# FIREFISH Part 1: Survival, ventilation and swallowing ability in infants with Type 1 SMA receiving risdiplam (RG7916) (1-year results)

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# Disclosures

- GB was a PI in F. Hoffmann-La Roche and AveXis SMA trials, and received consultancy fees from PTC therapeutics, Sarepta and F. Hoffmann-La Roche
- LS is a PI of SMA studies for Roche, Biogen, and AveXis; He has attended SAB of Biogen and AveXis and received consultancy fees from Biogen; He serves on the board for Cytokinetics
- JD reports grants from: AMO Pharmaceuticals, aTyr, AveXis, Biogen, Bristol Meyers Squibb, Cytokinetics, Ionis Pharmaceuticals, Roche Pharmaceuticals, Sanofi-Genzyme, and Sarepta Therapeutics; He has served as a consultant for: AMO Pharmaceuticals, AveXis, Biogen, Cytokinetics, Ionis Pharmaceuticals, Roche Pharmaceuticals, Pfizer, Sarepta Therapeutics, Santhera Pharmaceuticals; He has patents licensed to Athena Diagnostics for genetic testing of myotonic dystrophy type 2 (US patent 7442782) and spinocerebellar ataxia type 5 (US patent 7527931)
- ND is a PI of SMA studies for Roche, Novartis, Biogen and AveXis. He has received consultancy fees from Biogen
- EM is a consultant for F. Hoffmann-La Roche, AveXis, IONIS and Biogen, and PI for Biogen/IONIS and F. Hoffmann-La Roche studies
- AK has received speaker and consulting fees from Biogen, PTC, Roche Sarepta, AveXis and Santhera and is PI for F. Hoffmann-La Roche and Santhera studies
- BD is on advisory boards for AveXis, Biogen, Cytokinetics, PTC Therapeutics, Roche and Sarepta. He has received research support from the National Institutes of Health/National Institute of Neurological Disorders and Stroke, the Slaney Family Fund for SMA, Working on Walking Fund and the SMA Foundation; grants from CureSMA, Ionis Pharmaceuticals, Inc. and Biogen during ENDEAR, CHERISH, CS2, CS12, CS11 studies, Cytokinetics, Fibrogen, PTC, Roche, Santhera, Sarepta and Summit
- RM has no disclosures to report
- HK, YC, ME, TS, MG, CN, KG, and KG are current employees of F. Hoffmann-La Roche
- OK and CC are former employees of F. Hoffmann-La Roche
- OK is an employee of, and holds shares in, Voyager Therapeutics
- CC is an employee of Therachon AG, and holds shares in F. Hoffmann-La Roche

# Introduction

**41%**
**(7/17 infants in cohort B)**
**were able to sit without support for at least 5 seconds (as assessed by BSID-III)**

**1/17**
**infants in cohort B**
**were able to stand supporting their weight (as assessed by HINE-2)**

**59%**
**(10/17 infants in cohort B)**
**had a CHOP-INTEND score ≥40**

- 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]
- Reduced survival is often coupled with severe respiratory symptoms and swallowing difficulties that greatly impact patient and caregiver quality of life[2]
- Risdiplam (RG7916; RO7034067) is an oral (liquid formulation) *SMN2* splicing modifier that increases levels of SMN protein throughout the body[3]
- We present data on survival, ventilation and swallowing ability in infants who have received treatment with risdiplam for 12 months in FIREFISH Part 1

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; SMA, spinal muscular atrophy; SMN, survival motor neuron.

1. Mercuri E, et al. Lancet Neurol. 2012; 11:443–52; 2. Cruz R, et al. CureSMA Voice of the Patient Report 2018; 3. Ratni H, et al. J Med Chem. 2018; 61:6501–6517.

# Type 1 SMA: Natural history data

- Based on a prospective cohort study (N = 34) characterizing clinical features of Type 1 SMA over 36 months:

Median (IQR) age for **initiation of nutritional support**:*

8.0 (6–13) months

Median (IQR) age for **initiation of ventilation support:**†

11.0 (5–19) months

Median (IQR) age to **death or permanent ventilation:**‡

13.5 (8.1–22.0) months

*Defined as nasogastric tube or gastrostomy tube. †Defined as non-invasive ventilation or intubation leading to tracheostomy. ‡Event free is defined as alive and no need for permanent ventilation (defined as ≥16 hours per day continuously for ≥2 weeks).
IQR, interquartile range; SMA, spinal muscular atrophy.
Finkel R, et al. Neurology. 2014; 83:810–817.

# FIREFISH Part 1: Patient baseline characteristics

| | Cohort A (N = 4)<br>Low dose cohort | Cohort B (N = 17)<br>High dose cohort* | All infants (N = 21) |
|---|---|---|---|
| Female, n (%) | 4 (100) | 11 (65) | 15 (71) |
| Age at onset of symptoms (months) | | | |
| Median (range) | 2.7 (2.0–3.0) | 1.5 (0.9–3.0) | 2.0 (0.9–3.0) |
| Age at diagnosis (months) | | | |
| Median (range) | 3.3 (2.5–5.1) | 3.0 (0.9–5.4) | 3.0 (0.9–5.4) |
| Age at enrollment (months) | | | |
| Median (range) | 6.9 (6.7–6.9) | 6.3 (3.3–6.9) | 6.7 (3.3–6.9) |
| Weight at baseline (kg) | | | |
| Median (range) | 6.6 (5.7–7.6) | 6.7 (5.2–8.9) | 6.7 (5.2–8.9) |

*Dose adjusted per protocol. Part 1 included multiple doses. The three surviving infants from cohort A were dose adjusted per protocol at ages 24.4, 20.6, and 20.8 months, respectively for each patient.
Data cut-off: 27 February 2019.
kg, kilograms.

# FIREFISH Part 1: Summary of bulbar function results for patients receiving risdiplam for 12 months

**No infant has lost the ability to swallow***

**18/19 (94.7%) infants are able to feed orally or in combination with a feeding tube†**

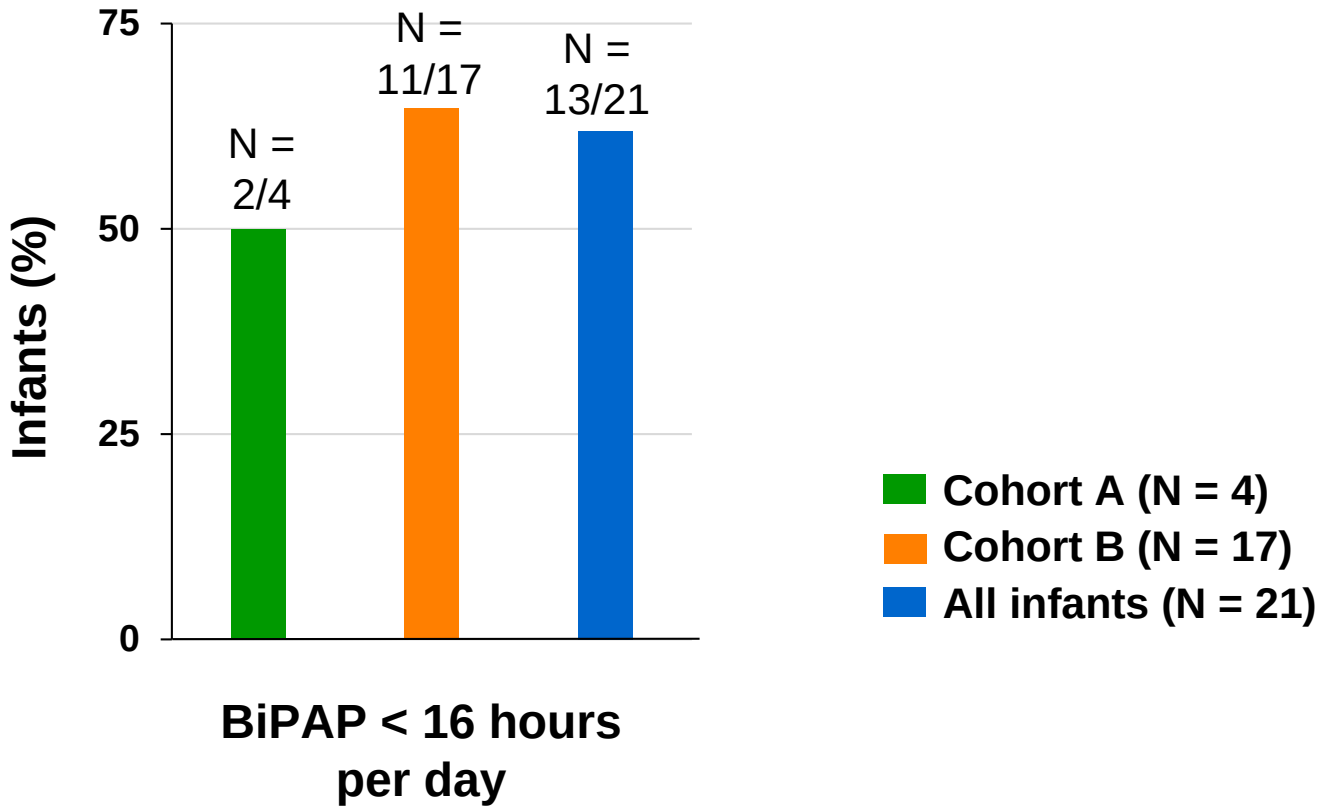
**16/19 (84.2%) infants did not experience coughing or choking during or after eating/drinking**

**15/19 (78.9%) infants are able to feed exclusively by mouth**

*1 patient was unable to swallow at baseline. †1/19 (5.3%) infants alive at Month 12 fed exclusively via a feeding tube.
Data cut-off: 27 February 2019.

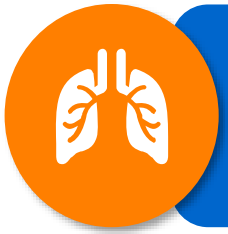
# FIREFISH Part 1: Following 12 months of risdiplam treatment, no infant required BiPAP support for ≥16 hours per day

**Level of respiratory support needed for patients receiving risdiplam at Month 12**




Cohort A: Low dose cohort. Cohort B: High dose cohort. Dose adjusted per protocol.
Data cut-off: 27 February 2019.
BiPAP, Bilevel Positive Airway Pressure.

# FIREFISH Part 1: Summary of respiratory results for patients receiving risdiplam for 12 months



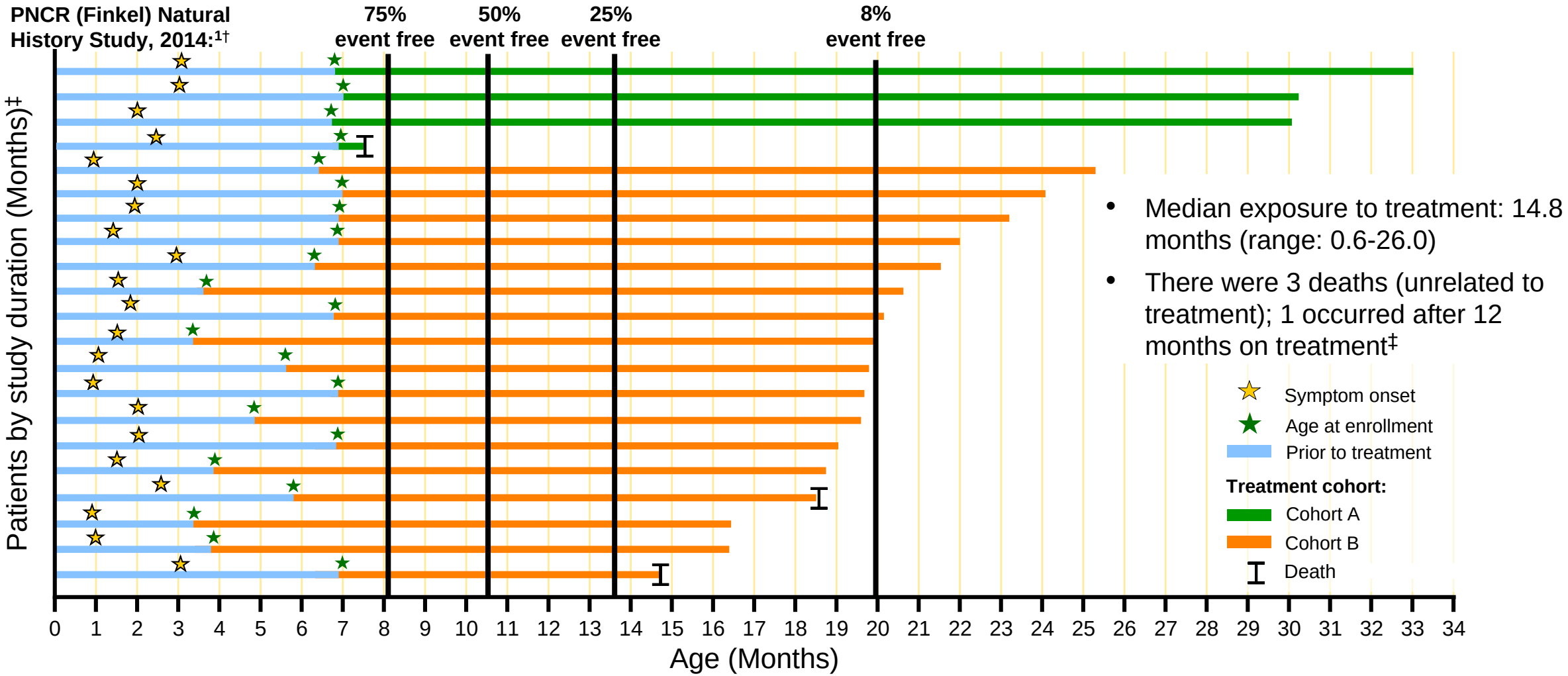
**No infant requiring permanent ventilation**

**No infant requiring BiPAP support ≥16 hours per day**

**No infant receiving awake-assisted ventilation**

Data cut-off: 27 February 2019.
BiPAP, Bilevel Positive Airway Pressure.

# FIREFISH Part 1: 19/21 (90.5%) of infants were event free* after receiving risdiplam for 12 months

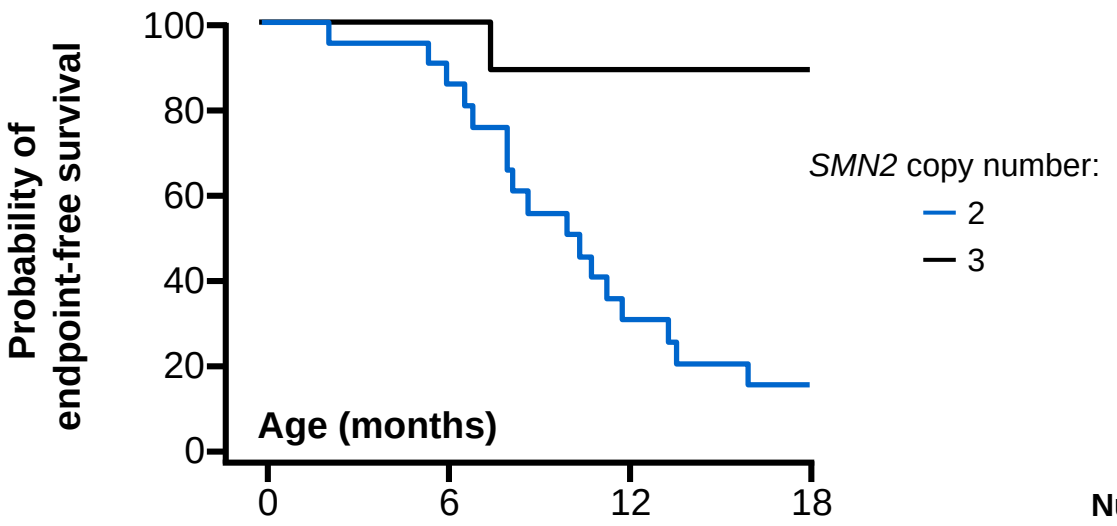



- Median exposure to treatment: 14.8 months (range: 0.6-26.0)
- There were 3 deaths (unrelated to treatment); 1 occurred after 12 months on treatment‡

Cohort A: Low dose cohort. Cohort B: High dose cohort. Dose adjusted per protocol. *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). †The median age at the combined endpoint for subjects with two *SMN2* copies was 10.5 months (IQR 8.1–13.6); event free is defined as alive and no need for permanent ventilation (defined as ≥16 hours per day continuously for ≥2 weeks). ‡Study duration is measured from the date of enrollment to the date of data cut-off. ‖Fatal events were reported in three infants: (1) Viral respiratory tract infection in female infant aged 7 months at enrollment. First symptoms started on Day 5 with fatal outcome on study Day 21. The event was complicated by bilateral atelectasis. (2) Fatal cardiac arrest and respiratory failure on study Day 236 in female infant aged 7 months at enrollment on concurrent night ventilation (BiPAP for less than 16 hours per day) in the context of suspected aspiration; (3) Respiratory tract infection with onset on study Day 386 in female infant aged 5 months and 3 weeks at enrollment. In the absence of fever and due to moderate symptomatology (nasal congestion and labored breathing) which seemed to improve the infant was not hospitalized and died 1 day after onset of respiratory tract infection. The third death occurred before the data cut-off, but after the Month 12 visit. Data cut-off: 27 February 2019. BiPAP, Bilevel Positive Airway Pressure; SMN, survival motor neuron. 1. Finkel R, et al. Neurology. 2014; 83:810–817.

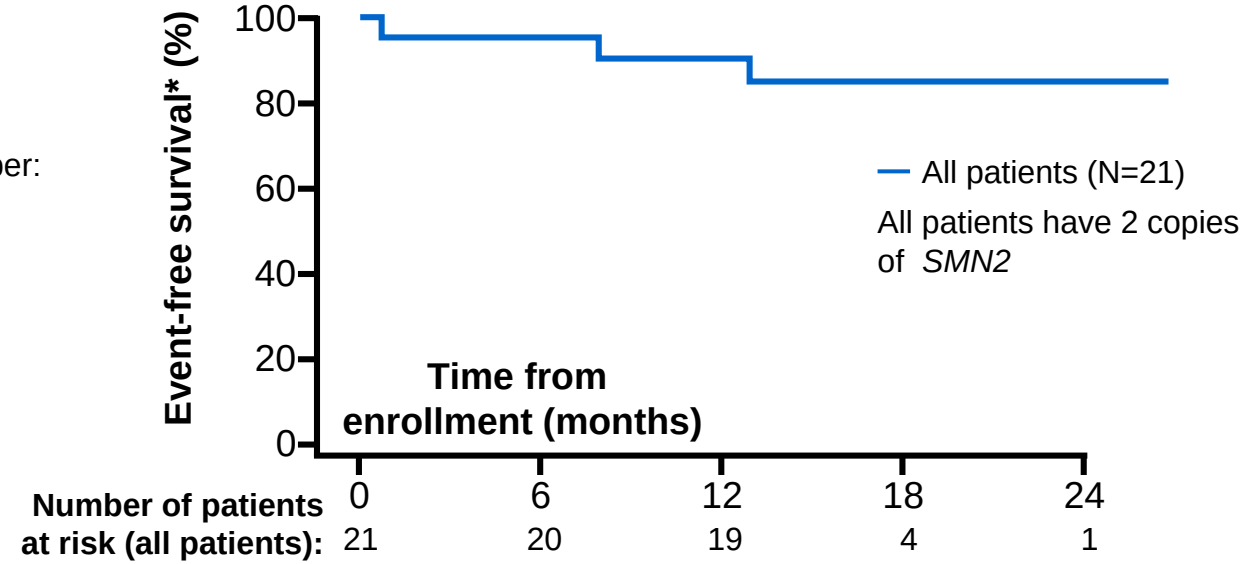
# FIREFISH Part 1: 19/21 (90.5%) of infants were event free* after receiving risdiplam for 12 months

**Natural history data for Type 1 SMA[1]**




- In natural history, median age for reaching death or permanent ventilation was 13.5 months[1]

**Data from FIREFISH Part 1**




- Deaths in the FIREFISH study were due to respiratory complications, which are commonly associated with Type 1 SMA disease
- There were 3 deaths (unrelated to treatment); 1 occurred after 12 months on treatment‡

*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). †Event free is defined as alive and no need for permanent ventilation (defined as ≥16 hours per day continuously for ≥2 weeks). ‡Fatal events were reported in three patients: (1) Viral respiratory tract infection in female infant aged 7 months at enrollment. First symptoms started on Day 5 with fatal outcome on study Day 21. The event was complicated by bilateral atelectasis. (2) Fatal cardiac arrest and respiratory failure on study Day 236 in female infant aged 7 months at enrollment on concurrent night ventilation (BiPAP for less than 16 hours per day) in the context of suspected aspiration; (3) Respiratory tract infection with onset on study Day 386 in female infant aged 5 months and 3 weeks at enrollment. In the absence of fever and due to moderate symptomatology (nasal congestion and labored breathing) which seemed to improve the patient was not hospitalized and died 1 day after onset of respiratory tract infection. The third death occurred before the data cut-off, but after the Month 12 visit. Data cut-off: 27 February 2019. BiPAP, Bilevel Positive Airway Pressure; SMA, spinal muscular atrophy.

1. Finkel R, et al. Neurology. 2014; 83:810–8.

# FIREFISH Part 1: No infants have left the study due to drug-related adverse events

| | | Infants (N = 21) |
|---|---|---|
| Total number of AEs, N | | 202 |
| Infants with at least one AE, N (%) | | 21 (100) |
| Most frequent AEs,* number of infants (%) | Pyrexia | 11 (52) |
| | Upper respiratory tract infection | 9 (43) |
| | Diarrhea | 6 (29) |
| | Cough | 5 (24) |
| | Vomiting | 5 (24) |
| | Constipation | 4 (19) |
| | Pneumonia | 4 (19) |
| | Ear infection | 3 (14) |
| | Eczema | 3 (14) |
| | Erythema | 3 (14) |
| | Nasopharyngitis | 3 (14) |
| | Respiratory tract infection | 3 (14) |
| | Rhinitis | 3 (14) |
| | Teething | 3 (14) |
| | Upper respiratory tract inflammation | 3 (14) |
| Infants with at least one serious AE, N (%) | | 10 (48) |
| Infants with at least one Grade 3–5 AE, N (%) | | 9 (43) |
| Discontinuations due to drug-related AEs, N | | 0 |

*Investigator text for AEs encoded using MedDRA version 21.1. Percentages based on N in column heading. Data cut-off: 27 February 2019.
AE, adverse event; MeDRA, Medical Dictionary for Regulatory Activities.

# FIREFISH Part 1: Safety summary

- In FIREFISH, as of February 2019, there have been no drug-related safety findings leading to withdrawal in any infants exposed to risdiplam
- Adverse events were reflective of the underlying disease:
  - All infants experienced at least 1 AE
    - Most frequent AEs were: pyrexia, upper respiratory tract infection, diarrhea, cough, vomiting, constipation, pneumonia, ear infection, eczema, erythema, nasopharyngitis, respiratory tract infection, rhinitis, teething, upper respiratory tract inflammation
  - 10 infants (47.6%) had at least one SAE
    - The most common SAE was pneumonia, reported in 3 patients (14.3%)
  - Three infants experienced fatal respiratory complications, characteristic of Type 1 SMA*
- There have been no drug-related ophthalmological findings to date

Data cut-off: 27 February 2019.
*Fatal events were reported in three infants: (1) Viral respiratory tract infection in female infant aged 7 months at enrollment. First symptoms started on Day 5 with fatal outcome on study Day 21. The event was complicated by bilateral atelectasis. (2) Fatal cardiac arrest and respiratory failure on study Day 236 in female infant aged 7 months at enrollment on concurrent night ventilation (BIPAP for less than 16 hours per day) in the context of suspected aspiration; (3) Respiratory tract infection with onset on study Day 386 in female infant aged 5 months and 3 weeks at enrollment. In the absence of fever and due to moderate symptomatology (nasal congestion and labored breathing) which seemed to improve the infant was not hospitalized and died 1 day after onset of respiratory tract infection. The third death occurred before the data cut-off, but after the Month 12 visit.
AE, adverse event; BiPAP, Bilevel Positive Airway Pressure; SAE, serious adverse event; SMA, spinal muscular atrophy.

# FIREFISH Part 1: 1 year results summary

## All infants

**90.5%**
**(19/21)**
of infants are alive and event free* after 12 months of treatment

**0**
infants lost the ability to swallow†

**0**
infants reached permanent ventilation/required tracheostomy

No drug-related safety findings leading to withdrawal to date

## Infants in cohort B

**41%**
**(7/17)**
were able to sit without support for at least 5 seconds (as assessed by BSID-III)

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**infants**
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# Acknowledgments

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