, University of São Paulo, São Paulo, Brazil; [11]Roche Products Ltd., Welwyn Garden City, UK; [12]Pharma Development Neurology, F. Hoffmann-La Roche Ltd., Basel, Switzerland; [13]Pharma Development, Safety, F. Hoffmann-La Roche Ltd, Basel, Switzerland; [14]PDMA Neuroscience and Rare Disease, F. Hoffmann-La Roche Ltd., Basel, Switzerland; [15]Roche Pharmaceutical Research and Early Development, Roche Innovation Center Basel, Basel, Switzerland; [16]Boston Children's Hospital, Harvard Medical School, Boston, MA, USA.

## Introduction

- Type 1 SMA is a severe, progressive neuromuscular disease, with untreated infants failing to achieve major motor milestones and typically dying before 2 years of age[1]
- Risdiplam (RG7916) is a centrally and peripherally distributed oral *SMN2* pre-mRNA splicing modifier that increases the levels of functional SMN protein[2,3]
- Here we present data for the first time from Part 2 of the FIREFISH trial in infants 1–7 months old* with Type 1 SMA who have received risdiplam for 12 months at the dose selected in Part 1
  - ➢ Primary endpoint, as well as additional motor milestone, survival and swallowing data will be presented

# A multicenter, global, open-label study




# Part 2 baseline characteristics are reflective of infants with symptomatic Type 1 SMA

| | Risdiplam (N=41) |
|---|---|
| Age at enrollment, months, median (range) | 5.3 (2.2–6.9) |
| Gender, n (%)<br>Female<br>Male | <br>22 (54)<br>19 (46) |
| Age at onset of symptoms, months, median (range) | 1.5 (1.0–3.0) |
| Disease duration, months, median (range)<br>≤3 months, n (%)<br>>3 months, n (%) | 3.4 (1.0–6.0)<br>14 (34)<br>27 (66) |
| CHOP-INTEND score, median (range) | 22.0 (8.0–37.0) |
| HINE-2 score, median (range) | 1.0 (0.0–5.0) |

# The study met its primary endpoint of the proportion of infants sitting at Month 12

**Without treatment, children with Type 1 SMA are never able to sit without support[1]**

**Sitting without support for at least 5 seconds***

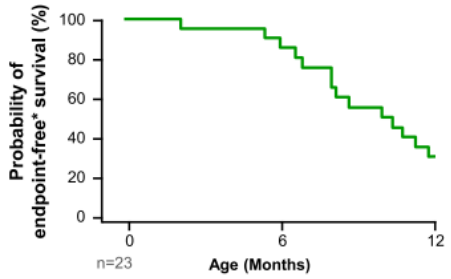
**29%**

**12/41 infants**

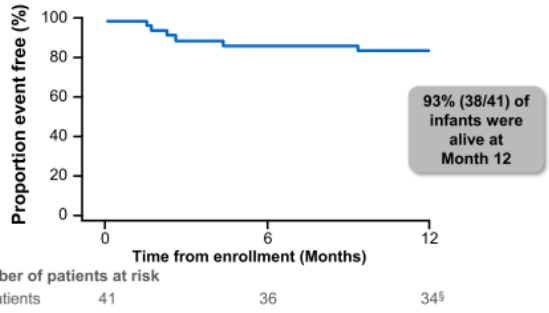
P<0.0001, performance criterion= 5%

# Event-free survival time was greatly improved in infants treated with risdiplam compared with natural history

**Natural history data (PNCR) for infants with Type 1 SMA and two *SMN2* copies[1]**




**85% (35/41) of infants were event free† at Month 12 in FIREFISH Part 2‡**




**In natural history, median age (IQR) for reaching death or permanent ventilation for infants with two *SMN2* copies was 10.5 (8.1–13.6) months[1]**

**In FIREFISH Part 2, median time to reaching death or permanent ventilation was not estimable due to lack of events**

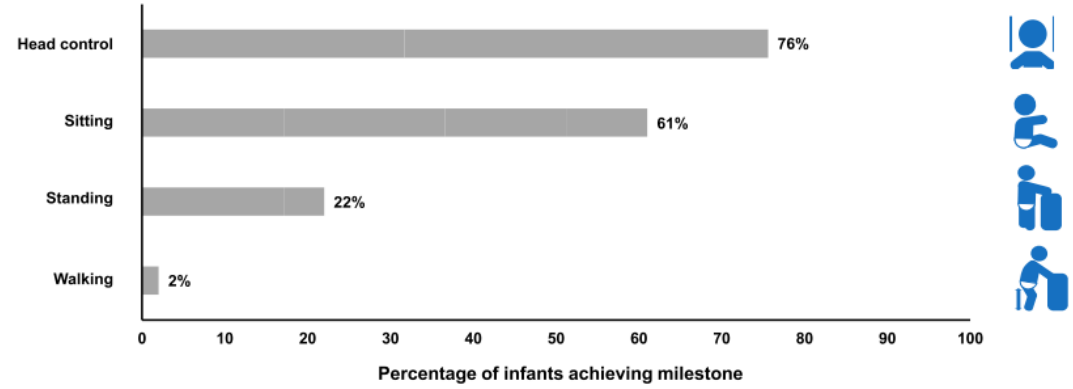
# The HINE-2 scale measures motor function in infants

| | Absence of activity | | | Normal activity | |
|---|---|---|---|---|---|
| **Head control** | Unable to maintain head upright | Wobbles | Maintain upright all the time | | |
| **Sitting** | Cannot sit | With support at hips | Props | Stable sit | Pivots (rotates) |
| **Voluntary grasp** | No grasp | Uses whole hand | Index finger and thumb but immature grasp | Pincer grasp | |
| **Ability to kick in supine** | No kicking | Kicks horizontally but legs do not lift | Upward (vertically) | Touches leg | Touches toes |
| **Rolling** | No rolling | Rolling to side | Prone to supine | Supine to prone | |
| **Crawling** | Does not lift head | On elbow | On outstretched hand | Crawling flat on abdomen | Crawling on hands and knees |
| **Standing** | Does not support weight | Supports weight | Stands with support | Stands unaided | |
| **Walking** | | Bouncing | Cruising (walks holding on) | Walking independently | |

**Used to assess posture, movements, tone and reflexes[1,2]**

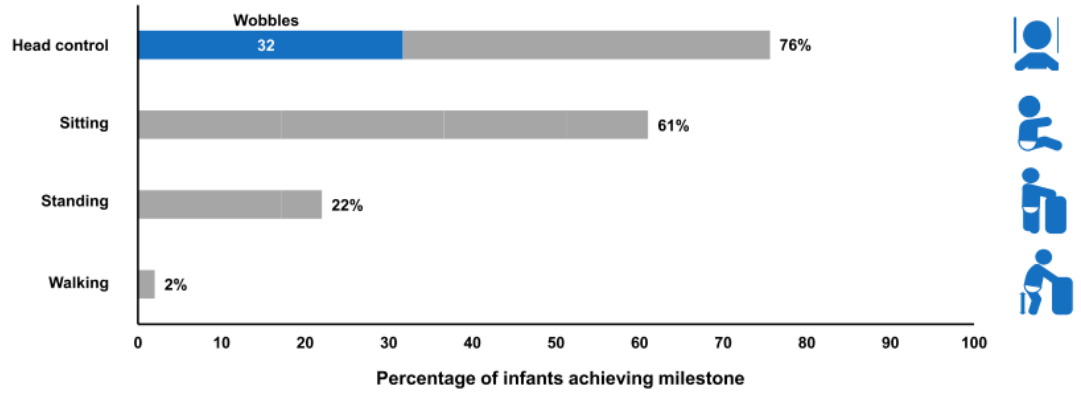
**Items are scored from 0–4 (0=unable, 4=able)[2]**

# Risdiplam treatment resulted in significant gains in motor milestones after 12 months (HINE-2 items)



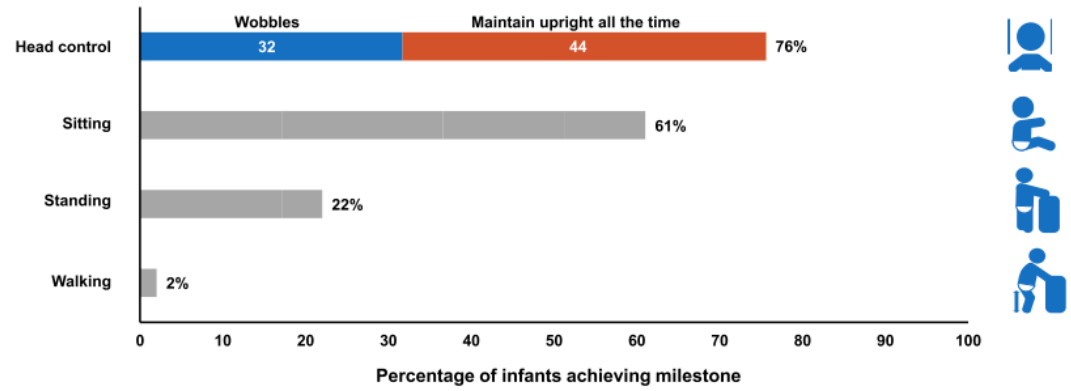

**78% of infants (32/41) responded to treatment using the HINE-2 scale and pre-specified response criteria*†**

# Risdiplam treatment resulted in significant gains in motor milestones after 12 months (HINE-2 items)



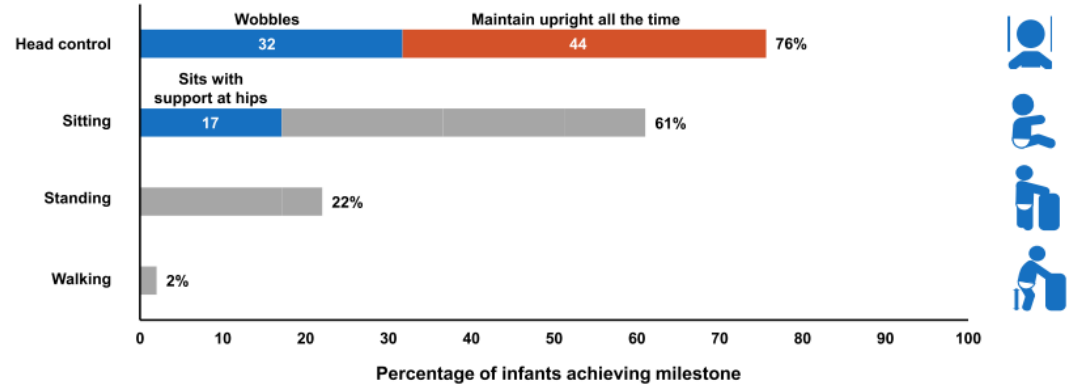

78% of infants (32/41) responded to treatment using the HINE-2 scale and pre-specified response criteria*†

# Risdiplam treatment resulted in significant gains in motor milestones after 12 months (HINE-2 items)



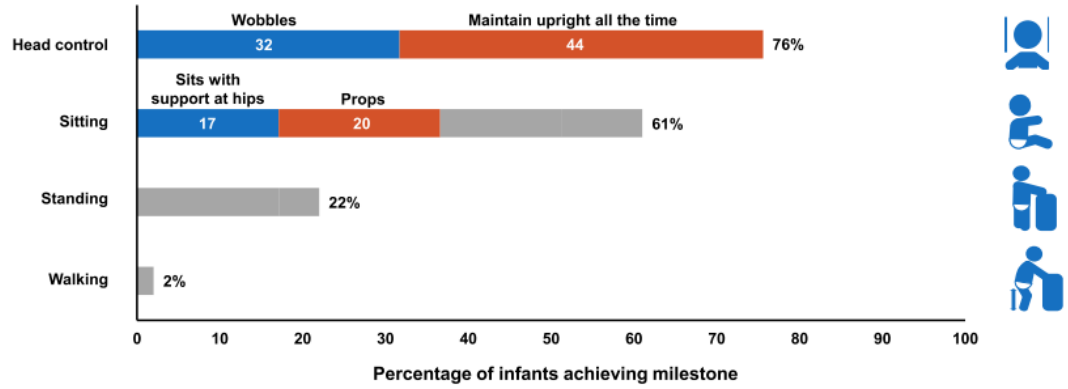

78% of infants (32/41) responded to treatment using the HINE-2 scale and pre-specified response criteria*†

# Risdiplam treatment resulted in significant gains in motor milestones after 12 months (HINE-2 items)



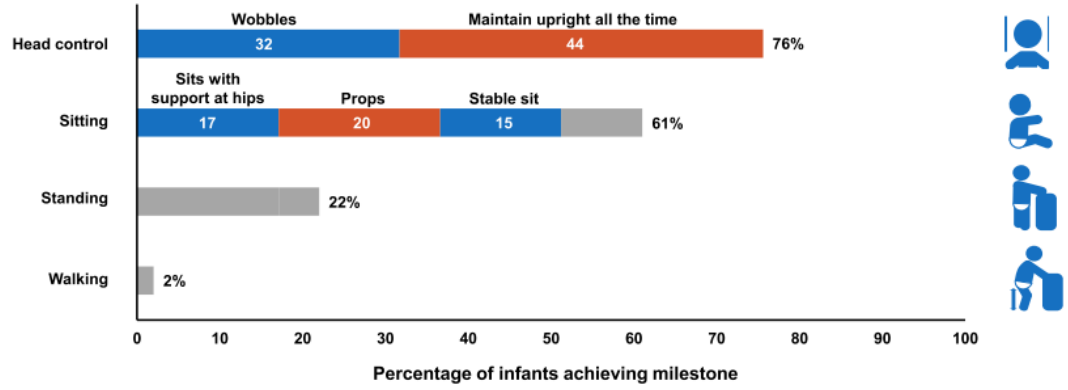

78% of infants (32/41) responded to treatment using the HINE-2 scale and pre-specified response criteria*†

# Risdiplam treatment resulted in significant gains in motor milestones after 12 months (HINE-2 items)



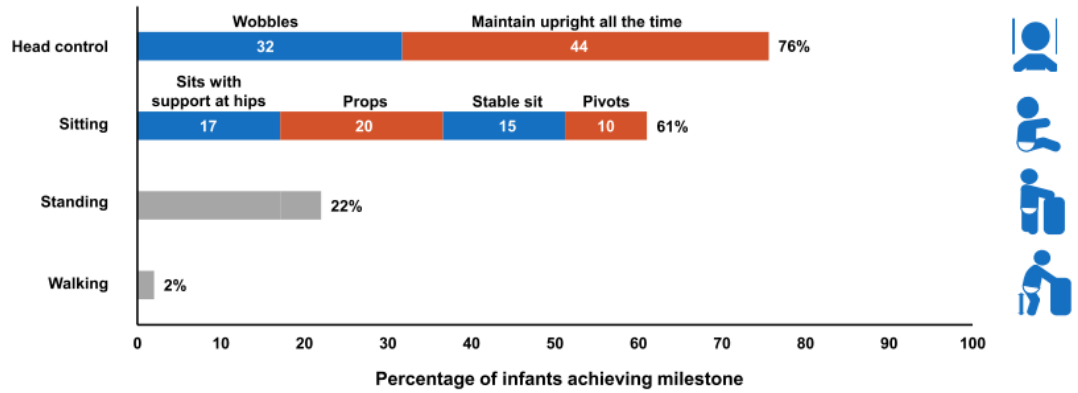

78% of infants (32/41) responded to treatment using the HINE-2 scale and pre-specified response criteria*†

# Risdiplam treatment resulted in significant gains in motor milestones after 12 months (HINE-2 items)



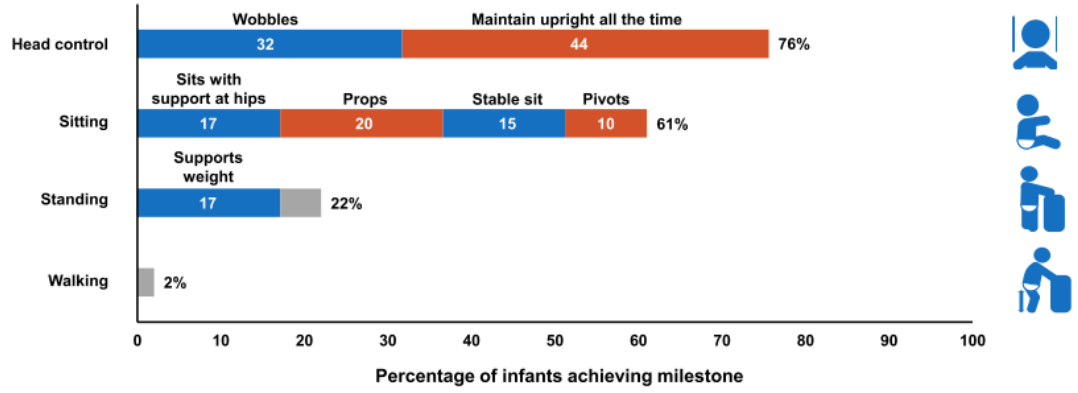

78% of infants (32/41) responded to treatment using the HINE-2 scale and pre-specified response criteria*†

# Risdiplam treatment resulted in significant gains in motor milestones after 12 months (HINE-2 items)



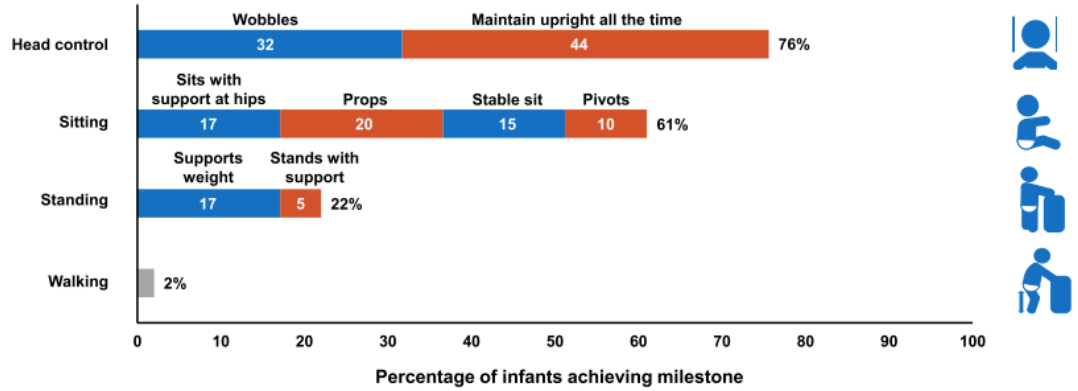

78% of infants (32/41) responded to treatment using the HINE-2 scale and pre-specified response criteria*†

# Risdiplam treatment resulted in significant gains in motor milestones after 12 months (HINE-2 items)



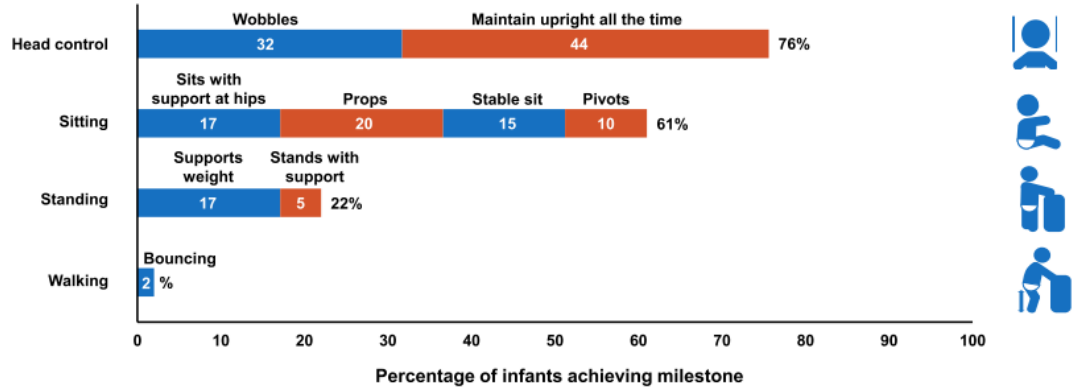

78% of infants (32/41) responded to treatment using the HINE-2 scale and pre-specified response criteria*†

# Risdiplam treatment resulted in significant gains in motor milestones after 12 months (HINE-2 items)




78% of infants (32/41) responded to treatment using the HINE-2 scale and pre-specified response criteria*†

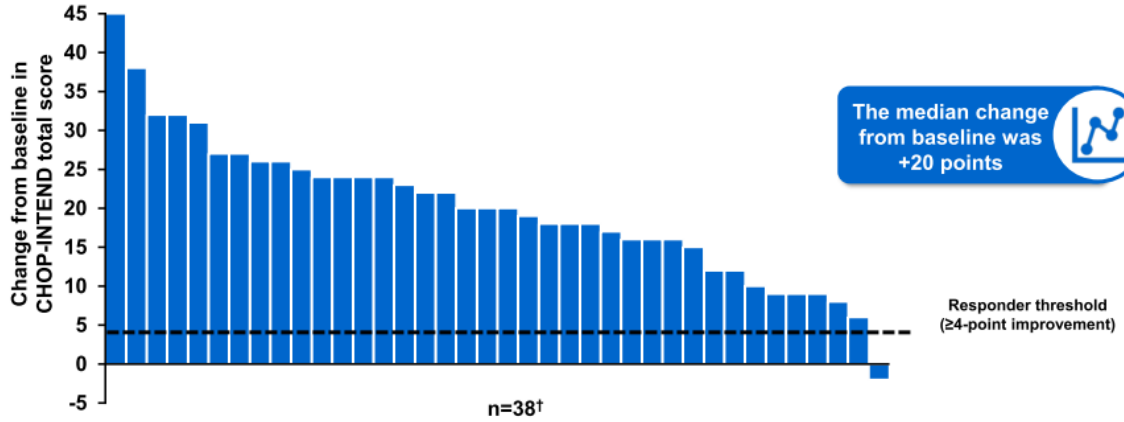
# Risdiplam treatment resulted in significant gains in motor milestones after 12 months (HINE-2 items)



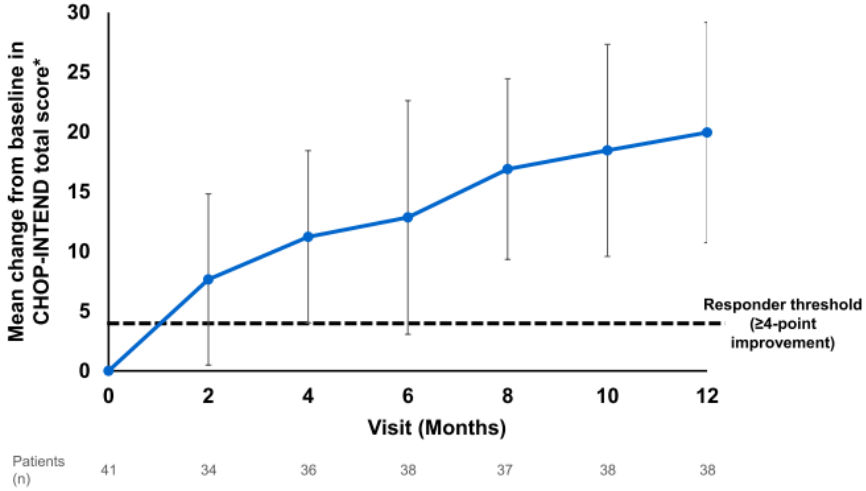

78% of infants (32/41) responded to treatment using the HINE-2 scale and pre-specified response criteria*†

## 90% (37/41) of infants achieved an increase of ≥4 points in CHOP-INTEND total score at Month 12*

**Without treatment, infants with Type 1 SMA show a steady decline in CHOP-INTEND scores over time[1]**



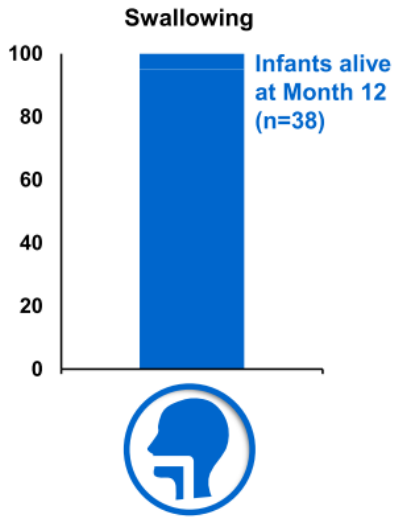

## CHOP-INTEND total score continued to improve over 12 months



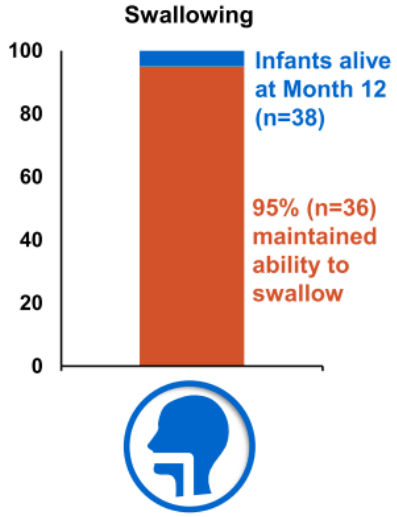

**In natural history, children with Type 1 SMA rarely reach a CHOP-INTEND total score of 40 points[1]**

**56% (23/41) achieved a CHOP-INTEND score ≥40 at Month 12† in FIREFISH Part 2**

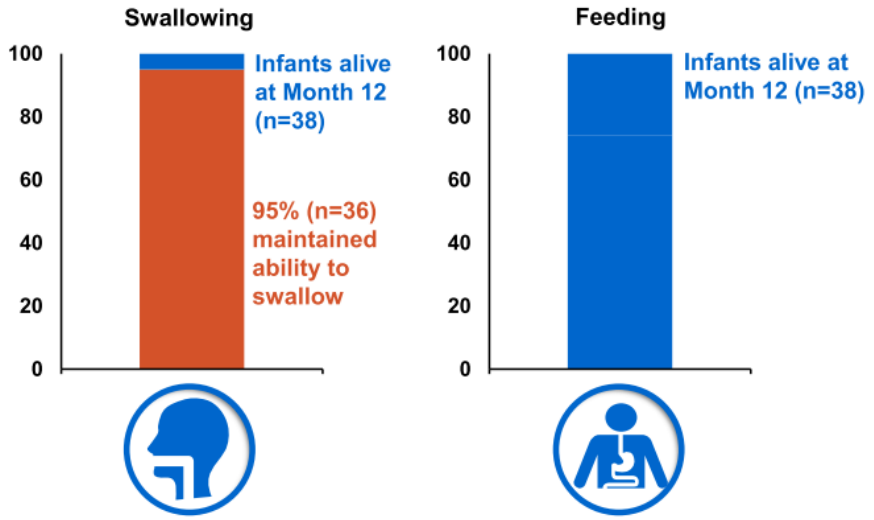
## Swallowing and feeding ability was maintained by the majority of infants alive at Month 12



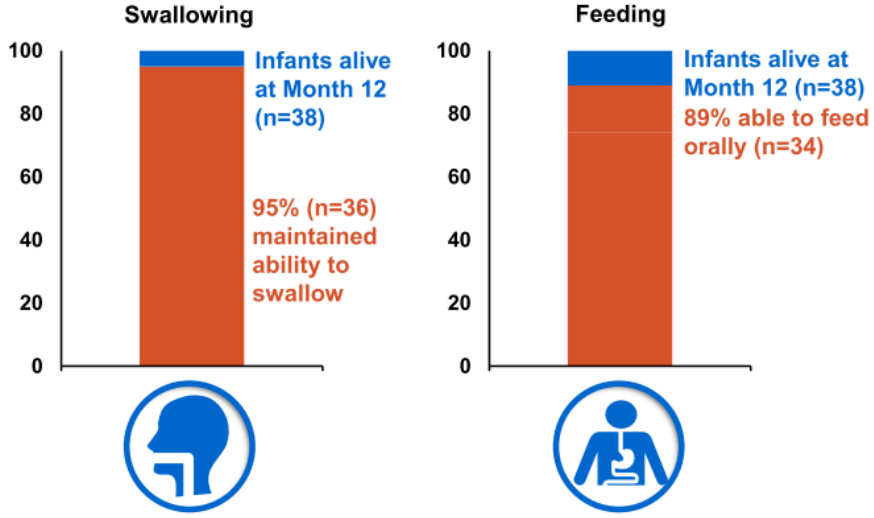

## Swallowing and feeding ability was maintained by the majority of infants alive at Month 12



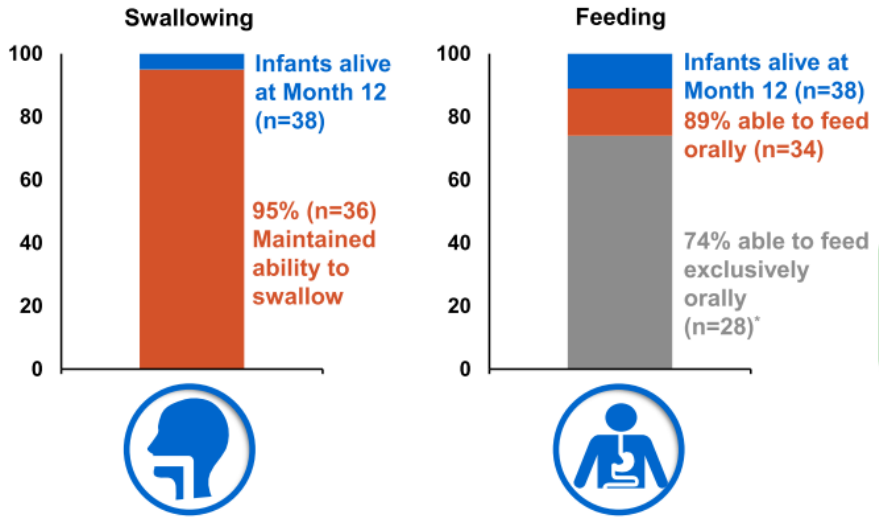
## Swallowing and feeding ability was maintained by the majority of infants alive at Month 12




## Swallowing and feeding ability was maintained by the majority of infants alive at Month 12

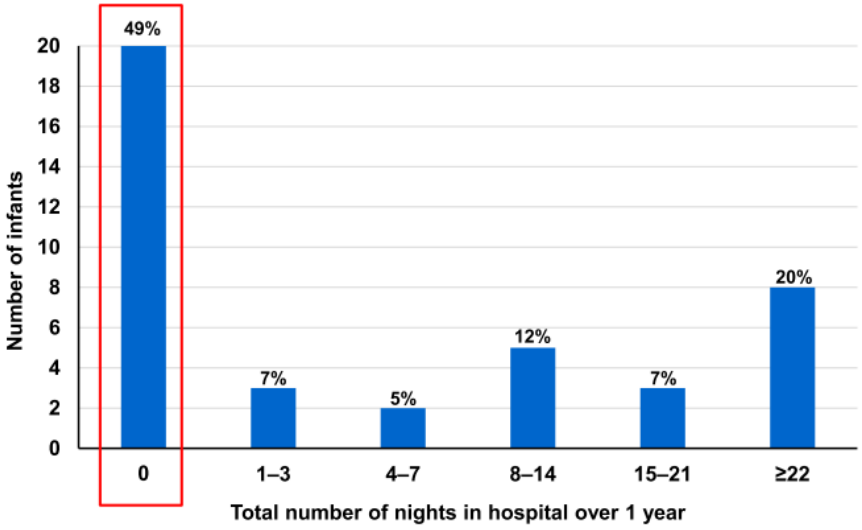


## Swallowing and feeding ability was maintained by the majority of infants alive at Month 12




In a natural history cohort, all infants with Type 1 SMA older than 12 months required feeding support[1]

## Nearly half of all infants (49%, 20/41) did not require hospitalization up to Month 12*




In natural history, children with Type 1 SMA experienced between ~4.2 and 7.6 hospitalizations every year[1,2]

There were 1.30 hospitalizations per patient-year in FIREFISH Part 2 (90% CI: 1.02, 1.65)

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

| | | Risdiplam (n=41) |
|---|---|---|
| Patients with at least one AE, n (%) | | 41 (100) |
| Total number of AEs | | 254 |
| Total number of deaths, n (%) | | 3 (7) |
| Total number of patients with at least one AE, n (%) | AE with fatal outcome† | 3 (7) |
| | SAE | 24 (59) |
| | SAE leading to withdrawal from treatment | 0 |
| | SAE leading to dose modification/interruption | 1 (2) |
| | Treatment-related SAE | 0 |
| | AE leading to withdrawal from treatment | 0 |
| | AE leading to dose modification/interruption | 2 (5) |
| | Treatment-related AE | 7 (17) |
| | Related AE leading to withdrawal from treatment | 0 |
| | Related AE leading to dose modification/interruption | 0 |
| | Grade 3–5 AE | 22 (54) |

# AEs and SAEs were reflective of underlying disease*

| | | Risdiplam (n=41) |
|---|---|---|
| Most common AEs, ≥4 patients, n (number of patients [%]) | Upper respiratory tract infection | 19 (46) |
| | Pneumonia | 16 (39) |
| | Pyrexia | 16 (39) |
| | Constipation | 8 (20) |
| | Nasopharyngitis | 5 (12) |
| | Rhinitis | 5 (12) |
| | Diarrhea | 4 (10) |
| | Rash maculo-papular | 4 (10) |
| Most common SAEs, ≥2 patients, n (number of patients [%]) | Pneumonia | 13 (32) |
| | Bronchiolitis | 2 (5) |
| | Respiratory failure | 2 (5) |
| | Hypotonia | 2 (5) |

**The incidence of serious pneumonia declined by approximately half between first and second 6-month periods**

**No risdiplam-associated ophthalmologic findings were observed**

- **The most frequent AE was upper respiratory tract infection**
- **The most common SAE was pneumonia**
- **Skin events were non-serious and resolved with ongoing treatment**

# Conclusions from FIREFISH Part 2 at 12 months

The primary endpoint was met (P<0.0001)*

**29%**
(12/41)

of infants were sitting without support for 5 seconds at Month 12, as measured by the BSID-III

Risdiplam treatment led to a significant improvement in motor function† (P<0.0001)‡

Infants achieved motor milestones, such as sitting and standing§ that would never be seen in untreated infants

**93%**
(38/41)
of infants were alive and

**85%**
(35/41)
of infants were event free‖ at Month 12

**95%**
(36/38)

of infants alive maintained the ability to swallow after 12 months of treatment

**49%**
(20/41)

of all infants did not require hospitalization¶ during 12 months of treatment

No drug-related safety findings led to withdrawal in FIREFISH Part 2

*Performance criterion=5%, exact binomial test. †As measured by CHOP-INTEND. ‡Performance criterion=12%, exact binomial test. §As measured by HINE-2; ‖Event-free in FIREFISH is defined as alive with no permanent ventilation (i.e. no tracheostomy or BiPAP ≥16 hours per day continuously for >3 weeks or continuous intubation >3 weeks, in the absence of, or following the resolution of, an acute reversible event). ¶Hospitalizations include hospital admissions ≥1 night.
BiPAP, Bilevel Positive Airway Pressure; BSID-III, Bayley Scales of Infant and Toddler Development, Third edition; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination, Module 2.

Roche in collaboration with SMA FOUNDATION and PTC THERAPEUTICS

**Risdiplam: Update on clinical development program in patients with Type 1, 2 & 3 SMA**

## Risdiplam in spinal muscular atrophy (SMA)

*Compelling benefit/risk profile in infants, children, teenagers, and adults*

- Durably increases SMN protein throughout the CNS and in peripheral tissues
- Positive efficacy in Type 1 infants (n=62 total)
- Positive efficacy in large (n=180) placebo-controlled study in a broad spectrum of Type 2/3 patients
- Consistent safety profile across trials
- No treatment-related safety findings have led to withdrawal in any study

**Over 450 patients treated with risdiplam to date**

| FIREFISH | SUNFISH | JEWELFISH | RAINBOWFISH |
|---|---|---|---|
| Type 1 SMA<br>1-7 months old<br>Two SMN2 gene copies | Type 2 or 3 SMA<br>2-25 years old | SMA<br>Non-naïve, aged 6 months to 60 years old | Birth-6 weeks old<br>presymptomatic |
| Primary analysis completed | Primary analysis completed | Enrollment completed | Enrolling |

**Potential to be the treatment of choice for a majority of patients living with SMA**

## Meaningful evidence being generated across a broad program

**Overview of the risdiplam development program**

- Spanning types 1, 2, & 3 SMA; naïve and pre-treated
- Newborns to 60 years old; randomized, placebo-controlled data in 2 – 25 years old
- Including real-world spectrum of SMA – scoliosis, joint contractures, low baseline motor scale scores, etc.

| Presymptomatic Newborns | Symptomatic Infants | Younger Children | Older Children | Teenagers | Adults |
|---|---|---|---|---|---|
| ≤ 5 years old | | | > 5 years old | | |
| ~15% prevalence* | | | ~85% prevalence* | | |
| Focus of many recent trials in SMA | | | Large prevalent population that remains underserved lacking treatment options and supporting evidence | | |

## JEWELFISH update

*Large open-label study of non-naïve patients completed enrollment*

| Prior SMA therapy | n |
|---|---|
| Olesoxime | 74 |
| Spinraza | 73 |
| AVXS-101 | 14 |
| RG7800 | 13 |
| **TOTAL** | **174** |

- **Primary objectives**: safety/tolerability and PK/PD
- Poster prepared for AAN 2020
  - Preliminary safety data from 45 patients (6 mo to 60 yrs) who had received risdiplam for up to 28.9 months
  - No drug-related AEs leading to withdrawal
  - Overall safety profile consistent with patients who have not received previous treatment
- Exploratory efficacy to be reported after 1 year of follow-up (2021)
- Data collected on reasons for switching therapy (to be presented later in 2020)

## Regulatory procedures moving at pace around the globe

- 24 August PDUFA date
- Additional time to enable review of newly submitted SUNFISH Part 2 data

- On track for mid 2020 EMA submission with Part 2 data fully integrated
- EU Prime designation

- Filed in China in April 2020

Risdiplam has also been filed in Brazil, Chile, Indonesia, Russia, South Korea, and Taiwan.


*Doing now what patients need next*