Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 30 (2020) 959–969

www.elsevier.com/locate/nmd

Long-term follow-up of patients with type 2 and non-ambulant type 3 spinal muscular atrophy (SMA) treated with olesoxime in the OLEOS trial

Francesco Muntoni[a,b,*], Enrico Bertini[c], Giacomo Comi[d], Janbernd Kirschner[e,f], Anna Lusakowska[g], Eugenio Mercuri[h], Mariacristina Scoto[a], W Ludo van der Pol[i], Carole Vuillerot[j,k], Alexander Burdeska[l], Muna El-Khairi[m], Paulo Fontoura[n], Jane Ives[m], Ksenija Gorni[o], Carol Reid[m], Sabine Fuerst-Recktenwald[n], on behalf of the OLEOS Study Group

[a] *Dubowitz Neuromuscular Centre, UCL Great Ormond Street Institute of Child Health and Great Ormond Street Hospital for Children, London, UK*
[b] *NIHR Biomedical Research Centre, UCL Great Ormond Street Institute of Child Health and Great Ormond Street Hospital NHS Trust, London, UK*
[c] *Unit of Neuromuscular and Neurodegenerative Disorders, Bambino Gesù Children's Research Hospital IRCCS, Rome, Italy*
[d] *Dino Ferrari Center, Department of Pathophysiology and Transplantation, University of Milan, Neurology Unit, I.R.C.C.S. Foundation Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy*
[e] *Department of Neuropediatrics and Muscle Disorders, Medical Center-University of Freiburg, Freiburg, Germany*
[f] *Department of Neuropediatrics, University Hospital Bonn, Bonn, Germany*
[g] *Department of Neurology, Medical University of Warsaw, Warsaw, Poland*
[h] *Paediatric Neurology and Nemo Center, Catholic University and Policlinico Gemelli, Rome, Italy*
[i] *Department of Neurology and Neurosurgery, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, the Netherlands*
[j] *Department of Paediatric Physical Medicine and Rehabilitation, Hôpital Femme Mère Enfant, Centre Hospitalier Universitaire de Lyon, France*
[k] *NeuroMyogene Institute, CNRS UMR 5310, INSERM U1217, Université de Lyon, Lyon, France*
[l] *Pharma Development, Safety, F. Hoffmann-La Roche Ltd, Basel, Switzerland*
[m] *Roche Products Limited, Welwyn Garden City, UK*
[n] *Neuroscience Product Development, F. Hoffmann-La Roche Ltd, Basel, Switzerland*
[o] *Roche Pharmaceutical Research and Early Development, Roche Innovation Center Basel, Basel, Switzerland*

Received 14 July 2020; received in revised form 15 October 2020; accepted 20 October 2020

Abstract

In a previous Phase 2 study, olesoxime had a favorable safety profile. Although the primary endpoint was not met, analyses suggested that olesoxime might help in the maintenance of motor function in patients with Types 2/3 SMA. This open-label extension study (OLEOS) further characterizes the safety, tolerability and efficacy of olesoxime over longer therapy durations. In OLEOS, no new safety risks were identified. Compared to matched natural history data, patients treated with olesoxime demonstrated small, non-significant changes in motor function over 52 weeks. Motor function scores were stable for 52 weeks but declined over the remainder of the study. The greatest decline in motor function was seen in patients ≤15 years old, and those with Type 2 SMA had faster motor function decline versus those with Type 3 SMA. Previous treatment with olesoxime in the Phase 2 study was not protective of motor function in OLEOS. Respiratory outcomes were stable in patients with Type 3 SMA >15 years old but declined in patients with Type 2 SMA and in patients with Type 3 SMA ≤15 years

* Corresponding author at: Dubowitz Neuromuscular Centre, UCL Great Ormond Street Institute of Child Health and Great Ormond Street Hospital for Children, London, UK.
E-mail address: f.muntoni@ucl.ac.uk (F. Muntoni).

https://doi.org/10.1016/j.nmd.2020.10.008

old. Overall, with no stabilization of functional measures observed over 130 weeks, OLEOS did not support significant benefit of olesoxime in patients with SMA.

Keywords: Olesoxime; Spinal muscular atrophy; Motor function measure; Natural history data; Longitudinal study.

1. Introduction

1.1. Spinal muscular atrophy (SMA)

5q-SMA is a rare, progressive neuromuscular disease characterized by motor neuron loss in the spinal cord and lower brainstem, which leads to muscle atrophy and disease-related complications [1,2]. SMA presents as a spectrum of motor and functional disabilities with five known types affecting infants, children, and adults [3,4]. SMA is caused by reduced levels of the survival of motor neuron (SMN) protein due to deletions and/or mutations of the *SMN1* gene [5,6]. A second SMN gene, *SMN2*, produces low levels of functional SMN protein that are not sufficient to fully compensate for the lack of the *SMN1* gene [7], but can modulate disease severity to produce a milder phenotype when the number of *SMN2* gene copies is increased [8-10].

In 2016, nusinersen (SPINRAZA®), an *SMN2* splicing modifier, became the first therapy approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of SMA [11,12]. More recently, the gene therapy onasemnogene abeparvovec-xioi (ZOLGENSMA®) was approved by both agencies [13,14]. However, despite these recent regulatory approvals, unmet needs remain.

The majority of patients with SMA are ineligible for onasemnogene abeparvovec, as it is currently only approved for children under the age of 2 years in the US and for patients with Type 1 SMA or $\leq$3 *SMN2* copies in the EU, and excludes patients positive for AAV9 antibodies [13,14]. Intrathecal (ITC) administration of nusinersen requires travel to specialist centers, which can place additional burden on caregivers in terms of travel time and cost [15]. Although generally well tolerated, the procedure itself is not without side-effects, which occur more frequently in older patients [16]. The procedure may need to be conducted under general anesthesia in younger children who cannot lie still throughout the procedure, and although generally safe [17], it is not yet fully understood how cumulative exposure to anesthesia affects the developing brain [18,19]. ITC procedures may also be challenging in patients with a complex spine and severe scoliosis [20]. In August 2020, risdiplam (EVRYSDI^{TM}), an orally administered small molecule *SMN2* splicing modifier, was approved by the FDA for the treatment of patients aged 2 months and older [21].

The reduction of SMN protein in SMA impairs fundamental cellular homeostatic pathways [see 22,23,24 for review]. Mitochondrial dysfunction leads to increased oxidative stress levels and impaired mitochondrial membrane potential in SMN-depleted neurons [25,26], with low energy levels and the accumulation of free radicals leading to progressive cell damage and cell death [25]. Biopsies taken from SMA patients also indicate reduced levels of mitochondrial biogenesis [27]. Taken together, these factors make mitochondrial preservation a potential therapeutic target for SMA.

1.2. Olesoxime and mechanism of action

Olesoxime (RO7090919; cholest-4en-3-one, oxime) is a cholesterol-like compound identified through its survival-promoting activity on cultured neurons deprived of trophic factors [28]. Olesoxime binds to proteins that have been implicated in the formation or modulation of the mitochondrial permeability transition pore complex, preserving essential mitochondrial functions, thereby reducing neuronal degeneration and death [28-30].

1.3. Clinical development of olesoxime

The safety and efficacy of olesoxime was previously investigated in an open-label, multiple dose Phase 1b trial (EudraCT 2006-006845-14) [31] and a Phase 2, double-blind, randomized, adaptive, parallel groups, placebo controlled study in patients with Type 2 or non-ambulatory Type 3 SMA (NCT01302600/ EudraCT 2010-020386-24) [32,33]. Eight patients were enrolled in the Phase 1b study and 165 patients were randomized to olesoxime 10 mg/kg once daily or placebo in a 2:1 ratio in the Phase 2 study [32].

The primary outcome measure in the Phase 2 study was the Motor Function Measure (MFM); a multidimensional motor function scale for assessing patients with neuromuscular disorders, that has been validated for use in SMA [34,35]. The MFM32 assesses a range of motor functions with 32 items across three domains: D1 measures standing position, transfers and ambulation; D2 measures axial and proximal motor function; and D3 measures distal motor function [34]. The raw summed score of the 32 items is converted to a 0–100 scale expressed as a percentage, with higher scores indicative of a higher level of motor function [35].

In this Phase 2 study, olesoxime was well tolerated and although the primary endpoint was not met, secondary endpoints and sensitivity analyses suggested that olesoxime

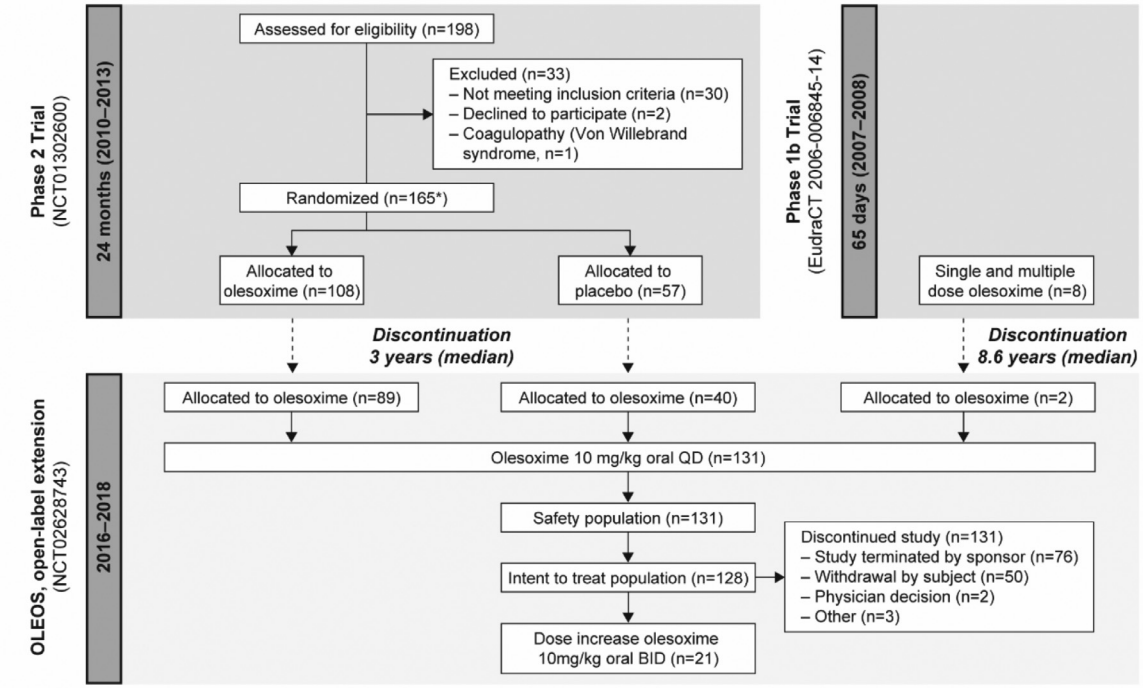


Fig. 1. CONSORT study diagram.
*Full analysis set, $n = 160$.
BID, twice daily; QD, once daily.

might help maintain motor function in patients with Types 2/3 SMA. Patients aged 6–15 years showed an improvement from baseline in MFM Domain D1+D2 scores throughout the entire treatment period of 24 months, whilst patients treated with placebo showed a consistent decline [32]. At Month 24, there was a significant difference in treatment ($p = 0.0362$) when compared to placebo [32]. Patients with SMA in this age group generally experience a decline in motor function due to changes associated with puberty [36,37]. The stabilization of these patients suggested that olesoxime may maintain motor function. The main objective of this open-label extension study (OLEOS) was to further characterize the safety, tolerability and efficacy of olesoxime in SMA, allowing a comparison of efficacy outcomes with natural history data in a matched population [38].

2. Patients and methods

2.1. Study design

This open-label, single arm, Phase 2 study (OLEOS; NCT02628743) [38] evaluating the long-term safety and efficacy of olesoxime in patients with SMA was an extension study of a Phase 1b (EudraCT 2006-006845-14) [31] and Phase 2 (NCT01302600/EudraCT2010-020386-24) trial (Fig. 1) [32,33]. One patient included in the study was diagnosed with Type 1b SMA. Eligible patients had previously participated in the olesoxime Phase 1b or blinded Phase 2 study, were able and willing to provide written informed consent, and in the investigators' judgment were able to comply with the study procedures. Target enrolment was a maximum of 171 patients. This study was conducted across 24 neuromuscular care centers in Belgium, France, Germany, Italy, Netherlands, Poland and the UK, which had previously participated in the Phase 1b and Phase 2 studies [38]. For women of childbearing potential, use of an acceptable birth control method during the treatment period and for at least 28 days after last dose was required [38]. Key exclusion criteria included: patients who had developed hypersensitivity to olesoxime, or one of its excipients; concomitant or previous participation in a *SMN2*-targeting antisense oligonucleotide study within 6 months prior to screening and the history or presence of an abnormal electrocardiogram (ECG) [38]. All patients or their parent or guardian provided written informed consent before screening. The study was approved by local institutional review boards and ethics committees. Informed consent was obtained prior to any study-related procedure.

2.2. Procedures

All enrolled patients received 10 mg/kg oral olesoxime (liquid suspension of 100 mg/mL) once daily with food either orally or via a nasogastric or gastrostomy tube for the duration of the study (manufactured and packaged by F. Hoffman-La Roche, Switzerland). Results from the previous Phase 2 trial showed an increase from baseline in MFM D1+D2 score after 2 years in patients who had higher olesoxime exposure (mean ≥7500 ng/mL). This informed an amendment to the protocol in November 2017 to increase the dose to 10 mg/kg oral olesoxime twice daily. After screening and baseline visits,

follow-up visits were scheduled for every 13 weeks until Week 52 and then every 26 weeks thereafter, up to a total treatment period of approximately 5 years. The study was terminated in December 2018 due to lack of evidence for olesoxime to provide clinically meaningful benefit in the context of the current therapeutic landscape. Final efficacy and safety analyses were completed using all data up to the end of the study.

2.3. Outcomes

The primary objective in this study was to evaluate the safety of olesoxime in patients with SMA, with adverse events (AEs), laboratory tests, vital signs, and ECG parameters as outcome measures. Investigator text for AEs was coded using MedDRA version 21.1. The secondary objectives were to evaluate the efficacy of olesoxime compared to the natural history of disease, as measured by MFM (32 item) D1+D2 and MFM total scores and the disease associated medical complications and procedures in olesoxime-treated patients compared to the natural history of the disease. Additional outcome measures included trough plasma olesoxime concentration and forced vital capacity (FVC)/theoretical capacity (TC). TC was calculated using an equation based upon patient height [39,40]. Height was measured directly, or derived from ulna length using published methods [41,42] if height could not be measured, e.g. due to scoliosis or contractures.

2.4. Natural history data matching

MFM data up to Week 52 were compared with natural history data collected from two sources: A natural history database consisting of Type 1, 2 and 3 SMA patients between 0 and 65 years of age with MFM data collected during real-life clinical practice in 29 pediatric physical medicine departments in France, Belgium, Switzerland and Argentina since 2002 [43] and NatHis-SMA, a prospective natural history study of patients between 2 and 30 years of age from 9 centers in France, Belgium and Germany sponsored by Roche and the Institute of Myology [44]. Patients remained in the study for up to 24 months between 2015 and 2018.

2.5. Analyses

Safety and efficacy data were summarized by visit. Safety analysis was based on the safety population, which includes all patients who received at least one dose of study medication. The data were summarized overall and by the dose being taken at the time of the assessment (10 mg/kg once or twice daily). Efficacy analysis was based on the intent to treat (ITT) population, which included all patients who received at least one dose of study medication and had at least one post-baseline assessment of MFM. Subgroup efficacy analyses performed included Type 2 vs. Type 3 SMA, high (mean $\geq$7500 ng/mL) vs. low (mean $<$7500 ng/mL) olesoxime pharmacokinetic (PK) exposure (exposure was calculated as the average over the whole study), age, treatment received in the previous study and the ability to sit at baseline (defined as achieving a score of >0 on Item 9 of the MFM32). Patients were matched with natural history data based on gender and SMA type. Mahalanobis distance matching, the distance between two points in multivariate space, was then applied for age and baseline MFM D1+D2 score within these groups. Optimal full matching was used: each treated patient was matched to only one untreated patient, but each untreated patient could be matched to more than one treated patient. A cap was set on the maximum number of times an untreated patient could be matched with a treated patient. Patients were matched using SAS Proc PSMATCH. The covariate balance between the two groups before and after matching was assessed using standardized mean differences and ratios of variances. The change from baseline in MFM D1+D2 was analysed using Mixed Models Repeated Measures (MMRM). The model included the treatment group, age at baseline, gender, SMA type, visit, treatment-by-visit interaction, and the baseline MFM D1+D2 score as covariates. Matched set was included in the model as a random effect.

3. Results

3.1. Patients

A total of 131 patients aged 8–34 years (mean age of 14.7 years) were enrolled between 6th January 2016 and 16th March 2017 and dosed in the study (Fig. 1). This included 129 patients previously enrolled in NCT01302600 and two patients from EudraCT 2006-006845-14. The ITT population included 128 patients. A total of 21 patients in the ITT population consented to the dose increase from 10 mg/kg oral olesoxime daily to 10 mg/kg twice daily. Demography and baseline characteristics (Table 1) were consistent with the entry criteria of the study, representing a broad range of patients with Types 2/3 SMA. A similar proportion of patients from both the olesoxime and placebo arms of the Phase 2 study (2:1 ratio) were included in this study who then all received olesoxime, indicating no selection bias. Overall, the majority of patients in the study (90/131, 68.7%) had Type 2 SMA.

Key differences between the patient populations enrolled from the previous Phase 1b and Phase 2 studies included age and period of treatment discontinuation (Table 1). Patients from the Phase 1b trial were older at baseline (mean age 24.5 [SD 13.4] years) compared with patients previously on either placebo (mean age 15.7 [SD 5.3] years) or olesoxime (mean age 14.0 [SD 5.7] years) in NCT01302600. The Phase 1b study completed 5 years earlier than the Phase 2 study and therefore patients in the Phase 1b trial had a longer discontinuation period (mean 8.56 [SD 0.91] years) than patients previously on placebo (mean 3.08 [SD 0.35] years) or olesoxime (mean 3.08 [SD 0.39] years) in NCT01302600. The difference in MFM D1+D2 score between the olesoxime and placebo arms at the end of the Phase 2 study was preserved [32] at baseline. The median treatment duration of

Table 1
Patient baseline characteristics at start of OLEOS study, safety-evaluable patients.

Baseline characteristics		Placebo in Phase 2 ($n=40$)	Olesoxime in Phase 2 ($n=89$)	Olesoxime in Phase 1b ($n=2$)	Total ($n=131$)
Age at baseline, years	Mean (SD)	15.7 (5.3)	14.0 (5.7)	24.5 (13.4)	14.7 (5.9)
	Range	8–26	8–30	15–34	8–34
Gender, *n* (%)	Male	17 (42.5)	46 (51.7)	2 (100.0)	65 (49.6)
	Female	23 (57.5)	43 (48.3)	0	66 (50.4)
SMA Type, *n* (%)	1b	0	0	1 (50.0)	1 (0.8)
	2	26 (65.0)	64 (71.9)	0	90 (68.7)
	3	14 (35.0)	25 (28.1)	1 (50.0)	40 (30.5)
Time off treatment (years)	Mean (SD)	3.1 (0.4)	3.1 (0.4)	8.6 (0.9)	3.2 (0.8)
	Range	2.6–4.8	2.4–5.1	7.9–9.2	2.4–9.2
MFM D1+D2 score	*n*	39	89	2	130
	Mean (SD)	29.2 (11.5)	30.6 (12.8)	22.0 (31.1)	30.0 (12.7)
	Range	6.7–48.0	0.0–66.7	0.0–44.0	0.0–66.7
FVC/TC, %	*n*	39	88	1	128
	Mean (SD)	51.5 (22.4)	57.3 (28.1)	86.70 (NA)	55.7 (26.5)
	Range	13.1–98.2	12.1–138.5	86.7–86.7	12.1–138.5
Functional status, *n* (%)	*n*	39	89	2	130
	Sitter*	28 (71.8)	57 (64.0)	1 (50.0)	86 (66.2)
	Non-sitter*	11 (28.2)	32 (36.0)	1 (50.0)	44 (33.8)

D, domain; FVC, forced vital capacity; MFM, Motor Function Measure; *n*, number; NA not applicable; SD, standard deviation; SMA, spinal muscular atrophy; TC, theoretical capacity.
* A sitter was defined as having achieved a score of >0 on Item 9 of the MFM scale; non-sitters achieved a score of 0.

Table 2
Patient baseline characteristics in OLEOS and a matched natural history population.

Baseline characteristics		Before matching		Matched,* weighted	
		Untreated $n=71$	Olesoxime $n=124$	Untreated $n=71$	Olesoxime $n=124$
Age at baseline, years	Mean (SD)	14.1 (7.9)	14.8 (5.9)	13.9 (6.8)	14.8 (5.9)
	Range	6–39	8–34	6–39	8–34
Gender, *n* (%)	Male	37 (52.1)	64 (51.6)	36.7 (51.6)	64.0 (51.6)
	Female	34 (47.9)	60 (48.4)	34.4 (48.4)	60.0 (48.4)
SMA Type, *n* (%)	2	54 (76.1)	84 (67.7)	48.1 (67.7)	84.0 (67.7)
	3	17 (23.9)	40 (32.3)	22.9 (32.3)	40.0 (32.3)
MFM D1+D2 score	Mean (SD)	30.2 (16.3)	30.3 (12.2)	32.8 (15.8)	30.3 (12.2)
	Range	4.0–72.0	5.3–66.7	4.0–72.0	5.3–66.7
MFM total score	Mean (SD)	40.6 (15.9)	41.7 (11.9)	43.2 (15.1)	41.7 (11.9)
	Range	6.3–76.0	12.5–74.0	6.3–76.0	12.5–74.0

D, domain; MFM, Motor Function Measure; *n*, number; SD, standard deviation; SMA, spinal muscular atrophy.
* Matching based on SMA type, age at baseline, MFM D1+D2 score at baseline and gender.

any dose of olesoxime was 817 days (range: 52–973) with a median compliance of 98.5%. The median treatment duration of olesoxime 10 mg/kg twice a day ($n=21$) was 177 days (range: 147–215) with a median compliance of 100%.

Of the 128 patients in the ITT population, 124 patients were included in the matched patient population (Table 2). Patients were excluded from the matched analysis where there was no suitable match to SMA type (Type 1b SMA, $n=1$), no MFM data at baseline ($n=1$) or where MFM20 was assessed at baseline instead of MFM32 ($n=2$). Seventy-one patients with Types 2/3 SMA were included in the natural history comparison population.

3.2. Safety

There were no deaths during the study and the majority of AEs experienced were classified as mild or moderate. All patients ($n=131$) discontinued the study and the most common reason for study discontinuation was study termination by sponsor (76 patients, 58.0%), followed by withdrawal by subject (50 patients, 38.2%), other (three patients, 2.3%) and physician decision (two patients, 1.5%). One patient (0.8%) withdrew prematurely from treatment due to non-serious AEs of asthenia and paraesthesia.

One hundred and twenty (91.6%) patients experienced an AE up to the final analysis (Table 3), and 36 (27.5%)

Table 3
Adverse events, safety-evaluable patients.

AEs (safety evaluable patients)	Placebo in Phase 2 $n=40$	Olesoxime in Phase 2 $n=89$	Olesoxime in Phase 1b $n=2$	Total patients $N=131$
Patients with ≥1 AE, *n* (%)	38 (95.0)	80 (89.9)	2 (100.0)	120 (91.6)
Total number of events	377	617	19	1013
Total number of deaths, *n* (%)	0	0	0	0
Total number of patients with ≥1:				
SAE, *n* (%)	13 (32.5)	22 (24.7)	1 (50.0)	36 (27.5)
SAE leading to withdrawal from treatment, *n* (%)	0	0	0	0
SAE leading to dose modification/interruption, *n* (%)	6 (15.0)	10 (11.2)	0	16 (12.2)
Related SAE, *n* (%)	1 (2.5)	0	0	1 (0.8)
Related AE, *n* (%)	7 (17.5)	10 (11.2)	0	17 (13.0)
Related AE leading to withdrawal from treatment, *n* (%)	1 (2.5)	0	0	1 (0.8)
Related AE leading to dose modification/interruption, *n* (%)	2 (5.0)	1 (1.1)	0	3 (2.3)
AE leading to withdrawal from treatment, *n* (%)	1 (2.5)	0	0	1 (0.8)
AE leading to dose modification/interruption, *n* (%)	14 (35.0)	28 (31.5)	0	42 (32.1)

AEs observed in SMA patients in the Placebo and Olesoxime arm in the Phase 2 study, and receiving Olesoxime in Phase 1b study. Percentages are based on N in column headings. Multiple occurrences of the same AE in one individual are counted only once except for 'total number of events' row in which multiple occurrences of the same AE are counted separately. Includes AEs with onset from first dose of study drug through 28 days after last dose of study drug.
AE, adverse event; *n*, number; SAE, serious AE.

patients experienced a serious AE (SAE). Overall, the most common AEs of any grade were upper respiratory tract infection (29.0%), nasopharyngitis (22.9%), pyrexia (21.4%), vomiting (18.3%) and headache (17.6%). AEs reported in ≥5% of patients are reported in Table S1. Overall, 74 SAEs were reported in 36 patients (27.5%). The most common SAEs were pneumonia and lower respiratory tract infection, occurring in 10/131 (7.6%) and 4/131 (3.1%) patients, respectively.

Forty-one patients reported 81 AEs leading to dose interruption of olesoxime treatment, of which the most common were vomiting (10 patients; 7.6%) and gastroenteritis (6 patients; 4.6%). The majority of these AEs resolved and were reported as not related to study medication. One patient reported a mild and non-serious AE of enteritis which led to a reduction of the olesoxime dose; this was reported as resolved at study termination.

Treatment-related AEs occurred in 17/131 (13.0%) patients; eleven were reported as not resolved, two were reported as resolving and one was reported as unknown outcome at study termination. The most common treatment-related AE was diarrhea, which was reported in four patients (3.1%). Two patients reported five mild/moderate AEs that were classified as treatment-related and led to dose interruption: vomiting in one patient and alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased and transaminases increased in another. All were reported as resolved at study termination.

One patient reported an SAE of respiratory distress that was assessed as related to olesoxime and led to dose interruption (two doses not taken, one on the day of event onset and one on Day 3 after event onset). The respiratory distress was reported as resolved after 8 days of treatment with amoxicillin/clavulanate potassium and did not recur under continuation of olesoxime.

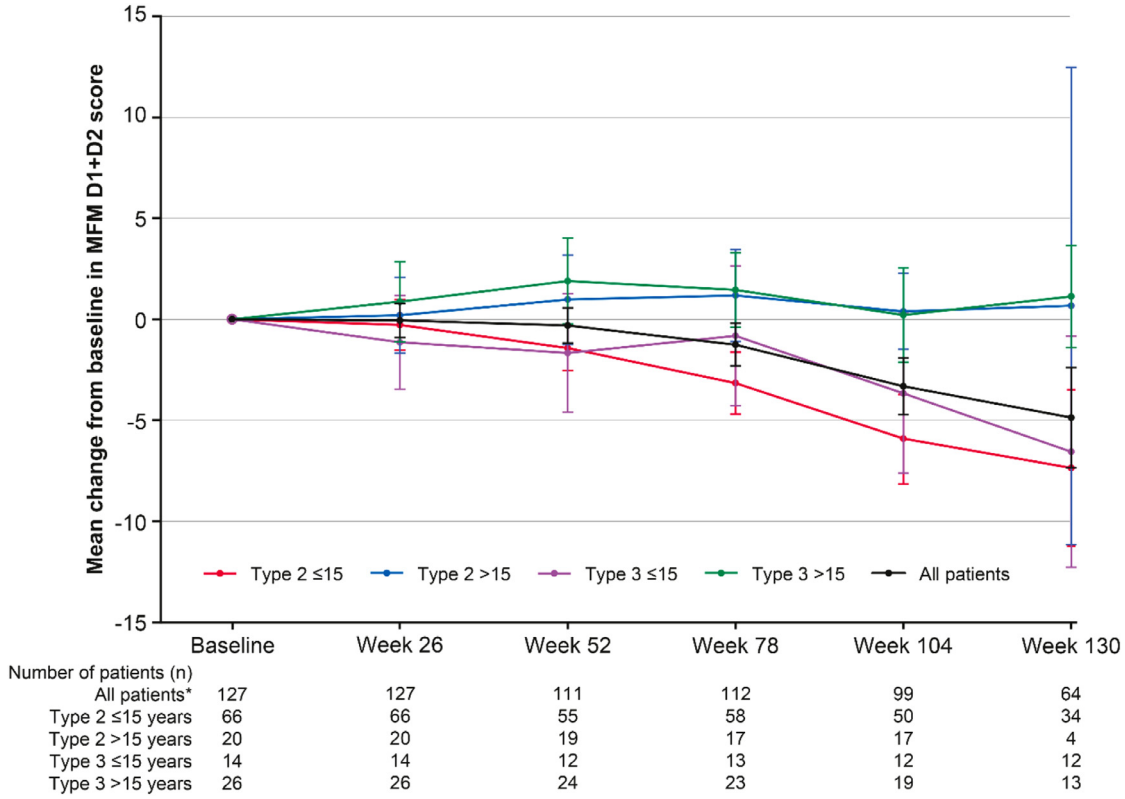
As only a small number of patients ($n=21$) switched to the 10 mg/kg twice daily dose, no comparison was performed, and no conclusions could be drawn based on dose increase. The most common AEs by dose are summarized in Table S1.

Analysis of all other safety parameters did not reveal any safety concerns.

3.3. Efficacy

The mean MFM D1+D2 score decreased in the ITT population over the course of the study (Fig. 2). Baseline motor function was maintained until Week 52; this was followed by a decline until the end of study where a mean decline of 4.87 points (95% confidence interval [CI]: −7.34, −2.39) in MFM D1+D2 score and a mean 4.02-point decline (95% CI: −6.39, −1.65) in total MFM was observed in patients remaining in the study at Week 130. Only 64/128 (50.0%) patients in the ITT population completed the assessment at Week 130. Individual patient changes from baseline in MFM D1+D2 score at Week 104 are shown in Fig. S1.

Subgroup analyses were performed to examine potential efficacy differences in olesoxime treatment due to SMA type,



Number of patients (n)						
All patients*	127	127	111	112	99	64
Type 2 ≤15 years	66	66	55	58	50	34
Type 2 >15 years	20	20	19	17	17	4
Type 3 ≤15 years	14	14	12	13	12	12
Type 3 >15 years	26	26	24	23	19	13

Fig. 2. Mean change from baseline in MFM D1+D2 score in patients treated with olesoxime by age group and SMA type in ITT population.
Mean change (±95% CIs) from baseline in MFM D1+D2 score in individuals treated with olesoxime by age group and by SMA type.
*All patients includes one patient with Type 1b SMA.
CI, confidence interval; D, domain; ITT, intent to treat; MFM, Motor Function Measure; SMA, spinal muscular atrophy.

PK exposure, age, prior exposure to olesoxime in earlier trials and the ability to sit at baseline. Results of subgroup analyses demonstrated that the greatest decline in motor function was seen in patients ≤15 years old in both Types 2 and 3 SMA, (Fig. 2), whereas in older patients (>15 years old) motor function was stable or slightly improved (Fig. 2). When age was not taken into account, there was a greater decline in patients with Type 2 SMA than in those with Type 3 SMA after Week 26 (Fig. S2). Patients who were able to sit had higher MFM scores at baseline and declined more than those who were unable to sit (Fig. S3).

The olesoxime-treated patient population was well matched to the natural history cohort with respect to gender and SMA type (Table 2). The matched olesoxime-treated population was slightly older on average, with a mean age of 14.8 years vs. 13.9 years. The matched untreated population also had higher MFM D1+D2 (32.8 vs. 30.3) and MFM total (43.2 vs. 41.7) scores. Absolute standardized mean differences were <0.2 for all variables and variance ratios ranged between 0.6 and 1.

Comparison of motor function between the natural history and olesoxime-treated patients in the matched population was carried out to Week 52. Between Week 52 and Week 104 the population of the NatHis-SMA study reduced by half as a result of patient withdrawal from that study; similarly, there was a limited number of eligible patients in the natural history database with 2-year data. Compared with the natural history data in the matched population, patients treated with olesoxime demonstrated small, non-significant changes in motor function over 52 weeks (Fig. 3). There were no significant differences in least squares means between the matched natural history and olesoxime-treated patients at Week 26 for the MFM D1+D2 score (1.03; 95% CI: −0.46, 2.52; $p=0.175$) or at Week 52 (0.74; 95% CI: −0.64, 2.12; $p=0.292$) or for the MFM total score at Week 26 (1.12; 95% CI: −0.18, 2.41; $p=0.092$) or at Week 52 (0.65; 95% CI −0.62, 1.92; $p=0.311$). At Week 52, the difference in MFM D1+D2 changes between patients treated with olesoxime and natural history data was similar for patients with Type 2 and Type 3 SMA (Fig. S4); however, due to the small number of patients with Type 3 SMA in the natural history cohort, these results should be interpreted with caution.

PK analysis (Fig. 4) demonstrated that the gradual decline observed in MFM D1+D2 score was similar in patients with higher PK exposure (mean ≥7500 ng/mL) compared with lower PK exposure (mean <7500 ng/mL). Up until Week 52 there was less decline in D1+D2 in patients previously treated with olesoxime but from Week 78 the differences diminished (Fig. S5).

Respiratory outcomes as measured by FVC/TC declined in patients over the course of the study (Fig. 5). FVC/TC was stable or improved in patients with Type 3 SMA >15 years

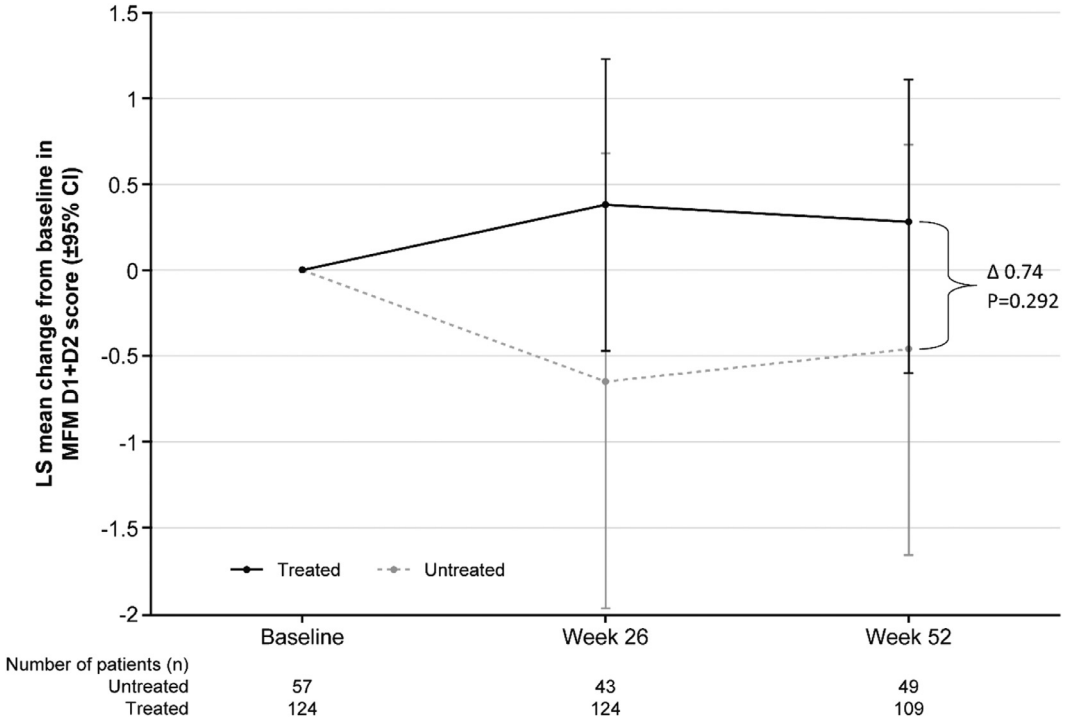


Fig. 3. LS mean change from baseline in MFM D1+D2 score in patients treated with olesoxime and a matched untreated natural history population (MMRM analysis; ITT population).
A comparison of the LS mean change (±95% CIs) from baseline in MFM D1+D2 score over 52 weeks in patients treated with olesoxime and a matched untreated natural history population. MMRM analysis. Matching based on SMA type, age at baseline, MFM D1+D2 score at baseline and gender.
CI, confidence interval; D, domain; ITT, intent to treat; LS, least squares; MFM, Motor Function Measure; MMRM, mixed models repeated measures; SMA, spinal muscular atrophy.

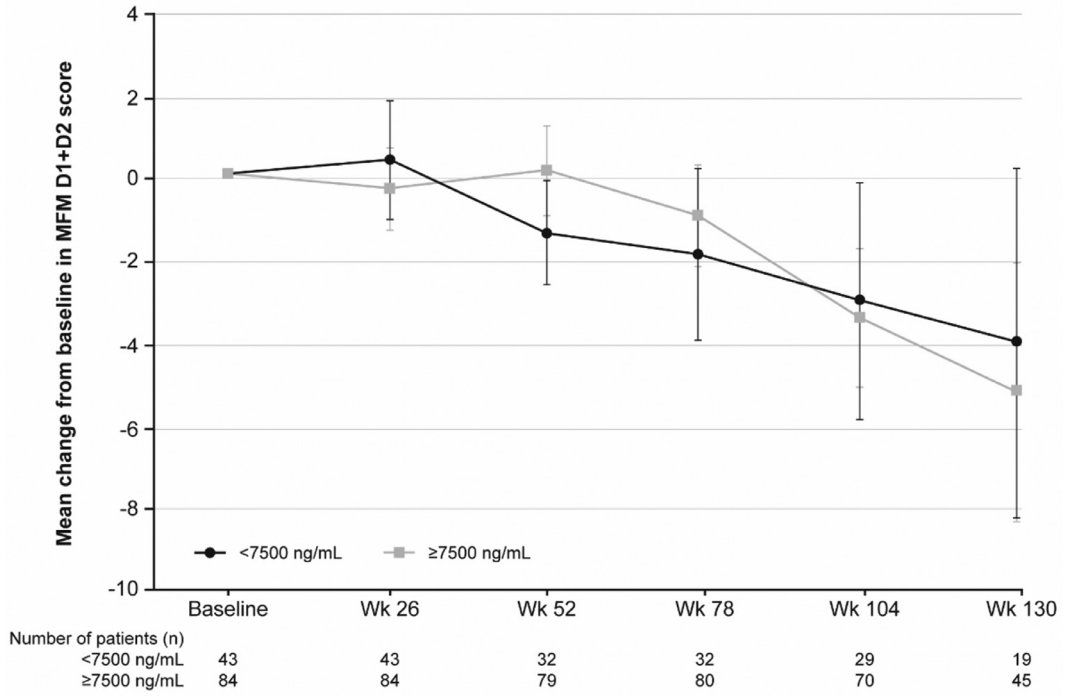
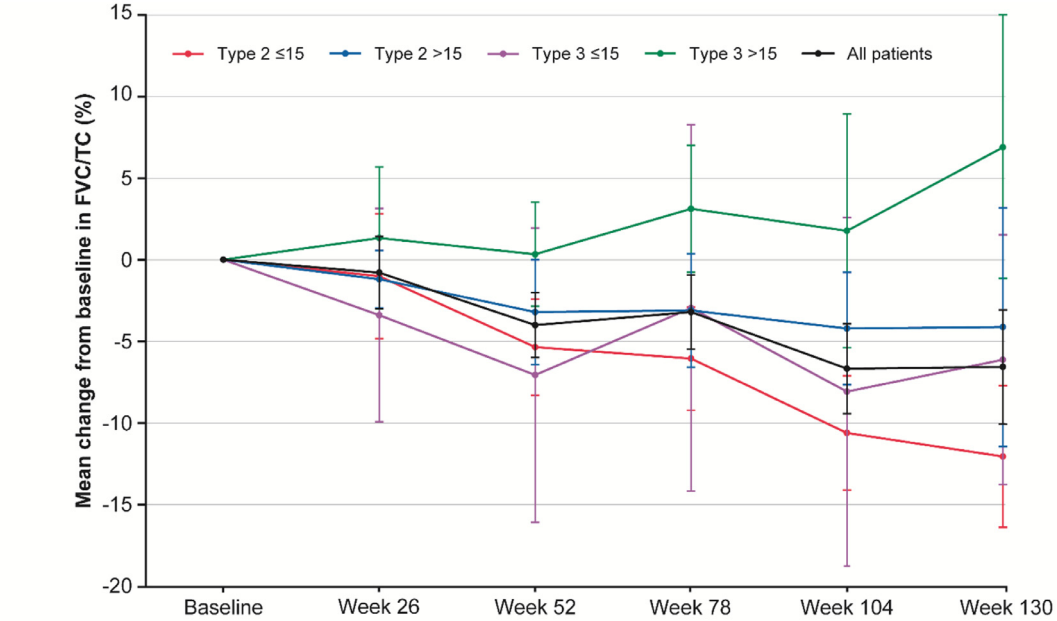


Fig. 4. Mean change from baseline in MFM D1+D2 score by PK exposure in ITT population.
Mean change (±95% CIs) from baseline in MFM D1+D2 score in individuals who have a higher PK exposure (mean ≥7500 mg/mL) or a lower PK exposure (mean <7500 mg/mL) to olesoxime.
CI, confidence interval; D, domain; ITT, intent to treat; MFM, Motor Function Measure; PK, pharmacokinetics.



Number of patients (n)						
All patients	125	118	112	107	94	65
Type 2 ≤15 years	65	60	56	53	46	35
Type 2 >15 years	21	21	18	18	16	5
Type 3 ≤15 years	14	12	14	13	13	12
Type 3 >15 years	25	25	24	23	19	13

Fig. 5. Mean change from baseline in FVC/TC by age group and SMA type in ITT population.
Mean change (±95% CIs) in FVC/TC (%) from baseline by age group and by SMA type.
CI, confidence interval; FVC, forced vital capacity; ITT, intent to treat; SMA, spinal muscular atrophy; TC, theoretical capacity.

old but declined in patients with Type 2 SMA and patients with Type 3 SMA ≤15 years old (Fig. 5).

4. Discussion

This study aimed to further characterize the safety, tolerability and efficacy of olesoxime in SMA. Olesoxime had a favorable safety profile; one patient discontinued treatment due to an AE. The most common SAE was pneumonia and the most common any grade AE was upper respiratory tract infection. Safety results were consistent with the previous Phase 2 study of olesoxime in patients with SMA [32]. The observed AE profile was consistent with the symptoms and disease history of patients with SMA [45]. The length of the study period and the number of patients ($n = 21$) exposed to olesoxime 10 mg/kg twice a day was insufficient to draw conclusions on comparative safety at higher doses.

Olesoxime treatment resulted in maintained motor function for 52 weeks; however, at study end (130 weeks), a 4.02-point mean decline in total MFM and a 4.87-point decline in D1+D2 score was observed. Some differences in MFM scores between patients treated with olesoxime and patients that received placebo in the previous Phase 2 trial were observed. During the initial 52 weeks, patients previously treated with placebo had a more prominent decline in MFM score than those previously treated with olesoxime, suggesting potential differences in the initial randomized groups. However, by Week 78, although patients treated with placebo did have larger declines in motor function, the numerical difference between the two groups had reduced.

Matched analyses showed only small, non-significant differences between untreated patients and patients treated with olesoxime, and even this small difference diminished over time. There was no clear evidence that olesoxime provides significantly better efficacy than natural history after 12 months.

Natural history study investigating changes in motor function in patients with Types 2 and 3 SMA, as assessed by the Hammersmith Functional Motor Scale, have demonstrated differing trajectories of motor function decline according to patient age, whereby patients between the ages of 5 and 15 years old showed the greatest negative change over 12 months compared with older age groups [46]. Longitudinal studies of pulmonary function in SMA have demonstrated that FVC correlates well with motor function and is an important determinant of survival in patients with SMA [47].

OLEOS patients demonstrated a steady decline in FVC/TC during the study, which has also been reported looking at % estimated FVC values in untreated patients of this age range with Types 2 and 3 SMA [48]. However, FVC/TC values appeared more stable in older patients (>15 years) with Type 3 SMA in OLEOS. Wijngaarde et al. [48] found % estimated FVC in untreated patients with Type 3a SMA continued to decline until a slightly older age (around 20 years), whereas % estimated FVC remained relatively stable

in untreated patients with Type 3b SMA. Estimated/theoretical FVC is derived from patient height, which can be difficult to measure in patients with SMA due to scoliosis. Differences in the method used to determine height could account for some of the difference between the two studies: Wijngaarde et al. [48] used arm span as a surrogate measure in these patients, whereas OLEOS derived patient height from ulna length. Patients in OLEOS were also not further classified into Types 3a and 3b.

In contrast to the observations from the previous Phase 2 trial, in which olesoxime treatment resulted in an increase in MFM score from baseline in patients with higher olesoxime exposure (mean $\geq$7500 ng/mL) after 2 years, no difference was observed in MFM score between high- and low-exposure groups. These results demonstrate that there is no clear evidence to support higher olesoxime exposure.

Overall, the results of OLEOS did not confirm the results observed in the Phase 2 study; there was no stabilization of motor function and FVC declined over the course of the study. There was also no effect of olesoxime treatment at a higher exposure or at a younger age. It is therefore difficult to determine a position for olesoxime in the SMA treatment landscape alongside recently approved SMN-upregulating treatments such as nusinersen, onasemnogene abeparvovec and risdiplam, which have dramatically altered the natural history of SMA.

As SMA primarily affects children, the long-term management of this disease is a key consideration for an effective therapy in this population. Treatment of SMA may proceed in the direction of combination therapies integrating treatments which increase SMN levels together with those that support muscle function and/or neuroprotection [49], particularly in patients who continue to lose muscle function on treatment and in those patients who are older with longer disease duration. An under-investigated concern in these patients is fatiguability, with SMA patients reporting that they fatigue easily when carrying out repetitive motions, such as when moving the arm up and down during eating or brushing teeth [50,51]. Although not investigated in OLEOS, it would be particularly important to ascertain how therapies that alter mitochondrial signaling pathways may impact muscle fatigue. However, while theoretically mitochondrial preservation might be a good partner for combination with other SMN-targeting therapies, the clinical effects obtained with olesoxime are not robust or stable enough to make it a good partner for combination studies.

Acknowledgments

This study was funded by F. Hoffmann-La-Roche Ltd, Basel, Switzerland. The authors would like to thank the patients and their families for participating in the OLEOS study, as well as the investigators and all trial staff. The authors would like to thank Dr Jean-Marie Cuisset for his contributions to the study. Medical writing support was provided by MediTech Media, which was funded by F. Hoffmann-La-Roche Ltd, in accordance with Good Publication Practice (GGP3) guidelines (http://www.ismpp.org/gpp3).

Qualified researchers may request access to individual patient level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here (https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2020.10.008.

References

[1] Farrar MA, Kiernan MC. The genetics of spinal muscular atrophy: progress and challenges. Neurotherapeutics 2015;12:290–302.
[2] Mercuri E, Bertini E, Iannaccone ST. Childhood spinal muscular atrophy: controversies and challenges. Lancet Neurol 2012;11:443–52.
[3] Russman BS. Spinal muscular atrophy: clinical classification and disease heterogeneity. J Child Neurol 2007;22(8):946–51.
[4] Zerres K, Rudnik-Schoneborn S. Natural history in proximal spinal muscular atrophy. Clinical analysis of 445 patients and suggestions for a modification of existing classifications. Arch Neurol 1995;52:518–23.
[5] Kolb SJ, Kissel JT. Spinal muscular atrophy: a timely review. Arch Neurol 2011;68:979–84. doi:10.1001/archneurol.2011.74.
[6] Lefebvre S, Burglen L, Reboullet S, Clermont O, Burlet P, Viollet L, et al. Identification and characterization of a spinal muscular atrophy-determining gene. Cell 1995;80:155–65.
[7] Lorson CL, Hahnen E, Androphy EJ, Wirth B. A single nucleotide in the SMN gene regulates splicing and is responsible for spinal muscular atrophy. PNAS USA 1999;96:6307–11.
[8] Feldkotter M, Schwarzer V, Wirth R, Wienker TF, Wirth B. Quantitative analyses of SMN1 and SMN2 based on real-time lightCycler PCR: fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy. Am J Hum Genet 2002;70:358–68.
[9] Harada Y, Sutomo R, Sadewa AH, Akutsu T, Takeshima Y, Wada H, et al. Correlation between SMN2 copy number and clinical phenotype of spinal muscular atrophy: three SMN2 copies fail to rescue some patients from the disease severity. J Neurol 2002;249:1211–19. doi:10.1007/s00415-002-0811-4.
[10] Crawford TO, Paushkin SV, Kobayashi DT, Forrest SJ, Joyce CL, Finkel RS, et al. Evaluation of SMN protein, transcript, and copy number in the biomarkers for spinal muscular atrophy (BforSMA) clinical study. PLoS ONE 2012;7:e33572 [doi]. doi:10.1371/journal.pone.0033572.
[11] Biogen Inc. SPINRAZA® (nusinersen) 2020 US prescribing information; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/209531lbl.pdf.
[12] Biogen Inc. SPINRAZA® (nusinersen) 2020 EMA prescribing information; Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004312/WC500229704.pdf.
[13] AveXis Inc. ZOLGENSMA® (onasemnogene abeparvovec-xioi) 2020, US prescribing information; Available from: https://www.fda.gov/media/126109/download.

[14] European Medicines Agency. Zolgensma. 2020 Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/zolgensma.
[15] Michelson D, Ciafaloni E, Ashwal S, Lewis E, Narayanaswami P, Oskoui M, et al. Evidence in focus: nusinersen use in spinal muscular atrophy: report of the guideline development, dissemination, and implementation subcommittee of the American academy of neurology. Neurology 2018;91:923–33. doi:10.1212/WNL.0000000000006502.
[16] Hache M, Swoboda KJ, Sethna N, Farrow-Gillespie A, Khandji A, Xia S, et al. Intrathecal injections in children with spinal muscular atrophy: nusinersen clinical trial experience. J Child Neurol 2016;31:899–906. doi:10.1177/0883073815627882.
[17] Bielsky AR, Fuhr PG, Parsons JA, Yaster M. A retrospective cohort study of children with spinal muscular atrophy type 2 receiving anesthesia for intrathecal administration of nusinersen. Paediatr Anaesth 2018;28:1105–8. doi:10.1111/pan.13500.
[18] Hansen TG. Use of anesthetics in young children consensus statement of the European society of anaesthesiology (ESA), the European society for paediatric anaesthesiology (ESPA), the European association of cardiothoracic anaesthesiology (EACTA), and the European safe tots anaesthesia research initiative (EuroSTAR). Paediatr Anaesth 2017;27:558–9. doi:10.1111/pan.13160.
[19] Psaty BM, Platt R, Altman RB. Neurotoxicity of generic anesthesia agents in infants and children: an orphan research question in search of a sponsor. JAMA 2015;313:1515–16. doi:10.1001/jama.2015.1149.
[20] Bortolani S, Stura G, Ventilii G, Vercelli L, Rolle E, Ricci F, et al. Intrathecal administration of nusinersen in adult and adolescent patients with spinal muscular atrophy and scoliosis: transforaminal versus conventional approach. Neuromusc Disord 2019;29:742–6. doi:10.1016/j.nmd.2019.08.007.
[21] Genentech. Evrysdi (risdiplam) US prescribing information 2020; Available from: https://www.gene.com/download/pdf/evrysdi_prescribing.pdf.
[22] Chaytow H, Huang YT, Gillingwater TH, Faller KME. The role of survival motor neuron protein (SMN) in protein homeostasis. Cell Mol Life Sci 2018;75:3877–94. doi:10.1007/s00018-018-2849-1.
[23] Burghes AH, Beattie CE. Spinal muscular atrophy: why do low levels of survival motor neuron protein make motor neurons sick? Nature reviews. Neuroscience 2009;10:597–609. doi:10.1038/nrn2670.
[24] Singh RN, Howell MD, Ottesen EW, Singh NN. Diverse role of survival motor neuron protein. Biochim Biophys Acta 2017;1860:299–315.
[25] Acsadi G, Lee I, Li X, Khaidakov M, Pecinova A, Parker GC, et al. Mitochondrial dysfunction in a neural cell model of spinal muscular atrophy. J Neurosci Res 2009;87:2748–56. doi:10.1002/jnr.22106.
[26] Miller N, Shi H, Zelikovich AS, Ma YC. Motor neuron mitochondrial dysfunction in spinal muscular atrophy. Hum Mol Genet 2016;25:3395–406. doi:10.1093/hmg/ddw262.
[27] Ripolone M, Ronchi D, Violano R, Vallejo D, Fagiolari G, Barca E, et al. Impaired muscle mitochondrial biogenesis and myogenesis in spinal muscular atrophy. JAMA Neurol 2015;72:666–75. doi:10.1001/jamaneurol.2015.0178.
[28] Bordet T, Berna P, Abitbol JL, Pruss RM. Olesoxime (TRO19622): a novel mitochondrial-targeted neuroprotective compound. Pharmaceuticals (Basel) 2010;3(2):345–68.
[29] Gouarne C, Giraudon-Paoli M, Seimandi M, Biscarrat C, Tardif G, Pruss RM, et al. Olesoxime protects embryonic cortical neurons from camptothecin intoxication by a mechanism distinct from BDNF. Br J Pharmacol 2013;168:1975–88. doi:10.1111/bph.12094.
[30] Gouarne C, Tracz J, Paoli MG, Deluca V, Seimandi M, Tardif G, et al. Protective role of olesoxime against wild-type alpha-synuclein-induced toxicity in human neuronally differentiated SHSY-5Y cells. Br J Pharmacol 2015;172:235–45. doi:10.1111/bph.12939.
[31] AG FH-LR. 2020 Clinical trial results: open-label phase Ib, dose-ranged, single and multiple dose study to assess safety and pharmacokinetics of TRO19622 in 6-25 year old spinal muscular atrophy (SMA) patients. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2006-006845-14/results.
[32] Bertini E, Dessaud E, Mercuri E, Muntoni F, Kirschner J, Reid C, et al. Safety and efficacy of olesoxime in patients with type 2 or non-ambulatory type 3 spinal muscular atrophy: a randomized, double-blind, placebo-controlled phase 2 trial. Lancet Neurol 2017;16:513–22. doi:10.1016/s1474-4422(17)30085-6.
[33] ClinicalTrials.gov. 2020 NCT01302600: safety and efficacy of Olesoxime (TRO19622) in 3-25 years SMA patients. Available from: https://clinicaltrials.gov/ct2/show/NCT01302600.
[34] Vuillerot C, Rippert P, Roche S, Berard C, Margirier F, de Lattre C, et al. Development and validation of a motor function classification in patients with neuromuscular disease: the NM-score. Ann Phys Rehabil Med 2013;56:673–86. doi:10.1016/j.rehab.2013.10.002.
[35] Bérard C, Girardot F, Payan C. User's manual: MFM-32 & MFM-20; Available from: https://mfm-nmd.org/get-a-user-manual/?lang=en.
[36] Crawford TO. Concerns about the design of clinical trials for spinal muscular atrophy. Neuromusc Disord 2004;14:456–60. doi:10.1016/j.nmd.2004.04.004.
[37] Mercuri E, Finkel R, Montes J, Mazzone ES, Sormani MP, Main M, et al. Patterns of disease progression in type 2 and 3 SMA: implications for clinical trials. Neuromusc Disord 2016;26:126–31.
[38] ClinicalTrials.gov. 2020 NCT02628743: a study to evaluate long term safety, tolerability, and effectiveness of olesoxime in patients with spinal muscular atrophy; Available from: https://clinicaltrials.gov/ct2/show/NCT02628743.
[39] Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Eur Respir J 1993;6(Suppl 16):5–40. doi:10.1183/09041950.005s1693.
[40] Quanjer PH, Borsboom GJ, Brunekreef B, Zach M, Forche G, Cotes JE, et al. Spirometric reference values for white European children and adolescents: polgar revisited. Pediatr Pulmonol 1995;19:135–42.
[41] Gauld LM, Kappers J, Carlin JB, Robertson CF. Height prediction from ulna length. Dev Med Child Neurol 2004;46:475–80. doi:10.1017/s0012162204000787.
[42] Elia M. *The 'MUST' report. Nutritional screening of adults: a multidisciplinary responsibility. Development and use of the 'malnutrition universal screening tool' ('MUST') for adults.* 2003, malnutrition advisory group (MAG), a standing committee of the British association of parenteral and enteral nutrition (BAPEN). Redditch; 2003.
[43] Vuillerot C, Payan C, Iwaz J, Ecochard R, Berard C, Group MFMS. Responsiveness of the motor function measure in patients with spinal muscular atrophy. Arch Phys Med Rehabil 2013;94:1555–61.
[44] Clinicaltrials.gov. 2020 NCT02391831: prospective study of the natural history of patients with Type 2 and 3 spinal muscular atrophy (NatHis-SMA). Available from: https://www.clinicaltrials.gov/ct2/show/NCT02391831?term=NCT02391831&draw=2&rank=1.
[45] Chabanon A, Seferian AM, Daron A, Pereon Y, Cances C, Vuillerot C, et al. Prospective and longitudinal natural history study of patients with type 2 and 3 spinal muscular atrophy: baseline data NatHis-SMA study. PLoS ONE 2018;13:e0201004.
[46] Mercuri E, Finkel R, Montes J, Mazzone ES, Sormani MP, Main M, et al. Patterns of disease progression in type 2 and 3 SMA: implications for clinical trials. Neuromuscul Disord 2016;26:126–31. doi:10.1016/j.nmd.2015.10.006.
[47] Samaha FJ, Buncher CR, Russman BS. Pulmonary function in spinal muscular atrophy. J Child Neurol 1994;9(3):326–9.
[48] Wijngaarde CA, Veldhoen ES, van Eijk RPA, Stam M, Otto LAM, Asselman FL, et al. Natural history of lung function in spinal muscular atrophy. Orphanet J Rare Dis 2020;15:88. doi:10.1186/s13023-020-01367-y.
[49] Waldrop MA, Kolb SJ. Current treatment options in neurology-SMA therapeutics. Neuromuscul Disord 2019;21(25):1–11.
[50] Bartels B, Habets LE, Stam M, Wadman RI, Wijngaarde CA, Schoenmakers M, et al. Assessment of fatigability in patients with spinal muscular atrophy: development and content validity of a set of endurance tests. BMC Neurol 2019;19:21. doi:10.1186/s12883-019-1244-3.
[51] Stam M, Wadman RI, Bartels B, Leeuw M, Westeneng HJ, Wijngaarde CA, et al. A continuous repetitive task to detect fatigability in spinal muscular atrophy. Orphanet J Rare Dis 2018;13:160. doi:10.1186/s13023-018-0904-5.