SUPPLEMENTARY MATERIAL

Long-Term Comparative Efficacy and Safety of Risdiplam and Nusinersen in Type 1 Spinal Muscular Atrophy

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Table S1 Clinical trials in Type 1 SMA identified in the updated SLR

Study identifier	SMA type	Intervention	Study design	Complete/ongoing (actual/estimated completion date)
Type 1 SMA				
FIH study (NCT02268552) [1]	Type 1	Branaplam	SA	Ongoing (Mar 2, 2023)
STR1VE-AP (NCT03837184) [2]	Type 1	Onasemnogene abeparvovec	SA	Ongoing (Jun 29, 2021)
STR1VE-EU (NCT03461289) [3]	Type 1	Onasemnogene abeparvovec	SA	Complete (Sep 11, 2020)
STR1VE-US (NCT03306277) [4]	Type 1	Onasemnogene abeparvovec	SA	Complete (Nov 12, 2019)
CS3A (NCT01839656) [5]	Type 1	Nusinersen	DC/DE	Complete (Aug 21, 2017)
START (NCT02122952) [6] Mendell et al. 2017 [7]	Type 1	Onasemnogene abeparvovec	DC/DE	Complete (Dec 15, 2017)
FIREFISH (NCT02913482) [8]	Type 1	Risdiplam	DC/DE (Part 1) SA (Part 2)	Ongoing (Nov 17, 2023)
ENDEAR (NCT02193074) [9]	Type 1	Nusinersen	RCT	Complete[a] (Nov 21, 2016)
Mixed SMA types				
JEWELFISH (NCT03032172) [10]	Type 1/2/3 (non-treatment-naïve patients)	Risdiplam	SA	Ongoing (Dec 27, 2024)
DEVOTE (NCT04089566) [11]	Type 1/2/3	Nusinersen	RCT	Ongoing (Aug 2, 2024)
EMBRACE (NCT02462759) [12]	Type 1/2/3	Nusinersen	RCT	Complete[a] (Sep 24, 2018)
SHINE[b] (NCT02594124) [13]	Type 1/2/3	Nusinersen	SA	Ongoing (Aug 29, 2023)
LTFU study (NCT04042025) [14]	Type 1/2/3	Onasemnogene abeparvovec	SA	Ongoing

				(December 29, 2035)

The SLR identified a total of eight clinical trials reporting data from a population of patients with Type 1 SMA, and five clinical trials reporting data from a population of patients with mixed SMA types, which included patients with Type 1 SMA

One study investigated branaplam, which is an unapproved treatment for SMA and not of interest in this study. Four SA trials were identified for onasemnogene abeparvovec: three in a Type 1 SMA population (STR1VE-AP, STR1VE-EU, STR1VE-US) and one in a mixed SMA-type population (LTFU study). Based on the results of a previous ITC [15], these studies were insufficient to control for differences in study characteristics, and thus an ITC against onasemnogene abeparvovec at 36 months was not considered feasible

One identified DC/DE trial of nusinersen was excluded from further consideration as RCT/SA data were available for nusinersen. Two RCTs of nusinersen in a mixed SMA-type population were excluded: DEVOTE, which was not considered feasible as it investigated an unapproved dose of nusinersen, and EMBRACE, which was a randomized trial with a small sample size (*n* = 21). EMBRACE did not report data on HINE-2 or CHOP-INTEND and so comparison with these studies was not feasible due to differences in outcome assessments

For risdiplam, JEWELFISH was excluded from inclusion in the analyses as it investigates risdiplam in patients who have already received a previous treatment for SMA, which includes nusinersen and onasemnogene abeparvovec

CHOP-INTEND Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, *DC* dose comparison, *DE* dose escalation, *FIH* first-in-human, *HINE-2* Hammersmith Infant Neurological Examination, Module 2, *ITC* indirect treatment comparison, *LTFU* long-term follow-up, *RCT* randomized controlled trial, *SA* single-arm, *SMA* spinal muscular atrophy

[a]The study was terminated early to roll over participants to SHINE (NCT02594124)

[b]SHINE was an open-label extension study that enrolled patients from ENDEAR (and from CS3A [NCT01839656], CS12 [NCT02052791], CHERISH [NCT02292537], and EMBRACE [NCT02462759])

Table S2 Definition of endpoints in FIREFISH and SHINE-ENDEAR

Endpoint	FIREFISH definition	SHINE-ENDEAR definition
Overall survival	• Time to death	• Time to death • Kaplan–Meier plot reporting up to day 1,800
Event-free survival	• Time to death or permanent ventilation, where permanent ventilation was defined as ≥16 hours of non-invasive ventilation/day or intubation for >21 consecutive days in the absence of, or following the resolution of, an acute reversible death or tracheostomy	• Time to death or permanent ventilation, where permanent ventilation was defined as either tracheostomy or ≥16 hours of ventilation/day continuously for >21 days • Kaplan–Meier plot reporting up to day 1,800

Time to achievement of a HINE-2 response	• A response was defined as a ≥2-point increase in the ability to kick (or maximal score) or a 1-point increase in head control, rolling, sitting, crawling, standing, or walking • Worsening was defined as a ≥2-point decrease in the ability to kick (or lowest score) or a 1-point decrease in head control, rolling, sitting, crawling, standing, or walking • Children are classified as a responder if more motor milestones showed improvement than showed worsening; children who died or withdrew were classified as non-responders • Patients are censored at the latest recorded visit • Deaths are censored (recorded as 0, rather than as an event)	• (i) subject demonstrates ≥2-point increase in the motor milestone category of ability to kick or achievement of maximal score in that category (touching toes), or a 1-point increase in the motor milestone category of head control, rolling, sitting, crawling, standing, or walking, and (ii) among the motor milestone categories, with the exclusion of voluntary grasp, there are more categories where there is improvement as defined in (i) than worsening (for the ability to kick category, worsening is defined as a ≥2-point decrease or decrease to the lowest possible score of no kicking. For the other categories, worsening is defined as a ≥1-point decrease.) • Cumulative density plot reporting up to ~day 990

Time to achievement of a CHOP-INTEND response	• A response was defined as a ≥4-point improvement from baseline in CHOP-INTEND score • Patients are censored at the latest recorded visit • Deaths are censored (recorded as 0, rather than as an event)	• A participant was considered a CHOP-INTEND responder if the change from baseline in CHOP-INTEND score was ≥4 points • Cumulative density plot reporting up to day 1650
Time to first SAE[a]	• Time to first SAE • Patients are censored at earliest date from: CCOD, death date, study withdrawal date, and last treatment dose + 30 days	• Time to first SAE • Kaplan–Meier plot reporting up to day 1500

CCOD clinical cut-off date, *CHOP-INTEND* Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, *HINE-2* Hammersmith Infant Neurological Examination, Module 2, *SAE* serious adverse event

[a]An SAE is defined as any adverse event that is fatal (i.e., actually causes or leads to death); life-threatening (i.e., in the view of the Investigator, places the patient at immediate risk of death); requires or prolongs inpatient hospitalization; results in persistent or significant disability/incapacity (i.e., results in substantial disruption of the patient's ability to conduct normal life functions); or is a significant medical event in the Investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

Table S3 Summary of key eligibility criteria and study design of FIREFISH and SHINE-ENDEAR

	Risdiplam (FIREFISH)	**Nusinersen (SHINE-ENDEAR)**
Study design	• Phase 2/3 • Open label • Multicenter, single-arm, two cohorts: – Part 1: dose finding, – Part 2: dose confirming	• ENDEAR: A randomized, double-blind, multicenter, Phase 3, sham procedure-controlled study • SHINE: An open-label extension study that enrolled patients from ENDEAR (and from CS3A [NCT01839656], CS12 [NCT02052791], CHERISH [NCT02292537], and EMBRACE [NCT02462759])
Inclusion criteria	• Diagnosis of 5q-SMA: – Clinical history, signs, or symptoms attributable to Type 1 SMA (i.e., hypotonia) – Genetic confirmation of homozygous deletion or compound heterozygosity predictive of loss of function of the *SMN1* gene – Two *SMN2* gene copies • Gestational age of 37–42 weeks • Onset of SMA after 28 days but prior to 3 months • Aged between 28 days and 210 days at enrollment • Measuring to at least the 3rd percentile in body weight using the appropriate country-specific guidelines Receiving adequate nutrition and hydration support (with or without gastrostomy)	According to ENDEAR: • Symptomatic children with Type 1 SMA • Two copies of the *SMN2* gene • Gestational age of 37–42 weeks • Younger than 6 months of age (180 days) at SMA symptom onset • Younger than 7 months of age (210 days) at screening • Body weight equal to or greater than 3rd percentile for age using appropriate country-specific guidelines • Receiving adequate nutrition and hydration (with or without gastrostomy)

Exclusion criteria	• Requiring invasive ventilation or tracheostomy, requiring awake NIV, or with awake hypoxemia (arterial oxygen saturation <95%) with or without ventilator support	• Peripheral oxygen desaturation (O_2 saturation <96% without ventilation support)

NIV non-invasive ventilation, *SMA* spinal muscular atrophy, *SMN* survival of motor neuron

Table S4 Post-matching distributions of re-scaled weights in FIREFISH for both the primary and scenario analyses[a]

	Mean	SD	Median	Min	Max
Primary analysis	1	0.7	0.8	0.2	3.4
Primary analysis + ventilatory support[b]	1	0.7	0.8	0.3	3.3
Primary analysis + nutritional support[b]	1	0.7	0.8	0.3	3.3
Primary analysis + ventilatory & nutritional support[b]	1	0.7	0.8	0.2	3.2
Primary analysis + gender	1	0.7	0.9	0.2	3.2
Primary analysis + HINE-2	1	0.7	0.8	0.2	3.8
Primary analysis + gender & HINE-2	1	0.7	0.8	0.2	3.4

BiPAP Bilevel Positive Airway Pressure, *CHOP-INTEND* Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, *ESS* effective sample size, *GI* gastrointestinal, *HINE-2* Hammersmith Infant Neurological Examination, Module 2, *MAIC* matching-adjusted indirect comparison, *NIV* non-invasive ventilation, *SD* standard deviation

[a]Primary analyses were conducted using MAIC methodology with the following adjustment factors: age at first dose, baseline CHOP-INTEND score and disease duration. In the scenario analyses, additional adjustment factors were included separately for each covariate and in combination, to evaluate the extent to which they affected the matching process individually and to prevent overfitting of the results.

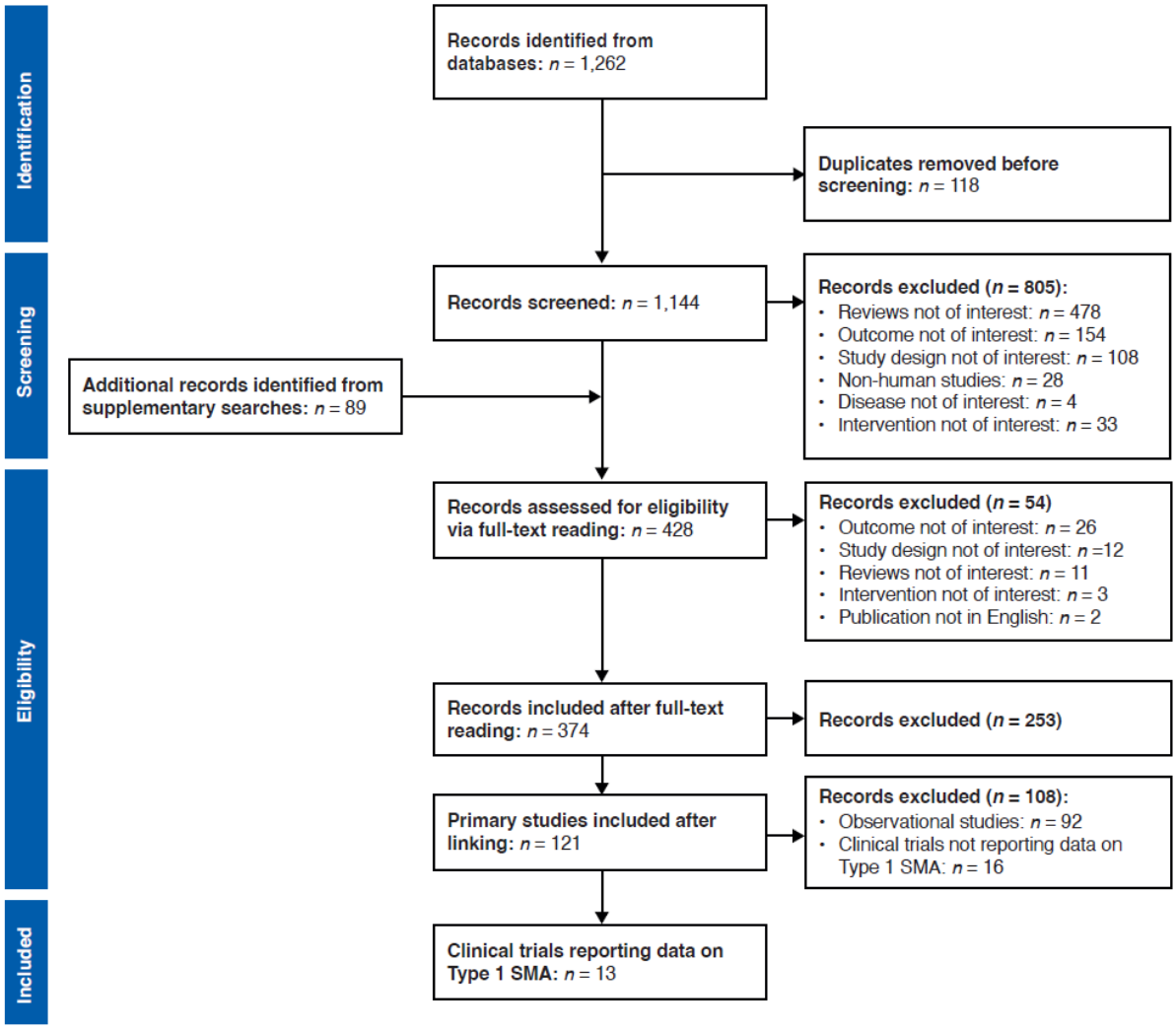
[b]The definition and assessment method for ventilatory and nutritional support were unclear in the SHINE-ENDEAR publications [9, 13, 16, 17] and in the submission dossier to the Federal Joint Committee in Germany [18], and thus it remains unclear whether definitions and assessment methods varied between FIREFISH and SHINE-ENDEAR. After careful consideration, the authors considered that the most likely comparators or proxies of ventilatory and nutritional support were the use of BiPAP (<16h per day) and the use of a GI tube. Therefore, ventilatory and nutritional support may only serve as proxies, and their use

as adjustment factors in our study should be interpreted only as an investigational approach to assess the matching performance of our primary scenario

Table S5 Number of death events, and death or permanent ventilation events, in FIREFISH and SHINE-ENDEAR

Month	Death, *N* (%)			Death or permanent ventilation events, *N* (%)		
	ENDEAR *N* = 81	**FIREFISH *N* = 58**	**FIREFISH re-weighted *N* = 58**	**ENDEAR *N* = 81**	**FIREFISH *N* = 58**	**FIREFISH re-weighted *N* = 58**
0 (baseline)	0	0	0	0	0	0
3	8 (9.9)	3 (5.2)	2 (2.7)	19 (23.5)	4 (6.9)	2 (4.1)
6	11 (13.6)	3 (5.2)	2 (2.7)	24 (29.6)	5 (8.6)	4 (6.6)
9	13 (16.1)	4 (6.9)	2 (3.3)	32 (39.5)	6 (10.3)	4 (7.1)
12	14 (17.3)	4 (6.9)	2 (3.3)	36 (44.4)	7 (12.1)	5 (9.2)
15	15 (18.5)	5 (8.6)	3 (5.3)	37 (45.7)	8 (13.8)	6 (11.2)
18	17 (21.0)	5 (8.6)	3 (5.3)	40 (49.4)	8 (13.8)	6 (11.2)
21	18 (22.2)	5 (8.6)	3 (5.3)	40 (49.4)	9 (15.5)	7 (12.5)
24	18 (22.2)	5 (8.6)	3 (5.3)	40 (49.4)	9 (15.5)	7 (12.5)
27	18 (22.2)	5 (8.6)	3 (5.3)	40 (49.4)	9 (15.5)	7 (12.5)
30	18 (22.2)	5 (8.6)	3 (5.3)	40 (49.4)	9 (15.5)	7 (12.5)
33	18 (22.2)	5 (8.6)	3 (5.3)	40 (49.4)	9 (15.5)	7 (12.5)
36	18 (22.2)	5 (8.6)	3 (5.3)	40 (49.4)	9 (15.5)	7 (12.5)
39	18 (22.2)	5 (8.6)	3 (5.3)	40 (49.4)	10 (17.2)	8 (13.3)
42	18 (22.2)	5 (8.6)	3 (5.3)	40 (49.4)	11 (19.0)	8 (14.0)
45	18 (22.2)	5 (8.6)	3 (5.3)	40 (49.4)	11 (19.0)	8 (14.0)
48	18 (22.2)	5 (8.6)	3 (5.3)	40 (49.4)	11 (19.0)	8 (14.0)
51	18 (22.2)	5 (8.6)	3 (5.3)	40 (49.4)	11 (19.0)	8 (14.0)
54	18 (22.2)	5 (8.6)	3 (5.3)	40 (49.4)	11 (19.0)	8 (14.0)
57	18 (22.2)	5 (8.6)	3 (5.3)	40 (49.4)	11 (19.0)	8 (14.0)
60	18 (22.2)	5 (8.6)	3 (5.3)	40 (49.4)	11 (19.0)	8 (14.0)

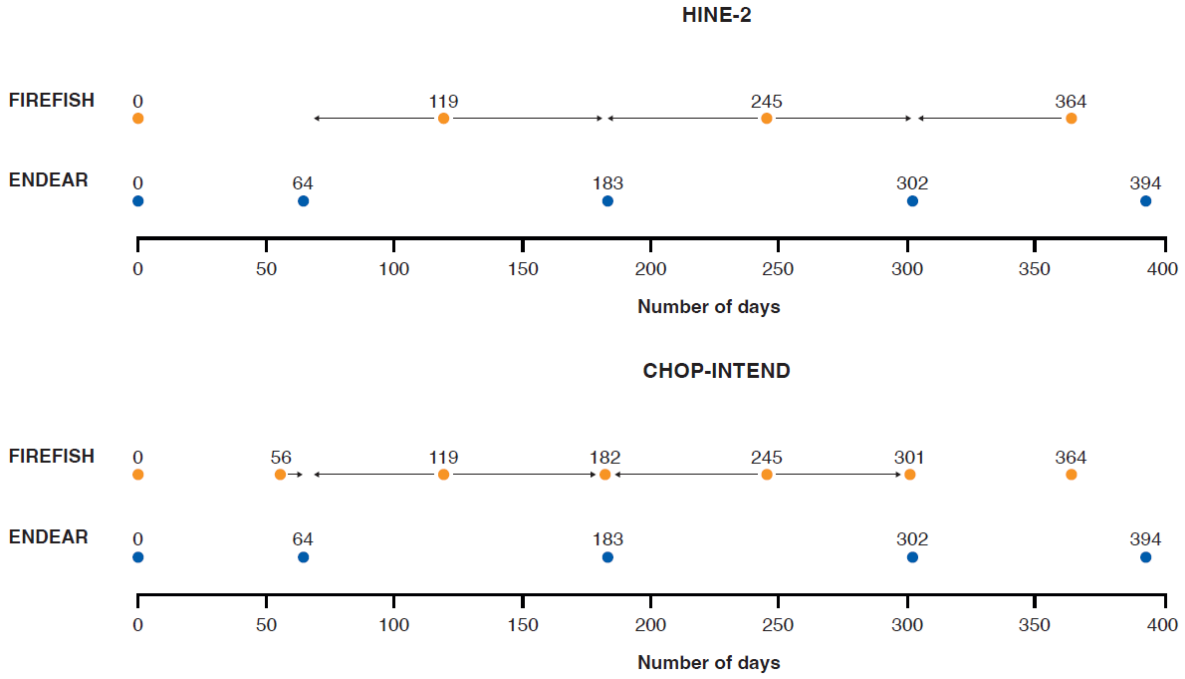
Fig. S1 PRISMA flow diagram



From Page et al., 2020 [19]. For more information, visit: http://www.prisma-statement.org/

PRISMA Preferred Reporting Items for Systematic reviews and Meta-Analyses, *SMA* spinal muscular atrophy

Fig. S2 HINE-2 and CHOP-INTEND assessment schedule for FIREFISH and SHINE-ENDEAR and ASM

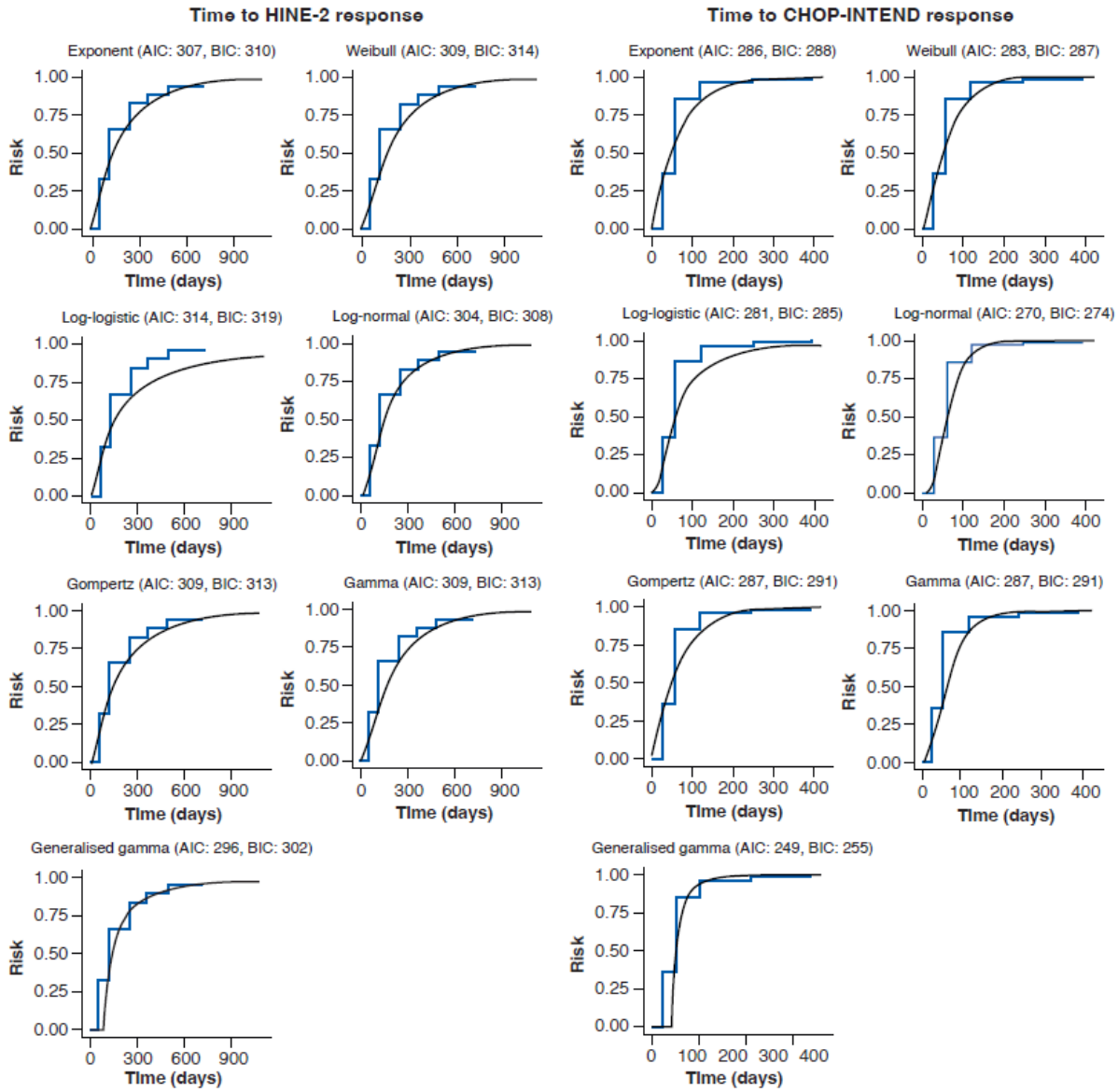


For the HINE-2, all FIREFISH scheduled visits required redistribution of patients. A proportion of patients at visit 1 (day 119) of FIREFISH were shifted back to visit 1 (day 64) of SHINE-ENDEAR, and another proportion of patients were advanced to visit 2 (day 183) of SHINE-ENDEAR. Similarly, patients at visit 2 (day 245) of FIREFISH were redistributed to visits 2 and 3 (days 183 and 302, respectively) of SHINE-ENDEAR. Patients at visit 3 (day 364) of FIREFISH were shifted back to visit 3 (day 302) of SHINE-ENDEAR. The final scheduled visits used corresponded to day 302 of SHINE-ENDEAR

For the CHOP-INTEND, many of the scheduled visits in FIREFISH were close to those of SHINE-ENDEAR (i.e., 56 vs 64, 182 vs 182, and 301 vs 302). Patients at visit 1 (day 56) of FIREFISH were advanced to visit 1 (day 64) of SHINE-ENDEAR. A proportion of patients at visit 1 (day 119) of FIREFISH were shifted back to visit 1 (day 64) of SHINE-ENDEAR, and another proportion of patients were advanced to visit 2 day 183) of SHINE-ENDEAR. Similarly, patients at visit 4 (day 245) of FIREFISH were redistributed to visits 2 and 3 (days 183 and 302, respectively) of SHINE-ENDEAR. The final scheduled visits used were day 301 of FIREFISH, and day 302 of SHINE-ENDEAR

ASM assessment-schedule matching, *CHOP-INTEND* Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, *HINE-2* Hammersmith Infant Neurological Examination, Module 2

Fig. S3 Curve fitting for HINE-2 and CHOP-INTEND responses (MAIC with ASM analyses)

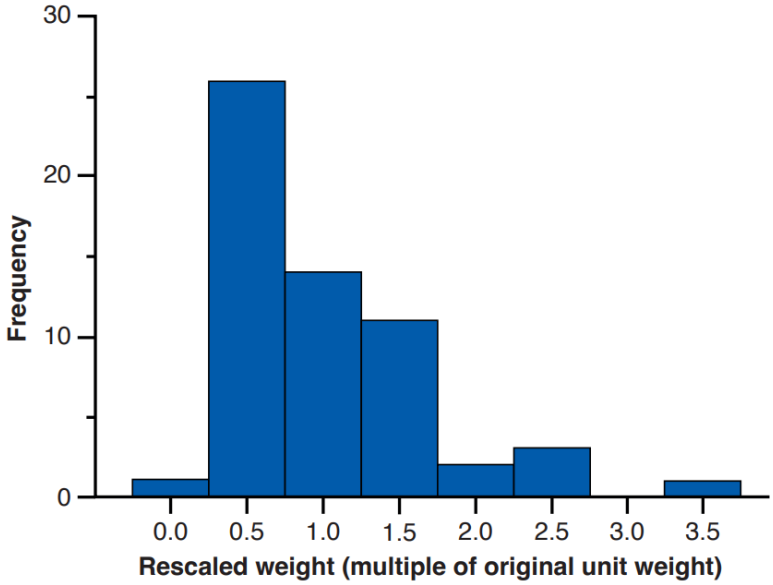


Log-normal was selected for analysis of HINE-2 results (top). Children were classed as a HINE-2 responder if more motor milestones showed improvement than showed worsening. Improvement was defined as a ≥2-point increase in the ability to kick (or maximal score) or a ≥1-point increase in head control, rolling, sitting, crawling, standing, or walking. Worsening was defined as a ≥2-point decrease in the ability to kick (or lowest score) or a ≥1-point decrease in head control, rolling, sitting, crawling, standing, or walking

Generalized gamma was selected for the analysis of CHOP-INTEND responses (bottom). A response was defined as a ≥4-point increase in CHOP-INTEND score from baseline

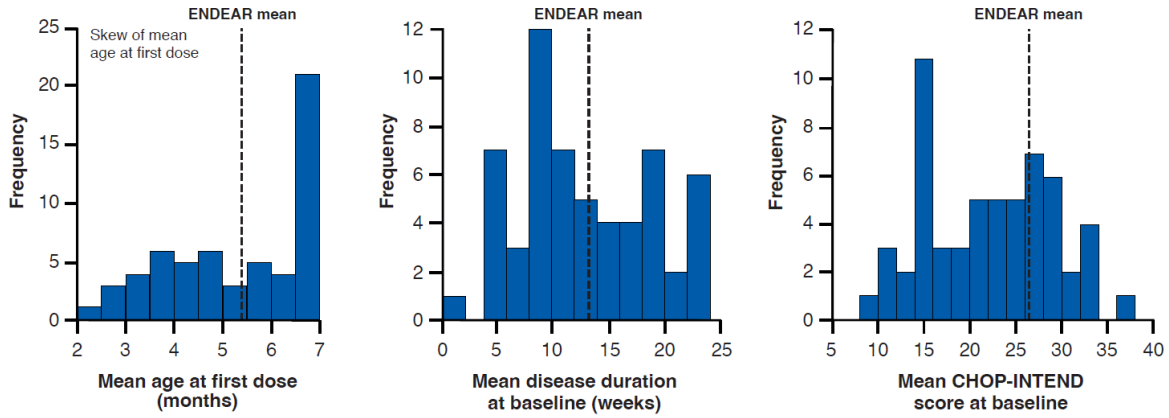
AIC Akaike information criterion, *ASM* assessment schedule matching, *BIC* Bayesian information criterion, *CHOP-INTEND* Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, *HINE-2* Hammersmith Infant Neurological Examination, Module 2

Fig. S4 Distribution of re-scaled weights for the ESS post-matching



ESS effective sample size

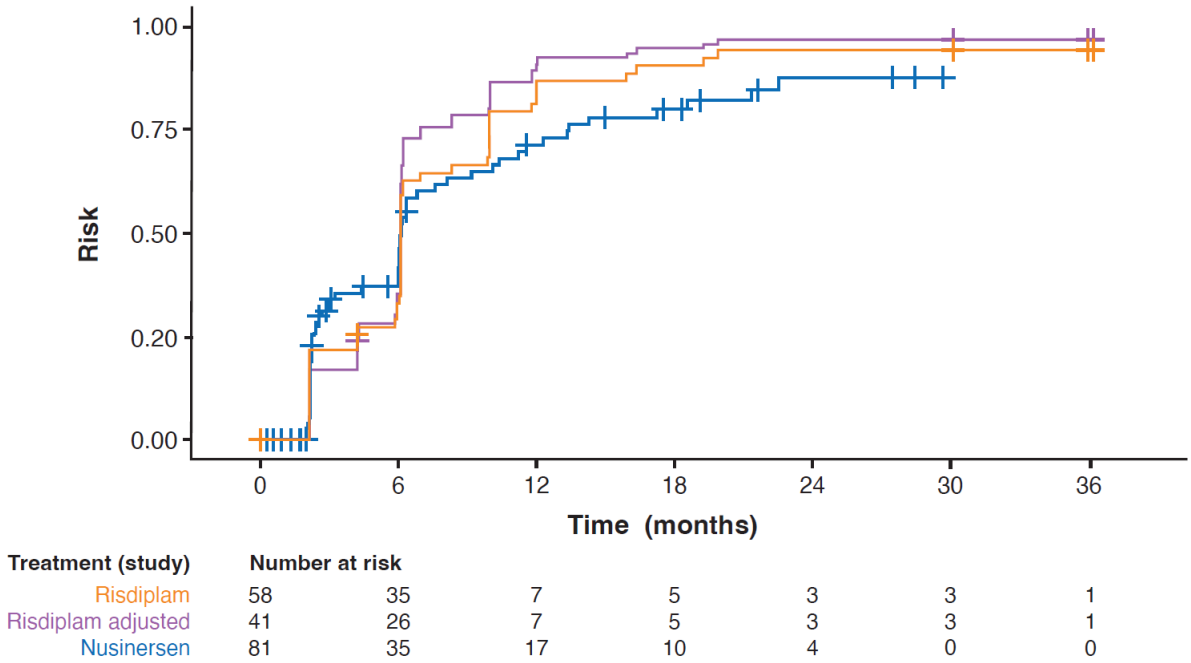
Fig. S5 Post-matching distributions of age at first dose, disease duration, and baseline CHOP-INTEND score in FIREFISH



Dashed line corresponds to the mean of ENDEAR

CHOP-INTEND Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders

Fig. S6 Time to a HINE-2 response with risdiplam and nusinersen (MAIC with ASM analysis)



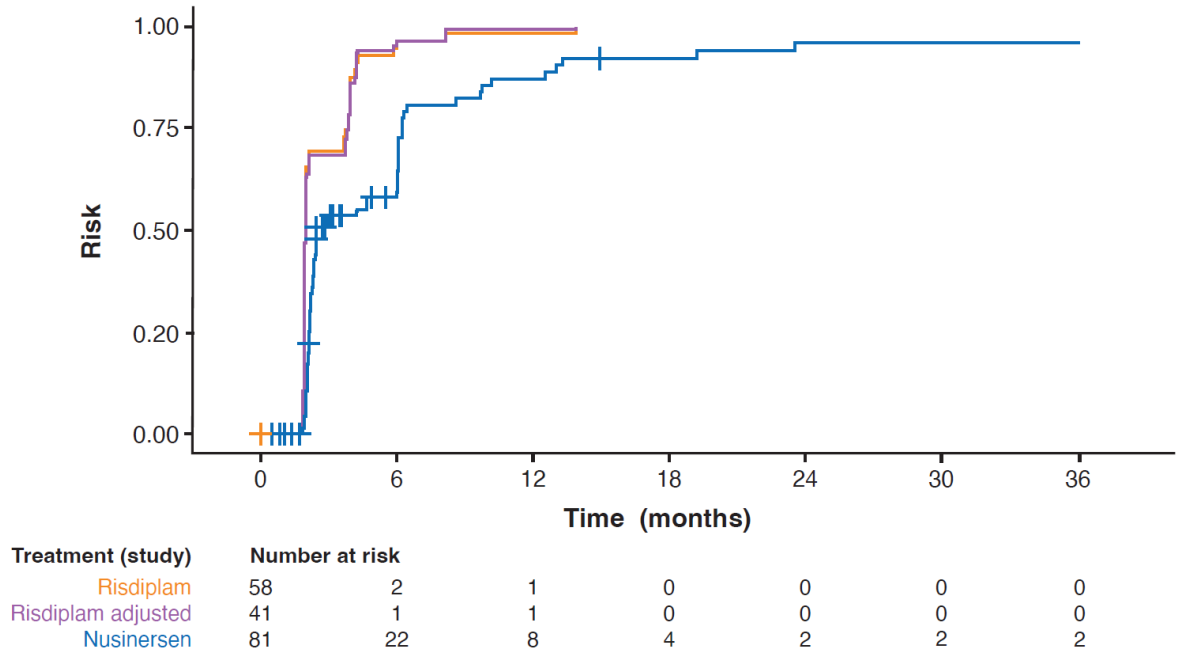
Children were classed as a HINE-2 responder if more motor milestones showed improvement than showed worsening. Improvement was defined as a ≥2-point increase in the ability to kick (or maximal score) or a ≥1-point increase in head control, rolling, sitting, crawling, standing, or walking. Worsening was defined as a ≥2-point decrease in the ability to kick (or lowest score) or a ≥1-point decrease in head control, rolling, sitting, crawling, standing, or walking

Unadjusted survival data from the pooled FIREFISH cohort (orange line) were plotted alongside the data from SHINE-ENDEAR (blue line). Patient baseline characteristics in FIREFISH were matched to the mean values of the baseline characteristics of the nusinersen arm in SHINE-ENDEAR using MAIC methodology, thus generating risdiplam-adjusted data (purple line). Characteristics that were used as adjustment factors in the MAIC analysis were age at first dose, disease duration, and baseline CHOP-INTEND score. Patients in FIREFISH were redistributed according to the timings of the scheduled visits from SHINE-ENDEAR using ASM methodology

PH test: $p = 0.067$, not rejecting the null hypothesis

ASM assessment schedule matching, *CHOP-INTEND* Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, *HINE-2* Hammersmith Infant Neurological Examination, Module 2, *MAIC* matching-adjusted indirect comparison, *PH* proportional hazard

Fig. S7 Time to a CHOP-INTEND response with risdiplam and nusinersen (MAIC with ASM analysis)



A CHOP-INTEND response was defined as a ≥4-point improvement in CHOP-INTEND score from baseline

Unadjusted survival data from the pooled FIREFISH cohort (orange line) were plotted alongside the data from SHINE-ENDEAR (blue line). Patient baseline characteristics in FIREFISH were matched to the mean values of the baseline characteristics of the nusinersen arm in SHINE-ENDEAR using MAIC methodology, thus generating risdiplam-adjusted data (purple line). Characteristics that were used as adjustment factors in the MAIC analysis were age at first dose, disease duration, and baseline CHOP-INTEND score. Patients in FIREFISH were redistributed according to the timings of the scheduled visits from SHINE-ENDEAR using ASM methodology

PH test: $p = 0.726$, not rejecting the null hypothesis

ASM assessment schedule matching, *CHOP-INTEND* Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, *MAIC* matching-adjusted indirect comparison, *PH* proportional hazard

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