Roche - Rainbowfish

An Open-Label Study of Risdiplam in Infants With Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy

Summary

This is a Phase 2 trial that looks at the safety, efficacy, and tolerability of Risdiplam in infants aged from birth to 6 weeks old. This study involves infants who have been diagnosed with SMA, but do not yet show any symptoms (pre-symptomatic). Risdiplam will be given orally (by mouth) to each participant, once daily, for 2 years. After this, participants will continue taking Risdiplam in an open-label extension for 3 years with follow-up, resulting in at least 5 years of treatment for each participant.

Study Number: NCT03779334

Description by Hoffmann-La Roche

The study is an open-label, single-arm, multicenter clinical study to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of risdiplam in infants aged from birth to 6 weeks who have been genetically diagnosed with SMA but are not yet presenting with symptoms. There will be a screening, treatment, open-label extension (OLE) and a follow-up. All participants will receive risdiplam orally once daily for 2 years followed by an OLE phase of at least 3 years and a follow-up, for a total treatment duration of at least 5 years for each participant enrolled.

Primary Outcome Measures

- Percentage of participants with two copies of the survival motor neuron (SMN) 2 gene (excluding the known SMN2 gene modifier mutation c.859G>C) and baseline compound muscle action potential (CMAP) >=1.5 millivolt (mV) who are sitting without support [Time Frame: At Month 12]
- Sitting is defined as "sits without support for 5 seconds" as assessed in Item 22 of the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) Gross Motor Scale

Secondary Outcome Measures

- Percentage of participants developing clinically manifested SMA [Time Frame: At Month 12 and 24]
- Time to permanent ventilation and/or death [Time Frame: Up to 7 years]
- Percentage of participants who are alive without permanent ventilation [Time Frame: At Month 12 and 24]
- Percentage of participants alive [Time Frame: At Month 12 and 24]
- Percentage of participants who achieve the attainment level of the motor milestones as assessed in the Hammersmith Infant Neurological Examination-2 (HINE-2) [Time Frame: At Month 12 and 24]

  HINE-2 assessment includes head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking
- Percentage of participants with two copies of the SMN2 gene sitting without support for 5 seconds (independent of the CMAP value at baseline). [Time Frame: At Month 12]

  Assessed with BSID-III Gross Motor Scale.
- Percentage of participants sitting without support for 5 seconds [Time Frame: At Month 24]

  Assessed with BSID-III Gross Motor Scale
- Percentage of participants sitting without support for 30 seconds [Time Frame: At Month 12 and 24]

  Assessed with BSID-III Gross Motor Scale
- Percentage of participants standing for at least 3 seconds [Time Frame: At Month 24]

  Assessed with BSID-III Gross Motor Scale
- Percentage of participants walking (takes at least 3 steps) [Time Frame: At Month 24]

  Assessed with BSID-III Gross Motor Scale
- Percentage of participants demonstrating the ability to achieve a scaled score on BSID-III Gross Motor Subtests within 1.5 standard deviations of chronological reference standard [Time Frame: At Month 24 and 42]

  Assessed through BSID-III Gross Motor Scale
- Change from baseline score in the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) motor function scale [Time Frame: At Month 12]
- Percentage of participants who achieve a score of 40 or higher, 50 or higher, and 60 or higher in the CHOP INTEND motor function scale [Time Frame: At Month 12]
- Percentage of participants who meet CHOP INTEND stopping criteria at any point [Time Frame: Up to Month 24]
- Change from baseline in the Hammersmith Functional Motor Scale Expanded (HFMSE) score [Time Frame: At Month 60]
- Number and percentage of participants within 3rd percentile of normal range for weight-for-age, length/height-for-age and weight-for-length/height [Time Frame: At Month 12, 24, 36, 48 and 60]

  Based on the WHO Child Growth Standards (WHO 2019)

AUSNMD

Trial Status
Fully recruited

Locations
Sydney - Children's Hospital, Fully recruited

Trial Sponsor
Hoffmann-La Roche

Age
Less than 6 weeks

SMASubtype
Type 1

SMN2 Copy Numbers Required
No restriction

Mode of delivery
Oral

MRI
No

Phase
2

Length Of Participation
Up to 7 years

Recruitment Target
25

Therapeutic Category
SMN2 Gene upregulation

- Number and percentage of participants within 3rd percentile of normal range for head circumference-for-age [Time Frame: At Month 12 and 24]

  Based on the WHO Child Growth Standards (WHO 2019)

- Change from baseline percentiles for weight-for-age, length/height-for-age, and weight-for- length/height [Time Frame: At Month 12, 24, 36, 48 and 60]
- Change from baseline percentiles for head circumference- for-age [Time Frame: At Month 12 and 24]
- Change from baseline in chest circumference [Time Frame: At Month 12 and 24]
- Ratio between chest and head circumferences [Time Frame: At Month 12 and 24]
- Percentage of participants with the ability to swallow and to feed orally [Time Frame: At Month 12, 24, 36, 48 and 60]
- Change from baseline in compound muscle action potential (CMAP) amplitude [Time Frame: At Month 12 and 24]

  Measured by CMAP

- Measurement of pharmacodynamic marker levels in blood [Time Frame: Day 1, 56, 196, 364, 728 and at early withdrawal]
- Percentage of participants with adverse events [Time Frame: Up to 7 years]

  Adverse event severity is determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5 (NCI CTCAE) v5

- Ophthalmological examination as appropriate for age [Time Frame: Up to 7 years]
- Plasma concentration of risdiplam and its metabolites to characterize the PK profile [Time Frame: Up to 7 years]

Can I take part?

Inclusion Criteria

- Males and females aged from birth (1 day) to 6 weeks (42 days) of age at the time of first dose (Day 1); a minimum age of 7 days at first dose is required for the first infant to be enrolled
- Gestational age of 37-42 weeks for singleton births; gestational age of 34-42 weeks for twins
- Body weight >= 3rd percentile for age, using appropriate country-specific guidelines
- Genetic diagnosis of 5q-autosomal recessive SMA, including confirmation of homozygous deletion or compound heterozygosity predictive of loss of function of the SMN1 gene
- Absence of clinical signs or symptoms at screening (Day -42 to Day -2) or at baseline (Day -1) that are, in the opinion of the investigator, strongly suggestive of SMA
- Receiving adequate nutrition and hydration at the time of screening, in the opinion of the investigator
- Adequately recovered from any acute illness at baseline and considered well enough to participate in the study, in the opinion of the investigator
- Able and expected to be able to safely travel to the study site for the entire duration of the study and in accordance to the frequency of required study visits, in the opinion of the investigator
- Able to complete all study procedures, measurements, and visits, and the parent (or caregiver), in the opinion of the investigator, has adequately supportive psychosocial circumstances
- Parent (or caregiver) is willing to consider nasogastric, naso-jejunal, or gastrostomy tube placement during the study to maintain safe hydration, nutrition, and treatment delivery, if recommended by the investigator
- Parent (or caregiver) is willing to consider the use of non-invasive ventilation during the study, if recommended by the investigator

Exclusion Criteria

- Concomitant or previous participation in any investigational drug or device study at any time
- Concomitant or previous administration of an SMN2-targeting antisense oligonucleotide, SMN2-splicing modifier, or gene therapy either in a clinical study or as part of medical care
- Presence of significant concurrent syndromes or diseases
- In the opinion of the investigator, inadequate venous or capillary blood access for the study procedures
- Requiring invasive ventilation, tracheostomy or awake non-invasive ventilation
- Awake hypoxemia (SaO2 < 95%) with or without ventilator support
- Multiple or fixed contractures and/or hip subluxation or dislocation at birth
- Systolic blood pressure or diastolic blood pressure or heart rate considered to be clinically significant by the investigator
- Presence of clinically relevant ECG abnormalities before study drug administration; corrected QT interval using Bazett's method > 460 ms; personal or family history (first degree relatives) of congenital long QT syndrome indicating a safety risk for patients as determined by the investigator. First-degree

atrioventricular block or isolated right bundle branch block are allowed

- The infant (and the mother, if breastfeeding the infant) taking any inhibitor of CYP3A4 taken within 2 weeks, any inducer of CYP3A4 taken within 4 weeks, any OCT 2 and MATE substrates within 2 weeks and known FMO1 or FMO3 inhibitors or substrates
- Clinically significant abnormalities in laboratory test results
- Ascertained or presumptive hypersensitivity to risdiplam or to the constituents of its formulation
- Treatment with oral salbutamol or another beta-2 adrenergic agonist taken orally for SMA is not allowed. Use of inhaled beta-2 adrenergic agonists is allowed
- Infants exposed to drugs with known retinal toxicity given to mothers during pregnancy (and lactation) should not be enrolled. Anticipated need for drugs known to cause retinal toxicity during the study.
- Diagnosis of ophthalmic diseases

Other inclusion/exclusion criteria applies.

For contact details and to find out more, please refer to ausnmd.org.