Supplementary Material

Risdiplam in patients previously treated with other therapies for spinal muscular atrophy: an interim analysis from the JEWELFISH study

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Ethics Committee and Internal Review Board sites

Country	PI Last Name	CENTRAL EC / IRB	LOCAL EC / IRB	Approval waived or not required (Y/N/NA)	IRB / EC reference number (if applicable)
Belgium	Deconinck	UZ Leuven campus Gasthuisberg Ethische commissie onderzoek	NA	NA	S62114
Belgium	De Waele (former Goemans)	UZ Leuven campus Gasthuisberg Ethische commissie onderzoek	NA	NA	S62114
France	Cances	CPP [Ethics committee/EC] Nord-Ouest II Bât Pharmacie -1er étage CHU d'Amiens	NA	NA	3438
France	Davion (former Cuisset)	CPP [Ethics committee/EC] Nord-Ouest II Bât Pharmacie -1er étage CHU d'Amiens	NA	NA	3438
France	Desguerre	CPP [Ethics committee/EC] Nord-Ouest II Bât Pharmacie -1er étage CHU d'Amiens	NA	NA	3438
France	Vuillerot	CPP [Ethics committee/EC] Nord-Ouest II Bât Pharmacie -1er étage CHU d'Amiens	NA	NA	3438
France	Walther-Louvier	CPP [Ethics committee/EC] Nord-Ouest II Bât Pharmacie -1er étage CHU d'Amiens	NA	NA	3438
Germany	Pechmann (former Borell)	Ethikkommission der Albert-Ludwigs-Universität Freiburg	NA	No (CEC approval in place)	CEC reference: 21-1028
Germany	Koelbel (former Schara)	Ethikkommission der Albert-Ludwigs-Universität Freiburg	Ethikkommission der Universität Duisburg-Essen	NA (In GER only the CEC provides the approval)	LEC Reference: 8522-AB
Italy	Bertini	Comitato Etico del Policlinico "A. Gemelli"	Comitato Etico OPBG, Viale Ferdinando	Y	NA
Italy	Bruno	Comitato Etico del Policlinico "A. Gemelli"	Comitato Etico Regionale della Liguria	Y	ID Sperimentazione 4265
Italy	Comi	Comitato Etico del Policlinico "A. Gemelli"	Comitato Etico Milano Area 2	Y	ID4321
Italy	Mercuri	Comitato Etico del Policlinico "A. Gemelli"	NA	Y	ID 1528
Italy	Messina (former Vita)	Comitato Etico del Policlinico "A. Gemelli"	Comitato Etico Interaziendale della Provincia di Messina,	Y	NA
Netherlands	Van der Pol	UMC Utrecht T.a.v. De Medisch Ethische Toetsingscommissie (METC)	NA	Y	18/763
Poland	Kostera-Pruszczyk	Komisja Bioetyczna przy Warszawskim Uniwersytecie Medycznym	NA	NA (SA approval is required)	EC opinion number: KB/20/2019
Switzerland	Fischer	Ethikkommission Nordwest- und Zentralschweiz (EKNZ)	NA	No (CEC approval in place)	2017-00360
UK	Guglieri (former Lochmuller, Straub)	North East – Newcastle and North Tyneside 1 Research Ethics Committee, NHSBT	NA	Applicable approval in place	17/NE/0176

UK	Parasuraman (former Roper)	North East – Newcastle and North Tyneside 1 Research Ethics Committee, NHSBT	NA	Applicable approval in place	17/NE/0176
UK	Scoto	North East – Newcastle and North Tyneside 1 Research Ethics Committee, NHSBT	NA	Applicable approval in place	17/NE/0176
USA	Chiriboga	NA	Columbia University Medical Center Institutional Review Board	Y	IRB-AAAR1270
USA	Darras	NA	Office of Clinical Investigation at Boston's Children's Hospital	Y	IRB-P00030854
USA	Day	NA	Stanford University Research Compliance Office	Y	47834
USA	Navas Nazario (former Finkel)	NA	Nemours Office of Human Subjects Protection (NOHSP)	Y	1414557

INCLUSION/EXCLUSION CRITERIA

Inclusion criteria

Patients must meet the following criteria for study entry:

- Males and females 6 months–60 years of age inclusive (at screening)
- Confirmed diagnosis of 5q-autosomal recessive spinal muscular atrophy (SMA), including:
  - Genetic confirmation of homozygous deletion or heterozygosity predictive of loss of function of the survival of motor neuron 1 (*SMN1*) gene;
  - Clinical history, signs, or symptoms attributable to SMA.
- Previous enrollment in RG7800 (MOONFISH) with the splicing modifier RO6885247 or previous treatment with any of the following:
  - Nusinersen (defined as having received ≥ 4 doses of nusinersen, provided that the last dose was received ≥ 90 days prior to screening);
  - Olesoxime (provided that the last dose was received ≤ 18 months and ≤ 90 days prior to screening);
  - AVXS-101 (provided that the time of treatment was ≥ 12 months prior to screening).
- Able and willing to provide written informed consent and to comply with the study protocol according to International Conference on Harmonization (ICH) guidelines and local regulations. Alternatively, a legally authorized representative must be able to give consent for the patient according to ICH guidelines and local regulations, and assent must be given whenever possible.
- Adequately recovered from any acute illness at the time of screening and considered well enough to participate, in the opinion of the Investigator.
- For women of childbearing potential: negative blood pregnancy test at screening, agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, as defined below:
  - Women must remain abstinent (refrain from heterosexual intercourse) or use two adequate methods of contraception, including at least one method with a failure rate of < 1% per year, during the treatment period and for at least 28 days after the final dose of study drug. Women must refrain from donating eggs during this same period;
  - A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations;
  - Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, established and proper use of hormonal contraceptives that inhibit ovulation, hormone-

releasing intrauterine devices, and copper intrauterine devices;
  - A vasectomy is a highly effective birth control method provided that the partner is the sole sexual partner of the woman of childbearing potential trial participant, and provided the vasectomized partner has received medical assessment of surgical success;
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.
- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:
  - With a female partner of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least 4 months after the final dose of the study drug. Men must refrain from donating sperm during this same period. This period is required for small molecules with potential for genotoxic effect and includes the spermatogenic cycle duration and drug elimination process;
  - With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for at least 28 days after the final dose of the study drug;
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- For patients aged ≤ 2 years at screening:
  - Receiving adequate nutrition and hydration (with or without gastrostomy) at the time of screening, in the opinion of the Investigator;
  - Medical care meets local accepted standard of care, in the opinion of the Investigator;
  - Would be able to complete all study procedures, measurements and visits, and the parent or caregiver of the patient has adequately supportive psychosocial circumstances, in the opinion of the Investigator;
  - Parent or caregiver of patient is willing to consider nasogastric, naso-jejunal or gastrostomy tube placement, as recommended by the Investigator, during the study (if not already in place at the time of screening) to maintain safe hydration, nutrition and treatment delivery;
  - parent or caregiver of patient is willing to consider the use of non-invasive ventilation, as recommended by the Investigator, during the study (if not already in place at the time of screening).

Exclusion criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Inability to meet study requirements;
- Concomitant participation in any investigational drug or device study;
- With the exception of studies of olesoxime, AVXS-101, or nusinersen: Previous participation in any investigational drug or device study ≤ 90 days prior to screening, or 5 half-lives of the drug, whichever is longer;
- Any history of gene or cell therapy, with the exception of AVXS-101;
- Unstable gastrointestinal, renal, hepatic, endocrine, or cardiovascular system diseases as considered to be clinically significant by the Investigator;
- Inadequate venous or capillary blood access for the study procedures, in the opinion of the Investigator;
- For patients aged < 2 years, hospitalization for a pulmonary event within 2 months prior to screening and pulmonary function not fully recovered at the time of screening;
- Lactating women;
- Suspicion of regular consumption of drugs of abuse;
- For adults and adolescents only, i.e., aged > 12 years, positive urine test for drugs of abuse or alcohol at screening or Day –1 visit;
- Cardiovascular, blood pressure, and heart rate:
  - Adults: Sustained resting systolic blood pressure (SBP) > 140 mmHg or < 80 mmHg, and/or diastolic blood pressure (DBP) > 90 mmHg or < 40 mmHg; a resting heart rate < 45 bpm or >100 bpm if considered to be clinically significant by the Investigator;
  - Adolescents (aged 12−17 years): SBP and/or DBP outside the 95th percentile for age; resting heart rate < 50 bpm or > 100 bpm if considered to be clinically significant by the Investigator;
  - Children (aged 6−11 years): SBP and/or DBP outside the 95th percentile for age; resting heart rate < 60 bpm or > 120 bpm if considered to be clinically significant by the Investigator;
  - Children (aged 2−5 years): SBP and/or DBP outside the 95th percentile for age; resting heart rate < 70 bpm or > 140 bpm if considered to be clinically significant by the Investigator;
  - Children (aged 6 months−< 2 years of age): SBP and/or DBP outside the 95th percentile for age; resting heart rate < 70 bpm or > 170 bpm if considered to be clinically significant by the Investigator.
- Presence of clinically significant electrocardiogram (ECG) abnormalities before study drug administration (e.g., second or third degree atrioventricular block), confirmed QTcF > 460 msec for patients aged ≥ 10 years, or QTcB > 460 ms for children aged ≤10 years (Bazett's correction is more appropriate inyoung children) from the average of triplicate measurements, or cardiovascular disease (e.g., cardiac insufficiency, coronary artery disease, cardiomyopathy, congestive heart failure, family

history of congenital long QT syndrome, family history of sudden death) indicating a safety risk for the patient as determined by the Investigator;

- History of malignancy if not considered cured;
- For patients aged > 6 years, significant risk for suicidal behavior in the opinion of the Investigator, as assessed by the Columbia-Suicide Severity Rating Scale (C-SSRS);
- Any major illness within 1 month before the screening examination or any febrile illness within 1 week prior to screening and up to first dose administration;
- Use of any organic cation transporter-2 and multidrug and toxic compound extrusion substrates within 2 weeks before dosing (including but not limited to: amantadine, cimetidine, memantine, amiloride, famotidine, metformin, pindolol, ranitidine, procainamide, varenicline, acyclovir, ganciclovir, oxaliplatin, cephalexin, cephradine, fexofenadine) including the mother, if breastfeeding the patient;
- Use of the following medications within 90 days prior to enrollment: riluzole, valproic acid, hydroxyurea, sodium phenylbutyrate, butyrate derivatives, creatine, carnitine, growth hormone, anabolic steroids, probenecid, agents anticipated to increase or decrease musclestrength, agents with known or presumed histone deacetylase inhibitory effect, and medications with known phototoxicity liabilities (e.g., oral retinoids including over-the-counter formulations, amiodarone, phenothiazines and chronic use of minocycline). (Patients who are on inhaled corticosteroids, administered either through a nebulizer or an inhaler, will be allowed in the study);
- Recently initiated treatment for SMA (≤ 6 weeks prior to enrollment) with oral salbutamol or another β2-adrenergic agonist taken orally is not allowed. Patients who have been on oral salbutamol (or another β2-adrenergic agonist) for ≥ 6 weeks before enrollment and have shown good tolerance are allowed. The dose of β2-adrenergic agonist should remain stable as much as possible for the duration of the study. Use of inhaled β2-adrenergic agonists (e.g., for the treatment of asthma) is allowed;
- Any prior use of chloroquine, hydroxychloroquine, retigabine, vigabatrin or thioridazine, is not allowed. Use of other medications known to or suspected of causing retinal toxicity within 1 year prior to enrollment is not allowed;
- Clinically significant abnormalities in laboratory test results, e.g., alanine amino transferase values exceeding 1.5-fold the upper limit of normal, unless the elevated alanine amino transferase level is considered of muscular origin (i.e., in the absence of other evidence of liver disease), which is supported by elevated creatine kinase and lactate dehydrogenase. Out-of-range creatine kinase levels should be reviewed in light of the underlying SMA pathology of the patient; elevated levels per se do not disqualify the patient from the study. In the case of uncertain or questionable results, tests performed during screening may be repeated before enrollment to confirm eligibility;
- Donation or loss of blood ≥ 10% of blood volume within 3 months prior to screening;
- Ascertained or presumptive hypersensitivity (e.g., anaphylactic reaction) to risdiplam or to the constituents of its formulation;
- A concomitant disease or condition, or treatment of a concomitant disease

or condition that could interfere with the conduct of the study, or that would, in the opinion of the Investigator, pose an unacceptable risk to the patient in this study;

- Recent history (< 1 year) of an ophthalmological disease (e.g., glaucoma not controlled by treatment, central serous retinopathy, inflammatory/infectious retinitis unless clearly inactive, retinal detachment, retinal surgery, intraocular trauma, retinal dystrophy or degeneration, optic neuropathy, or optic neuritis) that would interfere with the conduct of the study as assessed by the ophthalmologist. Any other abnormalities detected at screening (e.g., retinal layer abnormalities, edema, cystic or atrophic changes) should be discussed with the Investigator, the ophthalmologist, and with the Sponsor, who will jointly make the decision of whether the patient may be enrolled in the study. Patients in whom spectral-domain optical coherence tomography measurement of sufficient quality cannot be obtained at screening will not be enrolled;
- Any prior use of an inhibitor or inducer of flavin monooxygenase 1 (FMO1) or FMO3 taken within 2 weeks (or within 5 elimination half-lives, whichever is longer) prior to dosing.

Outcome measures

SAFETY OUTCOME MEASURES

The safety outcome measures for this study are as follows:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events scale, Version 4.0;
- Incidence of treatment discontinuations due to adverse events;
- Incidence of abnormal laboratory values;
- Incidence of abnormal ECG values;
- Incidence of abnormal vital signs (body temperature, systolic and diastolic blood pressure, heart rate, respiratory rate);
- Physical examination. For patients aged 9–17 years, physical examination will include formal Tanner staging for pubertal status;
- Neurological examination;
- Height, weight, and head and chest circumference;
- Incidence of emergence or worsening of symptoms as measured by the C-SSRS (adult version for adults and adolescents, pediatric version for patients aged 6–11 years);
- Ophthalmological assessments as appropriate for age;
- Adverse events and concomitant medications will be monitored throughout the entire study.

Pharmacokinetic (PK) outcome measures

The PK outcome measures for this study are as follows:

- Concentration per timepoint listed;

- Cmax;
- Area under the curve;
- Concentration at the end of a dosing interval (Ctrough) to assess steady-state;
- Other PK parameters as appropriate.

Pharmacodynamic (PD) outcome measures

The PD outcome measures for this study are as follows:

- SMN mRNA in blood: Blood samples will be collected at the times specified in the Schedules of Assessments and detailed tables, to isolate mRNA and measure the relative amount of SMN mRNA and its splice forms. Housekeeping genes for the quantitative analysis of RNA will also be measured;
- SMN protein levels in blood.

Exploratory outcome measures

The exploratory outcomes measures for this study are:

- Disease-related adverse events;
- 32-item Motor Function Measure (patients aged 2-60 years);
- Hammersmith Functional Motor Scale – Expanded (patients aged 2-60 years);
- Revised Upper Limb Module (patients aged 2-60 years);
- Gross Motor Scale of the Bayley Scales of Infant and Toddler development, Third Edition (patients aged 6 months to <2 years);
- Hammersmith Infant Neurological Examination, Module 2 (patients aged 6 months to ≤ 2 years);
- Six-minute walk test (for ambulant patients only in patients aged 6–60 years);
- Sniff nasal inspiratory pressure (patients aged 2–60 years);
- Forced vital capacity, forced expiratory volume in 1 second, and peak cough flow (patients aged 6–60 years);
- To evaluate time-matched QT profiles in patients treated with risdiplam (patients aged 12–60 years)
- To evaluate the efficacy of treatment with risdiplam in terms of patient-reported independence (patients aged 12–60 years) and caregiver-reported independence as assessed through the SMA Independence Scale (SMAIS) upper limb total score (patients aged 2–60 years);
- Time to death (patients aged 6 months to < 2 years)
- Time to permanent ventilation (patients aged 6 months to < 2 years)

Supplementary Table 1. Reported reasons why patients began treatment with risdiplam following previous treatments[a]

Primary reasons to enroll in JEWELFISH	**Patients previously treated with Nusinersen[b] (n = 77) n (%)**
Treatment-related tolerability concerns[c]	24 (31)
Treatment response: Lack of efficacy	14 (18)
Treatment response: Loss of efficacy	8 (10)
Caregiver preference	7 (9)[d]
Patient preference	6 (8)
Other[e]	18 (23)
Primary reasons to enroll in JEWELFISH	**Patients previously treated with onasemnogene abeparvovec[d] (n = 14) n (%)**
Hopes of additional benefit	8 (57)
Caregiver preference	4 (29)
Treatment response: lack of efficacy	2 (14)

[a]Reasons were self-reported for patients aged ≥ 5 years and caregiver reported for patients aged < 5 years. [b]Three patients in the nusinersen group had also received olesoxime previously. [c]Tolerability generally refers to challenges associated with intrathecal administration in patients with scoliosis or those who have undergone spinal surgery and the inability to receive a lumbar puncture. [d] One patient in the onasemnogene abeparvovec group received treatment with onasemnogene abeparvovec first followed by nusinersen. This patient is included in both tables here but included only in the 'previously treated with onasemnogene abeparvovec' group for safety and efficacy. [e]Other reasons include treatment-related safety concerns, treatment reimbursement/insurance policy challenge, access infrastructure challenges (e.g., accessibility to sites), injection procedures, inconvenience of treatment, or missing. Data cut-off: 29 Jan 2021.

Supplementary Table 2. Adverse events and serious adverse events reported in ≥1% of all patients

Adverse events	**Previous treatment**				**All patients (*N* = 174)**
	Olesoxime (*n* = 71)[a]	**MOONFISH study (*n* = 13)[a, b]**	**Nusinersen (*n* = 76)[c]**	**Onasemnogene abeparvovec (*n* = 14)[d]**	
Infections and infestations					
Upper respiratory tract infection	14 (20.0)	0	14 (18.4)	2 (14.3)	30 (17.3)
Nasopharyngitis	6 (8.6)	2 (15.4)	7 (9.2)	2 (14.3)	17 (9.8)
Gastroenteritis	3 (4.3)	0	10 (13.2)	0	13 (7.5)
Pneumonia	3 (4.3)	1 (7.7)	5 (6.6)	1 (7.1)	10 (5.8)
Urinary tract infection	4 (5.7)	2 (15.4)	4 (5.3)	0	10 (5.8)
Influenza	2 (2.9)	2 (15.4)	4 (5.3)	1 (7.1)	9 (5.2)
Bronchitis	3 (4.3)	0	5 (6.6)	0	8 (4.6)
Viral infection	0	0	7 (9.2)	1 (7.1)	8 (4.6)
Ear infection	2 (2.9)	0	2 (2.6)	2 (14.3)	6 (3.5)
COVID-19	3 (4.3)	0	1 (1.3)	1 (7.1)	5 (2.9)
Conjunctivitis	0	0	4 (5.3)	1 (7.1)	5 (2.9)

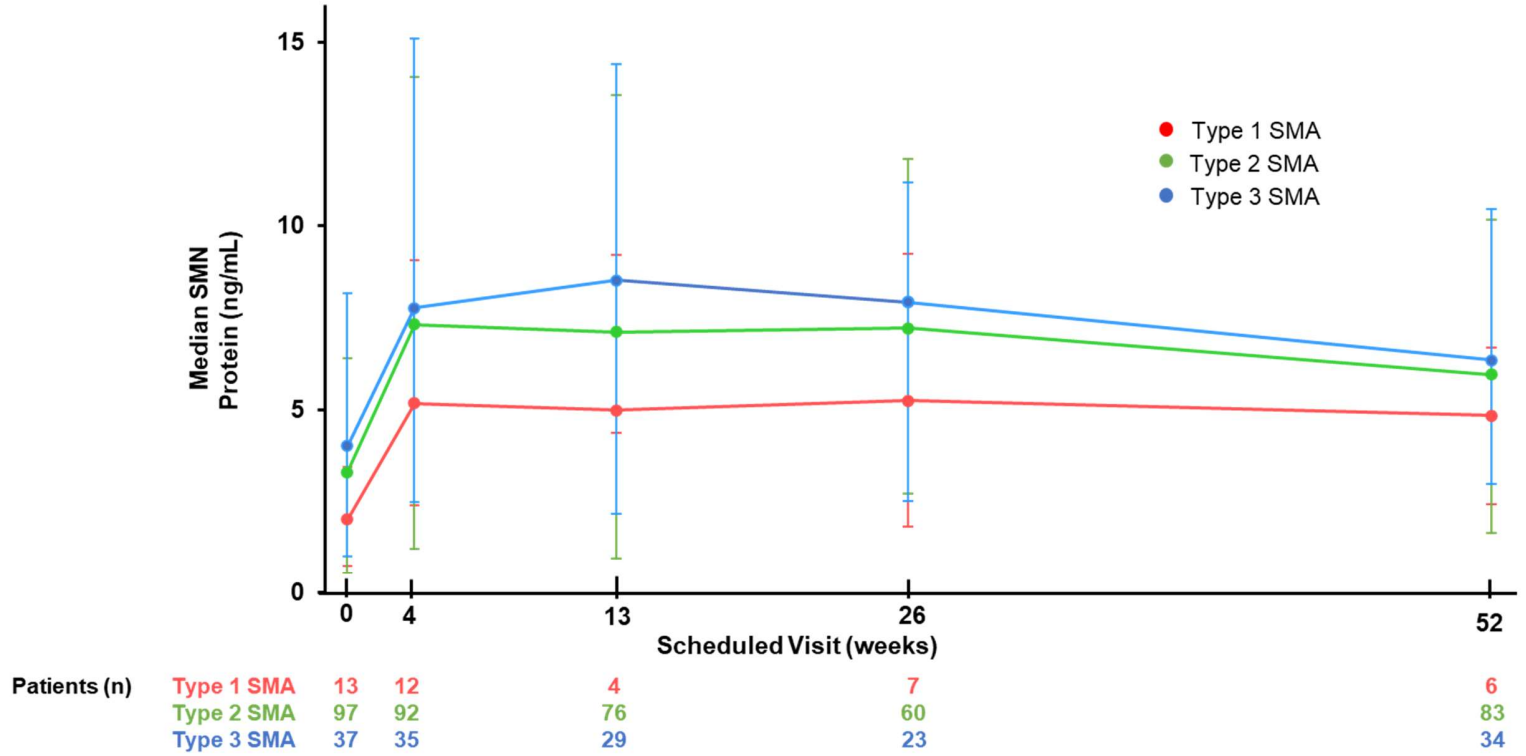
Sinusitis	1 (1.4)	0	4 (5.3)	0	5 (2.9)
Respiratory tract infection	3 (4.3)	0	1 (1.3)	0	4 (2.3)
Gingivitis	2 (2.9)	0	1 (1.3)	0	3 (1.7)
Lower respiratory tract infection	2 (2.9)	0	1 (1.3)	0	3 (1.7)
Otitis media	0	0	1 (1.3)	2 (14.3)	3 (1.7)
Pharyngitis	2 (2.9)	0	1 (1.3)	0	3 (1.7)
Viral upper respiratory tract infection	0	0	3 (3.9)	0	3 (1.7)
Cellulitis	0	0	2 (2.6)	0	2 (1.2)
Cystitis	0	0	2 (2.6)	0	2 (1.2)
Diverticulitis	1 (1.4)	0	1 (1.3)	0	2 (1.2)
Herpes virus infection	2 (2.9)	0	0	0	2 (1.2)
Herpes zoster	0	0	2 (2.6)	0	2 (1.2)
Localized infection	0	0	2 (2.6)	0	2 (1.2)
Oral fungal infection	2 (2.9)	0	0	0	2 (1.2)
Pneumonia viral	0	0	1 (1.3)	1 (7.1)	2 (1.2)
Rhinitis	0	0	2 (2.6)	0	2 (1.2)
Suspected COVID-19	2 (2.9)	0	0	0	2 (1.2)
Gastrointestinal disorders					
Nausea	5 (7.1)	0	14 (18.4)	1 (7.1)	20 (11.6)
Diarrhea	4 (5.7)	0	14 (18.4)	1 (7.1)	19 (11.0)
Vomiting	6 (8.6)	1 (7.7)	5 (6.6)	2 (14.3)	14 (8.1)
Aphthous ulcer	1 (1.4)	2 (15.4)	6 (7.9)	0	9 (5.2)
Abdominal pain	2 (2.9)	1 (7.7)	5 (6.6)	0	8 (4.6)
Abdominal pain upper	2 (2.9)	1 (7.7)	3 (3.9)	1 (7.1)	7 (4.0)
Constipation	1 (1.4)	0	4 (5.3)	0	5 (2.9)
Gastroesophageal reflux disease	0	0	2 (2.6)	1 (7.1)	3 (1.7)
Abdominal discomfort	0	1 (7.7)	1 (1.3)	0	2 (1.2)
Abdominal distension	1 (1.4)	0	1 (1.3)	0	2 (1.2)
Gastritis	1 (1.4)	0	1 (1.3)	0	2 (1.2)
Odynophagia	1 (1.4)	0	1 (1.3)	0	2 (1.2)
Respiratory, thoracic, and mediastinal disorders					
Cough	3 (4.3)	0	8 (10.5)	0	11 (6.4)
Oropharyngeal pain	8 (11.4)	0	3 (3.9)	0	11 (6.4)
Rhinorrhea	2 (2.9)	1 (7.7)	1 (1.3)	1 (7.1)	5 (2.9)
Epistaxis	2 (2.9)	0	1 (1.3)	1 (7.1)	4 (2.3)
Nasal congestion	0	1 (7.7)	2 (2.6)	1 (7.1)	4 (2.3)
Lower respiratory tract congestion	1 (1.4)		2 (2.6)	0	3 (1.7)
Respiratory distress	1 (1.4)	0	1 (1.3)	1 (7.1)	3 (1.7)
Respiratory failure	0	0	3 (3.9)	0	3 (1.7)
Catarrh	0	0	2 (2.6)	0	2 (1.2)
Respiratory tract congestion	0	0	2 (2.6)	0	2 (1.2)
Rhinitis allergic	1 (1.4)	0	1 (1.3)	0	2 (1.2)
General disorders and administration site conditions					
Pyrexia	8 (11.4)	1 (7.7)	17 (22.4)	4 (28.6)	30 (17.3)
Fatigue	2 (2.9)	1 (7.7)	8 (10.5)	0	11 (6.4)
Asthenia	2 (2.9)	0	1 (1.3)	0	3 (1.7)
Malaise	3 (4.3)	0	0	0	3 (1.7)
Pain	1 (1.4)	0	2 (2.6)	0	3 (1.7)
Chest pain	1 (1.4)	0	1 (1.3)	0	2 (1.2)
Edema peripheral	1 (1.4)	0	1 (1.3)	0	2 (1.2)

Skin and subcutaneous tissue disorders					
Rash	4 (5.7)	2 (15.4)	7 (9.2)	0	13 (7.5)
Acne	3 (4.3)	0	2 (2.6)	0	5 (2.9)
Dry skin	2 (2.9)	1 (7.7)	1 (1.3)	0	4 (2.3)
Erythema	2 (2.9)	0	2 (2.6)	0	4 (2.3)
Alopecia	2 (2.9)	0	0	1 (7.1)	3 (1.7)
Eczema	1 (1.4)	0	2 (2.6)	0	3 (1.7)
Skin exfoliation	2 (2.9)	1 (7.7)	0	0	3 (1.7)
Blister	0	0	2 (2.6)	0	2 (1.2)
Pruritus	1 (1.4)	1 (7.7)	0	0	2 (1.2)
Seborrheic dermatitis	2 (2.9	0	0	0	2 (1.2)
Nervous system disorders					
Headache	12 (17.1)	1 (7.7)	15 (19.7)	0	28 (16.2)
Tremor	1 (1.4)	1 (7.7)	1 (1.3)	0	3 (1.7)
Dizziness	1 (1.4)	0	1 (1.3)	0	2 (1.2)
Migraine	1 (1.4)	0	1 (1.3)	0	2 (1.2)
Syncope	1 (1.4)	0	1 (1.3)	0	2 (1.2)
Injury, poisoning, and procedural complications					
Fall	1 (1.4)	3 (23.1)	3 (3.9)	0	7 (4.0)
Limb injury	2 (2.9)	0	1 (1.3)	0	3 (1.7)
Arthropod bite	1 (1.4)	0	1 (1.3)	0	2 (1.2)
Contusion	0	0	2 (2.6)	0	2 (1.2)
Femur fracture	1 (1.4)	0	0	1 (7.1)	2 (1.2)
Procedural pain	0	0	0	2 (14.3)	2 (1.2)
Tibia fracture	1 (1.4)	1 (1.7)	0	0	2 (1.2)
Wound dehiscence	0	0	2 (2.6)	0	2 (1.2)
Musculoskeletal and connective tissue disorder					
Arthralgia	4 (5.7)	3 (23.1)	2 (2.6)	0	9 (5.2)
Back pain	5 (7.1)	2 (15.4)	1 (1.3)	0	8 (4.6)
Pain in extremity	2 (2.9)	2 (15.4)	3 (3.9)	0	7 (4.0)
Muscular weakness	1 (1.4)	0	5 (6.6)	0	6 (3.5)
Investigations					
Alanine aminotransferase increased	1 (1.4)	1 (7.7)	1 (1.3)	0	3 (1.7)
Aspartate aminotransferase increased	1 (1.4)	1 (7.7)	1 (1.3)	0	3 (1.7)
Blood triglycerides increased	2 (2.9)	1 (7.7)	0	0	3 (1.7)
Lipase increased	2 (2.9)	0	1 (1.3)	0	3 (1.7)
C-reactive protein increased	2 (2.9)	0	0	0	2 (1.2)
Prothrombin time prolonged	2 (2.9)	0	0	0	2 (1.2)
Eye disorders					
Vision blurred	3 (4.3)	0	1 (1.3)	0	4 (2.3)
Eye irritation	1 (1.4)	0	1 (1.3)	1 (7.1)	3 (1.7)
Conjunctivitis allergic	1 (1.4)	0	1 (1.3)	0	2 (1.2)
Ocular hyperemia	1 (1.4)	0	1 (1.3)	0	2 (1.2)
Metabolism and nutrition disorders					
Vitamin D deficiency	1 (1.4)	1 (7.7)	2 (2.6)	0	4 (2.3)
Decreased appetite	0	0	2 (2.6)	0	2 (1.2)
Dehydration	0	0	2 (2.6)	0	2 (1.2)
Hyperglycemia	1 (1.4)	0	1 (1.3)	0	2 (1.2)

Psychiatric disorder					
Anxiety	1 (1.4)	1 (7.7)	3 (3.9)	0	5 (2.9)
Depression	1 (1.4)	0	1 (1.3)	0	2 (1.2)
Mood swings	1 (1.4)	0	1 (1.3)	0	2 (1.2)
Panic attack	0	0	2 (2.6)	0	2 (1.2)
Renal and urinary disorders					
Hematuria	2 (2.9)	0	2 (2.6)	0	4 (2.3)
Nephrolithiasis	2 (2.9)	0	2 (2.6)	0	4 (2.3)
Renal colic	3 (4.3)	0	0	0	3 (1.7)
Reproductive system and breast disorders					
Dysmenorrhea	5 (7.1)	0	1 (1.3)	0	6 (3.5)
Blood and lymphatic system disorder					
Anemia	1 (1.4)	1 (1.7)	1 (1.3)	0	3 (1.7)
Neutropenia	1 (1.4)	0	1 (1.3)	0	2 (1.2)
Ear and labyrinth disorders					
Cerumen impaction	0	0	3 (3.9)	0	3 (1.7)
Ear pain	1 (1.4)	0	1 (1.3)	0	2 (1.2)
Vertigo	0	0	2 (2.6)	0	2 (1.2)
Cardiac disorders					
Tachycardia	3 (4.3)	0	0	0	3 (1.7)
	Previous treatment				
Serious adverse events	**Olesoxime (*n* = 71)[a]**	**MOONFISH study (*n* = 13)[a, b]**	**Nusinersen (*n* = 76)[c]**	**Onasemnogene abeparvovec (*n* = 14)[d]**	**All patients (*N* = 174)**
Infections and infestations					
Pneumonia	1 (1.4)	0	2 (2.6)	1 (7.1)	4 (2.3)
Lower respiratory tract infection	2 (2.9)	0	1 (1.3)	0	3 (1.7)
Upper respiratory tract infection	0	0	3 (3.9)	0	3 (1.7)
Pneumonia viral	0	0	1 (1.3)	1 (7.1)	2 (1.2)
Respiratory, thoracic, and mediastinal disorders					
Respiratory failure	0	0	3 (3.9)	0	3 (1.7)
Respiratory distress	0	0	1 (1.3)	1 (7.1)	2 (1.2)
Injury, poisoning, and procedural complications					
Tibia fracture	1 (1.4)	1 (1.4)	0	0	2 (1.2)

[a]No longer in clinical development. [b]Three patients who were previously enrolled in the MOONFISH study (NCT02240355) received placebo treatment and were never switched to RG7800. [c]Three patients in the nusinersen group had also received olesoxime (NCT01302600) previously. [d]One patient in the onasemnogene abeparvovec group received treatment with onasemnogene abeparvovec first followed by nusinersen. Ten patients were enrolled in STRONG (NCT03381729), three patients in STR1VE (NCT03306277) and one patient in STR1VE-EU (NCT03461289) prior to enrollment in JEWELFISH.

Supplementary Figure 1. Median SMN protein in blood by SMA type



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