Safety and efficacy of olesoxime in patients with type 2 or non-ambulatory type 3 spinal muscular atrophy: a randomised, double-blind, placebo-controlled phase 2 trial

*Enrico Bertini, Eric Dessaud, Eugenio Mercuri, Francesco Muntoni, Janbernd Kirschner, Carol Reid, Anna Lusakowska, Giacomo P Comi, Jean-Marie Cuisset, Jean-Louis Abitbol, Bruno Scherrer, Patricia Sanwald Ducray, Jeppe Buchbjerg, Eduardo Vianna, W Ludo van der Pol, Carole Vuillerot, Thomas Blaettler, Paulo Fontoura, for the Olesoxime SMA Phase 2 Study Investigators**

*Members listed in the Acknowledgments

Department of Neurosciences and Neurorehabilitation, Bambino Gesù Children's Research Hospital IRCCS, Rome, Italy (Prof E Bertini MD); **Trophos, Marseille, France** (E Dessaud PhD, J-L Abitbol MD); **Paediatric Neurology and Nemo Center, Catholic University and Policlinico Gemelli, Rome, Italy** (Prof E Mercuri MD); **Dubowitz Neuromuscular Centre, UCL Great Ormond Street Institute of Child Health and Great Ormond Street Hospital for Children, London, UK** (Prof F Muntoni MD); **Department of Neuropediatrics and Muscle Disorders, Medical Center-University of Freiburg, Freiburg, Germany** (Prof J Kirschner MD); **Biostatistics, Roche Products Limited, Welwyn Garden City, UK** (C Reid PhD); **Department of Neurology, Medical University of Warsaw, Warsaw, Poland** (A Lusakowska MD); **Dino Ferrari Center, Department of Pathophysiology and Transplantation, University of Milan, Neurology Unit, IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy** (Prof G P Comi MD); **Department of Neuropediatrics, Neuromuscular Disease Reference Centre, Roger-Salengro Hospital, Regional University Teaching Hospital, Lille, France** (J-M Cuisset MD); **Bruno Scherrer Conseil, Saint-Arnoult-en-Yvelines,**

Summary

Background **Spinal muscular atrophy (SMA) is a progressive motor neuron disease causing loss of motor function and reduced life expectancy, for which limited treatment is available. We investigated the safety and efficacy of olesoxime in patients with type 2 or non-ambulatory type 3 SMA.**

Methods **This randomised, double-blind, placebo-controlled, phase 2 study was done in 22 neuromuscular care centres in Belgium, France, Germany, Italy, Netherlands, Poland, and the UK. Safety and efficacy of olesoxime were assessed in patients aged 3–25 years with genetically confirmed type 2 or non-ambulatory type 3 SMA. A centralised, computerised randomisation process allocated patients (2:1 with stratification by SMA type and centre) to receive olesoxime (10 mg/kg per day) in an oral liquid suspension or placebo for 24 months. Patients, investigators assessing outcomes, and sponsor study personnel were masked to treatment assignment. The primary outcome measure was change from baseline compared with 24 months between the two treatment groups in functional domains 1 and 2 of the Motor Function Measure (MFM D1 + D2) assessed in the full analysis population. A shorter, 20-item version of the MFM, which was specifically adapted for young children, was used to assess patients younger than 6 years. Safety was assessed in the intention-to-treat population. The trial is registered with ClinicalTrials.gov, number NCT01302600.**

Findings **The trial was done between Nov 18, 2010, and Oct 9, 2013. Of 198 patients screened, 165 were randomly assigned to olesoxime (n=108) or placebo (n=57). Five patients in the olesoxime group were not included in the primary outcome analysis because of an absence of post-baseline assessments. The change from baseline to month 24 on the primary outcome measure was 0·18 for olesoxime and –1·82 for placebo (treatment difference 2·00 points, 96% CI –0·25 to 4·25, p=0·0676). Olesoxime seemed to be safe and generally well tolerated, with an adverse event profile similar to placebo. The most frequent adverse events in the olesoxime group were pyrexia (n=34), cough (n=32), nasopharyngitis (n=25), and vomiting (n=25). There were two patient deaths (one in each group), but these were not deemed to be related to the study treatment.**

Interpretation **Olesoxime was safe at the doses studied, for the duration of the trial. Although the primary endpoint was not met, secondary endpoints and sensitivity analyses suggest that olesoxime might maintain motor function in patients with type 2 or type 3 SMA over a period of 24 months. Based on these results, olesoxime might provide meaningful clinical benefits for patients with SMA and, given its mode of action, might be used in combination with other drugs targeting other mechanisms of disease, although additional evidence is needed.**

Funding **AFM Téléthon and Trophos SA.**

Introduction

Spinal muscular atrophy (SMA) is a rare and severely debilitating neuromuscular disease that manifests predominantly in infancy and childhood.[1,2] In type 2 and type 3 SMA, the deterioration of motor function results in substantial disability and in patients and a high burden for their caregivers.[3] SMA is caused by loss-of-function mutations in the Survival of Motor Neuron 1 (*SMN1*) gene. The absence of the *SMN1* gene results ininsufficient levels of SMN protein in cells, which particularly affect motor neurons and neuromuscular junctions, leading to muscle weakness, hypotonia, and atrophy.[1,4]

Although reduced SMN protein levels impair many fundamental neuronal processes and are the triggering event in all SMA types, the downstream pathological consequences of atrophy and denervation are also related to mitochondrial dysfunction, which also affects other cell types.[5–8] Given their role on energy production, mitochondria are vital for cells with a high energy demand, including motor neurons and muscle fibres that are central to the pathophysiology of SMA.[5,7,9,10]

Current therapies in clinical development have aimed to increase SMN production systemically, either by replacing SMN1 (eg, gene therapy with AVXS-101) or by SMN2 splicing modulators (eg, RO6885247, RO7034067, and LMI070). Nusinersen, a SMN2 splicing modulator for intrathecal administration, has been approved by the US Food and Drug Administration for treatment of SMA.[11]

France (B Scherrer PhD); **Roche Pharma Research and Early Development, Clinical Pharmacology, Roche Innovation Center Basel, Switzerland** (P Sanwald Ducray PhD); **Neuroscience Product Development, F Hoffmann-La Roche Ltd, Basel, Switzerland** (J Buchbjerg MSc, E Vianna PhD, T Blaettler MD, P Fontoura MD); **Department of Neurology and Neurosurgery, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, Netherlands** (W Ludo van der Pol MD); **Department of Paediatric Physical Medicine and Rehabilitation, Hôpital Femme Mère Enfant, Centre Hospitalier Universitaire de Lyon, France** (C Vuillerot MD)

Correspondence to: Prof Enrico Bertini, Department of Neurosciences and Neurorehabilitation, Bambino Gesù Children's Research Hospital IRCCS, Piazza Sant'Onofrio, 4-00165 Rome, Italy
enricosilvio.bertini@opbg.net

x

Research in context

Evidence before this study

Approved treatment for spinal muscular atrophy (SMA) is limited to nusinersen, an intrathecal-administered, antisense oligonucleotide intended to restore deficient SMN protein concentrations in motor neurons. However, unmet medical need remains in patients with SMA for additional, potentially complementary therapies that delay disease progression or augment the benefit of other therapies; substantial efforts have been invested to identify the key mechanisms of disease and test potential compounds. There is growing evidence that mitochondrial dysfunction is a key mechanism and a valid therapeutic target in neurological diseases, including SMA. In-vitro studies showed that olesoxime localises at the mitochondrial membrane, where it increases functional integrity of mitochondria in cortical neurons, and protects against apoptosis by preventing release of pro-apoptotic cytochrome C. At the time of study design for the present trial, only one large multicentre efficacy study had been done, assessing riluzole in patients with type 1 SMA (NCT00774423), for which results had not been published.

Added value of this study

This study is the largest and longest international study done so far in patients with SMA, and evaluates the safety and efficacy of olesoxime in a population of patients with type 2 or type 3 SMA. Although the study did not meet the primary endpoint, secondary endpoints and sensitivity analyses of the primary endpoint suggest some indications of efficacy in terms of maintenance of motor function over 2 years. Recent evidence suggests that maintenance of motor function is a key aspiration for patients with SMA as it preserves activities of daily living. The study also allowed, for the first time, the prospective assessment of motor function using both the Motor Function Measure and Hammersmith Functional Motor Scale, providing novel data for these measures in a large controlled study setting over a 24-month period.

Implications of all available evidence

The results of this study support the continued development of olesoxime as a therapy for SMA, a progressive, debilitating disease with reduced life expectancy, for which only one approved therapy exists. The clinical development of olesoxime will continue with an open-label extension study for patients previously treated in the phase 2 study (NCT02628743), and a phase 3 trial is being planned. Given the paucity of approved treatments for patients with SMA, the results of this study provide both invaluable information for future trial design and encouraging evidence on the part that olesoxime might play as a novel drug for SMA.

However, therapies that augment SMN levels might not benefit all patients, based on evidence from mouse models.[12] Consequently, an important role might exist for systemic non-SMN therapies that target alternative mechanisms, possibly in a complementary or synergistic manner, which might maintain motor units, muscle cells, and other affected cell types, particularly in the slow degenerative phase of the disease.

Olesoxime prevents excessive permeability of the mitochondrial membrane under stress conditions,[13–15] preventing apoptosis by reducing the release of pro-apoptotic factors and maintaining energy production.[13–15] Olesoxime showed neuroprotective and neuro-regenerative effects in several animal models of motor nerve degeneration, reducing pro-apoptotic factor release from neuronal mitochondria.[13,16] In a transgenic mouse model of severe SMA ($SMN^{F7/F7}$; NSE-Cre mice), daily olesoxime administration extended survival compared with vehicle-treated mice.[13] Taken together, these data suggest that olesoxime might maintain motor neuron function and might be a therapeutic drug in the treatment of SMA.[13,16]

Following a phase 1 study in SMA that assessed preliminary safety, tolerability, and pharmacokinetics,[17] accompanied by safety data in a phase 2/3 trial in amyotrophic lateral sclerosis,[18] this phase 2 study aimed to assess the safety, tolerability, and efficacy of olesoxime in patients with type 2 or non-ambulatory type 3 SMA.

Methods

Study design and participants

We did a randomised, double-blind, placebo-controlled phase 2 study in 22 neuromuscular care centres in Belgium, France, Germany, Italy, Netherlands, Poland, and the UK (appendix). All sites were centres with expertise in treating patients with SMA in line with the published standards of care for SMA.

Patients aged 3–25 years with type 2 or non-ambulatory type 3 SMA were recruited mainly via information disseminated through the TREAT-NMD website, patient registries, and in the clinics at each site, and were eligible for inclusion if they had weakness and hypotonia consistent with a clinical diagnosis of SMA type 2 or 3; genetic diagnosis of SMA with homozygous deletion of *SMN1* exon 7, or a heterozygous deletion accompanied by a point mutation on the other allele; Motor Function Measure (MFM) relative score (percentage of the maximum sum of both dimensions) of 15% or higher (functional domain 1 [D1] plus functional domain 2 [D2] score); Hammersmith Functional Motor Scale (HFMS) score at baseline between 3 and 38 (non-ambulatory); onset of symptoms at 3 years of age or younger; and ability to take the study treatment (tested at screening after informed consent). Key exclusion criteria included substantial central nervous system impairment, neuro-degenerative or neuromuscular disease other than SMA, and use of drugs intended for the treatment of SMA. A full

list of criteria is available in the appendix. 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.

Randomisation and masking

Patients were randomly assigned in a 2:1 ratio to receive olesoxime or placebo, with stratification by SMA type and centre. A 2:1 randomisation as a means to limit placebo exposure was deemed more ethically acceptable in a progressive, debilitating disease with no available treatment options. Randomisation lists were generated centrally by an independent statistician (Business & Decision Life Sciences, Montrouge, France) using validated randomisation software (SAS version 9.2, SAS Institute Inc, Cary, NC, USA). To maintain masking, active and placebo treatments were supplied in brown glass bottles, and randomisation details were provided using secure procedures to the clinical research organisation that did the packaging of the treatment units and to the laboratory that did the olesoxime pharmacokinetics bioanalysis assay. All investigators, site personnel, patients, and the sponsor study personnel were masked to treatment assignment until completion of the study.

Procedures

Patients received oral olesoxime 100 mg/mL liquid suspension formulation (manufactured by Minakem, Beuvry-la-Forêt, France, and packaged by CRID PHARMA, Saint-Gély-du-Fesc, France) at a weight-based fixed dose of 10 mg/kg once a day or matching placebo with their main daily meal for 24 months. After screening and baseline visits, follow-up visits were scheduled for week 4 and week 13 after randomisation, after which participants were assessed every 13 weeks for a total of nine visits over the 24-month treatment period. The full schedule of assessments is provided in the appendix. An interim efficacy analysis was done by an independent statistician when all patients had been treated for 12 months, to assess the need to continue the study to reach the planned objective. In the event of positive and significant results in favour of olesoxime, the study was to be considered successful and all patients were to be switched to olesoxime to allow assessment of the sustainability of the treatment effect and safety. If the results were significantly in favour of placebo, the study was to be discontinued for failure (futility). The interim efficacy analysis was reviewed by an independent Data Monitoring Committee. The final efficacy and safety analysis was done using data at 24 months.

Outcomes

The primary outcome measure was the change from baseline between treatment groups to month 24 as assessed by D1 + D2 of the 32-item MFM (MFM32).[19] A shorter 20-item version (MFM20) specifically adapted for young children[20] was used to assess children aged younger than 6 years. The MFM assesses standing, ambulation and transfers, and axial, proximal, and distal function (appendix).

Secondary outcomes were responder analyses of the change from baseline to month 24 in total MFM score, individual MFM domains (D1, D2, and D3), and HFMS from baseline to month 21; the proportion of patients showing maintenance or improvement in scores on MFM D1 + D2, MFM total score (D1 + D2 + D3), and HFMS change from baseline to month 21. Secondary endpoints assessing non-motor function were maximum compound muscle action potential (CMAP) and motor unit number estimation (MUNE); clinical global impression of change (CGI-C) assessed by the patient or caregiver and a physician; forced vital capacity (FVC); and Pediatric Quality of Life Inventory (PEDsQL) Neuromuscular Module (appendix).[21]

Safety assessments were adverse events, standard laboratory assessments, electrocardiograms, and vital signs. The independent Data Monitoring Committee was responsible for monitoring the safety of patients by reviewing data every 13 weeks. The committee also reviewed olesoxime plasma trough concentrations at weeks 4 and 13, and reviewed the efficacy data at week 52 to make a recommendation on study continuation.

Sensitivity analyses of the primary endpoint, which were prespecified in the statistical analysis plan following the interim analysis, were subgroup analyses of MFM D1 + D2 score to assess the overall treatment effect at month 24, and effect of age, country, and SMA type. In post-hoc sensitivity analysis, we assessed the effect of olesoxime exposure on the primary outcome measure (appendix).

Statistical analysis

Based on natural history studies,[22] we estimated that a mean decrease of 1·9 points in the MFM D1 + D2 score would be observed over 24 months in the placebo group, and no worsening of motor function in the olesoxime group, with an assumed SD of 3·32. To test whether olesoxime would prevent worsening of motor function over 24 months, we calculated that 150 patients (100 receiving olesoxime and 50 receiving placebo) would be needed to reach a power of at least 85% (α=0·04 to take into account the interim efficacy analysis done after 12 months [α=0·01]), assuming 5% of patients would be lost to follow-up.

All efficacy analyses were based on the full analysis set, which includes all randomly assigned patients who received at least one dose of olesoxime or placebo and who had at least one post-randomisation assessment of MFM available. All safety analyses are based on the safety evaluable population (all randomly assigned patients who received at least one dose of the study drug).

In 17 patients (olesoxime n=12, placebo n=5) who were younger than 6 years at enrolment, MFM32 was used at all visits instead of the protocol-defined MFM20. To account for this, we did two separate analyses of MFM

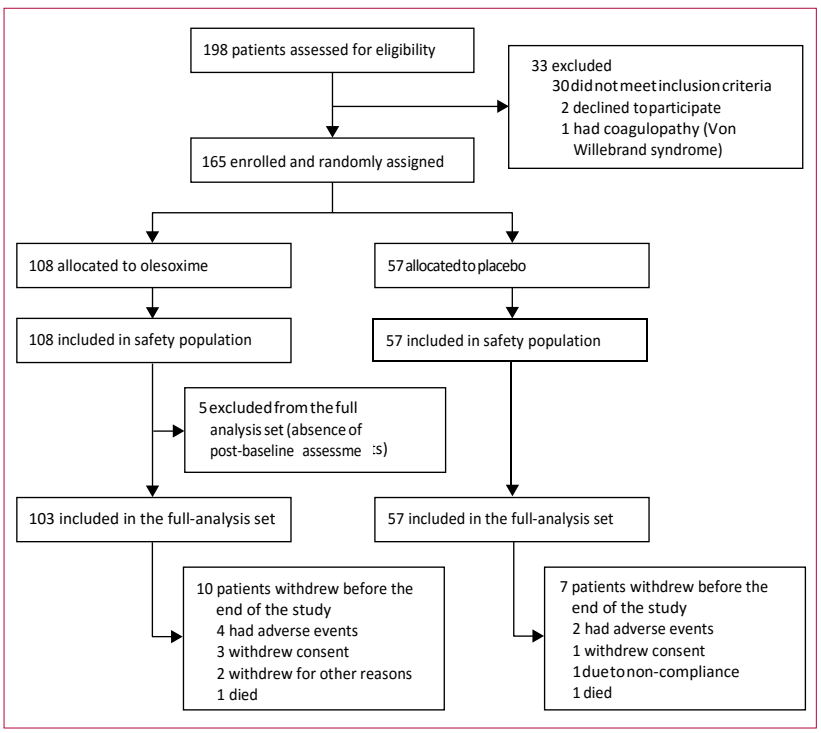


Figure 1: **Trial profile**

	Olesoxime (n=103)	Placebo (n=57)	Total (n=160)
Male	55 (53%)	25 (44%)	80 (50%)
Female	48 (47%)	32 (56%)	80 (50%)
Age (years)			
Mean	9·1 (5·5)	11·2 (6·0)	9·9 (5·7)
Median (range)	7 (3–25)	11 (3–27)	8 (3–27)
Age			
<6 years	35 (34%)	13 (23%)	48 (30%)
≥6 years	68 (66%)	44 (78%)	112 (70%)
SMA type			
Type 2	74 (72%)	39 (68%)	113 (71%)
Type 3	29 (28%)	18 (32%)	47 (29%)

Data are n (%) or mean (SD), unless otherwise stated. SMA=spinal muscular atrophy.

Table 1: **Baseline demographic and clinical characteristics**

score. In the primary analysis, a score for the MFM20 was calculated from the MFM32 score for these 17 patients by using only the 20 items that are featured in MFM20. A secondary sensitivity analysis included data from whichever form of the MFM that was used.

The primary outcome, change from baseline to month 24 in MFM D1 + D2 between treatment groups, was analysed using a mixed-effects repeated measures (MMRM) model. Covariates in the primary model were MFM score (D1 + D2) at baseline, SMA type, country, treatment group, visit, and treatment group by visit interaction. Further detail on the model is provided in the appendix. Least-square means, SEs, and the 96% CIs of treatment difference between olesoxime and placebo were reported. Statistical tests for the primary analysis were done with a two-sided test with a significance level (α) of 4%.

CGI-C ratings were analysed with a van Elteren test, a non-parametric test that compares the ranks of responses, stratified by country. Other secondary endpoints were tested with two-sided tests with a significance level (α) of 5% (appendix).

For the post-hoc analysis of the primary outcome measure according to olesoxime exposure, the time course of the mean change from baseline (standard error of mean [SEM]) of the MFM D1 + D2 score was graphically compared between patients with low and high olesoxime exposure and the placebo group (appendix). A post-hoc responder analysis of CGI-C mirroring the responder analyses for the MFM and HFMS was also done. Patients rated as no change or better (ie, stability or improvement) were considered to be responders, and patients rated as minimally worse or worse (ie, deterioration) were considered to be "non-responders". The proportion of responders and non-responders was then compared across treatment groups with a log binomial model, controlling for SMA type.

Adverse events were reported at each patient visit and traced in source documents, which were then monitored, with all adverse events reported in an electronic case report form by the investigation sites. Additionally, a post-hoc analysis was done on a series of adverse events clusters defined as SMA-related complications (appendix).

All analyses were done with SAS software (version 9.2). This study is registered with ClinicalTrials.gov, number NCT01302600.

Role of the funding source

AFM-Téléthon designed the study. J-LA was an employee of Trophos SA and was responsible for protocol development and study supervision until enrolment was completed. ED was an employee of Trophos SA and participated in the study management, data collection, data management, and data analysis. Five authors (TB, PF, CR, PSD and EV) are employed by F Hoffman La Roche and did primary, sensitivity, and exploratory analyses of this study. The funders of the study had no other role in data interpretation or in the decision to submit the manuscript for publication. Roche also supported reporting of study results by funding medical writing support. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between Nov 18, 2010, and Sept 6, 2011, 165 patients were enrolled and randomly assigned to treatment. Of these, 108 patients received olesoxime and 57 patients received placebo (figure 1). The final visit occurred on Oct 9, 2013.

17 patients withdrew prematurely, ten (12%) from the olesoxime group and seven (9%) from the placebo group. Of 108 patients allocated to olesoxime, five patients were excluded from the full analysis set because of the absence of post-baseline assessments. Protocol violations occurred in 30 patients (19 [18%] receiving olesoxime, 11 [19%] receiving placebo), including the 17 patients younger than 6 years at enrolment who did the MFM32 assessment at all visits instead of the protocol-defined MFM20. Other major protocol violations (olesoxime n=7 and placebo n=6) included deviation from the inclusion screening criteria (use of forbidden drugs and spinal rod or fixation for scoliosis within 6 months of enrolment), abnormal liver enzymes (alanine aminotransferase or aspartate aminotransferase >3 times the upper limits of normal), treatment compliance of 50% for at least two visits, and delayed visit dates. The full analysis set used for all efficacy analyses comprised 160 patients (table 1).

Patient demographic and baseline characteristics were mainly well balanced between the treatment groups, including proportions of patients with type 2 or type 3 SMA. However, both mean and median ages were lower in the olesoxime group than in the placebo group, with a difference of 2·1 years in mean ages and a difference of 4 years in median ages across treatment groups (table 1). Additionally, there were slight differences in the proportion of males and females between groups. The interim efficacy analysis done at month 12 did not find a significant difference between treatment groups. Therefore, the study continued with the full 2-year treatment period.

For the primary outcome, patients receiving olesoxime treatment had a mean change in MFM D1 + D2 score from baseline to month 24 of 0·18 points, whereas the placebo group had a mean change of –1·82 points. The difference was not significant (2·00 points, 96% CI –0·25 to 4·25, p=0·0676; table 2).

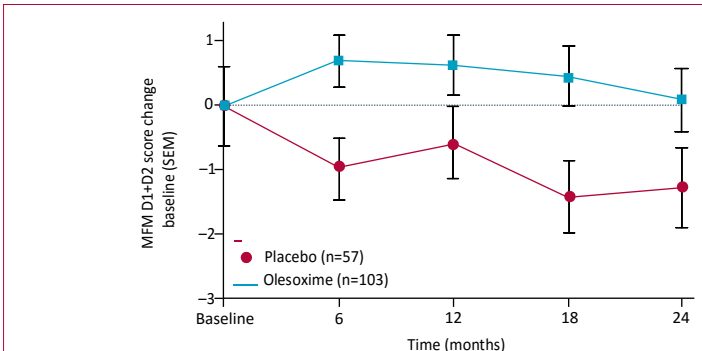
The secondary outcome examining overall treatment difference across all visits was 2·23 points (96% CI 0·50–3·96), and was statistically significant in favour of olesoxime (p=0·0084; figure 2). All other secondary MFM and HFMS endpoints were not significantly different between groups (table 3, appendix). In the responder analysis, the percentage of responders was significantly higher in the olesoxime group than in the placebo group for the MFM total score (56% for olesoxime, and 39% for placebo; p=0·0419; table 4). The proportion of patients who improved or remained stable over 21 months (response rate) on the HFMS was significantly higher in the olesoxime group than in the placebo group (50% for olesoxime and 28% for placebo, p=0·0091; table 4). Secondary outcomes assessing non-motor function with CMAP, MUNE, CGI-C, FVC, and PEDsQL Neuromuscular Module were not significantly different between groups (appendix).

Olesoxime seemed generally safe and well tolerated, and approximately equivalent proportions of patients in each group experienced at least one adverse event during the study (table 5); several adverse events were frequently reported (>5%), with fairly equal frequency in both treatment groups (appendix). Two patients died during the study, with one death in each treatment group, but these deaths were not deemed to be related to treatment by the treating physicians (attributed to cardiac arrest in the patient in the olesoxime group; and attributed to increased bronchial secretion in the patient in the placebo group; appendix). A greater proportion of patients experienced serious adverse events in the placebo group than in the olesoxime group (table 5). The proportion of patients withdrawing from treatment because of adverse events was low (4% for both olesoxime and placebo

	Olesoxime (n=103)	Placebo (n=57)	Estimate (SE)	96% CI	p value
Primary analysis					
Mean baseline	39·58 (11·701)	38·99 (11·905)	..	..	..
Least-squares mean change from baseline to week 104	0·18 (0·717)	–1·82 (0·901)	..	..	..
96% CI	–1·30 to 1·66	–3·68 to 0·04	..	..	..
Difference from placebo (primary outcome)	..	..	2·00 (1·088)	–0·25 to 4·25	0·0676
Sensitivity analysis					
Mean baseline	39·01 (11·472)	38·69 (11·689)	..	..	..
Least-squares mean change from baseline to week 104	0·24 (0·696)	–1·96 (0·872)	..	..	..
95% CI	–1·14 to 1·61	–3·68 to –0·24	..	..	..
Difference from placebo	..	..	2·20 (1·050)	0·12 to 4·27	0·0379
Overall treatment effect	..	..	2·36 (0·817)	0·74 to 3·97	0·0044

Data are least-squares mean (SE) or mean (SD), unless otherwise stated. Primary analysis: comparison between treatment groups on change from baseline at month 24 in MFM D1+D2 score (MMRM; full analysis set). For children aged <6 years who erroneously did the MFM32 assessment, MFM20 score was calculated from MFM32 score. Sensitivity analysis: data as collected from whichever form of the MFM was used (see appendix for methods). D1+D2 MFM=domains 1 and 2 of the Motor Function Measure. MMRM=mixed model-repeated measures.

Table 2: **Primary and prespecified sensitivity analyses**



Difference between treatment groups at timepoint	2·41	1·77	2·74	2·00*
p value	0·0039	0·0711	0·0075	0·0676*

Overall treatment difference 2·23, p=0·0084

Figure 2: **Adjusted mean change in MFM D1 + D2 score from baseline to months 6, 12, 18, and 24**
For children younger than 6 years who erroneously did the MFM32 assessment, MFM20 score was calculated from MFM32 score. Error bars represent standard error of the mean. MFM=Motor Function Measure. *Primary outcome.

groups). A post-hoc analysis investigating disease-related adverse events (appendix) showed a higher incidence in the placebo group than in the olesoxime group, with a lower frequency of the following disorders with olesoxime treatment: lower respiratory tract infections, gastrointestinal disorders (reflux disorders and constipation), and other joint-related disorders (table 5).

	Olesoxime (n=103)	Placebo (n=57)	Estimate (SE)	95% CI	p value
MFM total score (to month 24)					
Mean baseline	49·32 (10·993)	49·11 (11·432)	..	..	..
Least-squares mean change from baseline to week 104	0·59 (0·751)	−1·45 (0·943)	..	..	..
95% CI	−0·90 to 2·07	−3·31 to 0·41	..	..	..
Difference from placebo	..	..	2·04 (1·138)	−0·21 to 4·28	0·0755
MFM D1 (to month 24)					
Mean baseline	6·76 (7·933)	7·28 (7·543)	..	..	..
Least-squares mean change from baseline to week 104	0·07 (0·554)	−0·90 (0·706)	..	..	..
95% CI	−1·02 to 1·16	−2·29 to 0·49	..	..	..
Difference from placebo	..	..	0·97 (0·854)	−0·72 to 2·66	0·2582
MFM D2 (to month 24)					
Mean baseline	74·10 (18·610)	72·64 (18·882)	..	..	..
Least-squares mean change from baseline to week 104	0·38 (1·217)	−2·78 (1·524)	..	..	..
95% CI	−2·02 to 2·78	−5·79 to 0·23	..	..	..
Difference from placebo	..	..	3·16 (1·838)	−0·47 to 6·79	0·0873
MFM D3 (to month 24)					
Mean baseline	85·41 (13·147)	86·05 (15·412)	..	..	..
Least-squares mean change from baseline to week 104	2·27 (1·264)	0·15 (1·606)	..	..	..
95% CI	−0·22 to 4·76	−3·02 to 3·32	..	..	..
Difference from placebo	..	..	2·12 (1·945)	−1·72 to 5·96	0·2773
HFMS (to month 21)					
Mean baseline	16·47 (10·576)	14·86 (10·514)	..	..	..
Least-squares mean change from baseline to week 91	−0·78 (0·416)	−1·72 (0·515)	..	..	..
95% CI	−1·60 to 0·04	−2·74 to −0·70	..	..	..
Difference from placebo	..	..	0·94 (0·622)	−0·28 to 2·17	0·1309

Data are least-squares mean (SE) or mean (SD), unless otherwise stated. Primary analysis: for children aged younger than 6 years who erroneously did the MFM32 assessment, MFM20 score was calculated from MFM32 score. Sensitivity analysis: data as collected from whichever form of the MFM was used (appendix). MFM=Motor Function Measure. D1=MFM domain 1 (standing position and transfers). D2=MFM domain 2 (axial and proximal motor function). D3=MFM domain 3 (distal motor function). HFMS=Hammersmith Functional Motor Scale.

Table 3: **Secondary motor function outcomes**

	Olesoxime (n=103)	Placebo (n=57)	Relative risk (95% CI)	p value
MFM D1 + D2 (to month 24)	56 (54%)	22 (39%)	1·43 (0·98–2·08)	0·0609
MFM total score (to month 24)	58 (56%)	22 (39%)	1·46 (1·01–2·10)	0·0419
HFMS (to month 21)	51 (50%)	16 (28%)	1·82 (1·16–2·86)	0·0091

For children younger than 6 years who erroneously did the MFM32 assessment, MFM20 score was calculated from MFM32 score. MFM=Motor Function Measure. D1=MFM domain 1 (standing position and transfers). D2=MFM domain 2 (axial and proximal motor function). HFMS=Hammersmith Functional Motor Scale.

Table 4: **Secondary analysis of responders according to motor function scores**

In the sensitivity analysis of the primary outcome, taking into account erroneous use of the MFM32 version in some patients younger than 6 years, the difference in change from baseline between the two treatment groups was statistically significant in favour of olesoxime (2·20, 95% CI 0·12–4·27, p=0·0379). The change from baseline in MFM D1 + D2 score is shown separately for three different age groups: younger than 6 years, 6–15 years, and older than 15 years (figure 3). In the 6–15 years group, patients in the olesoxime group showed improvements in scores compared with baseline at all timepoints and patients in the placebo group showed a consistent decline (>3-point difference between treatments at all visits; overall mean p=0·0107). In the other age groups, no significant differences were observed between the treatment groups.

Prespecified sensitivity analyses of the MFM D1+D2 score revealed effects of olesoxime across country (data not shown), SMA type, sex, and disease severity at baseline (appendix). Analysis of the primary endpoint that included age as a continuous covariate revealed no significant effect of age on MFM D1 + D2 scores (p=0·2481; data not shown). The effects of olesoxime on the HFMS were observed across country (data not shown), age, SMA type, and sex (appendix).

In a post-hoc sensitivity analysis, the difference between olesoxime-treated and placebo-treated patients at month 24 was 3·61 points (p=0·036; figure 3). In the post-hoc responder analysis of CGI-C, a statistically significant effect favouring olesoxime over placebo was observed for CGI-C with physician-reported data (relative risk [RR] 1·23, 95% CI 1·01–1·49, p=0·036).

In post-hoc MMRM analyses, changes from baseline in MFM D1 + D2 score were repeated with systematic, one-by-one exclusion of patients with the lowest pharmacokinetic exposure values (C_{avg}; appendix). The smallest MMRM p value (p=0·0088) was obtained for a C_{avg} of 7500 ng/mL. This value was reached after exclusion of 37 patients with the lowest exposure C_{avg} values for the overall olesoxime treatment group and two groups with exposure levels below or above this value (7500 ng/mL) are shown in the appendix. Patients with olesoxime exposure 7500 ng/mL or more showed improvements in MFM D1 + D2 score at all visits, with a 2·0-point improvement from baseline at month 24 (appendix). The group with olesoxime exposure of less than 7500 ng/mL showed a decrease in MFM D1+D2 score.

Discussion

This phase 2 clinical trial tested the hypothesis that oral administration of olesoxime (10 mg/kg per day) would at least prevent decline of, and potentially improve, motor function in patients with type 2 or non-ambulatory type 3 SMA over a treatment period of 2 years, while patients in the placebo group would show a decline in motor function in line with the natural history of the disease. The trial did not meet the primary outcome of improved

motor function, compared with placebo, as measured by change from baseline to month 24 in MFM D1 + D2 score. However, several positive secondary outcomes suggest that olesoxime might be helpful in the maintenance of motor function.

First, the overall treatment effect in terms of change from baseline on MFM D1 + D2 across all visits was significantly better with olesoxime than with placebo. Additionally, the difference between the two treatment groups was significantly in favour of olesoxime at months 6 and 18, as well as in a sensitivity analysis taking into account erroneous use of MFM32 assessment in some patients younger than 6 years. Second, the change from baseline on MFM D1 + D2 scores was significantly better with olesoxime treatment than with placebo in patients aged 6–15 years during the entire treatment period. Patients with SMA in this age group generally experience profound declines in motor function associated with puberty.[23,24] Given that the expected effect of olesoxime was primarily maintenance of function, and that demonstration of a treatment effect would therefore depend on functional decline in the placebo group, we might expect that the greatest effect would be observed in this age group. In fact, the results might suggest a change in the trajectory of motor function with olesoxime in 6–15 year olds exists, from decline to improvement. Such differences between treatment groups were not observed in the youngest (<6 years) and oldest (>15 years) age groups. This might be because children younger than 6 years might experience improvements in motor function as they develop and achieve motor function milestones,[25] whereas patients older than 15 years might experience periods of fairly stable function over 2–3 years of observation.[23,24] Third, in a post-hoc sensitivity analysis, we observed that response on the primary outcome measure was associated with olesoxime exposure, with patients that experienced higher olesoxime exposure also showing improved responses. Finally, we also observed positive effects of olesoxime treatment in the responder analyses of the MFM total score and HFMS, in which a significantly greater proportion of patients receiving olesoxime than patients receiving placebo showed stable or improved motor function over the study period. These results were supported by the post-hoc responder analysis of CGI-C, a measure of global change relative to baseline, in which a significant benefit of olesoxime treatment compared with placebo was observed in the proportion of patients with stable or improved overall status as assessed by physicians. This benefit might represent additional evidence supportive of a clinically relevant effect of olesoxime, although further study is needed.

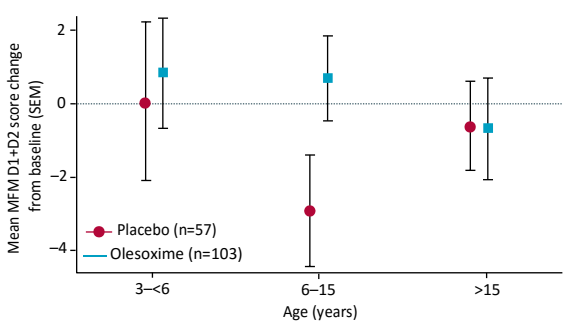
Given that many of the analyses showed signs of efficacy for olesoxime, it is perhaps surprising that olesoxime did not achieve significance on the primary outcome measure. A potential explanation relates with the higher than anticipated variability observed on the primary outcome measure in the study population, which caused the study to be underpowered. Our sample size calculation was based on a change of –1·9 points in MFM score in the placebo group over 24 months, with no worsening in the olesoxime group, and an assumed SD of 3·3. In fact, we observed a standard deviation for MFM D1 + D2 of 6·8 points in the placebo group, with a treatment difference of 2·0, in a population of 160 patients; this was greater than the variability reported in two previous longitudinal studies of motor function measures in patients with SMA.[3,26]

The greater variability observed in our population might have arisen from several causes, including

	Olesoxime (n=108)	Placebo (n=57)	Total (n=165)
Patients with ≥1 adverse event	103 (95%)	57 (100%)	160 (97%)
Number of adverse events	1104	612	1716
Deaths	1 (1%)	1 (2%)	2 (1%)
Patients who withdrew from the study due to an adverse event	4 (4%)	2 (4%)	6 (4%)
Patients with ≥1 adverse event with fatal outcome	1 (1%)	1 (2%)	2 (1%)
Patients with ≥1 serious adverse event	34 (31%)	29 (51%)	62 (38%)
Patients with ≥1 adverse event leading to withdrawal from study	9 (8%)	2 (4%)	11 (7%)
Patients with ≥1 severe adverse event	18 (17%)	14 (25%)	32 (19%)
Disease-related adverse events (post-hoc)			
Lower respiratory tract infections	13 (12%)	10 (18%)	23 (14%)
Respiratory failure	2 (2%)	2 (4%)	4 (2%)
Reflux disorders	4 (4%)	4 (7%)	8 (5%)
Constipation	5 (5%)	4 (7%)	9 (5%)
Scoliosis	14 (13%)	6 (11%)	20 (12%)
Other joint-related disorders	13 (12%)	17 (30%)	30 (18%)
Surgical procedure	9 (8%)	5 (9%)	14 (8%)

Data are n (%). See appendix for breakdown of adverse events by type.

Table 5: **Adverse events**



Placebo (n)	13	25	19
Olesoxime (n)	35	54	14
p value for treatment difference	0·7459	0·0362	0·9602
Placebo, mean MFM D1+D2 (SD)	44·07 (10·65)	36·48 (12·14)	38·81 (11·95)
Olesoxime, mean MFM D1+D2 (SD)	45·89 (10·67)	37·53 (11·07)	31·71 (9·29)

Figure 3: **Adjusted mean change in MFM D1 + D2 scores from baseline to month 24, by age group**
For children younger than 6 years who erroneously did the MFM32 assessment, MFM20 score was calculated from MFM32 score (see appendix for full explanation). Error bars represent standard error of the mean. MFM=Motor Function Measure.

imputation of scores in cases of death or missing data, erroneous use of the MFM32 in some patients younger than 6 years, and a relatively wide age range with significant variation in stages of development and differences in potential motor function decline.[24] Our study also lacked an inclusion criterion relating to standard of care, which might have resulted in a heterogeneous population in terms of previous intervention. Assessment and comparison of non-pharmacological management was not possible. However, all patients were treated in Europe and the cohort was stratified across countries, with no significant effect of country observed in the subgroup analyses. However, it is possible that the increased variability might arise from the differing contexts of the previous studies versus the present one. The previous studies[4,26] did not include any treatment, and the absence of any expectation of improvement by the patients might in itself produce more homogeneous results. Furthermore, because the overall aim of the previous studies was to validate motor function scales, the methods would have been more closely focused on demonstrating repeatability and reproducibility, again leading to more homogeneous data.

On the secondary endpoints CMAP, MUNE, PEDsQL, and FVC, no clear benefit of olesoxime treatment was observed (appendix). The correlation between CMAP and MUNE measurements and disease progression in SMA is uncertain and differences have been observed between SMA types,[27] so these measures might not be expected to show any evidence of consistent changes across the study. Furthermore, gaps exist in establishing the validation and sensitivity of the PEDsQL in patients with SMA because factor analysis to explore construct validity and dimensionality has not been done yet.[22] For FVC, post-baseline height was not measured, which prevented accurate calculation of predicted FVC after this time, and intersite variation might have played a part with different equipment used to perform this measure. On CGI-C, the initial analysis might not have been powerful enough to detect differences when the majority of responses reported no change. The results at month 24 relied on the accuracy of a 2-year recall, which might be too long for optimum assessment.[28] Additionally, no instructions were provided to assessors on how to rate clinical change when completing the scale (eg, what should be considered a minimum improvement or worsening), resulting in potential inconsistency among respondents. These endpoints will require refinement before use in future trials of SMA, and intercentre performance would be improved by using standardised methods across study sites.

Olesoxime seemed safe and well tolerated, and a post-hoc analysis suggested that fewer patients receiving olesoxime experienced disease-related complications, including pulmonary, gastrointestinal, and joint-related disorders.

An ongoing difficulty with research in SMA is translating available trial endpoints for measurement of motor function into clinically meaningful benefits for patients. Further investigations are ongoing to investigate the treatment effects of olesoxime on specific items of the motor function scales that can be better related to a patient's activities of daily living and developmental needs. However, there are strong indications from physician experience of treating patients with SMA and from direct discussions with patients and caregivers that maintenance of function is regarded by patients and their families as a meaningful outcome.[3,29]

A limitation of the study was the interindividual variability in olesoxime exposure. Daily doses approaching 1000 mg administered over 2 years were well tolerated, suggesting that the therapeutic window might be sufficiently wide for the administration of higher doses of olesoxime, to maximise benefit. Additional trials exploring higher doses might offer the opportunity to conclusively assess the efficacy of olesoxime. A further limitation is the absence of biomarkers to measure disease progression and the expected biological function of olesoxime. Despite the acknowledged limitations, this study represents a landmark, being the longest and largest international, controlled study so far to collect prospective assessments with both the MFM and HFMS motor scales. These novel data are useful to improve the design of future studies in similar populations of patients with SMA. Based on these results, olesoxime might provide meaningful clinical benefits for patients with SMA and, given its mode of action, might be used in combination with other drugs targeting other mechanisms of disease.

Contributors

EB, ED, EM, FM, JK, AL, GPC, J-MC, J-LA, BS, WLvdP, and CV were involved in study design and data collection, and provided guidance on the data analysis, interpretation, and presentation of the data. CR and PSD did the data analyses and provided guidance for the interpretation and presentation of the data. EV, JB, PF, and TB provided guidance for the data analysis, interpretation, and presentation of the data. All authors critically reviewed and edited the manuscript.

Declaration of interests

EB receives grant support from AFM Téléthon and the Italian Ministry of Health; he also served as scientific adviser for AveXis, Biogen, F Hoffmann-La Roche, Novartis, and Edison Pharmaceutics. FM reports grants from Biogen, Ionis Pharmaceuticals, F Hoffmann-La Roche, Trophos, SMA Europe, SMA Trust, Muscular Dystrophy UK, Wellcome Trust, EU FP7 (skip NMD), AFM, NIHR, NIH, Medical Research Council, British Heart Foundation, EU Horizon 2020 (Neuomics, Bioimage, eNHANCE), and Genethon; he has served on scientific advisory boards for AveXis, Sarepta, Biogen, Trivorsan, Catabasis, Capricor, Wave Therapeutics, PTC, GSK, F Hoffmann-La Roche, Nicox, Italfarmaco, Ashaki and Summit, and the rare disease scientific advisory board for Pfizer. He has received payment for lectures for PTC, Sarepta, and Biogen. AL and BS received consultant fees from Trophos SA. CV has received consultancy fees from F Hoffmann-La Roche. EM has received consultancy fees from Biogen, Ionis Pharmaceuticals, F Hoffmann-La Roche, and Avexis. JK reports grants from Ionis Pharmaceuticals, Biogen, F Hoffmann-La Roche, and Trophos, and has received consultant fees from Biogen, LabConsult, and F Hoffmann-La Roche. ED is a former employee of Trophos SA and reports grants from AFM Téléthon. J-LA is a former employee of, and holds stock in, Trophos SA. PF, PSD, TB, CR,

JB, and EV are current employees of F Hoffmann-La Roche; PF, TB, and PSD also hold stock in F Hoffmann-La Roche. TB and PSD are named on a patent pending for olesoxime (EP16172972), but receive no royalties. GPC, WLdvP, and J-MC declare no competing interests.

Acknowledgments

We thank all patients and family members who participated in this study. Communication and recruitment into the study was supported by the TREAT-NMD network (EU 6th Framework Programme #LSHM-CT-2006-036825), the Care and Trial Site Registry (Freiburg, Germany), and associated national SMA patient registries. This study was funded by AFM-Téléthon and Trophos SA. Since March 3, 2015, Trophos SA has been a wholly owned member of the Roche Group. We acknowledge the contributions and support of our colleagues, the Olesoxime SMA Phase 2 Study Investigators: Carole André (AFM-Téléthon, Evry, France); Claudio Bruno (Istituto Giannina Gaslini, Genova, Italy); Brigitte Chabrol (Hôpital Enfant La Timone, Marseille, France); Nicolas Deconinck (UZ GENT, Gent, Belgium); Brigitte Estournet (Centre Hospitalier Universitaire Paris, Hôpital Raymond Poincaré, Garches, France); Stephanie Fontaine-Carbonnel (Hôpital Femme Mère Enfant, Centre Hospitalier Universitaire de Lyon, Lyon, France); Nathalie Goemans (Department of Pediatric Neurology UZ Gasthuisberg, Leuven, Belgium); Ksenija Gorni (Centro Clinico Nemo, Milan, Italy); Alessandra Govoni (Dino Ferrari Center, University of Milan, Milan, Italy); Michela Guglieri (MRC Centre for Neuromuscular Diseases, Newcastle, UK); Hanns Lochmuller (MRC Centre for Neuromuscular Diseases, Newcastle, UK); Francesca Magri (Dino Ferrari Center, University of Milan, Milan, Italy); Michele Mayer (Hospital Trousseau, Paris, France); Wolfgang Müller-Felber (Von Haunersches Kinderspital, Munchen, Germany); François Rivier (Hôpital Gui de Chauliac, Montpellier, France); Helen Roper (Birmingham Heartlands Hospital, Birmingham, UK); Ulrike Schara (Universitätsklinikum Essen, Essen, Germany); Mariacristina Scoto (UCL Institute of Child Health & Great Ormond Street Hospital, London, UK); Leonard van den Berg (Department of Neurology and Neurosurgery, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, Netherlands); Giuseppe Vita (Policlinico Universitario G Martino, Messina, Italy); and Maggie C Walter (Friedrich-Baur-Institute, Department of Neurology, LMU Munich, Germany). In addition, we acknowledge the following people for their advice and support: Rebecca Pruss (Trophos SA, Marseille, France) contributed substantially to the study, including to design and protocol development, and initial analysis and interpretation of results; Christine Payan (AFM, Institute of Myology, Hôpital Pitié-Salpêtrière, Paris, France) and Carole Bérard (Centre Hospitalier Universitaire de Lyon, Hospices Civils de Lyon, Lyon, France) provided guidance on the use of the MFM, data from natural history studies for MFM in patients with SMA, and the MFM database used to calculate sample sizes required during the design of this study; Petra Kaufmann (National Institute of Neurological Disorders and Stroke at the National Institutes of Health, USA), Louis Viollet (Centre Hospitalier Universitaire Paris, Hôpital Necker-Enfants Malades, Paris, France), and Richard Finkel (Nemours Children's Hospital, Orlando, USA) provided guidance in the study protocol development; and Valérie Cuvier (Trophos SA) provided study management. We also acknowledge the following people for their assistance with the study: Johann Laurent, Nicolas Frey, and Franziska Schaedeli Stark (Roche Pharma Research and Early Development, Basel, Switzerland); Adele D'Amico and Michela Catteruccia (Bambino Gesù Children's Research Hospital IRCCS, Rome, Italy); Maria Carmela Pera and Marika Pane (Paediatric Neurology and Nemo Center, Catholic University and Policlinico Gemelli, Rome, Italy); Renske I Wadman (Department of Neurology and Neurosurgery, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, Netherlands); and Patrick Berna and Wilfried Hauke (Trophos SA, Marseille, France). We also thank the iDMC members: Corinne Alberti (methodologist; Université Paris Diderot and Hôpital Robert Debré, Paris, France), Evelyne Jacqz-Aigrain (clinical pharmacologist; Centre d'Investigation Clinique, CIC, Paris, France), and Odile Boespflug-Tanguy (neuropaediatrician, Chair; Service de Neurologie Pédiatriqueet des Maladies Métaboliques, Hôpital Robert Debré, Paris, France). We also acknowledge support from the founders of Trophos: Antoine Beret, Chris Henderson, and Michel Delaage. Editorial support for the development of this manuscript was provided by Lucy Craggs and Ben Caldwell (MediTech Media), and funded by F Hoffmann-La Roche Ltd. FM is supported by the National Institute for Health Research Biomedical Research Centre at Great Ormond Street Hospital for Children NHS Foundation Trust and University College London. The support of Muscular Dystrophy UK and The SMA Trust to the Dubowitz Neuromuscular Centre is also gratefully acknowledged.

References

1 Lunn MR, Wang CH. Spinal muscular atrophy. *Lancet* 2008; **371:** 2120–33.

2 Crawford TO, Pardo CA. The neurobiology of childhood spinal muscular atrophy. *Neurobiol Dis* 1996; **3:** 97–110.

3 Qian Y, McGraw S, Henne J, Jarecki J, Hobby K, Yeh WS. Understanding the experiences and needs of individuals with Spinal Muscular Atrophy and their parents: a qualitative study. *BMC Neurol* 2015; **15:** 217.

4 Lefebvre S, Burlet P, Liu Q, et al. Correlation between severity and SMN protein level in spinal muscular atrophy. *Nat Genet* 1997; **16:** 265–69.

5 Acsadi G, Lee I, Li X, et al. Mitochondrial dysfunction in a neural cell model of spinal muscular atrophy. *J Neurosci Res* 2009; **87:** 2748–56.

6 Katsetos CD, Koutzaki S, Melvin JJ. Mitochondrial dysfunction in neuromuscular disorders. *Semin Pediatr Neurol* 2013; **20:** 202–15.

7 Ripolone M, Ronchi D, Violano R, et al. Impaired muscle mitochondrial biogenesis and myogenesis in spinal muscular atrophy. *JAMA Neurol* 2015; **72:** 666–75.

8 Miller N, Shi H, Zelikovich AS, Ma YC. Motor neuron mitochondrial dysfunction in spinal muscular atrophy. *Hum Mol Genet* 2016; **25:** 3395–406.

9 Shababi M, Lorson CL, Rudnik-Schoneborn SS. Spinal muscular atrophy: a motor neuron disorder or a multi-organ disease? *J Anat* 2014; **224:** 15–28.

10 Procaccio V, Bris C, Chao de la Barca JM, et al. Perspectives of drug-based neuroprotection targeting mitochondria. *Rev Neurol (Paris)* 2014; **170:** 390–400.

11 US Food and Drug Administration. Prescribing Information SPINRAZA. http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/209531lbl.pdf (accessed Jan 30, 2017).

12 Gabanella F, Carissimi C, Usiello A, Pellizzoni L. The activity of the spinal muscular atrophy protein is regulated during development and cellular differentiation. *Hum Mol Genet* 2005; **14:** 3629–42.

13 Bordet T, Berna P, Abitbol JL, Pruss RM. Olesoxime (TRO19622): a novel mitochondrial-targeted neuroprotective compound. *Pharmaceuticals* 2010; **3:** 345–68.

14 Gouarne C, Giraudon-Paoli M, Seimandi M, et al. Olesoxime protects embryonic cortical neurons from camptothecin intoxication by a mechanism distinct from BDNF. *Br J Pharmacol* 2013; **168:** 1975–88.

15 Gouarne C, Tracz J, Paoli MG, 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.

16 Bordet T, Buisson B, Michaud M, et al. Identification and characterization of cholest-4-en-3-one, oxime (TRO19622), a novel drug candidate for amyotrophic lateral sclerosis. *J Pharmacol Exp Ther* 2007; **322:** 709–20.

17 Estournet B, Chabrol B, Cuisset J, et al. Safety and pharmacokinetics (PK) of TRO19622 in spinal muscular atrophy (SMA) children and adults. *Neurology* 2009; **72** (suppl 3)**:** A276.

18 Lenglet T, Lacomblez L, Abitbol JL, et al. A phase II-III trial of olesoxime in subjects with amyotrophic lateral sclerosis. *Eur J Neurol* 2014; **21:** 529–36.

19 Berard C, Payan C, Hodgkinson I, Fermanian J, MFM Collaborative Study Group. A motor function measure for neuromuscular diseases. Construction and validation study. *Neuromuscul Disord* 2005; **15:** 463–70.

20 de Lattre C, Payan C, Vuillerot C, et al. Motor function measure: validation of a short form for young children with neuromuscular diseases. *Arch Phys Med Rehabil* 2013; **94:** 2218–26.

21 Iannaccone ST, Hynan LS, Morton A, Buchanan R, Limbers CA, Varni JW, for the AmSMART Group. The PedsQL in pediatric patients with spinal muscular atrophy: feasibility, reliability, and validity of the Pediatric Quality of Life Inventory Generic Core Scales and Neuromuscular Module. *Neuromuscul Disord* 2009; **19:** 805–12.

22 Vuillerot C, Payan C, Iwaz J, Ecochard R, Berard C, for the MFM Spinal Muscular Atrophy Study Group. Responsiveness of the motor function measure in patients with spinal muscular atrophy. *Arch Phys Med Rehabil* 2013; **94:** 1555–61.

23 Crawford TO. Concerns about the design of clinical trials for spinal muscular atrophy. *Neuromuscul Disord* 2004; **14:** 456–60.

24 Mercuri E, Finkel R, Montes J, et al. Patterns of disease progression in type 2 and 3 SMA: implications for clinical trials. *Neuromuscul Disord* 2016; **26:** 126–31.

25 Iannaccone ST, Browne RH, Samaha FJ, Buncher CR. Prospective study of spinal muscular atrophy before age 6 years. DCN/SMA Group. *Pediatr Neurol* 1993; **9:** 187–93.

26 Mazzone E, De Sanctis R, Fanelli L, et al. Hammersmith Functional Motor Scale and Motor Function Measure-20 in non ambulant SMA patients. *Neuromuscul Disord* 2014; **24:** 347–52.

27 Kang PB, Gooch CL, McDermott MP, et al. The motor neuron response to SMN1 deficiency in spinal muscular atrophy. *Muscle Nerve* 2014; **49:** 636–44.

28 Schneider LS, Raman R, Schmitt FA, et al. Characteristics and performance of a modified version of the ADCS-CGIC CIBIC+ for mild cognitive impairment clinical trials. *Alzheimer Dis Assoc Disord* 2010; **23:** 260–67.

29 CureSMA. The Voices of SMA: the experiences of individuals and families and their views on living with spinal muscular atrophy. http://www.curesma.org/documents/research-documents/voices-of-sma-booklet.pdf (accessed Sept 22, 2016).