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HEALTH TECHNOLOGY BRIEFING
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rAAVrh74.MHCK7.micro-dystrophin for Duchenne muscular dystrophy

NIHRIO ID	24153	**NICE ID**	10167
Developer/Company	Roche Products Ltd	**UKPS ID**	658531

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

SUMMARY

rAAVrh74.MHCK7.micro-dystrophin is a medicinal product in clinical development for the treatment of children aged 3 months to 7 years with Duchenne muscular dystrophy (DMD). DMD is a rare progressive neuromuscular disorder caused by a gene mutation (change). DMD is caused by an absence of dystrophin, a protein that helps keep muscle cells intact. It affects mainly boys and symptoms often start before the age of five. DMD is a fatal condition with no cure. It causes progressive muscle weakness and often leads to loss of walking ability by the age of twelve, as well as problems with the heart and lungs. rAAVrh74.MHCK7.micro-dystrophin is a type of gene therapy, which delivers a functional version of the dystrophin gene via intravenous injection. rAAVrh74.MHCK7.micro-dystrophin, is based on a viral carrier to deliver a shorter version of the DMD gene, called micro-dystrophin. This shorter gene contains enough information to produce a protein that restores the function of dystrophin. If licensed, rAAVrh74.MHCK7.micro-dystrophin will provide a treatment option for male patients aged 3 months to 7 years with DMD.

PROPOSED INDICATION

For the treatment of male ambulatory DMD patients aged 3 months to 7 years old.[1,2]

TECHNOLOGY

DESCRIPTION

Gene therapy using rAAVrh74.MHCK7.micro-dystrophin (SRP-9001) is in clinical development to increase the production of micro-dystrophin, a shorter version of the dystrophin protein that is missing in DMD patients. Using an adeno-associated virus, or AAV, to deliver micro-dystrophin, this shorter gene contains enough information to produce and restore the function of dystrophin.[3] The therapy directs the delivery of the micro-dystrophin gene specifically to muscle tissue in particular the heart muscle (while avoiding other tissues), which is important as around 90% DMD patients develop heart disease and many die from it.[4,5] Preclinical data suggests that intravascular AAV micro-dystrophin delivery can significantly ameliorate muscle pathology, enhance muscle force, and attenuate dystrophic cardiomyopathy in animals.[3]

rAAVrh74.MHCK7.micro-dystrophin is in clinical development for the treatment of male ambulatory DMD patients aged 3 months to 7 years old.[1,2] In the phase I/II clinical trial cohort A (patients aged 3 months to 3 years) are given prednisolone 1mg/kg for 30 days, whilst monitoring immune response, and rAAVrh74.MHCK7.micro-dystrophin intravenously 2x1014 vg/kg in 10 mL/kg. If these patients display negative immune response on day 30, they are weaned off prednisolone over one week. In cohort B (patients aged 4 to 7 years) are maintained on corticosteroids throughout the trial and given rAAVrh74.MHCK7.micro-dystrophin intravenously 2x1014 vg/kg in 10 mL/kg.[1]

In the phase II clinical trial all subjects will be on a stable dose of oral corticosteroids for at least 12 weeks before the screening visit. On Day 1, subjects will be given rAAVrh74.MHCK7.micro-dystrophin (1.33×1014 vg/kg) by single IV infusion. Subjects will remain on their stable dose of oral corticosteroids (except for modifications to accommodate changes in weight) through the remainder of the study.[a]

INNOVATION AND/OR ADVANTAGES

Current treatment options do not treat the underlying cause of the disease and focus on alleviating symptoms and maintaining muscle strength.[6] rAAVrh74.MHCK7.micro-dystrophin is designed to address the underlying cause of DMD in patients by enabling the production of a shorter dystrophin protein.[3]

[a] Information provided by Roche Products Ltd

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

rAAVrh74.MHCK7.micro-dystrophin does not currently have Marketing Authorisation in the UK/EU for any indication.

In February 2020 rAAVrh74.MHCK7.micro-dystrophin received EU orphan drug designation for the treatment of DMD.[7]

PATIENT GROUP

DISEASE BACKGROUND

The muscular dystrophies are a group of inherited genetic conditions caused by changes (mutations) in the genes responsible for the structure and functioning of a person's muscles. The mutations cause changes in the muscle fibres that interfere with the muscles' ability to function. There are many different types of muscular dystrophies, one of the most common and severe forms is DMD.[8]

DMD is a muscle-wasting condition caused by the lack of a protein called dystrophin.[9] The Duchenne gene is found in the X-chromosome, thus primarily affecting boys (only ⩽1% of those with DMD are female).[10] Symptoms start in early childhood, generally between ages 2 and 3, first affecting the proximal muscles of the hips, pelvic area, thighs and shoulders, and later the distal limb muscles in the arms, legs and trunk.[11] Progressive muscular damage and degeneration occurs in people with DMD, resulting in muscular weakness, associated motor delays, loss of ambulation, respiratory impairment, and cardiomyopathy.[12] With medical care, most people with DMD die from heart or respiratory failure before or during their 30s.[10,13]

DMD is also associated with a substantial cost burden to society and to affected families and significantly impairs quality of life in both patients and caregivers.[14]

CLINICAL NEED AND BURDEN OF DISEASE

DMD affects an estimated 1 in every 3,500 to 5,000 live male births, and around 2,500 boys and young men in the UK have DMD. Each year, about 100 boys with DMD are born in the UK.[15]

In 2019/20 there were 2,251 hospital admissions for muscular dystrophy (ICD-10 G71.0, which includes DMD) in England, resulting in 2,369 finished consultant episodes and 3,441 bed days.[16]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Clinical care is provided by a multi-disciplinary team comprised of a range of healthcare professionals depending on local services, including neurologists or paediatric neurologists/neuromuscular specialists, rehabilitation specialists, neurogeneticists, paediatricians and primary care physicians.[12] Interventions include cardiac and respiratory monitoring and support, occasional inpatient orthopaedic intervention, spinal surgery and rehabilitation. In addition, dietetic advice (and, in some cases, gastric feeding), prevention and treatment of bone fragility, management of the complications of long-term corticosteroid therapy and psychosocial support may be needed.[17]

Prolonged survival of patients with DMD has meant a shift to more anticipatory diagnostic and therapeutic strategies to achieve prevention, early identification, and treatment of predictable and potentially modifiable disease complications. The expectation of longer survival has in turn led to increasing emphasis on quality of life and psychological management.[12]

CURRENT TREATMENT OPTIONS

Current management of DMD includes treatment with corticosteroids, which is associated with delay in loss of walking but significant adverse effects.[17] Ataluren is available for patients 5 years or older who can walk. This is administered orally via a dissolvable powder in liquid or semi-solid food and restores dystrophin synthesis.[18]

PLACE OF TECHNOLOGY

If licensed, rAAVrh74.MHCK7.micro-dystrophin will provide a treatment option for male patients aged 3 months to 7 years with DMD.

CLINICAL TRIAL INFORMATION

Trial	NCT03769116; **A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial for Duchenne Muscular Dystrophy Using SRP-9001** **Phase II –** Active, not recruiting **Location(s):** US **Primary completion date:** December 2020
Trial design	Randomised, quadruple-masked, parallel assignment.
Population	N= 41 (actual); 4 to 7 years; male with Duchenne Muscular Dystrophy
Intervention(s)	All subjects will be on a stable dose of oral corticosteroids for at least 12 weeks before the screening visit. On Day 1,

	subjects will be given SRP-9001 (1.33 × 1014 vg/kg) by single IV infusion. Subjects will remain on their stable dose of oral corticosteroids (except for modifications to accommodate changes in weight) through the remainder of the study.[b]
Comparator(s)	Matched placebo.
Outcome(s)	• Change From Baseline in Quantity of Micro-dystrophin Protein Expression as Measured by Western Blot [Time Frame: Baseline up to Week 12 (Part 1)] • Change From Baseline in North Star Ambulatory Assessment (NSAA) Total Score [Time Frame: Baseline up to Week 48 (Part 1)] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**NCT03375164; Systemic Gene Delivery Phase I/IIa Clinical Trial for Duchenne Muscular Dystrophy Using rAAVrh74.MHCK7.micro-dystrophin** **Phase I/II –** Active, not recruiting **Location(s):** US **Primary completion date:** April 2023
Trial design	Non-randomised, open label, parallel assignment.
Population	N= 4; 3 months to 7 years; male with Duchenne Muscular Dystrophy
Intervention(s)	• Cohort A: Patients 3 months to 3 years. One-day prior to gene transfer subjects in Cohort A will be started on prednisolone (prednisone or deflazacort acceptable) 1 mg/kg and maintained for 30 days while monitoring immune response. If negative at day 30, steroids will be weaned over 1 week. rAAVrh74.MHCK7.micro-dystrophin vector intravenously 2x1014 vg/kg in 10 mL/kg • Cohort B: Patients 4 to 7 years. Patients will be maintained on stable dose of corticosteroids throughout trial and rAAVrh74.MHCK7.micro-dystrophin vector intravenously 2x1014 vg/kg in 10 mL/kg
Comparator(s)	No comparator.
Outcome(s)	• Safety based on number of participants with adverse events. [Time Frame: 3 years] AEs will be monitored and scored for severity and relatedness to the study article. See trial record for full list of other outcomes

[b] Information provided by Roche Products Ltd

Results (efficacy)	All patients had confirmed vector transduction and showed functional improvement of North Star Ambulatory Assessment (NSAA) scores and reduced creatine kinase levels.[19]
Results (safety)	All adverse events (n = 53) were considered mild (33 [62%]) or moderate (20 [38%]), and no serious adverse events occurred. Eighteen adverse events were considered treatment related, the most common of which was vomiting (9 of 18 events [50%]).[19]

ESTIMATED COST

The cost of rAAVrh74.MHCK7.micro-dystrophin is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Idebenone for treating Duchenne muscular dystrophy (ID1092). Expected publication date: May 2021
- NICE highly specialised technologies guidance. Ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene (HST3). July 2016
- NICE guideline. Suspected neurological conditions: recognition and referral (NG127). May 2019

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS Standard Contract (2013/2014). For Diagnostic Service for Rare Neuromuscular Disorders (all ages). D04/S(HSS)/a

OTHER GUIDANCE

- Birnkrant DJ, Bushby K, Bann CM, Apkon SD, Blackwell A, Brumbaugh D, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management (2018).[12]
- Birnkrant DJ, Bushby K, Bann CM, Alman BA, Apkon SD, Blackwell A, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management (2018).[20]
- Birnkrant DJ, Bushby K, Bann CM, Apkon SD, Blackwell A, Colvin MK, et al. Diagnosis and management of Duchenne muscular dystrophy, part 3: primary care, emergency management, psychosocial care, and transitions of care across the lifespan (2018).[21]

ADDITIONAL INFORMATION

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