Official Title: Multicenter, Open-Label, Single-Arm Study to Evaluate Long-Term Safety, Tolerability, and Effectiveness of 10 mg/kg BID Olesoxime in Patients With Spinal Muscular Atrophy

NCT Number: NCT02628743

Document Date: Protocol Version 4: 14-Nov-2017

PROTOCOL

TITLE:	**MULTICENTER, OPEN-LABEL, SINGLE-ARM STUDY TO EVALUATE LONG-TERM SAFETY, TOLERABILITY, AND EFFECTIVENESS OF 10 MG/KG *BID* OLESOXIME IN PATIENTS WITH *SPINAL MUSCULAR ATROPHY***
PROTOCOL NUMBER:	BN29854
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DATE FINAL:	Version 1: 2 July 2015 Version 2: 9 September 2015 Version 3: 19 August 2016
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PROTOCOL AMENDMENT APPROVAL

Approver's Name	**Title**	**Date and Time (UTC)**
[redacted]	Company Signatory	14-Nov-2017 08:28:22

PROTOCOL AMENDMENT, VERSION 4:
RATIONALE

Protocol BN29854 has been amended to incorporate a dose increase of olesoxime from 10 mg/kg once daily (QD) to 10 mg/kg twice daily (BID). Changes to the protocol, along with a rationale for each change, are summarized below:

- Background information on spinal muscular atrophy (SMA) and olesoxime has been updated (see Sections 1.1 and 1.2).
- A dose increase of olesoxime from 10 mg/kg QD to 10 mg/kg BID was included based on information from an exploratory population pharmacokinetic (PK)/pharmacodynamic-efficacy analysis using data from Study TRO19622CLEQ1275-1, which suggests that a higher daily dose of olesoxime may potentially increase the benefit of the drug (see Sections 1.2.3, 1.3, 1.4, 3.1, 3.3.1, and 4.2.2.1). The total daily dose in this study will not exceed 2000 mg. Thus, for patients with body weight >100 kg, the administered dose will be 1000 mg BID (see Sections 3.1.1.3 and 4.2.2.1). All patients agreeing to dose increase must have signed informed consent (see Section 4.4.1.1).
- A newly developed scale assessing function-related independence has been introduced as a patient-reported outcome measure: the SMA Independence Scale (SMAIS) (see Sections 2.4, 2.5, 4.4.10, and 6.10).
- Three new exploratory outcome measures have been introduced: Clinical Global Impression of Change (CGI-C), digital biomarker assessment, and Olesoxime Fatigability Survey (OFS) (see Sections 2.6, 3.1.1.4, 3.3.4, 4.4.8.4, 4.4.12, 4.4.13, and 6.12 and Appendix 1).
- Appropriate safety monitoring procedures to assess any potential risk related to the dose increase have been included. These are reflected in two visits: a dose increase visit and a dose increase follow-up safety visit. These visits include predose increase and follow-up steady-state safety blood sampling (see Section 3.1.1.4 and Appendix 1), as well as predose increase and follow-up steady state 24-hour Holter ECG monitoring based on preclinical findings of rare and isolated arrhythmias (see Sections 3.1.1.4 and 4.4.9.1 and Appendix 1).
- As part of the dose increase and dose increase follow-up safety visits, blood samples for PK and biomarker assessments will be taken, which will help to understand the PK and biomarker profile at the steady state of the new dose (see Section 3.1.1.4 and Appendix 1).
- Two additional DNA samples for exploratory biomarker assessments will be collected. The current baseline and two additional longitudinal DNA samples may be used for additional exploratory biomarker analysis to measure dynamic changes due to disease severity, progression, and treatment response, including, but not limited to, mitochondrial DNA levels and genes related to survival motor neuron protein function, such as genetic modifiers (see Sections 3.3.4 and 4.4.8.2 and Appendix 1).

- The permission of concomitant use of nusinersen (Spinraza®) has been clarified (Section 4.3.1).
- The use of fish oils and niacin (vitamin B3) as prohibited medications was removed to align with the Olesoxime Investigator's Brochure (see Section 4.3.1.1).
- The timing for when biomarker samples will be destroyed has been clarified (see Section 4.4.8.1).
- It has been clarified that if a patient performs a 24-hour Holter ECG as part of the dose increase on a regular visit and an ECG assessment is scheduled at this regular visit, only the 24-hour Holter ECG will be performed (see Section 4.4.9 and Appendix 1).
- The timing for when Roche Clinical Repository specimens will be destroyed has been clarified to be 15 years after the date of final clinical study report (see Section 4.4.19.3).
- The reporting of the term "sudden death" has been updated to also require the presumed cause of death (see Section 5.3.5.7).
- Event reporting for hospitalization has been clarified (see Section 5.3.5.9).
- Emergency medical contact information has been updated (see Section 5.4.1).
- It has been clarified that data for analysis will be summarized by the dose being taken at the time of the assessment (see Sections 6.6, 6.7, 6.10, 6.11, and 6.12).
- The process for reviewing and handling protocol deviations has been updated per internal standard operating procedures (see Section 9.2).
- The Web site for Roche Global Policy on Sharing of Clinical Trials Data has been updated (see Section 9.5).
- The reference section has been updated to reflect changes to the protocol (see Section 10).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 4:
SUMMARY OF CHANGES

PROTOCOL SYNOPSIS

The protocol synopsis has been updated to reflect the changes to the protocol, where applicable.

GLOBAL CHANGES

A dose increase of olesoxime from 10 mg/kg once daily to 10 mg/kg twice daily was incorporated throughout the protocol.

SECTION 1.1: BACKGROUND ON SPINAL MUSCULAR ATROPHY (SMA)

~~There is no effective pharmacological treatment for SMA.~~

The medical need for patients with SMA is very high, and several drug candidates are currently under investigation in the nonclinical and clinical setting. The SMN2-targeting antisense oligonucleotide nusinersen (Spinraza®) has been recently approved by the U.S. Food and Drug Administration (FDA) and the European Commission for the treatment of pediatric and adult patients with SMA. This treatment is administered by intrathecal injection, and its effects are limited to CNS tissues. ~~and marketing applications have been submitted to other regulatory authorities for approval.~~ Alternative management strategies focus on ~~Current management~~ *~~of SMA~~* ~~is focused on~~ prevention and treatment of comorbidities, such as failure to thrive, surgical and non-surgical treatment for scoliosis and contractures, pulmonary hygiene, non-invasive ventilation, mobility and seating support, and physical and occupational therapy. *There is still a high unmet need with regard to oral therapies as well as limited access to treatment with nusinersen, depending on country and disease type. In addition, not all patients benefit from the treatment or tolerate it.* ~~Treatment is supportive with the goals being to improve the patient's quality of life and to minimize disability (Wang et al. 2007).~~

SECTION 1.2: BACKGROUND ON OLESOXIME

~~Seventeen~~*As of September 2017, there have been 17 completed* clinical Phase I, II, and II/III studies ~~were~~ performed with olesoxime, including ~~one~~*a* Phase ~~2/3~~*Ib single- and multiple-dose, open-label, multicenter, pharmacokinetic (PK) and safety study (TRO19622CLEQ1115-1) and a Phase II/III* double-blind study in SMA (TRO19622CLEQ1275-1). *More than 900*~~849~~ healthy subjects and patients have been exposed to olesoxime.

SECTION 1.2.1: <u>Study TRO19622CLEQ1115-1</u>

Study TRO19622CLEQ1115-1 was a Phase Ib single- and multiple-dose, open-label multicenter, PK and safety study conducted with pediatric and adult patients (6–25 years of age) with SMA, at the dose of 125 mg olesoxime once a day (QD) (hard capsule formulation). ~~This was a Phase II, adaptive, parallel group, double blind,~~

~~randomized, placebo-controlled, multicenter, multinational study designed to assess the efficacy and safety of olesoxime over 24 months in 3-25 year-old Type 2 and non-ambulatory Type 3 SMA patients. One hundred and sixty five patients were randomized in a 2:1 ratio to olesoxime 10mg/kg or placebo.~~ The first patient was enrolled on *7 January 2008* ~~November 18, 2010~~, and the last patient, last visit occurred ~~*in* October~~*on 6 November* 2013.

Olesoxime 125 mg QD, administered first in a single dose and then in repeated doses during 9 to 11 days, was safe and well tolerated.

~~The primary outcome measure was the Motor Function Measure (MFM) which is a multidimensional motor function scale for use in patients with neuromuscular disorders, and has been validated in SMA, and it has been divided into 3 sub-domains: D1, which evaluates functions related to standing and transfer; D2, which evaluates axial and proximal function in supine and sitting position on mat and chair; and D3, which evaluates distal motor function (). As SMA primarily affects proximal muscles, the primary endpoint of the study was change from baseline at month 24 on the MFM D1+D2 score. The result for the primary outcome, motor function loss over two years based on the MFM D1+D2 score, was in favor of olesoxime and close to statistical significance when compared with placebo (treatment effect: 20 [96% CI: 0.25 ; 4.25]; p=0.0676) (Clinical Study Report in preparation).~~

SECTION 1.2.2: Study TRO19622CLEQ1275-1

Study TRO19622CLEQ1275-1 was a Phase II/III, adaptive, parallel-group, double-blind, randomized, placebo-controlled, multicenter, multinational study designed to assess the efficacy and safety of olesoxime over 24 months in pediatric and adult patients (3–25 years of age) with Type 2 and non-ambulatory Type 3 SMA. There were 165 patients randomized in a 2:1 ratio to olesoxime 10 mg/kg QD or placebo. The first patient was enrolled on 18 November 2010, and the last patient, last visit occurred in October 2013.

The primary outcome measure was the Motor Function Measure (MFM), which is a multidimensional motor function scale for use in patients with neuromuscular disorders. The MFM has been validated in SMA and has been divided into three sub-domains: D1, which evaluates functions related to standing and transfer; D2, which evaluates axial and proximal function in supine and sitting positions on a mat and a chair; and D3, which evaluates distal motor function (Bérard et al. 2005). As SMA primarily affects proximal muscles, the primary endpoint of the study was change from baseline at Month 24 in the MFM D1 + D2 score. The result for the primary outcome was in favor of olesoxime and close to statistical significance when compared with placebo (treatment effect: 2.0 [96% CI: –0.25, 4.25]; p = 0.0676) (Bertini et al. 2017).

The secondary endpoints included the MFM Total score (D1+D2+D3), the Hammersmith Functional Motor Scale (HFMS), and a responder analysis on both functional motor scales. Electromyography (maximum compound muscle action potential [CMAP] / motor unit number estimation [MUNE]), Forced Vital Capacity (FVC), Pediatric Quality of Life ~~Questionnaire~~ *Inventory™* (PedsQL™), Clinical Global Impression (CGI), and safety were formally tested using analysis of covariance (ANCOVA) or other methods. The magnitude of the treatment effect based on the total MFM score (D1+D2+D3) was quite similar to the D1+D2 analysis. The change in HFMS after 21 months treatment showed a positive trend for the olesoxime treatment arm over time.

Natural history studies in Type 2 and Type 3 SMA (Vuillerot et al. 2013; Mercuri at al. 2016) have shown that patients 6–15 years of age have a greater likelihood of substantial worsening of their condition within 12–24 months of the observation period, which is likely related to growth and weight gain without an increase in muscle strength. Thus, the 6–15 years age group may be appropriate for demonstrating maintenance of motor function. A post hoc analysis conducted in this age group showed a statistically significant separation of 3.61 points (p=0.036) on the MFM D1+D2 scores at 24 months.

A responder analysis was performed by comparing the MFM score at Month 24 with the score at baseline. Patients were considered responders if their motor function score did not worsen at Month 24 compared to baseline. A similar approach was used for the HFMS by comparing the score at Month 21 with the score at baseline. For the MFM total score, olesoxime treatment for 24 months resulted in a higher responder rate (56.3%) compared to placebo (38.6%, p = 0.0419). When the analyses were performed on the HFMS score, the relative risk was 1.82 [95% CI: 1.16; 2.86] in favor of olesoxime (p = 0.0091), with 28.1% responders in the placebo arm, compared to 49.5% in the olesoxime arm. *The pre-specified analysis of electromyography* ~~Analyses of Electromyography~~ (CMAP / MUNE), FVC, PedsQL, and CGI were inconclusive. *However, a post hoc responder analysis of the CGI using a responder definition, which mirrors the stable or improved MFM/HFMS responder, showed a statistically significant effect favoring olesoxime (relative risk of 1.23 [CI: 1.01, 1.49]; p=0.0361). For the patient-/parent-reported CGI, a similar pattern was identified, with a trend favoring olesoxime (relative risk of 1.19 [CI: 0.99, 1.44]; p=0.0640).*

SMA-related complications were reported as adverse events in ~~*fewer*~~*a lower proportion of* patients in the olesoxime group compared ~~to~~ *with* placebo. Most importantly, ~~fewer~~*a lower proportion of* patients treated with olesoxime reported severe lower respiratory infections. All other adverse events were equally distributed in nature and severity: ~~62~~ ~~(37.6~~*63 (38.2*%) patients experienced at least one serious adverse event, with a lower rate in the olesoxime arm compared ~~to~~ *with* placebo (~~*33* [*30.6*~~*34 [31.5*%] *patients* vs. 29 [50.9%] *patients*).

~~Average trough concentrations at steady state observed in 3–25 year-old patients with Type 2 and Type 3 SMA (n = 103 [Full Analysis Set (FAS)]) treated with 10 mg/kg of olesoxime as a liquid suspension for 104 weeks were within the ranges anticipated based on data from healthy volunteers (mean individual average olesoxime plasma concentration [Caverage] was 8590 ng/mL, SD was 2400 ng/mL, and range was 4130–16600 ng/mL).~~

The PK and efficacy data from Study TRO19622CLEQ1275-1 were used to investigate the relationship between olesoxime PK exposure (i.e., average trough concentration [$C_{average}$]) and the primary efficacy outcome (i.e., MFM D1+D2 score). The results of this analysis indicated that the effect of olesoxime did not reach a plateau at the dose of 10 mg/kg QD and that higher doses may lead to an increase in efficacy (see PK/pharmacodynamic [PD] report) (see Section 3.3.1).

Baseline samples from 119 patients previously enrolled in Study TRO19622CLEQ1275-1 (81 patients in olesoxime arm and 38 patients in placebo arm) were analyzed. All patients previously on olesoxime in Study TRO19622CLEQ1275-1 had detectable predose olesoxime concentrations at baseline of Study BN29854. Olesoxime concentrations ranged from 23 to 801 ng/mL, corresponding to 0.3% to 9.5% of $C_{average}$ observed in Study TRO19622CLEQ1275-1. The time after last dose from Study TRO19622CLEQ1275-1 was 2.4–4.0 years. Olesoxime was not detected in the OLEOS baseline samples from any of the 38 patients previously randomized to placebo arm in Study TRO19622CLEQ1275-1. Roche currently assumes that these residual concentrations are secondary to the accumulation of olesoxime, a cholesterol derivative, in a deep compartment.

~~As of 2 June 2016, baseline samples from 38 patients previously enrolled in Study TRO19622CLEQ1275-1 (26 olesoxime and 12 placebo) were available. All patients previously on olesoxime in Study TRO19622CLEQ1275-1 had detectable predose olesoxime concentrations at baseline of the OLEOS study. Olesoxime concentrations ranged from 45.7 to 801 ng/mL, corresponding to 0.6% to 9.5% of the average trough concentration observed in Study TRO19622CLEQ1275-1. The time after last dose from Study TRO19622CLEQ1275-1 was 2.4–4.0 years. Olesoxime was not detected in the OLEOS baseline samples from any of the 12 patients previously randomized to placebo in Study TRO19622CLEQ1275-1. Roche currently assumes that these residual concentrations are secondary to the accumulation of olesoxime mainly in a deep compartment.~~

SECTION 1.2.3: *Study BP39378* ~~TRO19622CLEQ1115-1~~

~~This was a phase 1b single and multiple dose, open label, multicenter, pharmacokinetic and safety study conducted in 8 children and adults (6 to 25 years of age), at the dose of 125 mg (hard capsule formulation). The first patient was enrolled on 07 January, 2008, and the last patient, last visit occurred on 06 November, 2013. Olesoxime 125 mg once~~

~~daily *was* administered first in single dose and then in repeated doses during 9 to 11 days *and* was safe and well tolerated.~~

Study BP39378 is an ongoing Phase I relative bioavailability study in healthy volunteers comparing the systemic exposure (area under the concentration–time curve from Time 0 to infinity [$AUC_{0-\infty}$] and maximum concentration observed [C_{max}]) of olesoxime when administered as a single dose or in two divided doses (~12 hours apart) with food in the form of a suspension or solution formulation. Preliminary PK results revealed that doubling the dose of olesoxime from 10 mg/kg to 20 mg/kg (in solution form) resulted in only ~20% increase in AUC and ~11% increase in C_{max}. This finding is in line with animal data and is likely based on saturation of absorption of olesoxime. When the dose was divided into a morning and an evening dose, 10 mg/kg each, the increase in AUC was ~100%, while C_{max} only increased by ~20%. Similarly, a dose of 30 mg/kg of olesoxime in suspension formulation divided into two doses (15 mg/kg each) resulted in ~120% increase in AUC and ~56% increase in C_{max}, compared to a single dose of 10 mg/kg as suspension. The preliminary results of the study indicated that a twice a day (BID) dosing regimen of olesoxime produces higher systemic exposure, whereby potentially improving the efficacy outcome of the treatment. In this study, single or divided doses up to 30 mg/kg were well tolerated.

Taken together with the data from the PK/PD analysis of Study TRO19622CLEQ1275-1, the olesoxime dose will be increased to 10 mg/kg BID in this study (BN29854) to maximize efficacy for participating patients. The total daily dose of Study BN29854 will not exceed 2000 mg. This maximum dose of 2 g/day forms the basis of the technical investigational medicinal product (IMP) specifications in the drug manufacturing process and cannot be exceeded for this reason. Therefore, all patients with a body weight >100 kg will receive a dose of 1000 mg BID.

SECTION 1.2.4 (NEW SECTION): *Study BN29854 (OLEOS)*

The 12-month analysis of the OLEOS BN29854 study (Muntoni et al. 2017) demonstrated that olesoxime was generally safe and well tolerated at the dose assessed, with a safety profile comparable to placebo groups of previous studies. Despite a substantial decline in MFM D1 + D2 score (>2 points/year) since stopping study drug at the end of the previous clinical trial (median 3 years), the observed treatment difference between placebo and olesoxime was maintained at OLEOS baseline. Olesoxime sustained motor function over 12 months in patients treated open-label in the OLEOS study. These data suggest that olesoxime offers the potential to provide meaningful clinical benefit to patients with SMA by preventing loss of motor function.

SECTION 1.3: STUDY RATIONALE

The study was initiated at a dose of 10 mg/kg QD; after Protocol BN29854, Version 4 is in effect, the dose will be increased from 10 mg/kg QD to 10 mg/kg BID with the aim of increasing the exposure to olesoxime and thereby increasing a possible therapeutic benefit of olesoxime, while maintaining appropriate safeguards using a thorough

clinical safety monitoring plan. The total daily dose in this study will not exceed 2000 mg. For details on the dose increase rationale, see Section 3.3.1.

SECTION 1.4: BENEFIT–RISK ASSESSMENT

The main objective of this study is to evaluate long-term safety and efficacy to support long-term treatment with olesoxime in patients with SMA and to continue to provide access to olesoxime to patients enrolled in Study TRO19622CLEQ1275-1.

Patients with SMA have a high background incidence of comorbidities associated with their underlying disease and have decreased mobility (e.g., wheelchair bound). ~~SMA is also a highly debilitating condition with no pharmacotherapeutic options. The main objective of the study is to evaluate long-term safety and effectiveness to support long-term treatment with olesoxime in SMA patients.~~*The antisense oligonucleotide nusinersen (Spinraza®) was recently approved in the United States and the European Union for the treatment of pediatric and adult patients with SMA. This treatment is administered by intrathecal injection and targets the CNS tissues. Despite this first disease-modifying therapy, the medical need in SMA is still very high.*

Olesoxime *targets the CNS as well as peripheral tissues and* has demonstrated beneficial neuroprotective activity in numerous preclinical models at doses between 3 and 30 mg/kg. Although the primary endpoint was not met, Study TRO19622CLEQ1275-1 indicated that treatment with daily doses of olesoxime 10 mg/kg maintained motor function in *patients with Type 2 and non-ambulatory Type 3 SMA over the course of 2 years (see Section 1.2.2).* ~~in SMA Type 2 and non-ambulatory Type 3 patients.~~ These results support the use of olesoxime in *patients with*~~SMA~~ Type 2 and non-ambulatory Type 3 *SMA.* ~~, a disease for which there is currently no approved treatment. The main objective of the study is to evaluate long-term safety and effectiveness to support long-term treatment with olesoxime in SMA patients.~~

~~To date, there are no identified risks with olesoxime therapy in humans.~~

As described in Section 1.2.4, the recent 12-month analysis of the OLEOS (BN29854) study (Muntoni et al. 2017) continues to demonstrate that olesoxime offers the potential to provide meaningful clinical benefit to patients with SMA by preventing loss of motor function.

Based on a retrospective exposure/efficacy analysis described in Section 1.2.2, Study TRO19622CLEQ1275-1 indicated that the effect of olesoxime did not reach a plateau at the dose of 10 mg/kg QD and that higher exposure levels may lead to an increase in efficacy. The results are consistent with previous trends of better effect in subjects with medium-to-high exposure.

Therefore, an increased exposure to olesoxime with a doubling of the current dose given twice daily is seen as a meaningful step to provide patients with the possibility of an improved therapeutic effect from the treatment with olesoxime.

As described in Section 3.3.1, the 10 mg/kg BID dose is seen as the advisable dose regimen to be able to reach the targeted, higher exposure levels that may lead to an increase in efficacy. The total daily dose in this study will not exceed 2000 mg. This maximum dose of 2 g/day forms the basis of the technical IMP specifications in the drug manufacturing process and cannot be exceeded for this reason. Therefore, all patients with a body weight >100 kg will receive a dose of 1000 mg BID.

During clinical development of olesoxime, *over 900*~~, 849~~ healthy volunteers and patients have been exposed to ~~study drug~~ *olesoxime, with a daily dose ranging between 50 mg to 1000 mg and treatment duration up to 43 months*. Olesoxime has shown to be well tolerated at all tested dose regimens including co-administration with riluzole or beta-interferons. Atrioventricular conduction abnormalities observed in dogs have not been observed to date in humans. *To date, there are no identified risks with olesoxime therapy in humans.*

As mentioned above, the accumulating data from the open-label extension study BN29854 continues to demonstrate that olesoxime is generally safe and well tolerated at the dose assessed, with a safety profile comparable to the placebo goup of Study TRO19622CLEQ1275-1 (see Section 1.2.4) (Muntoni et al. 2017).

From a safety perspective, the 10 mg/kg BID dose appears appropriate as the expected exposure at 10 mg/kg BID is covered by chronic preclinical toxicity studies. Nevertheless, considering preclinical findings of arrhythmias observed in the 39-week toxicity studies in dogs that started at the lowest dose (50, 250, and 1000 mg/kg/day) and in order to ensure the safeguards of patients participating in this study, a 24-hour Holter ECG monitoring will be performed prior to the dose increase to 10 mg/kg BID and 4 weeks later when steady-state is expected to be reached.

Based on *the existing preclinical data, clinical data (including analysis of the* efficacy data from the completed trials *and results of the BP39378 study)* ~~and based on~~, the safety profile *of the 10 mg/kg QD dose* observed to date, *and the results of the BP39378 study,* the Sponsor considers the benefit–risk balance to be positive for the continuation of the *olesoxime* development program ~~with olesoxime~~ *and for an olesoxime dose increase to 10 mg/kg BID*.

SECTION 2.4: PATIENT-REPORTED OUTCOME OBJECTIVES

The patient-reported outcome (PRO) objectives for this study are as follows:

- *To explore changes in level of independence and health-related quality of life following treatment with olesoxime*

- ~~To compare changes in Health Related Quality of Life and the relationship to other measures of disease status (such as motor function scales), following treatment with olesoxime versus the natural history of disease in patients with SMA, as measured by PedsQL core, and neuromuscular sub-scales.~~
- To assess health-related quality of life and conduct economic modeling using the *EuroQol 5-Dimension, 5-Level Questionnaire (*EQ-5D-5L*)*

SECTION 2.5: CAREGIVER-REPORTED OUTCOME OBJECTIVES

The caregiver-reported outcome objectives for this study are as follows:

- *To assess caregiver-reported changes in patient health outcomes, as measured by the caregiver-report versions of the PedsQL™ Generic Core Scales (Version 4.0), PedsQL™ Neuromuscular Module (Version 3.0), SMA Independence Scale (SMAIS), and EQ-5D-5L*
- ~~To assess caregiver related~~ *To assess changes in caregiver* quality of life and conduct economic modeling using the caregiver resource use: Work Productivity and Activity Impairment: Caregiver (WPAI:CG) and caregiver generic health-related quality of life Short Form-36 ~~questionnaire~~ *Health Survey, Version 2 (SF-36v2*)

SECTION 2.6: EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To explore olesoxime treatment response of FVC in patients with SMA
- To evaluate the percentage of responders in patients with SMA, defined as patients who did not have a decrease from baseline in MFM scores
- To investigate the impact of SMN2 copy number *and other genes*, transcripts, and ~~protein~~*proteins* involved in pathological pathways of SMA in patients with SMA on the safety, pharmacokinetics, pharmacodynamics, and efficacy of olesoxime
- To explore olesoxime treatment response to levels of SMN2 mRNA and SMN protein in blood
- To evaluate potential relationships between drug exposure, efficacy, and safety
- *To assess clinician-reported change in overall health status, as measured by the Clinical Global Impression of Change (CGI-C)*
- *To evaluate potential correlations between the collected sensor data from smartphone-based monitoring and MFM scores and to assess patients' adherence to smartphone-based monitoring*
- *To explore the potential effect of olesoxime on patient experience of fatigability, as measured by the clinician-reported Olesoxime Fatigability Survey (OFS)*

SECTION 3.1.1: Study Design

This is an open-label, single-arm study to further evaluate long-term tolerability, safety, and efficacy outcomes in patients with SMA who previously participated in one of the following two clinical studies:

- Open-label Phase Ib, *multicenter,* ~~dose ranged,~~ single- and multiple-dose study to assess safety and pharmacokinetics of olesoxime in ~~6-25 year old~~*pediatric and adult* ~~Spinal Motor Atrophy (SMA)~~ patients *(6–25 years of age) with SMA* (TRO19622CLEQ1115-1), and*/or*
- Phase II*/III, adaptive, parallel-group, double-blind, randomized, placebo-controlled, multicenter, multinational* ~~multicenter, randomized, adaptive, double blind, placebo controlled~~ study to assess safety and efficacy of olesoxime in ~~3-25 year old Spinal Muscular Atrophy (SMA)~~ *pediatric and adult* patients *(3–25 years of age) with Type 2 and non-ambulatory Type 3 SMA* (TRO19622CLEQ1275-1)

SECTION 3.1.1.3: Treatment Period

Patients who have consented to the dose increase specified in Protocol BN29854, Version 4 ~~All eligible patients~~ will receive liquid formulation of olesoxime ~~either orally or via naso-gastric tube or gastrostomy tube~~ at a dose of 10 mg/kg ~~once daily with the main meal~~ *BID either orally or via a naso-gastric or gastrostomy tube with breakfast and dinner*, preferably at the same time of the day *throughout the study. If drug administration does not coincide with one of the scheduled meals, a snack should be taken prior to drug administration. Preferably there should be at least 10 hours between the morning and evening dose. The total daily dose in this study will not exceed 2000 mg. Therefore, patients with a body weight >100 kg will receive a dose of 1000 mg BID. This maximum dose of 2 g/day forms the basis of the technical IMP specifications in the drug manufacturing process and cannot be exceeded for this reason.*

Patients who have not consented to the dose increase specified in Protocol BN29854, Version 4 will be administered olesoxime at 10 mg/kg QD orally or via a naso-gastric or gastrostomy tube with the main meal throughout the study.

Patients′ visits will occur at 3 months, 6 months, 9 months, 12 months, and every 6 months thereafter for medical examination, and safety and efficacy assessments~~. For treatment period duration, please refer to Section 3.2.~~ *Related to the dose increase per Protocol BN29854, Version 4, one or two additional visits will occur (see the Schedule of Assessments in Appendix 1). For treatment period duration, please refer to Section 3.2.*

SECTION 3.1.1.4: Dose Increase per Protocol BN29854, Version 4

This section has been added.

SECTION 3.3.1: Rationale for the Dose Increase

This section has been added.

SECTION 3.3.3: Rationale for PK Sample Collection Schedule

Based on the PK characteristics of olesoxime (for more details, please refer to the Olesoxime Investigator's Brochure), it is believed that the collection of ~~one~~ PK sample*s* ~~in every patient~~ as outlined in Schedule of Assessments (Appendix 1) would allow appropriate characterizing of the PK of olesoxime in this study using a population PK modeling approach (see Section 6.8).

SECTION 3.3.4: Rationale for Biomarker Assessments

In order to explore the role of potential biomarkers and to better understand treatment response of olesoxime in SMA, the following analyses of biomarker data will be performed:

- Relationship of several SMA related biomarkers to olesoxime treatment response and progression of the disease in the patients, ~~such as~~ *which may include,* ~~(~~but *are* not restricted to~~)~~:
  - *SMN1 and* SMN2 copy number
  - SMN mRNA splicing and SMN protein levels in blood

    SMN1 and SMN2 copy number, SMN mRNA splicing, and protein levels in the blood have been linked with SMA type and disability progression.
  - Correlation *and dynamic changes* of genes, transcripts, and protein involved in pathological pathways of SMA to functional parameters, such as, but not restricted to cholesterol*, molecular mitochondrial analyses (e.g., mitochondrial DNA), and genetic modifiers*

For this study, a digital biomarker approach has been developed using high-quality smartphone sensors that enable remote, non-invasive, frequent, and precise measurement of motor and non-motor symptoms. Smartphone sensors have been successful for monitoring movement disorders such as Parkinson's disease (Maetzler et al. 2013; Arora et al. 2015; Ossig et al. 2016) and several of the clinical motor measures for patients with SMA are tractable to smartphone-based measurement. The smartphone assessments were designed with clinician, physiotherapist, and patient input and are based on the MFM (Bérard et al. 2009).

A smartphone will be provided to each patient aged 6 years and older. The smartphone will be used to complete a selection of tests and surveys:

- *Force tests to assess hypotonia*
- *Fine-hand motor tests to evaluate distal weakness*
- *Arm lifting tests to assess axial and proximal motor function*
- *Sustained phonation test, including voice pitch variation as an indicator of muscular fatigue, central hypotonia, and ventilation problems*
- *Questions on the patients' health*

Patients will receive the study smartphone during the dose increase visit and subsequently perform a subset of the smartphone tests each day at home, based on their ability and an automatic scheduler on the smartphone. In addition, patients will conduct the tests at selected visits as per the Schedule of Assessments (see Appendix 1). The tests take about 5 minutes per day. Additional details are available in the SMA Digital Biomarker Manual.

SECTION 4.2.1.1: Olesoxime

Patients who do not consent to the dose increase will continue with the previous dosage and receive a dose of 10 mg/kg QD.

SECTION 4.2.2.1: Olesoxime

Olesoxime will be given as a 100-mg/mL liquid formulation. The drug will be administered at 10 mg/kg ~~once a day~~*BID* orally or via a naso-gastric or gastrostomy tube with ~~the main meal~~*breakfast and dinner*, preferably at the same time of the day throughout the study. *If drug administration does not coincide with one of the scheduled meals, a snack should be taken prior to drug administration. Preferably there should be at least 10 hours between the morning and evening dose. The total daily dose in this study will not exceed 2000 mg. Therefore, patients with a body weight >100 kg will receive a dose of 1000 mg BID.*

For the dose increase procedures of the patients who consent to Protocol BN29854, Version 4, please refer to Section 3.1.1.4.

Patients who do not consent to the dose increase will continue with the previous dosage and receive a dose of 10 mg/kg QD orally or via a naso-gastric or gastrostomy tube with the main meal, preferably at the same time of the day, throughout the study.

[…]

Any overdose or incorrect administration of study drug should be documented in the patient's ~~notes~~*diary* and recorded in the eCRF.

SECTION 4.3.1: Permitted Therapy and Medical Procedures

Therapies for the treatment of SMA or agents anticipated to increase or decrease muscle strength are permitted, which include, but are not restricted to:

> *Nusinersen (Spinraza®),* riluzole, valproic acid, hydroxyurea, sodium phenylbutyrate, butyrate derivatives, growth hormone, anabolic steroids, probenecid, agents anticipated to increase or decrease muscle strength or presumed histone deacetylase inhibition activity

Use of nusinersen (Spinraza®) does not exclude patients from continued participation and treatment with olesoxime in Study BN29854.

SECTION 4.3.1.1: Prohibited Therapy

Use of the following therapies is prohibited during the study treatment:

- Investigational therapy
- Medications that could interfere with olesoxime absorption: ezetimibe, bile salts chelators (cholesteramine), fibrates, phytosterols, ~~fish oils, niacin (vitamin B3)~~

Medication that could interfere with olesoxime pharmacodynamics: tamoxifen

SECTION 4.4: STUDY OBJECTIVES

Laboratory safety samples should be collected first at each visit, *preferably* under fasted conditions.

SECTION 4.4.1.1 (NEW SECTION): *Informed Consent Form for Protocol BN29854, Version 4*

All patients, or if appropriate, legal guardians, must have signed informed consent for the new schedule of assessments and related procedures (see Section 3.1.1.4). If the patient agrees to the 10 mg/kg BID dose, as well as all procedures and assessments per Protocol BN29854, Version 4, this must be documented in the informed consent.

In case the patient or his/her caregiver initially declines receiving the dose increase and subsequently reconsiders the decision, new written informed consent must be obtained.

SECTION 4.4.4: Anthropometric Measurements

Anthropometric measurements include body weight at every visit, and height at baseline, and every 6 months thereafter *as well as at a possible early discontinuation visit*.

The patient's body weight will be measured to the nearest kilogram using a calibrated scale. For wheelchair-bound patients, weight of the patient will be obtained with a wheelchair balance scale with the patient in the wheelchair. The wheelchair should be also weighed by itself and subtracted from total weight.

The patient's height will be measured or derived *from ulna length* to the nearest centimeter. ~~Height may be derived from the measurement of ulna length using the formulas of Gauld et al. ():~~

- ~~Males: Height (cm)=4.605 *ulna length (cm) + 1.308*age (years) + 28.003~~
- ~~Females: Height (cm)= 4.459*ulna length (cm) + 1.315*age (years) + 31.485~~

SECTION 4.4.8: Laboratory, Pharmacokinetic, Biomarker, and Other Biological Samples

- Plasma samples for PK analysis

A ~~1 mL~~ blood sample will be collected at timepoints specified in the Schedule of Assessments (Appendix 1).

SECTION 4.4.8.1: Biomarker Assessments

All biomarker samples will be destroyed no later than 5 years after the date of the final clinical study report.

SECTION 4.4.8.1.1: SMN Protein Levels

Whole blood for SMN protein analysis ~~(approximately 3 mL)~~ will be collected from every patient.

SECTION 4.4.8.1.2: In Vivo Splicing of SMN2 mRNA

Two whole blood samples ~~(approximately 2.5 mL)~~ will be taken from every patient at the timepoints specified in the Schedule of Assessments (Appendix 1) to measure the relative amounts of ~~FL~~ *SMN1,* SMN2-*FL, and SMNΔ7* mRNA transcript ~~and splice forms thereof~~ during the course of the study. In addition, housekeeping genes for the quantitative analysis of RNA will be measured. Additional mRNA may be ~~measured to study~~ *used for exploratory analysis/assay development related to SMA, including, but not limited to,* pathways related to SMN function, SMA disease severity, ~~and~~ progression, and treatment response.

SECTION 4.4.8.1.3: Fluid Biomarkers

The following fluid biomarker samples will be used to assess treatment response in patients. Serum ~~(approximately 6 mL)~~ for the analysis of biomarkers related to SMA or to the response from treatment (e.g., muscle damage or insulin-like growth factor system) will be collected.

These samples will be destroyed no later than 5 years after the date of *the* final ~~lock of the~~ clinical ~~database~~ *study report* and may be used for additional exploratory analysis/assay development ~~with respect~~ *related to SMA including, but not limited* to, pathways related to SMN function or treatment response.

SECTION 4.4.8.2: Clinical Genotyping Samples

A mandatory ~~3 mL~~ whole blood sample will be taken for DNA extraction from every patient at ~~baseline.~~ *three timepoints, as indicated in the Schedule of Assessments (see Appendix 1).* The *baseline* DNA will be used to determine the copy number of SMN2 and may also be used to confirm the SMN1 mutation or deletion. *The baseline and longitudinal DNA samples may be used for additional exploratory analysis/assay development related to SMA including, but not limited to, mitochondrial DNA levels and genes related to SMN function (especially genetic modifiers of SMA, SMN mRNA splicing, or SMN protein expression), which might be dynamically changed due to disease severity, progression, and treatment response.* ~~In addition, the DNA may be used to analyze modifier of SMA disease severity and progression and modifiers of SMN mRNA splicing or SMN protein expression.~~

These samples will be destroyed no later than 5 years after the date of *the* final ~~lock of the~~ clinical ~~database and may be used for additional exploratory analysis/assay development with respect to the SMN genes.~~ *study report.*

SECTION 4.4.8.4 (NEW SECTION): *Spinal Muscular Atrophy Digital Biomarkers*

Each patient will receive a preconfigured smartphone at the first visit after Protocol BN29854, Version 4 has been initiated and after the new Informed Consent Form has been signed. The device and software will be used to regularly assess motor behavior, as well as to intermittently answer questions related to health and activities associated with routine daily living. The smartphone must be returned to the clinical site in case of study withdrawal, end of the study, or upon request.

Digital Biomarker Remote Monitoring

Patients will be provided with and trained on the device. During the study, patients will be instructed to conduct "Active Tests" every day, at approximately the same time (ideally in the morning after breakfast). The "Active Test" consists of a short, preconfigured sequence of tasks that assess motor symptoms.

Device sensor data will be recorded continuously throughout the "Active Tests." Audio will only be recorded during the sustained phonation test. Data are encrypted and uploaded to secure servers whenever the smartphone is connected to WiFi.

Digital Biomarker In-Clinic Assessments

Patients will be instructed to bring the smartphone to every clinic visit to check adherence and the technical status of the device.

At selected clinic visits, patients will be asked to conduct the "Active Tests" tasks under the supervision of a person trained on the digital biomarker approach.

The smartphone must be returned to the clinic in cases where the patient does not meet eligibility criteria, study withdrawal, end of the study, or upon request.

At the end of the study or at the time when the subject has completed the study, patients will be asked to complete a pen and paper satisfaction survey on their experience using the smartphone during the study.

Additional details are available in the SMA Digital Biomarker Manual.

SECTION 4.4.9: Electrocardiograms

If a patient performs a 24-hour Holter ECG as part of the dose increase per Protocol BN29854, Version 4 on a regular visit (see Option 2 in Section 3.1.1.4) and an ECG assessment is scheduled at this regular visit, only the 24-hour Holter ECG will be performed.

SECTION 4.4.9.1 (NEW SECTION): *24-Hour Holter ECG Monitoring*

All patients who have consented to the 10 mg/kg BID dose increase will be requested to have 24-hour Holter ECG monitoring (see Section 3.1.1.4) before the dose increase and 4 weeks after the dose increase. The Holter ECG monitor will be placed on the patient at the dose increase visit and at the dose increase safety follow-up visit. After the first predose 24-hour Holter ECG monitoring at the dose increase visit, patients will return the Holter ECG monitor to the site at the dose increase safety follow-up visit (at the latest). After the second 24-hour Holter ECG monitoring, which is performed at the dose increase safety follow-up visit, the recording data must be sent to the central laboratory, and the site will be informed of the results within 1 week. Any abnormality in the Holter ECG data will be assessed on a case-by-case basis between Sponsor and investigator, and appropriate measures will be taken as needed.

SECTION 4.4.10: Patient-Reported Outcomes

To ensure instrument validity and that data standards meet health authority requirements, the questionnaires scheduled for administration during a clinic visit should be completed *after the laboratory safety samples have been taken and* prior to administration of study treatment and to the performance of non-PRO assessments, in the order defined below ~~and in the Schedule of Assessments (). Whenever possible~~. *Where appropriate,* both caregiver and patient should complete the PedsQL ~~modules~~*Generic Core Scales*. The self-report version of EQ-5D-5L should be completed by patients ≥12 years of age, and the proxy version completed by caregivers of patients <12 years of age. *The SMAIS self-report version should be completed by patients aged ≥ 12 years, and the SMAIS caregiver-report version should be completed by a caregiver for all patients, where possible. The form used in the baseline assessment should be used at all subsequent visits and the dose increase visit (e.g., patients aged <12 years will not complete the EQ-5D-5L or the SMAIS even if their 12th birthday occurs during the study, and patients aged 8-12 years will continue to use the PedsQL forms for ages 8-12 years even if their 13th birthday occurs during the study).*

The PRO measures for this study are as follows:

- *The EQ-5D-5L conducted at all visits except screening, Visit 2, and Visit 4:*

  The EQ-5D-5L is a self-report health status questionnaire that consists of six questions used to calculate a health utility score for use in health economic analysis (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; van Hout et al. 2012; Janssen et al. 2013, Oppe et al. 2014). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analog scale (VAS) that measures overall health status. Published weighting systems allow for creation of a single summary score. Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction; for some countries (e.g., United Kingdom), scores below zero are possible. The EQ-5D-5L will be utilized in this study for economic modeling.

Patients who participate in the digital biomarker assessment will also complete an electronic version of the EQ-5D-5L every 2 weeks.

The PedsQL *Generic Core Scales (Version 4.0) and PedsQL Neuromuscular Module (Version 3.0)* conducted at all visits, with the exception of *screening,* Visit 2*,* and Visit 4.

[…]

Age bands for the instrument are as follows, and within a scale or module, the appropriate age band should be used based on the age of the patient at ~~the time of completion~~*enrollment*:

Young child (5–7 years)

Child (8–12 years)

Teen (13–18 years)

Young Adult (18–25 years) [Core scales only]

Adult (>25 years) [Core scales only]

[…]

- ~~The EuroQol 5 Dimension Questionnaire, 5 level version (EQ 5D 5L) conducted at all visits, with the exception of Visit 2 and Visit 4:~~

  ~~The EQ 5D 5L is a self report health status questionnaire that consists of six questions used to calculate a health utility score for use in health economic analysis (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013, Oppe et al. 2014, van Hout et al. 2012). There are two components to the EuroQol EQ 5D 5L: a five item health state profile that assesses mobility, self care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analogue scale (VAS) that measures overall health status. Published weighting systems allow for creation of a single summary score. Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction; for some countries (e.g., UK), scores below zero are possible. The EQ 5D 5L will be utilized in this study for economic modeling.~~

- *The SMAIS was developed specifically for SMA in order to assess function-related independence. The SMAIS contains 29 items, assessing the amount of assistance required from another individual to perform daily activities, such as eating or transferring to/from a wheelchair. Each item is scored on a 0–4 scale (with an additional option to indicate that an item is non-applicable). Item scores are summed to create the total score. Lower scores indicate greater dependence on another individual. The SMAIS will be completed by patients aged ≥12 years. The SMAIS will be conducted at all visits including the dose increase visit, with the exception of screening, Visit 2, and Visit 4.*

The PROs should be completed in the following order (caregivers should also follow this order when completing these questionnaires about the patient):

1. *SMAIS*
2. *EQ-5D-5L*
3. *PedsQL Neuromuscular Module*
4. *PedsQL Generic Core Scale*

SECTION 4.4.11: Caregiver-Reported Outcomes

The caregiver-reported outcome measures for this study are as follows:

- Caregiver resource use: WPAI:CG, conducted at all visits, with the exception of *screening,* Visit 2, and Visit 4

  Occupational work productivity and activity impairment in caregiver will be assessed using the WPAI:CG. The WPAI:CG consists of 6 questions about the effects of SMA on the following: employment status; hours missed due to patient caregiving; hours missed due to other reasons; hours actually worked; and two questions that measure the degree to which health problems affected productivity due to caregiving (presenteeism) and regular daily activities.

- Caregiver generic health-related quality of Life SF-36v2, conducted at all visits, with the exception of *screening,* Visit 2, and Visit 4

  SF-36v2 is widely used across databases and is a well-established generic scale with 36 questions grouped into eight domains *and two summary scores* covering aspects of functioning and physical and mental health in caregiver.

SECTION 4.4.12 (NEW SECTION): *Clinical Global Impression of Change*

The CGI-C is a single-item measure of change in global health that uses seven response options: Very Much Improved, Much Improved, Minimally Improved, No Change, Minimally Worse, Much Worse, and Very Much Worse. It is a widely used endpoint in clinical trials across a variety of disease areas. Clinicians will score patients using this scale based on their impression of change in the patient's global health since baseline. To enhance inter-rater consistency, an instructions document (developed with input from clinical experts) will be provided, which includes examples for each of the response options.

The same clinician should complete the CGI-C at all specified visits for an individual patient. The CGI-C will be administered at the dose increase visit and study Visits 5, 6, and 7.

SECTION 4.4.13 (NEW SECTION): *Olesoxime Fatigability Survey*

The OFS is a brief survey designed to explore potential benefit of olesoxime on fatigability (i.e., endurance). This survey will be completed once, at the dose increase visit. The data will be used to aid assessment of options for further clinical development of olesoxime. The survey will be completed by clinicians following discussions with the patient and their family/caregivers.

SECTION 4.4.16: Early Discontinuation Visit

Patients who decide to discontinue study treatment will be asked to return to the clinic for an early discontinuation visit 28 (± 5) days after last dose, regardless of reason of discontinuation *(safety follow-up, as described in Section 3.1.1.5).*

SECTION 4.4.18: Telephone Calls

The telephone interview is shown in Appendix 3 and will be conducted after Visit 5 by site personnel familiar with the patient(s) every 12 weeks (± 7 days) ~~between the~~*after each* study ~~visits~~*visit*.

SECTION 4.4.19.3: Sample Collection

The following samples will be collected from eligible patients who provide consent for research purposes, including but not limited to research on dynamic (non-inherited) biomarkers, and on genetic (inherited) biomarkers related to olesoxime, spinal muscular atrophy:

- DNA specimens for genetic biomarker (inherited) discovery and validation ~~(approximately 3 mL)~~ will be collected at baseline.
  NB If the sampling for DNA Specimens was missed during baseline, it may be collected in the next scheduled visit.
- Blood samples (~~approximately 2.5 mL total~~ collected in PAXgene vacutainers) will be collected for RNA analysis at timepoints specified in the Schedule of Assessments (Appendix 1).
- Blood ~~(approximately 6 mL)~~ for plasma isolation will be obtained at the timepoints indicated in the Schedule of Assessments (Appendix 1) for identification of dynamic (non-inherited) biomarkers.

These specimens will be used for research purposes and will help to better understand the pathogenesis, course, and outcome of SMA and related diseases. For all samples, dates of consent should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RCR specimens will be destroyed no later than 15 years after the date of final ~~closure of the associated clinical database~~*clinical study report*.

SECTION 4.5.1: Patient Discontinuation

The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn *(except for safety follow-up, as described in Section 3.1.1.5).*

SECTION 5.3.5.7: Deaths

~~The term **"sudden death"** should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case~~

~~of an unwitnessed death, within 24 hours after the patient was last seen alive and stable.~~ If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. *The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").*

SECTION 5.3.5.9: Hospitalization or Prolonged Hospitalization

~~The following~~ *An event that leads to* hospitalization ~~scenarios are~~*under the following circumstances should* not ~~considered to~~ be *reported as an* adverse ~~events~~*event or a serious adverse event*:

- Hospitalization for respite care
- Planned hospitalization required by the protocol , e.g., for study drug administration or insertion of access device for study drug administration
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

~~The following~~ *An event that leads to* hospitalization ~~scenarios are~~*under the following circumstances is* not considered to be *a* serious adverse ~~events~~*event*, but should be reported as *an* adverse ~~events~~*event* instead:

- Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available.

SECTION 5.4.1: Emergency Medical Contacts

Medical Monitor: [redacted], MD (primary)

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

SECTION 6.3: HISTORICAL DATA

~~Analyses will occur after last patient is enrolled in the study BN29854. The results will be reported in a document separate from the clinical study report.~~

SECTION 6.6: PRIMARY ANALYSES

Safety variables (e.g., laboratory tests, vital signs, and ECG) will be summarized for each assessment time (including follow-up) using descriptive statistics. *The data will be summarized by the dose being taken at the time of the assessment (10 mg/kg QD or 10 mg/kg BID). Data from the two 24-hour Holter ECG assessments will also be summarized.*

[…]

Adverse events will be summarized by the dose being taken at the onset date of the adverse event.

SECTION 6.7: SECONDARY ANALYSES

The change from baseline in MFM D1+D2 and MFM Total Score will be summarized at each visit using descriptive statistics. *The data will be summarized by the dose being taken at the time of the assessment.*

[…]

The incidence of disease associated medical complications and procedures will be summarized. *The data will be summarized by the dose being taken at the onset date of the event.*

SECTION 6.10: PATIENT-REPORTED OUTCOME ANALYSES

Data will be presented separately for child/patient report and parent report. *The data will be summarized by the dose being taken at the time of the assessment.*

[…]

For the SMAIS, total scores will be summarized for each assessment time by the dose being taken at the time of the assessment. Each item is scored on a 0-4 scale (with an additional option to indicate that an item is non-applicable), and item scores are summed to create the total score.

SECTION 6.11: CAREGIVER-REPORTED OUTCOME ANALYSES

The data will be summarized by the dose being taken at the time of the assessment.

SECTION 6.12: EXPLORATORY ANALYSES

Responder rates, where a responder is defined as no worsening from baseline in MFM D1 + D2, will be summarized *by the dose being taken at the time of the assessment.*

Change from baseline in FVC will be summarized *by the dose being taken at the time of the assessment.*

The CGI-C responses at each assessment visit will be summarized by the dose being taken at the time of the assessment. Clinicians will score patients using the CGI-C based on their impression of change in the patient's global health since baseline.

Smartphone sensor data collected as part of the digital biomarker approach will be analyzed. Patient adherence will be evaluated. From the sensor data, features will be developed for each smartphone-based test and correlated with the MFM and other

clinical endpoints. Further exploratory analyses may be conducted. The results will be separately reported from the clinical study report.

SECTION 9.2: PROTOCOL DEVIATIONS

The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

SECTION 9.5: PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf
~~http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf.~~

APPENDIX 1: Schedule of Assessments

Appendix 1 has been updated to reflect the changes to the protocol.

APPENDIX 3: Telephone Interviews

Appendix 3 has been updated to reflect the changes to the protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**MULTICENTER, OPEN-LABEL, SINGLE-ARM STUDY TO EVALUATE LONG-TERM SAFETY, TOLERABILITY, AND EFFECTIVENESS OF 10 MG/KG *BID* OLESOXIME IN PATIENTS WITH *SPINAL MUSCULAR ATROPHY***
PROTOCOL NUMBER:	BN29854
VERSION NUMBER:	4
EUDRACT NUMBER:	2015-001589-25
IND NUMBER:	IND119645
TEST PRODUCT:	Olesoxime (RO7090919)
MEDICAL MONITOR:	[redacted], *MD*
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy as instructed by your local study monitor.

PROTOCOL SYNOPSIS

TITLE:	**MULTICENTER, OPEN-LABEL, SINGLE-ARM STUDY TO EVALUATE LONG-TERM SAFETY, TOLERABILITY, AND EFFECTIVENESS OF 10 MG/KG *BID* OLESOXIME IN PATIENTS WITH *SPINAL MUSCULAR ATROPHY***
PROTOCOL NUMBER:	BN29854
VERSION NUMBER:	4
EUDRACT NUMBER:	2015-001589-25
IND NUMBER:	IND119645
TEST PRODUCT:	Olesoxime (RO7090919)
PHASE:	Phase II
INDICATION:	Spinal Muscular Atrophy
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives

Primary Objective

- To evaluate the safety of olesoxime in patients with SMA, focusing on the nature, frequency, and severity of adverse events, as well as effects on laboratory values, vital signs and electrocardiogram (ECG) parameters

Secondary Objectives

- To evaluate effectiveness of olesoxime compared to the natural history of disease in patients with SMA, as measured by MFM D1+D2 and MFM Total scores.
- To evaluate the disease associated medical complications and procedures in olesoxime treated patients compared to the natural history of disease, focusing on their nature, frequency of occurrence, and severity.
- To evaluate the disease course between last visit of the studies TRO19622CLEQ1275-1 and TRO19622CLEQ1115-1, and baseline assessment in this study, as measured by motor functional scales (e.g. MFM) and as measured by nature, frequency, and severity of medical procedures.

Pharmacokinetic Objectives

- To investigate the pharmacokinetics of olesoxime in the target population using Bayesian feedback analysis based on a population pharmacokinetic model (as appropriate and permitted by the data).

Patient-Reported Outcome Objectives

- *To explore changes in level of independence and health-related quality of life following treatment with olesoxime*
- To assess health-related quality of life and conduct economic modeling using the *EuroQol 5-Dimension, 5-level Questionnaire* (EQ-5D-5L)

Caregiver-Reported Outcome Objectives

- *To assess caregiver-reported changes in patient health outcomes, as measured by the caregiver-report versions of the PedsQL™ Generic Core Scales (Version 4.0), PedsQL™ Neuromuscular Module (Version 3.0), SMA Independence Scale (SMAIS), and EQ-5D-5L*

- *To assess changes in caregiver* quality of life and conduct economic modeling using the Caregiver resource use: Work Productivity and Activity Impairment: Caregiver (WPAI:CG) and Caregiver generic health-related quality of Life Short Form-36 *Health Survey, Version 2 (SF-36v2*)

Exploratory Objectives

- To explore olesoxime treatment response of Forced Vital Capacity (FVC) in patients with SMA
- To evaluate the percentage of responders in patients with SMA, defined as patients who did not have a decrease from baseline in MFM scores
- To investigate the impact of genes, transcripts, and *proteins* involved in pathological pathways of SMA in patients with SMA on the safety, pharmacokinetics, pharmacodynamics, and efficacy of olesoxime
- To explore olesoxime treatment response to levels of SMN2 mRNA and SMN protein in blood
- To evaluate potential relationships between drug exposure, efficacy, and safety
- *To assess clinician-reported change in overall health status, as measured by the Clinical Global Impression of Change (CGI-C)*
- *To evaluate potential correlations between the collected sensor data from smartphone-based monitoring and MFM scores and to assess patients' adherence to smartphone-based monitoring*
- *To explore the potential effect of olesoxime on patient experience of fatigability, as measured by the clinician-reported Olesoxime Fatigability Survey (OFS)*

Study Design

Description of Study

This is an open-label, single arm study to further evaluate long-term tolerability, safety and efficacy outcomes in patients with SMA who previously participated in one of the following two clinical studies:

- Open-label Phase Ib, *multicenter,* single- and multiple-dose study to assess safety and pharmacokinetics of olesoxime in *pediatric and adult* patients *(6–25 years of age) with SMA* (TRO19622CLEQ1115-1), and*/or*
- Phase II*/III, adaptive, parallel-group, double-blind, randomized, placebo-controlled, multicenter, multinational* study to assess safety and efficacy of olesoxime in *pediatric and adult* patients *(3–25 years of age) with Type 2 and non-ambulatory Type 3 SMA* (TRO19622CLEQ1275-1)

The study will consist of Historical Data Collection, screening, treatment, and safety follow-up periods. The study will occur in approximately 23 sites in 7 countries in Europe.

During the screening period, patients and their treating physicians will be requested to provide data for the Historical Data Collection, including detailed medical history information between the last visit of the above mentioned trials and the screening period, such as medical procedures and therapies. Patients and/or their treating physicians will also be requested to provide further information, such as documentation regarding their disability status, including motor and disabilities scales (e.g. MFM, HFMS; Brooke and Vignos, among others). This request for Historical Data Collection will be documented in a separate Informed Consent Form. Patients (or their legal representatives) who decline to provide detailed medical history information are still eligible to participate in the treatment phase of the study.

Number of Patients

The maximum number of patients in this study will be 171, the number of patients enrolled in studies TRO19622CLEQ1115-1 and TRO19622CLEQ1275-1 and alive at the end of the studies.

Target Population

All patients who participated in TRO19622CLEQ1115-1 *and/*or TRO19622CLEQ1275-1 trials will be invited to participate in the current trial.

Patients who screen fail may be rescreened if the underlying reason for previous screen failure has changed status in the investigator's clinical judgment. The rescreening can occur up to 6 months after the first screening attempt. Additionally, a patient may be rescreened if the inclusion/exclusion criteria leading to previous non-eligibility have been amended in the protocol, rendering the patient potentially eligible for the study. If a patient is rescreened, all screening assessments must be repeated using a new screening number. If rescreening occurs within a period of 4 weeks, and there has been no significant change in the patient status which affects the eligibility criteria, only the safety assessments must be repeated.

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Have participated in *either of* the studies TRO19622CLEQ1115-1 or TRO19622CLEQ1275-1.
- Are able and willing to provide written or verbal witnessed informed consent; Alternatively, a legally authorized representative must be able to consent for the patient according to International Conference on Harmonisation (ICH) and local regulations and assent must be given by the subject whenever possible.
- Able to comply with the study protocol, in the investigator's judgment, including ability to take study treatment and perform study visits.
- For women of childbearing potential: agreement to use an acceptable birth control method during the treatment period and for at least 28 days after the last dose of olesoxime.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  The following are acceptable contraceptive methods: progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, male or female condom with or without spermicide, and cap, diaphragm, or sponge with spermicide. A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods) is considered acceptable.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

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

- Pregnant or lactating, or intending to become pregnant during the study
- Patients who, in the opinion of the investigator, are not suitable to participate in this open-label study
- Patients who have developed study drug hypersensitivity to olesoxime or one of the formulation excipients, including sesame oil.
- Concomitant or previous participation in any investigational drug or device study within 90 days prior to screening
- Concomitant or previous participation in a SMN2-targeting antisense oligonucleotide study within 6 months prior to screening
- History of HIV infection, history of Hepatitis B infection within the past year, history of Hepatitis C infection which has not been adequately treated
- History of illicit drug or alcohol abuse within 12 months prior to screening, in the investigator's judgment
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study

- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion.

Length of Study

The study will continue until olesoxime is commercially available in the patient's country, or as per local regulation, or per the Sponsor's decision to terminate the olesoxime program for SMA, but will not exceed 4 years after the last patient was enrolled in the study.

NB In the UK, the study will last for a fixed period of 3 years.

End of Study

The end of this study is defined as the date when the last patient, last visit (LPLV) of the treatment period occurs.

Outcome Measures

Safety Outcome Measures

- Adverse events
- Laboratory tests
- Vital signs
- ECG
- *24-hour Holter ECG*
- Physical examination

Efficacy Outcome Measures

- Motor Function Measure (MFM)
- Forced Vital Capacity (FVC)
- *Clinical Global Impression of Change (CGI-C)*

Pharmacokinetic Outcome Measures

- Predose (trough) plasma olesoxime concentration at each visit

Patient-Reported Outcome Measures

- The PedsQL™ 4.0 Generic Core *Scales* and *PedsQL 3.0* Neuromuscular *Module (Version 3.0)*
- The EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L)
- *The SMA Independence Scale (SMAIS)*

Caregiver-Reported Outcome Measures

- Caregiver resource use: Work Productivity and Activity Impairment: Caregiver (WPAI:CG)
- Caregiver generic health-related quality of life (Short Form-36 questionnaire)
- *Caregiver-reported versions of the PedsQL™ Generic Core Scales (Version 4.0), PedsQL™ Neuromuscular Module (Version 3.0), SMA Independence Scale (SMAIS), and EQ-5D-5L*

Other Outcome Measures

- *Olesoxime Fatigability Survey (OFS)*

Investigational Medicinal Products

Test Product (Investigational Drug)

Olesoxime will be given as a 100–mg/mL liquid formulation. The drug will be administered at 10 mg/kg *twice a day* orally or via a naso-gastric or gastrostomy tube *with breakfast and dinner*, preferably at the same time of the day throughout the study.

If drug administration does not coincide with one of the scheduled meals, a snack should be taken prior to drug administration.

Preferably there should be at least 10 hours between the morning and evening dose.

Patients who have not consented to the dose increase specified in Protocol BN29854, Version 4 will be administered olesoxime at 10 mg/kg QD orally or via a naso-gastric or gastrostomy tube with the main meal throughout the study.

Statistical Methods

Primary Analysis

Safety analysis will be based on the safety population.

*S*afety variables (e.g., laboratory tests, vital signs, and ECG) will be summarized for each assessment time (including follow-up) using descriptive statistics. *The data will be summarized by the dose being taken at the time of the assessment (10 mg/kg QD or 10 mg/kg BID). Data from the two 24-hour Holter ECG assessments will also be summarized.*

Determination of Sample Size

The sample size will be determined by the number of patients who participated in studies TRO19622CLEQ1275-1 and*/or* TRO19622CLEQ1115-1 and who meet the enrolment criteria. The primary objective of the study is to assess the safety and tolerability of olesoxime.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{0-24}	Area under the plasma concentration curve from administration to 24 hours
AUC0-∞	*area under the concentration–time curve from Time 0 to infinity*
BID	*twice a day*
BMI	body mass index
BP	blood pressure
$C_{average}$	*average trough concentration*
CGI-C	*Clinical Global Impression of Change*
CL/F	apparent clearance
C_{max}	*maximum concentration observed*
EC	Ethics Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EQ-5D-5L	EuroQol 5-Dimension*, 5-Level* Questionnaire
FDA	Food and Drug Administration
FFM	fat free mass
FM	fat mass
FMI	fat mass index
FVC	Forced Expiratory Vital Capacity
HDL	High-density lipoprotein
HFMS	Hammersmith Functional Motor Scale
HN	home nursing
ICH	International *Council for* Harmonisation
IMP	investigational medicinal product
IxRS	Interactive Voice/Web Response System
LDL	low-density lipoprotein
LPLV	last patient, last visit
MFM	Motor Function Measure
OFS	*Olesoxime Fatigability Survey*
PD	*pharmacodynamics*
PedsQL™	Pediatric Quality of Life Inventory™

PK	pharmacokinetic
PQ	PQ interval: duration in milliseconds from the beginning of P wave to onset of ventricular depolarization (Q and R)
PRO	patient-reported outcome
QD	*once a day*
QRS	QRS interval: duration in milliseconds of the QRS-complex
QT	QT interval: duration in milliseconds from the beginning of Q wave to the end of T wave
QTcF	QT interval corrected using Fridericia's formula
RCR	Roche Clinical Repository
SF-36v2	*Short Form-36 Health Survey, Version 2*
SMA	spinal muscular atrophy
SMAIS	*SMA Independence Scale*
SMN	survival motor neuron protein
$t_{1/2}$	plasma concentration half-life
ULN	upper limit of normal
VAS	*visual analog scale*
WPAI:CG	Work Productivity and Activity Impairment: Caregiver

1. BACKGROUND

1.1 BACKGROUND ON SPINAL MUSCULAR ATROPHY (SMA)

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder clinically characterized by progressive muscular weakness and atrophy. SMA is the most common genetic cause of infant mortality with an estimated incidence of 1 in 6,000 to 10,000 live births (Prior 2010). In most patients, the disease results from homozygous deletion or mutation of the survival motor neuron protein (SMN) gene SMN1 (Lefebvre et al. 1995). In humans, there are two SMN genes, the telomeric SMN1 gene and the centromeric SMN2 gene, resulting from intra-chromosomal duplication of 5q13. The only critical difference is an 840 C-to-T mutation in the SMN2 gene that excludes exon 7 from approximately 85-90% of transcripts, resulting in an unstable protein (Markowitz et al. 2012). Clinical severity is inversely correlated with SMN2 gene copy number (Kolb and Kissel 2011).

SMA leads to predominantly proximal muscle atrophy and weakness and the potential for medical complications such as scoliosis, joint contractures and restrictive lung disease due to respiratory muscle weakness. Progressive respiratory failure and frequent pulmonary infections are common in SMA Type 1 and 2, so that in severe phenotypes non-invasive respiratory support is often needed. Other common comorbidities include failure to thrive, sleep difficulties, pneumonia, osteopenia and osteoporosis with pathological fractures, poor cough and secretion clearance, reduced vital capacity, gastro esophageal motility disorder, urinary incontinence, hip dislocation, and joint and muscle pain.

The continuous clinical spectrum of SMA has been divided into three types based on the age of onset and highest motor milestone achieved. Patients with SMA Type 1 become symptomatic in infancy, never achieve the ability to sit, and often require a feeding tube. Even with proactive respiratory management, they typically have a shortened life expectancy. The most common form of SMA by prevalence is Type 2. Children present between 12 and 24 months of age with failure to walk or stand independently. Patients may live into their third decade, but life expectancy is shortened because of the risk of respiratory complications. Age of onset of Type 3 SMA is variable, although diagnosis typically occurs before the age of 3, symptoms in mild cases may not be noticeable until late childhood. Patients with Type 3 SMA achieve independent ambulation and are able to stand and walk without assistance, at least for some time in their lives (Kolb and Kissel 2011, Shababi et al. 2014).

The medical need for patients with SMA is very high, and several drug candidates are currently under investigation in the nonclinical and clinical setting. The SMN2-targeting antisense oligonucleotide nusinersen (Spinraza®) has been recently approved by the U.S. Food and Drug Administration (FDA) and the European Commission for the treatment of pediatric and adult patients with SMA. This treatment is administered by intrathecal injection, and its effects are limited to CNS

tissues. Alternative management strategies focus on prevention and treatment of comorbidities, such as failure to thrive, surgical and non-surgical treatment for scoliosis and contractures, pulmonary hygiene, non-invasive ventilation, mobility and seating support, and physical and occupational therapy. *There is still a high unmet need with regard to oral therapies as well as limited access to treatment with nusinersen, depending on country and disease type. In addition, not all patients benefit from the treatment or tolerate it.*

1.2 BACKGROUND ON OLESOXIME

Olesoxime (RO7090919, cholest-4en-3-one, oxime), is a cholesterol-like compound identified through its survival-promoting activity on trophic factor deprived motor neurons in culture. Olesoxime showed neuroprotective effects in four animal models of motor nerve degeneration as well as anti-nociceptive and neuroprotective effects in experimental models of painful peripheral neuropathies induced by diabetes or chemotherapy. Olesoxime binds to proteins that have been implicated in the formation or modulation of the mitochondrial permeability transition pore complex. By binding to these proteins, olesoxime may preserve essential mitochondrial functions such as calcium buffering in stressed neurons, thereby reducing neuronal degeneration and death (Bordet et al. 2010).

As of September 2017, there have been 17 completed clinical Phase I, II, and II/III studies performed with olesoxime, including *a* Phase *Ib single- and multiple-dose, open-label, multicenter, pharmacokinetic (PK) and safety study (TRO19622CLEQ1115-1) and a Phase II/III* double-blind study in SMA (TRO19622CLEQ1275-1). *More than 900* healthy subjects and patients have been exposed to olesoxime.

Information on nonclinical pharmacology, nonclinical safety, and clinical experience can be found in the Olesoxime Investigator's Brochure.

1.2.1 *Study TRO19622CLEQ1115-1*

Study TRO19622CLEQ1115-1 was a Phase Ib single- and multiple-dose, open-label multicenter, PK and safety study conducted with pediatric and adult patients (6–25 years of age) with SMA, at the dose of 125 mg olesoxime once a day (QD) (hard capsule formulation). The first patient was enrolled on *7 January 2008*, and the last patient, last visit occurred *on 6 November* 2013.

Olesoxime 125 mg QD, administered first in a single dose and then in repeated doses during 9 to 11 days, was safe and well tolerated.

1.2.2 Study TRO19622CLEQ1275-1

Study TRO19622CLEQ1275-1 was a Phase II/III, adaptive, parallel-group, double-blind, randomized, placebo-controlled, multicenter, multinational study designed to assess the efficacy and safety of olesoxime over 24 months in pediatric and adult patients (3–25 years of age) with Type 2 and non-ambulatory Type 3 SMA.

There were 165 patients randomized in a 2:1 ratio to olesoxime 10 mg/kg QD or placebo. The first patient was enrolled on 18 November 2010, and the last patient, last visit occurred in October 2013.

The primary outcome measure was the Motor Function Measure (MFM), which is a multidimensional motor function scale for use in patients with neuromuscular disorders. The MFM has been validated in SMA and has been divided into three sub-domains: D1, which evaluates functions related to standing and transfer; D2, which evaluates axial and proximal function in supine and sitting positions on a mat and a chair; and D3, which evaluates distal motor function (Bérard et al. 2005). As SMA primarily affects proximal muscles, the primary endpoint of the study was change from baseline at Month 24 in the MFM D1 + D2 score. The result for the primary outcome was in favor of olesoxime and close to statistical significance when compared with placebo (treatment effect: 2.0 [96% CI: –0.25, 4.25]; p = 0.0676) (Bertini et al. 2017).

The secondary endpoints included the MFM Total score (D1+D2+D3), the Hammersmith Functional Motor Scale (HFMS), and a responder analysis on both functional motor scales. Electromyography (maximum compound muscle action potential [CMAP] / motor unit number estimation [MUNE]), Forced Vital Capacity (FVC), Pediatric Quality of Life *Inventory™* (PedsQL™), Clinical Global Impression (CGI), and safety were formally tested using analysis of covariance (ANCOVA) or other methods. The magnitude of the treatment effect based on the total MFM score (D1+D2+D3) was quite similar to the D1+D2 analysis. The change in HFMS after 21 months treatment showed a positive trend for the olesoxime treatment arm over time.

Natural history studies in Type 2 and Type 3 SMA (Vuillerot et al. 2013; Mercuri at al. 2016) have shown that patients 6–15 years of age have a greater likelihood of substantial worsening of their condition within 12–24 months of the observation period, which is likely related to growth and weight gain without an increase in muscle strength. Thus, the 6–15 years age group may be appropriate for demonstrating maintenance of motor function. A post hoc analysis conducted in this age group showed a statistically significant separation of 3.61 points (p=0.036) on the MFM D1+D2 scores at 24 months.

A responder analysis was performed by comparing the MFM score at Month 24 with the score at baseline. Patients were considered responders if their motor function score did not worsen at Month 24 compared to baseline. A similar approach was used for the HFMS by comparing the score at Month 21 with the score at baseline. For the MFM total score, olesoxime treatment for 24 months resulted in a higher responder rate (56.3%) compared to placebo (38.6%, p = 0.0419). When the analyses were performed on the HFMS score, the relative risk was 1.82 [95% CI: 1.16; 2.86] in favor of olesoxime (p = 0.0091), with 28.1% responders in the placebo arm, compared to 49.5% in the olesoxime arm. *The pre-specified analysis of electromyography* (CMAP / MUNE), FVC,

PedsQL, and CGI were inconclusive. *However, a post hoc responder analysis of the CGI using a responder definition, which mirrors the stable or improved MFM/HFMS responder, showed a statistically significant effect favoring olesoxime (relative risk of 1.23 [CI: 1.01, 1.49]; p=0.0361). For the patient-/parent-reported CGI, a similar pattern was identified, with a trend favoring olesoxime (relative risk of 1.19 [CI: 0.99, 1.44]; p=0.0640).*

SMA-related complications were reported as adverse events in *a lower proportion of* patients in the olesoxime group compared *with* placebo. Most importantly, *a lower proportion of* patients treated with olesoxime reported severe lower respiratory infections. All other adverse events were equally distributed in nature and severity: *63 (38.2*%) patients experienced at least one serious adverse event, with a lower rate in the olesoxime arm compared *with* placebo (*34 [31.5*%] *patients* vs. 29 [50.9%] *patients*).

The PK and efficacy data from Study TRO19622CLEQ1275-1 were used to investigate the relationship between olesoxime PK exposure (i.e., average trough concentration [$C_{average}$]) and the primary efficacy outcome (i.e., MFM D1 + D2 score). The results of this analysis indicated that the effect of olesoxime did not reach a plateau at the dose of 10 mg/kg QD and that higher doses may lead to an increase in efficacy (see PK/pharmacodynamic [PD] report) (see Section 3.3.1).

Baseline samples from 119 patients previously enrolled in Study TRO19622CLEQ1275-1 (81 patients in olesoxime arm and 38 patients in placebo arm) were analyzed. All patients previously on olesoxime in Study TRO19622CLEQ1275-1 had detectable predose olesoxime concentrations at baseline of Study BN29854. Olesoxime concentrations ranged from 23 to 801 ng/mL, corresponding to 0.3% to 9.5% of $C_{average}$ observed in Study TRO19622CLEQ1275-1. The time after last dose from Study TRO19622CLEQ1275-1 was 2.4–4.0 years. Olesoxime was not detected in the OLEOS baseline samples from any of the 38 patients previously randomized to placebo arm in Study TRO19622CLEQ1275-1. Roche currently assumes that these residual concentrations are secondary to the accumulation of olesoxime, a cholesterol derivative, in a deep compartment.

Based on currently available data, residual exposure to olesoxime for periods up to 6 years does not appear to be associated with any newly emerging safety risks.

Study TRO19622CLEQ1275-1 indicated that treatment with olesoxime maintained motor function in SMA Type 2 and non-ambulatory Type 3 patients, as measured by the MFM, and decreased disease-related complications.

1.2.3 Study *BP39378*

Study BP39378 is an ongoing Phase I relative bioavailability study in healthy volunteers comparing the systemic exposure (area under the concentration–time curve from Time 0 to infinity [$AUC_{0-\infty}$] and maximum concentration observed [C_{max}]) of

olesoxime when administered as a single dose or in two divided doses (~12 hours apart) with food in the form of a suspension or solution formulation. Preliminary PK results revealed that doubling the dose of olesoxime from 10 mg/kg to 20 mg/kg (in solution form) resulted in only ~20% increase in AUC and ~11% increase in C_{max}. This finding is in line with animal data and is likely based on saturation of absorption of olesoxime. When the dose was divided into a morning and an evening dose, 10 mg/kg each, the increase in AUC was ~100%, while C_{max} only increased by ~20%. Similarly, a dose of 30 mg/kg of olesoxime in suspension formulation divided into two doses (15 mg/kg each) resulted in ~120% increase in AUC and ~56% increase in C_{max}, compared to a single dose of 10 mg/kg as suspension. The preliminary results of the study indicated that a twice a day (BID) dosing regimen of olesoxime produces higher systemic exposure, whereby potentially improving the efficacy outcome of the treatment. In this study, single or divided doses up to 30 mg/kg were well tolerated.

Taken together with the data from the PK/PD analysis of Study TRO19622CLEQ1275-1, the olesoxime dose will be increased to 10 mg/kg BID in this study (BN29854) to maximize efficacy for participating patients. The total daily dose of Study BN29854 will not exceed 2000 mg. This maximum dose of 2 g/day forms the basis of the technical investigational medicinal product (IMP) specifications in the drug manufacturing process and cannot be exceeded for this reason. Therefore, all patients with a body weight >100 kg will receive a dose of 1000 mg BID.

1.2.4 *Study BN29854 (OLEOS)*

The 12-month analysis of the OLEOS BN29854 study (Muntoni et al. 2017) demonstrated that olesoxime was generally safe and well tolerated at the dose assessed, with a safety profile comparable to placebo groups of previous studies. Despite a substantial decline in MFM D1 + D2 score (>2 points/year) since stopping study drug at the end of the previous clinical trial (median 3 years), the observed treatment difference between placebo and olesoxime was maintained at OLEOS baseline. Olesoxime sustained motor function over 12 months in patients treated open-label in the OLEOS study. These data suggest that olesoxime offers the potential to provide meaningful clinical benefit to patients with SMA by preventing loss of motor function.

1.3 STUDY RATIONALE

This study is a Phase II trial for SMA patients who participated in previous studies TRO19622CLEQ1275-1 and/*or* TRO19622CLEQ1115-1. The current study includes collecting retrospective data between last visit of the above mentioned trials and screening period of this study. As the last patient of study TRO19622CLEQ1275-1 received the last dose in October 2013, the retrospective data collection will serve to understand the disease course of SMA patients after withdrawal of olesoxime treatment for at least 2 years.

The study's main period is an open-label, single arm period in which the patients will receive olesoxime *at the dose of* 10 mg/kg *BID*, and it will serve to further characterize the safety, tolerability and effectiveness profile of olesoxime in SMA. The outcomes of the study may be compared to natural history data of similar population and outcomes.

The study was initiated at a dose of 10 mg/kg QD; after Protocol BN29854, Version 4 is in effect, the dose will be increased from 10 mg/kg QD to 10 mg/kg BID with the aim of increasing the exposure to olesoxime and thereby increasing a possible therapeutic benefit of olesoxime, while maintaining appropriate safeguards using a thorough clinical safety monitoring plan. The total daily dose in this study will not exceed 2000 mg. For details on the dose increase rationale, see Section 3.3.1.

1.4 BENEFIT–RISK ASSESSMENT

The main objective of this study is to evaluate long-term safety and efficacy to support long-term treatment with olesoxime in patients with SMA and to continue to provide access to olesoxime to patients enrolled in Study TRO19622CLEQ1275-1.

Patients with SMA have a high background incidence of comorbidities associated with their underlying disease and have decreased mobility (e.g., wheelchair bound). *The antisense oligonucleotide nusinersen (Spinraza®) was recently approved in the United States and the European Union for the treatment of pediatric and adult patients with SMA. This treatment is administered by intrathecal injection and targets the CNS tissues. Despite this first disease-modifying therapy, the medical need in SMA is still very high.*

Olesoxime *targets the CNS as well as peripheral tissues and* has demonstrated beneficial neuroprotective activity in numerous preclinical models at doses between 3 and 30 mg/kg. Although the primary endpoint was not met, Study TRO19622CLEQ1275-1 indicated that treatment with daily doses of olesoxime 10 mg/kg maintained motor function in *patients with Type 2 and non-ambulatory Type 3 SMA over the course of 2 years (see Section 1.2.2).* These results support the use of olesoxime in *patients with* Type 2 and non-ambulatory Type 3 *SMA.*

As described in Section 1.2.4, the recent 12-month analysis of the OLEOS (BN29854) study (Muntoni et al. 2017) continues to demonstrate that olesoxime offers the potential to provide meaningful clinical benefit to patients with SMA by preventing loss of motor function.

Based on a retrospective exposure/efficacy analysis described in Section 1.2.2, Study TRO19622CLEQ1275-1 indicated that the effect of olesoxime did not reach a plateau at the dose of 10 mg/kg QD and that higher exposure levels may lead to an increase in efficacy. The results are consistent with previous trends of better effect in subjects with medium-to-high exposure.

Therefore, an increased exposure to olesoxime with a doubling of the current dose given twice daily is seen as a meaningful step to provide patients with the possibility of an improved therapeutic effect from the treatment with olesoxime.

As described in Section 3.3.1, the 10 mg/kg BID dose is seen as the advisable dose regimen to be able to reach the targeted, higher exposure levels that may lead to an increase in efficacy. The total daily dose in this study will not exceed 2000 mg. This maximum dose of 2 g/day forms the basis of the technical IMP specifications in the drug manufacturing process and cannot be exceeded for this reason. Therefore, all patients with a body weight >100 kg will receive a dose of 1000 mg BID.

During clinical development of olesoxime, *over 900* healthy volunteers and patients have been exposed to *olesoxime, with a daily dose ranging between 50 mg to 1000 mg and treatment duration up to 43 months*. Olesoxime has shown to be well tolerated at all tested dose regimens including co-administration with riluzole or beta-interferons. Atrioventricular conduction abnormalities observed in dogs have not been observed to date in humans. *To date, there are no identified risks with olesoxime therapy in humans.*

As mentioned above, the accumulating data from the open-label extension study BN29854 continues to demonstrate that olesoxime is generally safe and well tolerated at the dose assessed, with a safety profile comparable to the placebo goup of Study TRO19622CLEQ1275-1 (see Section 1.2.4) (Muntoni et al. 2017).

From a safety perspective, the 10 mg/kg BID dose appears appropriate as the expected exposure at 10 mg/kg BID is covered by chronic preclinical toxicity studies. Nevertheless, considering preclinical findings of arrhythmias observed in the 39-week toxicity studies in dogs that started at the lowest dose (50, 250, and 1000 mg/kg/day) and in order to ensure the safeguards of patients participating in this study, a 24-hour Holter ECG monitoring will be performed prior to the dose increase to 10 mg/kg BID and 4 weeks later when steady-state is expected to be reached.

Based on *the existing preclinical data, clinical data (including analysis of the* efficacy data from the completed trials *and results of the BP39378 study),* the safety profile *of the 10 mg/kg QD dose* observed to date, *and the results of the BP39378 study,* the Sponsor considers the benefit–risk balance to be positive for the continuation of the *olesoxime* development program *and for an olesoxime dose increase to 10 mg/kg BID.*

2. OBJECTIVES

The main objective of this open-label, single arm study is to further characterize the safety, tolerability and effectiveness profile of olesoxime in SMA.

2.1 PRIMARY OBJECTIVE

The primary safety objective for this study is as follows:

- To evaluate the safety of olesoxime in patients with SMA, focusing on the nature, frequency, and severity of adverse events, as well as effects on laboratory values, vital signs and electrocardiogram (ECG) parameters

2.2 SECONDARY OBJECTIVES

The secondary objectives for this study are as follows:

- To evaluate effectiveness of olesoxime compared to the natural history of disease in patients with SMA, as measured by MFM D1+D2 and MFM Total scores.
- To evaluate the disease associated medical complications and procedures in olesoxime treated patients compared to the natural history of disease, focusing on their nature, frequency of occurrence, and severity.
- To evaluate the disease course between last visit of the studies TRO19622CLEQ1275-1 and TRO19622CLEQ1115-1, and baseline assessment in this study, as measured by motor functional scales (e.g., MFM) and as measured by nature, frequency, and severity of medical procedures.

2.3 PHARMACOKINETIC OBJECTIVES

The pharmacokinetic (PK) objectives for this study are as follows:

- To investigate the pharmacokinetics of olesoxime in the target population using Bayesian feedback analysis based on a population pharmacokinetic model (as appropriate and permitted by the data).

2.4 PATIENT-REPORTED OUTCOME OBJECTIVES

The patient-reported outcome (PRO) objectives for this study are as follows:

- *To explore changes in level of independence and health-related quality of life following treatment with olesoxime*
- To assess health-related quality of life and conduct economic modeling using the *EuroQol 5-Dimension, 5-Level Questionnaire (*EQ-5D-5L*)*

2.5 CAREGIVER-REPORTED OUTCOME OBJECTIVES

The caregiver-reported outcome objectives for this study are as follows:

- *To assess caregiver-reported changes in patient health outcomes, as measured by the caregiver-report versions of the PedsQL™ Generic Core Scales (Version 4.0), PedsQL™ Neuromuscular Module (Version 3.0), SMA Independence Scale (SMAIS), and EQ-5D-5L*
- *To assess changes in caregiver* quality of life and conduct economic modeling using the caregiver resource use: Work Productivity and Activity Impairment: Caregiver (WPAI:CG) and caregiver generic health-related quality of life Short Form-36 *Health Survey, Version 2 (SF-36v2*)

2.6 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To explore olesoxime treatment response of FVC in patients with SMA
- To evaluate the percentage of responders in patients with SMA, defined as patients who did not have a decrease from baseline in MFM scores
- To investigate the impact of SMN2 copy number *and other genes*, transcripts, and *proteins* involved in pathological pathways of SMA in patients with SMA on the safety, pharmacokinetics, pharmacodynamics, and efficacy of olesoxime
- To explore olesoxime treatment response to levels of SMN2 mRNA and SMN protein in blood
- To evaluate potential relationships between drug exposure, efficacy, and safety
- *To assess clinician-reported change in overall health status, as measured by the Clinical Global Impression of Change (CGI-C)*
- *To evaluate potential correlations between the collected sensor data from smartphone-based monitoring and MFM scores and to assess patients' adherence to smartphone-based monitoring*
- *To explore the potential effect of olesoxime on patient experience of fatigability, as measured by the clinician-reported Olesoxime Fatigability Survey (OFS)*

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Study Design

This is an open-label, single-arm study to further evaluate long-term tolerability, safety, and efficacy outcomes in patients with SMA who previously participated in one of the following two clinical studies:

- Open-label Phase Ib, *multicenter,* single- and multiple-dose study to assess safety and pharmacokinetics of olesoxime in *pediatric and adult* patients *(6–25 years of age) with SMA* (TRO19622CLEQ1115-1), and*/or*
- Phase II*/III, adaptive, parallel-group, double-blind, randomized, placebo-controlled, multicenter, multinational* study to assess safety and efficacy of olesoxime in *pediatric and adult* patients *(3–25 years of age) with Type 2 and non-ambulatory Type 3 SMA* (TRO19622CLEQ1275-1)

The study will consist of Historical Data Collection, screening, treatment, and safety follow-up periods. The study will occur in approximately 23 sites in 7 countries in Europe. All patients who participated in the studies mentioned above will be invited to participate in this study. The maximum number of patients in this study will be 171.

A schedule of assessments is provided in Appendix 1.

3.1.1.1 Historical Data Collection

All patients who participated in TRO19622CLEQ1115-1 *and/*or TRO19622CLEQ1275-1 will be asked to provide medical history and information of all relevant medical procedures that occurred between the patient's last study visit of TRO19622CLEQ1115-1 or TRO19622CLEQ1275-1 studies and the screening visit of this current study, including:

- Motor Function Assessment using any SMA validated motor function scale, such as the MFM and HFMS;
- patient disability status as assessed during routine clinical visits, such as Brooke or Vignos scales;
- any documented medical procedures and therapies related to the natural course of SMA disease according to the opinion of the treating investigator.

The request to provide detailed medical history information will be documented in a separate Informed Consent Form (please refer to Appendix 2).

Patients (or their legal representatives) who decline to provide detailed medical history information are still eligible to participate in the treatment phase of the study.

3.1.1.2 Screening Period

After written informed consent from the patient, parent or legal guardian, and if appropriate, assent from the child, is obtained, the patients will be screened for eligibility.

NB. Enrollment in the open-label treatment period of the study is independent from Historical Data Collection, and a separate informed consent for the following periods should be signed. It is possible for the patient or legal representative to decline participation in the Historical Data Collection and still be eligible to participate in the open-label period. It is also possible for the patient to decline participation in the open-label period, but still consent to the Historical Data Collection.

The screening period will last a maximum of 6 weeks. Procedures at screening will include: medical examination including a thorough neurological exam, MFM scales, ECG, blood and urine sampling and medical history.

3.1.1.3 Treatment Period

Patients who have consented to the dose increase specified in Protocol BN29854, Version 4 will receive liquid formulation of olesoxime at a dose of 10 mg/kg *BID either orally or via a naso-gastric or gastrostomy tube with breakfast and dinner*, preferably at the same time of the day *throughout the study. If drug administration does not coincide with one of the scheduled meals, a snack should be taken prior to drug administration. Preferably there should be at least 10 hours between the morning and evening dose. The total daily dose in this study will not exceed 2000 mg. Therefore, patients with a body weight* >*100 kg will receive a dose of 1000 mg BID. This*

maximum dose of 2 g/day forms the basis of the technical IMP specifications in the drug manufacturing process and cannot be exceeded for this reason.

Patients who have not consented to the dose increase specified in Protocol BN29854, Version 4 will be administered olesoxime at 10 mg/kg QD orally or via a naso-gastric or gastrostomy tube with the main meal throughout the study.

Patients' visits will occur at 3 months, 6 months, 9 months, 12 months, and every 6 months thereafter for medical examination, and safety and efficacy assessments. *Related to the dose increase per Protocol BN29854, Version 4, one or two additional visits will occur (see the Schedule of Assessments in Appendix 1). For treatment period duration, please refer to Section 3.2.*

3.1.1.4 *Dose Increase per Protocol BN29854, Version 4*

All patients enrolled in the study must be contacted about the planned dose increase per Protocol BN29854, Version 4, and a discussion should take place between the patient or caregiver and the investigator.

Procedure for Dose Increase

All patients are asked to attend an unscheduled dose increase visit as early as possible, to increase their dose to the recommended level. Patients will be required to re-consent prior to dose increase and related assessments. If the medical condition of a patient does not allow an additional study visit or the date of the next regular study visit is scheduled close to when Protocol BN29854, Version 4 becomes in effect, the option to increase the dose at the next scheduled study visit will be offered.

Dose increase visit procedure options:

1. *Patients attend an additional dose increase visit to increase their dose to the recommended level as early as possible. Only the specified assessments for the dose increase visit will be performed (see the Schedule of Assessments in Appendix 1).*
2. *Patients attend their next scheduled regular visit to increase their dose to the recommended level. Specified assessments for the dose increase visit (see Appendix 1) and scheduled assessments for the regular visit will be performed.*

Prior to the dose increase, specified assessments need to be performed (see Schedule of Assessments in Appendix 1). These assessments include 24-hour Holter ECG monitoring (see Section 4.4.9.1) as well as blood sampling for PK and biomarker assessments (Section 4.4.8.1). If a patient performs the procedure for dose increase as part of a regular study visit and an ECG assessment is scheduled for this visit, only the 24-hour Holter ECG needs to be performed. If PK and biomarker samples are scheduled for this regular study visit, the relevant sample types need to be collected only once.

Blood samples shall be taken predose. Therefore, before attending the dose increase visit, patients should be reminded not to take the drug at home, as they will have it administered with their next meal after the assessments are conducted.

Starting on the day after the removal of the Holter ECG monitor, patients will receive olesoxime at a dose of 10 mg/kg to be taken twice daily with breakfast and dinner.

In addition to the dose increase procedure, the investigator will fill out the OFS and the CGI-C. The OFS is a brief survey designed to explore potential benefit of olesoxime on fatigability (i.e., endurance). The CGI-C assesses the clinician-reported change in the patients overall health status.

The digital biomarker study smartphone will be provided to the patient and training given on the performance of the tests therein.

Dose Increase Safety Follow-Up Visit

Patients who have consented to receiving the 10 mg/kg dose BID will return for a dose increase safety follow-up visit 4 weeks after the dose increase. During this follow-up visit, patients will also be requested to have 24-hour Holter ECG monitoring and blood sampling for safety and PK assessments. Blood samples should be taken predose.

After the dose increase safety follow-up visit, patients will return to the site for their next visit at the next scheduled timepoint per protocol. In the case of an unscheduled dose increase visit, the next visit should not be delayed and should take place at the next scheduled visit per the protocol.

Procedure for Continuing in the Study for Patients Who Do Not Consent to Protocol BN29854, Version 4

In case a patient does not consent to Protocol BN29854, Version 4, the dose increase and all new assessments and procedures (see the Summary of Changes and Appendix 1) per Protocol BN29854, Version 4 should not be performed. This includes the 24-hour Holter ECG monitoring as well as blood sampling for safety, PK, and additional biomarker assessments. It also includes all additional outcome measures per Protocol BN29854, Version 4.

Non-consenting patients do not need to attend the dose increase safety follow-up visit 4 weeks later, and they will continue to be administrated olesoxime at 10 mg/kg QD.

3.1.1.5 Safety Follow-Up

Patients who withdraw from study drug treatment during the open-label period of the study will be observed for a period of 28 days after last dose.

3.2 END OF STUDY

The study will continue until olesoxime is commercially available in the patient's country, or as per local regulation, or per the Sponsor's decision to terminate the olesoxime

program for SMA, but will not exceed 4 years after the last patient was enrolled in the study.

NB In the UK, the study will last for a fixed period of 3 years.

The end of this study is defined as the date when the last patient, last visit (LPLV) of the treatment period occurs.

3.3 RATIONALE FOR STUDY DESIGN

Given the very high unmet medical need in patients with SMA and following the results of study TRO19622CLEQ1275-1 that indicated that olesoxime maintained motor function in patients with SMA, this study was designed as a long-term, open-label study to further characterize the safety and efficacy profile of olesoxime. The study also provides an opportunity for SMA patients who participated in previously completed TRO19622CLEQ1115-1 and TRO19622CLEQ1275-1 studies to receive further olesoxime treatment.

A further goal of the study is to assess the course of the disease after drug withdrawal that occurred at the end of the studies TRO19622CLEQ1115-1 and TRO19622CLEQ1275-1.

The open-label design and long-term duration of the study will allow evaluation of tolerability and safety of the drug to support long-term treatment with olesoxime in SMA patients. Efficacy results will be compared with the natural history of the disease based on information obtained from SMA natural history databases. The study is considered an effectiveness study because it is a single arm study and during the course of the study, patients will be allowed to continue or start any symptomatic therapy or medical procedures needed to improve survival and quality of life. Thus, the information obtained from this study will reflect real-world conditions for patients with SMA.

Due to the open-label design of this study, it is not deemed necessary to have an Independent Data Monitoring Committee.

3.3.1 *Rationale for the Dose Increase*

The initial drug dosage in this study was consistent with the drug dosage in Study TRO19622CLEQ1275-1 (i.e., a dose of 10 mg/kg QD).

The PK and efficacy data from the TRO19622CLEQ1275-1 study were used to investigate the relationship between olesoxime PK exposure (i.e., $C_{average}$) and the primary efficacy outcome (i.e., MFM D1 + D2 score). A longitudinal PK-PD approach was applied. In the placebo group, the progression of the disease over time was best described by a linear function (slope of –1.05 units/year with a relative standard error of 27%). The exposure-response relationship was also best described by a linear function (slope of 0.281 units/mg/L with a relative standard error of 36%), indicating

that the effect of olesoxime did not reach a plateau at the dose of 10 mg/kg and that higher doses may lead to an increase in efficacy (see PK/PD report).

The proposed dose increase from 10 mg/kg QD to 10 mg/kg BID is based on an exploratory PK-PD analysis of the results of the Phase II study TRO19622CLEQ1275-1, along with the interim results from the ongoing relative bioavailability study BP39378. The PK-PD analysis suggested that the effect did not reach a plateau at the dose of 10 mg/kg QD and that higher exposures can potentially lead to an increase in efficacy.

Attempts to increase the systemic exposure of olesoxime by increasing the daily dose from 10 mg/kg QD to 20 mg/kg QD (using a solution formulation) produced a marginal (~20%) increase in $AUC_{0-\infty}$. The limited increase in bioavailability is thought to be due to saturable absorption of olesoxime. However, when the 20 mg/kg dose was divided into two doses, 10 mg/kg each, administered approximately 12 hours apart, an increase in the $AUC_{0-\infty}$ of 100% was observed, while C_{max} was only increased by ~20%. The preliminary results of the study also indicated that a dose of 30 mg/kg of olesoxime in suspension formulation divided into two doses (15 mg/kg each) resulted in an increase of ~120% in AUC and ~56% increase in C_{max}, compared with a single dose of 10 mg/kg as suspension. Therefore, although a dose of 10 mg/kg BID in suspension form was not tested in Study BP39378, this dose is projected to produce a ~100% increase in AUC and the average steady-state plasma concentration of olesoxime, while C_{max} should only increase by 20% to 30%. The increase in exposure is assumed to lead to a clinically meaningful increase in motor function for patients (2-point increase in the MFM D1 + D2 efficacy score) as detailed before.

The total daily dose in this study will not exceed 2000 mg. Thus, for patients with body weight >100 kg, the administered dose will be 1000 mg BID. The maximum dose of 2 g/day forms the basis of the technical IMP specifications in the drug manufacturing process and cannot be exceeded for this reason.

The drug will be provided as liquid suspension formulation of olesoxime (100 mg/mL) for oral administration or via gastrostomy tube. Due to the weight-based dosing, it is required that body weight be measured and recorded at every study visit. The study drug should be administered BID orally or via a naso-gastric or gastrostomy tube with breakfast and dinner, preferably at the same time of the day throughout the study.

3.3.2 Rationale for Effectiveness Outcome Measures

Efficacy assessments in this study are consistent with Study TRO19622CLEQ1275-1. The MFM outcome measure that was used in the TRO19622CLEQ1275-1 study is one of the most frequently used quantitative scales for measurement of functional motor abilities of individuals affected by neuromuscular disease. During Study TRO19622CLEQ1275-1, the MFM D1+D2 was defined as the primary outcome measure. Thus, to maintain consistency with the primary outcome measure of study TRO19622CLEQ1275-1, the MFM is included in this clinical trial.

The MFM (Berard et al. 2005) is an ordinal scale constructed for use in patients with neuromuscular disorders, and has been validated in SMA. The scale evaluates motor function in three dimensions:

- D1: evaluates functions related to standing and transfer,
- D2: evaluates axial and proximal function in supine and sitting position on mat and chair,
- D3: evaluates distal motor function.

The scoring of each task uses a 4-point Likert scale based on the patient's maximal abilities without assistance: 0, cannot initiate the task or maintain the starting position; 1, performs the task partially; 2, performs the task incompletely or imperfectly (with compensatory/uncontrolled movements or slowness); and 3, performs the task fully and "normally." The scores are summed to yield a total score expressed as the percentage of the maximum possible score (the one obtained with no physical impairment); the lower the total score, the more severe the impairment. The MFM is free and available in most common European languages. Users' manual and scoring sheet will be provided to the sites prior to study start.

Validation studies for MFM were performed in many neurodegenerative disorders including Duchenne muscular dystrophy, Spinal Muscular Atrophy, congenital myopathies, hereditary neuropathies, myotonic dystrophy, limb girdle muscular dystrophy, congenital muscular dystrophies. These studies showed good psychometric properties (face validity and scale completion), excellent scores of reproducibility (intra-rater and inter-rater reliability). The internal consistency was high for the global scale and for the three dimensions subscales. A good correlation between the MFM scores and the evaluations of the severity of the disability was shown by the physical therapists or the physicians using the Visual Analog Scale and the Brooke and Vignos grades of disability (convergent validity and discriminant validity studies) (Berard et al. 2005). Reassessment of the MFM scale after one year in a subgroup of 152 neuromuscular patients demonstrated a good overall sensitivity to change of the MFM-32, especially in Duchenne muscular dystrophy patients (Payan et al. 2009).

3.3.2.1 Efficacy Outcome Measures

Due to progressive proximal muscle weakness, study TRO19622CLEQ1275-1 considered the MFM D1 + D2 score as the most appropriate measure in patients with SMA Type 2 and non-ambulatory Type 3 and as such it was used as the primary endpoint in the study. As this open-label study aims to provide further clinical information and complement the results of study TRO19622CLEQ1275-1 consistency in primary endpoint is appropriate. The primary outcome measure is therefore MFM D1 + D2.

Although MFM D1+D2 is considered to be the most appropriate measure for the study population and defined as primary efficacy endpoint in study TRO19622CLEQ1275-1

and in this study, it is important to evaluate the Total MFM score that includes D3 reflecting distal motor function. The Total MFM, D1+D2+D3 score is therefore included as a secondary efficacy outcome measure.

An additional secondary efficacy measure is the proportion of patients with disease associated medical complications and procedures. An effective treatment for SMA is expected to reduce the incidence of comorbidities and thus the need for medical interventions and procedures.

Consistent with TRO19622CLEQ1275-1, this study will use Forced Vital Capacity (FVC) to assess pulmonary function as an exploratory outcome. Pulmonary measures have been validated in SMA in a previous study and the FVC was the most reliable measure (Iannaccone et al. 2003).

3.3.3 Rationale for PK Sample Collection Schedule

In this study, PK samples will be collected to characterize the PK of olesoxime in the target population.

Based on the PK characteristics of olesoxime (for more details, please refer to the Olesoxime Investigator's Brochure), it is believed that the collection of PK samples as outlined in Schedule of Assessments (Appendix 1) would allow appropriate characterizing of the PK of olesoxime in this study using a population PK modeling approach (see Section 6.8). The collection of sparse PK samples will require an accurate collection of the dosing history prior to collecting the PK sample (see Section 4.4.8).

3.3.4 Rationale for Biomarker Assessments

The rationale for biomarker assessments applies to all mandatory biomarker samples in this study, including genetic sampling.

SMA is a disease that presents in a heterogeneous manner with a spectrum of motor function (from not being able to sit up to not being able to walk) and variability in disease onset (from birth to the third decade of life). The severity of SMA is variable, partially due to differences in SMN2 copy numbers. However, different factors may exist which modify the severity of the disease, its progression or the response to therapy. The analysis of SMA related biomarkers may have important implications in therapeutic development timelines and patients could be allocated more efficiently into studies with the greatest probability of success. It will also increase our understanding of the disease and the underlying pathological mechanisms.

Biomarkers can help predict and measure responses to drugs in SMA patients in simple blood specimens. The potential advantages of development of biomarkers for SMA are many and largely can be applied to any new drugs that are tested. In order to explore

the role of potential biomarkers and to better understand treatment response of olesoxime in SMA, the following analyses of biomarker data will be performed:

- Relationship of several SMA related biomarkers to olesoxime treatment response and progression of the disease in the patients, *which may include,* but *are* not restricted to:
  - *SMN1 and* SMN2 copy number
  - SMN mRNA splicing and SMN protein levels in blood

    SMN1 and SMN2 copy number, SMN mRNA splicing, and protein levels in the blood have been linked with SMA type and disability progression.
  - Correlation *and dynamic changes* of genes, transcripts, and protein involved in pathological pathways of SMA to functional parameters, such as, but not restricted to cholesterol*, molecular mitochondrial analyses (e.g., mitochondrial DNA), and genetic modifiers*

For this study, a digital biomarker approach has been developed using high-quality smartphone sensors that enable remote, non-invasive, frequent, and precise measurement of motor and non-motor symptoms. Smartphone sensors have been successful for monitoring movement disorders such as Parkinson's disease (Maetzler et al. 2013; Arora et al. 2015; Ossig et al. 2016) and several of the clinical motor measures for patients with SMA are tractable to smartphone-based measurement. The smartphone assessments were designed with clinician, physiotherapist, and patient input and are based on the MFM (Bérard et al. 2009).

A smartphone will be provided to each patient aged 6 years and older. The smartphone will be used to complete a selection of tests and surveys:

- *Force tests to assess hypotonia*
- *Fine-hand motor tests to evaluate distal weakness*
- *Arm lifting tests to assess axial and proximal motor function*
- *Sustained phonation test, including voice pitch variation as an indicator of muscular fatigue, central hypotonia, and ventilation problems*
- *Questions on the patients' health*

Patients will receive the study smartphone during the dose increase visit and subsequently perform a subset of the smartphone tests each day at home, based on their ability and an automatic scheduler on the smartphone. In addition, patients will conduct the tests at selected visits as per the Schedule of Assessments (see Appendix 1). The tests take about 5 minutes per day. Additional details are available in the SMA Digital Biomarker Manual.

4. MATERIALS AND METHODS

4.1 PATIENTS

The current clinical trial will include SMA patients who participated in TRO19622CLEQ1115-1 *and/*or TRO19622CLEQ1275-1 trials.

4.1.1 Recruitment Procedures

All patients who participated in TRO19622CLEQ1115-1 or TRO19622CLEQ1275-1 trials will be invited to participate in the current trial. During the screening period, patients and their treating physicians will be requested to provide data for the Historical Data Collection (see Section 3.1.1.1), including detailed medical history information between the last visit of the above mentioned trials and the screening period, such as medical procedures and therapies. Patients and/or their treating physicians will also be requested to provide further information, such as documentation regarding their disability status, including motor and disabilities scales (e.g., MFM, HFMS; Brooke and Vignos, among others). This request for Historical Data Collection will be documented in a separate Informed Consent Form. Patients (or their legal representatives) who decline to provide detailed medical history information are still eligible to participate in the treatment phase of the study.

Patients who are candidates for enrollment into the study will be evaluated for eligibility by the Investigator to ensure they fulfill eligibility criteria (see Section 4.1.2 and Section 4.1.3). All patients must sign the informed consent form prior to screening and prior to any changes to their existing medication for the purposes of enrollment into the treatment period of the trial. Caregivers who may be completing Patient-reported outcomes questionnaires should also provide informed consent.

Patients who screen fail may be rescreened if the underlying reason for previous screen failure has changed status in the investigator's clinical judgment. The rescreening can occur up to 6 months after the first screening attempt. Additionally, a patient may be rescreened if the inclusion/exclusion criteria leading to previous non-eligibility have been amended in the protocol, rendering the patient potentially eligible for the study. If a patient is rescreened, all screening assessments must be repeated using a new screening number. If rescreening occurs within a period of 4 weeks, and there has been no significant change in the patient status which affects the eligibility criteria, only the safety assessments must be repeated.

4.1.2 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Have participated in *either of* the studies TRO19622CLEQ1115-1 or TRO19622CLEQ1275-1.
- Are able and willing to provide written or verbal witnessed informed consent; Alternatively, a legally authorized representative must be able to consent for the

patient according to International Conference on Harmonisation (ICH) and local regulations and assent must be given by the subject whenever possible.

- Able to comply with the study protocol, in the investigator's judgment, including ability to take study treatment and perform study visits.
- For women of childbearing potential: agreement to use an acceptable birth control method during the treatment period and for at least 28 days after the last dose of olesoxime.

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  The following are acceptable contraceptive methods: progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, male or female condom with or without spermicide, and cap, diaphragm, or sponge with spermicide. A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods) is considered acceptable.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.3 Exclusion Criteria

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

- Pregnant or lactating, or intending to become pregnant during the study
- Patients who, in the opinion of the investigator, are not suitable to participate in this open-label study
- Patients who have developed study drug hypersensitivity to olesoxime or one of the formulation excipients, including sesame oil.
- Concomitant or previous participation in any investigational drug or device study within 90 days prior to screening
- Concomitant or previous participation in a SMN2-targeting antisense oligonucleotide study within 6 months prior to screening
- History of HIV infection, history of Hepatitis B infection within the past year, history of Hepatitis C infection which has not been adequately treated
- History of illicit drug or alcohol abuse within 12 months prior to screening, in the investigator's judgment
- Any serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study

- History or presence of an abnormal ECG that is clinically significant in the investigator's opinion.

4.2 STUDY TREATMENT

4.2.1 Formulation, Packaging, and Handling

4.2.1.1 Olesoxime

The clinical formulation is a powder and solvent for preparation of an oral suspension. The drug product will be supplied by Roche. Final IMP kits will be delivered as one box containing one amber glass bottle containing 7.5 g olesoxime powder and one amber glass bottle containing sesame oil. The powder will be constituted on first use to yield a homogeneous suspension containing 100 mg/mL of olesoxime in sesame oil. IMP will be administered in *milliliters* at a dose of 10 mg/kg *BID* with suitable oral devices. *Patients who do not consent to the dose increase will continue with the previous dosage and receive a dose of 10 mg/kg QD.*

For more information, please refer to the Olesoxime Investigator's Brochure, the pharmacy manual, and the patient's instruction for use.

4.2.2 Dosage, Administration, and Compliance

4.2.2.1 Olesoxime

Olesoxime will be given as a 100-mg/mL liquid formulation. The drug will be administered at 10 mg/kg *BID* orally or via a naso-gastric or gastrostomy tube with *breakfast and dinner*, preferably at the same time of the day throughout the study. *If drug administration does not coincide with one of the scheduled meals, a snack should be taken prior to drug administration. Preferably there should be at least 10 hours between the morning and evening dose. The total daily dose in this study will not exceed 2000 mg. Therefore, patients with a body weight >100 kg will receive a dose of 1000 mg BID.*

For the dose increase procedures of the patients who consent to Protocol BN29854, Version 4, please refer to Section 3.1.1.4.

Patients who do not consent to the dose increase will continue with the previous dosage and receive a dose of 10 mg/kg QD orally or via a naso-gastric or gastrostomy tube with the main meal, preferably at the same time of the day, throughout the study.

Dose will be determined by weighing the patient at every visit (see Schedule of Assessments in Appendix 1), and recorded in the electronic Case Report Form (eCRF) Dose should be adjusted at every visit according to the weight changes.

In the event that the patient has to undergo medical procedures that impair the administration of study drug, sites can interrupt treatment at the discretion of the treating investigator. If interruption of treatment is prolonged (more than 8 weeks), the treating investigator should notify the Sponsor.

IMP administration should be recorded on the Study Drug Administration electronic Case Report Form (eCRF). Any overdose or incorrect administration of study drug should be documented in the patient's *diary* and recorded in the eCRF. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

4.2.2.2 Treatment Compliance

Patients will be asked to document drug administration in a patient diary. Compliance with study drug intake (dose, frequency, should be checked by the investigator at scheduled visits). The data from the patient's diary will be provided to the Sponsor.

4.2.3 Investigational Medicinal Product Accountability

The IMP, olesoxime, will be provided by the Sponsor. The study site will acknowledge receipt of IMP, using IxRS, to confirm the shipment condition and content. Any damaged shipments will be replaced.

At applicable sites, study drug may be shipped to patients home and receipt confirmed by a trained home nursing (HN) professional at the patient's home, if the patient has given written informed consent to participate in HN visits.

IMP will either be disposed at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.2.4 Post-Trial Access to Olesoxime

The Sponsor will offer post-trial access to the study drug olesoxime free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive study drug after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive study drug after completing the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or would not otherwise create a financial hardship for the patient).
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for SMA.
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for SMA.
- Provision of study drug is not permitted under the laws and regulations of the patient's country.

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.3 CONCOMITANT THERAPY AND FOOD

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements), as well as, e.g., prescribed exercise and physical therapy programs used or performed by a patient from at least 6 weeks prior to screening up to the study completion/discontinuation visit. All such medications and therapies should be reported to the investigator and recorded on the eCRF.

4.3.1 Permitted Therapy and Medical Procedures

Patients will be allowed to continue or start any symptomatic therapy or medical procedures needed to improve survival and quality of life, as judged by the treating physician. Dosing should always be used in the dose range according to the approved local prescribing information. Therapies for the treatment of SMA or agents anticipated to increase or decrease muscle strength are permitted, which include, but are not restricted to:

Nusinersen (Spinraza®), riluzole, valproic acid, hydroxyurea, sodium phenylbutyrate, butyrate derivatives, growth hormone, anabolic steroids, probenecid, agents anticipated to increase or decrease muscle strength or presumed histone deacetylase inhibition activity

Use of nusinersen (Spinraza®) does not exclude patients from continued participation and treatment with olesoxime in Study BN29854.

Patients should remain on stable dose throughout the study. However, in case it is medically recommended that a dose or therapy is modified, this should be recorded in the eCRF.

4.3.1.1 Prohibited Therapy

Use of the following therapies is prohibited during the study treatment:

- Investigational therapy
- Medications that could interfere with olesoxime absorption: ezetimibe, bile salts chelators (cholesteramine), fibrates, phytosterols
- Medication that could interfere with olesoxime pharmacodynamics: tamoxifen

4.3.2 Food and Drink

There are no specific dietary requirements or prohibited food in this study. The investigator may give or refer the subject for specific nutritional advice based on patients' health status. In case specific nutritional advice, such as enteric nutrition, is recommended, this should be recorded in the eCRF.

4.4 STUDY ASSESSMENTS

Please see Appendix 1 for Historical Data Collection.

Laboratory safety samples should be collected first at each visit, *preferably* under fasted conditions. After receiving food, the PRO assessments (in the pre-specified order) should be administered first. Then, all other assessments can be performed in the order convenient for the site. If it is not possible for the patient to perform all assessments during the day, the site may divide the assessments between 2 consecutive days.

At applicable sites, certain study assessments may be performed by a trained home nursing professional (HN) at the patient's home to improve access and convenience for patients participating in the study. The schedule of assessments (see Appendix 1) will specify the assessments that may be performed by an HN professional.

4.4.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained from the patient, parent or legal guardian and if appropriate, assent from the child, before any study-specific screening tests, Historical Data Collection or evaluations are performed. The study can have two main Informed Consent Forms signed from each patient: one for providing detailed historical information (Historical Data Collection), and one for the open-label period of this study. However, participation in one part of the study does not preclude or oblige the patient to participate in the other part of the study. For the Caregiver Reported Outcomes, written informed consent must be obtained from the the caregiver (please refer to Section 4.4.11). The signed Informed Consent Forms will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before initiation of treatment with olesoxime. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.4.1.1 *Informed Consent Form for Protocol BN29854, Version 4*

All patients, or if appropriate, legal guardians, must have signed informed consent for the new schedule of assessments and related procedures (see Section 3.1.1.4). If the patient agrees to the 10 mg/kg BID dose, as well as all procedures and assessments per Protocol BN29854, Version 4, this must be documented in the informed consent.

In case the patient or his/her caregiver initially declines receiving the dose increase and subsequently reconsiders the decision, new written informed consent must be obtained.

4.4.2 Historical Data Collection

Historical Data Collection includes any clinically significant diseases and medical complications that in the opinion of the treating investigator are related to the natural course of SMA (for instance, but not restricted to, pulmonary, gastrointestinal, orthopedic, nutritional), medical procedures (such as, but not restricted to, scoliosis surgery, gastrostomy feeding, use of ventilation, history of pulmonary infections/events), and its treatments used by the patient from the last visit in study TRO19622CLEQ1275-1 or TRO19622CLEQ1115-1 up to the screening visit for study BN29854.

Further information requested will be patient clinical status during routine clinical visits, that may include any SMA validated motor functional scale, such as the MFM and HFMS, and/or disability scale (e.g., Brooke, Vignos) performed during the above mentioned period.

The information will be collected at screening from patients who consent (Appendix 2).

NB The Historical Data Collection requires a separate informed consent.

4.4.3 Medical History and Demographic Data

Demographic data and other applicable medical history will be collected at screening to verify patient's eligibility. Demographic data will include age, sex, and self-reported race/ethnicity, education status, and employment status (if applicable).

Other applicable medical history will include reproductive status, smoking history, use of alchohol and drugs of abuse and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) and medical procedures not related to SMA in the opinion of the treating physician.

NB For other applicable medical history, patients should have provided informed consent for the open-label treatment period of the study.

4.4.4 Anthropometric Measurements

Anthropometric measurements include body weight at every visit, and height at baseline, and every 6 months thereafter *as well as at a possible early discontinuation visit.*

The patient's body weight will be measured to the nearest kilogram using a calibrated scale. For wheelchair-bound patients, weight of the patient will be obtained with a wheelchair balance scale with the patient in the wheelchair. The wheelchair should be also weighed by itself and subtracted from total weight.

The patient's height will be measured or derived *from ulna length* to the nearest centimeter.

Ulna length (from the tip of the olecranon process to that of the styloid process) will be measured using an anthropometer with the patient in sitting position, the left forearm resting comfortably on a table, elbow bent 90 to 110 , palm facing downwards and fingers extended but together.

The assessments will be performed as in the Schedule of Assessments Appendix 1, and the formula for calculation of BMI is provided in Appendix 4.

4.4.5 Physical Examinations

A complete physical examination should be performed at screening including the evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at screening or baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At baseline and subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.4.6 Vital Signs

Vital signs will include measurements of temperature, respiratory rate, pulse rate, and systolic and diastolic blood pressure (BP) while the patient is in a seated position, after the patient has rested for approximately 5 minutes. BP measurements should be done at the same arm and with the same cuff size using an automatic instrument with a digital readout throughout the study.

Vital signs should be measured prior to blood draw or at least 10 minutes after the last blood draw.

4.4.7 Tanner Staging

Tanner staging will be determined at the baseline visit in all patients aged from 9-17 years of age and yearly thereafter.

4.4.8 Laboratory, Pharmacokinetic, Biomarker, and Other Biological Samples

Laboratory safety tests will be collected at timepoints specified in the Schedule of Assessments (Appendix 1) and analyzed by a central laboratory. For safety monitoring purposes, the investigator must review, sign, and date all laboratory safety tests results.

Additional blood or urine samples may be taken at the discretion of the investigator if the results of any test falls outside the reference ranges, or clinical symptoms necessitate additional testing to monitor patient safety.

Samples for the following laboratory tests will be sent to one or several central laboratories for analysis:

- Hematology (WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count [neutrophils, eosinophils, basophils, monocytes, and lymphocytes)
- Blood chemistry: AST, ALT, γ-glutamyl transferase, creatine kinase, total and direct bilirubin, alkaline phosphatase (ALP), albumin, creatinine, urea, total protein, sodium, chloride, calcium, phosphorus, potassium, glucose, and additionally in adults and adolescents only, brain natriuretic peptide.
- Coagulation (INR, aPTT, PT).
- Lipids (cholesterol, low-density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides)
- Urinalysis: a midstream, clean-catch urine specimen will be collected for dipstick analysis of protein, blood, glucose and pH. If there is a clinically significant positive result, urine will be sent to the laboratory for microscopy and culture. If there is an explanation for the positive dipstick result, it should be recorded, and there is no need to perform laboratory for microscopy and culture.
- Hormones

  Patients aged 6-17 years: thyroid hormones (free thyroxine T4 and thyroid stimulating hormone.

  Female patients aged 12-17 years or younger who have menses: estradiol, follicle stimulating hormone, luteinizing hormone.
- Pregnancy test

  All women of childbearing potential (≤12 months of non-therapy-induced amenorrhea) or not surgically sterile will have urine pregnancy tests performed at all visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.
- Plasma samples for PK analysis

  A blood sample will be collected at timepoints specified in the Schedule of Assessments (Appendix 1). The time of the assessment will be recorded. If PK samples have been missed or taken in error, reasons for these discrepancies must be provided.

Actual date and time of the administration for the preceding two doses (except on V1) and the dosing date and time on the day of assessment must be documented in the eCRF. The most frequent time of drug intake (i.e., with evening, noon, or morning) in the weeks prior to the visit should also be recorded in the eCRF.

Laboratory kits will be provided for all central laboratory assessments. The procedures for the collection, handling, storage and shipping of samples will be detailed in the laboratory manual.

4.4.8.1 Biomarker Assessments

The following biomarker assessments will be performed as detailed in the Schedule of Assessments (Appendix 1). *All biomarker samples will be destroyed no later than 5 years after the date of the final clinical study report.*

4.4.8.1.1 SMN Protein Levels

Whole blood for SMN protein analysis will be collected from every patient.

4.4.8.1.2 In Vivo Splicing of SMN2 mRNA

Two whole blood samples will be taken from every patient at the timepoints specified in the Schedule of Assessments (Appendix 1) to measure the relative amounts of *SMN1,* SMN2-*FL, and SMNΔ7* mRNA transcript during the course of the study. In addition, housekeeping genes for the quantitative analysis of RNA will be measured. Additional mRNA may be *used for exploratory analysis/assay development related to SMA, including, but not limited to,* pathways related to SMN function, SMA disease severity, progression, and treatment response.

4.4.8.1.3 Fluid Biomarkers

The following fluid biomarker samples will be used to assess treatment response in patients. Serum for the analysis of biomarkers related to SMA or to the response from treatment (e.g., muscle damage or insulin-like growth factor system) will be collected.

These samples will be destroyed no later than 5 years after the date of *the* final clinical *study report* and may be used for additional exploratory analysis/assay development *related to SMA including, but not limited* to, pathways related to SMN function or treatment response.

4.4.8.2 Clinical Genotyping Samples

A mandatory whole blood sample will be taken for DNA extraction from every patient at *three timepoints, as indicated in the Schedule of Assessments (see Appendix 1).* The *baseline* DNA will be used to determine the copy number of SMN2 and may also be used to confirm the SMN1 mutation or deletion. *The baseline and longitudinal DNA samples may be used for additional exploratory analysis/assay development related to SMA including, but not limited to, mitochondrial DNA levels and genes related to SMN function (especially genetic modifiers of SMA, SMN mRNA splicing, or SMN protein*

expression), which might be dynamically changed due to disease severity, progression, and treatment response.

These samples will be destroyed no later than 5 years after the date of *the* final clinical *study report.* The procedures for the collection, handling, storage and shipping of samples will be detailed in the laboratory manual.

Data arising from clinical genotyping will be subject to the confidentiality standards described in Section 8.4.

4.4.8.3 Order of Sample Collection

Should the total blood volume to be collected at any timepoint according to this Schedule of Assessments exceed 1mL/kg or the volume collected over any 8-week period throughout the study exceeds 4 mL/kg, the blood sample prioritization described below should be followed:

- Any safety laboratory samples (scheduled or unscheduled and performed at the discretion of the investigator);
- PK samples;
- SMN protein levels
- In vivo splicing of SMN2 mRNA
- Clinical genotyping
- Fluid biomarkers assessing treatment response
- RCR samples if collected

4.4.8.4 *Spinal Muscular Atrophy Digital Biomarkers*

Each patient will receive a preconfigured smartphone at the first visit after Protocol BN29854, Version 4 has been initiated and after the new Informed Consent Form has been signed. The device and software will be used to regularly assess motor behavior, as well as to intermittently answer questions related to health and activities associated with routine daily living. The smartphone must be returned to the clinical site in case of study withdrawal, end of the study, or upon request.

Digital Biomarker Remote Monitoring

Patients will be provided with and trained on the device. During the study, patients will be instructed to conduct "Active Tests" every day, at approximately the same time (ideally in the morning after breakfast). The "Active Test" consists of a short, preconfigured sequence of tasks that assess motor symptoms.

Device sensor data will be recorded continuously throughout the "Active Tests." Audio will only be recorded during the sustained phonation test. Data are encrypted and uploaded to secure servers whenever the smartphone is connected to WiFi.

Digital Biomarker In-Clinic Assessments

Patients will be instructed to bring the smartphone to every clinic visit to check adherence and the technical status of the device.

At selected clinic visits, patients will be asked to conduct the "Active Tests" tasks under the supervision of a person trained on the digital biomarker approach.

The smartphone must be returned to the clinic in cases where the patient does not meet eligibility criteria, study withdrawal, end of the study, or upon request.

At the end of the study or at the time when the subject has completed the study, patients will be asked to complete a pen and paper satisfaction survey on their experience using the smartphone during the study.

Additional details are available in the SMA Digital Biomarker Manual.

4.4.9 Electrocardiograms

ECGs recordings will be performed at the time-points specified in the Schedule of Assessments (Appendix 1). *If a patient performs a 24-hour Holter ECG as part of the dose increase per Protocol BN29854, Version 4 on a regular visit (see Option 2 in Section 3.1.1.4) and an ECG assessment is scheduled at this regular visit, only the 24-hour Holter ECG will be performed.* All ECG recordings will be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting for at least 10 minutes. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. ECG tracings should also be submitted to a central laboratory. Results will be provided to sites within 72 hours or 48 hours if any signal is detected.

4.4.9.1 *24-Hour Holter ECG Monitoring*

All patients who have consented to the 10 mg/kg BID dose increase will be requested to have 24-hour Holter ECG monitoring (see Section 3.1.1.4) before the dose increase and 4 weeks after the dose increase. The Holter ECG monitor will be placed on the patient at the dose increase visit and at the dose increase safety follow-up visit. After the first predose 24-hour Holter ECG monitoring at the dose increase visit, patients will return the Holter ECG monitor to the site at the dose increase safety follow-up visit (at the latest). After the second 24-hour Holter ECG monitoring, which is performed at the dose increase safety follow-up visit, the recording data must be sent to the central laboratory, and the site will be informed of the results within 1 week. Any abnormality

in the Holter ECG data will be assessed on a case-by-case basis between Sponsor and investigator, and appropriate measures will be taken as needed.

4.4.10 Patient-Reported Outcomes

Patient Reported Outcomes (PRO) data will be collected via questionnaires to more fully characterize the clinical profile of olesoxime. The questionnaires will be in paper format, and translated as required in the local language. To ensure instrument validity and that data standards meet health authority requirements, the questionnaires scheduled for administration during a clinic visit should be completed *after the laboratory safety samples have been taken and* prior to administration of study treatment and to the performance of non-PRO assessments, in the order defined below. *Where appropriate,* both caregiver and patient should complete the PedsQL *Generic Core Scales*. The self-report version of EQ-5D-5L should be completed by patients ≥12 years of age, and the proxy version completed by caregivers of patients <12 years of age. *The SMAIS self-report version should be completed by patients aged ≥ 12 years, and the SMAIS caregiver-report version should be completed by a caregiver for all patients, where possible. The form used in the baseline assessment should be used at all subsequent visits and the dose increase visit (e.g., patients aged <12 years will not complete the EQ-5D-5L or the SMAIS even if their 12th birthday occurs during the study, and patients aged 8-12 years will continue to use the PedsQL forms for ages 8-12 years even if their 13th birthday occurs during the study).*

The PRO measures for this study are as follows:

- *The EQ-5D-5L conducted at all visits except screening, Visit 2, and Visit 4:*

  The EQ-5D-5L is a self-report health status questionnaire that consists of six questions used to calculate a health utility score for use in health economic analysis (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; van Hout et al. 2012; Janssen et al. 2013, Oppe et al. 2014). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analog scale (VAS) that measures overall health status. Published weighting systems allow for creation of a single summary score. Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction; for some countries (e.g., United Kingdom), scores below zero are possible. The EQ-5D-5L will be utilized in this study for economic modeling.

  Patients who participate in the digital biomarker assessment will also complete an electronic version of the EQ-5D-5L every 2 weeks.

- The PedsQL *Generic Core Scales (Version 4.0) and PedsQL Neuromuscular Module (Version 3.0)* conducted at all visits, with the exception of *screening,* Visit 2*,* and Visit 4.

The PedsQL is a modular instrument designed to measure health-related quality of life and disease-specific symptoms. The instrument integrates generic core scales and disease-specific modules into a single measurement system (a full listing of peer-reviewed journal publications is available at www.pedsql.org). The PedsQL Generic Core Scales (*Version* 4.0) and *PedsQL* Neuromuscular Module (*Version* 3.0) have been shown to be feasible, reliable, and valid in the SMA population (Iannaccone et al. 2009).

The PedsQL Generic Core Scales (Version 4.0) includes 23 items that can be completed in around 4 minutes, using self-report (ages 5+) and/or parent report (ages 5+). The instrument covers physical, emotional, social, and school functioning and can be summarized into three main scores (total scale score, physical health score, and psychosocial health score).

The PedsQL Neuromuscular Module (Version 3.0) includes 25 items that can be completed in around 4 minutes, using self-report (ages 5–18) and/or parent report (ages 5–18). The instrument covers problems related to neuromuscular disease, communication and family resources and can be summarized into total and domain scores.

For all PedsQL items, the recall period will be the past one month. PedsQL assessments will be performed using both parent report and child report where possible, dependent on age and ability to complete the questionnaire. An administrator is also required to develop rapport with respondents, emphasize the importance of the questionnaire, address concerns, and ensure accurate completion and confidentiality. Age bands for the instrument are as follows, and within a scale or module, the appropriate age band should be used based on the age of the patient at *enrollment*:

Young child (5–7 years)

Child (8–12 years)

Teen (13–18 years)

Young Adult (18–25 years) [Core scales only]

Adult (>25 years) [Core scales only]

For scoring purposes, scale items are linearly transformed to a 0–100 scale (0=100, 1=75, 2=50, 3=25, and 4=0) so that higher scores indicate better health-related quality of life. Scale scores are computed as the sum of the items divided by the number of items which were answered. It is recommended that if more than 50% of the items in the scale are missing, the scale score should not be computed.

- *The SMAIS was developed specifically for SMA in order to assess function-related independence. The SMAIS contains 29 items, assessing the amount of assistance required from another individual to perform daily activities, such as eating or transferring to/from a wheelchair. Each item is scored on a 0–4 scale (with an additional option to indicate that an item is non-applicable). Item scores are summed to create the total score. Lower scores indicate greater dependence on another individual. The SMAIS will be completed by patients aged ≥12 years. The*

SMAIS will be conducted at all visits including the dose increase visit, with the exception of screening, Visit 2, and Visit 4.

The PROs should be completed in the following order (caregivers should also follow this order when completing these questionnaires about the patient):

1. *SMAIS*
2. *EQ-5D-5L*
3. *PedsQL Neuromuscular Module*
4. *PedsQL Generic Core Scale*

4.4.11 Caregiver-Reported Outcomes

As noted above, caregivers will be required to complete questionnaires assessing the impact of disease on the patient. For the EQ-5D-5L Proxy and the PedsQL Generic Core Scale and Neuromuscular Module, the questionnaires should be completed by the primary caregiver of the patient. For adult patients who do not receive care from their parents (or other individuals close to the patient), the collection of caregiver-reported outcomes is not mandatory; however, it has to be fully documented in the appropriate eCRF form.

Caregiver Reported Outcomes data will be collected via questionnaires to understand the impact of disease on the caregiver. The questionnaires will be in paper format, and translated as required in the local language, and should be completed by the same caregiver throughout the study. Written informed consent must be obtained from the caregiver. In case the patient is an adult who does not receive care from a relative, partner, or close friend (i.e., someone who is not necessarily a professional caregiver), the collection of caregiver-reported outcomes is not mandatory; however, it has to be fully documented in the appropriate eCRF form. The caregiver-reported outcome measures for this study are as follows:

- Caregiver resource use: WPAI:CG, conducted at all visits, with the exception of *screening,* Visit 2, and Visit 4

  Occupational work productivity and activity impairment in caregiver will be assessed using the WPAI:CG. The WPAI:CG consists of 6 questions about the effects of SMA on the following: employment status; hours missed due to patient caregiving; hours missed due to other reasons; hours actually worked; and two questions that measure the degree to which health problems affected productivity due to caregiving (presenteeism) and regular daily activities.

- Caregiver generic health-related quality of Life *SF-36v2,* conducted at all visits, with the exception of *screening,* Visit 2, and Visit 4

  SF-*36v2* is widely used across databases and is a well-established generic scale with 36 questions grouped into eight domains *and two summary scores* covering aspects of functioning and physical and mental health in caregiver.

The same caregiver should complete the assessments at all specified visits (e.g., it is not permitted for the mother of one patient to complete an assessment at one visit, and for the father of the same patient to complete the same assessment at a subsequent visit).

4.4.12 *Clinical Global Impression of Change*

The CGI-C is a single-item measure of change in global health that uses seven response options: Very Much Improved, Much Improved, Minimally Improved, No Change, Minimally Worse, Much Worse, and Very Much Worse. It is a widely used endpoint in clinical trials across a variety of disease areas. Clinicians will score patients using this scale based on their impression of change in the patient's global health since baseline. To enhance inter-rater consistency, an instructions document (developed with input from clinical experts) will be provided, which includes examples for each of the response options.

The same clinician should complete the CGI-C at all specified visits for an individual patient. The CGI-C will be administered at the dose increase visit and study Visits 5, 6, and 7.

4.4.13 *Olesoxime Fatigability Survey*

The OFS is a brief survey designed to explore potential benefit of olesoxime on fatigability (i.e., endurance). This survey will be completed once, at the dose increase visit. The data will be used to aid assessment of options for further clinical development of olesoxime. The survey will be completed by clinicians following discussions with the patient and their family/caregivers.

4.4.14 SMA Disease Specific Assessments

4.4.14.1 Motor Function Measure (MFM)

The MFM (Berard et al. 2005) is an ordinal scale constructed for use in patients with neuromuscular disorders, and has been validated in SMA. The scale evaluates motor function in three dimensions:

- D1: evaluates functions related to standing and transfer,
- D2: evaluates axial and proximal function in supine and sitting position on mat and chair,
- D3: evaluates distal motor function.

The scoring of each task uses a 4-point Likert scale based on the patient's maximal abilities without assistance: 0, cannot initiate the task or maintain the starting position; 1, performs the task partially; 2, performs the task incompletely or imperfectly (with compensatory/uncontrolled movements or slowness); and 3, performs the task fully and "normally." The scores are summed to yield a total score expressed as the percentage of the maximum possible score (the one obtained with no physical impairment); the lower the total score, the more severe the impairment. The MFM is free and available in most

common European languages. Users' manual and scoring sheet will be provided to the sites prior to study start.

4.4.14.2 Forced Vital Capacity (FVC)

Pulmonary Function will be assessed in patients 5 years or older by measuring forced expiratory vital capacity (FVC) (as percent predicted for age and height). Pulmonary measures have been validated in SMA (Iannaccone et al. 2003). If height cannot be measured (e.g., with scoliosis or contractures), ulna length will be used to calculate a surrogate height measure.

4.4.15 Unscheduled Visits

Patients reporting new or worsening symptoms related to either the natural course of the disease or an adverse event should be seen at the investigational site, if deemed appropriate by the treating physician. Assessments performed at unscheduled visits will depend on the clinical needs of the patient.

Any unscheduled visits and procedures should be recorded in the eCRF.

4.4.16 Early Discontinuation Visit

Patients who decide to discontinue study treatment will be asked to return to the clinic for an early discontinuation visit 28 (± 5) days after last dose, regardless of reason of discontinuation *(safety follow-up, as described in Section 3.1.1.5).*

Remaining IMP delivered to the patient should be returned to the trial site during this visit.

4.4.17 Treatment Completion

Patients will be asked to come for a final study visit as early as possible but not later than 6 weeks after the end of the study at the patient's site (as described in Section 3.2).

If a patient had a regular visit prior to up to 3 months before announcement of the study end the last regular visit will be regarded as the final visit. However, remaining IMP delivered to the patient should be returned to the trial site within 6 weeks of announcement of study end.

4.4.18 Telephone Calls

The purpose of this semi-structured interview is to identify new or worsening symptoms that warrant an unscheduled visit. The telephone interview is shown in Appendix 3 and will be conducted after Visit 5 by site personnel familiar with the patient(s) every 12 weeks (± 7 days) *after each* study *visit*.

4.4.19 Samples for Roche Clinical Repository

4.4.19.1 Overview of the Roche Clinical Repository

The Roche Clinical Repository (RCR) is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid

tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and analysis of RCR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.4.19.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol (Section 4.4.18) will not be applicable at that site.

4.4.19.3 Sample Collection

The following samples will be collected from eligible patients who provide consent for research purposes, including but not limited to research on dynamic (non-inherited) biomarkers, and on genetic (inherited) biomarkers related to olesoxime, spinal muscular atrophy:

- DNA specimens for genetic biomarker (inherited) discovery and validation will be collected at baseline.
  NB If the sampling for DNA Specimens was missed during baseline, it may be collected in the next scheduled visit.
- Blood samples (collected in PAXgene vacutainers) will be collected for RNA analysis at timepoints specified in the Schedule of Assessments (Appendix 1).
- Blood for plasma isolation will be obtained at the timepoints indicated in the Schedule of Assessments (Appendix 1) for identification of dynamic (non-inherited) biomarkers.

These specimens will be used for research purposes and will help to better understand the pathogenesis, course, and outcome of SMA and related diseases. For all samples, dates of consent should be recorded on the associated RCR page of the eCRF. For

sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RCR specimens will be destroyed no later than 15 years after the date of final *clinical study report*. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens (RNA, plasma) will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

4.4.19.4 Confidentiality

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR specimens and associated data. Upon receipt by the RCR, each specimen is "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant are also labeled with this same independent number. A "linking key" between the patient identification number and this new independent number is stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

Data generated from RCR specimens must be available for inspection upon request by representatives of national and local health authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Patient medical information associated with RCR specimens is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient and/or legal guardian, unless permitted or required by law.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RCR data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

4.4.19.5 Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or authorized designee will explain to each patient and/or legal guardian the objectives, methods, and potential hazards of participation in the RCR. Patients and/or legal guardians will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's and/or legal guardian's agreement to provide optional RCR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate by completing the RCR Research Sample Informed Consent eCRF.

In the event of an RCR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RCR research.

4.4.19.6 Withdrawal from the Roche Clinical Repository

Patients and/or legal guardians who give consent to provide RCR specimens have the right to withdraw the specimens from the RCR at any time for any reason. If a patient and/or legal guardian wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal of Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study BN29854 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study BN29854.

4.4.19.7 Monitoring and Oversight

RCR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, Institutional Review Board/Ethics Committee (IRB/EC) review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

4.5 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.5.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn *(except for safety follow-up, as described in Section 3.1.1.5)*. Patients who withdraw from the study will not be replaced.

4.5.2 Study Treatment Discontinuation

Patients must discontinue study treatment if they experience any of the following:

- Ongoing pregnancy

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients should be invited to the site to perform a Study Discontinuation Visit. Patients who discontinue study treatment prematurely will not be replaced.

4.5.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the ICH guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Olesoxime is not approved and is currently in clinical development. Thus, the entire safety profile is not known at this time. Based on clinical experience to date there are no identified risks with olesoxime (for additional information please refer to the Olesoxime Investigator's Brochure). The safety plan for this study is designed to ensure patient safety and will include specific eligibility criteria (Section 4.1.2 and Section 4.1.3) and monitoring for adverse events and other safety parameters as described in the Schedule of Assessments (Appendix 1).

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Sections 5.2.2 and 5.2.3.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as blood draw).

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)

- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.9).
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4 for reporting instructions). Adverse events of special interest for this study are:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Section 5.3.5.6).
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle, pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4 to Section 5.6. The investigator is also responsible for reporting medical device complaints (see Section 5.4.4).

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 28 days after the last dose of study drug. After this period, the investigator should report any serious adverse events that are believed to be related to prior study drug treatment (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

Table 1 provides guidance for assessing adverse event severity.

Table 1 Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 $\times$ ULN (upper limit of normal) associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of SMA.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. *The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").*

If the death is attributed to progression of SMA, "SMA progression" should be recorded on the Adverse Event eCRF.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.9 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization *under the following circumstances should* not be *reported as an* adverse *event or a serious adverse event*:

- Hospitalization for respite care
- Planned hospitalization required by the protocol , e.g., for study drug administration or insertion of access device for study drug administration
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event

An event that leads to hospitalization *under the following circumstances is* not considered to be *a* serious adverse *event*, but should be reported as *an* adverse *event* instead:

- Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available.

5.3.5.10 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF page.

5.3.5.11 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events which must reported to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (see Section 5.4.2 for further details)
- Adverse events of special interest (see Section 5.4.2 for further details)
- Pregnancies (see Section 5.4.3 for further details)

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor Contact Information for all sites

Medical Monitor: [redacted], MD (primary)

Telephone No.: [redacted]

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be

available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor contact information, will be distributed to all investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 28 days after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 28 days after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. The investigator should counsel the patient. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In

addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Abortions

Any abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.4.4 Reporting Requirements for Medical Device Complaints

In this study, syringes, funnels, and press-in bottle adaptors are considered medical devices. The investigator must report all medical device complaints to the Sponsor. The investigator should document as much information as possible on the IMP Deviation Form, including the product batch number, and forward the form to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) (refer to the pharmacy manual for further details). If the medical device results in an adverse event to the study patient, the event must be reported on the Adverse Event eCRF and submitted through the EDC system. If the event is serious, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5.4.2.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case

details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 28 days after the last dose of study drug), if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the Olesoxime Investigator's Brochure.

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 ANALYSIS POPULATIONS

Safety Population

The safety population will consist of all patients who received at least one dose of study medication. All safety data will be summarized based on the safety population.

Intent-To-Treat Population

The intent-to-treat (ITT) population will include all patients who received at least one dose of study medication and have at least one post-baseline assessment of MFM. The ITT population will be the primary population for the efficacy analysis.

As this is an open-label study no formal hypothesis testing will be performed. Data will be summarized using descriptive statistics and will be compared with natural history data. Further details will be provided in the statistical analysis plan (SAP).

6.2 DETERMINATION OF SAMPLE SIZE

The sample size will be determined by the number of patients who participated in studies TRO19622CLEQ1275-1 and*/or* TRO19622CLEQ1115-1 and who meet the enrolment criteria. The primary objective of the study is to assess the safety and tolerability of olesoxime.

6.3 HISTORICAL DATA

Descriptive statistics will be used to describe the disease course of patients from the last visit of Studies TRO19622CLEQ1275-1 and TRO19622CLEQ1115-1 and the start of current study BN29854. Further exploratory analyses will be described in a separate SAP.

6.4 SUMMARIES OF CONDUCT OF STUDY

Descriptive statistics will be used to evaluate the conduct of the study. Patient disposition, compliance with medication and major protocol deviations will be assessed.

6.5 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic data collected at screening and baseline characteristics will be summarized. Summaries will be presented overall and by the treatment received in the previous study.

Summaries will be based on the safety population.

Where available, similar descriptive statistics may be provided for the natural history data.

6.6 PRIMARY ANALYSES

Safety analysis will be based on the safety population.

Safety variables (e.g., laboratory tests, vital signs, and ECG) will be summarized for each assessment time (including follow-up) using descriptive statistics. *The data will be summarized by the dose being taken at the time of the assessment (10 mg/kg QD or 10 mg/kg BID). Data from the two 24-hour Holter ECG assessments will also be summarized.*

Adverse events will be coded and summarized by body system and preferred term. Adverse events will also be summarized by intensity and relationship to trial treatment as assigned by the investigator. Serious adverse events will be summarized separately. *Adverse events will be summarized by the dose being taken at the onset date of the adverse event.*

6.7 SECONDARY ANALYSES

The change from baseline in MFM D1+D2 and MFM Total Score will be summarized at each visit using descriptive statistics. *The data will be summarized by the dose being taken at the time of the assessment.* Mean changes and 95% confidence intervals over time will be presented graphically. Summary statistics by age and SMA type will also be provided.

Where available, similar descriptive statistics may be presented for the Natural History Data.

Statistical modelling approaches may be used to explore the effects of differences in baseline covariates. Details will be provided in the SAP.

The incidence of disease associated medical complications and procedures will be summarized. *The data will be summarized by the dose being taken at the onset date of the event.*

6.8 PHARMACOKINETIC ANALYSES

A Bayesian feedback population pharmacokinetic analysis of olesoxime PK data collected in this open-label study will be performed using NONMEM. Individual olesoxime PK parameters (e.g., CL/F, Vss/F) will be estimated using a posterior Bayes analysis based on a previously developed population PK model. The results will be reported in a document separated from the clinical study report.

6.9 EXPOSURE-RESPONSE (EFFICACY, SAFETY, AND BIOMARKERS) EXPLORATORY ANALYSES

Graphical analyses of the relationship between exposure and response (efficacy, safety, and biomarkers) will be conducted. The efficacy parameter will be the MFM D1+D2 score. The safety parameters will include adverse events, relevant safety labs, and ECG parameters. The biomarkers will be those linked with the disease, such as SMN mRNA, SMN protein, or other biomarkers linked to the disease pathway.

In case a relevant exposure-response relationship is identified, an empirical exposure response model might be developed using a nonlinear mixed effects modeling approach. Classical hierarchical PK-PD models, like linear, Emax, or sigmoidal Emax models, will be used. The possibility of a delay between the time course of exposure and effects will be investigated.

Details of these graphical analyses and mixed-effects modeling analyses will be described and reported in a document separate from the clinical study report.

6.10 PATIENT-REPORTED OUTCOME ANALYSES

For the PedsQL, data will be presented for the core and neuromuscular modules, by total and sub-scores. Within modules data will be pooled across age bands. Data will be presented separately for child/patient report and parent report. *The data will be summarized by the dose being taken at the time of the assessment.* For scoring purposes, scale items are linearly transformed to a 0–100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, and 4 = 0) so that higher scores indicate better health-related quality of life. Scale scores are computed as the sum of the items divided by the number of items which were answered. It is recommended that if more than 50% of the items in the scale are missing, the scale score should not be computed.

For the SMAIS, total scores will be summarized for each assessment time by the dose being taken at the time of the assessment. Each item is scored on a 0-4 scale (with an additional option to indicate that an item is non-applicable), and item scores are summed to create the total score.

For EQ-5D-5L Index and VAS scores will be calculated for use in economic modeling, and will be reported separately.

6.11 CAREGIVER-REPORTED OUTCOME ANALYSES

For the WPAI:CG, data will be presented for occupational work productivity and activity impairment (employment status; hours missed due to patient caregiving; hours missed due to other reasons; hours actually worked; and two questions that measure the degree to which health problems affected productivity due to caregiving (presenteeism) and regular daily activities). *The data will be summarized by the dose being taken at the time of the assessment.*

For the SF-36, SF-6D health utility values will be calculated. Additionally, the eight domain scores and both component summary scores will be calculated as norm-based *T*-scores (general population norm mean = 50, SD = 10). The SF-6D and SF-36 scores will be used for economic modeling, and will be reported separately.

6.12 EXPLORATORY ANALYSES

The effect of olesoxime on the disease progression time-course will be investigated by applying model based approaches using, as appropriate, a disease progression model accounting for the time course of disease status with time being a continuous variable. The results will be reported in a document separate from the clinical study report.

Responder rates, where a responder is defined as no worsening from baseline in MFM D1 + D2, will be summarized *by the dose being taken at the time of the assessment*.

Change from baseline in FVC will be summarized *by the dose being taken at the time of the assessment*.

The CGI-C responses at each assessment visit will be summarized by the dose being taken at the time of the assessment. Clinicians will score patients using the CGI-C based on their impression of change in the patient's global health since baseline.

Smartphone sensor data collected as part of the digital biomarker approach will be analyzed. Patient adherence will be evaluated. From the sensor data, features will be developed for each smartphone-based test and correlated with the MFM and other clinical endpoints. Further exploratory analyses may be conducted. The results will be separately reported from the clinical study report.

For further exploratory analyses, please refer to the SAP for details.

6.13 INTERIM ANALYSES

Interim analyses of the data may be performed in response to information that may emerge during the course of the study, or for submissions to health authorities. Details of the analyses and timing will be documented in the SAP.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data and other electronic data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Data from paper PRO questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve

as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union (E.U.) or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor’s sample ICF for study participation and an ICF for the Historical Data Collection (i.e., the collection of data for the off-treatment period between studies TRO19622CLEQ1275-1 and TRO19622CLEQ1115-1 and screening for study BN29854 and ancillary sample Informed Consent Forms such as a Child’s Informed Assent Form or Home Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, ICFs will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample ICFs or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent

Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the ICF will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

At applicable sites, patients might receive the visit of a HN for drug delivery and selected procedures, if the patient has given written informed consent to participate in HN visits.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements,

policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., LPLV).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive

the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. *The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.*

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

The Sponsor of the trial is F. Hoffmann-La Roche Ltd. The Sponsor is responsible for the study management (monitoring), medical oversight, data management, statistical analysis, and medical writing for the Clinical Study Report.

An IxRS system will be used to register the screening/screening failures, enrolment, withdrawal, discontinuation, and completion of patients and for management of study drug inventory at trial sites.

A central laboratory will be used to provide sample kits to all sites and collect samples for the assessments listed in Section 4.4.8 and Section 4.4.19.

A central ECG laboratory will be used to assess all ECG tracings.

External consultants will provide training to site staff on various scales and assessments to ensure standardization across sites.

At applicable sites, certain study assessments may be performed by an HN professional at the patient's home to improve access and convenience for patients participating in the study.

The Sponsor will select a healthcare company that will be responsible for providing HN services for participating sites (the HN vendor). The HN vendor is responsible for ensuring that all HN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If

the investigator at a participating site determines that HN services are appropriate for a patient and the patient gives written informed consent to participate in HN visits, the HN network will communicate with the patient and the patient's site. HN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the HN professional.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

http://www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Assessments

	Screen.[a]	Baseline	Treatment Period									*Dose Increase Visit [b, c]*	*SFU Dose Increase Visit [c]*	Unsched. Visit [d]	Treat. Comp./ Early Discont.[e]	Safety Follow-Up [f]
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V9	V *N*[e]					
Week (Window; days)	–42 to –1	1	13 (±7)	26 (±7)	39 (±7)	52 (±7)	78 (±14)	104 (±14)	130 (±14)	156 (± 14)	Every 26 weeks[e] (±14)		*(+28 days after dose increase visit) (± 5)*			(+ 28 days after last dose) (± 5)
Informed consent	x[g]											*x*				
History data collection [h]	x															
Demographic data	x															
Medical history	x															
Weight [i]		x	x	x	x	x	x	x	x	x	*x*	*x*			x	
Height [i]		x		x		x	x	x	x	x	*x*				*x*	
Physical examination [j]	x	x	x	x	x	x	x	x	x	x	x			x	x	
Vital signs [k]	x	x	x	x	x	x	x	x	x	x	x			x	x	
Tanner staging [l]		x				x		x		x	(x) [l]					
Safety laboratory assessments [m]	x	x	x	x	x	x	x	x	x	x	x	*x*	*x*	x	x	

Appendix 1
Schedule of Assessments (cont.)

	Screen.[a]	Baseline	Treatment Period									*Dose Increase Visit* [b, c]	*SFU Dose Increase Visit* [c]	Unsched. Visit [d]	Treat. Comp./ Early Discont.[e]	Safety Follow-Up [f]
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V9	V *N*[e]					
Week (Window; days)	–42 to –1	1	13 (±7)	26 (±7)	39 (±7)	52 (±7)	78 (±14)	104 (±14)	130 (±14)	156 (± 14)	Every 26 weeks[e] (±14)		*(+28 days after dose increase visit) (± 5)*			(+ 28 days after last dose) (± 5)
Hormone assessments [n]		x				x		x		x	(x)[n]	*x*			x	
Pregnancy test [o]	x	x	x	x	x	x	x	x	x	x	x	*x*			x	
Urinalysis [p]	x					x		x		x	(x)[n]	*x*			x	
PK assessment [q]		x	x	x	x	x	x	x	x	x	x[r]	*x*	*x*		x	
SMN2 protein and SMN2 mRNA [q, s]		x	x	x			x		x	x	x	*x*				
Fluid biomarker [q, t]		x	x	x			x		x	x	x	*x*				
Clinical genotyping [q, u]		x								*x* [c]		*x*				
ECG [v]	x		x			x [w]		x [w]		x [w]	(x)				x	
Holter ECG [c]												*x*	*x*			
PedsQL[x]		x		x		x	x	x	x	x	x				x	
EQ-5D-5L[x]		x		x		x	x	x	x	x	x				x	
Caregiver Reported Outcomes [y]		x		x		x	x	x	x	x	x				x	

Appendix 1
Schedule of Assessments (cont.)

	Screen.[a]	Baseline	Treatment Period									*Dose Increase Visit* [b, c]	*SFU Dose Increase Visit* [c]	Unsched. Visit [d]	Treat. Comp./ Early Discont.[e]	Safety Follow-Up [f]
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V9	V *N*[e]					
Week (Window; days)	–42 to –1	1	13 (±7)	26 (±7)	39 (±7)	52 (±7)	78 (±14)	104 (±14)	130 (±14)	156 (± 14)	Every 26 weeks[e] (±14)		*(+ 28 days after dose increase visit)* *(± 5)*			(+ 28 days after last dose) (± 5)
CGI-C [c]						*x*	*x*	*x*				*x*				
OFS [c]												*x*				
SMAIS [c]				*x*		*x*	*x*	*x*	*x*	*x*	*x*	*x*			*x*	
MFM		x		x		x	x	x	x	x	x				x	
FVC		x		x		x	x	x	x	x	x				x	
IMP dispensation		x	x	x	x	x	x	x	x	x	x					
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	*x*	*x*	x	x	
Adverse events [z]		x	x	x	x	x	x	x	x	x	x	*x*	*x*	x	x	x
Telephone calls [aa]																
RCR mRNA and plasma sample [bb]		x				x		x								
RCR DNA [bb]		x														

Appendix 1
Schedule of Assessments (cont.)

	Screen.[a]	Baseline	Treatment Period									*Dose Increase Visit* [b, c]	*SFU Dose Increase Visit* [c]	Unsched. Visit [d]	Treat. Comp./ Early Discont.[e]	Safety Follow-Up [f]
Visit		V1	V2	V3	V4	V5	V6	V7	V8	V9	V *N*[e]					
Week (Window; days)	–42 to –1	1	13 (±7)	26 (±7)	39 (±7)	52 (±7)	78 (±14)	104 (±14)	130 (±14)	156 (± 14)	Every 26 weeks[e] (±14)		*(+28 days after dose increase visit)* *(± 5)*			(+ 28 days after last dose) (± 5)
Digital biomarker remote assessment [c, cc]		←														→
Digital biomarker in-clinic assessment [c, cc]		*x*		*x*		*x*	*x*	*x*	*x*	*x*	*x*	*x*			*x*	

CGI-C = Clinical Global Impression of Change; Comp. = Completion; Discont. = Discontinuation; eCRF = electronic Case Report Form; *EQ-5D-5L = EuroQol 5-Dimension, 5-Level Questionnaire; FVC = Forced Expiratory Vital Capacity; HN = home nursing; IMP = investigational medicinal product; MFM = Motor Function Measure; OFS = Olesoxime Fatigability Survey; PedsQL = Pediatric Quality of Life Inventory; PK = pharmacokinetic; PRO = patient-reported outcome;* RCR = Roche Clinical Repository*; SFU = Safety Follow-Up; Screen. = Screening; SMAIS = SMA Independence Scale; Treat. = Treatment; Unsched. = Unscheduled.*

Appendix 1
Schedule of Assessments (cont.)

Notes: All assessments should be performed within 14 days of the scheduled visit, unless otherwise specified. *Laboratory safety samples should preferably be collected first at each visit under fasting conditions.* Following food, the PRO assessments (in the pre-specified order) should be administered first. Then, all other assessment can be performed in the order convenient for the patient and site. *If it is not possible for the patient to perform all assessments during the day, the site may divide the assessments between 2 consecutive days.*
The following assessments may be performed by an HN professional: vital signs, urine pregnancy test, all lab assessments, and IMP dispensation.

[a] Screening can be prolonged up to 6 weeks for relevant clinical, administrative, or operational reasons. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 7 days prior to Day 1 may be used; such tests do not need to be repeated for screening.

[b] *Dose increase visit can be performed either at next scheduled visit or at unscheduled visit (as described in Section 3.1.1.4).*

[c] *Procedures should only be performed by patients that consent to Protocol BN29854, Version 4.*

[d] Unscheduled visit: If the patient reports new or worsening of symptoms related to the disease or an adverse event, the treating physician can request that the patient come for a clinical visit for further assessment or monitoring. Assessments should be performed as clinically indicated.

[e] The open-label treatment period can terminate at any time (please refer to End of Study Section 3.2). When the study is ended for a particular country, a completion visit should occur as soon as possible but no later than 6 weeks after study end. Patients who discontinue study drug prematurely will return to the clinic for a treatment discontinuation visit 28 (±5) days after the last dose of study drug. The assessments requested for Visit *N* represent the typical schedule of assessments during a scheduled visit.

[f] Required follow-up information will be collected via a phone call. An unscheduled follow-up visit may occur if the treating investigator deems it necessary.

[g] Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment. Please note that there is a separate consent form for historical data collection and for the open-label treatment period of the study. Please refer to Section 4.4.1.

[h] Refer to Appendix 2 and Section 4.4.2 (Historical Data Collection).

[i] Anthropometric measurement as described in Section 4.4.4.

[j] At screening, includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. At subsequent visits, limited, symptom-directed physical examinations should be performed. At baseline visit, record abnormalities observed *during* screening and *at* baseline on the General Medical History and Baseline Conditions eCRF. After baseline visit, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. Please refer to Section 4.4.5.

[k] Includes respiratory rate, pulse rate, and systolic and diastolic blood pressures while the patient is in a seated position, and temperature. Vital signs should be measured prior to blood draw or at least 10 minutes after the last blood draw. Record abnormalities on the Adverse Event eCRF.

Appendix 1
Schedule of Assessments (cont.)

[l] Only assessed in patients aged 9–17 years at Visit 1 and annually thereafter.

[m] For a list of all safety laboratory assessments, please refer to Section 4.4.8.

[n] For patients aged 6–17 years, *includes* thyroid hormones (free thyroxine T4 and thyroid-stimulating hormone); and for patients aged 12–17 years or younger who have menses, also includes estradiol, follicle-stimulating hormone, *and* luteinizing hormone. Hormone assessments should occur every 12 months.

[o] Urine pregnancy tests will be performed at all visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

[p] Includes dipstick (pH, specific gravity, glucose, protein, ketones, blood). If deemed necessary for further investigation, the treating physician can request microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria). Urinalysis should occur every 12 months.

[q] *Should be performed predose.*

[r] Actual PK sampling times must be documented. Actual date and time of study drug administration for the preceding two doses (except on V*isit* 1) must be documented in the eCRF.

[s] Separate whole blood samples for SMN protein and SMN2 mRNA assessment. Please refer to Section 4.4.8.1.

[t] Serum sample for fluid biomarkers. Please refer to Section 4.4.8.1.2.

[u] In case it was not possible to collect *the baseline* sample during Visit 1, a sample for clinical genotyping should be drawn at the next visit. Please refer to Section 4.4.8.2.

[v] ECG should be performed at screening and Visit 2 and then yearly from start of treatment.

[w] *If dose increase visit is performed at a scheduled visit, ECG does not need to be performed since a 24-hour Holter ECG monitoring is being performed.*

[x] Please refer to Section 4.4.10 for age-specific assessment and details. Complete before all other assessments during the study visit.

[y] Please refer to Section 4.4.11 for details on the Caregiver-Reported Outcomes.

[z] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 28 days after the last dose of study drug. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study drug treatment (see Section 5.6). The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[aa] Telephone calls: After Visit 5, telephone calls should occur every 12 weeks (±7 days). Please refer to Section 4.4.18 and Appendix 3.

[bb] Optional sample to be collected only for patients providing additional consent and not applicable for a site that has not been granted approval for RCR sampling. If the sampling for DNA specimens was missed during baseline, it may be collected in the next scheduled visit.

[cc] *The digital biomarker smartphone will be handed to patients at the first visit after the amendment. The smartphone must be returned to the clinical site in case of study withdrawal, end of the study, or upon request.*

Appendix 2
Historical Data Collection

The following information will be collected at screening from patients who sign separate consent.	Screening visit of BN29854	Possible assessments during all routine clinical visits [d]
Informed consent for Historical Data collection	x	
Last study visit date in previous study	x	
Clinical visit dates		x
Motor Function Measure at each visit [a]		x
Patient disability status [b]		x
Medical procedures [c]		x
Therapies [c]		x
Participation in other investigational studies	x	

[a] Motor Function Measure using any SMA validated motor function scale, such as the MFM and HFMS.

[b] e.g., using Brooke or Vignos scales.

[c] Medical procedures and therapies that in the opinion of the investigator are related to the natural course of SMA disease.

[d] The site should request to the patient and/or treating physician all possible assessment that occurred between last visit in TRO19622CLEQ1275-1 or TRO19622CLEQ1115-1 and enrollment in BN29854. It is possible that all information listed was not acquired during routine clinical visits.

Appendix 3
Telephone Interviews

The following semi-structured telephone interview should occur after Visit 5, 12 weeks ($\pm$7 days) *after each* study *visit*. The purpose of this interview is to identify any new or worsening symptoms that warrant an unscheduled visit or reporting of an adverse event.

Please ask the following questions and record patient's answers during the Telephone Interview:

1. Since the last time we talked (at site or over the telephone), have you had any worsening medical problems? If yes, what were they?

_____

_____

2. Since your last visit or telephone interview, have you taken any new medicines? If yes, what were they?

_____

_____

3. Have you had problems or issues with the preparation or handling of the study drug?

_____

_____

If the patient answered YES to any question, contact the Treating Investigator and review the patient's answers. The Investigator can determine if an unscheduled visit is required.

Record any pertinent comments made by the patient during the interview:

_____

_____

NAME:_____ Date:_____

Name of person completing the telephone interview.

Appendix 4
Formula for Calculation of Body Mass Index

Formula for Calculation of Body Mass Index (BMI)

$$BMI = \frac{Weight\ (kg)}{[Height(m)]^2}$$