FIREFISH Part 1: 1-year results on motor function in infants with Type 1 SMA receiving risdiplam (RG7916)

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**Current affiliation is Therachon AG; †Current affiliation is Voyager Therapeutics*

Disclosures

- GB was 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, Cytoknetics, 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

- Type 1 SMA is a severe neuromuscular disease, with untreated infants typically dying before 2 years of age[1]
- Reduced survival is coupled with infants failing to achieve major motor milestones[2]
- Risdiplam is an oral (liquid formulation) *SMN2* splicing modifier designed to increase levels of SMN protein throughout the body[2]
- We present motor milestone data (BSID-III, CHOP-INTEND and HINE-2) in infants who have received 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 of motor neuron.

1. Mercuri E, et al. Lancet Neurol. 2012; 11:443–452; 2. Ratni H, et al. J Med Chem. 2018; 61:6501–6517.

FIREFISH: Study overview

- FIREFISH is an ongoing, multicenter, open-label pivotal study
  - Part 1: Dose-finding period followed by open-label extension
    - Cohort A: Low dose cohort (N = 4)
    - Cohort B: High dose cohort* (N = 17)
  - Part 2: Efficacy and safety at the dose selected in Part 1
    - Open-label risdiplam treatment for 24 months

FIREFISH Type 1 SMA 1–7 months old Two *SMN2* gene copies		**Part 1 (N=21)†**	**Part 2 (N=41)†**
	Primary endpoint	• Safety, tolerability, PK and PD of risdiplam • Dose selection for Part 2	Proportion of infants sitting without support for 5 seconds after 12 months on treatment as assessed by Gross Motor Scale of the BSID-III
	Secondary endpoints		Motor function (HINE-2, CHOP-INTEND), PD/PK, safety, time to death or permanent ventilation, RP

- 19 infants received treatment with risdiplam (RG7916) for at least 12 months in FIREFISH Part 1 as of data cut-off 27 February 2019

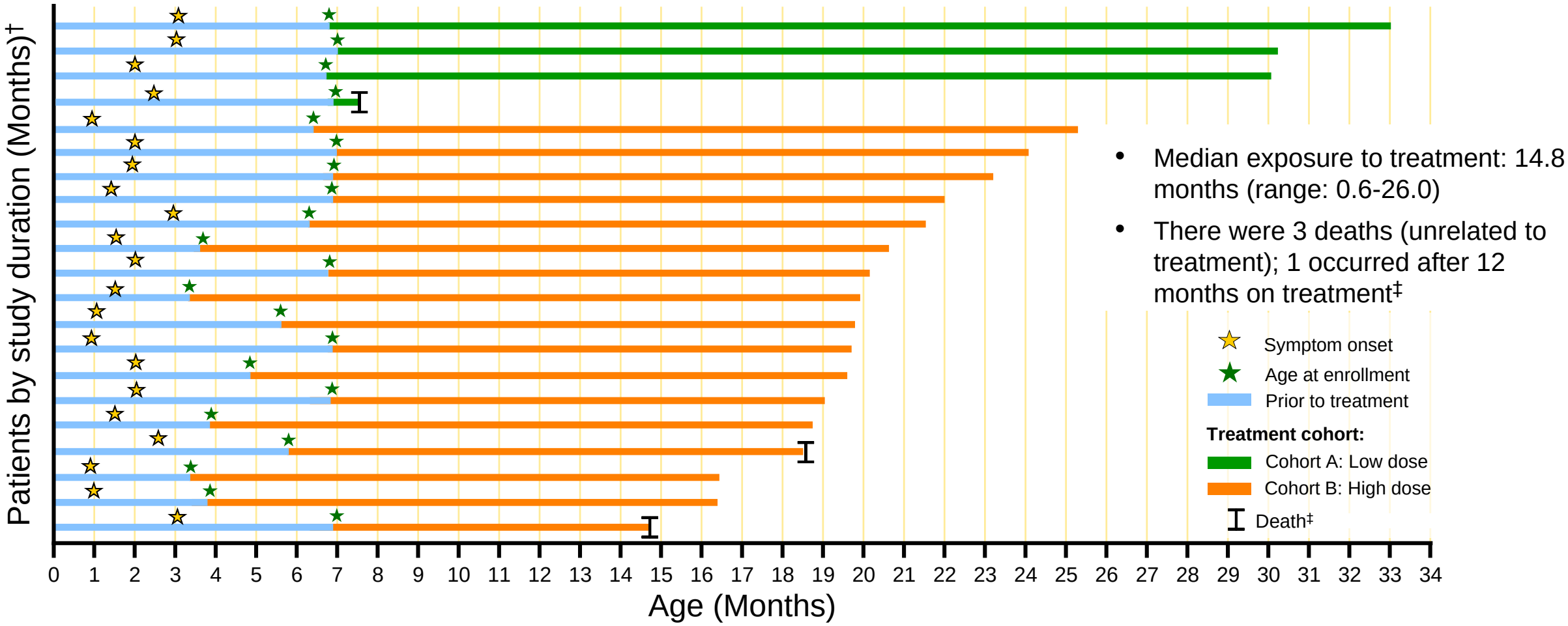
*Dose adjusted per protocol. Part 1 included multiple doses. †Actual number of infants enrolled
BSID-III, Bayley Scales of Infant and Toddler development Third Edition; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination Module 2; PD, pharmacodynamics; PK, pharmacokinetics; RP, respiratory plethysmography; SMA, spinal muscular atrophy.
Clinicaltrials.gov/ct2/show/NCT02913482 (Accessed April 2019).

FIREFISH Part 1: Patient baseline characteristics

	Cohort A (N = 4) Low-dose cohort	Cohort B (N = 17) 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)
CHOP-INTEND score			
Median (range)	23.5 (10.0–25.0)	24.0 (16.0–34.0)	24.0 (10.0–34.0)
HINE-2 score			
Median (range)	1.0 (0.0–3.0)	1.0 (0.0–2.0)	1.0 (0.0–3.0)
BSID-III: Infants sitting without support for 5 seconds			
n	0	0	0

*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.
BSID-III, Bayley Scales of Infant and Toddler Development Third Edition; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE, Hammersmith Infant Neurological Examination.

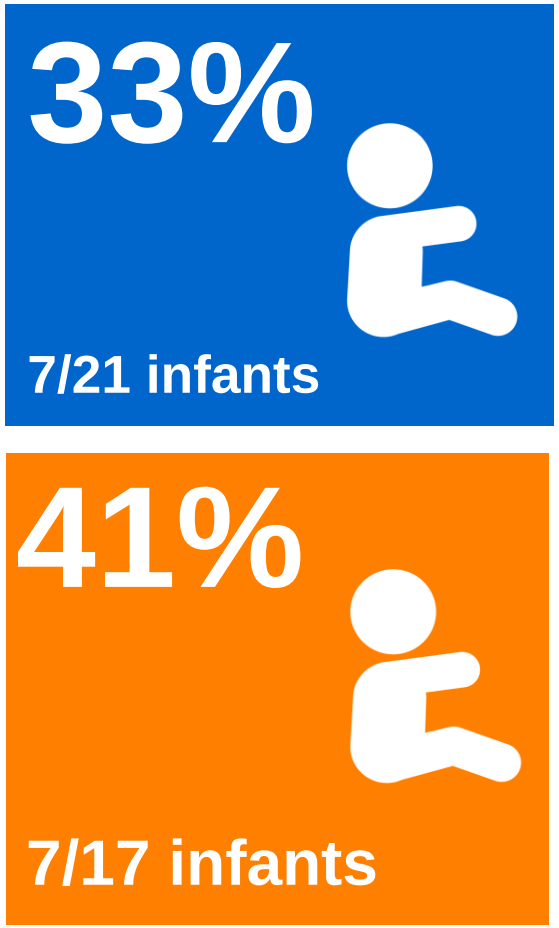
FIREFISH Part 1: 19/21 (90.5%) of infants were event free* after receiving risdiplam for 12 months



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). †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.

Motor milestones achieved in infants treated with risdiplam for 12 months, as assessed by BSID-III

Sitting without support for at least 5 seconds*



Treatment cohort

- All infants
- Cohort B

*Item 22 of the BSID-III gross motor scale.
Data cut-off: 27 February 2019.
BSID-III, Bayley Scales of Infant and Toddler Development Third Edition.

CHOP-INTEND scores: At Month 12, 86% of all infants showed a ≥4-point improvement in CHOP-INTEND score from baseline

75%

of infants in cohort A had a ≥4-point improvement in CHOP-INTEND score from baseline (N = 4)

88%

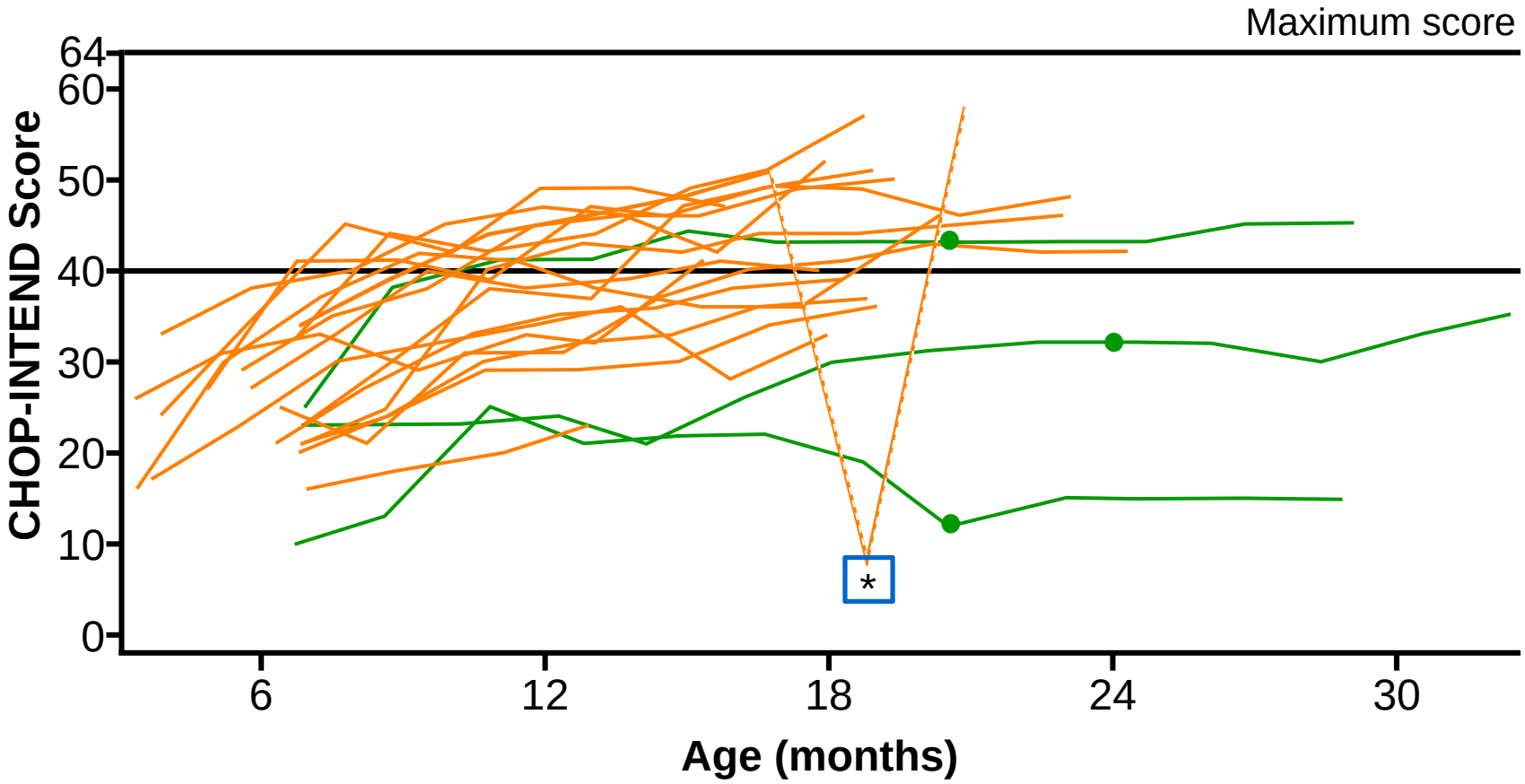
of infants in cohort B had a ≥4-point improvement in CHOP-INTEND score from baseline (N = 17)

86%

of All infants had a ≥4-point improvement in CHOP-INTEND score from baseline (N = 21)

12 months is the latest time point at which the majority of infants have follow-up data available. Cohort A: Low dose cohort. Cohort B: High dose cohort. Dose adjusted per protocol.
Cohort B includes data from one infant who did not cooperate at the 12 Month visit. Data cut-off: 27 February 2019.
CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders.

CHOP-INTEND Score: Improvement in CHOP-INTEND was seen over time with risdiplam treatment



Median change from baseline in CHOP-INTEND score at Month 12		
Cohort A (N = 3)	Cohort B (N = 16)	All infants (N = 19)
9	17.5	17

59% of Cohort B (high dose) had a CHOP-INTEND score ≥40

Treatment cohort

- Cohort A: Low dose
- Cohort B: High dose

*Denotes an infant who was uncooperative at CHOP-INTEND assessment

● Denotes when infants from cohort A dose adjusted per protocol

Cohort A: Low dose cohort. Cohort B: High dose cohort. Dose adjusted per protocol.
Each line represents an individual infant. Intent-to-treat infants from FIREFISH Part 1 (N=21).
Data cut-off: 27 February 2019.
CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders.

Improved motor function and milestones achieved in infants treated with risdiplam for 12 months, as assessed by HINE-2

Motor milestones		HINE-2 scores			
		Unable to maintain upright	Wobbles	Maintain upright	
Head control	Baseline (n=21)	3 green, 14 orange	1 green, 2 orange		
	Month 8 (n=19)				
	Month 12 (n=19)				
		No rolling	Roll to side	Prone to supine	Supine to prone
Rolling	Baseline (n=21)	4 green, 15 orange			
	Month 8 (n=19)				
	Month 12 (n=19)				
		Cannot sit	Sits with support at hips	Props	Stable sit
Sitting	Baseline (n=21)	4 green, 15 orange			
	Month 8 (n=19)				
	Month 12 (n=19)*				
		Does not support weight	Supports weight	Stands with support	Stands unaided
Standing	Baseline (n=21)	4 green, 15 orange			
	Month 8 (n=19)†				
	Month 12 (n=19)				

● Cohort A: Low dose

● Cohort B: High dose

*One infant from cohort A was not tested for sitting at Month 12. †One infant from cohort B was not tested for standing at Month 8. Each circle represents an individual infant. Cohort A: Low dose cohort. Cohort B: High dose cohort. Dose adjusted per protocol. Intent-to-treat infants from FIREFISH Part 1 (N=21); 'cannot test' results are not included. Data cut-off: 27 February 2019.
HINE-2, Hammersmith Infant Neurological Examination Module 2.

Improved motor function and milestones achieved in infants treated with risdiplam for 12 months, as assessed by HINE-2

Motor milestones		HINE-2 scores			
		Unable to maintain upright	Wobbles	Maintain upright	
Head control	Baseline (n=21)	●●● ●●●●●●●●●●●●●●	● ●●		
	Month 8 (n=19)	● ●●●●●	●● ●●●●	●●●●●●●	
	Month 12 (n=19)				
		No rolling	Roll to side	Prone to supine	Supine to prone
Rolling	Baseline (n=21)	●●●● ●●●●●●●●●●●●●●●			
	Month 8 (n=19)	●●● ●●●●●●●●	●●●●●●	●	
	Month 12 (n=19)				
		Cannot sit	Sits with support at hips	Props	Stable sit
Sitting	Baseline (n=21)	●●●● ●●●●●●●●●●●●●●●			
	Month 8 (n=19)	●●● ●●●●●●●	●●●	●●	●●●
	Month 12 (n=19)*				
		Does not support weight	Supports weight	Stands with support	Stands unaided
Standing	Baseline (n=21)	●●●● ●●●●●●●●●●●●●●●			
	Month 8 (n=19)†	●●● ●●●●●●●●●●●●	●		
	Month 12 (n=19)				

● Cohort A: Low dose

● Cohort B: High dose

*One infant from cohort A was not tested for sitting at Month 12. †One infant from cohort B was not tested for standing at Month 8. Each circle represents an individual infant. Cohort A: Low dose cohort. Cohort B: High dose cohort. Dose adjusted per protocol. Intent-to-treat infants from FIREFISH Part 1 (N=21); 'cannot test' results are not included. Data cut-off: 27 February 2019.
HINE-2, Hammersmith Infant Neurological Examination Module 2.

Improved motor function and milestones achieved in infants treated with risdiplam for 12 months, as assessed by HINE-2

Motor milestones		HINE-2 scores			
		Unable to maintain upright	Wobbles	Maintain upright	
Head control	Baseline (n=21)	●●● ●●●●●●●●●●●●●●	● ●●		
	Month 8 (n=19)	● ●●●●●	●● ●●●●	●●●●●●●	
	Month 12 (n=19)	● ●●●	●● ●●●●	●●●●●●●●●	
		No rolling	Roll to side	Prone to supine	Supine to prone
Rolling	Baseline (n=21)	●●●● ●●●●●●●●●●●●●●●			
	Month 8 (n=19)	●●● ●●●●●●●●	●●●●●●	●	
	Month 12 (n=19)	●●● ●●●●●●	●●●●●	●●●	●●
		Cannot sit	Sits with support at hips	Props	Stable sit
Sitting	Baseline (n=21)	●●●● ●●●●●●●●●●●●●●●			
	Month 8 (n=19)	●●● ●●●●●●●	●●●	●●	●●●
	Month 12 (n=19)*	● ●●●●●	● ●●	●●●	●●●●●●
		Does not support weight	Supports weight	Stands with support	Stands unaided
Standing	Baseline (n=21)	●●●● ●●●●●●●●●●●●●●●			
	Month 8 (n=19)†	●●● ●●●●●●●●●●●●	●		
	Month 12 (n=19)	●●● ●●●●●●●●●●●●●	●		

● Cohort A: Low dose

● Cohort B: High dose

*One infant from cohort A was not tested for sitting at Month 12. †One infant from cohort B was not tested for standing at Month 8. Each circle represents an individual infant. Cohort A: Low dose cohort. Cohort B: High dose cohort. Dose adjusted per protocol. Intent-to-treat infants from FIREFISH Part 1 (N=21); 'cannot test' results are not included. Data cut-off: 27 February 2019.
HINE-2, Hammersmith Infant Neurological Examination Module 2.

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

Infants in cohort B

41%

(7/17)

were able to sit without support for at least 5 seconds (as assessed by BSID-III)

1/17

infants

was able to stand supporting their weight (as assessed by HINE-2)

59%

(10/17 infants)

had a CHOP-INTEND score ≥40

All infants

90.5%

(19/21)

of infants are alive and event free* after 12 months of treatment

No drug-related safety findings leading to withdrawal to date

*Event free 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). †1 infant was unable to swallow at baseline. Cohort A: Low dose cohort. Cohort B: High dose cohort. Dose adjusted per protocol. Data cut-off: 27 February 2019.
BSID-III, Bayley Scales of Infant and Toddler Development Third Edition, Third Edition; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination, Module 2.

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