NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING
MAY 2019

Risdiplam for paediatric and adult patients with spinal muscular atrophy (SMA)

NIHRIO ID	13205	**NICE ID**	10144
Developer/Company	Roche Products Ltd	**UKPS ID**	651298

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Risdiplam is in clinical development for the treatment of spinal muscular atrophy (SMA). SMA is a severe, inherited, neuromuscular lethal disease that gets worse over time. Patients with the disease lack a survival motor neuron (SMN) 1 gene and fewer copies of SMN2. This gene produces a protein called SMN protein, which is essential for the normal functioning and survival of motor neurons (nerves from the brain and spinal cord that control muscle movements). SMA is usually diagnosed within the first few months of life for the most severe subtype (type I). Depending on the type of SMA, an individual's physical strength and their ability to walk, eat or breathe can be significantly diminished or lost. SMA causes the muscles to fall into disuse, leading to muscle wasting (atrophy) and weakness, and in its most common form (type I), loss of swallowing function, breathing failure and death within the first few years of life. There is currently no cure for SMA but there are treatments to help manage the symptoms.

Risdiplam is an investigational, oral medicine that is designed to increase SMN protein levels in the central nervous system and throughout the body and thereby reducing the symptoms of the disease. If licensed risdiplam will offer a treatment option for paediatric and adult patients with SMA.

PROPOSED INDICATION

Treatment of spinal muscular atrophy (SMA) in paediatric and adult patients[a]

TECHNOLOGY

DESCRIPTION

Risdiplam (RO7034067, RG7916) is an orally administered, small-molecule survival motor neuron-2 (SMN2) gene pre-mRNA splicing modifier that is systemically distributed and designed to durably increase SMN protein levels in the central nervous system and throughout the body.[1,2]

The SMN protein can be made by two genes, SMN1 and SMN2. Patients with SMA lack a working SMN1 gene but have the SMN2 gene, which mostly produces a short SMN protein that does not work as well as a full-length protein. Risdiplam enables the SMN2 gene to produce a full length and more functional protein, which is able to work normally. This is expected to increase survival of motor neurons and reduce symptoms of the disease.[3,4]

Risdiplam is in clinical development for treatment of SMA in paediatric and adult patients.[b]

In the phase II/III clinical trial for infants with type I SMA (FIREFISH; NCT02913482), there is an exploratory dose finding part (part 1) and a confirmatory part (part 2) which will investigate risdiplam for 24 months at the dose selected in part 1. For part 1, participants will receive multiple ascending doses of risdiplam administered orally once daily for 4 weeks followed by open-label extension phase. For part 2, participants will receive risdiplam administered orally at the dose defined in Part 1 and treatments will continue up to 24-months maximum.[5]
In the phase II/III (SUNFISH; NCT02908685) clinical trial for adult and paediatric participants with type 2 and type 3 SMA, the study consists of two parts, an exploratory dose finding part (Part 1) of risdiplam for 12 weeks and a confirmatory part (Part 2) of risdiplam for 24 months. Part 2 participants will be followed up in open-label extension (OLE) phase.[6]
In the phase II (JEWELFISH; NCT03032172) clinical trial, participants will receive multiple doses of risdiplam orally once daily for 24 months. After 24-month treatment, participants will be offered the opportunity to enter the OLE phase.[7]

INNOVATION AND/OR ADVANTAGES

Currently there is an unmet need for effective treatments that could slow disease progression.[8] Nusinersen is currently licensed in the EU for the treatment of SMA. Nusinersen is given by injection into the spine. Early data indicate that the risdiplam may improve patients' survival and muscle strength compared with nusinersen.[4] Since risdiplam is to be given by mouth, it may be used in a broader population providing a greater convenience to patients and carers.[c,4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

- Risdiplam does not currently have Marketing Authorisation in the EU/UK for any indication.

Ridisplam has the following regulatory designations:

[a] Information provided by Roche Product Ltd
[b] Information provided by Roche Product Ltd
[c] Information provided by Roche Products Ltd UK on UK PharmaScan

- An orphan designation in the EU in February 2019 for the treatment of SMA.[4]
- European Medicines Agency PRIME (PRIority MEdicines) status in December 2018 for SMA.[1]
- A PIM status for SMA by the MHRA in May 2019.[d]

PATIENT GROUP

DISEASE BACKGROUND

Spinal muscular atrophies (SMA) include a group of rare neuromuscular disorders characterized by degeneration of alpha motor neurons in the spinal cord with progressive muscle atrophy, weakness and paralysis.[9,10] SMA is an autosomal recessive neuromuscular disease, meaning two faulty copies of the disease gene, one from each parent, are needed in order to have the condition.[9] SMA is caused by a homozygous deletion or mutation of the survival of motor neuron 1 (SMN1) gene on chromosome 5q (locus 5q13) which encodes survival motor neuron protein (SMN), an essential protein for normal development and functional homeostasis in all species.[11] The defects in the gene SMN leads to degeneration of motor neurones in the spinal cord (this is termed '5q SMA'). 5q SMA is the most common form of SMA. There are also rarer forms of SMA that have different genetic (non-5q SMA) causes.[9]

SMA can be grouped into 5 main types (type 0 to IV), based on the age of onset and the maximum motor function achieved by the person, which correlates with prognosis.[8] SMA affects nerve cells involved in walking, crawling, arm, hand, head and neck movement, breathing and swallowing.[9] Type 0 SMA, the most severe, affects babies before birth. Babies with type 0 SMA do not develop any motor skills and often survive for only a few weeks after birth. Babies with SMA type I have severe muscle weakness which affects movement, swallowing and breathing. In type II SMA, the onset of symptoms is between 7 and 18 months of age, and people with this condition are often severely disabled and unable to walk unaided. Type III SMA is a condition in which varying degrees of muscle weakness appear between age 18 months and 18 years; most people with type III SMA can walk or sit unaided at some point, but many lose mobility over time.[8] SMA type III is less disabling and again many people live long and productive lives. This divided into type IIIa and IIIb with symptoms beginning between 18 months and 3 years for IIIa and after 3 years for IIIb. There is a wide spectrum of severity in SMA with each individual affected differently.[9,12] Type IV SMA, the least severe, affects adults. Adults with type IV SMA may have only mild motor impairment and live a normal lifespan. The clinical experts suggested that of all diagnosed cases of SMA, around 60% are type I and around 40% are types II and III; types 0 and IV are rarely diagnosed.[12]

Sometimes, as well as being diagnosed with a type of SMA, a child may also be described as 'strong' or weak' or having 'early onset' or 'later onset'.[9,10]Life expectancy is very varied between and within the different types of SMA. At present there is no cure. Treatment focuses on managing symptoms and maintaining the best quality of life for as long as possible.[9,12]

CLINICAL NEED AND BURDEN OF DISEASE

Approximately 1 in 40 people carry the faulty SMN1 gene, which means there are around 1.6 million carriers in the UK.[9]
Recent studies indicate that approximately one in every 10,000 babies worldwide are born with a type of SMA, and that type I SMA accounts for approximately 60% of cases. In the UK in 2017, there were 755,043 live births. This suggests that in that year approximately 76 babies were born with a

[d] Information provided by Roche Products Ltd UK

type of 5q SMA and that approximately 46 children were type I. Furthermore, between 1 and 2 people in every 100,000 worldwide have a type of SMA. It is thought that there are between some 1,200 – 2,500 children and adults in the UK living with SMA.[12]

Based on a 2019 European study data on prevalence and incidence of rare diseases, the incidence of proximal SMA type I, II, III and IV is estimated to be 0.26, 1.23, 1.1 and 0.32 per 100,000 respectively.[13] Applying this data to the 2017 mid-year population estimates for England, about 145, 684, 612 and 178 people would have SMA type I, II, III and IV respectively.[14]

In England, in 2017-2018, there were 4,773 finished consultant episodes (FCE) for spinal muscular atrophy and related symptoms (ICD 10 code G12), resulting in 3,182 hospital admissions and 24,830 FCE bed days.[15]

In England, between 2001 and 2014 there were a total of 366,728 deaths with a mention of neurological condition in people aged over 20 years old which is estimated to be 5.6% of all deaths. Between 2012 and 2014, directly age-standardised rate of mortality in persons (aged 20+) with motor neurone disease and spinal muscular atrophy was 5.7 per 100,000.[16]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

There is currently no cure for SMA. A range of options aimed at managing symptoms, reducing complications of muscle weakness and maintaining the best quality of life form the main treatment strategies.[9]
Care for patients with SMA should be tailored according to their current functional status rather than the original classification of SMA types. In SMA, functional status is classified in the form of non-sitters, sitters, and walkers.[17]
SMA is a complex disorder involving different aspects of care and professionals, and each of the aspects is approached as part of a multidisciplinary strategy. In the past families had to coordinate all the assessments and visits but it is now recommended that this should be coordinated by one of the physicians, generally the neurologist or paediatric neurologist, who is aware of the disease course and potential issues. This will allow monitoring of various aspects that are known to be part of the disease progression and, when possible, to provide anticipatory care. These management strategies include neuromuscular rehabilitation, orthopaedic and spinal management, nutritional, swallowing and gastrointestinal management, pulmonary management, palliative care, and medications.[10,18]

CURRENT TREATMENT OPTIONS

In the UK, the only potentially available drug treatment for SMA is nusinersen (Spinraza). Nusinersen has just been recommended by NICE and would be available immediately for type I SMA while it use in type II and III SMA would be available shortly after NICE guidance publication.[19] Nusinersen is available in Scotland if the medical team and family agree that an infant with SMA type I is eligible and may potentially benefit from the treatment.[9]

PLACE OF TECHNOLOGY

If licensed, risdiplam will offer a new treatment option for paediatric and adult patients with SMA.

CLINICAL TRIAL INFORMATION	
Trial	**SUNFISH, NCT02908685, BP39055, EudraCT-2016-000750-35; children and adults aged 2 to 25 years ; Risdiplam vs placebo; Phase II/III**
Sponsor	Hoffmann-La Roche
Status	Ongoing
Source of Information	Trial registry[6,20], manufacturer[1], poster[21]
Location	6 EU countries (incl UK), USA, Canada and other countries
Design	Randomised, double-blind, placebo-controlled
Participants	N=231, aged 2 to 25 years; For Part 1: Type 2 or 3 SMA ambulant or non-ambulant. For Part 2: Type 2 or 3 SMA non-ambulant; Confirmed diagnosis of 5q-autosomal recessive SMA, for Part 2: 1) revised upper limb module (RULM) entry item A greater than or equal to [>=] 2; 2) ability to sit independently as assessed by item 9 of the MFM; Negative blood pregnancy test at screening and agreement to comply with measures to prevent pregnancy and restrictions on sperm donation.
Schedule	Study is divided into: • Experimental: Part 1 Group A: Adolescents and Adults (risdiplam) Adolescent and adult participants aged 12-25 years will receive risdiplam for 12 weeks. Once 12-week treatment is completed and Part 2 dose is selected, participants will be switched to Part 2 dose and will be followed up in open-label extension (OLE) phase. Placebo Comparator: Part 1 Group A: Adults and Adolescents (Placebo) Adolescent and adult participants aged 12-25 years will receive placebo matching to risdiplam for 12 weeks. Once 12-week treatment is completed and Part 2 dose is selected, participants will be switched to Part 2 dose and will be followed up in OLE phase. • Placebo Comparator: Part 1 Group B: Children Children aged 2-11 years will receive placebo matching to risdiplam for 12 weeks. Once 12-week treatment is completed and Part 2 dose is selected, participants will be switched to Part 2 dose and will be followed up in OLE phase. Experimental: Part 1 Group B: Children Children aged 2-11 years will receive risdiplam for 12 weeks. Once 12-week treatment is completed and Part 2 dose is selected, participants will be switched to Part 2 dose and will be followed up in OLE phase. • Placebo Comparator: Part 2: Participants aged 2-25 years will receive placebo matching to risdiplam. After 12 months of treatment with placebo, participants will be switched to risdiplam and treatment will then continue until Month 24. After 24-month treatment, participants will be offered the opportunity to enter the OLE phase. Interventions: Experimental: Part 2: Participants aged 2-25 years will receive risdiplam at the dose selected based on the results from Part 1 of the study, for 24 months. After 24-month treatment, participants will be offered the opportunity to enter the OLE phase.

	Risdiplam/ placebo will be administered orally (via mouth) or through a feeding tube (naso-gastric or gastrostomy tube).
Follow-up	Treatments will continue up to 24-months. After 24-month treatment, participants will be offered the opportunity to enter the OLE phase.
Primary Outcomes	• Part 2: Change from baseline in the Total Motor Function Measure 32 (MFM-32) score at month 12 [Time Frame: baseline (day -1) and month 12] • Part 1: Recommended part 2 dose of risdiplam [time frame: 120 days]
Secondary Outcomes	• Survival of motor neuron 2 (smn2) messenger ribonucleic acid (MRNA) levels in blood [time frame: part 2: days -1, 1, 7, 28, 120, 246, 365, 729] • survival of motor neuron (SMN) protein levels in blood [time frame: part 2: days -1, 7, 28, 120, 246, 365, 729] • Change from baseline in total score of Hammersmith functional motor scale expanded (HFMSE) at month 12 [time frame: baseline (day-1) and month 12] • Change from baseline in the total score of the RULM at month 12 [time frame: baseline (day-1) and month 12] • Percentage of participants who achieve stabilization or improvement (defined as >= 0) in the total motor function measure (MFM) score at month 12 [time frame: baseline (day-1) and month 12] • Change from baseline in the best sniff nasal inspiratory pressure (SNIP) at month 12 [time frame: baseline (day-1) and month 12] • Change from baseline in forced expiratory volume in 1 second (fev1) at month 12 [time frame: baseline (day-1) and month 12] • Change from baseline in forced vital capacity (FVC) at month 12 [time frame: baseline (day-1) and month 12] • Change from baseline in the peak cough flow (PCF) at month 12 [time frame: baseline (day-1) and month 12] • Change from baseline in maximal inspiratory pressure (MIP) at month 12 [time frame: baseline (day-1) and month 12] • Change from baseline in maximal expiratory pressure (MEP) at month 12 [time frame: baseline (day-1) and month 12] • Percentage of participants who experience at least one disease-related adverse event [time frame: baseline up to month 12] • Part 1 and 2: maximum plasma concentration (Cmax) of risdiplam [time frame: part 1 and 2: 1, 2, 4, 6 hours post dose on day 1; pre-dose (hour 0) on days 7, 14, 56 (part 2), 120, 246, 490, 729; pre-dose (hour 0) and 1, 2, 4, 6 hours post dose on days 28, 56 (part 1), 365, 609] • Part 1 and 2: area under the curve (AUC) of risdiplam [time frame: part 1 and 2: 1, 2, 4, 6 hours post dose on day 1; pre-dose (hour 0) on days 7, 14, 56 (part 2), 120, 246, 490, 729; pre-dose (hour 0) and 1, 2, 4, 6 hours post dose on days 28, 56 (part 1), 365, 609] • Part 1 and 2: concentration at the end of a dosing interval (Ctrough) of risdiplam [time frame: part 1 and 2: pre-dose (hour 0) on days 7, 14, 28, 56, 120, 246, 365, 490, 609, 729] • Percentage of participants with adverse events (AEs) and serious adverse events (saes) [time frame: baseline up to 24 months] • Change from baseline in the MFM domain 1 (d1) score at month 12 [time frame: baseline (day-1) and month 12] • Change from baseline in the MFM domain 2 (d2) score at month 12 [time frame: baseline (day-1) and month 12]

	• Change from baseline in the MFM Domain 3 (d3) score at month 12 [time frame: baseline (day-1) and month 12] • Change from baseline in the total combined scores of MFM domains 1 and 2 at month 12 [time frame: baseline (day-1) and month 12] • Percentage of participants with suicidal ideation or behaviour based on Columbia-suicide severity rating scale (C-SSRS) score [time frame: baseline (day-1), day 120, day 248, day 386, day 647, day 729] • Percentage of participants by clinical global impression of change (CGI-C) scale ratings [time frame: month 12] • Change from baseline in SMA independence scale (SMAIS) total score at month 12 [time frame: baseline (day-1) and month 12] • Percentage of participants who achieve an improvement of at least one standard error of measurement on the total MFM score at month 12 [time frame: baseline (day-1) and month 12]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as May 2019.

Trial	**FIREFISH, NCT02913482, BP39056, EudraCT-2016-000778-40; children aged 1-7 months; Risdiplam; Phase II/III**
Sponsor	Hoffmann-La Roche
Status	Ongoing
Source of Information	Trial registry[5,22], poster[23], manufacturer[3]
Location	7 EU countries (incl UK), USA and other countries
Design	Non-randomised, open label
Participants	N=61, aged 1-7 months; Clinical history, signs or symptoms attributable to Type 1 SMA with onset after 28 days but prior to the age of 3 months; Gestational age of 37 to 42 weeks; Confirmed diagnosis of 5q-autosomal recessive SMA; Participants has two survival motor neuron 2 (SMN2) gene copies, as confirmed by central testing; Body weight greater than or equal to (>=) third percentile for age, using appropriate country-specific guidelines; Receiving adequate nutrition and hydration (with or without gastrostomy) at the time of screening, in the opinion of the investigator; Adequately recovered from any acute illness at the time of screening and considered well-enough to participate in the opinion of the Investigator
Schedule	Study is divided into: Part 1 (Dose Finding): Participants will receive multiple ascending doses of risdiplam administered orally once daily for 4 weeks followed by open-label extension phase. Part 2 (Confirmatory): Participants will receive risdiplam administered orally at the dose defined in Part 1 of the study.
Follow-up	Treatments will continue maximum up to 24-months.

Primary Outcomes	• Recommended Part 2 Dose of risdiplam [Time frame: 2 weeks] • Part 2: Percentage of infants who are sitting without support at 12-months of treatment assessed by the gross motor scale of the Bayley scales of infant and toddler development third edition (BSID-III) [Time frame: month 12]
Secondary Outcomes	• Percentage of participants with adverse events (AE) and serious adverse events (SAEs) [Time frame: baseline up to 25 months] • Part 1: maximum plasma concentration (Cmax) of risdiplam [time frame: pre-dose (PrD) (Hour 0) and 2, 4, 6, hour post-dose (PoD) on Days 1, 28, 84, 364, 546, 728; PrD on Day 2; PrD and 4 hours PoD on Days 7, 14, 56, 119, 182, 245, 301, 427, 490, 609, 672] • Part 2: Maximum plasma concentration (Cmax) of risdiplam [Time frame: 2, 4, 6, hours PoD on day 1; PrD (hour 0) on days 2, 14, 119, 245, 364, 427, 490, 609, 728; PrD and 2, 4, 6 hours PoD on days 28, 56, 182, 301, 546, 672] • Part 1: Area Under the Curve (AUC) of risdiplam [Time Frame: PrD (Hour 0) and 2, 4, 6, hour PoD on days 1, 28, 84, 364, 546, 728; PrD on day 2; PrD and 4 hours PoD on days 7, 14, 56, 119, 182, 245, 301, 427, 490, 609, 672] • Part 2: Area Under the Curve (AUC) of risdiplam [Time Frame: 2, 4, 6, hours PoD on Day 1; PrD (Hour 0) on Days 2, 14, 119, 245, 364, 427, 490, 609, 728; PrD and 2, 4, 6 hours PoD on Days 28, 56, 182, 301, 546, 672] • Part 1: concentration at the end of a dosing interval (Ctrough) of risdiplam [Time Frame: PrD (Hour 0) Days 1, 2, 7, 14, 28, 56, 84, 119, 364, 546] • Part 2: Concentration at the end of a dosing interval (Ctrough) of risdiplam [Time Frame: PrD (Hour 0) on Days 2, 14, 28, 56, 119, 182, 301, 546, 672] • Time to Death [Time Frame: Baseline up to 25 Months] • Time to permanent ventilation [time frame: month 12, month 24] • Survival of Motor Neuron (SMN) protein levels in blood [Time Frame: Days 1, 14 (Part 1 only), 28, 119, 245, 364, 609, 728] • Survival Motor Neuron (SMN) Messenger Ribonucleic Acid (mRNA) Levels in Blood [Time Frame: Days 1, 14 (Part 1 only), 28, 245, 364, 609, 728] • Change From Baseline in the Total Raw Score of the BSID-III Gross Motor Scale at Month 12 and 24 [Time Frame: Baseline, Month 12, Month 24] • Percentage of Infants who Achieve the Attainment Levels of the Motor Milestones Assessed in the Hammersmith Infant Neurological Examination Module 2 (HINE-2) at Month 12 and 24 [Time Frame: Month 12, Month 24] • Percentage of Infants who Achieve Highest Motor Milestone as Assessed in the BSID-III Gross Motor Scale [Time Frame: Month 12, Month 24] • Percentage of Infants who Achieve a Score of 40 or Higher in the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) at Month 12 [Time Frame: Month 12] • Percentage of Infants who Achieve a Reduction of At Least 30 Degrees in Phase Angle From Baseline, as Measured by Respiratory Plethysmography (RP) at Month 12 [Time Frame: Baseline, Month 12] • Time to Death or Permanent Ventilation, Whichever Occurred First [Time Frame: Baseline up to 25 Months] • Percentage of Infants who are Alive Without Permanent Ventilation at Month 12 and 24 [Time Frame: Month 12, Month 24] • Percentage of Infants who are Sitting Without Support for 5 Seconds at 24-months [Time Frame: Month 24] • Percentage of Infants who Stand Alone as Assessed in Item 40 of the BSID-III Gross Motor Scale at Month 24 [Time Frame: Month 24] • Percentage of Infants who Walk Alone as Assessed in Item 42 of the BSID-III Gross Motor Scale at Month 24 [Time Frame: Month 24]

	• Percentage of Infants who are Sitting Without Support for 30 Seconds at 24-months [Time Frame: Month 24] • Percentage of Infants that are Crawling at 24 Months [Time Frame: Month 24] • Proportion of Infants Achieving an Increase of >/= 4 Points from Baseline CHOP-INTEND Score [Time Frame: Baseline, 8 Months, 12 Months] • Proportion of Infants Achieving Head Control (Defined as a Score of >/= 3 for CHOP-INTEND Item 12) [Time Frame: 8, 12, and 24 Months] • Proportion of Infants not Requiring Respiratory Support (Invasive or Non-Invasive) at 12 and 24 Months [Time Frame: Months 12, Month 24] • Proportion of infants able to feed orally at 12 and 24 months [Time Frame: month 12, month 24]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as September 2019.

Trial	**JEWELFISH, NCT03032172, BP39054, EudraCT- 2016-004184-39; children and adults aged 6 months to 60 years; Risdiplam; Phase II**
Sponsor	Hoffmann-La Roche
Status	Ongoing
Source of Information	Trial registry[7]
Location	Italy, Switzerland, United States
Design	Single group assignment, open label
Participants	N=125, aged 6 months to 60 years ; Confirmed diagnosis of 5q-autosomal recessive SMA; Previous enrolment in Study BP29420 (Moonfish) with the splicing modifier RO6885247 or previous treatment with any of the following: 1.) Nusinersen (defined as having received >= 4 doses of nusinersen, provided that the last dose was received >= 90 days prior to screening) or 2.) Olesoxime (provided that the last dose was received <= 12 months and >= 90 days prior to screening); Adequately recovered from any acute illness at the time of screening and considered well enough to participate in the opinion of the Investigator; For women of childbearing potential: negative blood pregnancy test at screening, agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs; For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm; For patients aged 2 years or younger at screening: 1.) Parent or caregiver of patient is willing to consider nasogastric, naso-jejunal or gastrostomy tube placement, as recommended by the investigator, during the study (if not already in place at the time of screening) to maintain safe hydration, nutrition and treatment delivery. 2.) Parent or caregiver of patient is willing to consider the use of non-

	invasive ventilation, as recommended by the Investigator during the study (if not already in place at the time of screening).
Schedule	Participants will receive multiple doses of risdiplam orally once daily for 24 months
Follow-up	Treatments will continue up to 24-months. After 24-month treatment, participants will be offered the opportunity to enter the OLE phase
Primary Outcomes	• Percentage of participants with Adverse Events (AEs) and Serious AEs (SAEs) with severity determined according to national cancer institute common terminology criteria for adverse events scale, V 4.0 [Time Frame: Baseline up to 5 years] • Percentage of participants with emergence or worsening of symptoms as assessed using Columbia suicide severity rating scale (C-SSRS) (adult version for adults and adolescents, paediatric version for patients aged 6-11 years) [Time Frame: aged 6 to 60 years: screening, day-1, day 182, 364, 546, 728, at extension phase and follow-up visit 1 (Week 112)] • Percentage of participants with protocol defined clinically significant changes in ophthalmological assessments [Time Frame: baseline up to 5 years] • Percentage of participants with protocol defined clinically significant changes in neurological assessments [time frame: baseline up to 5 years] • tanner staging among all participants aged from 9 to 17 years [time frame: baseline up to 5 years] • Mean plasma concentration of RO7034067 [time frame: aged 2-60 years: at pre-defined intervals up to week 104; aged 6 months to 2 years: at pre-defined intervals up to extension phase (up to 4 years after the last patient is enrolled in the study)] • Maximum plasma concentration (Cmax) of RO7034067 [time frame: aged 2-60 years: at pre-defined intervals up to week 104; aged 6 months to 2 years: at pre-defined intervals up to extension phase (up to 4 years after the last patient is enrolled in the study)] • Area under the plasma concentration versus curve (AUC) of RO7034067 [Time frame: aged 2-60 years: at pre-defined intervals up to week 104; aged 6 months to 2 years: at pre-defined intervals up to extension phase (up to 4 years after the last patient is enrolled in the study)] • Concentration of RO7034067 at the end of dosing interval (Ctrough) [Time Frame: Aged 2-60 years: at pre-defined intervals up to Week 104; aged 6 months to 2 years: at pre-defined intervals up to extension phase (up to 4 years after the last patient is enrolled in the study)] • Mean plasma concentration of RO7034067 metabolite [Time Frame: Aged 2-60 years: at pre-defined intervals up to week 104; aged 6 months to 2

	years: at pre-defined intervals up to extension phase (up to 4 years after the last patient is enrolled in the study)] • Cmax of RO7034067 metabolite [Time Frame: Aged 2-60 years: at pre-defined intervals up to Week 104; aged 6 months to 2 years: at pre-defined intervals up to extension phase (up to 4 years after the last patient is enrolled in the study)] • AUC of RO7034067 metabolite [Time Frame: Aged 2-60 years: at pre-defined intervals up to Week 104; aged 6 months to 2 years: at pre-defined intervals up to extension phase (up to 4 years after the last patient is enrolled in the study)] • Ctrough of RO7034067 metabolite [Time Frame: Aged 2-60 years: at pre-defined intervals up to Week 104; aged 6 months to 2 years: at pre-defined intervals up to extension phase (up to 4 years after the last patient is enrolled in the study
Secondary Outcomes	• SMN messenger Ribonucleic Acid (mRNA) Level in Blood [Time Frame: Aged 2 to 60 Years: Days -1, 1, 28, 91, 183, 365, 729, at early withdrawal, and at follow-up visit 1; Patients Aged 6 Months to <2 Years: Day 1, 28, 182, 364 and 728 and at early withdrawal] • SMN Protein Levels in Blood [Time Frame: Aged 2 to 60 Years: Day -1, Day 28, 91, 183, 365, 729, at early withdrawal, and at follow-up visit 1; Patients Aged 6 Months to <2 Years: Day 1, 28, 182, 364 and 728 and at early withdrawal] No quality of life measurement included in trial outcomes
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as December 2020.

ESTIMATED COST

The cost of risdiplam is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Nusinersen for treating spinal muscular atrophy (GID-TA10281). Expected publication date TBC.

- NICE highly specialised technology guidance in development. Onasemnogene abeparvovec for treating spinal muscular atrophy type 1 (ID1473). Expected publication date TBC.
- NICE guideline. Motor neurone disease: assessment and management (NG42). February 2016.
- NICE quality standard. Motor neurone disease (QS126). July 2016.
- NICE interventional procedures guidance. Intramuscular diaphragm stimulation for ventilator dependent chronic respiratory failure caused by motor neurone disease (IPG593). September 2017.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Urgent Clinical Commissioning Policy Statement: Nusinersen for genetically confirmed Spinal Muscular Atrophy (SMA) type 1 for eligible patients under the Expanded Access Programme (EAP). 170038P. March 2018.
- NHS England. Service Specification: Neuropathology. 16074/S.
- NHS England. 2013/14 NHS Standard Contract for Neurosciences: Specialised Neurology (Adult). D04/S/a.
- NHS England. 2013/14 NHS Standard Contract for paediatric Neurosciences – Neurology. E09/S/b.
- NHS England. 2013/14 Standard Contract for Diagnostic Service for Rare Neuromuscular Disorders (All ages). D04/S(HSS)/a.

OTHER GUIDANCE

- SMA Care Group. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopaedic and nutritional care. 2018.[10]
- SMA Care Group. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. 2018.[18]
- Ching et al 2007. Consensus statement for standard of care in spinal muscular atrophy.[24]

ADDITIONAL INFORMATION

REFERENCES

1 F. Hoffmann-La Roche Ltd. *Media Release; PRIME designation granted by European Medicines Agency for Roche's risdiplam for treatment of spinal muscular atrophy (SMA).* 2018. Available from: https://www.roche.com/media/releases/med-cor-2018-12-17.htm [Accessed 15 April 2019].

2 Poirier A, Weetall M, Heinig K, Bucheli F, Schoenlein K, Alsenz J, et al. Risdiplam distributes and increases SMN protein in both the central nervous system and peripheral organs. *Pharmacol Res Perspect*. 2018 Dec;6(6):e00447. Available from: https://doi.org/10.1002/prp2.447.

3 F. Hoffmann-La Roche Ltd. *Media Release; Roche announces new data for risdiplam in Spinal Muscular Atrophy (SMA) at the World Muscle Society Congress.* 2018. Available from: https://www.roche.com/media/releases/med-cor-2018-10-03.htm [Accessed 16 April 2019].
4 European Medicines Agency. *EU/3/19/2145.* 2019. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3192145 [Accessed 16 April 2019].
5 ClinicalTrials.gov. *Investigate Safety, Tolerability, PK, PD and Efficacy of Risdiplam (RO7034067) in Infants With Type1 Spinal Muscular Atrophy (FIREFISH)*. *Trial ID: NCT02913482*. Status: Ongoing. Available from: https://clinicaltrials.gov/ct2/show/NCT02913482 [Accessed 16 April 2019].
6 ClinicalTrials.gov. *A Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of Risdiplam (RO7034067) in Type 2 and 3 Spinal Muscular Atrophy (SMA) Participants (SUNFISH)*. *Trial ID: NCT02908685*. Status: Ongoing. Available from: https://clinicaltrials.gov/ct2/show/NCT02908685 [Accessed 16 April 2019].
7 ClinicalTrials.gov. *A Study of Risdiplam (RO7034067) in Adult and Pediatric Participants With Spinal Muscular Atrophy (Jewelfish)*. *Trial ID: NCT03032172*. Status: Ongoing. Available from: https://clinicaltrials.gov/ct2/show/NCT03032172 [Accessed 16 April 2019].
8 National Institute for Health and Care Excellence. *Nusinersen for treating spinal muscular atrophy.* 2018. Available from: https://www.nice.org.uk/guidance/GID-TA10281/documents/appraisal-consultation-document [Accessed 29 April 2019].
9 Spinal Muscular Atrophy UK. *What is Spinal Muscular Atrophy?* Available from: https://smauk.org.uk/what-is-spinal-muscular-atrophy [Accessed 15 April 2019].
10 Mercuri E, Finkel RS, Muntoni F, Wirth B, Montes J, Main M, et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. *Neuromuscular Disorders*. 2018 2018/02/01/;28(2):103-15. Available from: https://doi.org/10.1016/j.nmd.2017.11.005.
11 Ratni H, Ebeling M, Baird J, Bendels S, Bylund J, Chen KS, et al. Discovery of Risdiplam, a Selective Survival of Motor Neuron-2 (SMN2) Gene Splicing Modifier for the Treatment of Spinal Muscular Atrophy (SMA). *Journal of Medicinal Chemistry*. 2018 2018/08/09;61(15):6501-17. Available from: https://doi.org/10.1021/acs.jmedchem.8b00741.
12 Spinal Muscular Atrophy UK. *Summary information about SMA.* Available from: https://smauk.org.uk/summary-information-about-sma [Accessed 15 April 2019].
13 Orphanet. *Prevalence and incidence of rare diseases: Bibliographic data Prevalence, incidence or number of published cases listed by diseases (in alphabetical order).* 2019. Available from: https://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf [Accessed 15 April 2019].
14 Office for National Statistics. *Population Estimates for UK, England and Wales, Scotland and Northern Ireland: mid-2017.* 2017. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland [Accessed Downloaded 24 August 2018].
15 NHS Digital. *Hospital Admitted Patient Care Activity, 2017-18.* 2017. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2017-18 [Accessed 17 December 2018].
16 Public Health England National Neurology Intelligence Network. *Deaths associated with neurological conditions in England 2001 to 2014.* Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/683112/Deaths_Associated_with_neurological_conditions_dataset.xlsx [Accessed 15 April 2019].
17 TREAT-NMD Neuromuscular Network. *Standards of Care for Spinal Muscular Atrophy.* 2007. Available from: https://smauk.org.uk/files/files/General%20Information%20and%20Support/sma_soc_brochure_en.pdf [Accessed 15 April 2019].
18 Finkel RS, Mercuri E, Meyer OH, Simonds AK, Schroth MK, Graham RJ, et al. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications,

supplements and immunizations; other organ systems; and ethics. *Neuromuscular Disorders*. 2018 2018/03/01/;28(3):197-207. Available from: https://doi.org/10.1016/j.nmd.2017.11.004.

19 National Institute For Health And Care Excellence. *NICE recommends first ever treatment for children with rare muscle-wasting condition.* Available from: https://www.nice.org.uk/news/article/nice-recommends-first-ever-treatment-for-children-with-rare-muscle-wasting-condition [Accessed 20 May 2019].

20 EU Clinical Trials Register. *A study to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of RO7034067 in type 2 and 3 spinal muscular atrophy patients*. *Trial ID: 2016-000750-35*. Status: Ongoing. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-000750-35/BE [Accessed 20 May 2019].

21 Mercuri E, Baranello G, Kirschner J, Servais L, Goemans N, Pera M, et al. *SUNFISH Part 1: Risdiplam (RG7916) treatment results in a sustained increase of SMN protein levels and improvement in motor function in patients with Type 2 or 3 SMA.* 2018. Available from: https://medically.roche.com/content/dam/pdmahub/non-restricted/neurology/wms-2018/WMS_2018_SUNFISH_risdiplam_poster_Mercuri.pdf [Accessed 16 April 2019].

22 EU Clinical Trials Register. *A Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of RO7034067 in Infants with Type1 Spinal Muscular Atrophy*. *Trial ID: 2016-000778-40*. Status: Ongoing. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2016-000778-40/BE [Accessed 20 May 2019].

23 Baranello G, Servais L, Day J, Deconinck N, Mercuri E, Klein A, et al. *FIREFISH: Risdiplam (RG7916) improves motor function in babies with Type 1 SMA.* 2018. Available from: https://medically.roche.com/en/search/pdfviewer.02a9d2b9-908e-4900-bbb2-ef66124f1f00.html?cid=slprxx1810nexxwms2018risdiplamrg7916 [Accessed 16 April 2019].

24 Wang CH, Finkel RS, Bertini ES, Schroth M, Simonds A, Wong B, et al. Consensus Statement for Standard of Care in Spinal Muscular Atrophy. *Journal of Child Neurology*. 2007;22(8):1027-49. Available from: https://doi.org/10.1177/0883073807305788.

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.