Supplementary Material for *CNS Drugs*

An Integrated Safety Analysis of Infants and Children with Symptomatic Spinal Muscular Atrophy (SMA) Treated with Nusinersen in Seven Clinical Trials

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Table S1 Time on study and exposure to nusinersen

	Nusinersen			Control		
	Infantile-onset SMA *n* = 100	Later-onset SMA *n* = 140	All nusinersen-treated participants *N* = 240	Infantile-onset SMA *n* = 41	Later-onset SMA *n* = 42	All control-treated participants *N* = 83
Median (range) number of doses received	5.0 (1–12)	4.0 (1–8)	4.0 (1–12)	4.0 (1–6)	4.0 (4–4)	4.0 (1–6)
Mean (SD) total amount of nusinersen received, mg	60.6 (26.5)	51.4 (14.9)	55.2 (21.0)	0	0	0
Median (range) time on study, days	308.0 (6–1429)	456.0 (31–1538)	449.0 (6–1538)	187.0 (20–423)	450.0 (364–482)	400.0 (20–482)
Total number of patient-years	108.65	267.20	375.85	25.39	50.99	76.38

Table S2 Respiratory, renal, and hepatic AEs[a]

	Nusinersen			Control		
	Infantile-onset SMA *n* = 100	Later-onset SMA *n* = 140	All nusinersen-treated participants *N* = 240	Infantile-onset SMA *n* = 41	Later-onset SMA *n* = 42	All control-treated participants *N* = 83
Respiratory, thoracic, and mediastinal disorders, n (%)[b]	79 (79)	62 (44)	141 (59)	36 (88)	17 (40)	53 (64)
Respiratory distress	30 (30)	4 (3)	34 (14)	12 (29)	2 (5)	14 (17)
Respiratory failure	27 (27)	1 (<1)	28 (12)	16 (39)	1 (2)	17 (20)
Atelectasis	24 (24)	1 (<1)	25 (10)	12 (29)	0	12 (14)
Acute respiratory failure	17 (17)	1 (<1)	18 (8)	10 (24)	0	10 (12)
Cough	16 (16)	27 (19)	43 (18)	8 (20)	9 (21)	17 (20)
Nasal congestion	15 (15)	6 (4)	21 (9)	5 (12)	2 (5)	7 (8)
Pneumonia aspiration	12 (12)	1 (<1)	13 (5)	7 (17)	0	7 (8)
Hypoxia	11 (11)	2 (1)	13 (5)	2 (5)	0	2 (2)
Dyspnea	9 (9)	0	9 (4)	6 (15)	0	6 (7)
Bronchial secretion retention	8 (8)	0	8 (3)	7 (17)	0	7 (8)
Respiratory arrest	6 (6)	0	6 (3)	4 (10)	0	4 (5)

Rhinorrhea	8 (8)	12 (9)	20 (8)	3 (7)	7 (17)	10 (12)
Sleep apnea syndrome	1 (1)	1 (<1)	2 (<1)	4 (10)	0	4 (5)
Renal and urinary disorders, n (%)	2 (2)	6 (4)	8 (3)	1 (2)	1 (2)	2 (2)
Urinary incontinence	0	2 (1)	2 (<1)	0	0	0
Urinary retention	1 (1)	1 (<1)	2 (<1)	0	1 (2)	1 (1)
Vesicoureteric reflux	0	2 (1)	2 (<1)	0	0	0
Dysuria	0	1 (<1)	1 (<1)	0	0	0
Hydronephrosis	1 (1)	0	1 (<1)	0	0	0
Glycosuria	0	0	0	1 (2)	0	1 (1)
Hepatobiliary disorders, n (%)	1 (1)	0	1 (<1)	0	0	0
Hepatomegaly	1 (1)	0	1 (<1)	0	0	0

AE adverse event, *SMA* spinal muscular atrophy

[a]Incidence of all AEs occurring under the respiratory, thoracic and mediastinal disorders; renal and urinary disorders; and hepatobiliary disorders System Organ Classes

[b]AEs shown occurred with ≥10% incidence in one group

Table S3 Shifts to abnormal in ECG results

	Nusinersen			Control		
	Infantile-onset SMA *n* = 100	Later-onset SMA *n* = 140	All nusinersen-treated participants *N* = 240	Infantile-onset SMA *n* = 41	Later-onset SMA *n* = 42	All control-treated participants *N* = 83
ECG shifts to abnormal[a]						
Clinically significant[b]	10/81 (12)	0/109	10/190 (5)[c]	0/34	2/33 (6)	2/67 (3)
Not clinically significant[d]	22/81 (27)	54/109 (50)	76/190 (40)	5/34 (15)	13/33 (39)	18/67 (27)

ECG electrocardiogram; *SMA* spinal muscular atrophy

[a]Number with a shift/number at risk (percentage); number at risk is the number of participants whose baseline value was not abnormal and who had at least one post-baseline value

[b]Shift to "abnormal, clinically significant" includes "unknown" or "normal" to "abnormal, clinically significant"

[c]Clinically significant abnormal findings in nusinersen-treated participants included: marked change in frontal plane axis almost certainly due to limb lead error at day 92 visit, next ECG result was normal; prominent right atrial and right ventricular forces at day 568 visit, next ECG result was normal (*n* = 1); right axis deviation and upright T wave in V1 abnormality at day 337 visit, echocardiogram results normal; right axis deviation with positive T wave in V1 and very small LV forces at day 568 visit (*n* = 1); right atrial enlargement likely biventricular hypertrophy at visit day 29, repeat testing showed biventricular hypertrophy mid precordial voltage and probably right atrial enlargement (*n* = 1); large increase in right ventricular forces in V6 at day 29 visit, next ECG result was normal (*n* = 1); left ventricular hypertrophy by voltage criteria on day 330 (*n* = 1); ventricular forces significantly increased, left ventricular hypertrophy and right ventricular forces close to right ventricular hypertrophy at day 148 (*n* = 1); right atrial enlargement, possible right ventricular hypertrophy linked to AE of right-sided cardiac strain on day 218 (*n* = 1); clear axis deviation and prominent right ventricular forces consistent with probable right ventricular hypertrophy at day 29 (*n* = 1); marked sinus tachycardia at day 29, next ECG result was normal (*n* = 1); marked and unusual ST elevations in almost every lead consistent with pericarditis if not an artifact on day 14, next ECG result was normal (*n* = 1)

[d]Shift to "abnormal, not clinically significant" includes "unknown" or "normal" to "abnormal, not clinically significant"

Fig. S1 Median, minimum, and maximum ALT and AST levels in nusinersen-treated and control participants from (**a**, **c**) ENDEAR and (**b**, **d**) CHERISH. Graph b study visit Day 2: nusinersen, *n* = 78; control, *n* = 40; graph c study visit Day 2: nusinersen, *n* = 69; control, *n* = 31. *ALT* alanine aminotransferase, *AST* aspartate aminotransferase