24 July 2025
EMA/CHMP/CAT/213364/2025
Committee for Medicinal Products for Human Use (CHMP)
Committee for Advanced Therapies (CAT)

Assessment report

Elevidys

International non-proprietary name: delandistrogene moxeparvovec

Procedure No. EMEA/H/C/005293/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Quality/Non-clinical

AAV	adeno-associated virus
BDS	bulk drug substance
CC	cell control
Cq	quantitation cycle
ddPCR	droplet digital polymerase chain reaction
DLS	dynamic light scattering
DMD^{MDX} mice	dystrophin-null mutant (C57BL/10ScSn-DMD^{MDX}/J) mice
IF/IA	immunofluorescence/image analysis
IM	intramuscular
ITR	inverted terminal repeat
ISH	in situ hybridization
IV	intravenous
NaN	not a number, no amplification
NC	negative control
NTC	no template control
OOS	out of specification
PC	positive control
PD	pharmacodynamic
PDPF	percentage dystrophin-positive fibers
PEI	Polyethyleneimine
PK/PD	pharmacokinetic-pharmacodynamic
qPCR	quantitative polymerase chain reaction
rcAAV	replication competent adeno-associated virus
RoA	route of administration
SEC	size exclusion chromatography
TSE	transmissible spongiform encephalopathy
Vg	vector genome
WB	Western blot
WCB	working cell bank
WRS	working reference standard
WT mice	wild-type (C57BL/6J) mice

Clinical

10MWR	10-meter walk/run timed test
100MWR	100-meter walk/run times test
4SC	time to ascend 4 stairs
AAV	adeno-associated virus
AAVrh74	adeno-associated virus serotype rh74
AE	adverse event
BMD	Becker muscular dystrophy
CCOD	clinical cutoff date
CI	confidence interval
CK	creatine kinase
CDP	clinical development plan
CSR	clinical Study Report
DAPC	dystrophin-associated protein complex
DMD	Duchenne muscular dystrophy
EC	external control

ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
FOR-DMD	Finding the Optimum Regimen for Duchenne Muscular Dystrophy
GGT	gamma-glutamyl transferase
IF	immunofluorescence
INFγ	interferon gamma
IRR	infusion-related reaction
LS	least squares
MCID	minimal clinically important difference
MHCK7	α-myosin heavy-chain creatine kinase 7
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy
NSAA	North Star Ambulatory Assessment
PIP	Paediatric Investigation Plan
RMP	risk management plan
SD	standard deviation
SAE	serious adverse event
SRP-9001	delandistrogene moxeparvovec
Study 101	SRP-9001-101
Study 102	SRP-9001-102
Study 103	SRP-9001-103
Study 301	SRP-9001-301
Study 305	SRP-9001-305
SV95C	Stride Velocity 95th Centil
T2	transverse relaxation
TMA	thrombotic microangiopathy
TTR	time to rise from floor
ULN	upper limit of normal
vg	vector genome

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Roche Registration GmbH submitted on 31 May 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Elevidys, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 17 September 2020.

Elevidys was designated as an orphan medicinal product EU/3/20/2250 on 28 February 2020 in the following condition: Duchenne muscular dystrophy.

The applicant applied for the following indication:

Elevidys is indicated for the treatment of Duchenne muscular dystrophy (DMD) in ambulatory patients aged 3 to 7 years old without elevated antibodies to adeno associated virus serotype rh74 (AAVrh74).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that Delandistrogene moxeparvovec was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0325/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's request(s) for consideration

1.5.1. Conditional marketing authorisation

The applicant requested consideration of its application for a conditional marketing authorisation in accordance with Article 14-a of the above-mentioned Regulation

1.5.2. New active substance status

The applicant requested the active substance delandistrogene moxeparvovec contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Protocol assistance

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
19/09/2019	EMEA/H/SA/4204/1/2019/PED/HTA/ADT/III	André Elferink, Mogens Westergaard, Mario Miguel Rosa
11/11/2021	EMA/SA/0000066340	Fernando de Andrés Trelles, Ewa Balkowiec Iskra
13/10/2022	EMA/SA/0000093176	Karl-Heinz Huemer, Fernando de Andrés Trelles
13/10/2022	EMA/SA/0000095793	André Elferink, Karl-Heinz Huemer
26/04/2023	EMA/SA/0000126027	Silvijus Abramavicius, Nathalie Morgensztejn
12/12/2024	Delandistrogene moxeparvovec (231197) - Scientific Advice Letter.docx	Nathalie Morgensztejn, Martin Walter

The scientific advice pertained to the following quality, non-clinical and clinical aspects:

EMEA/H/SA/4204/1/2019/PED/HTA/ADT/III - Non-clinical and clinical development

- Agreement that the completed 24-week toxicology study and bridging GLP toxicology study in mice are sufficient to characterise the non-clinical safety and no additional non-clinical safety studies are needed for MAA.
- The proposed viral shedding study plan; whether the proposed development programme adequately characterises the clinical effect and safety of the product; adequacy of the proposed data package for conditional marketing authorisation (CMA); the proposed long-term follow up of patients treated with SRP-9001; the statistical analysis methodology for Study-SRP-9001-301, including the sample size and the analysis methods for the primary and secondary endpoints; the proposed primary endpoint in study SRP-9001-301 to assess efficacy in ambulatory DMD patients; the choice of secondary endpoints for studies in ambulatory patients; the proposed efficacy endpoint(s) in study SRP-9001-303 to assess efficacy in non-ambulatory DMD patients; whether the proposal for assessing the efficacy of SRP-9001 adequately accounts for the expected improvement in patient score resulting from growth and maturation as well as steroid usage; the proposed endpoints that will be measured in the registries for assessing long-term effects.

EMA/SA/0000066340 – Quality, non-clinical and clinical development

- The proposed dose assignment method (qPCR assay) for SRP-9001 production lots; the acceptability of use of an in vitro potency assay matrix for release and stability measurement of drug product for pivotal trials and for commercial use; the control strategy for drug substance and drug product of SRP-9001; adequacy of in-use compatibility study based on laboratory tests to support the use of infusion bags as an alternative to syringes for the administration of SRP-9001; the comparability exercise that would support the manufacturing change from Process A (clinical) to Process B (commercial); adequacy of the proposed comparability plan designed to demonstrate comparability between the commercial Process B material produced at the current manufacturing site and the commercial Process B material produced at the new manufacturing site.
- Adequacy of the completed, ongoing, and planned non-clinical studies to support registration of SRP-9001 in all DMD patients, and in particular a) the completed and ongoing non-clinical toxicology studies, b) biodistribution assessment, c) the need for additional studies to investigate germline transmission, d) the need for specific genotoxicity, tumorigenicity, fertility, embryo-foetal toxicity, and pre- and post-natal toxicity studies.
- Whether a positive outcome of the pivotal Study 301, supported by results from the Phase I/II

Studies 101, 102, and 103, can support an initial full MAA for the treatment of ambulatory patients aged 4 to 7 years with Duchenne muscular dystrophy; appropriateness of a Conditional Marketing Authorisation application based on the totality of the data from Studies 101 and 102 and 103; adequacy of the estimated size of the safety database at time of submission of an initial full MAA or CMA; appropriateness of the multi-national, post-authorisation, observational, longitudinal study of patients with DMD to collect long-term follow-up data in patients treated with SRP-9001; the design of study 302 to support an indication of treatment of patients with Duchenne muscular dystrophy aged <4 years; whether a positive outcomes of the proposed Study 303 would support an extension of the initial MAA indication to treatment of all patients with Duchenne muscular dystrophy; the proposed testing of AAVrh74 antibodies prior to SRP-9001 administration.

EMA/SA/0000093176 – Clinical development

- The design of the proposed "early mutation" study in ambulatory boys, and in particular the study population and genetic rationale for the proposed cohort definition, study objectives and endpoints, statistical analysis, risk management, and safety monitoring; extrapolation from the proposed study in ambulatory patients to non-ambulatory DMD patients with the same genetic classes.

EMA/SA/0000095793 – Quality and clinical development

- Conduct of the in-vitro potency assay as part of the drug product release testing outside the EU until the method transfer to the EU; use of the available Clinical Trial Assay, used within a single accredited laboratory located in the US, as a temporary measure for testing of AAVrh74 antibodies prior to SRP-9001 administration.
- CMA in patients aged 4 to 7 years (excluding mutations in exons 1-17); size of the planned safety database and proposed pooling strategy for overall safety profiles.

EMA/SA/0000126027 – Non-clinical and clinical development

- The approach to investigate integration of SRP-9001 in animal tissues; the presentation and content of the environmental risk assessment (ERA); the proposed approach regarding blood and organ donation after the use of SRP-9001.
- The safety concerns proposed for the risk management plan (RMP); the proposed (a) pharmacovigilance plan, (b) risk minimisation measures, and (c) effectiveness measures; the design of the non-interventional PASS study to assess the long-term safety and effectiveness of SRP-9001; the clinical validation strategy for the IVD companion diagnostic and the samples to be used for the analytical concordance study; the proposed safety pooling strategy; the options for inclusion in the MAA of blinded safety data from the SRP-9001-303 study.

EMA/SA/0000231197 – Quality, non-clinical and clinical development

- Acceptability of the proposed plan to demonstrate comparability between materials manufactured with processes C (commercial) and B, in particular the suitability of the proposed analytical package.
- Suitability of the proposed nonclinical package.
- Feedback on the draft clinical study design to investigate Process C material in the course of a clinical study.

1.7. Steps taken for the assessment of the product

The CAT Rapporteur and Co-Rapporteur appointed by the CHMP were:

CAT Rapporteur: Silke Dorner CAT Co-Rapporteur: Jan Mueller-Berghaus

The application was received by the EMA on	31 May 2024
The procedure started on	20 June 2024
The CAT Rapporteur's first Assessment Report was circulated to all CAT and CHMP members on	10 September 2024
The CAT Co-Rapporteur's first Assessment Report was circulated to all CAT and CHMP members on	24 September 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	23 September 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CAT during the meeting on	03 October 2024
The CAT agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	11 October 2024
The applicant submitted the responses to the CAT consolidated List of Questions on	13 February 2025
The CAT Rapporteur circulated the Joint Assessment Report on the responses to the List of Questions to all CAT and CHMP members on	26 March 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 April 2025
The CAT agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	16 April 2025
The applicant submitted the responses to the CAT List of Outstanding Issues on	13 May 2025
The CAT Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CAT and CHMP members on	28 May 2025
The outstanding issues were addressed by the applicant during an oral explanation before the CAT during the meeting on	11 June 2025
The CAT, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Elevidys on	17 July 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Elevidys on	24 July 2025
The CAT and CHMP adopted a report on similarity of name of the medicinal product with name of the authorised orphan medicinal product(s) on (See Appendix on similarity)	24 July 2025
Furthermore, the CAT and CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	24 July 2025

2. Scientific discussion

2.1. Problem statement

The marketing authorisation application seeks conditional marketing authorisation of delandistrogene moxeparvovec (SRP-9001, tradename Elevidys) for the following indication:

Elevidys is indicated for the treatment of Duchenne muscular dystrophy (DMD) in ambulatory patients aged 4 to 7 years old without elevated antibodies to adeno associated virus serotype rh74 (AAVrh74).

Patients treated with Elevidys must have a confirmed mutation in the DMD gene that is expected to lead to absence of functional dystrophin protein.

2.1.1. Epidemiology and screening tools

The incidence of DMD is approximately 1 in 5000 live male births worldwide (Mendell et al. 2012; Crisafulli et al. 2020). Patients with DMD have a mutation that causes disruption of the reading frame of the dystrophin gene, which subsequently leads to a deficiency of this important structural protein. The types of mutations are varied across the DMD population and include deletions, duplications, point mutations and out-of-frame mutations. Dystrophin is expressed in multiple tissue types such as skeletal muscle (including diaphragm) and cardiac muscle. As dystrophin is also deficient in vital organ systems such as the cardiovascular and respiratory systems, the effect is thus inevitably fatal, with an average survival limited to the third decade of life.

Skeletal muscle tissue from children with DMD are characterized by histopathological changes such as a significantly greater variability in myofibres size, an increased frequency of central nucleation, fat substitution of muscle, and extensive zones of reactive myofibrosis (Zweyer et al. 2022). Pathological features that are initially only evident on histopathological examination become identifiable by using MRI, such as muscle wasting and fat substitution of muscles.

Increases in serum biomarkers of muscle damage (creatine kinase [CK]) and dystrophic histological changes are apparent consequences of DMD already evident from birth. Due to the elevated CK levels at birth, this serum biomarker has been previously trialled as an initial newborn screening test (Moat et al. 2013). Patients with DMD have grossly elevated serum CK values due to leakage of the enzyme from degenerating muscle fibers (Zatz et al. 1991). Early in the disease, between 2- and 5-years of age, CK levels in subjects with DMD are usually 50 to 300 times the upper limit of normal, and levels tend to decrease over time as muscle is lost and replaced by fibrotic tissue and fat. Increases in other enzymes originating from degenerating muscles are also generally observed in these patients (McMillan et al. 2011).

2.1.2. Biologic features

DMD is an X-linked, degenerative, and invariably fatal neuromuscular disease caused by mutations within the dystrophin gene. In muscle tissue, dystrophin is a critically important part of the protein complex connecting the cytoskeleton of a muscle fibers to the cell membrane and the extracellular matrix, providing muscle stability. Dystrophin is thought to function as a molecular spring, preventing muscle membrane damage during eccentric contraction. If dystrophin is deficient due a mutation that causes disruption of the reading frame of the dystrophin gene, the cell membrane of muscle cells becomes unstable and porous to cations leading to muscle cell damage. Macroscopically, this cellular damage results in chronic and progressive muscle inflammation and replacement of muscle by fat and fibrotic tissue (van Westering et al. 2015).

2.1.3. Clinical presentation, diagnosis and stage/prognosis

The first concern reported by parents of children with DMD is most commonly a delay in the developmental milestone of walking. Despite the irreversible early damage occurring at this early age and the early signs of the disease, there is often a delay in diagnosis, with children being diagnosed, on average, between 3 and 5 years of age (Ciafaloni et al. 2009, van Ruiten et al. 2014). As children with DMD get older, they lose the ability to rise from the floor or climb stairs typically within the first decade of life and subsequently lose ambulation at a median age of 13 years (McDonald et al. 2018). The early disease milestones, such as the loss of the ability to rise from the floor, significantly impact the quality of life of children with DMD as they already greatly restrict the children's autonomy and increase care needs. Upper limb function also progressively declines in children and adolescents with DMD, leading to increased care needs; this is a factor which may contribute to the high rates of comorbid anxiety and depression in children with DMD, as well as their parents and siblings (Steele et al. 2008, Read et al. 2010; Landfeldt et al. 2016).

Although DMD is often first diagnosed because of skeletal muscles weakness and difficulty walking, it is a multisystem disease impacting all muscle types, and a decline in the cardiac and respiratory systems is observed during the first to second decades of life. Cardiac manifestations of DMD include dilated cardiomyopathy, which is caused by progressive fibrosis within the cardiac muscle. The prevalence of cardiomyopathy in patients with DMD increases with age and disease progression, with the great majority of patients affected by age 20 years (Spurney et al. 2014). Due to reduced ambulation, the majority of patients are asymptomatic of cardiac failure until very late stage. Cardiac arrhythmias are more prevalent and can be life-threatening in DMD. Arrhythmias such as a fast-resting heart rate (sinus tachycardia) have been associated with increased risk of developing cardiomyopathy earlier (Thomas et al. 2012). Subclinical impairment of respiratory muscle function occurs in ambulatory patients but decline of respiratory function accelerates after loss of ambulation (Khirani et al. 2014, Mayer et al. 2015). Due to the progressive nature of the disease and cardiorespiratory weakness, despite the standard of care, life expectancy is severely reduced, with a median age of 28.1 years (Broomfield et al. 2021).

2.1.4. Management

Current management of DMD has been focused on supportive care using a multi-disciplinary team. The aim of supportive care, presented in consensus documents on the standard of care (Birnkrant et al. 2016; Passamano et al. 2012), is to reduce the effect of the disease on different systems. Supportive care includes management of respiratory, cardiac, endocrinological, orthopedic, gastroenterological, and psychological issues. Although these measures do provide symptomatic relief and modestly prolong ambulation and life span, the disease still causes a progressive and relentless decline in function and quality of life.

Corticosteroids, such as prednisolone and deflazacort, are widely used as part of the standard of care for the treatment of DMD. The exact mechanism of corticosteroids in DMD is unknown but likely includes immunomodulatory and anti-inflammatory actions. Chronic corticosteroid use in DMD delays loss of ambulation from approximately 9 years to a median age of 13 years, slows rate of decline in upper limb, reduces progression of scoliosis, and reduces respiratory complications and cardiac complications (McDonald et al. 2018; Mendell et al. 2012; Miller et al. 2020). Although there are clear benefits in the use of corticosteroids in terms of ameliorating some of the effects of the disease, they are associated with multiple significant side effects (most notably: weight gain, behavioral and mood effects, elevation in blood pressure, reduced growth, pubertal delay, cataracts, and osteoporosis), and patients still ultimately die in early adulthood or earlier (Biggar 2006; Moxley et al. 2010; Matthews et al. 2016, Broomfield et al. 2021).

Vamorolone (Agamree) is a modified corticosteroid that selectively binds to the glucocorticoid receptor, which triggers anti-inflammatory effects via inhibition of NF-κB-mediated gene transcripts but leads to less transcriptional activation of other genes. In addition, vamorolone also inhibits the activation of the mineralocorticoid receptor by aldosterone. This modified corticosteroid has the advantage of fewer side effects with similar functional gains compared with standard corticosteroids, however, as with the standard corticosteroid, it is not aimed at the underlying cause of DMD. Vamorolone is authorized for the treatment of DMD patients aged 4 years and older.

Givinostat (Duvyzat) is an oral histone deacetylase inhibitor targeting pathogenic processes to reduce inflammation and loss of muscles. Givinostat is currently authorized for use in the United States for the treatment of DMD patients aged 6 years and older with all genetic variants of DMD. At the time of this MAA, givinostat was under evaluation for MA at the CHMP and received a positive opinion on 25 April 2025.

Ataluren (Translarna) is an oral small molecule that promotes ribosomal read through of messenger ribonucleic acid containing a premature stop codon. Ataluren was granted conditional marketing authorization in the European Union in 2014 for the treatment of patients with DMD whose disease is caused by a 'nonsense mutation' in the dystrophin gene, however, the CHMP recommended not to renew the conditional marketing authorisation of ataluren. The recommendation follows the full re-evaluation of the benefits and risks of the medicine during the renewal of its marketing authorisation,

including results of a new study which failed to confirm ataluren's effectiveness. EC has re-confirmed non-renewal of the marketing authorisation.

Over the past years, more treatments aimed at partially correcting the underlying pathophysiology of DMD have been developed. These include anti-sense oligonucleotides, which promote production of an internally truncated dystrophin protein for specific genetic mutations, such as eteplirsen, golodirsen, viltolarsen, and casimersen. Exon-skipping therapies have shown very modest increases in dystrophin and functional benefit for a minority of patients with mutations amenable to their mechanism of action. In 2018, the CHMP considered that the efficacy and safety of eteplirsen was not sufficiently demonstrated and recommended the refusal of the granting of the conditional marketing authorization. None of these therapies are authorized for use in the European Union.

Effective treatment for DMD remains a highly unmet medical need as no current treatment options address the root cause of the disease and significantly modify the universally progressive declining disease trajectory resulting in a severely shortened life expectancy in patients with DMD.

2.2. About the product

SRP-9001 is a non-replicating, recombinant adeno-associated virus serotype rh74 (AAVrh74)-based vector containing the SRP-9001 human micro-dystrophin gene, under the control of the α-myosin heavy-chain creatine kinase 7 (MHCK7) promotor/enhancer.

The vector genome (vg) consists of several elements, which have replaced all DNA from the wild-type AAVrh74 vector. These elements include 5’ and 3’ AAV2 inverted terminal repeats, the MHCK7 promoter/enhancer, the codon-optimized human SRP-9001 micro-dystrophin complementary DNA, a chimeric simian virus (SV40) intron (including the splice donor/splice acceptor), and a synthetic polyadenylation signal.

A single IV infusion of SRP-9001 aims to replace dysfunctional or missing dystrophin protein with a functional shortened dystrophin (SRP-9001 micro-dystrophin) in cardiac and skeletal muscles.

The dystrophin gene is one of the largest human genes, totalling 2.3 megabases in size and is composed of 79 exons (Chamberlain and Chamberlain 2017). The full-length dystrophin coding sequence is > 11 kb, whereas AAV-based vectors have a gene-packaging size limit of 5 kb (Naso et al. 2017). Therefore, shorter dystrophin gene constructs that retain essential elements for function need to be designed for AAV vector-based gene therapies. A number of publications in the literature support that multiple regions of the full-length dystrophin protein could be deleted in various combinations, while still generating highly functional mini- and micro-dystrophins (Harper et al. 2002; Davies and Guiraud 2019). The SRP-9001 micro-dystrophin coding sequence contains key functional elements from the full-length wild-type human dystrophin gene and is designed to retain the most functional elements of dystrophin that would be expected to lead to slower disease progression.

The design of SRP-9001 was guided by examination of genotype-phenotype correlations in patients with Becker muscular dystrophy (BMD) indicating that large in-frame truncating mutations can lead to milder phenotypes. There are notable differences between BMD and DMD in terms of the underlying genetic defects in the dystrophin gene, the expressed truncated or absent dystrophin protein, and the resulting dystrophic phenotype. DMD is mostly caused by deletions (~65%) that disrupt the translational reading frame of dystrophin, resulting in truncated, non-functional dystrophin protein expressed at a very low level due to low mRNA and protein stability (Hoffman et al. 1987; Koenig et al. 1989). In contrast, patients with BMD have deletions that retain the translational reading frame and enable the muscle cells to produce shortened, but partially functional dystrophin, leading to a milder muscular dystrophy, longer ambulation, and longer average life expectancy (England et al. 1990; Koenig et al. 1989; Wells et al. 1995). The hypothesis that even large in-frame deletions cause only mild dystrophin phenotypes was demonstrated by clinical observations in a patient with BMD with a large in-frame deletion of exons 17 to 48, removing a significant portion of the rod domain (England et al. 1990). The patient remained ambulatory until the age of 61 years, despite the absence of 46% of the dystrophin gene. Other BMD patients with severely truncated genes but milder phenotypes have been described in the literature (Love et al. 1991).

These clinical observations form the basis that shortened dystrophin molecules can still possess significant functional properties. In addition, the modular structure of dystrophin allows for additional flexibility in the synthetic design of shortened dystrophins; removal of non-essential coding regions, namely spectrin-like repeats and the C-terminus, allow the shortened dystrophin to retain significant function if the reading frame remains intact (Rodino-Klapac et al. 2013).

2.2.1. Type of application and aspects on development

The applicant requested consideration of their application for a Conditional Marketing Authorisation in accordance with Article 14-a of the above-mentioned Regulation, based on the following argumentation:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data.

  The applicant is proposing to add a sub-study to the ongoing SRP-9001-305 study. SRP-9001-305 is a Phase III Long-Term Follow-Up Study to evaluate the safety and efficacy in subjects who have previously received SRP-9001 in a clinical study. The sub-study will run for up to 10 years and will have additional efficacy endpoints to confirm a positive benefit-risk balance.
- Unmet medical needs will be addressed, as very limited treatment options are available for patients with DMD and no treatments aim at treating the underlying pathobiological cause of this progressive, debilitating and ultimately fatal disease.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

  As a gene therapy product, SRP-9001 has the potential to deliver functional SRP-9001 micro-dystrophin in cardiac and skeletal muscle; the key tissues affected in this lethal degenerative disease, thus addressing the root cause of the disease, and potentially reversing the clinical course of decline. A delay in progression positively impacts the lives of DMD patients and their caregivers. With potential to slow disease progression, expeditious patient access to SRP-9001 would satisfy a significant unmet medical need.

2.3. Quality aspects

2.3.1. Introduction

The finished product (FP) Elevidys is presented as solution for intravenous infusion containing 1.33×10^{13} vector genomes(vg)/mL of delandistrogene moxeparvovec as active substance. Other ingredients are sodium chloride, tromethamine HCL, tromethamine, magnesium chloride hexahydrate, poloxamer 188, and water for injections. The product is available in a polymer vial (10 mL, crystal zenith) with rubber stopper (20 mm chlorobutyl rubber) and seal (aluminium shell with flip-off cap overseal).

The recommended dose of Elevidys is determined by body weight. A body weight of 10 - 70 kg requires a dose of 1.33×10^{14} vg/kg. At 70 kg or above a dose of 9.31×10^{15} vg/kg is applied. The total number of vials in each finished pack corresponds to the dosing requirement of the individual patient, depending on the body weight, and is provided on the package.

2.3.2. Active substance

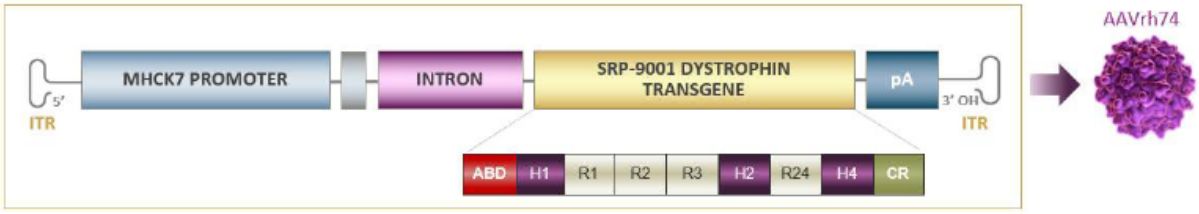
2.3.2.1. General information

Elevidys (INN: delandistrogene moxeparvovec, company code: SRP-9001) is a non-replicating, recombinant adeno-associated virus (AAV) encoding a human micro-dystrophy gene.

The SRP-9001 vector genome contains the minimal elements from the full length wild-type human dystrophin gene required for gene expression, including AAV2 inverted terminal repeats (ITR), the codon-optimized human SRP-9001-dystrophin complementary DNA, chimeric (SV40) intron, and synthetic polyadenylation (Poly A) signal, all under the control of the α-myosin heavy-chain creatine kinase 7 (MHCK7) promoter (Figure 1).

To prevent the formation of replication competent AAVs, a 3 kb human collagen intron was introduced into the *Rep* coding sequence resulting in a Rep-Cap coding sequence which is too large for encapsidation into the AAV.

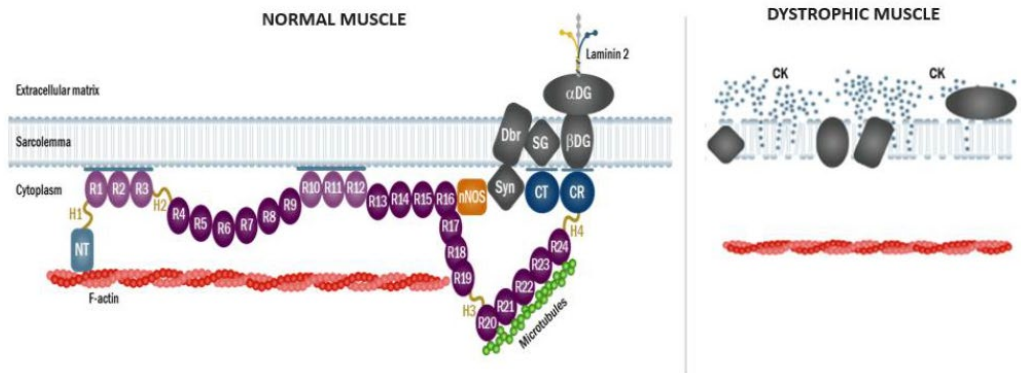
The AAVrh74 serotype has a high tropism for skeletal and cardiac muscle and the expression of SRP-9001 is restricted to these tissues by the MHCK7 promotor.



ABD = actin-binding domain; CR = cysteine-rich region; H = hinge; ITR = inverted terminal repeats; MHCK7 = α-myosin heavy-chain creatine kinase 7; pA = polyadenylation signal; R = spectrin-like repeat; rAAV = recombinant adeno-associated virus; rh74 = rhesus serotype 74.

Figure 1: SRP-9001 Vector Genome

The proposed indication of SRP-9001 is for treatment of Duchenne muscular dystrophy (DMD). In a normal muscle cell, dystrophin serves as a flexible structural protein linking the intracellular space with the sarcolemmal membrane in a complex called the Dystrophin-Associated Protein Complex (DAPC), which then links to the extracellular matrix via laminin. This link helps transmit force related to muscle contraction and to maintain sarcolemmal integrity during muscle use. Without functional dystrophin, normal muscle contraction in DMD patients results in chronic muscle breakdown and loss of function (Figure 2).



αDG = alpha dystroglycan; βDG = beta dystroglycan; CK = creatine kinase; CR = cysteine-rich region; CT = C-terminus; Dbr = dystrobrevin; DMD = Duchenne muscular dystrophy; SG = sarcoglycan complex; Syn = synthrophin.
Source: Figures adapted from Zhao 2016.

Figure 2: The Roles of Functional Dystrophin, Sarcolemma, and the DAPC in Healthy Muscle and Consequence of Their Loss in Dystrophic Muscle

Because the wild-type dystrophin gene is too large to be encapsidated into an AAV vector, the applicant designed the shortened SRP-9001-Dystrophin transgene variant. The clinical observations that form the basis of the shortened form of dystrophin in SRP-9001 are described in the dossier.

The design of the SRP-9001 transgene is based on its ability to halt muscle necrosis and increase muscle strength in the mouse model. Included and excluded critical elements in SRP-9001 are listed and respective literature is indicated.

Post-translational modifications as well as results of VP1/VP2/VP3 mass and peptide mapping (100% sequence coverage) were presented. General properties such as size of the capsid, viral protein primary structure and intact mass, molecular weight and primary structure and sequence of the therapeutic sequence as well as physicochemical and other properties are listed as well.

2.3.2.2. Manufacture, process controls and characterisation

The AS is manufactured, and release tested in the USA.

Name, address, responsibilities and test methods of all manufacturers involved in manufacture, in-process-, release- and stability testing of SRP-9001 active substance (AS) as well as manufacture and storage of cell banks are listed. A flow chart of manufacturers indicating all responsibilities and test methods is also provided.

Satisfactory GMP compliance has been provided for the sites performing manufacturing, control and storage activities for the active substance.

Description of manufacturing process and process controls

The applicant provided flow charts and a detailed description of the upstream and downstream manufacturing process steps including process parameters (critical/non-critical) and in-process controls (IPC/critical IPC) and their acceptable range/acceptance criteria as well as hold times. IPC´s relevant to safety sampling are implemented.

Delandistrogene moxeparvovec (SRP-9001) is manufactured by transient transfection.

Manufacture of an upstream batch starts from a single vial. After thawing, the cells are first expanded using Seed Train and Expansion Media. The cells are then further expanded using shake flasks. For final cell expansion prior to transfection, bioreactor is inoculated. During final expansion, the bioreactor is maintained under controlled conditions using bioreactor growth. The cells are transfected in two rounds with three plasmids (transgene, packaging and helper plasmid. The second transfection is performed. The harvest procedure involves the lysis of cells with lysis buffer and flushing the bioreactor with Bioreactor rinse buffer. The bioreactor harvest lysate is collected in a single use bioprocess bag. Bulk harvest clarification is performed using a two-stage filtration train with a depth filter followed by a polishing membrane filter equilibrated with AAVX buffer. To reduce volume and exchange the formulation, a tangential flow filtration step (TFF1) is performed. The harvest TFF1 retentate is defined as the only intermediate in the upstream process site.

Harvest TFF1 retentate intermediates are thawed and pooled into a single downstream purification batch. SRP-9001 is purified by two column chromatography steps, i.e. affinity chromatography (AAVX) and anion exchange (AEX – CIM Q) operated in bind-elute mode. A hold step of the un-neutralized eluate is validated as an adventitious agents reduction step. A virus removal filtration is performed. By tangential flow filtration (TFF2) the viral filtrate is then concentrated in a first step then and then finally concentrated. The formulated product is filtered to obtain Bulk active substance (BAS).

Definitions of batch and scale are provided. The numbering system for active substance manufactured before the current numbering system is also explained.

Overall, the process description is deemed in line with regulatory expectations. All used media, buffers and solutions are listed. Production, testing and storage of media and buffer solutions is indicated as well. Specifications for individual raw material components of media, buffers and solutions are

provided. are used in the cell culture process. Overall, the classification of the process parameters and in-process controls and their acceptable ranges/acceptance criteria are adequately justified.

Overall, the manufacturing process and controls is well described and issues were appropriately addressed. However, the respective development and validation data provided within 12 months post authorisation.

Control of materials

The starting materials for manufacture of active substance include the master cell bank (MCB) and working cell bank (WCB) and plasmids.

For each of the three plasmids, a plasmid map, the annotated nucleotide sequence and information on the source, history and generation of the plasmids was provided. The function of the different genetic elements is described in sufficient detail. The full expected DNA sequence for plasmids was confirmed For each plasmid was established under cGMP conditions using animal origin free reagents. Overall, the establishment complies with Ph. Eur. 5.14 on bacterial cells used for the manufacture of plasmid vectors for human use and the new general monograph on "Gene therapy medicinal products for human use" which is applicable since 04/2025.

For plasmid preparation a manufacturing flow chart as well as a description of the manufacturing process steps and process controls is presented. The analytical methods for release testing are shortly described. Used buffers and media are listed. The manufacturing process was slightly modified with minor changes for process enhancement and representative release test results provided. However, the applicant is recommended to formally demonstrate equal AS quality for both in a retrospective comparison as soon sufficient V2 AS release data are available. The purified plasmid release specification complies with Ph.Eur.5.14. Concerns with regard to the plasmid release testing acceptance criteria have been appropriately addressed. The applicant acknowledged that release acceptance criteria are rather broad and confirmed that the specification will be reassessed after about 30 batches, which is endorsed. Stability data of conditions is presented and no trends were detected. Overall, the construction, manufacturing and control of the plasmids and respective cell banks is mostly appropriately performed but an issue with the comparability between plasmid manufacturing process is recommended to be addressed.

A two-tiered cell bank system with Master Cell Bank (MCB) and Working Cell Bank (WCB) has been established from a pre-master cell bank lot. The information provided on the origin and history of the cell line is described in sufficient detail. Respective test reports were attached to the dossier.

Raw materials used in the upstream and downstream process are listed together with their quality standard (in-house specification, compliant with Ph. Eur., USP and/ or NF, JP, JPC, JPE), supplier (non-compendial materials), and their intended use. Acceptable in-house specifications are provided for the non-compendial raw materials. A risk assessment was performed to evaluate raw materials that potentially have an impact on process performance or AS and FP quality attributes. Upon request, a summary of this risk assessment was provided. For those critical raw materials additional measures were taken such as inclusion of an alternative supply source, comprehensive raw material testing, monitoring and periodic re-evaluation of raw materials by risk assessment. Internal specifications were provided for release of ancillary materials.

Control of critical steps and intermediates

In this section the final process control strategy is summarized. Critical process parameters (CPPs) in the upstream and downstream active substance manufacture are listed with their established proven acceptable range (PAR). IPCs and their alert limits are presented for the upstream and downstream manufacturing including a rational for testing. In the upstream process tests are designated critical IPCs (CIPCs – passing acceptance criteria is required for lot disposition). In the downstream process CIPCs are defined. The analytical procedures used for IPCs are described.

Process validation

In accordance with the Guideline on process validation for manufacture of biotechnology-derived active substances EMA/CHMP/BWP/187338/2014 the process validation activities for SRP-9001 AS manufacture include process development/characterisation, process verification studies, and continued process verification along the lifecycle.

Performance of the intended commercial AS manufacturing process was verified at the commercial manufacturing site. The applicant confirms that the raw material, single use equipment, materials, utilities, facility design and manufacturing process is the same in all suits. A matrix approach was applied to qualify both, the suites and the manufacture of upstream batches. The PPQ matrix approach is deemed acceptable and provides a sufficient number of PPQ batches.

All active substance PPQ lots met the release specification. All active substance PPQ lots were filled and met the finished product release specifications. All FP lots derived from AS PPQ lots were placed on stability monitoring.

Based on the PPQ assessment the applicant established the final process control strategy. Several changes to normal operating ranges (NOR) (tightened), IPCs and CPPs were implemented and appropriately justified.

In summary, the presented process validation data demonstrate that the intended commercial AS manufacturing process performs consistently and delivers SRP-9001 AS complying with the release specifications under commercial operating conditions. Additional information were provided and deemed appropriate. Respective reports should be provided.

Downstream lots derived from PPQ and full-scale post-PPQ batches were tested. Overall, the impurity clearance showed consistent removal of impurities to acceptable levels. The established control strategy is endorsed.

Shipping of the bulk active substance was performed. Maximum and minimum load shipment was tested in a laboratory environment. Container integrity was maintained when subjecting to physical stress conditions. A performance qualification with an active substance lot filled in the commercial AS packaging confirmed package integrity and temperature control during shipment. Overall, shipping validation is acceptable.

Manufacturing process development

Two manufacturing processes versions have been implemented to manufacture SRP-9001. Early clinical study material was manufactured according to Process A. Later-stage clinical material was manufactured according to Process B. Material derived from Process A and B was also used for animal toxicology- and stability studies. Manufacturing Process B is the validated intended commercial manufacturing process.

Most of the physicochemical and biological attributes are comparable between FP manufactured according to Process A and B.

The applicant summarized results from non-clinical and clinical studies performed with Process A and B material.

The assessment of the benefit risk of Elevidys should be mainly based on the non-clinical and clinical data obtained with Process B batches. Early non-clinical and clinical studies performed with material from Process A may be regarded as supportive.

The process control strategy was established based on risk assessment, product knowledge, process development, characterisation studies, and manufacturing experience. In line with ICH Q8 and Q11, the applicant performed a failure mode and effects analysis (FMEA) to evaluate process parameters and their potential impact on CQAs based on data from pilot runs, engineering runs and full-scale manufacturing batches. All critical process parameters are listed with their rationale and proven acceptable range. All process parameters that were not determined as CPPs in the FMEA were designated non-CPPs. Some of the non-CPPs were defined as key non-CPPs that are controlled in a narrow rage. The non-CCPs and key non-CPPs are listed with their rational and action limits. The overall process control strategy including the active substance CPPs is presented. The establishment of

the quality target product profile (QTPP) and the CQAs assessment is presented in the Control Strategy.

Characterisation

Elucidation of structure and other characteristics

Characterization was performed mainly on PPQ Lots. The applicant referred to recent scientific literature showing that VP ratios for recombinant AAV are dependent on serotype and production system and the ratios show some variability. Justification based on scientific literature appears acceptable.

Post-translational modifications were appropriately characterized.

The applicant did not show characterisation data on SRP-9001 e.g. under different stress conditions.

Impurities

Most of the impurities present in the active substance were appropriately analysed and characterised.

Several issues were appropriately addressed.

2.3.2.3. Specification

The active substance specification includes attributes with respect to quantity, identity, purity and safety.

The acceptance criteria have been established based on product knowledge and release/stability data according to Process B that have been used in non-clinical, clinical, process development and validation, stability- and comparability studies. The applicant calculated the quantitative parameters. The final acceptance criteria were based on method variability, range of observed results, regulatory guidelines, and pharmacopoeia procedures. The proposed acceptance criteria can be mostly regarded acceptable. Upon request some acceptance criteria were further justified.

Analytical methods

The analytical methods have been satisfactorily described and several issues were adequately addressed.

Validation data have been provided for the analytical AS release methods and issues have been appropriately addressed.

Batch analysis

Batch analysis data are presented for batches which have been used in clinical- and stability studies. Also, data from four batches manufactured after the PPQ are presented. Because manufacturing process A was continuous no active substance was released, and FP data is presented.

Overall, the presented results demonstrate that the manufacturing process provides SRP-9001 active substance with consistent quality meeting the specification acceptance criteria.

Container closure system

The volume container closure system (CCS) is a pre-sterilized single-use flexible freeze container with an integral port for fluid transfer, customized tubing and connector components. Specifications, test results and technical drawings, are presented. All components are sterilized with according to ISO 11135:2014 Annex B. All components of the CCS meet the biocompatibility requirements of USP<87> Biological Reactivity Tests In Vitro and USP <88> Biological Reactivity Tests In Vivo Class VI. Representative specification results were provided which show conformance to acceptance criteria for bacterial endotoxins (USP<85>) and particulate matter (USP<788>). Extractable and leachable evaluation of the CCS is presented. In summary, the CCS appears suitable for SRP-9001 stored at ≤-60°C.

2.3.2.4. Stability

The applicant proposes an active substance shelf-life of ≤ -60°C.

For stability studies, a scaled-down active substance container of the same material as the commercial active substance container closure is used. Long-term stability data at ≤ -60°C are provided for the remaining process validation batches. The testing frequency of quality attributes during long-term stability studies is in accordance with ICH Q5C.

The applicant commits to complete the ongoing stability studies. Post-approval, one active substance lot will be placed on stability on an annual basis and will be tested according to the shelf-life specification.

2.3.3. Finished medicinal product

2.3.3.1. Description of the product and Pharmaceutical Development

Description of the product

SRP-9001 finished product (FP) is a sterile solution for intravenous infusion containing delandistrogene moxeparvovec as active substance, and is supplied in a cyclic olefin polymer (COP) vial closed with a rubber stopper and sealed with an aluminium seal and plastic flip-off cap. One vial contains 10 mL of 1.33×10^{13} vg/mL of delandistrogene moxeparvovec (SRP-9001) formulated in a buffered solution of tromethamine/tromethamine-HCl, magnesium chloride, sodium chloride hexahydrate, and poloxamer 188. Each vial contains an extractable volume of not less than 10.0 mL. The total recommended dosage is based on patient weight and requires multiple vials per dose.

The vial and stopper comply with Ph. Eur. and USP requirements and the appropriateness of the container closure system is presented.

SRP-9001 finished product (Elevidys) and its composition is appropriately described.

Table 1: Composition of the SRP-9001 finished product

Component	Reference to Standard(s)	Function
Delandistrogene moxeparvovec	In-house specification	Active ingredient
Sodium chloride	USP, Ph. Eur., JP	Tonicifier
Tromethamine HCl (Trometamol HCl)	In-house specification	Buffer agent
Tromethamine (Trometamol)	USP, Ph Eur., JPC	Buffer agent
Magnesium chloride (Magnesium chloride hexahydrate)	USP, Ph. Eur., JPC	Stabilizer
Poloxamer 188	USP, Ph. Eur., JPE	Surfactant
Water for injection (Water for injections)	USP, Ph. Eur., JP	Solvent

Pharmaceutical development

The components of the finished product, active substance and excipients are adequately described. The choice of the excipients and their concentration are adequately justified. There are no novel excipients, and no excipients of human or animal origin.

Overall, the formulation chosen has been sufficiently justified based on the formulation and robustness studies.

Physiochemical and biological properties of SRP-9001 FP were adequately described.

The applicant defined the QTPP for SRP-9001 FP including a comprehensive list of FP attributes, followed by the identification of CQAs based on product and process development experience (process characterisation studies, see below), nonclinical and clinical experience and publicly available information on other AAV products. These CQAs, divided into safety, purity, potency and identity, are tested as release methods (AS and/or FP) or as IPCs during manufacturing. Release/stability specifications are discussed and appropriate. It is noted that no formal risk assessment or the application of risk assessment tools have been described. Nevertheless, the definition of CQAs appears reasonable and considered main elements of ICH Q8, Pharmaceutical Development.

CPPs and nCPPs were defined and characterized in development and process characterization (PC) studies to generate PARs; for CPPs) and action limits (for nCPPs). In the main, these ranges and limits for process parameters are sufficiently justified based on the process characterization/development studies as described below. The criticality assignment appears reasonable.

In general, the control strategy, consisting of control of incoming raw material, operating conditions and in-process controls and product specifications is considered adequate.

Comparability between the two process variants (process A for non-clinical and early clinical and process B for late clinical and PPQ batches) is discussed under the AS section.

Overall, the performed process characterization studies are sufficiently outlined and support the anticipated manufacturing process.

Surface materials used in FP manufacturing were evaluated for their risk to contributing extractables or leachables to the final product.

Container closure system:

Suitability of the container closure system is sufficiently described.

Microbial attributes:

The microbiological attributes of SRP-9001 FP are sufficiently described. The presented microbial control strategy is considered sufficient to ensure microbial integrity. The process design and microbial controls ensure adequate microbiological quality. The FP does not contain preservatives or antioxidants.

Compatibility:

The FP is a ready-to-use solution for IV infusion. The solution from the vial is to be transferred with a syringe for immediate use with an IV infusion assembly (syringe and infusion assembly are not co-packed; no antimicrobial preservatives included). For complete thawing of the FP vials storage at RT for approximately 2 hours is recommended by the applicant and described in the SmPC. Compatibility of the FP with the CCS is discussed above.

All other tested quality attributes further support compatibility of the IV administration components with the FP at room temperature for up to 32 hours (24 hours in the vial plus 6 hours in the syringe; after thawing of the FP vials at RT for approximately 2 hours). Upon request confirmation has been provided that specific instructions are provided for health care professionals to visually inspect each vial of FP.

2.3.3.2. Manufacture of the product and process controls

Manufacture:

The name, address and responsibility of each manufacturer, including contractors involved in finished product manufacture and testing are described and the site responsible for EU batch release is specified.

Satisfactory GMP compliance has been demonstrated for sites involved in finished product manufacturing activities (missing documentation was raised as a Major Objection and resolved).

The finished product is manufactured using standard pharmaceutical processing steps.

A flow chart of the manufacturing process steps, including in-process controls has been provided and a narrative description of each step is given. The FP manufacturing process is described in sufficient detail.

Process parameters including hold times and accompanying acceptable ranges have been provided in tables (for critical and non-critical process parameters: CPP and nCPP).

Process control:

Critical and non-critical IPC applied to control critical steps are appropriately described and are set in line with process characterization/development and validation studies. Upon request, the following items have been adequately addressed.

Process validation/verification:

In addition to the PPQ, following a traditional approach further studies were performed to support process robustness and validation of the finished product manufacturing process. These studies include process validation studies for formulation buffer hold and hold time characterization as well as studies that were performed during process development (see above).

The applicant has described that the FP PPQ process is the same as the process used to generate clinical trial supply material and has confirmed that the FP PPQ process is representative for the intended commercial process.

The PPQ batches were produced applying NORs and by monitoring all designated CPPs and IPCs. No additional testing has been done during PPQ batch production. In principle, all unit operations for the FP manufacturing process are covered. For the filling process, data demonstrating homogeneity during filling have been provided.

All results measured for during the PPQ met the validation criteria and were consistent throughout the PPQ lots. Post PPQ, changes to NORs for process parameters and acceptance criteria or classification of IPCs were introduced. These changes were appropriately justified and are acceptable.

Maximum process and hold times have been successfully validated.

Adequate shipping validation has been performed for transport of SRP-9001.

2.3.3.3. Product specification, analytical procedures, batch analysis

The finished product specification includes attributes with respect to appearance, identity, purity, potency and safety.

Unique method identifiers have been included in the list of specifications and analytical procedure descriptions and validations for all non-compendial in house methods have been provided. In addition, references to Ph. Eur. have been included in the list of specification for the compendial methods.

The list of specifications covers relevant quality attributes which are, mostly, in line with relevant guidance, EMA/CAT/80183/2014 and Ph. Eur. 5.14. A few deficiencies are noted and discussed.

Analytical procedures and reference standards

Analytical methods used for AS and FP are described and discussed in the respective AS sections.

Reference materials and standards used in other methods are sufficiently described.

Batch Analysis

Batch analyses results are shown for FP batches manufactured according to process A and used for clinical, comparability and stability studies, FP batch manufactured acc. to process B and used for

nonclinical/comparability/stability purposes, and a total of batches manufactured at the commercial manufacturer according to process B.

Changes in analytical methods and discontinuation of methods have also been adequately described in this section.

Characterisation of impurities

The provided information is sufficient.

Container Closure system

The container closure system for SRP-9001 FP consists of a 10 mL cyclic olefin polymer vial with chlorobutyl rubber stopper and an aluminium seal with flip-off plastic caps The vial and elastomeric stopper materials comply with Ph. Eur. 3.1.3, 3.2.21 and Ph. Eur. 3.2.9, respectively. In summary, sufficient information has been provided on the CCS.

Assurance of correct dosing and traceability has been adequately justified. Usage of the shortest expiry for the total patient specific pack in case of usage of FP vials from different batches has been confirmed.

2.3.3.4. Stability of the product

2.3.3.5. Adventitious agents

The applicant has implemented various steps into the manufacturing process to minimize the risk of contamination with adventitious agents. According to the applicant, no excipients, primary packaging material and product-contact materials used in finished product manufacture contain materials of animal or human origin and the finished product complies with the EMA/410/01 "Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products".

According to the applicant, an assessment was performed on animal derived components used in the manufacturing process and has concluded that manufacturing materials produced with low-risk animal-derived components, are safe and have appropriate certifications (including TSE/BSE certification).

The testing programme for adventitious agents, non-viral and viral, is generally in line with ICH Q5A and is acceptable.

There was no evidence for bacterial, fungal, or viral contamination. The original test reports have been filed in 3.2.A.2.

Viral clearance studies

The viral clearance studies are in compliance with ICH Q5A and CPMP/BWP/268/95.

GMO

SRP-9001 is an AAV vector with an expression cassette containing a codon-optimized human SRP-9001-dystrophin complementary DNA, chimeric (SV40) intron, and synthetic polyadenylation signal, all under the control of the α-myosin heavy-chain creatine kinase 7 promoter. SRP-9001 lacks all wildtype AAV genes with the exception of ITR sequences and is therefore replication incompetent.

As SRP-9001 is considered a GMO, a separate GMO environmental risk assessment report was submitted to estimate the risk of SRP-9001 to third parties and the environment.

The clinical use of SRP-9001 provides a negligible risk for the environment and for third parties.

2.3.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

A well organised Module 3 of overall good quality for Elevidys (SRP-9001; Delandistrogene moxeparvovec) was provided. SRP-9001 is a non-replicating, recombinant adeno-associated virus (AAV) encoding a shortened form of the human dystrophin gene. Two Major Objections were raised during the procedure, concerning GMP and potency assay. These 2 MOs could be resolved during the procedure. Following assessment of responses, further characterisation and tightening of acceptance limits of the potency assay is not further pursued. GMP compliance of manufacturing and testing sites has been provided. Additionally, a number of recommendations were identified in the event that Elevidys would become approvable.

Active substance

The active substance manufacturing process and control strategy of SRP-9001 was described in detail. Process parameters (CPPs, key non-CPPs and non-CPPs) and in-process controls (IPCs, critical IPCs) and their respective acceptance ranges are presented for every manufacturing process step. Sufficient detail on establishment, manufacturing and control of starting materials was provided. Raw materials used in the upstream and downstream process are listed together with their quality standard, supplier, and their intended use.

The manufacturing process of Elevidys has been described in sufficient detail and critical and non-critical process parameters (CPPs and nCPPs), in-process controls (IPCs) as well as operating ranges were defined based on available process development studies. Overall, an effective and robust clearance capacity for enveloped and non-enveloped adventitious viruses was confirmed. The risk of potential contamination and transmission of bacterial, viral, or TSE agents appears acceptably low.

The active substance specification is acceptable.

Several issues concerning product characterisation were appropriately addressed.

The description of the Container Closure System is considered acceptable.

Based on updated real-time stability data, the claimed shelf life at ≤-60°C for the active substance can be accepted.

Finished product

Elevidys (SRP-9001 FP) is a sterile liquid solution for intravenous infusion, containing 1.33×10^{13} vg/mL of delandistrogene moxeparvovec as active substance, and is supplied in a single-use cyclic olefin polymer vial. The delandistrogene moxeparvovec active substance is formulated in a buffered solution of tromethamine /tromethamine-HCl, magnesium chloride, sodium chloride, and poloxamer 188, at pH 8 ± 0.3. Each vial contains an extractable volume of not less than 10.0 mL. The total recommended dosage is based on patient weight and requires multiple vials per dose.

The vial and stopper comply with Ph. Eur. and USP requirements.

The chosen formulation is sufficiently supported by formulation development. There are no novel excipients, and no excipients of human or animal origin were used in the manufacture of Elevidys.

Critical process parameters (CPPs) and non-CPPs (nCPPs) were defined and characterized in development and process characterization (PC) studies to generate proven acceptable ranges (PARs; for CPPs) and action limits (for nCPPs). The control strategy, consisting of control of incoming raw material, operating conditions and in-process controls and product specifications is sufficiently shown.

Process parameters and in-process controls (IPCs) are appropriately described and justified and are set in line with process characterization/development and validation studies. The FP manufacturing process is described in sufficient detail.

Comparability between the two process variants (process A for non-clinical and early clinical and process B for late clinical and PPQ batches) is discussed under the AS section.

Process validation has been performed on consecutive large-scale SRP-9001 FP batches. In addition, further studies were performed to support process robustness and validation of the finished product manufacturing process. Process validation and batch data demonstrate that the manufacturing process reliably generates finished product meeting its predetermined specifications and quality attributes. The shipping validation was sufficiently described.

FP-specific methods are suitable for their intended purpose and specifications are mostly in line with relevant guidance, 'Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products', EMA/CAT/80183/2014 and 'Gene transfer medicinal products for human use', Ph. Eur. 5.14. The acceptance criteria have been established based on product knowledge and release/stability data of FP batches manufactured according to Process B, that have been used in non-clinical, clinical, process development/validation, stability and comparability studies.

Compatibility of the primary container closure system with SRP-9001 FP over the proposed shelf life has been demonstrated. Sufficient information on the sterilization of the container closure components has been provided.

Stability studies have been conducted on SRP-9001 FP vial according to ICH Q5C. The strategy presented is supported, and the proposed shelf-life of SRP-9001 vial stored at ≤-60°C for 24 months is endorsed by the real-time data provided. The provided post-approval stability protocol and commitments are acceptable. In-use stability for Elevidys has demonstrated that the product can be stored for 24 hours at room temperature (up to 25 °C).

There are no further impurities in the FP compared to those already discussed for the active substance. The risk as regards nitrosamines can be considered as low based on the provided summary of the risk assessment.

The risk as regards extractable/leachables, and elemental impurities can be considered as low.

Adventitious agents

The risk of contamination and for transmission of adventitious agents appears adequately controlled and minimised by complementary measures implemented at various stages of the manufacturing process.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The CHMP endorses the CAT assessment regarding the conclusions on the chemical, pharmaceutical and biological aspects as described above.

In conclusion, based on the review of the quality data provided, the CAT/CHMP consider that the quality dossier of Elevidys is satisfactory.

2.3.6. Recommendation(s) for future quality development

The CHMP endorses the CAT assessment regarding the recommendation(s) for future quality development as described above.

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CAT made a number of recommendations for further points for investigation.

2.4. Non-clinical aspects

2.4.1. Introduction

In order to investigate the pharmacology, pharmacokinetics and toxicology of SRP-9001, in vivo studies have been conducted in WT and DMD^{MDX} mice and rats as well as in rhesus macaques.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

In vitro pharmacology

The role and relevance of the included elements/domains of the microdystrophin gene included in the vector was thoroughly discussed. Specific attention was paid to the different domains within the construct and their proposed function. A summarizing table was included in the dossier describing all critical included and excluded elements of SRP-9001 microdystrophin. Sarcolemmal binding efficiency of the spectrin-like repeats was addressed in an *in vitro* study. Restoration of the DAPC was evaluated by immunofluorescent analysis, showing co-localization of microdystrophin and β-sarcoglycan at the sarcolemma of stained muscle sections, without further characterization of this complex at the molecular level, which would have strengthened this claim.

Studies in mice

In study 1111840 Process B SRP-9001 material, Lot no. A-634-SRP9001-20-0004, Lot no. A-634-SRP9001-20-0006, and Lot no. A-634-SRP9001-20-0008 was tested in regard to efficacy and expression after IM (5×10^{10} vg) and IV (1.33×10^{14} or 2.66×10^{14} vg) administration to C57BL/6J and DMD^{MDX} mice (4 weeks ± 5 days of age). Terminal analysis was performed 12 weeks post-administration. Specific force in TA and eccentric contraction (ECC) improved in DMD^{MDX} mice after IM and IV administration as compared to saline treated DMD^{MDX} mice but did not reach WT levels.

The applicant provided a tabulated comparison of the process materials used in non-clinical studies, revealing a functional improvement of 37.32% (Process A), 31.42% (initial Process B), and 26.24% (commercial Process B) in TA and 10.62% (Process A), 20.59% (initial Process B) and 25.66% (commercial Process B) in DIA. Thus, it is considered that the material from different processes did not induce a similar/comparable functional improvement across studies, neither for TA nor for DIA specific force output measurements. Thus, non-clinical studies performed with process A or initial Process B material will be considered as supportive, but could not be claimed as part of non-clinical efficacy and PoC.

Dystrophin and β-sarcoglycan expression in WT and DMD^{MDX} mice with and without SRP-9001 treatment was confirmed by immunofluorescence staining of skeletal muscle, diaphragm and heart. In this respect the complete absence of any signal in untreated DMD^{MDX} mice is not considered advantageous. Staining with a reference marker would have emphasized the integrity of the data. Micro-dystrophin expression in various organs was detected via Western Blot. No expression was detected in other tissues than skeletal muscle, liver, heart and diaphragm.

Immunofluorescence staining for micro-dystrophin showed expression in muscle fibers and correct localization in the cell membranes. In addition, co-localization with in β-sarcoglycan could be demonstrated, pointing towards restoration of DAPC. Dystrophin expression was quantified by determination of percent positive muscle fibers.

Neither by Western Blot nor by immunofluorescence differences in expression between the tested lots could be detected.

Overall, commercial Process B lots of SRP-9001 administered to juvenile DMD^{MDX} mice IM or IV improved muscular functionality and lead to muscular micro-dystrophin expression irrespective of the type of administration. All lots tested performed in a comparable manner.

In order to assess dose-dependent effects of SRP-9001 after systemic administration of Process A material in DMD^{MDX} mice animals were injected IV with 4.43×10^{13} vg/kg, 1.33×10^{14}vg/kg and 4.01×10^{14} vg/kg at 4-6 weeks of age (study 1107174). IF staining using anti-dystrophin and anti-beta-sarcoglycan antibodies was performed in order to investigate restoration of DAPC in skeletal muscles and a dose-dependent increase of dystrophin positive fibers.

Histopathological assessment demonstrated the reduction of muscular pathologies after SRP-9001 administration as well as an increase in fiber diameter as compared to negative controls. Functional assessment revealed restoration of the diaphragm specific force in a dose-dependent manner with WT-levels being reached in the high dose group 12 weeks post-treatment. Long-term observation after 24 weeks of the mid-dose group indicated maintenance or even further increase of the effect. Similarly, the specific force in TA increased dose-specifically, however, it appears to a lesser extent than in the diaphragm. Also, a slight decrease in the long-term group was observed as compared to the 12-week time point.

In study 1107173 functional effects as well as biodistribution and protein expression were assessed at different doses of SRP-9001 (initial Process B material) 12 weeks after administration. Juvenile mice of 6-8 weeks of age were administered IV with $4.43x10^{13}$ vg/kg (low dose), $1.33x10^{14}$ vg/kg (mid dose) and $4.01x10^{14}$ vg/kg (high dose) as well as 0.9% sodium chloride for the vehicle control.

Micro-dystrophin expression was assessed by immunofluorescence in six skeletal muscles, i.e. PSO, TA, GAS, QD, TRI, GLUT, as well as in diaphragm and heart. Dose-dependent expression was observed in all investigated muscles, however, wild-type levels were not reached. Muscle pathology, such as fiber diameter, central nucleation and collagen deposition improved. However, the effects were not dose-dependent for all parameters and all muscles and can – in some instances – be regarded as moderate in comparison to the DMD^{MDX} vehicle controls. A dose-dependent improvement in the force output of the diaphragm was registered and it appeared that a plateau of the effect was reached at the mid-dose. The following percentages as compared to WT were achieved: vehicle 65.05%, low dose 60.05%, mid-dose 78.38%% and high dose 77.86%. Virtually no effect was observed at the low dose level. Regarding the force output of TA, no group data in numbers have been provided. However, from the graphical display it can be concluded that the deficiency in DMD^{MDX} as compared is considerably higher that the deficiency in the diaphragm force output. Also, the effect mediated by SRP-9001 on the specific force appears rather moderate and the meaning of the magnitude of the effect for a clinical benefit is not clear.

Western blot analysis revealed micro-dystrophin expression in skeletal muscles and heart. Of organs investigated, only the liver exhibited micro-dystrophin protein – presumably due to expression in the smooth muscle cells of the liver. Serum analysis revealed elevated levels of ALT, ALK/P and AST in DMD^{MDX} mice when compared to WT-mice. Reduction to WT-levels was achieved by SRP-9001 administration over almost all dose groups for ALT and ALK/P, but not for AST.

A further dose level of $7.00x10^{13}$ vg/kg of initial Process B material was tested in addition to the low and high dose in previous studies in order to identify potential differences in efficacy (study 1107193). Juvenile DMD^{MDX} and WT mice 7-8 weeks of age were injected IV and analysed in respect to micro-dystrophin expression and functional improvements 10-weeks post-administration.

IF staining of various skeletal muscles, heart and diaphragm revealed a dose-dependent increase in the percentage of micro-dystrophin positive muscle fibers. The overall percentages across all skeletal muscles for the 4.43×10^{13}, 7.00×10^{13}, 1.33×10^{14} and 4.01×10^{14} vg/kg dose groups were 18.34±1.28%, 42.36±2.30%, 54.47±1.81% and 71.74±2.54% of WT, respectively, and the differences between the dose groups were statistically significant.

Analysis of functional improvement of the specific force output was performed for diaphragm and TA. In diaphragm, an improvement in specific force output was reported starting from the 7.00×10^{13} vg/kg dose, which is not supported as the reported value is 70.39±7.07 mN/mm^2 as compared to 74.47±3.56 mN/mm^2 in the vehicle DMD^{MDX} group. In the highest dose group, the specific force was restored to 73.83% of WT, in the vehicle group the specific force output was reduced to 64.19%. Measurements in the TA revealed statistically significant improvement in the 7.00×10^{13} vg/kg dose group that also somehow represents the start of a plateau that was not exceeded by the two higher doses. The highest improvement of specific force output in TA was 63.72% as compared to WT and achieved with the 1.33×10^{14} dose. Reduction in the vehicle group was to 49.24% of WT.

Overall, the 7.00 x 10^{13} vg/kg dose individually investigated in this study did not significantly add to the previously tested studies in regard to clinical dosing. Of note, comparison of different dose-levels of different studies is considered critical in respect to comparability and regarded of limited significance for the overall assessment.

In the safety study 1111842 expression, biodistribution and functional PD endpoints, i.e. specific TA force and eccentric contraction (ECC), were included for a dose of 2.0x10^{14} vg/kg IV of commercial Process B material administered to WT and DMD^{MDX} mice 4 weeks of age.
A moderate improvement in specific TA force was observed in SRP-9001-treated as compared to saline treated DMD^{MDX} mice.

In study 1107194 4-week-old DMD^{MDX} mice were injected IM with doses of 2.36 x 10^{12} vg/kg of three different materials, i.e. Nationwide Children's Hospital (Process A), Thermo Fisher Scientific (Process B), or Catalent Pharma Services (Process B), to compare the potency of the employed lots.
Muscular functionality was assessed in TA and resulted in similar and statistically significant improvement over all three materials as compared to untreated DMD^{MDX} mice. Highest significance was reached in the Catalent Process B group. However, wild-type functionality was not reached.
Additionally, micro-dystrophin expression in muscle fibers was evaluated by IF. The percentage of micro-dystrophin positive muscle fibers was similar in animals treated with NCH process A and Thermo Fisher process B material. Lower expression was observed in Catalent process B treated animals.

In study 1119830 lot # A-634-SRP9001-21-0021 of commercial process B material was investigated regarding protein expression by IF and functional improvement after IM administration of 2.36 x 10^{12}vg/kg to DMD^{MDX} mice. Biological activity was observed in respect to both parameters with improvement of the specific force output with no statistically significant difference to WT animals. Whether the observed effect also translates to a significant clinical effect is not clear.

Studies in rats

Evaluation of myocardial and functional efficacy of the commercial Process B material was conducted in DMD^{MDX} rats 3-5 weeks of age that received an IV dose of 1.33 x 10^{14} vg/kg of SRP-9001 (study 1107185).

Cardiac function was evaluated 12 and 24 weeks after administration. As compared to saline controls heart rate, ejection fraction and fractional shortening were elevated, whereas left ventricular internal diameter diastole and systole as well as end-diastolic volume were decreased at both time points, however, without statistical significance 24 weeks after administration. The heart and body weight ratio decreased over time in both, the saline control as well as the SRP-9001 group.
Ambulation measurement of vertical and horizontal movement revealed a statistically significant improvement in comparison to saline controls 12 and 24 weeks after treatment. However, the difference between control and treatment group was clearly reduced at the 24 weeks time point as compared to the 12 weeks time point.

To evaluate changes in heart and muscle damage toponin I and CK plasma levels were evaluated. After rather inconsistent results at weeks 1 and 12, a decrease in both parameters without statistical significance was observed for both parameters 24 weeks after administration.
Consistent dystrophin expression was demonstrated in various muscle types by IF 12 and 24 weeks after administration. Histological parameters such as fiber diameter and central nucleation were statistically significantly improved as compared to saline controls throughout the study period. Similar results were obtained for the assessment of muscular fibrosis.

Five out of six SRP-9001 dosed animals survived a minimum of 26 months as compared to a median survival of 13 months in the saline group.

In summary, administration of the proposed clinical dose of 1.33 x 10^{14} vg/kg process B material resulted in improved heart function and ambulation as well as decreased biomarkers for cardiac and

muscular damage, troponin I and CK. Statistically significant improvement as compared to control animals was observed in regard to histological parameters. Also, survival of SRP-9001 treated animals increased as compared to untreated controls.

Efficacy in older rats displaying a more pronounced phenotype was analysed in 3-5 months old DMD^{MDX} rats at a dose of 1.33×10^{14} vg/kg (Study 1119829; commercial Process B material). Several deaths occurred directly after dosing in the test and control group that were probably not associated with SRP-9001 but with the poor health condition of the aged DMD^{MDX} rats.

Twelve weeks after administration, animals that received SRP-9001 displayed improvements in ambulation and vertical activity as compared to the control group.
The conducted echocardiography could not be evaluated as due to the development of the method during this study, variable approaches were used.

Serum troponin I levels did not differ between test and control group pointing towards a lack of cardioprotective effect of SRP-9001 in this study. However, the significance of troponin I regarding the effect expected from SRP-9001 is not clear. Serum CK levels, on the other hand, were decreased after administration of SRP-9001 as compared to controls pointing to a reduction of muscle damage. Quantitative dystrophin expression revealed levels less than 50% of normal in various muscle types except for the heart that exhibited ~ 175% dystrophin expression as compared to normal tissue. IF showed dystrophin expression at the sarcolemma of skeletal muscle and heart.

Histopathological examination of medial gastrocnemius, heart and diaphragm demonstrated that the percentage of central nuclei did not improve after SRP-9001 treatment, whereas a slight improvement of fiber diameter was observed after treatment.

The long term efficacy of SRP-9001 for up to 52 was evaluated in DMD^{MDX} rats 3-6 weeks of age after administration of 7.0×10^{13} vg/kg and 1.33×10^{14} vg/kg, respectively (Study 1112486).
Ambulation was statistically significantly improved in the SRP-9001 groups as compared to the saline controls 12-weeks after administration and even reached wild-type levels. After 52 weeks ambulation declined in all cohorts and as the saline control group also the treatment groups statistically significantly differed from wild-type levels and showed only moderate improvement.

Vertical activity was moderately improved after 12 weeks with no statistical significance in comparison to the control group. The effect was no longer observed after 52 weeks and even appeared to fall below negative control levels in the low dose group.

Cardiac parameters such as left ventricle anterior wall thickness, left ventricle posterior wall thickness, ejection fraction fractional shortening largely improved over time and were maintained throughout the whole study period or became only apparent at the 52-week time point in case of deficiencies that only developed at a later time point.

Cardiomyocytes isolated from rats necropsied 12 weeks after treatment were subjected to in vitro functional evaluation. Sarcomere length and contractility were statistically significantly improved in SRP-9001 treated cardiomyocytes and dysregulated calcium handling significantly shifted towards normal.

Histopathologic analysis revealed dose-dependent reduction of fibrosis after SRP-9001 treatment in tibialis anterior, medial gastrocnemius, triceps as well as in the heart. The difference between the dosing groups was pronounced 12 weeks after treatment and reduced at 52 weeks. Wild-type levels were reached in the heart but not in the skeletal muscle. Similarly, the percentage of central nuclei and fiber diameter improved as compared to saline controls.

Serum biomarkers of liver dysfunction, i.e. alanine aminotransferase and aspartate aminotransferase, were elevated in saline controls but reduced in SRP-9001 treated animals 12 weeks post-treatment. Creatine kinase and cardiac troponin I were also clearly reduced as compared to untreated controls. Micro-dystrophin levels quantified by western blot increased in a dose- and time-dependent manner in skeletal muscle and heart, whereby the highest amounts even exceeding wild-type levels were detected in the heart. In cardiomyocytes isolated after 52 weeks the amount of micro-dystrophin was statistically significantly different between the two dose groups. Quantification of dystrophin positive muscle fibers revealed that the percentage of positive fibers was dose-dependent but not time-dependent as the maximum percentage was already reached after 12 weeks.

Studies in monkeys

An exploratory study in a 4.75-year-old rhesus macaque that received a dose of 1.33×10^{14} vg/kg of a surrogate transgene containing a FLAG tag at the C-terminus via the cephalic vein was conducted in order to examine safety and efficacy in a large animal model (study 1107175). At necropsy 12 weeks after infusion FLAG positive muscle fibers were assessed by IF, however, quantification was not provided. In addition, micro-dystrophin was quantified by western blot without specification whether the endogenous dystrophin was also detected by this method. The efficacy after re-dosing under immunosuppression and therapeutic plasma exchange was evaluated in rhesus macaques that received 1.33×10^{14} vg/kg SRP-9001 (1107181). The results point towards the possibility of efficient re-dosing after TPE.

2.4.2.2. Secondary pharmacodynamic studies

Studies on secondary pharmacology were not conducted with SRP-9001 which is acceptable.

2.4.2.3. Safety pharmacology programme

No dedicated safety pharmacology studies were conducted with SRP-9001. Functional cardiac endpoints were evaluated in rat PD studies and results point towards an improvement of various parameters in DMD^{MDX} rats treated with SRP-9001 as compared to saline controls. Similarly, cardiomyocytes isolated from SRP-9001 treated DMD^{MDX} rats showed improved functionality as compared to saline controls. In addition, troponin I levels have been monitored in order to demonstrate a protective effect on the cardiac phenotype that develops during the course of the disease. However, results were equivocal between studies. No data from WT rats treated with SRP-9001 have been provided and data from disease models are only regarded supportive. According to the applicant, SRP-9001-related but non-adverse deficits in locomotor activity and maximum acoustic startle response parameters were observed in males administered 4.01×10^{14} vg/kg in the pivotal juvenile toxicity study in WT mice [1107187]. Overall, no adverse effects on neurobehavioral endpoints were reported. No dedicated safety pharmacology parameters were assessed in NHPs.

2.4.2.4. Pharmacodynamic drug interactions

Studies on pharmacodynamic drug interactions have not been conducted.

2.4.3. Pharmacokinetics

Pharmacokinetics assessment of SRP-9001 was incorporated in pharmacodynamics and toxicological studies conducted in mice, rats and non-human primates. Biodistribution was assessed in WT and DMD^{MDX} mice, in DMD^{MDX} rats and rhesus monkeys. In addition, plasma pharmacokinetics and viral shedding were analysed in DMD^{MDX} and WT mice.

An analytical qPCR method was developed for the determination of **vector genome copy numbers** in tissues, plasma, urine and feces to be measured in mouse GLP studies.

In addition, an exploratory digital droplet PCR method was established to evaluate absolute linearized SRP-9001 vg copy numbers without the need for a calibration curve in tissues.

Anti-capsid antibodies in mouse serum were measured in an electro luminescence immunoassay (ECLIA) or an ELISA method in mouse and monkey serum. An exploratory mRNA in situ hybridization assay was applied to determine transcripts in mouse ovary and testis.

The definitive assays were validated according to recent guidance.

Absorption was not specifically assessed for SRP-9001. However, in a single-dose toxicity study in mice (1107172) plasma exposure was evaluated in DMD^{MDX} as well as WT animals. This revealed a distribution phase of up to 10 days post dose and a slower terminal elimination phase. Exposure (C_{max} and AUC) were dose-proportional between 4.01×10^{14} and 1.33×10^{14} vg/kg, whereas total plasma clearance, central volume and volume of distributions associated with the terminal phase were dose-independent. $T_{1/2}$ was about 5 hours in the initial phase and 178 h in the terminal phase for both doses. This is consistent with quantifiable plasma concentrations for up to 40 days after administration in the high dose group.

In Study 1119827 a population PK model was established based on these in vivo data and resulted in a linear two-compartmental distribution model, linear elimination from the central compartment, correlated inter-individual variability was estimated for central volume and plasma clearance, an absolute error model for log-transformed concentrations was used.

Biodistribution was assessed in mice, rats and rhesus macaques predominantly 12 weeks after IV administration but occasionally also after 24 or 52 weeks. A panel of target as well as off-target tissues were analysed.

Vg levels in *mouse* tissues were largely dose-dependent and in a similar range in WT and DMD^{MDX} tissues. Throughout all studies contributing to biodistribution data, tissues with highest numbers were the liver, adrenal glands, heart and muscle tissue. Occasionally, higher vg numbers have also been detected in off target tissues such as esophagus and bone, however, only at higher doses than the clinical dose. On average a vg number of 2-3 was found in the skeletal muscle of animals treated with the clinical dose 12 weeks after administration.

In study 1107173 vg numbers only ranged from 0.06 to 0.32 vg/nucleus in the skeletal muscles of DMD^{MDX} mice 12 weeks after having received the clinical dose of initial process B and, thus, no difference to off-target tissues in terms of vg/nucleus exists. Similar low vg levels were observed in the skeletal muscle of study 1111840 throughout all initial process B lots tested.

Biodistribution in newborn WT mice administered on PND1 with 1.33×10^{14} or 4.01×10^{14} vg/kg assessed in liver, heart and skeletal muscle four weeks after treatment was clearly lower than in older animals (1107191). Exposure increased more than dose-proportional. Like in older mice highest levels were detected in the liver followed by heart and skeletal muscle. According to the applicant, when normalized to liver exposures the exposure in heart and muscle was comparable to that in juvenile mice.

Overall, prominent distribution to off-target organs did not become apparent from the data provided.

In *rat* tissues with highest exposure were liver, heart, spleen, fat and lymph node. Muscle exposure was with few exceptions < 1 vg/nucleus and vg numbers in same tissues were generally comparable, when analysis was performed at two different time points.

In *rhesus macaques* biodistribution was comparable to mouse and rat tissues. Interestingly, redosing did not result in higher vg/nucleus levels in muscle tissues when compared to levels after the first dose (1107181).

Low distribution to *gonads* was observed in mice, rats and monkeys 12 weeks after administration of the clinical dose. In rat study 1107185 where tissues were analysed 12 and 24 weeks after treatment a clear decrease in vg/nucleus was observed at the later time point.

Distribution to *brain* and *spinal cord* was negligible in most mouse studies when the clinical dose was administered. Only in study 1111842 vg levels > 1 were detected in both tissues. Very low vg levels were observed in rat brains. Cerebellum, frontal lobe and mid cortex exhibited vg levels comparable to muscle tissues examined in rhesus macaques (1107181).

The **metabolism** of SRP-9001 was not analysed which is acceptable due to the composition of protein and DNA.

Excretion of SRP-9001 was evaluated in the urine and feces of WT and DMD^{MDX} mice that received doses of either 1.33 x 10^{14} and 4.01 x 10^{14} vg/kg (1107172). Samples were collected starting from day 2 up to day 44 after administration every 3 days and evaluated for SRP-9001 by qPCR. Peak concentrations in both urine and feces were determined 2 days post-administration. The vector was detectable in urine for about 10 days with a tendency to longer detectability in the high dose group. and in feces through 44 days. No difference in excretion became apparent between WT and DMD^{MDX} mice, however, the detected vg level were roughly dose-related.

No **pharmacokinetic drug interaction** studies have been conducted.

The applicant conducted an analysis on the **PK/PD relationship** between tissue vector exposure and biological as well as functional response and established maximum effect models based on the existing results from studies 1107173, 1107174, 1107172, and 1111840 (study 1119828). The whole dose range of 0.443, 0.7, 1.33, 2.66, and 4.01 x 10^{14} vg/kg was included in the analysis.

Analysis of the relation of tissue vector exposure (vg/nucleus) to the percent positive micro-dystrophin fibers in triceps, gastrocnemius and quadriceps revealed a dose-response effect with regard to exposure. In addition, a context between vg/nucleus and micro-dystrophin positive fibers is noted. A plateau effect regarding protein expression was observed starting from the dose of 2.66 x 10^{14} vg/kg. Of note, the applicant stated that a similar correlation between WB data and vg/nucleus could not be established due to high variance of WB results.

In principle, IF is not considered to be of comparable accuracy to WB for protein quantitation. A less pronounced correlation was observed between vg/nucleus and functional improvement expressed as the relative specific force in the diaphragm and tibialis anterior.

Overall, the correlation of biological and functional endpoints is acknowledged. However, due to various shortcomings in study design and data pooling the study is rated explorative and supportive.

2.4.4. Toxicology

Two non-GLP single-dose toxicity studies were conducted to evaluate the potential toxicity of research-grade SRP-9001 manufactured with Process A. Study [1107174] evaluated the efficacy, toxicity, and biodistribution of SRP-9001 in DMD^{MDX} and WT mice following a single IV dose followed by either a 6-, 12-, or 24-week observation period. An exploratory study in one rhesus macaque [1107175] examined biodistribution, preliminary safety, and immunological responses following a single IV dose of a FLAG-tagged version of SRP-9001 with a 12-week endpoint. Subsequently, a dual-dose evaluation examined the biodistribution, immunological response and efficacy of SRP-9001 in rhesus macaques. Both NHP studies were conducted with material from Process A.

A GLP-compliant study [1107172] examined the toxicity, biodistribution, shedding, and immunogenicity of SRP-9001 manufactured with initial Process B (Thermo Fisher) after a single IV dose in DMD^{MDX} and WT mice with 12- and 24-week endpoints. Next, a GLP-compliant study [1107192] evaluated the single IV dose toxicity and biodistribution of SRP-9001 manufactured with the intended commercial Process B (Catalent) in DMD^{MDX} and WT mice following a 12-week observation period. Finally, a DRF [1107191] and a definitive [1107187] juvenile toxicity study evaluated the safety of a single IV injection of SRP-9001 intended commercial Process B (Catalent) material to neonatal WT mice.

Further, a study to examining vector integration in NHP liver tissue study [1128231] and two studies on impurities [1107176], [1107180] were conducted.

Single dose toxicity was evaluated in WT and *mdx* mice after single doses of 1.33 to 4.01 x 10^{14} vg/kg with an observation period from 12 to 24 weeks.

2.4.4.1. Single dose toxicity

Study 11070174 was conducted with research grade Process A material and was only exploratory in nature with regards to toxicity evaluations. A variety of skeletal muscles including the diaphragm, along with the heart and five major organs (kidney, liver, lung, spleen and testis) were harvested for histopathology. The test article did not induce anatomic lesions in any skeletal muscle or the heart of young adult, male DMD^{MDX} or wild-type mice at 12 or 24 weeks after administration. Further, serum chemistry and hematology evaluations indicated normal values across all parameters tested. Overall, no SRP-9001-related adverse findings were observed, and the high dose of 4.01×10^{14} vg/kg was considered to represent the NOAEL.

In the GLP-compliant pivotal study 11070172, male WT or DMD^{MDX} mice were administered vehicle control article or 1.33×10^{14} or 4.01×10^{14} vg/kg SRP-9001 via a single IV injection and observed for either 12 or 24 weeks. Toxicity evaluation was based on mortality, clinical observations, body weight, and clinical and anatomic pathology. Blood, urine, and faecal samples were collected for viral shedding analysis. Blood samples were collected for AAV antibody analysis and frozen tissues were collected for biodistribution analysis. There were 8 unscheduled deaths in this study; for three of them, the cause of death was undetermined; one death was considered accidental in relation to blood sampling; the remaining four animals displayed signs of brain ventricle dilatation.

Decreased, reversible, body weight gains were observed for DMD^{MDX} mice administered 4.01×10^{14} vg/kg. Clinical pathology changes noted in both strains included minimally higher mean corpuscular haemoglobin concentration on Day 85 in mice administered $\geq 1.33 \times 10^{14}$ vg/kg. The effect was no longer observed on Day 169, which indicated reversibility. According to the applicant, other SRP-9001-related clinical pathology effects were noted only in DMD^{MDX} mice, and some were attributable to the pharmacologic action of the test article. Most of the effects exhibited evidence of reversibility by Day 169. However, at Day 169, lower AST and GLDH levels were observed in DMD^{MDX} mice. The decrease in AST appeared to be dose dependent with 3 out of 4 animals having a mild decrease in the low dose group, and 4 out of 5 animals having a moderate decrease in the high dose group. GLDH activity was mildly affected in all animals in both dose groups at both, the interim sacrifice and on Day 169. Platelet count was also mildly decreased at both time points.

SRP-9001-related microscopic liver findings (hepatocyte hypertrophy/necrosis and mitosis as well as oval cell hyperplasia) were noted at the interim sacrifice in WT mice administered $\geq 1.33 \times 10^{14}$ vg/kg. At the terminal sacrifice increased incidence and/or severity of minimal to moderate hepatocyte vacuolation was still present. The finding had no clinical pathology correlates at the terminal sacrifice indicating a lack of functional impact on the liver.

In the GLP-compliant pivotal study 11070192, male WT or DMD^{MDX} mice were administered vehicle control article (0.9% sodium chloride) or 1.33×10^{14} or 4.02×10^{14} vg/kg SRP-9001 via a single IV injection and were observed for 12 weeks. Toxicity evaluation was based on mortality, clinical observations, body weights, food consumption, and clinical and anatomic pathology. Frozen tissue samples were collected from biodistribution animals for qPCR biodistribution analysis. The findings in WT mice were restricted to alterations in body weight or body weight gain in the high dose group and a test article-related increase in spleen weights in the low dose group without macroscopic or microscopic correlates. No SRP-9001-related mortality, clinical observations, food consumption, clinical pathology, or macroscopic or microscopic findings were noted in C57BL/6J mice administered up to 4.02×10^{14} vg/kg and this dose is considered the NOAEL for the WT mice in that study.

Three unscheduled deaths occurred in mdx mice; one low dose animal was found dead on Day 79. No abnormal observations were noted prior to the unscheduled death of this animal. At necropsy, bilateral, large iliac lymph nodes were noted. The cause of death was not determined and was considered not related to test article due to the lack of similar macroscopic observations in other animals. Two high dose animals were sacrificed in moribund condition. Upon microscopic examination, moderate or marked dilatation of the brain ventricles was noted for both animals and was considered the cause of moribundity (see below). There were no other SRP-9001-related clinical observations in mdx animals. *Mdx* mice administered 1.33×10^{14} or 4.02×10^{14} vg/kg gained 9% or 29% less body weight, respectively, compared with controls, over the duration of the study.

With regard to clinical pathology, low and high dose *mdx* mice showed slightly decreased mean reticulocyte counts, platelet counts, WBC counts and neutrophils compared to the control group. Additionally, decreases in mean AST and ALT compared to the control group were observed in both dose groups (≥1.33 x 10^{14} vg/kg). According to the study director, these findings were not considered adverse due to the small magnitude of the changes. The observed AST and ALT changes in SRP-9001-administered *mdx* mice were attributed to decreased muscle injury, consistent with the histopathology observations of reduced muscle degeneration in heart and skeletal muscles of SRP-9001-administered *mdx* mice compared to control mice. Further, SRP-9001-related, decreased liver/gall bladder weights were noted for *mdx* mice administered ≥1.33 x 10^{14} vg/kg, but without a microscopic correlate.

Two exploratory, non-GLP compliant, in vivo studies were conducted in NHP with initial process A material to investigate the toxicity, immunogenicity and biodistribution of SRP-9001.

Study 1107175 investigated the biodistribution and immune response to SRP-9001 in a single rhesus macaque after a single dose of 1.33 x 10^{14} vg/kg. To enable specific detection of micro-dystrophin expression in the presence of endogenous dystrophin expressed in healthy monkey, a FLAG-tagged SRP-9001 analogue was used. Baseline chemistries and several immunological assessments were performed every 2 weeks during the 3 months observation period of the study.

Transient and expected increases were observed in T-cell response to the AAV capsid but levels returned to baseline by 8 weeks post-delivery. No relevant T-cell responses against SRP-9001 transgene protein were observed. Anti-AAVrh74 antibodies increased after the Week 2 sample and reached the highest levels in the sample taken shortly after Week 8; consecutively anti-AAVrh74 antibody levels declined at Week 12. Immunofluorescence staining for the FLAG tagged human micro-dystrophin protein was used to determine transgene expression in skeletal muscle. However, expression in off-target tissues was not examined.

Complete blood count (CBC) and chemistry panels showed elevated liver enzymes. ALT increased approximately 4.5-fold with a maximum at Week 6. AST increased approximately 3.5-fold with a maximum at Week 8. Both values decreased but were still elevated at the end of the 12-weeks observation period. Histopathologic changes in the liver comprised minimal fibrosis and mild lymphocytic infiltration of periportal regions, sometimes with penetration into the adjacent hepatic parenchyma. According to the study report, the changes were fairly widespread but not accompanied by overt tissue destruction. Due to the lack of concurrent control animals the relationship of the liver changes to rAAVrh74.MHCK7. Microdystrophin.FLAG injection could not be defined.

The purpose of study 1107181 was to evaluate safety and efficacy of re-dosing SRP-9001 (Process A Material) using different methods of immunosuppression regimens or therapeutic plasma exchange (TPE). In brief, the gene therapy and immunosuppression treatments were administered safely to all animals (n=14) at the single dose of 1.33 x 10^{14} vg/kg in part 1 of the study. There was no significant inhibition of immune response with any of the immune suppression regimes applied (prednisone or triple immunosuppression by prednisone, rituximab and sirolimus). In Part 2, TPE was well tolerated and led to a decrease in anti-AAVrh74 antibody (IgG) levels. Re-dosing was well tolerated for all animals that underwent TPE and led to increased transduction and expression. A second dose of SRP-9001 was not tolerated when animals were not sufficiently immune suppressed and anti-AAV antibodies remained high.

Toxicity findings comprised transient liver enzyme elevations, minimal to moderate atrophy of the marginal zone of the spleen, minimal to mild decreased lymphocytes in splenic follicles, mild lymphoid follicular atrophy of the inguinal and mesenteric lymph nodes, and minimal and moderate bile duct hyperplasia.

Toxicity in juvenile mice (wildtype, strain C57BL/6) was evaluated in two single dose studies. In both studies intended commercial Process B material was used.

Study 1107191 was a non-GLP compliant dose range study, in which SRP-9001 was administered as a single IV dose to male neonatal WT mice at 1.33 x 10^{14} or 2.50 x 10^{14} vg/kg on PND1 followed by a 4-week observation period. Assessment of toxicity was based on mortality, clinical observations, body

weights, food consumption, and macroscopic observations. Additionally, tissue samples from the liver, heart, and skeletal muscle were collected and analyzed for biodistribution analysis.

A dose dependent increase of vector distribution in liver, heart and skeletal muscles was observed during the 28-day study duration.

Overall mean body weight gains during the course of the study were reduced by up to 18.4%. However, based on the attribution to a single litter, lack of dose response and no corresponding reductions in mean food consumption, the reductions in mean body weight gains for SRP-9001-treated animals were considered incidental and not SRP-9001-related.

It was concluded that there was no SRP-9001-related mortality, clinical or macroscopic observations, or effects on body weight or food consumption.

In the pivotal, GLP compliant, study 1107187, male and female neonatal WT mice received a single temporal vein injection of 1.33×10^{14} or 4.01×10^{14} vg/kg SRP-9001 on PND1 to assess efficacy, biodistribution and toxicity including neurobehavioral functionality after a 13-week post-dosing phase.

Overall, no SRP-9001-related mortality or clinical observations were noted. Body weight gain and body weight were significantly decreased in male mice of both dose groups in the neurobehavioral subgroup, as well as in females of the high dose group. Due to the dose-responsive manner, the lower mean body weight gain and mean body weight were considered SRP-9001 related but non-adverse due to the low magnitude of change. Of note, these effects were only observed in one of the three subgroups in the study (neurobehavioral group).

A significant increase in total femur BMD was observed in females at both dose levels, whereas no such effect was noted in males. The evaluation of bone growth indicated that SRP-9001 caused no effects in male femur bones but increased BMD in female femur bones in juvenile WT mice.

2.4.4.2. Repeat dose toxicity

Not available

2.4.4.3. Genotoxicity

Vector integration was evaluated in liver tissue from cynomolgus monkeys.

Five animals were treated with 1.33 x 10E14 vg/kg ssAAV rh74.CMV.eGFP vector and necropsied 12 weeks post test item administration. Liver tissues were collected from a sampling of 2 liver regions per animal. DNA isolated from all liver samples was used for target enrichment sequencing (TES) in a triplicate analysis, which is considered an acceptable method for this purpose.

In total, 35385 unique exactly mappable ISs were detected across all samples with 1504 to 8204 unique exactly mappable IS for each transduced sample. The highest relative contribution was found for the FARSB gene (Phenylalanyl-TRNA Synthetase Subunit Beta) constituting 0.166% of all IS sequence counts. Common integration site (CIS) analysis revealed that 25324 IS (71.57% of all IS) were detected in a total of 8618 CIS across different chromosomes. CIS analysis revealed a diverse composition of clusters, in line with the IS integration profile, without any evident IS hotspots.

The frequency of IS harboured in 100 kb proximity to a transcription start site (TSS) of selected cancer-associated genes revealed that 7.1% of all uniquely mappable ISs were close to predefined, well-characterized genes listed in the Cancer Gene Census database. The strongest relative contribution per sample was found for three cancer-associated genes (*EXT2*, *FLT4*, *MAP2K1*), each constituting to 0.13% of all IS read counts from the respective sample.

2.4.4.4. Carcinogenicity

Not available

2.4.4.5. Reproductive and developmental toxicity

No dedicated reproductive and developmental toxicity studies have been conducted.

Toxicity in juvenile mice is described above.

Further, a discussion on potential germline transmission has been provided.

2.4.4.6. Toxicokinetic data

Biodistribution data have been provided and are summarized in the section on Pharmacokinetics.

2.4.4.7. Other toxicity studies

Study [1121960]

Seropositivity for anti-AAVrh74 antibodies following both IM and mucosal (ocular) delivery was investigated in a model of male C57BL/6J mice (wildtype). The doses examined were based on expected levels of shed vector and ranged from 1 x 10^2 to 1 x 10^{10} vg. Following IM administration, seroconversion occurred at doses of 10^8 vg or higher. Seropositivity levels and vector genome levels in the injected muscle increased with the dose. With increasing dose, vector genome levels became detectable in adjacent muscle and within the liver. No antibodies against AAVrh74 developed (seroconversion) following the topical application to the conjunctiva (i.e., a mucous membrane) up to a dose of 10^{10} vg. There were no notable vector genome levels in the tissues of animals treated by ocular administration.

Studies on impurities

A dedicated short term nonclinical safety study in DMD^{MDX} mice was conducted to evaluate the potential expression, clearance and persistence of four DNA contaminants detected in the course of an out-of-specification (OOS) observation. Further, the clearance and persistence of the DNA contaminants in the affected vector lot was examined in blood and tissue samples of DMD^{MDX} mice in an additional nonclinical study.

In conclusion, no toxicity was observed and no safety concerns are raised. Of note, the affected vector lot was used for the manufacturing of research-grade Process A material; the intended commercial Process B material was not affected by the OOS event.

2.4.5. Ecotoxicity/environmental risk assessment

Delandistrogene moxeparvovec (SRP-9001) is a single-administration (one-time) gene therapy product designed to treat the underlying biological cause of Duchenne muscular dystrophy (DMD) by delivering a functional shortened dystrophin, called SRP-9001 micro-dystrophin, to cardiac and skeletal muscle; the key tissues affected in this lethal degenerative disease. The intended patient population is patients with a confirmed mutation in the DMD gene.

Delandistrogene moxeparvovec consists of a vector genome ITRs derived from human AAV Serotype 2 and a capsid from non-human primate-specific AAV Serotype 74 (i.e., AAVrh74). AAVrh74 was isolated from rhesus monkeys and selected on the basis of high tropism for skeletal and cardiac muscle. The rh74 serotype has only been found in primates with wide tissue propensity. It shares 93% amino acid identity with AAV serotype 8 and is most similar to a related clade E virus rh10 with 99% amino acid identity.

Delandistrogene moxeparvovec has been constructed to be replication-incompetent for the administration to patients with DMD. The inserted sequence for expression of human SRP-9001 micro-dystrophin is not hazardous. Delandistrogene moxeparvovec is still susceptible to immune response. Delandistrogene moxeparvovec does not contain viral coding sequences and does not express Rep proteins to avoid not only DNA replication but also prevent site-specific integration into the patient's genome.

2.4.6. Discussion on non-clinical aspects

Pharmacology

In vitro pharmacology was limited to the assessment of the lipid-binding capacity of three differently designed peptides in order to evaluate the sarcolemmal binding efficiency. Co-localization of micro-dystrophin and β-sarcoglycan at the sarcolemma of IF-stained muscle sections was interpreted as restoration of the DAPC by the applicant. In the light of the fact that not the full-length but a shortened form of dystrophin is expressed by SRP-9001 and a rather complex molecular interaction is required for a functional formation of the DAPC, further investigation would substantially support the demonstration of a PD effect.

In vivo studies on pharmacology, biodistribution and toxicity of SRP-9001 were predominantly conducted in DMD^{MDX} mice and a DMD rat model, the latter also exhibits DMD-related cardiomyopathy, as well as in WT mice and rhesus macaques. In the light of the childhood onset of DMD, non-clinical studies addressing the efficacy, biodistribution and safety of SRP-9001 were conducted in animals 4-6 or 6-8 weeks of age corresponding to children of 5-12 years. One study was performed in adult rats (3-5 months of age). The administered doses ranged from 2.36×10^{12} vg/kg to 6×10^{14} vg/kg. Three different materials, i.e. research Process A, initial Process B and commercial Process B, have been employed in the in vivo PD studies. In general, SRP-9001 was administered intravenously, however, some experiments with intramuscular administration were also performed.

Pharmacodynamic endpoints variably analysed throughout the in vivo studies were: assessment of microdystrophin protein expression via immunofluorescence and western blot, histopathological parameters such as muscle fiber diameter and central nucleation, functional assessment via specific force output of tibialis and diaphragm in mice as well as mobility in rats and serum creatine kinase as well as troponin I levels. Endpoints were mainly evaluated 12 weeks post dosing. In some cases the observation period was extended to 24 weeks or 52 weeks.

The **percentage of microdystrophin positive fibers** was in general dose-dependent and ranged from around 20% to > 90% over all doses and materials tested. For commercial process B material administered at the clinical dose of 1.33×10^{14} vg/kg the percentage of positive fibers in DMD^{MDX} mice was around 75% 12 weeks after administration (study 1111840). A similar range for microdystrophin positive fibers was observed in rats treated with commercial process B material after 12 weeks. A tendency for a decrease in microdystrophin positive fibers was noted after 24 weeks (study 1107185; administration to young rats), however, not in Study 1112486 after 52 weeks (administration to adolescent rats).

Restoration of the DAPC was addressed by immunofluorescent analysis of co-localization of microdystrophin and β-sarcoglycan (surrogate marker) at the sarcolemma of stained muscle sections of skeletal muscles, diaphragm, and heart. However, concerns regarding single staining as well as co-localization of dystrophin and β-sarcoglycan in heart and diaphragm across the referenced studies exist. While a qualitative match of dystrophin and β-sarcoglycan is supported and each staining is considered specific in skeletal muscle, the staining in heart and diaphragm is not deemed specific due to high background staining being detected also in the no-primary control staining. Overall, a qualitative claim on the presence or absence of dystrophin and β-sarcoglycan staining might be supported by the provided data. However, based on the assay variability and only low specificity of the staining (especially in heart and diaphragm tissue), a quantitative evaluation of either transgene expression or co-localization with β-sarcoglycan is not regarded valid. However, a qualitative interpretation of the provided data on IF staining appears possible (yes-or-no), but limits the interpretation of data with respect to efficacy or functional benefit.

Evaluation of the **muscular fiber diameter** in comparison to saline treated DMD^{MDX} mice resulted in the observation of almost no effect in the diaphragm (study 1107173; initial Process B material; 4.43×10^{13} vg/kg) up to 20% improvement in the tibialis anterior (study 1107173; initial Process B material; 4.01×10^{14} vg/kg). An increase in overall muscular fiber diameter was also observed in rats (Studies 1112486 and 1107185; commercial Process B material; 1.33×10^{14} vg/kg) with a tendency to further increase at the 24 weeks time point as compared to 12 weeks. At the 52 weeks time point in

Study 1112486 WT levels are almost reached – no comparative WT data were provided in Study 1107185. A clear reduction in **central nucleation** from around 50% (saline controls) to 20% (SRP-9001) was registered in rats 12 and 24 weeks after administration (Study 1107185). Similar results were observed 12 weeks after administration in rat study Study 1112486, however, the effect was maintained also through the 52 weeks time point. Nevertheless, WT levels were not reached.

Functional assessment was performed in mice by analysis of specific force outputs of diaphragm and tibialis anterior. Measurement at the tibialis anterior was conducted in anaesthetised mice with surgically exposed muscle that was stimulated by a single electrical impulse. The maximum absolute isometric tetanic force normalized to the cross-sectional area of the muscle was defined as the specific force. Diaphragm tetanic contraction was measured in dissected and stabilized sections from the diaphragm. Similar to the tibialis the specific force was defined. In rats, ambulation and rearing activity was detected in an activity cage.

In mice muscle function was reduced to a minimum of about 50% of WT in DMD^{MDX} saline controls. Functional improvement over all doses and materials employed, was largely low to moderate as compared to WT or DMD^{MDX} saline controls. A comparison between all three process materials provided by the applicant revealed a functional improvement of 37.32%, 31.42% and 26.24% for Process A, initial Process B and commercial Process B material in TA. Diaphragm specific force in saline controls was improved to similar levels as TA force at the clinical dose of 1.33×10^{14} vg/kg. The improvement in the diaphragm was clearly lower, i.e. 10.62%, 20.59% and 25.66%. Of note, the highest percentage of dystrophin positive fibers was achieved with commercial Process B material, which did, however, only achieve the highest functional effect in diaphragm, but the lowest in TA as compared to the other lots tested.

An additional cohort of young animals from study 1107185 was dosed to examine the potential long-term survival benefits of SRP-9001; treatment with 1.33×10^{14} vg/kg SRP-9001 extended the survival of the DMD^{MDX} rats beyond 20 months. Ambulation and vertical activity were, however, not assessed in the scope of this long-term study. Persistence of the vector (qPCR) and transgene expression analysed by WB analysis at the survival timepoint were assessed. Subject to concerns for numerical analysis of the WB data, a durable expression is only observed in the heart of SRP-9001 treated animals, while virtually no dystrophin is found in skeletal muscle and diaphragm. The median survival of SRP-9001-treated young DMD^{MDX} rats doubled compared to controls (median survival of saline-treated rats was 13 months post-treatment, while SRP-9001-treated rats showed a median survival of 26 months post−treatment), almost reaching the WT median survival age of 29-30 months. However, no data on functional improvement are available and an improved functional outcome in terms of ambulation may not be deduced from a longer survival.

Ambulation and vertical activity in rats improved to statistically significant levels compared to DMD^{MDX} saline controls 12 weeks after administration in Studies 1107185 and 1112486 and showed a tendency to improvement in adult rats in Study 1119829. Of note, the observed improvement was clearly reduced at the 24-weeks timepoint as compared to the 12-weeks timepoint in study 1107185 and further declined to only minimal improvement being detected at 52 weeks post-treatment in study 1112486, suggesting the loss of functional improvement over time. Interestingly, functional improvement was lost at 52 weeks post-dosing in study 1112486, despite stable vector and protein expression. These observations are explained by an age-related decline in ambulation and vertical activity and are also linked to natural causes like increased size of animals as activity also declined in wt-animals. Also, functionality is likely to be influenced by to progressive replacement of functional muscle tissue by non-functional fibrotic tissue and fat as disease is progressing. This might explain the stable transgene expression throughout the study period and at the same time a decrease in functional improvement. The applicant further points out that the functional tests applied in the rat studies are not comparable to clinical functionality assessment. In order to confirm therapeutic improvement of DMD^{MDX} rats that had been dosed with SRP-9001 at the age of 4 weeks, the applicant submitted new survival data generated in study 1107185. Results demonstrate a prolonged survival of treated animals as compared to saline controls from a median of 13 months to a median of 26 months. In addition, the percentage of dystrophin positive muscle fibers was evaluated at the terminal survival endpoint and was comparable to the 12- and 24-week time points for several muscles except for diaphragm, where

the percentage of dystrophin positive muscles was clearly higher at the terminal survival time point. However, it remains unclear whether this improved survival is associated with a functional improvement and a delayed progression of disease.

Creatine kinase and troponin I were evaluated in rat serum as biomarkers for damage of skeletal or heart muscle, respectively (Studies 1107185, 1119829, 1112486). A decrease in CK was detectable in all studies after 12 weeks. Results for TP I were equivocal. 24 and 52 weeks after administration, both markers were reduced as compared to saline controls. Similarly, **ALT and AST** evaluated in rats and mice (Studies 1112486 and 1107174) were reduced in SRP-9001 treated DMD^{MDX} animals as compared to saline controls 12 weeks after delivery.

Cardiac function and structure were evaluated in rats in studies 1107185 and 1112486 after 12 and 24 or 12 and 52 weeks, respectively. Beneficial effects on cardiac remodelling and function were observed, however, effects were distinctly pronounced between different studies. The improvements were more pronounced after 24 weeks and 52 weeks, respectively, as compared to 12 weeks. In study 1112486 cardiomyocytes were isolated from mice of all cohorts 12 weeks after treatment and subjected to functional in vitro analysis regarding sarcomere contractility and calcium handling. Functionality to WT levels was restored in cardiomyocytes isolated from SRP-9001 treated DMD^{MDX} rats.

A **bridging study** was performed with research-grade Process A, initial Process B, and the intended commercial Process B material in mice that were intramuscularly dosed with $2.36x10^{12}$ vg/kg (Study 1107194). Analyzed endpoints were muscular dystrophin expression via IF as well as functional assessment of the TA specific force. The applicant claimed that the three different materials applied across all non-clinical studies are similar based on the non-clinical data package, which is not endorsed, since relevant differences with regard to functional improvements in TA and DIA specific force output were acknowledged. In terms of functional comparability of the three different process materials employed in non-clinical in vivo studies, the applicant provided a detailed statistical re-evaluation of results from the bridging study where 2.36×10^{12} vg/kg were administered IM. Statistically significant differences were not detected when comparing biodistribution, dystrophin positive fibers and dystrophin protein levels when comparing process A, initial process B and commercial process B material. Similarly, the increase of specific force output did not statistically significantly differ between the three process materials.

Correlation analysis for dystrophin positive fibers either in TA or all muscles and specific force output in TA pointed towards a weak, statistically not significant correlation for both process B materials as well as no difference between all three materials.

Finally, potential differences between IM and IV administration were evaluated for all materials in respect to dystrophin positive fibers and TA specific force output. No differences related to the route of administration were detected for specific force output TA for process A and initial process B material. However, statistically significantly higher improvement was observed after IM administration of commercial process B material. This observation was reversed when assessing dystrophin positive fibers: statistically significant higher values were observed in animals that were treated IM with process A or initial process B material whereas no differences between the routes of administration were observed for commercial process B material. Subsequent analysis revealed no statistically significant correlation between dystrophin positive fibers and improvement in specific force output after IV administration of commercial process B material.

Overall, no apparent differences were observed between the employed process materials after thorough analysis of various PD endpoints and routes of administration. This might be partially attributable to inherent weaknesses of the animal model as well methods of analysis, as discussed previously, to be taken into account. The applicant also points out that dystrophin expression is not a direct indicator for the improvement of muscle strength. Also, biodistribution of AAV vectors is not homogenous throughout all muscles hampering reliable quantification of vg/cell as well as influencing the PD effects.

Neither the clinical route of administration (i.v.) nor the clinical dose (1.33×10^{14} vg/kg) were selected for the bridging study 1107194. Due to lower variability and higher robustness of results upon IM

injection of SRP-9001 as compared to IV administration, the IM RoA was chosen for the bridging study, which is considered acceptable in light of *in vivo* potency evaluation in terms of batch consistency. A lower dose ($2.36x10^{12}$ vg/kg) was used for IM administration as compared to IV dosing ($1.33x10^{14}$ vg/kg). It was reasoned that IV dosing requires a high viral dose to achieve widespread muscle transduction, whereas IM is designed to target specific muscles, which is reasonable and could be followed in terms of *in vivo* potency. It is assumed that optimal doses (for IM administration) were applied for the bridging study, which might not allow a comprehensive detection of discrepancies of the different process materials. Thus, IM administration does qualify to compare *in vivo* potency and to estimate batch consistency, but does not provide valid information to conclude on comparability of the process A/B materials from a non-clinical perspective. Overall, the provided discussion does not support comparability of process A and process B material from a non-clinical perspective, but comparability in terms of in vivo potency (batch quality) might be claimed. Regarding safety, the totality of non-clinical and clinical data indicates no differences in the safety profile.

Other studies in mice with intramuscular administration were Studies 1111840 and 1119830 both with $2.36x10^{12}$ vg/kg administered intramuscularly (LTA). Functional evaluation as well as analysis of IF stained muscle sections were comparable to IV administered animals.

Quantitative analysis of microdystrophin expression by **western blot** revealed expression up to WT levels in all muscles investigated. Highest protein levels that exceeded even WT levels were detected in the heart of DMD^{MDX} rats in Study 1112486. Most western blot data originated from 12 weeks after administration, however, stable expression was demonstrated in rats through weeks 24 and 52. As Western Blot analysis is a highly variable method and the accuracy of the positive as well as negative control play a crucial role; along the same line, the equal distribution of the loading control is considered crucial for interpretation of the integrity of the data. It was stated that a quantitative robust cross-study comparison is not possible based on the generated data throughout the non-clinical development. The applicant further claimed that a semi-quantitative data interpretation might be possible based on the provided additional data on precision and accuracy for both the wildtype NHP protein standard (used in study 1107181) and the recombinant SRP-9001 micro-dystrophin protein standard (used in studies 1111840, 1107185, 1119829, and 1112486). Based on the calculations and explanations provided, the rationale could be followed, whereby a similar level of precision and accuracy across all standards was achieved. However, based on the above-mentioned limitations, a fully quantitative evaluation of expression is not possible. Qualitative transgene expression evaluation is supported for individual studies, but nor for inter-study comparison.

In order to examine the safety and efficacy of SRP-9001 in a large animal model rhesus macaques were dosed with 1.33×10^{14} vg/kg FLAG-tagged SRP-9001 in two exploratory studies (Study 1107175 and 1107181). Protein expression in various muscle types was confirmed by IF and western blot. Moreover, the efficacy after re-dosing under immunosuppression and therapeutic plasma exchange was evaluated in rhesus macaques that received $1.33x10^{14}$ vg/kg SRP-9001. The results might point towards the possibility of re-dosing after TPE, but should be considered with care due to the various drawbacks of the study

The C57BL/10ScSn-DMDMDX/J mouse model employed in non-clinical testing of SRP-9001 is described in the literature to be of a rather mild phenotype and, thus, of limited representativeness of the human course of disease (De Luca, 2012; Van Putten et al., 2019). Its use is, however, adequately justified by the limited availability of suitable animal models at the start of the in vivo development of SRP-9001 as well as the elaborate knowledge of its strengths and limitations. In regard to clinical relevance, the DMD^{MDX} mouse model mimics the progressive muscle degeneration of DMD patients but has a higher regenerative capacity with reduced accumulation of connective and adipose tissue. Mouse data were complemented by the rat DMD model included in the panel of non-clinical in vivo studies that exhibits a more severe phenotype comparable to DMD patients and covers aspects such as survival and cardiac effects. Thus, the use of two animal models covering different aspects of the clinical phenotype is acknowledged. However, despite results from animal studies pointing towards improvement in muscle and cardiac function as well as survival data, gaps remain especially in terms of long-term effects and maintenance of the effects which makes translatability to patients difficult.

The time points of evaluation chosen for the mouse model, i.e. 12 and 24 weeks post-dose, were selected to cover the degenerative phase and evaluate a potential restorative capacity of SRP-9001 as the model is characterized by major muscle weakness from 24 weeks of age. Therefore, and also based on the interpretation of stable transduction and efficacy at the 12 and 24 week time points, no additional evaluation beyond that period was conducted. Due to the differences in the disease phenotype, behavioural endpoints were considered more relevant in rats as compared to mice.

The clinical route of administration is via intravenous infusion. Most of the pharmacology studies were performed with intravenous (IV) administration, but some experiments were also performed with intramuscular (IM) route of administration, i.e. also the bridging study. It was confirmed that studies performed with the IM RoA served exclusively to compare *in vivo* potency of the different process materials and might only be considered as supportive for batch quality. Thus, all non-clinical studies performed with IM administration might not be taken into consideration for evaluating non-clinical proof-of-concept or safety.

Studies on **secondary pharmacology** were not conducted with SRP-9001 which is acceptable.

Dedicated **safety pharmacology** studies have not been conducted with SRP-9001, but limited safety pharmacology endpoints were included in the juvenile GLP toxicity study in WT mice and in exploratory safety studies in DMD^{MDX} rats and rhesus macaques. Decrease in locomotor activity was observed in male juvenile mice (WT) administered the high dose of 4.01×10^{14} vg/kg in the juvenile toxicity study 1107187. According to the applicant, it is conceivable that in healthy mice SRP-9001 micro-dystrophin may hypothetically compete with full-length dystrophin and may lead to somewhat reduced muscle function compared to healthy, untreated animals. DMD^{MDX} mice were not used in the juvenile toxicity study due to feasibility issues. No decreases in locomotor activity were observed at the proposed therapeutic dose of 1.33×10^{14} vg/kg in healthy mice. The decrease in locomotor activity was considered non-adverse, which was further supported by an increased swim speed in the Morris water maze in these animals and a general lack of clinical observations.

Reduced auditory startle response was observed at the low and high dose level males of the juvenile toxicity study 1107187, with individual animals often being affected in all parameters. Based on the absence of pre-pulse inhibition and intra-session startle habituation the reduction in startle response was considered non-adverse due to the small magnitude.

The applicant further demonstrated that cardiac effects were sufficiently examined in the nonclinical development program, especially in the studies in DMD^{MDX} rats. CNS effects were assessed in the juvenile toxicity study in WT mice and the results have been discussed in an adequate way.

Effects on the respiratory system have not been addressed in the nonclinical development program. The applicant noted that in the exploratory study in NHPs (1107181), animals experienced acute side effects after the second dose including elevated respiratory rates and heart rates. This may be related to the dual dosing of the IMP and would thus be irrelevant for the clinical setting where only single dosing is intended. In general, clinical observation of animals is not considered sufficient to assess respiratory function, and thus respiratory function should be evaluated by using appropriate methodologies in nonclinical studies. In the present case of a gene therapy medicinal product, on the other hand, a dedicated safety pharmacology assessment could be waived if appropriately justified. Given the availability of pivotal data on clinical safety, this issue is not further pursued from a nonclinical perspective.

Pharmacokinetics

No specific PK studies were conducted for SRP-9001 but biodistribution, plasma PK and viral shedding were incorporated into PD and toxicology studies.

Pharmacokinetic endpoints incorporated in pharmacodynamic and toxicology studies revealed dose-proportional plasma exposure and abundant biodistribution to a wide range of tissues in WT and DMD^{MDX} mice, in DMD^{MDX} rats and rhesus macaques. In WT and in DMD^{MDX} mouse plasma SRP-9001 was detectable up to 40 days. In line with this, elimination via urine and feces was completed 10 or 44 days, respectively, after administration. Tissues with highest vg/nucleus in all species tested were

liver, adrenal glands, heart, fat, lymph nodes and muscle. Higher distribution to off-target tissues was generally only observed at doses exceeding the intended clinical dose of 1.33 x 10^{14} vg/kg.

In terms of observed increases in vg numbers between 12 and 24 weeks time points the applicant provided various points to be considered in that respect. These include aspects related to the in vivo study itself as well as assay limitations. Thus, samples for both time points were obtained from different animal cohorts and vector DNA is not evenly distributed within tissues.

As far as the qPCR method is concerned limitations have been acknowledged regarding the reference material spiking procedure in liver and other tissue homogenates and, in turn, high variability in precision and accuracy between various tissue samples. In addition, different studies were performed with different PCR assays throughout the individual studies. All these differences make the comparison of vg numbers between the conducted non-clinical studies difficult.

Based on the preclinical biodistribution data of Process A material compared to initial or commercial Process B material, a skewing from a more balanced transduction efficiency level of skeletal muscle and heart towards lower transduction levels in skeletal muscle in comparison to heart transduction was noticed. In addition, in the rhesus monkey pre-clinical studies, which were only conducted with Process A material also a higher transduction level of the heart as compared to skeletal muscle was noticed. Considerable shortcomings in the PCR methods as well as in the sample size of non-clinical animal studies impede a definite extrapolation of this observation to a potential imbalance between heart and skeletal muscle transduction.

It was noted in the PK/PD correlation study 1119828 that same lots and doses lead to different extents of functional improvements in TA and diaphragm. It was clarified that data points correspond to results pooled by study and muscle type. Correlation of specific force separated by muscle types, i.e. tibialis anterior and diaphragm, and PDPF was provided which gave a clearer picture of the relationship.

Toxicology

The toxicologic profile of SRP-9001 was assessed primarily in wild-type C57BL/6J (WT) mice and in the dystrophin-null DMD^{MDX} (C57BL/10ScSn-DMDmdx/J) mouse model of DMD. Data in these mouse models were supplemented with data from rhesus monkeys (NHP). The majority of the studies was conducted as single dose studies. The absence of repeat-dose toxicity studies is acceptable as only a single administration of delandistrogene moxeparvovec is intended in patients.

In the GLP-compliant pivotal study 11070172, clinical pathology changes were observed in both strains of mice administered ≥1.33 x 10^{14} vg/kg. According to the applicant, some of the SRP-9001-related clinical pathology effects that were noted only in DMD^{MDX} mice were attributable to the pharmacologic action of the test article. Most but not all of the effects exhibited evidence of reversibility by Day 169. Further, SRP-9001-related microscopic liver findings (hepatocyte hypertrophy/necrosis and mitosis, oval cell hyperplasia), as well as mild increases in AST, ALT, GLDH, and ALP activities, were noted at the interim sacrifice in WT mice administered ≥1.33 x 10^{14} vg/kg. At the terminal sacrifice increased incidence and/or severity of minimal to moderate hepatocyte vacuolation was still present. The finding had no clinical pathology correlates at the terminal sacrifice indicating a lack of functional impact on the liver. However, these observations might be indicative of liver toxicity, which occurred in a high rate of patients in the pivotal clinical trial and throughout the clinical development program, as discussed in the respective sections of this report.

According to the study report, the no observed adverse effect level (NOAEL) in study 11070172 is considered to be 4.01x10^{14} vg/kg for both strains due to the lack of impact on the health and wellbeing of both strains of mice administered 4.01x10^{14} vg/kg, and all effects for this dose were considered non-adverse. This is debatable, due to the persistent alterations in GLDH, platelet count and hepatocyte vacuolation, as well as the dose dependent effects on AST. It is, however, acknowledged that a NOAEL of 4.01 × 10^{14} vg/kg was derived by the study director and further discussion on this NOAEL is not deemed meaningful.

In the GLP-compliant pivotal study 11070192, two high dose animals were sacrificed in moribund condition. Moderate or marked dilatation of the brain ventricles was noted for both animals and was

considered the cause of moribundity. Low and high dose *mdx* mice showed slightly decreased mean reticulocyte counts, platelet counts, WBC counts and neutrophils compared to the control group. Additionally, decreases in mean AST and ALT compared to the control group observed in both dose groups were attributed to decreased muscle injury, consistent with the histopathology observations of reduced muscle degeneration in heart and skeletal muscles of SRP-9001-administered *mdx* mice compared to control mice. Further, SRP-9001-related, decreased liver/gall bladder weights were noted for *mdx* mice administered ≥1.33 x 10^{14} vg/kg, but without a microscopic correlate.

Based on the increased incidence and severity of ventricular dilatation in high-dose DMD^{MDX}, the NOAEL was defined at 1.33 x 10^{14} vg/kg in DMD^{MDX} mice in this study.

Ventricular dilatation of the brain occurred in *mdx* mice across all groups, including control animals, in both pivotal GLP-compliant single dose studies. In study 11070172, four unscheduled deaths were attributed to moderate to marked brain ventricle dilatation. All affected animals were *mdx* mice, 1 in the control group, 2 in the low dose group and 1 in the high dose group. Overall, 13 *mdx* mice displayed brain ventricle dilatation in that study across all groups (5/20 control, 4/6 low dose, 4/20 high dose animals). Thus, no pattern or dose relationship was discernible.

In study 11070192, brain ventricle dilatation was determined in 12 *mdx* mice across all groups (4/15 control, 2/15 low dose, 6/15 high dose); in the control and low dose groups all affected animals had minimal ventricle dilatation, whereas the effect was graded 3 to 4 (moderate to severe) in 4 animals of the high dose group. As a result, two of the affected animals in the high dose group had to be euthanized before schedule in moribund condition. For the purposes of NOAEL determination, these findings were considered adverse and the NOAEL was determined to be 1.33 x 10^{14} vg/kg in study 11070192. This was not the case in study 11070172, where the effects on the brain ventricles in the *mdx* strain where not taken into account for the NOAEL determination. This was based on evidence in the published literature demonstrating naturally occurring enlargement of brain ventricles in the DMD^{MDX} mouse model of muscular dystrophy compared with age-matched WT mice (Bagdatlioglu et al. 2020, Xu et al. 2015). The notion that the findings were indeed related to the background rate occurring in the *mdx* mouse strain is supported by the fact that no such findings were observed in WT mice under equivalent exposure in the same studies.

To further examine this phenomenon, a dedicated safety study was conducted to specifically evaluate dilatation of brain ventricles in *mdx* mice. In that study (1111842), screening for hydrocephalus was performed by removing any mouse with a domed head prior to dosing, thus minimizing the risk for spontaneous brain ventricle dilatation after dosing. A higher incidence of normal or minimal dilatation of lateral ventricles compared to more severe lateral ventricle dilatation scores (mild, moderate, marked or severe) was observed in study animals that received either SRP-9001, saline or formulation buffer. Pathological changes in the brain parenchyma due to dilatation of lateral ventricles were only observed in two animals – one having received saline and the other SRP-9001. It was therefore concluded that SRP-9001 administered up to 4.01 x 10^{14} vg/kg did not exacerbate the incidence of brain ventricular dilatation at 12 weeks post-delivery compared to saline or formulation buffer administration.

Hence, based on the weight of evidence, the applicant concluded that SRP-9001 is not believed to have exacerbated the dilated brain ventricles in study 1107192 and the imbalance was more likely incidental. This conclusion is acceptable.

Two exploratory, non-GLP compliant studies were conducted in NHP with initial process A material to investigate the toxicity, immunogenicity and biodistribution of SRP-9001.

Study 1107175 investigated the biodistribution and immune response to SRP-9001 in a single rhesus macaque after a single dose of 1.33 x 10^{14} vg/kg. Immunofluorescence staining for the FLAG tagged human micro-dystrophin protein was used to determine transgene expression in skeletal muscle. However, expression in off-target tissues was not examined. Relevant findings included elevated liver enzymes (4.5-fold ALT increase with a maximum at Week 6; 3.5-fold AST increase with a maximum at Week 8) and histopathologic changes in the liver (minimal fibrosis and mild lymphocytic infiltration of periportal regions, partly with penetration into the adjacent hepatic parenchyma). According to the

study report, the changes were fairly widespread but not accompanied by overt tissue destruction. Due to the lack of concurrent control animals, the relationship of the liver changes to study drug could not be defined.

In the following study 1107181, efficacy of re-dosing SRP-9001 with different methods of immunosuppression regimens or therapeutic plasma exchange (TPE) was evaluated.

Toxicity findings comprised transient liver enzyme elevations, minimal to moderate atrophy of the marginal zone of the spleen, minimal to mild decreased lymphocytes in splenic follicles, mild lymphoid follicular atrophy of the inguinal and mesenteric lymph nodes, and minimal and moderate bile duct hyperplasia.

Neither of the two NHP studies included untreated animals and neither was designed to derive a proper NOAEL; thus, no safety margin can be deducted for human exposure. As both NHP studies were conducted with Process A Material and as significant differences are present between material from Processes A and B, the obtained data are of limited value for the safety and especially immunogenicity of the final drug product. Additionally, also the immunogenicity aspects can only be relevant for the anti-AAVrh74 response; the absence of an intact dystrophin gene with no or only partial expression in DMD-patients can lead to immune response against micro-dystrophin and rejection of the transgene and modified cells. A fact which is reflected in the exclusion of patients with a deletion of dystrophin Exons 1-17. Interestingly, the non-GLP NHP study 1107181 showed that the vg/nucleus levels were not significantly increased after re-dosing, but the expression level of Delandistrogene moxeparvovec micro-dystrophin was markedly increased in TA and GAS skeletal muscles. Further, it demonstrates that re-dosing is per se possible in combination with a TPE treatment but not with a peri immune suppression. More so, the applicant does not intend re-dosing of Delandistrogene moxeparvovec for DMD patients.

Toxicity in juvenile mice (wildtype, strain C57BL/6) was evaluated in two single dose studies. In both studies intended commercial Process B material was used.

In Study 1107191, SRP-9001 was administered as a single IV dose to male neonatal WT mice at 1.33 x 10^{14} or 2.50 x 10^{14} vg/kg on PND1 followed by a 4-week observation period. A dose dependent increase of vector distribution in liver, heart and skeletal muscles was observed. Overall, there was no SRP-9001-related mortality, clinical or macroscopic observations, or effects on body weight or food consumption.

In the pivotal, GLP compliant study 1107187, male and female neonatal WT mice received a single temporal vein injection of 1.33 x 10^{14} or 4.01 x 10^{14} vg/kg SRP-9001 on PND1 to assess efficacy, biodistribution and toxicity including neurobehavioral functionality after a 13-week post-dosing phase. Overall, no SRP-9001-related mortality or clinical observations were noted. Significant decreases in body weight gain and body weight were observed in a dose-responsive manner and were considered SRP-9001 related but non-adverse due to the low magnitude of change. However, these effects were only observed in one of the three subgroups in the study.

The applicant states that males and females administered 1.33 x 10^{14} or 4.01 x 10^{14} vg/kg developed antibodies to SRP-9001 with titre loads ranging from a negative titre (-2) to as high as 64. Based on toxicity evaluation including neurobehavioral functionality, the NOAEL was concluded to be 4.01 x 10^{14} vg/kg in this study in neonatal wildtype mice. This conclusion is agreed.

Biodistribution data are summarised for liver, heart, leg muscles and adrenals in Module 2.6.7 showing comparable levels for heart, leg muscles and adrenals. Vg levels in liver are generally by one or two orders of magnitude higher than in the other organs. Dorsal root ganglia (DRG) delivery was analyzed in three, non-GLP efficacy studies (1107173, 1107193, 1111840) in DMD^{MDX} mice. Additionally, in the two GLP toxicity studies 1107172 and 1107192 brain tissues were analyzed microscopically, with no signs for adverse effects in the brain of either C57Bl6 WT or DMD^{MDX} mice using initial or commercial Process B material. Although DRG toxicity after AAV application can occur in rodents, the frequency is low. The most relevant species to evaluate DRG toxicity by AAV application are non-human primates, as shown by several recent studies. The applicant has not analyzed DRG histopathology in detail of the two rhesus macaque studies 1107175 and 1107181 with the initial Process A material. It is

acknowledged that clinical observations indicative of clinically relevant DRG toxicity (such as posture changes, reflex changes, or tremors) were absent in the NHP studies, however, a final conclusion on DRG toxicity cannot be drawn from the presented data.

During the EMA Scientific advice from September 2019 it was already discussed that the change in production process and location may influence the quality, especially the safety profile of the product. This request is crucial, as the production Process A and B are considered not comparable from the quality assessment, especially in respect to the empty-to-full-ratio. In the pre-clinical studies differences between the efficacy and functional improvement were noticed, as well as a skewing toward a more heart favoured delivery of Process B compared to Process A in WT and DMD^{MDX} mice. These points contest the relevance of the NHP studies performed with Process A material with respect to safety and especially immunogenicity of the final drug product. No preclinical study in NHP or other higher animals like golden retriever (Dystrophin-deficient muscular dystrophy, DD-MD) was conducted with intended commercial Process B material, which limits the predictability of possible altered tissue tropism, immune response transgene expression and its duration.

No dedicated genotoxicity or carcinogenicity studies were performed with SRP-9001. It is acknowledged that dystrophin is unlikely to contribute to tumour formation. However, vector integration as such, independent of the target gene and protein to be synthesised, carries a theoretical risk for carcinogenesis dependent on integration site.

Vector integration was evaluated in liver tissue from cynomolgus monkeys. Since availability of tissues from previous studies with SRP-9001 in NHPs was limited, a surrogate approach was chosen using tissue from a recent NHP study with a surrogate gene therapy product. The surrogate product used is AAVrh74.CMV.eGFP, in which a cytomegalovirus (CMV) promoter drives the expression of GFP. Like SRP-9001, this product contains the rAAVrh74 capsid and AAV2 ITRs. This approach has been discussed during the Scientific Advice procedure and is considered acceptable. Based on the results of the integration analysis in the Target Enrichment Sequencing (TES) study 1128231, it can be concurred that SRP-9001 is not expected to pose an increased cancer risk based on the low frequency and random distribution of insertions mutations, and general lack of proximity to cancer-associated genes. However, the overall high level of vector integration in the liver is of concern as it may contribute to hepatotoxicity, as observed in the clinical trials. This issue is further discussed in the clinical sections and benefit-risk assessment.

An additional risk is the expected higher expression of micro-dystrophin in cardiac tissue in relation to cardiotoxic risk in the clinical setting. In a very recent study by Hart et al., a potential life shortening risk with micro-dystrophin gene therapy for Duchenne muscular dystrophy was identified by acceleration of cardiomyopathy [Hart et al 2024; https://doi.org/10.1172/jci.insight.165869]. At Day 120, the applicant was asked to discuss whether overexpression of micro-dystrophin in the heart as observed in rats and rhesus macaques seen in the pre-clinical studies 1107185, 1112486 and 1107181 could have an impact on the function of utrophin in cardiomyocytes and thereby accelerate cardiac disfunction. In reply, the applicant highlighted differences between the setup used in Hart et al for the MDC1 construct (which was built to reflect SRP-9001 µDystrophin transgene) versus SRP-9001. (Please see Nonclinical D150 AR for details.) Of note, a 2- to 4-fold higher expression in heart (for both DMD^{MDX} mice and rats) is reported for SRP-9001, while a 5- to 10-fold overexpression was found by Hart et al for D2.mdx mice. According to the applicant this difference is due to the different promoters used. The applicant further evaluated the expression levels in young (1107185) and adolescent (1112486) DMD^{MDX} rats by conventional Western Blot. The over expression levels were comparable between DMD^{MDX} rats and DMD^{MDX} mice (1107193). To exclude a displacement of Utrophin by µ-Dystrophin -seen as one reason for of the enhanced cardiomyopathy in Hart et al. - Utrophin levels after 12 and 24 weeks SRP-9001 treatment were re-evaluated the in heart. The applicant retested samples from 1 saline (12 weeks), 2 DMD^{MDX} rats at 12 weeks and 3 rats at 24 weeks treated with 1.33×10^{14} vg/kg SRP-9001 for both µDystrophin and Utrophin expression. Especially in respect to the availability of samples from other animals of this study, the very low number of samples is seen as a clear weak point for the informative value of the presented data. Further, the presentation of data as ng µDyst on total protein amount on µDystrophin and as % of WT for Utrophin allow no direct comparison of expression level. However, based on the provided capillary bands µ-Dystrophin was roughly 3-fold higher than Utrophin levels, while for

rats it is reported that in healthy heart the levels are similarly strong. Therefore, the data fit to the other expression analyses made prior where a 2- to 4-fold overexpression was documented. In conclusion, there is no sign of Utrophin displacement by µ-Dystrophin expression in the heart of DMD^{MDX} rats.

To address the possibility that cardiotoxicity relates to the overexpression of the transgene protein, the applicant summarized the Nonclinical Pharmacology and Safety Assessments on the heart from the DMD^{mdx} mice and DMD^{MDX} rats. In the 6-month safety study (1107172) minimal cardiomyocyte degeneration was only noted in 5 saline control DMD^{MDX} mice but not in SRP-9001-treated DMD^{MDX} mice. In young DMD^{MDX} rats fibrosis was analysed in several muscle tissues, diaphragm, heart, skeletal muscle (1107185). In all analysed tissues fibrosis was reduced in the SRP-9001-treated DMD^{MDX} rats compared to saline treated controls. Median long-term survival was doubled in the SRP-9001 treated DMD^{MDX} rats from 13 to 26 months compared to saline treated animals. In an exploratory pharmacology study in rhesus macaques (1107181), a roughly 2-fold overexpression in heart compared to skeletal muscle was detected but no signs for cardiac events and histopathological findings were seen 24 weeks after the first dose. Therefore, the applicant concludes, SRP-9001 treatment may lead to a cardioprotective effect as indicated by echocardiography, histopathology data, and long−term survival in three different species mice rats and rhesus macaques.

In conclusion, the re-evaluation of rodent studies with SRP-9001 did not confirm the high overexpression of micro-dystrophin in the heart or the reduced utrophin expression by MDC1 construct as reported by Hart et al. The applicant suggests this is due to the use of the weak more balance MHCK7 promoter used in SRP-9001 compared to the CK8 promoter in MDC1.

Reproductive toxicity studies were not performed because the patient population in DMD is almost exclusively males. This approach is in line with feedback from the EMA Scientific Advice 2021 (EMA/SA/0000066340) and is considered acceptable. As a consequence, actual germline transmission has not been studied but the potential risk of germline transmission has been discussed by the applicant.

In the GLP juvenile toxicity study in WT mice (1107187) one epididymis, testis, or ovary were collected from male and female animals in one subgroup. Tissues were analyzed by RNAScope ISH to detect SRP-9001 micro-dystrophin transgene and AAV vector MHCK7 in the mouse testes and ovaries. Six of 16 testis samples were mildly positive, with ≥1% to 1-10% positive cells, independent of dose. All ovarian samples were collected from low-dose animals only and were scored negative, despite the presence of low levels of vector genome. Considering that the overall number of positive samples was low, did not score relevantly above control values (controls 0.5 versus 1 treated), and that no dose-dependency was observed, the applicant concluded that germline transmission is not expected.

In one of the efficacy and biodistribution studies (1107173), AAV vector MHCK7 scores were increased in all SRP-9001-treated DMD^{MDX} mice compared with vehicle controls. SRP-9001 micro-dystrophin transgene scores increased dose dependently. Staining for both the vector and the transgene was most reliably observed in the interstitial space. Staining in Sertoli cells, spermatogonia, and primary spermatocytes was similar to the negative control for both probes.

Though vector biodistribution to muscle tissue was more than 10-fold higher compared to testes in *mdx* mice, the ratio in wildtype mice was only 3.6 to 6.7. Thus, the biodistribution to the target tissue is only by less than one order of magnitude higher than the biodistribution to testes. This observation was independent of dose and thus also observed at the intended clinical dose of 1.33×10^{14} vg/kg.

In summary, AAV vector MHCK7 expression scores were increased in testes of SRP-9001-treated animals compared with vehicle controls in two studies in mice. However, there was no reliable ISH staining above the negative control background for neither the MHCK7 vector nor the SRP-9001 micro-dystrophin transgene observed in Sertoli cells, spermatogonia and primary spermatocytes. Thus, no conclusive results on germline transmission can be drawn.

Biodistribution to gonads in NHP occurred at similar levels as in mice as observed in study 1107175 in a male macaque.

In that study, protein expression was only determined in selected skeleton muscles but since the SRP-9001 promotor is muscle specific, no or negligible expression is expected to occur in germline cells.

No dedicated local tolerance studies were conducted with SRP-9001. This is acceptable. No obvious local intolerability was reported in clinical observations or in macro- or microscopic investigations at scheduled or unscheduled termination of the different groups across the toxicity studies.

Seropositivity for anti-AAVrh74 antibodies following both IM and mucosal (ocular) delivery was investigated in model of male C57BL/6J mice (wildtype). No antibodies against AAVrh74 developed (seroconversion) following the topical application to the conjunctiva (i.e., a mucous membrane) up to a dose of 1 x 10^{10} vg. There were no notable vector genome levels in the tissues of animals treated by ocular administration. It can be concluded that inadvertent topical or mucosal exposure that may occur, e.g., in caregivers, does not lead to anti-AAVrh74 antibody formation. Of note, a SRP-9001 surrogate (vector AAVrh74.CMV.eGFP) was used in this study.

Dedicated immunogenicity studies have not been conducted but anti-drug antibodies were assessed in selected toxicity studies. Antibody formation to the AAVrh74 vector capsid was investigated in DMD^{MDX} and WT mice in studies 1107172 and 1107187 as well as in rhesus macaques in studies 1107175 and 1107181.

In the GLP compliant toxicity Study 1107172, SRP-9001 was administered as a single IV dose at 0, 1.33 x 10^{14}, or 4.01 x 10^{14} vg/kg to male WT or DMD^{MDX} mice. All WT and DMD^{MDX} mice injected with 1.33 x 10^{14} or 4.01 x 10^{14} vg /kg of SRP-9001 developed anti−AAVrh74 antibodies, starting approximately 72 hours post-dose and rapidly reaching high titers that persisted through the last timepoint collected during Week 25. There was a statistically significant difference in titers between the low- and high-dose groups in WT mice ($p = 0.026$), but not in DMD^{MDX} mice. Unexpectedly, samples collected from some of the control mice also tested positive for anti−AAVrh74 antibodies, although with lower titers than in the treated animals.

In the GLP compliant juvenile toxicity study 1107187, SRP-9001 was administered as a single IV dose at 0, 1.33 x 10^{14}, or 4.01 x 10^{14} vg/kg to post-natal WT mice. Overall, the antibody titers in the SRP-9001-treated groups remained extremely low, compared to those measured in adult WT and DMD^{MDX} mice in study 1107172 and there was no trend toward an increase in antibody titers over time. The low antibody levels in this study can be explained by the fact that neonatal immune response is impaired during the first weeks after birth.

Study 1107175 investigated the immune response to SRP-9001 in a single rhesus macaque administered a single IV dose of 1.33 x 10^{14} vg/kg. Transient increases were observed in T-cell response to the AAV capsid, but levels returned to baseline by 8 weeks post-delivery. No relevant T-cell responses against SRP-9001 transgene protein were observed. Anti-AAVrh74 antibodies increased after the Week 2 sample and reached the highest levels in the sample taken shortly after Week 8. Anti-AAVrh74 antibody levels declined at Week 12.

In study 1107181, rhesus macaques received 2 × 10^{14} vg/kg of SRP-9001 with or without immunosuppressants. Prophylactic treatment with prednisone did not inhibit the formation of anti-AAVrh74 antibodies. Even a "triple immunosuppression" regimen combining rituximab, sirolimus and prednisone did not prevent antibody formation; re-dosing of animals with high anti-AAVrh74 antibody titers led to safety findings. In the second part of the study, plasmapheresis was found to efficiently decrease anti-AAVrh74 antibody titers 12 weeks after SRP-9001 administration to NHPs, allowing safe re-dosing of the product.

As outlined before, both NHP studies were conducted with Process A Material, therefore the obtained data are of limited value for the immunogenicity assessment of the final drug product.

Interspecies comparison and exposure margins to clinical exposure

Across the nonclinical development programme for SRP-9001, the following two dose levels were assessed in pivotal, GLP-compliant toxicity studies: 1.33 x 10^{14} and 4.01 x 10^{14} vg/kg. The selected high dose was driven by the maximum dose volume of administration and the viral titer of the dose formulation. The high dose tested corresponds to 3-times the clinical dose of 1.33 x 10^{14} vg/kg. The

applicant presented the NOAELs established in the pivotal toxicology studies in *mdx* and WT mice. The lowest NOAEL is equal to the intended therapeutic dose (1.33×10^{14} vg/kg). NOAELs from other species are not available (no toxicity study was conducted in rats; toxicity was only studied in exploratory manner in NHP).

Conclusions on ERA:

All potential hazards for both unintended recipients and the environment have been identified. On the one hand the nature of the GMO is a replication-defective adeno-associated virus vector. However, even if a recombinant virus is formed capturing back the deleted rep and cap genes, the result will still be replication-defective (as the wild-type AAV). Therefore, the only mechanism by which there could be mobilisation is that the same cell would be the unlikely situation in which a cell is infected simultaneously with the clinical vector, a wild-type AAV virus and a helper virus (triple infection).

In any case, the applicant has put in place risk management measures to further reduce any potential exposure, including safe transport containers with adequate labelling, hospital administration by specialized personnel trained in its administration and in biosafety practices to manage this medicinal product, and instructions for patients on the best hygiene practices after having been treated so as to minimize any exposure of contact persons.

In addition delandistrogene moxeparvovec, fulfills all requirements laid down in the Specific ERA of the Document "Good Practice on the assessment of GMO related aspects in the context of clinical trials with AAV clinical vectors" (Version 3, January 2022).

Provided that the control measures described by the applicant are implemented, the overall risks of delandistrogene moxeparvovec for human health and the environment can be considered **negligible**.

2.4.7. Conclusion on non-clinical aspects

In vivo pharmacology studies in DMD^{MDX} mice and rats that were IV or IM administered with SRP-9001 demonstrated improvements in microdystrophin expression, histopathological parameters and muscle function. However, especially functional improvements measured by specific force output across all studies are regarded mostly moderate. Despite stable vector and protein expression at later timepoints, the functional improvements declined over time, which is at least partially relatable to natural aging and decrease in activity of animals. Even if the median survival of SRP-9001-treated young DMD^{MDX} rats doubled compared to controls, an improved functional outcome in terms of ambulation may not be deduced from these data. Thus, the clinical relevance of these data is considered limited. The relevance of the mouse model used is debatable according to published literature as the phenotype is considered to be moderate. Also, a clear proof of concept demonstrating the correct restoration of the DAPC has not been provided. IF as well as WB measurements are considered surrogate markers.

No specific PK studies were conducted for SRP-9001 but biodistribution, plasma PK and viral shedding were incorporated into PD and toxicology studies conducted in mice, rats, and non-human primates. In WT and in DMD^{MDX} mouse plasma SRP-9001 was detectable up to 40 days. In line with this elimination via urine and feces was completed 10 or 44 days, respectively, after administration. SRP-9001 was abundantly distributed to virtually all tissues investigated in all three non-clinical species with highest levels detected in liver, adrenal glands, heart, fat, lymph nodes and muscle. Overall, the PK of SRP-9001 is considered adequate. Biodistribution analysis showed differences between preclinical animal studies especially between species, which raised some concerns, however, could be a consequence of inconsistencies regarding the employed detection methods.

A comprehensive toxicology assessment has been conducted in wildtype and DMD^{MDX} mice following a single dose of SRP-9001. Major findings relate to clinical pathology and histological findings in the liver. The lowest NOAEL across the single dose studies is considered to be 1.33×10^{14} vg/kg, which corresponds to the proposed clinical dose.

Data obtained in NHPs are only exploratory and do not contribute to the NOAEL determination, which is a shortcoming of the preclinical development programme.

Overall, the non-clinical studies conducted in support of the development of SRP-9001 are considered comprehensive, despite a limited clinical relevance of non-clinical efficacy data.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

- **Tabular overview of clinical studies**

Table 2: Summary of clinical studies in scope of efficacy evaluation

Study (Phase)	Population	Study Design	Efficacy-Evaluable Subjects (N)	Dose, Route, Regimen	Clinical Cutoff Date	Actual / Planned Follow-Up Time [a]
Study 301 *(Phase III)*	Ambulatory DMD, aged ≥ 4 to < 8 years	Double-blind, randomized (1:1), placebo-controlled, 2-part study	125 [b] *SRP-9001: 63* *Placebo: 62*	1.33×10^{14} vg/kg (IV) or placebo	13 Sep 2023 (Part 1)	52 weeks / Up to 104 weeks
Study 103 *(Phase Ib)*	Ambulatory DMD **Cohort 1:** aged ≥ 4 to < 8 years; **Cohort 4:** aged ≥ 3 to < 4 years	Open-label	27 *Cohort 1: 20;* *Cohort 4: 7*	1.33×10^{14} vg/kg (IV)	24 Jul 2023	104 weeks (Cohort 1), 52 weeks (Cohort 4) / Up to 160 weeks
Study 102 *(Phase II)*	Ambulatory DMD, aged ≥ 4 to < 8 years	Double-blind, randomized (1:1), placebo-controlled, 3-part study	41 **Part 1** *SRP-9001: 20* *Placebo: 21* **Part 2** *SRP-9001: 21* *Placebo: 20* **Part 3:** *SRP-9001 in Part 1: 20* *SRP-9001 in Part 2: 21*	**Part 1 [c]:** 6.29×10^{13} vg/kg, or 8.94×10^{13} vg/kg, or 1.33×10^{14} vg/kg (IV) or placebo **Part 2:** Subjects previously on placebo: 1.33×10^{14} vg/kg (IV) Subjects previously on SRP-9001: placebo **Part 3:** No treatment	16 Aug 2023	156 weeks / Up to 260 weeks
Study 101 *(Phase I/IIa)*	Ambulatory DMD, aged 4 to 7 years	Open-label	4	2×10^{14} vg/kg [d] (IV)	25 Apr 2023	260 weeks / Up to 260 weeks
External Control Study (WN44594)	Ambulatory DMD, aged 4 to 8 years	Retrospective, cohort study to contextualize the effect of SRP-9001 treatment against an external historical control cohort at 1- and 2-years.	Subjects who received target dose of SRP-9001 from Studies 101, 102, and 103	Tadalafil (clinical trial placebo group), FOR-DMD (clinical trial), CINRG (natural history study)	SRP-9001 Clinical Trial Sources Study 101: 12 May 2020 Study 102: 20 February 2023 Study 103: 26 April 2023 External Data Sources: Tadalafil (placebo): 01 July 2022 FOR-DMD: 01 July 2022 CINRG: 03 May 2023	SRP-9001: 52 External Control: 181 [e]

CINRG = Cooperative International Neuromuscular Research Group; DMD = Duchenne muscular dystrophy; EC = external control; FOR-DMD = Finding the Optimum Regimen for Duchenne Muscular Dystrophy; IV = intravenous; qPCR = quantitative polymerase chain reaction; vg = vector genome

[a] Follow-up time was calculated from Day 1 to last planned assessment visit, regardless of when infusion of SRP-9001 was administered.

[b] One subject for whom Part 1 efficacy data are presented in the Addendum Clinical Study Report (1124892, Section 3.1), is not in scope of this efficacy evaluation.

[c] Two methods were used to quantify the dose of clinical product which resulted in three doses of clinical product being administered (see Section 1.5.3.1)

[d] SRP-9001 at a dose of 2×10^{14} vg/kg as measured using a qPCR method using a supercoiled plasmid standard in 10 mL/kg is equivalent to 1.33×10^{14} vg/kg as measured with linear standard (see Section 1.5.4.1).

[e] Number of eligible external control subjects prior to propensity score weighting

2.5.2. Clinical pharmacology

Due to the nature of the product, no conventional clinical pharmacology studies were conducted.

SRP-9001 drug exposure was determined by detection of SRP-9001 vector DNA and quantified using droplet digital polymerase chain reaction (ddPCR). A PK assessment of SRP-9001 vector exposure in the systemic circulation (serum) and excreta (feces, saliva, urine) was performed in Cohorts 1 to 4 of Study 103, whereas the assessment in target muscle tissues was performed in all four clinical studies. A summary of viral vector shedding results is shown in the Safety Section.

SRP-9001 exposure in the target muscle tissues was quantified through tissue biopsies obtained from gastrocnemius or biceps femoris approximately 12 weeks after dosing. The results from Studies 101 (n = 4), 102 Cohort 1, subset who received the dose of 1.33 x 10^{14} vg/kg (n = 8), and Cohort 2 (n = 21), 103 (Cohorts 1-4) (n = 39), and 301 (Cohort 1) (n = 17) (total of N = 89) demonstrate effective SRP-9001 drug biodistribution and successful muscle tissue transduction following SRP-9001 treatment at the dose of 1.33 x 10^{14} vg/kg with an average of 3 vector genome copies per nucleus (Figure 3).

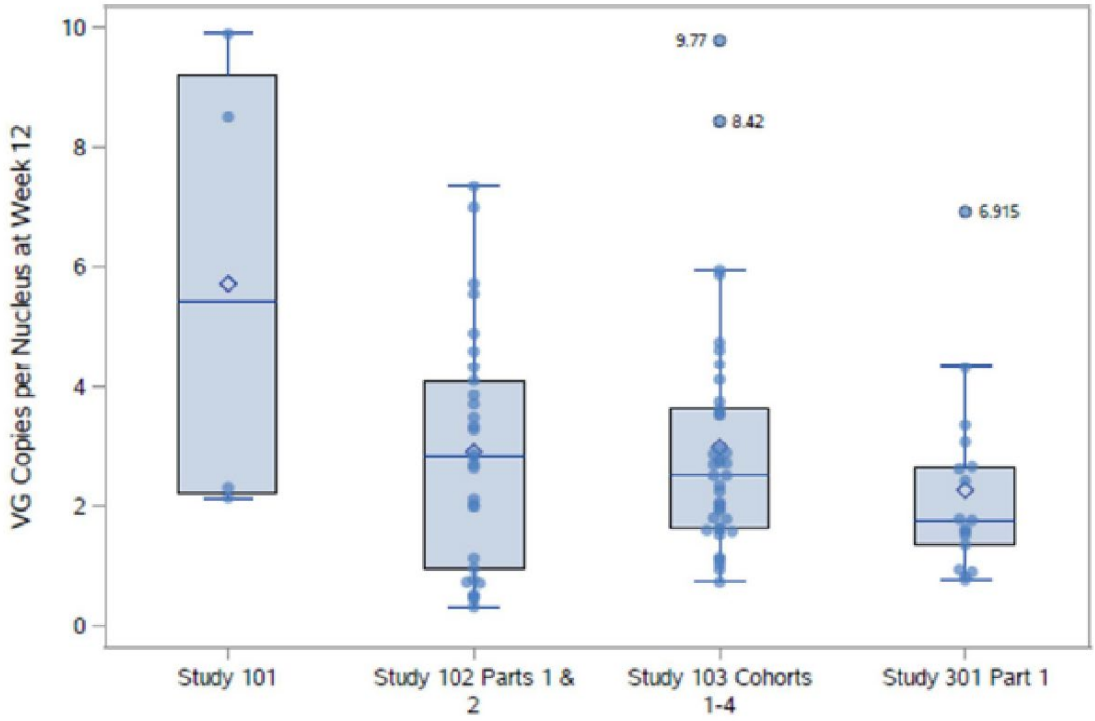


Figure 3: Vector Genome Copies per Nucleus at Day 90 (Study 101) or Week 12 (Part 1 and Part 2 of Study 102, Study 103, and Study 301) after SRP-9001 Administration

2.5.2.1. Pharmacokinetics

Bioanalytical Methods

Quantitative droplet digital polymerase chain reaction (ddPCR) was used for the evaluation of the presence of SRP-9001 vector DNA in serum, muscle tissue and excreta (salvia, stool, and urine).

For analysis of the SRP-9001 micro-dystrophin transgene, the amount of total micro-dystrophin protein expression was analyzed using immunoblotting (western blot analysis). Masson's Trichome staining of tissue from the same muscle biopsies were performed as used for western blot analysis and the percentage of muscle tissue determined. This value was used to determine a muscle adjusted value for the amount of micro-dystrophin expressed in a particular biopsy. Further the fraction of membrane-localized micro-dystrophin was evaluated using immunostaining techniques.

2.5.2.2. Pharmacodynamics

Mechanism of action

After administration, SRP-9001 enters the tissues and is taken up into cells. The SRP-9001 micro-dystrophin vector translocates into the nucleus and disassembles to form larger double stranded DNA concatemers. For AAV-based vectors in general, these concatemers persist in the cell as stable extrachromosomal episomal structures rather than integrating into the host cell genomes (McCarty et al. 2004; Kimura et al. 2019) and are transcriptionally active. The delivered expression cassette is transcribed and translated by the host cell leading to expression of SRP-9001 micro-dystrophin. Once transduced, persistent expression is anticipated in the target tissues, according to the applicant.

Primary and secondary pharmacology

Study SRP-9001-101

This was a Phase 1/2a open-label, first-in-human, single-arm, single-dose study in 4 subjects with DMD aged 4 to 7 years. Subjects received 1.33 x 10^{14} vg/kg SRP-9001 intravenously (IV; Process A material). The study duration was ~5 years. The purpose of this study was to assess the safety of SRP-9001 administered IV to subjects with DMD. As secondary objective, micro-dystrophin expression was assessed in all subjects.

All 4 subjects in this study were male. Mean age was 5.14 years, with 3 (75.0%) subjects in the 4 to 5 years age group and 1 (25.0%) subject in the 6 to 7 years age group. Mean NSAA total score was 20.5 (range: 18.0 to 26.0).

A mean increase (improved) from Baseline to Day 90 post-SRP-9001 infusion was observed in micro-dystrophin expression by western blot (70.52%), IF fiber intensity (93.59%), and IF PDPF (81.18%).

The mean decreases in CK levels from Baseline to Year 1, Year 2, Year 3, Year 4, and Year 5 were 15133.0 U/L, 11345.5 U/L, 9037.0 U/L, 11623.3 U/L, and 9309.5 U/L, respectively.

Study SRP-9001-102

This was a randomized, double-blind, placebo-controlled, 3-part Phase 1/2 study of systemic gene delivery of IV SRP-9001 (1.33 × 10^{14} vg/kg, Process A material) in DMD subjects 4 to 7 years of age. Subjects randomized to SRP-9001 in Part 1 (48 weeks) of the study crossed over to receive placebo in Part 2 (48 weeks). Subjects randomized to placebo in Part 1 of the study crossed over to receive SRP-9001 in Part 2. Part 3 of the study included an open-label follow-up period (up to 5 years). The main objectives were to assess the safety and efficacy of SRP-9001 in DMD patients by measuring biological (micro-dystrophin expression, CK levels) and clinical (NSAA, time to rise from the floor, 10-meter walk/run test, time to ascend 4 stairs, 100-meter walk test) endpoints.

A total of 41 subjects were enrolled: 20 subjects received SRP-9001 in Part 1 and 21 subjects received SRP-9001 in Part 2. Retrospectively, it was determined that 3 different dose amounts had been administered during Part 1 of the study (1.33 × 10^{14} vg/kg (n=8), 6.29 × 10^{13} vg/kg (n=6), and 8.94 × 10^{13} vg/kg (n=6)). During Part 2 of the study all doses of SRP-9001 in Part 2 were 1.33 × 10^{14} vg/kg. Mean age was 6.27 years, with 16 (39.0%) subjects in the 4 to 5 years age group and 25 (61.0%) subjects in the 6 to 7 years age group. Subjects in the SRP-9001 group had a numerically lower mean NSAA score at Part 1 Baseline (19.8) than subjects in the placebo group (22.6).

For the subjects who received SRP-9001 in Part 1, the mean micro-dystrophin level (% control) by western blot adjusted by muscle content was 4.23% at Baseline of Part 1, 28.05% at Week-12 in Part 1, and 23.59% at Week-12 in Part 2. The mean micro-dystrophin expression by IF fiber intensity (% control) was 37.90% at Baseline of Part 1 and 76.77% at Week-12 of Part 2.

For the subjects who received SRP-9001 in Part 2, the mean (SD) CK at Baseline of Part 1 was 24888.3 U/L (11884.5 U/L) and was 12943.3 U/L (7790.6 U/L) at Part 2Week-48; the mean change in CK from Baseline of Part 1 to Week-48 in Part 2 was -11945.0 U/L (10603.5 U/L).

For the subjects who received SRP-9001 in Part 2, the mean (SD) CK improved from Part 2 Day -1 (N=18;18346.1 U/L [10254.6 U/L]) to Part 2 Week-48 (N=21; 12943.3 [7790.6]).

For the subjects who received SRP-9001 in Part 1, the mean (SD) CK at Baseline of Part 1 was 18845.0 U/L (10421.0 U/L) and was 13979.5 U/L (9068.2 U/L) at Part 2 Week-48; the mean change in CK from Baseline of Part 1 to Week-48 in Part 2 was -4865.5 U/L (13638.2 U/L).

Study SRP-9001-103

Design of this study is described in the Clinical efficacy Section (3.3.4.7).

Study SRP-9001-301 (EMBARK)

Design of this study is described in the Clinical efficacy Section (3.3.4.2).

Quantity of Micro-dystrophin Protein Expression at Week 12 (Part 1) as Measured by Western Blot

At week 12 post-treatment, expression of micro-dystrophin protein was confirmed for the subset of biopsied SRP-9001 patients (n=17), but not for the subset of biopsied placebo-treated patients (n=14).

Table 3: Summary of micro-dystrophin level (% control) by western blot adjusted by muscle content, modified intent-to-treat population (part 1)

Visit / Statistics	**SRP-9001 (N = 63)**	**Placebo (N = 62)**
Week 12		
N	17	14
Mean (SD)	34.29 (41.04)	0.00 (0.00)
Median	19.11	0.00
Q1, Q3	7.58, 45.49	0.00, 0.00
Min, Max	0.00[a], 161.88	0.00, 0.00

Source: Table 14.2.1.1.1

BLOQ = below the limit of quantification; Max = maximum; Min = minimum; N = number of subjects; Q1 = first quartile; Q3 = third quartile; SD = standard deviation

a A visible band at the correct kD size was evident on the gel but was quantified as BLOQ and therefore numerically imputed as a zero per computational convention.

Change in Creatine Kinase from Baseline Over 52 Weeks (Part 1)

Mean baseline CK levels were 18,143.42 U/L (range: 6652, 39390) for the SRP-9001 group and 18,188.89 U/L (range: 6607, 40338) for the placebo group. A mean decrease (improvement) from Baseline over 52 weeks in CK levels was observed in the SRP-9001 group and placebo groups as early as Day 2 post-infusion. The LSM change difference between SRP-9001 and placebo groups at Week 52 was -4343.59 (95% CI: -6616.04, -2071.15; p = 0.0002), favoring SRP-9001.

Quantity of Micro-dystrophin Protein Expression at Week 12 by Immunofluorescence Fiber Intensity and Immunofluorescence Percent Dystrophin Positive Fibers (Part 1)

The mean (SD) micro-dystrophin expression by IF fiber intensity (% Control) at Week 12 was higher in the SRP-9001 group [54.70 (13.14)] compared to the placebo group [31.92 (9.43)](p < 0.0001). The mean (SD) micro-dystrophin expression by IF PDPF at Week 12 was higher in the SRP-9001 group [28.13 (26.10)] than in the placebo group [0.61 (1.27)](p < 0.0001).

2.5.3. Discussion on clinical pharmacology

Due to the nature of the product, no conventional clinical pharmacology studies were conducted. This is in line with the Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (EMA/CAT/80183/2014), which specifies that classical pharmacokinetic studies based on absorption, distribution, metabolism and excretion (ADME) studies are usually not required for GTMPs. Therefore, the lack of clinical pharmacology studies in this dossier is acceptable. The same guideline further clarifies that on a case by case basis, pharmacokinetics studies may be needed depending on the specific GTMPs, which is however not the case for SRP-9001.

No formal clinical dose-response study was performed, which is considered acceptable for a GTMP. A clinical dose of 1.33×10^{14} vg/kg and a maximum total dose of 9.31×10^{15} vg in patients >70 kg is proposed. In non-clinical studies in DMD^{MDX} mice, a dose-response relationship was observed between vector genome copies per nucleus, protein expression, and moderately with functional responses. However, the NOAEL is defined at 1.33×10^{14} vg/kg in DMD^{MDX} mice, resulting in a safety margin of 1 which was considered in the determination of the target dose in the clinical setting (see Nonclinical Section).

Vector shedding is discussed in the safety part of this AR and in the ERA. Across studies, SRP-9001 muscle tissue transduction following SRP-9001 treatment at the dose of 1.33×10^{14} vg/kg was demonstrated with an average of 3 vector genome copies per nucleus.

Based on the characteristics of the product, clinical pharmacology is primarily addressed as pharmacodynamics, with particular emphasis on the transgene expression including its kinetics and clinical monitoring of biological function of the via laboratory assays, and immunogenicity, the latter being discussed in the safety section.

Clinical pharmacology data submitted in the MAA dossier has been generated in four clinical trials, i.e. trials SRP-9001-101, -102, -103, and -301. For details on the trials, also refer to section 3.3. Of note, manufacturing process A has been used for product administered in studies SRP-9001-101 and -102, while process B has been used for product administered in studies SRP-9001-103 and -301. As material from Process A and B are not comparable, trials 101 and 102 are not considered supportive in terms of efficacy of SRP-9001.

Quantification of micro-dystrophin in muscle biopsies is considered an adequate biomarker for primary pharmacology to confirm transduction of cells and subsequent transgene protein expression. However, functionality of the transgenic protein and durability of protein expression are crucial. For pharmacology assessment of functionality of the transgenic protein, serum creatine kinase (CK) levels reflecting sarcolemma damage are assessed.

In trial 301 a muscle biopsy for evaluation of micro-dystrophin expression was collected from a subset of subjects (n=31) at Week 12 post-treatment only. Biopsies were limited to 31 subjects (17 treated with SRP-9001, as agreed with the PDCO not to exceed 30% of subjects and to have as few biopsies as possible) at one timepoint and in one muscle. Micro-dystrophin protein expression at Week 12 by Western blot was confirmed in all tested patients treated with SRP-9001, confirming transduction of the target tissue and transgene protein expression.

However, in study 102, several subjects had considerably high (up to 30.18%) micro-dystrophin protein expression levels detected at baseline. This is in contrast to study 301 results, where all tested subjects had no micro-dystrophin protein expression detected at baseline, and lacks plausibility, as per inclusion criteria no dystrophin protein expression is expected in eligible subjects. Similarly, baseline micro-dystrophin levels were measured by IF. However, for the assays used, a high variability was observed, which might be due to the sampling procedure itself, the known AAV-associated variability, or the heterogeneity of the underlying disease. Overall, these observations do not indicate that micro-dystrophin expression is suitable as surrogate for clinical benefit.

Regarding durability of transgene expression, w12 or equivalent data of micro-dystrophin expression in skeletal muscle biopsies has been generated in all four trials, but only for trial 102 data of three timepoints is available: Baseline, week 12, and approx. week 64. Week 12 and approx. week 64 data

are also available from trial 301. Durability of the transgenic protein expression has been confirmed in a relevant portion of trial participants, but with high interindividual variability.

For pharmacological assessment of functionality of the transgenic protein, i.e. secondary pharmacology, the exploratory endpoint serum CK was assessed, with a decrease considered to result from muscle membrane stabilisation following micro-dystrophin expression. A mean decrease of serum CK levels over the first 52 weeks has been observed in trials 101, 102, 103, and 301, however, the applicant acknowledged at least part of the CK decrease is attributable to the additional corticosteroids administered for immunosuppression. This might explain comparable magnitudes of CK decrease in both SRP-9001 and placebo treated patients in trial 102, but this has not been reproduced in trial 301. Longer-term data in the absence of temporary increase of corticosteroids might be more suited to confirm functionality of the transgenic protein. However, the only available longer-term data has been generated in trial 101 in n=4, thus a very limited data set of patients treated with Process A material. There, an initial decrease of serum CK levels, but increase of serum CK levels over time up to year 5 had been reported. Considering serum CK in DMD patients is expected to peak at 1-6 years of age, but patients in study 101 were 4-6 years at treatment, an increase of CK due to the initial natural course of disease is not the most likely explanation. Also, serum CK increase may have several reasons, including activity related muscle injury. In conclusion, the utility of CK is limited and difficult to interpret.

Currently, the provided data is confirming target tissue transduction, short-term transgene expression, and short-term membrane stabilisation, although the latter is not solely attributable to SRP-9001.

2.5.4. Conclusions on clinical pharmacology

Pharmacology data has been generated in all four clinical trials, i.e. trials 101&102 using manufacturing process A material, and trials 103&301 using manufacturing process B material. As neither analytical comparability has been shown, nor "high similarity" of manufacturing processes can be derived from non-clinical data or clinical pharmacology data, trials 101 and 102 are not considered supportive in terms of efficacy of SRP-9001.

The available data confirms micro-dystrophin expression after SRP-9001 administration, but no correlation with clinical outcome has been established. A reduction of serum CK levels has been observed following SRP-9001 administration, which cannot completely be attributed to SRP-9001 but also to the concomitant increase of glucocorticoids, and longer-term data is not yet available for process B material. Longer-term data on micro-dystrophin expression over time triggers relevant concerns on high interindividual variability in the expression of micro-dystrophin. Hence, relying purely on micro-dystrophin expression to conclude on efficacy is not considered appropriate, with impact on B/R of SRP-9001.

2.5.5. Clinical efficacy

2.5.5.1. Dose-response studies

No formal clinical dose-response study was performed. The clinical dose selection of 1.33×10^{14} vg/kg was based on PK/PD analyses from nonclinical studies, as well as clinical considerations:

- Across a log unit range of doses studied in mice (0.443, 0.7, 1.33, 2.66, and 4.01×10^{14} vg/kg), an apparent dose-proportionality of SRP-9001 tissue exposure was observed. A PK/PD analysis integrating biodistribution, biological response based on percentage of dystrophin-positive fibers (% PDPF), and functional response across the nonclinical studies conducted in DMD^{MDX} mice demonstrated a nonlinear PK/PD relationship with a saturable response observed at the high range of tissue drug exposure. There was a dose-response relationship observed between vector genome copies per nucleus, protein expression, and moderately with functional responses, supporting the functional muscle activity of SRP-9001 micro-dystrophin protein. Muscle exposures of approximately 1 vg/nucleus saturated protein expression (PDPF, % of fibers stained for SRP-9001 micro-dystrophin protein), translated into functional effects in DMD^{MDX} mice and rats, and were achieved at the clinically proposed dose of 1.33×10^{14} vg/kg.

In agreement with this PK/PD relationship, in young DMD^{MDX} rats treated with the clinically proposed dose of 1.33×10^{14} vg/kg and resulting in approximately 1 vg/nucleus in muscle cells, a high % of fibers stained for SRP-9001 micro-dystrophin protein and trends of cardiac efficacy were observed (see 3.2 Non-clinical aspects).

- Muscle tissue drug biodistribution is consistent across the studied DMD population (age 3-20 years old).
- Subjects with DMD who were treated with a dose of 1.33×10^{14} vg/kg achieved tissue transduction and SRP-9001 micro-dystrophin protein expression.

Patients with up to 50.5 kg have been treated in the target indication with the body weight-based dosing approach.

2.5.5.2. Main study

SRP-9001-301 (EMBARK)

This is a Phase 3, 1:1 randomized, double-blind, placebo-controlled, 2-part study of systemic gene delivery of SRP-9001 in 125 male ambulatory subjects with DMD, who are ≥ 4 to < 8 years of age. The total duration of each subject's participation in the study is expected to be approximately 108 weeks, inclusive of an up to 4-week pre-infusion period and a 52-week treatment and follow-up period in Part 1 and in Part 2. All eligible subjects have the opportunity to receive IV SRP-9001 (1.33×10^{14} vg/kg) in either Part 1 or Part 2.

Methods

Study participants

Main inclusion criteria

1. Is male at birth, ambulatory, and ≥ 4 to < 8 years of age at the time of randomization.
2. Has a definitive diagnosis of DMD prior to Screening based on documentation of clinical findings and prior confirmatory genetic testing using a clinical diagnostic genetic test. Genetic report must describe a frameshift deletion, frameshift duplication, premature stop ("nonsense"), canonical splice site mutation, or other pathogenic variant in the DMD gene fully contained between exons 18 to 79 (inclusive) that is expected to lead to absence of dystrophin protein.

    a. Mutations between or including exons 1-17 are not eligible.

    b. In-frame deletions, in-frame duplications, and variants of uncertain significance ("VUS") are not eligible.

    c. Mutations fully contained within exon 45 (inclusive) are not eligible.
3. Able to cooperate with motor assessment testing.
4. Has an NSAA score > 16 and < 29 at the Screening visit.
5. Has a time to rise from floor < 5 seconds at the Screening visit.
6. Stable daily dose equivalent of oral corticosteroids for at least 12 weeks before Screening and the dose is expected to remain constant (except for modifications to accommodate changes in weight) throughout the study.
7. Has rAAVrh74 antibody titers < 1:400 (ie, not elevated) as determined by an ELISA.

Main exclusion criteria

1. Has left ventricular ejection fraction < 40% on the screening ECHO or clinical signs and/or symptoms of cardiomyopathy.
2. Has a symptomatic infection (eg, upper respiratory tract infection, pneumonia, pyelonephritis, meningitis) within 4 weeks prior to Day 1.
3. Treatment with any of the following therapies according to the time frames specified:
    - Any time:
        - Gene therapy
        - Cell based therapy (eg, stem cell transplantation)
        - CRISPR/Cas9, or any other form of gene editing
    - Within 12 weeks of Day 1 and any time during the study:
        - Use of human growth factor or vamorolone
    - Within 6 months of Day 1 and any time during the study:
        - Any investigational medication
        - Any treatment designed to increase dystrophin expression (eg, Translarna™, EXONDYS 51™, VILTEPSO™)
4. Has abnormal laboratory values considered clinically significant by the Investigator including but not limited to:
    - Gamma-glutamyl transferase > 2 x ULN
    - Glutamate dehydrogenase (GLDH) > 15 U/L
    - Total bilirubin > ULN. Note; elevations in total bilirubin confirmed to be due to Gilbert' s syndrome are not exclusionary.
    - White blood cell count > 18,500 per µl
    - Platelets ≤ 150,000 per µl

Treatments

Subjects were randomized in a 1:1 ratio by the IRT to one of the following treatment groups:

- SRP-9001 (1.33×10^{14} vg/kg) by single IV infusion
- Placebo (saline, 0.9% sodium chloride solution) by single IV infusion

As required by the inclusion criterion, all subjects were to be on a stable daily dose of oral corticosteroids for at least 12 weeks before the Screening visit. The day before the infusion (SRP-9001 or placebo), the subject was started on additional steroid for immunosuppression and continued at this level for at least 60 days after the infusion. Following these 60 days, subjects were tapered from the added steroid and returned to their baseline dose of corticosteroids for DMD and remained on their stable dose (except for modifications to accommodate changes in weight) through the remainder of the study.

Post-infusion added glucocorticoid for immunosuppression should be increased if GGT level is confirmed to be ≥ 150 U/L or there are other clinically significant liver function abnormalities following infusion.

Objectives

Primary

To evaluate the effect of SRP-9001 on physical function as assessed by the NSAA score

Secondary

To evaluate the effect of SRP-9001 on physical function as assessed by the number of skills gained or improved on the NSAA

To evaluate micro-dystrophin expression from SRP-9001 at 12 weeks (Part 1) as measured by western blot of biopsied muscle tissue

To evaluate the effect of SRP-9001 on timed function tests as assessed by measuring: Time to rise from the floor, 100MWR, Time to ascend 4 steps, 10MWR

To evaluate the effect of SRP-9001 on SV95C as measured by a wearable device

To evaluate subject (parent/caregiver proxy) reported Mobility and Upper Extremity Function using the PROMIS® tool

For the primary efficacy endpoint of change in NSAA total score from Baseline to Week 52 (Part 1), the null hypothesis is that the population means for the 2 treatments are equal and the alternative hypothesis is that the population means for the 2 treatments are not equal. Even though the alternative hypothesis is 2-sided, only superiority of SRP-9001 over placebo will be of interest.

The statistical hypotheses for secondary efficacy endpoints can be stated in a similar manner as those for change in NSAA total score from Baseline to Week 52 (Part 1).

Outcomes/endpoints

Primary

Change in NSAA total score from Baseline to Week 52 (Part 1)

Secondary

- Number of skills gained or improved at Week 52 (Part 1) as measured by the NSAA
- Quantity of micro-dystrophin protein expression at Week 12 (Part 1) as measured by western blot
- Timed function tests:
    - Change in time to rise from the floor from Baseline to Week 52 (Part 1)
    - Change in time of 100MWR from Baseline to Week 52 (Part 1)
    - Change in time to ascend 4 steps from Baseline to Week 52 (Part 1)
    - Change in time of 10MWR from Baseline to Week 52 (Part 1)
- Change in SV95C from Baseline to Week 52 (Part 1)
- Change in PROMIS score in Mobility and Upper Extremity from Baseline to Week 52 (Part 1)

Sample size

The sample size of this study was based on the power for the primary efficacy endpoint, change in NSAA total score from Baseline to Week 52. Assumptions were: a standard deviation of 3.5 NSAA total score in all subjects, a 10% dropout rate, significance level of 0.05, two-sided and a sample size of 120 subjects randomized 1:1 to the two treatment arms. With these assumptions the study has a power of approximately 90% to detect a mean difference of 2.2 in change in NSAA total score from Baseline to Week 52.

Randomisation and blinding (masking)

Subjects were randomized in a 1:1 ratio by the IRT to receive either SRP-9001 or placebo by single IV infusion. Subjects who received SRP-9001 in Part 1 of the study received placebo in Part 2. Subjects who received placebo in Part 1 of the study had the opportunity to receive SRP-9001 in Part 2.

Randomization was stratified by age group at the time of randomization (≥ 4 to < 6 years or ≥ 6 to < 8 years) and NSAA total score (≤ 22 or > 22) at Screening; approximately 50% of subjects were randomized to the ≥ 4 to < 6 years age group.

All subjects, parents/caregivers, Investigators, and site staff were blinded to the treatment the subject received (SRP-9001 or placebo) with the exception of the unblinded site pharmacist. The unblinded pharmacist (or designee) performed drug preparation according to the randomized treatment assigned.

The blind of the treatment may be broken only in exceptional circumstances, such as when knowledge of the study treatment is essential for management of a subject's medical condition or AE.

Statistical methods

The population used for the primary analysis was the set of subjects who were randomized and received study treatment.

MMRM models for the difference in mean change from baseline at 52 weeks with prognostic and demographic covariates as well as baseline values were used for most endpoints. A re-randomisation test was used to test for differences in micro-dystrophin expression.

No interim analyses were conducted. A hierarchical testing procedure was used to account for multiplicity due to the testing of multiple endpoints. NSAA change from baseline at week 52 was the first endpoint in the hierarchy key-secondary and secondary endpoints were to be tested had NSAA change from baseline been significant.

Results

Recruitment and participant flow

Study SRP-9001-301 began on 14 October 2021 and as of 13 September 2023, the clinical cutoff date (CCOD) for this report, the study was still ongoing. Efficacy data up to 1-year post-infusion of SRP-9001 from the pre-specified primary analysis of the completed double-blind, placebo-controlled period (Part 1) of the study are presented in 125 subjects (CCOD: 13 September 2023); Part 2 of the study is ongoing.

In total, 126 subjects received study treatment in Study 301 at the time of CCOD of the primary analysis. One subject for whom Part 1 efficacy data are presented in the Addendum CSR (CCOD: 11 October 2023, Study 301 Addendum CSR, 1124892, Section 3.1), is not in scope of this efficacy evaluation as the subject was enrolled under a regional addendum. As such, efficacy data are presented on 125 subjects.

As of the data cutoff date, a total of 173 subjects were screened for the study; however, 42 subjects were screen failures, mainly due to having elevated rAAVrh74 antibody titers (> 1:400). A total of 131 subjects were randomized, however, of these 6 subjects were not dosed. A total of 125 subjects (SRP-9001: N = 63; placebo: N = 62) received study treatment and completed Part 1 of this study. No subjects discontinued from the study prior to Part 1 completion.

Conduct of the study

The primary changes in the conduct of the study that were implemented by global protocol amendments are summarized below. The original protocol and all protocol amendments are available for review.

Protocol/Amendments, Date	Changes	Rationale
Original Protocol, 17 NOV 2020	Not applicable	Not applicable
Protocol Amendment 1, 02 AUG 2021	Added a blinded crossover design	To provide equal opportunity for subjects to receive SRP-9001, either in Part 1 or Part 2 of the study, but remain blinded
Protocol Amendment 2, 30 AUG 2021	Updated/refined the exon language for inclusion criterion #2; and safety monitoring and adverse events of special interest language	To mitigate the risk of immune response to the transgene; and update the identified risk based on recent clinical safety data
Protocol Amendment 3, 29 AUG 2022	Updated the randomization language	To allow approximately 50% of subjects to be randomized in the ≥ 4 to < 6 years age group
Letter of Administrative Changes #3, 08 SEP 2023	Removal of GLDH from safety monitoring and reporting. This USA-specific change is being implemented because GLDH is not approved by the FDA for diagnostic use in the USA. GLDH does not provide Sarepta, or the investigator, clinically actionable data for the purposes of medical management, nor is it a direct measure of liver dysfunction. The protocol includes other, more actionable measures of hepatic health and function, such as AST, ALT, GGT, bilirubin, albumin, and INR. Therefore, Sarepta has determined that it is most appropriate, and safe, to remove GLDH from safety monitoring and reporting language.	GLDH is not approved by the FDA for diagnostic use in the USA. GLDH does not provide Sarepta, or the investigator, clinically actionable data for the purposes of safety monitoring, nor is it a direct measure of liver dysfunction.

Prior to the start of Study SRP-9001-301, the Sponsor performed a comprehensive risk assessment to identify any specific COVID-19 pandemic risks relating to trial disruption and implemented corresponding mitigation actions, for the defined critical variables (data and processes) of the study, which could have impacted participant safety and/or data integrity. According to the applicant, the COVID-19 pandemic had minimal impact on Study SRP-9001-301.

Baseline data

Table 4: Demographics and baseline characteristics, modified intent-to-treat population (part 1)

Parameter	SRP-9001 N = 63	Placebo N = 62	Total N = 125
Age (years) at randomization [a]			
N	63	62	125
Mean (SD)	5.98 (1.06)	6.08 (1.05)	6.03 (1.05)
Median	6.20	6.06	6.10
Q1, Q3	5.07, 6.72	5.16, 7.01	5.12, 6.80
Min, Max	4.07, 7.87	4.03, 7.99	4.03, 7.99
Age group at randomization – n (%)			
4-5 years old	30 (47.6)	29 (46.8)	59 (47.2)
6-7 years old	33 (52.4)	33 (53.2)	66 (52.8)
Sex – n (%)			
Male	63 (100.0)	62 (100.0)	125 (100.0)
Race – n (%)			
American Indian or Alaska Native	0	0	0
Asian	8 (12.7)	11 (17.7)	19 (15.2)
Black or African American	0	2 (3.2)	2 (1.6)
Native Hawaiian or other Pacific Islanders	0	0	0
White	49 (77.8)	46 (74.2)	95 (76.0)
Multiple	1 (1.6)	0	1 (0.8)
Other	2 (3.2)	1 (1.6)	3 (2.4)
Not reported	3 (4.8)	2 (3.2)	5 (4.0)
Race group – n (%)			
White	49 (77.8)	46 (74.2)	95 (76.0)
Non-White	11 (17.5)	14 (22.6)	25 (20.0)
Missing	3 (4.8)	2 (3.2)	5 (4.0)
Ethnicity – n (%)			
Hispanic or Latino	15 (23.8)	8 (12.9)	23 (18.4)
Not Hispanic or Latino	47 (74.6)	53 (85.5)	100 (80.0)
Not reported	0	1 (1.6)	1 (0.8)
Unknown	1 (1.6)	0	1 (0.8)
Height (cm)			
N	63	62	125
Mean (SD)	108.64 (6.74)	110.68 (7.44)	109.65 (7.14)
Median	109.00	110.15	109.30

Parameter	SRP-9001 N = 63	Placebo N = 62	Total N = 125
Q1, Q3	104.00, 112.00	104.50, 116.50	104.50, 113.50
Min, Max	93.5, 127.0	95.2, 127.5	93.5, 127.5
Dosing weight (kg)			
N	63	62	125
Mean (SD)	21.29 (4.62)	22.37 (6.42)	21.83 (5.59)
Median	20.20	20.55	20.20
Q1, Q3	18.50, 23.40	17.40, 25.00	18.20, 23.80
Min, Max	13.5, 38.5	14.1, 41.6	13.5, 41.6
Body Mass Index (kg/m^2)[b]			
N	63	62	125
Mean (SD)	17.85 (2.20)	17.89 (3.20)	17.87 (2.73)
Median	17.36	16.56	17.26
Q1, Q3	16.20, 19.01	15.85, 19.11	15.97, 19.01
Min, Max	13.69, 24.92	13.45, 26.86	13.45, 26.86
BMI category (kg/m^2) – n (%)			
< 20	53 (84.1)	52 (83.9)	105 (84.0)
≥ 20	10 (15.9)	10 (16.1)	20 (16.0)
Years since diagnosis of DMD[c]			
N	63	62	125
Mean (SD)	2.62 (1.73)	2.60 (1.78)	2.61 (1.75)
Median	2.40	2.12	2.27
Q1, Q3	1.31, 3.81	1.15, 3.69	1.29, 3.69
Min, Max	0.00, 6.71	0.24, 7.55	0.00, 7.55
Years since corticosteroid treatment started			
N	63	62	125
Mean (SD)	1.07 (0.92)	0.97 (0.83)	1.02 (0.88)
Median	0.96	0.66	0.77
Q1, Q3	0.40, 1.38	0.42, 1.19	0.42, 1.33
Min, Max	0.23, 6.17	0.24, 4.01	0.23, 6.17
Genetic mutation type – n (%)[e]			
Large deletion	45 (71.4)	41 (66.1)	86 (68.8)
Large duplication	3 (4.8)	3 (4.8)	6 (4.8)

Parameter	SRP-9001 N = 63	Placebo N = 62	Total N = 125
Small mutation	15 (23.8)	18 (29.0)	33 (26.4)
NSAA total score at Screening			
N	63	62	125
Mean (SD)	23.03 (3.24)	22.56 (3.79)	22.80 (3.52)
Median	23.00	23.00	23.00
Q1, Q3	20.00, 26.00	19.00, 26.00	19.00, 26.00
Min, Max	17, 28	17, 28	17, 28

Source: Table 14.1.3

BMI = body mass index; DMD = Duchenne muscular dystrophy; Max = maximum; Min = minimum; NSAA = North Star Ambulatory Assessment; Q1 = first quartile; Q3 = third quartile; SD = standard deviation.

a Age at Randomization = ([date at Randomization - date of birth] +1)/365.25.

b Body Mass Index = weight in kg / (height in m2).

c Years since diagnosis of DMD = (date of informed consent - date of DMD diagnosis)/365.25.

d Years since corticosteroid treatment started = (date of informed consent - date of start of corticosteroid intake)/365.25.

e Large deletion and Large duplications are the two types of larger structural variants, which extend one or more exons and/or are 50 nucleotides or more in length, inclusive of any nucleotides affected in intronic regions. Small mutations include single nucleotide variants, small insertions and small deletion mutations. 425-1323 has two mutations (a large duplication and a large inversion) and it is listed in the large duplication mutation category. Mutation data will be updated at the next database lock for clarity.

All subjects had at least one medical history finding. The most frequent medical history findings by SOC were congenital, familial, and genetic disorders (100.0%), musculoskeletal and connective tissue disorders (25.6%), surgical and medical procedures (22.4%), and infections and infestations (21.6%).

The most frequently reported Preferred Term other than the condition under study were blood CK increased (12.0%), muscle weakness (12.0%), seasonal allergy (11.2%), Vitamin D deficiency (11.2%), muscle hypertrophy (10.4%), and constipation (10.4%).

All subjects (100%) in both treatment groups were treated with corticosteroid medications prior to and/or following administration of SRP-9001 or placebo (Table 5).

Table 5: (excerpt): Concomitant medications (modified intent-to-treat population)(part 1)

ATC Dictionary Level Preferred Term [a]	SRP-9001 (N=63) n (%)	Placebo (N=62) n (%)	Total (N=125) n (%)
Corticosteroids for systemic use, plain	63 (100.0)	62 (100.0)	125 (100.0)
Deflazacort	43 (68.3)	28 (45.2)	71 (56.8)
Prednisone	36 (57.1)	28 (45.2)	64 (51.2)
Prednisolone	31 (49.2)	36 (58.1)	67 (53.6)
Methylprednisolone	6 (9.5)	1 (1.6)	7 (5.6)

Hydrocortisone sodium succinate	3 (4.8)	0	3 (2.4)
Methylprednisolone sodium succinate	3 (4.8)	0	3 (2.4)
Prednisolone sodium phosphate	3 (4.8)	3 (4.8)	6 (4.8)
Dexamethasone	2 (3.2)	2 (3.2)	4 (3.2)
Hydrocortisone	2 (3.2)	7 (11.3)	9 (7.2)

Concomitant medications are defined as medications that (1) started before the first dose of study drug and continued into the treatment period, or (2) started on or after the date of the first dose of study drug.

[a] ATC Dictionary Level and Preferred Name are coded using WHO Drug Version WHODrug Global B3 SEP 2021. ATC are sorted in descending order of frequency and preferred terms (PTs) are listed in descending order of frequency within each ATC in SRP-9001 column. A subject is counted only once for multiple events within each ATC/PT.

Other concomitant medications frequently (at least 50% of subjects) used were Vitamin A and D (71.2%) and other analgesics and antipyretics (53.6%).

Numbers analysed

Table 6: Subject disposition, All Subjects population (part 1)

	SRP-9001	**Placebo**	**Total**
Subjects who were screened	173		
Subjects who were randomized[a]	65	64	131
Safety population	63	62	125
ITT population[a]	65	64	131
mITT population[b]	63	62	125
Subjects who were treated in Part 1	63	62	125
Subjects who completed Part 1	63	62	125
Treated subjects who discontinued from Part 1	0	0	0

Source: Table 14.1.1
ITT = intent-to-treat; mITT = modified intent-to-treat
[a] Two subjects who were randomized but not dosed did not have planned randomization recorded.
[b] The mITT population included all randomized subjects who received study treatment (not including those enrolled under a regional addendum), with treatment group designated according to randomization.

Outcomes and estimation

Primary efficacy endpoint

Change in North Star Ambulatory Assessment Total Score from Baseline to Week 52 (Part 1)

A mean increase (improvement) from Baseline to Week 52 in NSAA total scores was observed in SRP-9001 and placebo groups (Table 6). The LSM change difference between SRP-9001 and placebo groups at Week 52 was not statistically significant (p = 0.2441).

Table 7: NSAA total score, modified intent-to-treat population (part 1)

Results from MMRM analysis:

Timepoint	Treatment	N1	LSM Change (SE)	95% CI	Within-group P-value	Versus Placebo LSM Change Diff (SE)	95% CI	P-value
Week 52	SRP-9001	63	2.57 (0.39)	1.80, 3.34	< 0.0001	0.65 (0.55)	-0.45, 1.74	0.2441
	Placebo	61	1.92 (0.39)	1.14, 2.70	< 0.0001			

Source: Table 14.2.2.1.1

CI = confidence interval; Diff = difference; LSM = least squares mean; MMRM = mixed model of repeated measures; N1 = number of subjects with non-missing change from Baseline data at a specific timepoint; NSAA = North Star Ambulatory Assessment; SE = standard error.

As the NSAA (primary endpoint) p value did not reach 0.05, the gatekeeping procedure stopped. For subsequent secondary and exploratory endpoints in this CSR, raw p values are reported, without adjustment for multiplicity.

Secondary efficacy endpoints

Key secondary endpoints

Quantity of Micro-dystrophin Protein Expression at Week 12 (Part 1) as Measured by Western Blot

Results of this endpoint are shown in the Clinical pharmacology section.

Time to Rise From the Floor

A mean decrease (improvement) from Baseline to Week 52 in time to rise from the floor was observed in the SRP-9001 group but not in the placebo group (Table 8).

Table 8: Time to rise from the floor (sec), modified intent-to-treat population (part 1)

Results from MMRM analysis:								
Timepoint	**Treatment**	**N1**	**LSM Change (SE)**	**95% CI**	**Within-group P-value**	**Versus Placebo LSM Change Diff (SE)**	**95% CI**	**P-value**
Week 52	SRP-9001	63	-0.27 (0.15)	-0.56, 0.02	0.0669	-0.64 (0.21)	-1.06, -0.23	0.0025
	Placebo	61	0.37 (0.15)	0.08, 0.67	0.0133			

Source: Table 14.2.2.4.1

CI = confidence interval; Diff = difference; LSM = least squares mean; MMRM = mixed model of repeated measures; N1 = number of subjects with non-missing change from Baseline data at a specific timepoint; SE = standard error.

Time of 10-meter Timed Test

A mean decrease (improvement) from Baseline to Week 52 in time of 10-meter timed test was observed in the SRP-9001 group but not in the placebo group (Table 9).

Table 9: Time of 10-meter timed test (sec), modified intent-to-treat population (part 1)

Results from MMRM analysis:

Timepoint	Treatment	N1	LSM Change (SE)	95% CI	Within-group P-value	Versus Placebo LSM Change Diff (SE)	95% CI	P-value
Week 52	SRP-9001	63	-0.34 (0.10)	-0.55, -0.14	0.0013	-0.42 (0.15)	-0.71, -0.13	0.0048
	Placebo	61	0.08 (0.10)	-0.13, 0.29	0.4431			

Source: Table 14.2.2.5.1

CI = confidence interval; Diff = difference; LSM = least squares mean; MMRM = mixed model of repeated measures; N1 = number of subjects with non-missing change from Baseline data at a specific timepoint; SE = standard error.

Other secondary endpoints

Change in SV95C From Baseline to Week 52 (Part 1)

A mean increase (improvement) from Baseline to Week 52 in SV95C was observed in the SRP-9001 group but not in the placebo group. The LSM change difference between SRP-9001 and placebo groups at Week 52 was 0.10 (95% CI: 0.00, 0.19; p = 0.0402), favoring SRP-9001.

Time of 100-meter Timed Test

A mean decrease (improvement) from Baseline to Week 52 in time of 100-meter timed test was observed in both the SRP-9001 and placebo groups. The LSM change difference between SRP-9001 and placebo groups at Week 52 was -3.29 (95% CI: -8.28, 1.70; p = 0.1942).

Percent Predicted 100-meter Timed Test

A mean increase (improvement) from Baseline to Week 52 in % predicted 100-meter timed test was observed in both the SRP-9001 and placebo groups. The LSM change difference between SRP-9001 and placebo groups at Week 52 was 3.52 (95% CI: -0.12, 7.16; p = 0.0576).

Time to Ascend 4 Steps

A mean decrease (improvement) from Baseline to Week 52 in time to ascend 4 steps was observed in both the SRP-9001 and placebo groups. The LSM change difference between SRP-9001 and placebo groups at Week 52 was -0.36 (95% CI: -0.71, -0.01; p = 0.0412), favoring SRP-9001.

Change in PROMIS Score in Mobility and Upper Extremity From Baseline to Week 52 (Part 1)

A mean increase (improvement) from Baseline to Week 52 in PROMIS score in mobility was observed in the SRP-9001 group but not in the placebo group. The LSM change difference between SRP-9001 and placebo groups at Week 52 was 0.05 (95% CI: -0.08, 0.19; p = 0.4272).

A mean increase (improvement) from Baseline to Week 52 in PROMIS score in upper extremity was observed for both the SRP-9001 and placebo groups. The LSM change difference between SRP-9001 and placebo groups at Week 52 was -0.04 (95% CI: -0.24, 0.17; p = 0.7324).

Number of Skills Gained or Improved at Week 52 (Part 1) as Measured by the NSAA

As measured by NSAA, the number of skills gained (the average item score is 0 at Baseline and > 0 at Part 1 Week 52) or improved (the average item score at Baseline is > 0 but less than the average item score at Part 1 Week 52) was positive in both the SRP-9001 and placebo groups. The LSM change difference between SRP-9001 and placebo groups at Week 52 was 0.19 (95% CI: -0.67, 1.06; p = 0.6554).

Exploratory endpoints

Vector Genome Copies at Week 12 (Part 1) Using Polymerase Chain Reaction in Muscle Tissue Biopsy

A mean of 2.26 vector genome copies per nucleus by ddPCR at Week 12 was observed in the SRP-9001 group compared to 0 in the placebo group ($p < 0.0001$), favoring SRP-9001. Vector genome copies using polymerase chain reaction in serum has not been analyzed at the time of this report.

Change in Creatine Kinase from Baseline Over 52 Weeks (Part 1)

Results of this endpoint are shown in the Clinical pharmacology section (2.6.2.).

Change in Linearized NSAA Score From Baseline to Week 52 (Part 1)

A mean increase (improvement) from Baseline to Week 52 in linearized NSAA total scores was observed in SRP-9001 and placebo groups. The LSM change difference between SRP-9001 and placebo groups at Week 52 was 1.37 (95% CI: -1.61, 4.34; $p = 0.3645$).

Change in PROMIS Score in Fatigue From Baseline to Week 52 (Part 1)

A mean decrease (improvement) from Baseline to Week 52 in PROMIS score in fatigue was observed in SRP-9001 and placebo groups. The LSM change difference between SRP-9001 and placebo groups at Week 52 was -0.14 (95% CI: -0.38, 0.11; $p = 0.2756$).

Change in Cardiac MRI Findings From Baseline to Week 52 (Part 1)

There were no clinically significant changes in cardiac MRI findings from Baseline to Week 52 in a subset of subjects (n = 39) who participated in this sub-study.

Change in Musculoskeletal MRI Findings From Baseline to Week 52 (Part 1)

A subset of study participants (n = 39) underwent musculoskeletal MRI images, including 8-point Dixon and magnetic resonance spectroscopy sequences to derive fat fraction, and transverse relaxation time (T2) sequences to detect inflammation. For all 5 muscle groups, the placebo group demonstrated longer (worsening) T2 relaxation times compared to the SRP-9001-treated group.

Change in Ambulation Variables as Measured by Wearable Device From Baseline to Week 52 (Part 1)

A mean increase (improvement) from Baseline to Week 52 in the number of stairs climbed per hour was observed in the SRP-9001 group but not in the placebo group. The LSM change difference between SRP-9001 and placebo groups at Week 52 was 0.29 (95% CI: -0.13, 0.71, $p = 0.1747$).

A mean increase (improvement) from Baseline to Week 52 in the 95th percentile of stair climbing velocity was observed in the SRP-9001 group but not in the placebo group. The LSM change difference between SRP-9001 and placebo groups at Week 52 was 0.06 (95% CI: 0.02, 0.11, $p = 0.0081$).

A mean increase (improvement) from Baseline to Week 52 in the distance walked per hour was observed in the SRP-9001 and placebo groups. The LSM change difference between SRP-9001 and placebo groups at Week 52 was 14.05 (95% CI: -7.11, 35.21; $p = 0.1910$).

A mean increase (improvement) from Baseline to Week 52 in the 95th percentile of stride length was observed in the SRP-9001 group and placebo groups. The LSM change difference between SRP-9001 and placebo groups at Week 52 was 0.02 (95% CI: -0.01, 0.05, $p = 0.2119$).

Ancillary analyses

Primary endpoint:

Change in North Star Ambulatory Assessment Total Score From Baseline to Week 52 (Part 1)

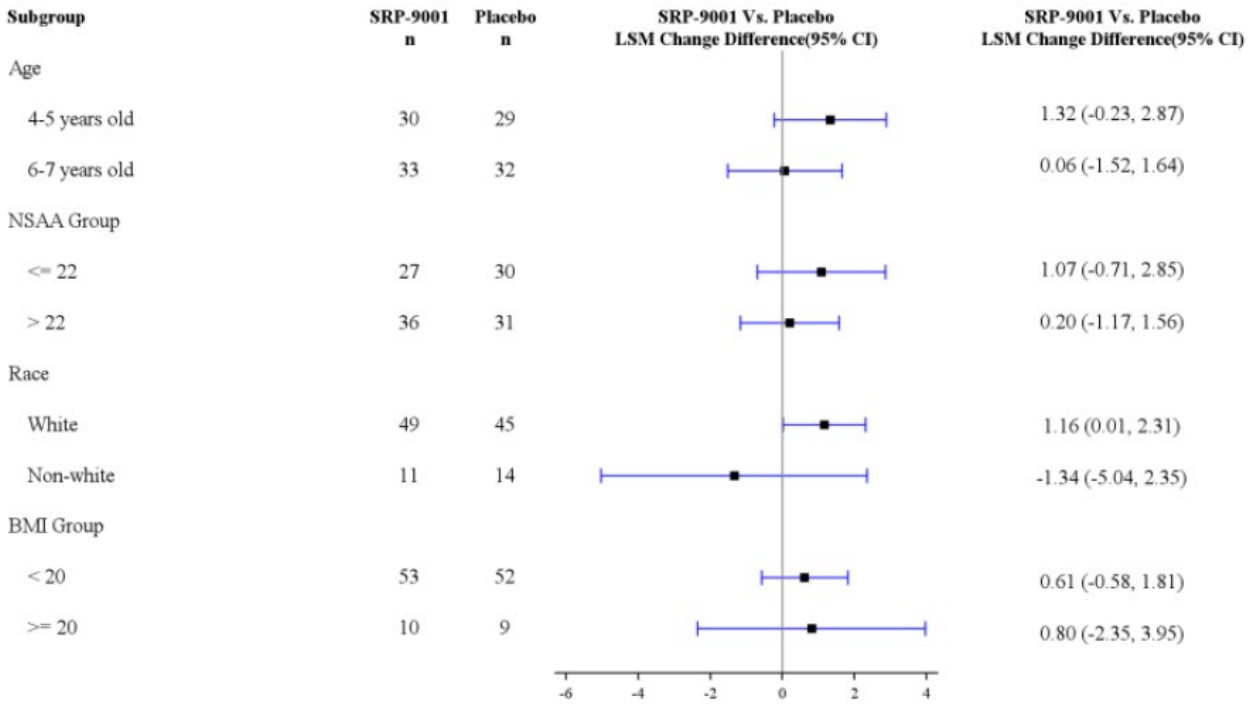


Figure 4: Forest plot of change from baseline in NSAA total score at week 52, modified intent-to-treat population (part 1)

Source: Figure 14.2.2.8

BMI = body mass index; CI = confidence interval; LSM = least squares mean; NSAA = North Star Ambulatory Assessment; vs = versus.

Key secondary endpoints:

Micro-dystrophin Level (% control) by Western Blot Adjusted by Muscle Content by Age and Baseline NSAA Total Score

Micro-dystrophin expression adjusted by muscle content at Week 12 was observed in the SRP-9001 group for age groups 4 to 5 years old and 6 to 7 years old; and for subjects with Baseline NSAA total scores of ≤ 22 and > 22 but not in the placebo group.

Change in Functional Assessments (Time to Rise From the Floor, 10-meter Timed Test) From Baseline to Week 52 (Part 1)

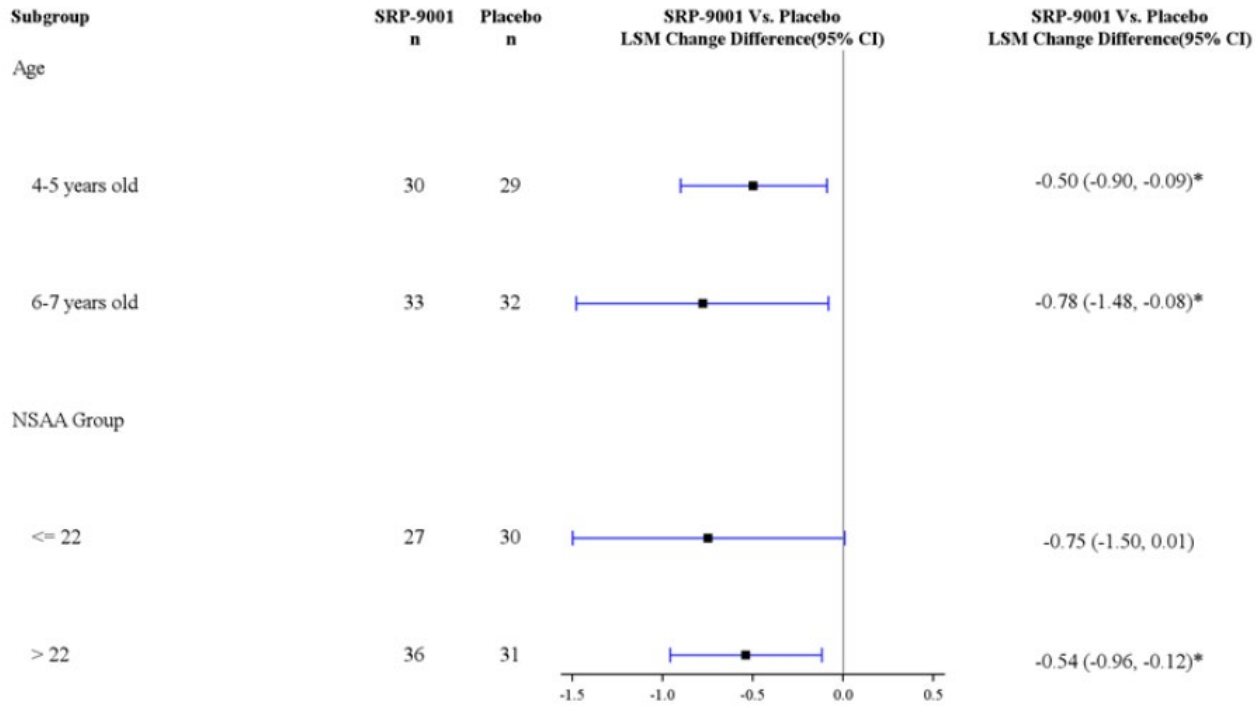


Figure 5: Forest plot of change from baseline in time to rise from floor (sec) at week 52 by age subgroup and NSAA subgroup, modified intent-to-treat population (part 1)

Source: Figure 14.2.2.8.1

CI = confidence interval; LSM = least-square mean; NSAA = North Start Ambulatory Assessment.

* p < 0.05, ** p < 0.01, *** p < 0.001

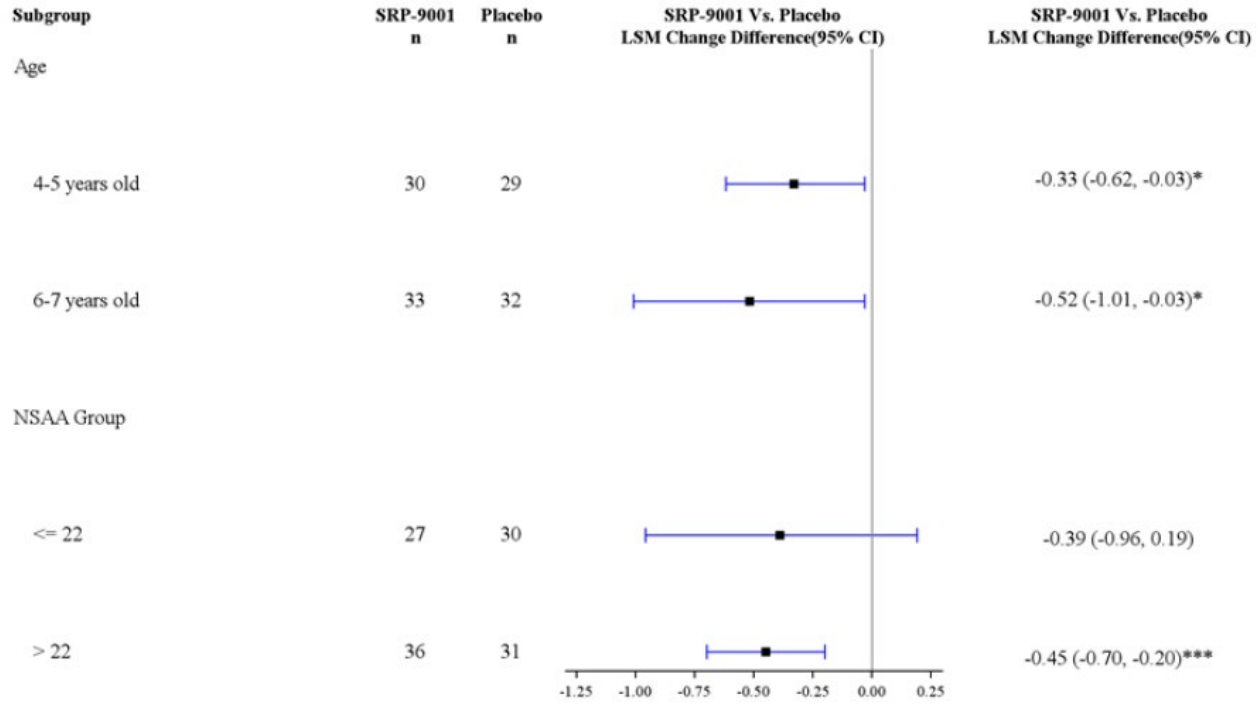


Figure 6: Forest plot of change from baseline in time of 10meter timed test (sec) at week 52 by age subgroup and NSAA subgroup, modified intent-to-treat population (part 1)

Source: Figure 14.2.2.8.2

CI = confidence interval; LSM = least-square mean; NSAA = North Star Ambulatory Assessment.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

2.5.5.3. Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 10: Summary of efficacy for trial SRP-9001-301

Title: A Phase 3, Multinational, Randomized, Double-blind, Placebo-Controlled Systemic Gene Delivery Study to Evaluate the Safety and Efficacy of SRP-9001 in Subjects With Duchenne Muscular Dystrophy (EMBARK)		
Study identifier	SRP-9001-301, EMBARK, BN44841 ClinicalTrials.gov Identifier: NCT05096221 EudraCT: 2019-003374-91	
Design	Multicenter, randomized, double-blind, placebo-controlled, 2-part study of systemic gene delivery of SRP-9001 in 125 male ambulatory subjects with Duchenne's muscular dystrophy, who are ≥ 4 to < 8 years of age. The total duration of each subject's participation in the study is expected to be approximately 108 weeks, inclusive of an up to 4-week pre-infusion period and a 52-week treatment and follow-up period in Part 1 and in Part 2. Subjects were randomized in a 1:1 ratio to receive either SRP-9001 (1.33×10^{14} vg/kg) or placebo by single IV infusion. Subjects who received SRP-9001 in Part 1 of the study received placebo in Part 2. Subjects who received placebo in Part 1 of the study had the opportunity to receive SRP-9001 in Part 2.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	104 weeks (Part 1: 52 weeks [completed]; Part 2: 52 weeks [ongoing]) Up to 31 days Not applicable
Hypothesis	For the primary endpoint of change in NSAA total score from Baseline to Week 52 (Part 1), the null hypothesis was that the population means for the two treatments were equal and the alternative hypothesis was that the population means for the two treatments were not equal. Even though the alternative hypothesis was two-sided, only superiority of SRP-9001 over placebo was of interest.	
Treatment groups	SRP-9001 group	SRP-9001 (1.33×10^{14} vg/kg) by single IV infusion. All subjects were to be on a stable daily dose of oral corticosteroids for at least 12 weeks before the Screening visit. The day before the infusion (SRP-9001 or placebo), the subject was started on additional steroid for immunosuppression and continued at this level for at least 60 days after the infusion.
	Placebo group	Placebo (saline, 0.9% sodium chloride solution) by single IV infusion. All subjects were to be on a stable daily dose of oral corticosteroids for at least 12 weeks before the Screening visit. The day before the infusion (SRP-9001 or placebo), the subject was started on additional steroid for immunosuppression and continued at this level for at least 60 days after the infusion.

Endpoints and definitions	Primary endpoint:	CfBL in NSAA at Week 52	Change in North Star Ambulatory Assessment (NSAA) total score from Baseline to Week 52 (Part 1)
	Secondary endpoint:	WB micro-dystrophin at Week 12	Quantity of micro-dystrophin protein expression at Week 12 (Part 1) as measured by western blot (WB)
	Secondary endpoint:	CfBL in TTR at Week 52	Change in time to rise from the floor (TTR) from Baseline to Week 52 (Part 1)
	Secondary endpoint:	CfBL in 10MWR at Week 52	Change in time of 10-meter walk/run timed test (10MWR) from Baseline to Week 52 (Part 1)
	Secondary endpoint:	Number of skills gained or improved at Week 52	Number of skills gained or improved at Week 52 (Part 1) as measured by the NSAA
	Secondary endpoint:	CfBL in 100MWR at Week 52	Change in time of 100-meter walk/run timed test (100MWR) from Baseline to Week 52
	Secondary endpoint:	CfBL in 4SC at Week 52	Change in time to ascend 4 stairs (4SC) from Baseline to Week 52
	Secondary endpoint:	CfBL in SV95C at Week 52	Change in Stride Velocity 95th Centile (SV95C) from Baseline to Week 52 (Part 1)
Database lock	Database lock for Part 1 of the study occurred on 13 September 2023 for the primary analysis of efficacy data through Week 52 (Part 1). The final database lock will occur once all subjects have completed Part 2 of the study, which is currently ongoing.		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Modified intent to treat: All randomized subjects who received study treatment (not including those enrolled under a regional addendum [such as the local Japan protocol addendum]), with treatment group designated according to randomization. The mITT population was the analysis population used for efficacy endpoints. The primary analysis of the study was performed after all subjects had completed Part 1 of the study or had withdrawn early from Part 1.		
Descriptive statistics and estimate variability	Treatment group	SRP-9001	Placebo
	Number of subjects (N)	63	62
	Primary Endpoint: CfBL in NSAA at Week 52 n Mean (SD)	 63 2.52 (3.31)	 61 1.86 (3.18)
	Secondary Endpoint: WB micro-dystrophin at Week 12 (% control) n Mean (SD)	 17 34.29 (41.04)	 14 0.00 (0.00)
	Secondary Endpoint: CfBL in TTR at Week 52 (seconds) n Mean (SD)	 63 -0.26 (0.95)	 61 0.39 (1.39)
	Secondary Endpoint: CfBL in 10MWR at Week 52 (seconds) n Mean (SD)	 63 -0.34 (0.69)	 61 0.09 (1.03)

	Secondary Endpoint: Number of skills gained or improved at Week 52 n Mean (SD)	 63 4.16 (2.38)	 61 3.97 (2.55)
	Secondary endpoint: CfBL in 100MWR at Week 52 (seconds) n Mean (SD)	 59 -6.65 (14.54)	 57 -4.18 (18.46)
	Secondary endpoint: CfBL in 4SC at Week 52 (seconds) n Mean (SD)	 62 -0.41 (0.85)	 60 -0.12 (1.28)
	Secondary Endpoint: CfBL in SV95C at Week 52 (m/second) n Mean (SD)	 57 0.06 (0.30)	 61 -0.03 (0.26)
Effect estimate per comparison	Primary Endpoint: CfBL in NSAA at Week 52	Comparison groups	SRP-9001 group vs. placebo group
		Difference in least square means	0.65
		95% confidence interval	-0.45, 1.74
		P-value (MMRM analysis)	0.2441
	Secondary Endpoint: WB micro-dystrophin at Week 12 (% control)	Comparison groups	SRP-9001 group vs. placebo group
		P-value (2-sample Welch t-test)	< 0.0001
	Secondary Endpoint: CfBL in TTR at Week 52 (seconds)	Comparison groups	SRP-9001 group vs. placebo group
		Difference in least square means	-0.64
		95% confidence interval	-1.06, -0.23
		P-value (MMRM analysis)	0.0025
	Secondary Endpoint: CfBL in 10MWR at Week 52 (seconds)	Comparison groups	SRP-9001 group vs. placebo group
		Difference in least square means	-0.42
		95% confidence interval	-0.71, -0.13
		P-value (MMRM analysis)	0.0048
	Secondary Endpoint: Number of skills gained or improved at Week 52	Comparison groups	SRP-9001 group vs. placebo group
		Difference in least square means	0.19
		95% confidence interval	-0.67, 1.06
		P-value (MMRM analysis)	0.6554

	Secondary endpoint: CfBL in 100MWR at Week 52 (seconds)	Comparison groups	SRP-9001 group vs. placebo group
		Difference in least square means	-3.29
		95% confidence interval	-8.28, 1.70
		P-value (MMRM analysis)	0.1942
	Secondary endpoint: CfBL in 4SC at Week 52 (seconds)	Comparison groups	SRP-9001 group vs. placebo group
		Difference in least square means	-0.36
		95% confidence interval	-0.71, -0.01
		P-value (MMRM analysis)	0.0412
	Secondary Endpoint: CfBL in SV95C at Week 52 (m/second)	Comparison groups	SRP-9001 group vs. placebo group
		Difference in least square means	0.10
		95% confidence interval	0.00, 0.19
		P-value (MMRM analysis)	0.0402
Notes	The primary endpoint of change in NSAA total score from Baseline to Week 52 did not reach statistical significance. Therefore, secondary endpoints are not Type I error controlled and nominal p-values are presented.		

2.5.5.4. Clinical studies in special populations

No studies in special populations have been conducted and no data on special populations are available.

2.5.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Study WN44594 was a retrospective non-interventional study comparing functional endpoints (NSAA total score, 10MWR and TTR) in selected patients exposed to SRP-9001 from a set of clinical trials (Studies 101, 102 and 103 Cohort 1) conducted by the applicant to a pooled cohort of patients that were never treated with SRP-9001 derived from external secondary data sources (CINRG Duchenne Natural History Study (DNHS), Finding the Optimum Regimen for Duchenne Muscular Dystrophy (FOR-DMD) study, and a placebo cohort from Eli Lilly and Company-sponsored Phase 3 clinical study). Inverse probability of treatment weighting (IPTW) was used to create a pseudo-population with similar covariate distributions in the SRP-9001 and EC cohorts. Propensity scores were estimated using logistic regression analyses that included pre specified prognostic independent covariates with a dependent variable of whether a patient received the treatment of SRP-9001 or not. The treatment effect of SRP-9001 was assessed via comparison to the EC cohort using a weighted linear regression model.

The estimated least-square (LS) mean difference in NSAA total score change from baseline compared to EC was 2.5 points at 1 year ($p < 0.0001$), and 1.8 points at 2 years ($p = 0.0429$). Mean gains from baseline of 2.3 points on NSAA total score at 1 year and 1.1 points at 2 years were estimated for patients treated with SRP-9001, while no gains were estimated for the EC patients (LS mean change from baseline -0.2 and -0.7 points respectively at 1 and 2 years). Signs of positive efficacy were observed on TTR and 10MWR at both 1 and 2 years after treatment (TTR difference in LS mean change from baseline at 1 year -2.37 seconds [$p < 0.0001$], 2 years -2.82 seconds [$p = 0.0273$]), (10MWR difference in LS mean change from baseline at 1 year -0.76 seconds [$p = 0.0105$], 2 years -1.80 seconds [$p = 0.0107$]).

2.5.5.6. Supportive study

Study **SRP-9001-103** is an ongoing, open-label, single-arm, single-dose, Phase 1b study with seven cohorts and a two-part follow-up period. Cohorts within scope of this evaluation are as follows:

• Cohort 1, which consists of 20 male DMD ambulatory subjects aged ≥ 4 to < 8 years, NSAA score >17 and ≤ 26 at Screening.

• Cohort 4, which consists of 7 male DMD ambulatory subjects aged ≥ 3 and <4 years at Screening.

A single infusion of open-label SRP-9001 was administered (1.33×10^{14} vg/kg; IV; Process B). Following administration of SRP-9001, subjects were planned to be followed up from Day 1 through Week 12 (Part 1) and Week 12 through Week 260 (Part 2). The main scope of the efficacy evaluation includes assessment of micro-dystrophin expression, NSAA, time to rise from floor and time of 10MWR.

As of the CCOD (24 July 2023), 48 subjects are currently enrolled. Efficacy data from the subjects enrolled in Cohorts 1 (n=20) and 4 (n=7) are presented. All subjects enrolled in the study were male. In Cohort 1, the mean age was 5.81 years (range: 4.38, 7.94), and 5 subjects had mutations fully or partially contained within exons 1−17. In Cohort 4, the mean age was 3.48 years (range: 3.24, 3.95).

Mean increase (improvement) in SRP-9001 micro-dystrophin expression as measured using western blot adjusted by muscle content from Baseline to Week 12 was observed in Cohorts 1 and 4 (see Clinical pharmacology Section 2.6.2.).

For subjects in Cohort 1, mean (SD) improvements in the NSAA at Week 52 (4.0 [3.5] points) were observed and sustained through Week 104 (3.6 [4.3] points), indicating improvement in function. Mean (SD) improvements in the TTR and 10MWR were also observed at Week 52 (-0.48 [1.47] seconds and -0.77 [0.84] seconds, respectively), and the majority of subjects who had an available TTR assessment at Week 104 (17/19) had a TTR < 5 seconds.

No subject in Cohort 4 (≥ 3 to < 4 years of age) was able to complete all NSAA items at both Baseline and Week 52. For the 7 subjects with an available NSAA total score assessment at Baseline and Week 52, the mean (SD) scores were 12.9 (2.1) and 18.9 (2.1) points, respectively. For the 6 subjects who completed the TTR assessments at Baseline and Week 52, the mean (SD) times were 5.17 (1.02) seconds and 4.22 (0.90) seconds, respectively. For the 6 subjects who completed the 10MWR at Baseline and Week 52, the mean (SD) times were 7.55 (1.29) seconds and 5.95 (0.95) seconds, respectively.

As of July 2024, provided with the D120 responses, subjects enrolled in Study SRP-9001-103 Cohort 1 have reached 3-years of follow up post-treatment with SRP-9001. For the NSAA, the LSM Change (SE) from Baseline was 4.00 (0.45), 3.60 (0.65) and 1.00 (1.00) for Year 1, Year 2, and Year 3, respectively. For Velocity of Rise from the Floor (m/sec), the LSM Change (SE) from Baseline was 0.07 (0.01), 0.03 (0.01), and -0.02 (0.01) for Year 1, Year 2, and Year 3, respectively. For Velocity of 10-meter walk/run (m/sec), the LSM Change (SE) from Baseline was 0.40 (0.05), 0.11 (0.07), and -0.06 (0.09) for Year 1, Year 2, and Year 3, respectively.

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development programme comprises one Phase 3 study (SRP-9001-301 or EMBARK, subsequently referred to as Study 301), three Phase 1/2 studies (Studies 103 [Cohorts 1 and 4], 102, and 101), and an External Control study (WN44594). The intended commercial material is Process B, which was used in Studies 301 and 103. Process A, for which considerable differences have been identified on the quality level (see Quality Section), was used in Studies 102 and 101. Therefore, results from these studies are not deemed supportive for clinical efficacy. The retrospective external control study (WN44594) may be considered supportive, but cannot supersede results from the RCT. Hence, Phase 3 Study 301 is considered the only pivotal study, and *Points To Consider On Application With 1. Meta-Analyses; 2. One Pivotal Study* (CPMP/EWP/2330/99) applies. Statistically compelling (a

p-value stronger than p<0.05) and clinically relevant results are expected, with an estimated size of treatment benefit that is large enough to be clinically valuable.

The pivotal Phase 3 Study 301 is an ongoing 1:1 randomized, double-blind, placebo-controlled, 2-part study of systemic gene delivery of SRP-9001 in 125 male ambulatory subjects with DMD, who are ≥ 4 to < 8 years of age. Due to the cross-over design (introduced with Amendment 1: 2 August 2021), all subjects have the opportunity to receive IV SRP-9001 (1.33×10^{14} vg/kg) in either Part 1 or Part 2. The design of Study 301 has been discussed in Scientific Advice EMA/CHMP/SAWP/492702/2019 and EMA/SA/0000066340, where the overall approach to first establish short term (52 Weeks) efficacy and safety in ambulatory DMD patients aged 4-7 years was supported. The originally intended inclusion of patients 3-4 years old was not justified by the study population and removed from the indication upon request.

Patients with mutations within exon 45 were to be excluded due to a possibly milder phenotype. This was understood in Scientific Advice (EMA/CHMP/SAWP/492702/2019), but it was recommended to still include these patients in clinical trials. Information that patients with mutations within exon 45 were excluded from the pivotal trial was included in the SmPC upon request. Additionally, the indication wording was further amended to reflect that only patients with a confirmed mutation in the DMD gene *that is expected to lead to absence of functional dystrophin protein* are eligible.

Other inclusion criteria to define DMD based on confirmatory genetic testing, restricting the NSAA score to > 16 and < 29 and time to rise from floor < 5 seconds at Screening visit, are in general considered appropriate. All patients are required to be on a stable dose of corticosteroids for at least 12 weeks before Screening and have rAAVrh74 antibody titers < 1:400. This ensures all patients receive comparable standard of care and have no pre-existing antibodies to the delivery vector. Depending on the validated CE-marked assay finally used to assess eligibility for treatment, appropriate criteria to exclude patients with pre-existing rAAVrh74 antibodies need to be reflected in the SmPC. Exclusion criteria are overall appropriate to consider important safety aspects or potentially interfering treatments. Randomization is stratified by age group at the time of randomization (≥ 4 to < 6 years or ≥ 6 to < 8 years) and NSAA total score (≤ 22 or > 22) at Screening; approximately 50% of subjects were randomized to the ≥ 4 to < 6 years age group. This is considered appropriate to ensure balanced enrolment. Randomization and blinding are adequately described, as well as criteria for emergency unblinding.

Concomitant treatment with additional corticosteroids (on top of baseline stable oral corticosteroids for DMD) is adequately pre-specified, starting the day before infusion for approximately 60 days, tapering for 2 weeks if the patient has stable GGT levels and no signs of acute liver injury. No rescue treatment as such is foreseen as patients are required to be on stable corticosteroids to be eligible for enrolment.

The primary endpoint was to evaluate the effect of SRP-9001 on physical function assessed by the NSAA score at Week 52 (Part 1). This is considered appropriate and clinically relevant, as also discussed in EMA/CHMP/SAWP/492702/2019, where it was also the applicant's opinion that the NSAA is validated and can be reliably assessed in the DMD patients aged 4-7 years of age. Similarly, secondary endpoints are overall appropriate to support the clinical efficacy of SRP-9001, including number of skills gained or improved at Week 52 (NSAA) and timed function tests at Week 52 (time to rise from the floor (TTR), time of 100MWR, time to ascend 4 steps (4SC), time of 10MWR). Quantity of micro-dystrophin protein expression at Week 12 (Western blot) may also support the efficacy of SRP-9001, provided that surrogacy with clinically relevant endpoints has been established. However, there are several issues with this endpoint to be used as surrogate for clinical efficacy in DMD. As a general principle, surrogate endpoints may be considered, when direct assessment of the clinical benefit to the subject through observing actual clinical efficacy is not practical (ICH E9), but in Study 301 clinical efficacy could be appropriately assessed. Moreover, so far no correlation of micro-dystrophin protein expression with clinically relevant endpoints has been established. As micro-dystrophin lacks large parts of human full-length dystrophin, its mere presence cannot predict functionality in a patient with DMD, and demonstration of functionality in non-clinical models is considered limited. Furthermore, in study 301, expression data from only a subset of patients already early at 12 weeks after administration of SRP-9001 is available, which is at best suitable as pharmacodynamic marker (see Clinical pharmacology section 2.6.2). Patients who underwent muscle biopsies in Study 301 were

selected based on their enrolment site. All subjects that were enrolled at one of 9 preselected sites to perform muscle biopsies also had muscle biopsies.

Yet, micro-dystrophin protein expression, as well as TTR and time of 10MWR, are defined as key secondary endpoints in the SAP, but have not been taken into account for sample size planning, as recommended in EMA/CHMP/SAWP/492702/2019, and are not defined as such in the study protocol. Further secondary endpoints comprise SV95C, PROMIS score in Mobility and Upper Extremity, Safety Endpoints, which are considered appropriate. Importantly, SV95C has been qualified as secondary endpoint to quantify a patient's ambulation ability directly and reliably (EMA/CHMP/SAWP/178058/2019). Exploratory endpoints include quantity of micro-dystrophin protein expression (IF), vector genome copies (PCR), CK, linearized NSAA, PROMIS score in Fatigue, cardiac and musculoskeletal MRI, ambulation variables as measured by a wearable device, and immunogenicity of SRP-9001. These are considered appropriate.

The null hypothesis (primary and secondary endpoints) is that the population means for the 2 treatments are equal and the alternative hypothesis is that the population means for the 2 treatments are not equal. The alternative hypothesis is 2-sided, but only superiority of SRP-9001 over placebo will be of interest. This is considered appropriate. The estimand for the primary objective is considered appropriately described. Because SRP-9001 is a one-off treatment and there is no curative treatment for DMD, treatment discontinuation and start of rescue medication are not applicable. The analysis of the main endpoint was done in the modified intention to treat (mITT) analysis set, excluding patients who were randomized but did not receive study treatment. Changes in background corticosteroid treatment were handled using a treatment policy strategy.

For the primary endpoint an MMRM was used to compare SRP-9001 with placebo. In this model, the response vector consists of the change from baseline in NSAA total score at each post-baseline visit in Part 1. The model includes the covariates of treatment group (categorical), visit (categorical), treatment group by visit interaction, age group at the time of randomization (categorical), baseline NSAA total score, age group at the time of randomization by visit interaction, and baseline NSAA total score by visit interaction as fixed effects. The primary endpoint and success criterion was LS estimate on the treatment difference at Week 52 (Part 1). The efficacy was to be demonstrated if the change from baseline in the NSAA total score to Week 52 (Part 1) comparing SRP-9001 group with placebo group had demonstrated a statistically significant improvement at a two sided alpha level of alpha=0.05. LS means for treatment group means and differences and their respective CIs are reported by visit. Missing data was assumed to be missing at random. A multiple imputation based tipping point analysis was provided to investigate robustness of the missing data assumption.

The study was powered to detect a mean difference of 2.2 points in NSAA change from baseline.

Secondary endpoints (except micro-dystrophin expression) were analysed with a model similar to the model for the primary endpoint. In each of the analyses baseline NSAA raw total score was replaced with the baseline value of the respective secondary endpoint variable. NSAA group at the time of screening (≤ 22 vs. > 22) was added as covariate. The difference in the quantity of micro-dystrophin protein expression at Week 12 was tested using a re-randomisation test with the Welch t-test statistic as test statistic using 10000 re-randomized datasets.

A hierarchical testing (gatekeeping) procedure was used to account for multiplicity. The order of tests was pre-specified with the primary endpoint as first endpoint followed by key-secondary and secondary endpoints. Since the primary endpoint was not statistically significant the gatekeeping procedure stopped. Reported p-values for all other (key-)secondary endpoints are nominal/descriptive only and do not correspond to statistical tests under family wise error control.

For eligibility testing and as part of ADA assessment the amount of total anti-AAVrh74 IgG binding antibody titers were determined using a single tier anti-AAVrh74 antibody enzyme-linked immunosorbent assay (ELISA). A neutralizing antibody assay against AAVrh74 and an assay to determine anti-AAVrh74 IgM binding antibody titers have not been used. This is acceptable.

Efficacy data and additional analyses

As of the data cutoff date (13 September 2023), a total of 173 subjects were screened for the study. Of those, 42 subjects were screen failures, mainly due to having elevated rAAVrh74 antibody titers (> 1:400). Patients with rAAVrh74 antibody titer = 1:400 were excluded from study 301. Of 131 randomized subjects, 6 subjects were not dosed. Of those, each 2 subjects were assigned to the SRP-9001 and placebo treatment arm, respectively. Although it is not known why no randomization records were available for the remaining 2 subjects, no concern is raised, as this is considered a minor issue and unlikely to impact study conduct or validity of results.

A total of 125 subjects (SRP-9001: N = 63; placebo: N = 62) received study treatment and completed Part 1 of this study (mITT). As SRP-9001 is a one-off treatment, no treatment discontinuations or issues with treatment compliance are anticipated. Three subjects in the placebo arm had an important protocol deviation of IP administration/study treatment (2 unintended unblinding in Part 1, 1 incorrect dose/drug administered in Part 2). As requested, the applicant provided sensitivity analyses for the primary endpoint and timed function tests excluding 2 subjects with unintended unblinding during Part 1 in the placebo group, indicating no impact on the efficacy analyses in favour of SRP-9001. No subjects discontinued from the study prior to Part 1 completion. One additional subject was enrolled under a regional (Japan-specific) addendum and is not included in this efficacy analysis. Sensitivity analyses showed that including the additional subject did not impact the interpretation of the efficacy results. There were considerably more protocol deviations due to AE/SAE in the SRP-9001 treatment arm (7.9% vs 1.6%), which is expected due to adverse events being more frequent compared to the placebo arm (see Safety section).

All subjects in this study were male with a mean age of 6.03 years (range: 4.03-7.99 years), 59 (47.2%) subjects were in the 4 to 5 years age group and 66 (52.8%) subjects were in the 6 to 7 years age group. The race and ethnicity of most of the subjects were White (76.0%) and not Hispanic or Latino (80.0%), respectively. The overall mean time since DMD diagnosis was 2.61 years (range: 0-7.55 years). Genetic mutations of subjects with DMD were mostly large deletions (68.8%). The mean NSAA total score at Screening was 22.80 (range: 17-28). Overall, baseline characteristics were similar across treatment groups, including mean NSAA, which was slightly lower in the placebo arm (22.56 vs 23.03). Similarly, other baseline evaluations (TTR, 100MWR, 4SC, 10MWR, SV95C, PROMIS score) indicate slightly poorer mean performance in the placebo group.

As required per inclusion criteria, all subjects were treated with corticosteroid medications prior to and/or following administration of SRP-9001 or placebo. More patients in the SRP-9001 treatment group received deflazacort (68.3% vs 45.2% in placebo group), which is associated with reduced growth and lower weight gain compared to prednisone, but may result in prolonged ambulation (Griggs et al, 2016), and was associated with increased median age at loss of three milestones in comparison with prednisone or prednisolone (McDonald et al, 2018) and significantly lower functional decline over 48 weeks (McDonald et al, 2020). Yet, another study found no significant difference between the 2 daily corticosteroid regimens (Guglieri et al, 2020). Still, baseline characteristics of Study 301 may suggest a potential impact of more frequent deflazacort use in the SRP-9001 group: slightly lower mean/median height and weight, and slightly higher mean NSAA compared to the placebo group. Reassuringly, requested subgroup analyses did not indicate a treatment advantage of patients in the SRP-9001 group due to more frequent deflazacort use.

The primary efficacy endpoint, Change in NSAA from Baseline to Week 52, was not met: LSM change difference (SE) between SRP-9001 and placebo was 0.65 (0.55), and not statistically significant (95% CI: -0.45, 1.74; p=0.2441). In order to allow an accurate interpretation of the primary endpoint, also in the context of previously reported studies, the exploratory secondary endpoint, Change in linearized NSAA score from Baseline to Week 52, is considered relevant as well. The linearized scale takes account of the fact that fixed changes in non-linear ordinal-level scores (0–34 in raw NSAA) may hide or amplify a true change, as a one-point change does not mean the same across the breadth of the scale (Mayhew et al, 2013). A mean increase from Baseline to Week 52 in linearized NSAA total scores was observed in SRP-9001 and placebo groups. The LSM change difference (SE) between SRP-9001 and placebo groups at Week 52 was 1.37 (1.50), and did not reach nominal statistical significance

(95% CI: -1.61, 4.34; nominal p = 0.3645). A 10 unit (ranging between 7 and 14) change on the linearized NSAA scale was estimated to be the MCID for males with DMD at different levels of ability (Mayhew et al, 2013). Using different calculation parameters, the estimated MCID was suggested to be 2.3 points on the raw NSAA scale (5.6 points on the linearized scale) for age 7 years (Ayyar Gupta et al, 2023). Thus, in addition to the lack of statistical significance for both the raw and linearized NSAA score, the magnitude of LSM change difference to placebo (raw NSAA: 0.65, linearized NSAA: 1.37) was clearly below a clinically relevant change.

Since the primary endpoint was not statistically significant, and in line with the SAP, the gatekeeping procedure stopped. For subsequent secondary endpoints, nominal p values are reported, without adjustment for multiplicity. Therefore, results for secondary endpoints were tested outside of Type I error control. The probability of falsely claiming efficacy in one or more of the secondary endpoints is therefore not controlled at the nominal level of 5%, calling into question the relevance of any *nominally* significant differences in secondary endpoints.

The following key secondary endpoints (micro-dystrophin protein expression, TTR and 10MWR) have not been taken into account for sample size planning. A nominal statistically significant result in any of the key secondary endpoints cannot supersede the lack of statistical significance in the primary efficacy endpoint NSAA.

Micro-dystrophin protein expression is discussed in the Clinical pharmacology section (2.6.2). As expression in the SRP-9001 group was highly variable, no correlation with clinical function has been established, and no threshold for functionality is known, the relevance for clinical efficacy is unknown. At Week 52, the LSM change difference between SRP-9001 and placebo groups for TTR was -0.64 (95% CI: -1.06, -0.23; nominal p = 0.0025), and for 10MWR was -0.42 (95% CI: -0.71, -0.13; nominal p = 0.0048). While both endpoints are nominally statistically significant, results are not type I error controlled, and are both below their respective MCID of 3.6-3.7 seconds for TTR, and 1.4-2.3 seconds for 10MWR (McDonald et al, 2013). When converted to a velocity metric, a TTR of 0.04 rise/s would exceed the reported MCID of 0.023 rise/s, but not 10MWR (observed difference: 0.17 m/s; MCID: 0.212 m/s; Duong et al, 2021).

Among other secondary endpoints, nominal statistical significance was observed between groups at Week 52 for Change in SV95 from baseline (LSM change difference 0.10 [95% CI: 0.00, 0.19; p = 0.0402]) and Time to ascend 4 steps (LSM change difference -0.36 [95% CI: -0.71, -0.01; p = 0.0412]). The observed LSM change difference in SV95 (0.10 m/s) would be in the range of the MCID (EMA/CHMP/SAWP/178058/2019), but not the LSM change difference in Time to ascend 4 steps (-0.36; MCID: 2.1-2.2 seconds; McDonald et al, 2013). Again, when converted to a velocity metric, Time to ascend 4 steps or 0.16 tasks/s exceeds the reported MCID of 0.035 tasks/s (Duong et al, 2021). All other secondary endpoints (100MWR, Percent predicted 100MWR, PROMIS score in mobility and upper extremity, Number of skills gained or improved as measured by NSAA), did not reach nominal statistical significance. The exploratory clinical endpoint 95th percentile of stair climbing velocity was nominally statistically significant (LSM change difference 0.06 [95% CI: 0.02, 0.11, p = 0.0081)]. All other exploratory clinical endpoints (linearized NSAA score, PROMIS score in fatigue, number of stairs climbed per hour, distance walked per hour, 95th percentile of stride length), did not reach nominal statistical significance.

As far as the applicant argues SRP-9001-treated subjects were shown to have a 91% reduction in odds of reaching a TTR>5 seconds by Week 52 compared to the placebo group, with TTR being a predictive factor for loss of ambulation. However, the limitations of sample size and follow-up in combination with concerns on durability of transgene expression render this claimed clinical meaningfulness speculative at best, and not suited to overrule the missing demonstration of efficacy by the agreed primary endpoint.

Further exploratory endpoints aimed at quantifying micro-dystrophin protein expression by immunofluorescence and vector genome copies using PCR in muscle tissue biopsy at Week 12, and change in CK over 52 Weeks (see Clinical pharmacology section 2.6.2). Structural endpoints measured the change in cardiac and musculoskeletal MRI to Week 52. No clinically significant changes were observed in cardiac MRI. In the subset of subjects who participated in the MRI sub-study (SRP-9001:

n=19; placebo: n=20), musculoskeletal MRI images indicated longer (worsening) T2 relaxation times for 5 muscle groups (biceps femoris, hamstring, quadriceps, vastus lateralis, soleus) in the placebo group compared to the SRP-9001 group. These results are descriptive trends.

Predefined subgroup analyses were conducted for the primary and key secondary endpoints. Overall, inverse trends were observed in subgroups by age between the primary efficacy endpoint, where 4-5 year old subjects performed better in terms of LSM change difference in the SRP-9001 group, and key secondary clinical endpoints, where 6-7 year old subjects performed better in terms of LSM change difference in the SRP-9001 group. Similarly, neither baseline NSAA group (≤22, >22) showed consistently favourable results over the other. For non-white children there is even a detrimental effect (placebo better than SRP-9001), but sample size is low, resulting in a wide CI. Hence, the subgroup analyses do not indicate a single subgroup for which the totality of data supports a favourable effect.

In conclusion, the primary efficacy endpoint, Change in NSAA from Baseline to Week 52, failed to show statistically significant or clinically relevant superiority of SRP-9001 over SoC. Although key secondary clinical endpoints TTR and 10MWR showed nominally statistically significant improvement, their relevance is not fully understood. Results are not type I error controlled, and differences are mostly below the MCID. In the totality of data, improvements in clinical function were modest in the SRP-9001 group compared to SoC. In a subset of patients tested, vector genome copies and micro-dystrophin protein expression adjusted to muscle content were detected in the SRP-9001 group, indicating successful delivery of the vector and expression of micro-dystrophin. However, a correlation with clinical function has not been demonstrated.

With the D120 Responses, additional responder analyses have been provided for the primary and the secondary endpoints in which the proportion of patients who achieved meaningful within-patient change (MWPC) were compared between the treatment arms. From these analyses, it appears that there may be some patients who could benefit from SRP-9001 treatment in the primary endpoint NSAA. For any subgroup to be the basis for an MAA, an additional confirmatory trial would be expected. All provided post-hoc subgroup analyses can be considered hypothesis-generating only and will have to be confirmed by independent clinical data in order to lead to an indication in any such subgroup. To substantiate the efficacy claim introduced in the response by the applicant, i.e. survival that is currently based on NC data only, and considering the SmPC changes claiming transduction of skeletal AND CARDIAC muscle cells, the applicant was asked to submit all relevant cardiac function parameters generated in trials 103 and 301 on its own as well as compared post-hoc with the same external controls as used for the motor function comparisons. Determination of relevant parameters is up to the applicant, but must include LVEF. Following this request, the applicant proposed a rewording of the SmPC subsection 'Mechanism of action', now clearly stating the clinical significance of the NC findings (transduction and transgene protein expression in cardiac [and diaphragm] muscle cells) was unknown. Further, the applicant provided the available clinical data on LVEF; not unexpectedly, the data is not suited to demonstrate a beneficial effect of SRP-9001 in a population too young for significant cardiac dysfunction to be expected. This would need to be investigated over an extended time.

Supportive Studies

Three Phase 1/2 studies are described: Phase 1/2a study 101, Phase 1/2 study 102 and Phase 1b study 103. As Process A, for which considerable differences have been identified on the quality level, was used in Studies 102 and 101, results from these studies are not considered supportive for efficacy.

Study 103 is an ongoing, single-arm, open-label, single-dose study. The protocol of this study has been amended repeatedly as well, including revisions to endpoint hierarchy, sample size and addition of cohorts. Results from two (of seven in total) cohorts may be considered supportive for the intended indication: Cohort 1 (20 ambulatory DMD subjects aged ≥ 4 to < 8 years) and Cohort 4 (7 ambulatory DMD subjects aged ≥ 3 and <4 years). In Cohort 1, five subjects had mutations fully or partially contained within exons 1-17. Thus, study 103 currently provides the only efficacy data in subjects aged ≥ 3 and <4 years and subjects with mutations within exons 1-17. With the D120 responses, results from Cohort 1 for NSAA, TTR velocity and 10MWR velocity over time were submitted. All three declined over time, with year 3 findings approximating baseline data. The single-arm design hampers

evaluation of the overall results, which might indicate a delay of progression, but do not indicate a stabilisation in terms of a plateau, and in any case do not supersede the failed pivotal trial.

Study WN44594 was a retrospective non-interventional study comparing functional endpoints in selected patients exposed to SRP-9001 from a set of clinical trials conducted by the applicant to a pooled cohort of patients that were never treated with SRP-9001 derived from external secondary data sources. A retrospective study comparing selected patients exposed to SRP-9001 from a set of clinical trials to a pooled cohort from external secondary data sources cannot supersede the results from the failed pivotal trial.

A compelling, clinically relevant result allowing for conclusion of efficacy irrespective of statistical significance would be preservation of ambulation beyond the age loss of ambulation is expected for in the DMD population. This is around 12 years of age. The available follow-up in neither clinical trial is long enough (yet) to assess this.

Additional efficacy data needed in the context of a conditional MA

The applicant considered that the totality of the data supports a favourable benefit-risk profile for SRP-9001 that can form the basis of an application to support the conditional approval of SRP-9001 for the treatment of DMD with the proposed conversion plan to confirm the benefit of SRP-9001 in the 10-year Study 305 sub-study including patients as per the proposed indication. This was not agreed by CAT/CHMP, as the benefit-risk was considered negative.

Regarding the concern on durability of a (yet to be demonstrated) beneficial effect over time triggered both by non-clinical, clinical pharmacology data, and patients' organisations' feedback, the overall follow-up would need to ensure the age of expected loss of ambulation is definitely covered. The initial plans, to follow each patient for a minimum of 5 years post-infusion of delandistrogene moxeparvovec in a previous clinical study plan of study 305, would have been insufficient. This has already been outlined in an EMA scientific advice, where also a proposal of 10 years of follow-up in a registry was discussed. A 10 year follow-up post-infusion is proposed in the *Protocol Synopsis* submitted for sub-study 305. The proposed sub-study of Study 305 is not deemed suitable to robustly demonstrate clinical efficacy in the study population, as it is not placebo-controlled. The applicant proposes time to loss of ambulation as the primary endpoint for the study. Besides the conceptional shortcomings of the definition of the success criterion, the issue that a treatment effect cannot be differentiated from a change in standard of care and concomitant medication persists. No strategy was proposed to account for additional treatments becoming available and being used by the study participants and it is questionable if such an adjustment is even possible without the use of contemporaneous control subjects. The follow-up of said sub-study is to be extended to cover 15 years post-SRP-9001, and efficacy endpoints need to include both age of loss of ambulation and LVEF over time. In addition, the planned NIS is to be considered a PAES with respective changes to the protocol, with mandatory monitoring of the same key effectiveness parameters as requested for study 305 in addition to the effectiveness parameters already defined for BN44090. In light of the failed pivotal RCT it is doubtful that the proposed sub-study will provide more comprehensive clinical data. In the response to the D180 LoOI, reported LOA occurred at 9-10 years of age. In the previous round, the applicant pointed to the "most conservative estimate of 13.4 years" for LoA in glucocorticoid treated patients. A delayed LoA following SRP-9001 treatment cannot be agreed based on this (very limited) data, while the safety profile includes the identified risk hepatotoxicity and at least a potential risk for cardiomyopathy. For the LTFU sub-study, however, the applicant agreed to it being a PAES, agreed to an external contemporaneous control, and agreed to monitor LOA as primary efficacy endpoint as well as LVEF for efficacy, though the latter is only considered as exploratory endpoint. While all the methodological issues regarding LVEF determination are acknowledged, it should be upgraded to a secondary endpoint. LOA determination, when following the patients to age 16 years as proposed, is acceptable. Submission of the final PAES protocol following CHMP opinion also would be acceptable. However, a positive B/R is not agreed, rendering follow-up questions on the LTFU obsolete.

2.5.7. Conclusions on clinical efficacy

Efficacy was not demonstrated. In the single pivotal trial, the primary efficacy endpoint, change in NSAA from Baseline to Week 52, was not met. The difference to placebo (0.65) was not statistically significant (p=0.2441) and clearly below the estimated MCID of 2.3 points (Ayyar Gupta et al, 2023). Since the primary endpoint was not statistically significant, results for secondary endpoints are not Type I error controlled, and false positive results cannot be excluded. Demonstration of clinical benefit is mainly based on post-hoc analyses of timed function tests. Micro-dystrophin protein expression, which was detected in the tested subset of patients treated with SRP-9001, but not in the tested subset of patients in the placebo group at Week 12. However, no correlation of micro-dystrophin protein expression with clinical function has been established, and no threshold for functionality is known. Hence, clinical efficacy could not be demonstrated in the overall study population.

As far as the proposed indication was concerned, it was initially considered too broad, and was amended to reflect the study population of the pivotal trial. During the procedure, the applicant has proposed to further restrict the indication to a subgroup of patients with a time to rise of 3.6 to 5 seconds at baseline, as the probability of improvement on the NSAA at week 52 was higher than in other enrolled patients with a faster TTR. However, all provided post-hoc subgroup analyses can be considered hypothesis-generating only and will have to be confirmed by independent clinical data in order to lead to an indication in any such subgroup. The currently available data is not suited to conclude on efficacy even in the restricted population.

2.5.8. Clinical safety

2.5.8.1. Patient exposure

Table 11: Number of subjects treated with SRP-9001 included in pooled populations (exposure analysis set)

Study	Process B 4 to 8 Years [f]	All Subjects
Studies Using Process B Material:		
SRP-9001-301		
Part 1 (ambulatory, 4 to < 8 years) [a, d]	64	64
Part 2 (ambulatory, 4 to < 8 years at time of randomization to placebo in Part 1)	47 [e]	50
SRP-9001-103		
Cohort 1 (ambulatory, 4 to < 8 years) [b]	20	20
Cohort 2 (ambulatory, 8 to < 18 years [b]		7
Cohort 3 (non-ambulatory, no age restriction)	—	6
Cohort 4 (ambulatory, 3 to < 4 years [b]		7
Cohort 5a (ambulatory, 4 to < 9 years) [b]	—	6
Cohort 5b (non-ambulatory, no age restriction)	—	2
Studies Using Process A Material:		
SRP-9001-102		
All Subjects (ambulatory, 4 to < 8 years) [b]	—	41
SRP-9001-101		
All Subjects (ambulatory, 4 to < 8 years) [c]	—	4
TOTAL	**131**	**207**

[a] Age at randomization.
[b] Age at screening.
[c] Age at enrollment.
[d] The pools include 1 additional subject in comparison to the results reported in the Study 301 interim CSR. This subject was enrolled in Japan and used a database lock of 11-Oct-2023 rather than 13-Sep-2023.
[e] Three of 50 subjects were just above 9 years old at the time of dosing in Part 2 of Study 301. Therefore, they were excluded from the Process B 4 – 8 years population but are included in the All Subjects population.
[f] Age at time of SRP-9001 infusion.

The **pivotal trial 301**, used a dose of 1.33 x 10^{14} vg/kg of process B material for each subject. In **Study 103**, subjects up to 70 kg of body weight received weight-based dosing at 1.33 x 10^{14} vg/kg (Process B). Subjects over 70 kg of body weight were treated with a fixed dose of 9.31x 10^{15} vg, corresponding to a clinical dose cap at 70 kg.

In **study 102**, 3 different dose levels of Process A material had been administered during Part 1 of the study (1.33 x 10^{14}, 6.29 x 10^{13}, and 8.94 x 10^{13} vg/kg), which was retrospectively ascertained using the validated linear standard method for dose determination after the dose was titrated using the supercoiled plasmid standard in the beginning. During Part 2 of the study, the vector genome concentrations for the doses were determined using the linear standard, therefore, all doses of SRP-9001 in Part 2 were 1.33 x 10^{14} vg/kg. **First in human study 101** employed a dose of 1.33 x 10^{14} of Process A material.

Table 12: Patient exposure (cut off Sep 2023)

Process B – commercial	Patients enrolled	Patients exposed*	Patients exposed to the proposed dose range	Patients with long term** safety data
Blinded study (placebo-controlled) 301 Part 1	131	63 (+1 Japanese patient included into the pooled analysis set)	63 (+1 Japanese patient included into the pooled analysis set)	All subjects have accrued approx. 52 weeks (min, max 51.14, 63 wks)
301 Part 2		50	50	Median FU: 8.64 weeks (min: 0.14, max: 40.29)
Open study 103	48	48	48	9: 1-< 2 years 31: ≥ 2 years
Process A – supportive				
Blinded study (placebo-controlled) 102	43	41 (20[x] Part 1, 21 Part 2)	N=8 Part 1 N= 21 Part 2	In summary: 11: 2-< 4 years 30: ≥ 3 years
Open study 101	4	4	4	4 (5 years)
Post marketing		61	61	
Compassionate use				

* Received at least 1 dose of active treatment
** In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.
[x] There was a retrospectively identified issue with quantifying the active ingredient for 12 of the 20 subjects in Part 1 of Study 102. These subjects therefore received a lower dose (6.29 $\times 10^{13}$ vg/kg or 8.94 $\times 10^{13}$ vg/kg [6 subjects each]) rather than the targeted dose of 1.33 $\times 10^{14}$ vg/kg.

2.5.8.2. Adverse events

Study 301 Part 1

Nearly all subjects experienced at least one AE during the study: 62 subjects (98.4%) on SRP-9001 vs 57 (91.9%) on placebo. The most frequently affected System Organ Classes were infections and infestations in 91 (72.8%) of all trial subjects, followed by gastrointestinal disorders (83 of total subjects, 66.4%), general disorders and administration site conditions (54, 43.2%), and investigations (47, 37.6%).

Table 13: Most frequent AEs (≥ 10% in entire study population) by preferred term (301 part 1, safety analysis set)

Preferred Term	SRP-9001 (N=63) n (%)	Placebo (N=62) n (%)	Total (N=125) n (%)
Vomiting	40 (63.5)	12 (19.4)	52 (41.6)
Nausea	25 (39.7)	8 (12.9)	33 (26.4)
Decreased appetite	20 (31.7)	3 (4.8)	23 (18.4)
Pyrexia	20 (31.7)	15 (24.2)	35 (28.0)
COVID-19	17 (27.0)	9 (14.5)	26 (20.8)
Glutamate dehydrogenase increased	17 (27.0)	2 (3.2)	19 (15.2)
Cough	12 (19.0)	18 (29.0)	30 (24.0)
Upper respiratory tract infection	12 (19.0)	17 (27.4)	29 (23.2)
Abdominal pain upper	10 (15.9)	9 (14.5)	19 (15.2)
Fatigue	9 (14.3)	6 (9.7)	15 (12.0)
Influenza	9 (14.3)	4 (6.5)	13 (10.4)
Irritability	9 (14.3)	4 (6.5)	13 (10.4)
Nasopharyngitis	9 (14.3)	12 (19.4)	21 (16.8)
Contusion	7 (11.1)	9 (14.5)	16 (12.8)
Headache	7 (11.1)	8 (12.9)	15 (12.0)
Pain in extremity	7 (11.1)	12 (19.4)	19 (15.2)
Diarrhoea	6 (9.5)	13 (21.0)	19 (15.2)

Source: t-14-3-2-3-teaept.

The majority of AEs were of mild or moderate intensity. The proportion of subjects who experienced severe AEs was higher in the SRP-9001 group (13 subjects [20.6%] with at least one severe event) than in the placebo group (5 subjects, 8.1%). There were no life-threating or fatal events in any group. Of the severe AEs, none occurred more than once within a treatment group, with the exception of hepatic enzyme increased (2 subjects on SRP−9001 vs 0 on placebo) and vomiting (2 subjects on SRP-9001 vs 1 on placebo).

Pooled Analyses

As observed for the subjects in Part 1 of Study 301, nearly all subjects in the pooled populations experienced at least one AE during the study: 198 subjects (95.7%) in the All Subjects population and 122 (93.1%) in the Process B 4 −8 Years subpopulation. The most frequently affected System Organ Classes were gastrointestinal disorders (175 subjects of the All Subjects population, 84.5%), followed by infections and infestations (133, 64.3%), investigations (105, 50.7%), and general disorders and administration site conditions (99, 47.8%). The proportions of AEs in the Process B 4−8 Years subpopulation were overall comparable to those in the All Subjects population.

Table 14: Most frequent AEs (≥ 10% in all subjects) by preferred term (exposure analysis set)

Preferred Term	Process B 4-8 Years (N=131) n (%)	All Subjects (N=207) n (%)
Vomiting	83 (63.4)	136 (65.7)
Nausea	52 (39.7)	88 (42.5)
Decreased appetite	44 (33.6)	74 (35.7)
Upper respiratory tract infection	22 (16.8)	63 (30.4)
Pyrexia	34 (26.0)	53 (25.6)
COVID-19	24 (18.3)	52 (25.1)
Cough	24 (18.3)	49 (23.7)
Abdominal pain upper	24 (18.3)	47 (22.7)
Pain in extremity	17 (13.0)	46 (22.2)
Glutamate dehydrogenase increased	34 (26.0)	43 (20.8)
Headache	21 (16.0)	40 (19.3)
Fatigue	21 (16.0)	34 (16.4)
Irritability	12 (9.2)	34 (16.4)
Gamma-glutamyltransferase increased	16 (12.2)	31 (15.0)
Diarrhoea	11 (8.4)	28 (13.5)
Procedural pain	3 (2.3)	28 (13.5)
Constipation	15 (11.5)	25 (12.1)
Influenza	13 (9.9)	25 (12.1)
Rhinorrhoea	10 (7.6)	24 (11.6)
Viral infection	8 (6.1)	23 (11.1)
Arthralgia	9 (6.9)	21 (10.1)

Adverse events are coded using MedDRA Version 26.0. Preferred terms (PTs) are listed in descending order of frequency in All Subjects column. A subject is counted only once for multiple events within each PT.
All included AEs are treatment emergent AE (TEAE) that occurred or increased in severity since the study treatment.
N = number of subjects in the analysis set mentioned in the column heading. n = number of subjects within a specific category. Percentages calculated as 100 * (n / N).

An analysis of the time periods in which AEs occurred showed that 185 (89.4%) of the subjects in the All Subjects population had their first AE within the initial 2 weeks after SRP-9001 infusion. The temporal pattern for gastrointestinal disorders showed that most events occurred within 60 days (usually within 2 weeks of study drug administration). Most of these events included nausea and/or vomiting. Hepatobiliary disorders predominantly occurred between 2 weeks and 60 days of SRP-9001 administration. The number of AEs tended to decrease in the long term after SRP-9001 infusion.

Table 15: Adverse events by intensity (exposure analysis set)

System Organ Class Preferred Term	Maximum Severity	Process B 4-8 Years (N=131)	All Subjects (N=207)
Subjects with any AE	Mild	54 (41.2)	69 (33.3)
	Moderate	49 (37.4)	98 (47.3)
	Severe	19 (14.5)	31 (15.0)
	Total	122 (93.1)	198 (95.7)

A subject is counted only once for multiple events within each SOC/PT at the maximum severity.
All included AEs are treatment emergent AE (TEAE) that occurred or increased in severity since the study treatment.
N = number of subjects in the analysis set mentioned in the column heading. n = number of subjects within a specific category. Percentages calculated as 100 * (n / N).

Treatment-related adverse events

Study 301 Part 1

In total, the proportion of subjects with AEs considered related to treatment was higher in the SRP-9001 group (48 subjects, 76.2%) than in the placebo group (17 subjects, 27.4%).

Table 16: Most frequent treatment-related adverse events (≥10% in entire study population) by preferred term (301 part1, safety analysis set)

Preferred Term	SRP-9001 (N=63) n (%)	Placebo (N=62) n (%)	Total (N=125) n (%)
Vomiting	34 (54.0)	0	34 (27.2)
Nausea	20 (31.7)	5 (8.1)	25 (20.0)
Decreased appetite	17 (27.0)	1 (1.6)	18 (14.4)
Glutamate dehydrogenase increased	15 (23.8)	2 (3.2)	17 (13.6)

Source: 301 CSR t-14-3-3-3-traept.

Pooled Analyses

In the All Subjects population, 171 subjects (82.6%) had at least one AE that the investigator considered related to treatment; in the Process B 4 −8 Years subpopulation, there were 104 subjects (79.4%) with a related AE. Overall, the proportions of individual treatment-related AEs were comparable across both pooled populations. In the All Subjects population, 831 of the total of 2633 AEs were considered related; in the Process B 4 −8 Years subpopulation, 515 of a total of 1302 were related to treatment (Table 17).

As for all AEs, it was observed that many subjects experienced AEs within the first 2 weeks after SRP-9001 infusion that were considered to be related to treatment: 161 subjects (77.8%) in the All Subjects population and 98 (74.8%) in the Process B 4−8 Years subpopulation.

Table 17: Most frequent treatment-related adverse events (≥ 5%) by preferred term (exposure analysis set)

Preferred Term	Process B 4-8 Years (N=131) n (%)	All Subjects (N=207) n (%)
Vomiting	70 (53.4)	120 (58.0)
Nausea	44 (33.6)	77 (37.2)
Decreased appetite	36 (27.5)	63 (30.4)
Glutamate dehydrogenase increased	32 (24.4)	41 (19.8)
Gamma-glutamyltransferase increased	16 (12.2)	31 (15.0)
Abdominal pain upper	16 (12.2)	30 (14.5)
Pyrexia	19 (14.5)	27 (13.0)
Fatigue	14 (10.7)	17 (8.2)
Thrombocytopenia	7 (5.3)	14 (6.8)
Abdominal pain	7 (5.3)	12 (5.8)
Alanine aminotransferase increased	7 (5.3)	12 (5.8)

Adverse events are coded using MedDRA 26.0. Preferred terms (PTs) are listed in descending order of frequency in All Subjects column. A subject is counted only once for multiple events within each PT.
All included AEs are treatment emergent AE (TEAE) that occurred or increased in severity since the study treatment.
N = number of subjects in the analysis set mentioned in the column heading. n = number of subjects within a specific category. Percentages calculated as 100 x (n / N).

2.5.8.3. Serious adverse events, deaths, and other significant events

Serious adverse events

Study 301 Part 1

For 7 subjects on SRP-9001 (11.1%) vs 0 on placebo the SAEs were considered related to treatment. All events occurred only once. They included:• Transaminases increased • Liver injury • Hepatotoxicity • Rhabdomyolysis • Vomiting, myocarditis, pyrexia, nausea (all events in the same subject) • Hepatic enzyme increased • Gamma-glutamyltransferase increased. All events have resolved.

Table 18: Serious adverse events by system organ class and preferred term (301 part 1, safety analysis set)

System Organ Class Preferred Term	SRP-9001 (N=63) n (%)	Placebo (N=62) n (%)	Total (N=125) n (%)
Subjects with any SAE	14 (22.2)	5 (8.1)	19 (15.2)
Infections and infestations	5 (7.9)	3 (4.8)	8 (6.4)
COVID-19	2 (3.2)	1 (1.6)	3 (2.4)
Appendicitis	1 (1.6)	0	1 (0.8)
Pneumonia	1 (1.6)	0	1 (0.8)
Rotavirus infection	1 (1.6)	0	1 (0.8)
Anal abscess	0	1 (1.6)	1 (0.8)
Influenza	0	1 (1.6)	1 (0.8)
Toxic shock syndrome streptococcal	0	1 (1.6)	1 (0.8)
Investigations	3 (4.8)	0	3 (2.4)
Gamma-glutamyltransferase increased	1 (1.6)	0	1 (0.8)
Hepatic enzyme increased	1 (1.6)	0	1 (0.8)
Transaminases increased	1 (1.6)	0	1 (0.8)
Gastrointestinal disorders	2 (3.2)	1 (1.6)	3 (2.4)
Vomiting	2 (3.2)	1 (1.6)	3 (2.4)
Abdominal pain	1 (1.6)	0	1 (0.8)
Nausea	1 (1.6)	0	1 (0.8)
Hepatobiliary disorders	2 (3.2)	0	2 (1.6)
Hepatotoxicity	1 (1.6)	0	1 (0.8)
Liver injury	1 (1.6)	0	1 (0.8)
Injury, poisoning and procedural complications	2 (3.2)	2 (3.2)	4 (3.2)
Craniocerebral injury	1 (1.6)	0	1 (0.8)
Prescription drug used without a prescription	1 (1.6)	0	1 (0.8)
Arterial injury	0	1 (1.6)	1 (0.8)
Upper limb fracture	0	1 (1.6)	1 (0.8)
Cardiac disorders	1 (1.6)	1 (1.6)	2 (1.6)
Myocarditis	1 (1.6)	0	1 (0.8)
Left ventricular dysfunction	0	1 (1.6)	1 (0.8)
General disorders and administration site conditions	1 (1.6)	1 (1.6)	2 (1.6)
Pyrexia	1 (1.6)	1 (1.6)	2 (1.6)
Musculoskeletal and connective tissue disorders	1 (1.6)	0	1 (0.8)
Rhabdomyolysis	1 (1.6)	0	1 (0.8)
Nervous system disorders	1 (1.6)	0	1 (0.8)
Haemorrhage intracranial	1 (1.6)	0	1 (0.8)

Pooled analyses

Nearly all SAEs were of severe intensity. Only a case of rotavirus infection and another one of COVID-19 were considered moderate, and 1 case of pyrexia was assessed of mild intensity.

An analysis of the occurrence of SAEs over time showed that 19 subjects (9.2%) of the All Subjects population experienced an SAE in the initial 12 weeks after SRP-9001 administration, followed by 10

subjects (5.6%) during the period between 12 weeks and 1 year. Three subjects experienced SAEs after 1 year. The distribution over time was comparable with the one noted for the Process B 4 −8 Years subpopulation.

Table 19: Serious adverse events by system organ class and preferred term (exposure analysis set)

System Organ Class Preferred Term	Process B 4-8 Years (N=131) n (%)	All Subjects (N=207) n (%)
Subjects with any Serious AE	19 (14.5)	30 (14.5)
Hepatobiliary disorders	4 (3.1)	6 (2.9)
PT Hepatotoxicity	2 (1.5)	2 (1.0)
PT Hypertransaminasaemia	1 (0.8)	2 (1.0)
PT Liver injury	1 (0.8)	2 (1.0)
Infections and infestations	5 (3.8)	6 (2.9)
PT Appendicitis	1 (0.8)	2 (1.0)
PT COVID-19	2 (1.5)	2 (1.0)
PT Pneumonia	1 (0.8)	1 (0.5)
PT Rotavirus infection	1 (0.8)	1 (0.5)
Musculoskeletal and connective tissue disorders	1 (0.8)	6 (2.9)
PT Rhabdomyolysis	1 (0.8)	4 (1.9)
PT Immune-mediated myositis	0	2 (1.0)
PT Muscular weakness	0	1 (0.5)
Injury, poisoning and procedural complications	2 (1.5)	5 (2.4)
PT Femur fracture	0	2 (1.0)
PT Craniocerebral injury	1 (0.8)	1 (0.5)
PT Prescription drug used without a prescription	1 (0.8)	1 (0.5)
PT Torus fracture	0	1 (0.5)
Gastrointestinal disorders	3 (2.3)	4 (1.9)
PT Vomiting	3 (2.3)	4 (1.9)
PT Abdominal pain	1 (0.8)	1 (0.5)
PT Nausea	1 (0.8)	1 (0.5)
Investigations	4 (3.1)	4 (1.9)
PT Gamma-glutamyltransferase increased	2 (1.5)	2 (1.0)
PT Hepatic enzyme increased	1 (0.8)	1 (0.5)
PT Transaminases increased	1 (0.8)	1 (0.5)
Cardiac disorders	1 (0.8)	2 (1.0)
PT Myocarditis	1 (0.8)	2 (1.0)
General disorders and administration site conditions	2 (1.5)	2 (1.0)
PT Pyrexia	2 (1.5)	2 (1.0)
Nervous system disorders	1 (0.8)	1 (0.5)
PT Haemorrhage intracranial	1 (0.8)	1 (0.5)

Adverse events are coded using MedDRA Version 26.0. System organ classes (SOCs) are presented descending order of frequency and preferred terms (PTs) are listed in descending order of frequency within each SOC in All Subjects column. A subject is counted only once for multiple events within each SOC/PT.
All included AEs are treatment emergent AE (TEAE) that occurred or increased in severity since the study treatment.
N = number of subjects in the analysis set mentioned in the column heading. n = number of subjects within a specific category. Percentages calculated as 100 x (n / N).

Table 20: Treatment-related serious adverse events (SAE) by system organ class and preferred term (exposure analysis set)

System Organ Class Preferred Term	Process B 4-8 Years (N=131) n (%)	All Subjects (N=207) n (%)
Subjects with any Treatment-Related Serious AE	12 (9.2)	18 (8.7)
Hepatobiliary disorders	4 (3.1)	6 (2.9)
PT Hepatotoxicity	2 (1.5)	2 (1.0)
PT Hypertransaminasaemia	1 (0.8)	2 (1.0)
PT Liver injury	1 (0.8)	2 (1.0)
Musculoskeletal and connective tissue disorders	1 (0.8)	5 (2.4)
PT Rhabdomyolysis	1 (0.8)	3 (1.4)
PT Immune-mediated myositis	0	2 (1.0)
PT Muscular weakness	0	1 (0.5)
Investigations	4 (3.1)	4 (1.9)
PT Gamma-glutamyltransferase increased	2 (1.5)	2 (1.0)
PT Hepatic enzyme increased	1 (0.8)	1 (0.5)
PT Transaminases increased	1 (0.8)	1 (0.5)
Gastrointestinal disorders	2 (1.5)	3 (1.4)
PT Vomiting	2 (1.5)	3 (1.4)
PT Nausea	1 (0.8)	1 (0.5)
Cardiac disorders	1 (0.8)	2 (1.0)
PT Myocarditis	1 (0.8)	2 (1.0)
General disorders and administration site conditions	2 (1.5)	2 (1.0)
PT Pyrexia	2 (1.5)	2 (1.0)

Adverse events are coded using MedDRA Version 26.0. System organ classes (SOCs) are presented descending order of frequency and preferred terms (PTs) are listed in descending order of frequency within each SOC in All Subjects column. A subject is counted only once for multiple events within each SOC/PT.
All included AEs are treatment emergent AE (TEAE) that occurred or increased in severity since the study treatment.
N = number of subjects in the analysis set mentioned in the column heading. n = number of subjects within a specific category. Percentages calculated as 100 x (n / N).

Deaths

No deaths occurred in study 101, 102, 103 or 301.

AESI

Hepatotoxicity

Study 301 Part 1

Across the entire study population in Part 1 of Study 301, 31 subjects reported AEs that were retrieved in the search for events indicative of hepatotoxicity (Table 22). The proportion was higher in the SRP-9001 group (26 subjects, 41.3%) than in the placebo group (5 subjects, 8.1%). Of these, 6 subjects (9.5%) on SRP-9001 vs 1 (1.6%) on placebo had severe events, while the remainder was mild or moderate. Most of the reported events were considered related to treatment: 24 subjects (38.1%) for the SRP-9001 group and 3 subjects (4.8%) in the placebo group. The ALI events were serious in 5 (7.9%) of the SRP-9001 subjects; there were no serious events in the placebo group.

The majority of hepatotoxicity events occurred within 90 days of the study drug infusion. One subject (1.6%) in the SRP-9001 group and 3 subjects (4.8%) in the placebo group experienced events with an

onset later than 90 days of infusion. None of these 4 subjects had an increase in steroid dose relating to the events.

The proportion of subjects identified by the laboratory parameters indicating hepatotoxicity as defined for the 301 study matched closely to that identified using AE search terms.

Overall, among the subjects meeting any ☐ -fold definition of ALI, the mean time to onset was 42.5 days post SRP-9001 infusion and the mean time to peak was 7.4 days after onset; the median time to resolution was 24 days in the SRP-9001 group and 11.5 days in the placebo group. One subject treated with SRP-9001 experienced ALI with an onset after Day 90 (Day 106), identified by GLDH of 3.7 ☐ ULN with normal GGT. The minimum duration of ALI was 6 days and the maximum duration 77 days (median 44) in the SRP-9001 group. In 5 subjects in the SRP-9001 group IV steroids were used to manage ALI.

Pooled analyses

Searching for AEs indicating acute liver injury identified at least one such event in 80 subjects (38.6%) in the All Subjects population. There was a multitude of preferred terms, with glutamate dehydrogenase increased being the most frequent individual term. The numbers were overall comparable between the All Subjects population and the Process B 4 −8 Years subpopulation, except for the term of "GLDH increased", which was reported more frequently in the Process B 4 −8 Years subpopulation (26.0%) than in the All Subjects population (20.8%). This reflects the fact that regular GLDH measurements were conducted from the beginning only for studies 301 and 103.

The events of biochemical acute liver injury were all responsive to treatment with corticosteroids. Doses of corticosteroids (oral or intravenous) given to treat adverse events increased in the period from Day -1 to Day 60 in comparison to the period of 12 weeks before SRP-9001 infusion. In the period between Day 61 to 90, the median doses were essentially twice as high in subjects receiving additional corticosteroids to treat AEs than in those subjects who received corticosteroids just for DMD as well as immunosuppression. In the period from Month 6 to Month 12, the corticosteroid doses returned to their baseline levels.

In the All Subjects population, 14 subjects had AEs of hepatotoxicity and consequently received IV corticosteroids to treat them. High dose IV pulses of steroids (> 5 mg/kg/d methylprednisolone) were used for the treatment of hepatotoxicity in 13 of these subjects.

A weak positive correlation between maximum GGT values and maximum antigen-specific T-cell response to AAVrh74 within 12 weeks after SRP-9001 infusion was observed.

Immune-mediated myositis

Study 301 Part 1

Four subjects each in the SRP-9001 (6.3%) and placebo (6.5%) group experienced a total of 8 AEs that were potentially indicative of immune-mediated myositis. One of these events (reported as "myositis" with an onset at Day 92 in an SRP-9001 subject) was of moderate severity, all other events were mild. Three events in the SRP-9001 and 1 event in the placebo group were considered related to treatment. None of these potential events was serious. All but one event (in the placebo group) had resolved by the time of the analysis

Pooled analyses

In the All Subjects population, 12 subjects (5.8%) reported 14 events potentially indicative of immune-mediated myositis. In half of these subjects, the events had an onset within 60 days after administration. In 8 subjects, the events were considered related to treatment (asthenia, 5 subjects; immune-mediated myositis, 2 subjects; muscular weakness and myositis, 1 subject each).

In 10 of the subjects, the identified events were of mild or moderate severity; the affected subjects carried mutations in between exons 18 and 58. No additional immunosuppressants were given. In general, the events resolved. An event of muscular weakness (onset: Day 631) was not resolved. An

event of asthenia in another subject occurred on the day of the CCOD (Day 37) and was thus recorded as ongoing at the time analysis.

In 2 subjects, a total of 3 events were severe; all these events were also reported as SAEs and resolved with sequelae. A subject in Cohort 2 of Study 103 carrying an exon 3-43 deletion mutation experienced treatment-related life-threatening events of immune-mediated myositis and muscular weakness, both with an onset on Day 35. A subject in Cohort 5A of Study 103 and with an exon 8 − 9 deletion mutation developed treatment-related immune-mediated myositis with an onset on Day 27. Both subjects were treated with tacrolimus in addition to corticosteroids. The highest number of spot forming units (SFU) against the transgene product, as measured in the IFNγ ELISpot assay in the 2 subjects with serious immune mediated myositis, was clearly higher than in subjects who had other mutations than the mutations in exon 1-17 and who had events of mild or moderate severity. In addition, ex vivo epitope mapping was available for the two subjects with the SAE of immune-mediated myositis identifying peptides coded by exons 8 and 9 as the most immunogenic epitopes.

Immune response to transgene product

Cellular immune responses to 3 pools of micro-dystrophin as well as measurements of antibody titers against micro-dystrophin were determined for a total of 207 subjects in the All Subjects set at time points specified in the schedule of assessments of the respective studies. The dystrophin antigen pool 1 used in the ELISpot assay consists of peptides 1-52, pool 2 consists of peptides 53-113 and pool 3 consists of peptides 114-169.

The All Subjects set is analyzed in this section to better characterize the serious adverse event of immune-mediated myositis for SRP-9001, as this population includes subjects with potentially relevant mutations (i.e., those with mutations in exons 1-17 and 59-79).

The SRP-9001-dystrophin transgene contains portions of the N-terminus (exons 1-17 are present in the SRP-9001 construct) and C-terminus (exons 59-71/79 are present in the SRP-9001 construct) of the naturally occurring full-length dystrophin gene. Regarding the putative mechanism, mutations in the transgene portion of the construct may impart higher immunogenic risk, as mutations in these exons can result in a lack of immune-tolerance to the 1-17 and 59-71/79 regions present in SRP-9001 dystrophin protein. In particular, mutations that delete a portion of that genetic sequence (known as deletions) may confer risk, due to the inability to produce a possibly immunogenic portion of dystrophin that is encoded by SRP-9001, at the relevant early stage in life when immune-tolerance to auto-antigens is developed.

IFN Cytokine ELISpot

Maximum ELISpot response and antibody response directed against micro-dystrophin within 12 weeks after SRP-9001 infusion for subjects with mutations in exons 1-17 and for subjects with mutations in exons 59-79 were analyzed.

Exons 1-17 large deletion mutations

☐ Nine subjects with exon 1-17 mutations had deletion mutations, and in 5 of those, the deletion mutation affected exons 8 and/or 9. These 5 subjects included the 2 subjects who reported the serious adverse event of immune-mediated myositis (with an exon 3-43 deletion and an exon 8-9 deletion) while the other 3 subjects had deletions in exons 8-12, an exon 8-9 deletion and an exon 8 deletion. Four subjects had deletions not affecting exons 8 and 9. This group consisted of subjects with an exon 10-11 deletion, an exon 12-16 deletion, an exon 12-30 deletion, and an exon 3-7 deletion.

☐ The maximum SFUs from ELISpot of 1083.3 and 1447.5 were reported for the 2 subjects who reported the serious adverse event of immune-mediated myositis at Week 12 and Week 4, respectively. The next highest value reported in this group was 134.2 SFU in a subject with an exon 10-11 deletion. In these 3 subjects pool 1 was the affected peptide pool.

☐ Maximum antibody titers within the first 12 weeks after SRP-9001 infusion varied. The 2 subjects who reported the serious adverse event of immune-mediated myositis reported maximum titers of 1:5120 at Week 10 (subject with exon 3-43 deletion) and 1:320 at Week 4 (subject with exon 8-9

deletion). Of the remaining 7 subjects, 4 reported maximum titers of ≥ 1:400, and the highest titer reported was 1:2560 at Week 12 in a subject with an exon 12-16 deletion.

Exons 1-17 mutations (other than large deletion mutations)

☐ There were 8 subjects with mutations in exons 1-17 including 5 subjects with large duplications in exons 12-16, exon 2, exons 2-9, exons 8-11, and exons 14-19.

☐ Maximum SFUs of 211.25 and 322.5 both at Week 6 and directed against peptide pool 2 were reported in 2 subjects, one subject with a small mutation in exon 9, and one subject with a small mutation in exon 11. In the remaining 6 subjects, the maximum SFU number within 12 weeks after SRP-9001 infusion did not exceed 100 SFU.

☐ The highest antibody titer against micro-dystrophin reported was 1:640 at Week 12 in a subject with a small mutation in exon 14.

☐ No clinical symptoms meeting the criteria for immune-mediated myositis were reported.

Exons 59-79 mutations

☐ There were 16 subjects with mutations in exons 59-79, including 2 subjects with a large deletion (exons 52-70, and exons 53-60) and a subject with a large duplication (exons 53-62). Seven subjects had small mutations in exon 59, exon 61 (3 subjects), exon 66 (2 subjects), and exon 67. Six subjects had small mutations affecting introns.

☐ The highest maximum SFU value of 220 was reported in 1 subject with a small mutation in exon 61 at Week 8 that was directed against peptide pool 2 and not against peptide pool 3 which covers the C-terminal portion of the SRP-9001 transgene construct. There was another SFU value exceeding 100 directed against peptide pool 1, in a subject with a small mutation referring to intron 62. The highest antibody titer against micro-dystrophin was found in a subject with a small exon 66 mutation at Week 12. In the other subjects there was no antibody titer exceeding 1:100 within 12 weeks following SRP-9001 infusion.

☐ No clinical symptoms meeting the criteria for immune-mediated myositis were reported

<u>Troponin Elevation / Myocarditis</u>

Study 301 Part 1

A search for troponin I elevations >3×ULN (or 3 ×baseline for subjects with elevated baseline values) showed that 2 subjects each (3.2%) in both treatment groups had experienced at least one increase. The earliest such episode was at Day 130 in a placebo patient (note that the subject with an SAE of myocarditis described below only had reports of 3× troponin from Day 189 onwards).

An analysis by searching for various terms related to troponin increases and resulting myocarditis showed as well that 2 subjects in each treatment group reported at least 1 such event (Table 21). One subject in the SRP-9001 group had an SAE of treatment-related myocarditis on Day 1. More than 6 months later, the same subject had 3 episodes of mild troponin increase.

Pooled analyses

Troponin elevations ≥3×ULN were observed in 17 subjects (8.2%) of the All Subjects population. The events were distributed evenly over the entire study duration, i.e., they were not obviously associated with the SRP-9001 infusion and are thus in most instances a reflection of the underlying DMD rather than of developing myocarditis.

Table 21: Troponin I elevations >3 x ULN or 3 x baseline by visit (exposure analysis set)

Troponin I > 3 x ULN or 3 x Baseline for subjects with elevated Baseline value	Process B 4-8 Years (N=131) n (%)	All Subjects (N=207) n (%)
Overall	12 (9.2)	17 (8.2)
Day 4	2 (1.5)	2 (1.0)
Week 1	2 (1.5)	3 (1.4)
Week 2	1 (0.8)	1 (0.5)
Week 3	0	0
Week 4	0	1 (0.5)
Week 5	0	1 (0.5)
Week 6	0	0
Week 8	0	0
Week 12	0	2 (1.0)
Week 24	2 (1.5)	4 (1.9)
Week 36	1 (0.8)	1 (0.5)
Year 1	2 (1.5)	3 (1.4)
Month 18	3 (2.3)	3 (1.4)
Year 2	1 (0.8)	1 (0.5)
Month 30	2 (1.5)	2 (1.0)

N = number of subjects in the Exposure Analysis Set. n = number of subjects within a specific category. Percentages calculated as 100 x (n / N).

Source: root/clinical_studies/RO7494222/CDT30328/share/pool_SCS/prod/program/t_lb_troponin.sas
Date/time of run: 20JAN2024:11:19.
Adapted from t_lb_troponin_EAS.

The range of post-baseline troponin I elevation within and after 4 weeks post SRP-9001 infusion is provided in Table 22. The summary excludes the maximum troponin I values as observed in the 2 subjects with SAEs of myocarditis (troponin I elevations of 11,28 pg/mL and 3,561 pg/mL).

Table 22: Patients with troponin elevations >3 x ULN (or > baseline value if exceeding ULN) – excluding 2 subjects with myocarditis SAEs

Time period*	N	Age range (years)	Peak range (pg/mL)	Time of onset range (Day**)
≤4 weeks	4	7 - 8	234 - 1336	4 - 30
> 4 weeks	14	3 - 9	175 - 1686 (outlier: 11209)	81 - 905

* Onset of troponin I elevation, post SRP-9001 infusion

** Study day (Day = Date - SRP-9001 dose date + 1. If date < SRP-9001 dose date, Day = Date – SRP-9001 dose date).

Source: l_lb_tropo_pcs_EAS.

A wider AE search to identify potential cases of myocarditis identified 26 subjects (12.6%) in the All Subjects population (Table 41). Of these, events in 9 (4.3%) subjects were considered related to treatment (the differences between all AEs in this search and those considered related were driven by events of cardiomyopathy, and of troponin I or troponin increased). The proportions of related AEs in the Process B 4 −8 Years subpopulation were similar to those in the All Subjects population. Most of the events were mild or moderate in severity. Two events (both with the PT of myocarditis) were severe, and they were also reported as SAEs. All the subjects with related AEs included in the search for potential myocarditis events were also identified in the search for events with troponin increases ≥3×ULN.

Two severe myocarditis events were also reported as SAEs.

Thrombotic Microangiopathy

Study 301 Part 1

No incidents of TMA were identified in the SRP-9001 group during Part 1 of Study 301.

In the placebo group, 1 subject experienced acute kidney injury, which could have indicated TMA. The event was moderate in severity, not considered treatment-related, and had an onset 148 days after placebo infusion. It occurred in the context of a serious streptococcal toxic shock syndrome.

Pooled analyses

To identify potential cases of thrombotic microangiopathy (TMA) defined in the protocol as acute kidney injury, and/or atypical hemolytic uremic syndrome the search was widened for the purpose of this SCS as to include more manifestations of complement-mediated reactions as identified by the following search terms: PTs of haemolytic uraemic syndrome, atypical haemolytic uraemic syndrome, thrombotic microangiopathy, acute kidney injury, microangiopathic haemolytic anaemia, or red cell fragmentation syndrome. Searches for AEs indicative of TMA did not identify any events related to these terms.

A review of laboratory parameters also suggests that there were no cases of TMA. Laboratory parameters of hemoglobin (< 10 g/dL and ≥ 8 g/dL) and lactate dehydrogenase (LDH) (≥ 2.0 ×baseline) during the first two weeks following administration of SRP-9001 were reviewed for signs of a potential TMA. There were no subjects with hemoglobin< 8 g/dL at any timepoint.

A total of 5 subjects presented with a lactate dehydrogenase value ≥ 2.0 ×baseline up to the Week 2 visit following administration of SRP-9001; there were no subjects with decreases in hemoglobin< 10 g/dL:

At Week 1, 3 (1.4%) subjects reported hemoglobin value of < 1.0 ×LLN and ≥ 10 g/dL; no subjects had a decrease in hemoglobin< 10 g/dL. At the same study visit, there were 5 subjects (2.4%) with

increases in LDH of ≥ 2.0 ×baseline. Neither of these patients reported hemoglobin value of < 1.0 ×LLN and ≥ 10 g/dL and an increase in LDH of≥2.0 ×baseline simultaneously at Week 1.

At Week 2, no subjects reported decreases in hemoglobin, while 2 subjects (1.0%) reported increases in LDH of ≥ 2.0 ×baseline.

Hypersensitivity

Study 301 Part 1

Potential hypersensitivity events were observed in 19 subjects of the SRP-9001 group and in 21 subjects of the placebo group. Most of these events were considered not related to treatment.

Pooled analyses

A search for potential events of hypersensitivity identified 63 subjects (30.4%) in the All Subjects population with such events. In 15 subjects (7.2%), the events had an onset in the initial 2 weeks of the study, and in 11 subjects (5.3%) in the period of >2 weeks to 60 days. In the remaining subjects (more than half of those with events), onset was after 60 days. Most of these events were considered not related to treatment.

When focusing on treatment-related events of hypersensitivity, 8 subjects (6.1%) in the Process B 4-8 Years subpopulation and 10 (4.8%) in the All Subjects population were identified.

Most of the potential hypersensitivity events were of mild or moderate severity. Only 2 out of the 3 myocarditis events identified in the search for hypersensitivity events were considered to be severe.

Thrombocytopenia

Study 301 Part 1

Two subjects (both in the SRP-9001 group) reported 1 AE each retrieved with the searching criteria of "SMQ haematopoietic thrombocytopenia" (MedDRA preferred terms: platelet count decreased, thrombocytopenia) (Table 44). One of these events occurred within 2 weeks of study drug infusion (platelet count: 86 $\times 10^9$/L) and was considered related to treatment and mild in severity; it started on Day 8 and was resolved by Day 14. The other event occurred on Day 43 post-infusion (platelet count: 29×10^9/L), it was considered not related to treatment, was also mild in severity, and had resolved 2 days later; as per the Investigator, the sample was clotted at the time of collection

In a search for subjects with platelet counts $<75 \times 10^9$/L, 2 episodes were identified in the SRP-9001 group one was the event on Day 43 described above. The other one involved a reading of 26 $\times 10^9$/L at Day 74. This was associated with an AE of "false positive investigation result" (verbatim term: pseudothrombocytopenia; as per reporter, platelets were seen to be clumping). No other significant laboratory abnormalities or symptom were reported. At a follow-up 4 days later, the platelet count was $>75 \times 10^9$/L.

Pooled analyses

A search for the SMQ hematopoietic thrombocytopenia identified similar proportion of subjects in the pooled populations; 10 subjects (7.6%) in Process B 4−8 Years and 18 subjects (8.7%) in the All Subjects populations. The majority of these events occurred in the initial 2 weeks following the SRP-9001 administration (Table 45). The events were all mild or moderate in severity. None of these events was an SAE. Except for 2 events, all reported thrombocytopenia AEs were considered by the investigator to be related to treatment. There was no obvious correlation between thrombocytopenia and bleeding AEs reported within the first 2 weeks after SRP-9001 administration.

Mean platelet counts underwent a transient decrease in the treated subjects shortly after they were administered SRP-9001, with the most pronounced change from baseline observed at Week 1.

A search for subjects with platelet counts $<75 \times 10^9$/L was conducted to identify patients with the most pronounced decrease in platelets. The proportion of subjects identified was overall smaller than that in the search for thrombocytopenia AEs: 4 subjects (3.1%) in Process B 4 −8 Years and 8 (3.9%) in the

All Subjects population. Seven of these 8 subjects with low platelet counts have had these low values reported as a thrombocytopenia AE and are included in the analysis described above. The 8th subject is the one with an AE of "false positive investigation result" described above.

Five of the 8 events occurred within the first 16 days after SRP−9001 dosing. One platelet count of 64×10^9/L was measured for one subject in his second year after SRP-9001 dosing. The other 2 events were the low platelet counts of 29×10^9/L on Day 43 and 26×10^9/L on Day 74 mentioned above and in which the clotting samples indicated that the measurements of low platelets were most likely not accurate.

Six of the 8 subjects with platelet counts $<75\times10^9$/L reported no bleeding events. One subject had an AE of thrombocytopenia from Days 7 − 15 and he had epistaxis from Days 13 − 186, which was mild and considered to be not related to treatment. The second subject reported epistaxis on Day 4, which resolved on the same day; it was mild and reported as not related to treatment. The subject had then thrombocytopenia on Day 43, with a platelet count of 29×109/L.

Rhabdomyolysis

Study 301 Part 1

An analysis of rhabdomyolysis events on the basis of the rhabdomyolysis/myopathy SMQ identified a total of 10 subjects (15.9%) with such events in the SRP-9001 group vs 14 (22.6%) in the placebo group. The majority of these events were not related to treatment and most of them were mild in severity. Two rhabdomyolysis events in one SRP-9001 subject were severe (and serious) and are described below. An event of blood CK increased reported in a subject on placebo was also severe in intensity. Three subjects (4.8%) in the SRP-9001 group and 2 (3.2%) in the placebo group had events within 2 weeks after the infusion, while all other events occurred later.

When summarizing rhabdomyolysis on the basis of the protocol-defined PTs of myalgia, rhabdomyolysis, chromaturia, or myoglobinuria for the "rhabdomyolysis" AESI, there were 8 subjects (12.7%) in the SRP-9001 group and 9 subjects (14.5%) on placebo with at least one such event. These events were analyzed further to determine the likelihood that they were true representations of rhabdomyolysis: if the subject showed acute CK elevation (≥2×baseline value) and exhibited 3 (probable rhabdomyolysis), 2 (possible rhabdomyolysis), or 1 (rhabdomyolysis unlikely or unassessable) of the following signs/symptoms: i) myalgia or muscle pain; ii) weakness or inability to walk; and iii) dark urine or myoglobinuria (Gabow 1982; Giannoglou 2007). Based on this definition, no case met the probable category, 3 AEs in 2 subjects met the possible category (see below), and the remaining AEs met the unlikely category.

Of the subjects in the "possible rhabdomyolysis" category, one subject in the SRP-9001 group experienced 2 SAEs reported as rhabdomyolysis with onsets on Day 3 and Day 171, respectively. The other subject was in the placebo group and experienced a non-serious AE reported as rhabdomyolysis on Day 28.

Pooled analyses

A search of AEs for the preferred terms used for the definition in the Study 301 protocol of AESIs of rhabdomyolysis identified 15 (11.5%) subjects in the Process B 4 −8 Years subpopulation and 24 (11.6%) subjects in the All Subjects population.

Using a search strategy based on the rhabdomyolysis/myopathy SMQ, which includes additional preferred terms potentially indicative of rhabdomyolysis, identified 20 (15.3%) subjects in the Process B 4 −8 Years subpopulation and 36 (17.4%) subjects in the All Subjects population (Table 47). Approximately half of the events were considered related to treatment (Process B 4 −8 Years: 10, 7.6%; All Subjects: 18, 8.7%).

Most events were mild or moderate in intensity; 6 of them were severe and they were all considered as SAEs (see below). Most resolved without sequelae. One event (in a subject with an SAE) resolved with sequelae, 3 events were unresolved at the time of CCOD. No subject with one of the identified events

reported an event related to renal, cardiac, or electrolyte abnormalities. The value of creatinine and cystatin were within the normal range.

Five subjects in the All Subjects population (2.4%) experienced SAEs: in 4 of them, they were reported with the preferred term of rhabdomyolysis. In the 5th subject, this was reported as muscular weakness in the context of a parallel event of immune-mediated myositis.

The time to onset of the SAEs with the preferred term of rhabdomyolysis varied widely, 2 occurred shortly after SRP-9001 infusion (Days 3 and 16), and 3 events had a late onset (Days 156, 171, and 790). The 5 SAEs recovered with IV fluids within 2 to 4 days; there were no sequelae. There was a reported increase in physical activity preceding the SAEs in 2 of the subjects.

Nausea and Vomiting

Study 301 Part 1

A total of 76 subjects, with more in the SRP-9001 group (49, 77.8%) than on placebo: (27, 43.5%) experienced AEs indicating nausea and/or vomiting. Most of these occurred within 2 weeks post-infusion. During that time period, the imbalance was most pronounced, with 44 subjects (69.8%) in the SRP-9001 group vs 13 (21.0%) on placebo.

These events were serious in 2 subjects in the SRP-9001 group (one subject with vomiting and nausea on Day 1, another subject with vomiting and abdominal pain on Day 173). In the placebo group, one subject reported an SAE of vomiting on Day 184.

Pooled analyses

Vomiting and nausea were the most frequent AEs observed. In the All Subjects population, 73 (35.3%) subjects experienced episodes of both vomiting and nausea, 63 (30.4%) had only events of vomiting, while 15 (7.2%) reported only nausea but had no vomiting (Table 49). These numbers were similar to those in the Process B 4-8 Years subpopulation.

Most of the events were mild or moderate in intensity. Severe events, with an onset between 1 and 3 days occurred in 3 subjects; these severe events were considered serious and related to treatment. A fourth subject had AEs of abdominal pain and vomiting that were both considered severe and were reported as serious; they had an onset at Day 173 and were considered not related to treatment. A listing of all nausea and vomiting events is appended. All events resolved with standard of care and there have been no complications or sequelae from vomiting.

The median time to onset of the first vomiting and/or nausea event was 3 days and most cases had a first onset within the initial 2 weeks after SRP-9001 administration.

In the All Subjects population, 78 (37.7%) of the subjects received ondansetron as a treatment of their nausea/vomiting, and 6 (2.9%) received another medication as anti-emetic.

Sixteen subjects of the All Subjects population received ondansetron/anti-emetic from Day -1 to Day 1 as prophylaxis. Of these, 6 subjects (37.5%) had vomiting/nausea in the first week after SRP-9001 administration. In the subjects who received no such prophylaxis, 124 (64.9%) experienced vomiting/nausea in Week 1.

There was no difference in BMI at baseline or total dose of SRP-9001 (vg) between subjects with AEs of vomiting and those without. Because of the high sodium content of the infusion solution, the sodium concentrations in serum approximately 24 hours after infusion were compared between patients with and without vomiting. No difference was found in serum sodium concentrations in subjects with and without vomiting AEs.

Pyrexia

Study 301 Part 1

A search for the PTs pyrexia and temperature increased, identified 20 subjects (31.7%) in the SRP−9001 group and 15 (24.2%) in the placebo group (Table 52). Pyrexia with onset within 2 weeks

occurred in 11 (17.5%) subjects in the SRP-9001 group and 0 in the placebo group; pyrexia with onset later than 2 weeks occurred in 10 (15.9%) subjects in the SRP−9001 group and 15 (24.2%) subjects in the placebo group.

Two subjects developed an SAE of pyrexia: one in the SRP-9001 group at Day 1 (same subject with SAEs of nausea and vomiting described above) and one in the placebo group with an onset at Day 184 (same subject with SAE of vomiting described above).

Pooled analyses

In the All Subjects population, 53 (25.6%) subjects experienced pyrexia (Table 53). Most of the events were mild or moderate in intensity; one event, with an onset on Day 1, was severe in intensity. In about half of the subjects with pyrexia (27, 13.0%), the events were considered related to treatment.

Two subjects developed pyrexia on Day 1 or 2 that was reported as an SAE. One of these events occurred in Study 301 Part 1; this event was severe in intensity. The other SAE occurred in Study 301 Part 2 and was mild in intensity.

All events resolved with standard of care and there have been no complications or sequelae from pyrexia. The median time to onset of the first event of pyrexia was 4.0 days in the All Subjects population and 4.5 days in the Process B 4 −8 Years subpopulation.

More than half of the pyrexia cases had a first onset within the initial 2 weeks after SRP−9001 administration.

No correlation could be established between vomiting and pyrexia. Within the first 7 days after SRP-9001 infusion, 29 subjects in the All Subjects population had pyrexia and 111 subjects had vomiting. Of those, 24 subjects had both vomiting and pyrexia: 17 subjects had vomiting and pyrexia on the same day, 2 subjects first had vomiting then pyrexia on the following day, 4 subjects had pyrexia, then vomiting followed the next day and two days later in 1 subject.

Infusion-Related Reactions

Study 301 Part 1

During Part 1 of Study 301, 24 (38.1%) subjects in the SRP-9001 group and 16 (25.8%) on placebo reported any AE with onset within 24 hours of the start of infusion. The most commonly reported AEs were decreased appetite (SRP-9001: 10; placebo: 1), vomiting (SRP-9001: 9; placebo: 0), fatigue (SRP-9001: 5; placebo: 1) and nausea (SRP-9001: 5; placebo: 2).

Pooled analyses

Potential infusion-related reactions were identified based on a search for all AEs with an onset within 24 hours of SRP-9001 infusion. In the All Subjects population, such events were reported in 74 (35.7%) subjects. Nausea (12.6%), vomiting (10.6%), decreased appetite (8.7%), and fatigue (5.3%) were the most frequent types of AEs.

Most events were mild or moderate in intensity. In 3 subjects, 6 events were severe and reported as SAEs (one subject with SAE of vomiting and another one with 4 SAEs [vomiting, nausea, pyrexia]) and one patient with mild pyrexia. Drug administration was temporarily interrupted due to AE in 2 subjects (injection site extravasation, device dislocation). Among the events indicative of a possible IRR (i.e. with onset within 24 hours after SRP−9001 administration, the following adverse event preferred terms were considered to be clinically more specific as to indicate a possible IRR in the All Subjects population: pyrexia (8 subjects, 3.9%), chills, flushing, sinus tachycardia, skin irritation, and tachycardia (all events with 1 subject each, 0.5%). In most of the 8 subjects who experienced pyrexia, this was of mild or moderate severity and resolved either on the same day or the following day. In one subject, pyrexia was severe and resolved on the third day. In another subject mild pyrexia was considered serious; it lasted for 6 days. In all subjects, pyrexia was reported as recovered/resolved.

In the subjects with AE preferred terms considered to be clinically more specific as to indicate a possible IRR, the events of chills, flushing, and sinus tachycardia were all considered mild and resolved on the same or the next day. The events of tachycardia or skin irritation were also considered mild and

resolved on Days 6 or 9, respectively. Monitoring of blood pressure (including intense monitoring in the 45 subjects in Studies 101 and 102) showed no consistent decreases within the first 5 hours following the start of SRP-9001 administration.

Side Effects of Additional Steroid Use

Study 301 Part 1

No analyses were conducted for the subjects of Study 301 alone.

Pooled analyses

Occurrence of infections, body weight increase, hypertension, diabetes, cushingoid, and decreases in ALP as a rather non-specific bone marker were investigated by comparing frequencies during the first 60-90 days after infusion with subsequent time periods. There was no indication that the increased use of corticosteroids early in the study led to an increase in infections. The number of infections in the All Subjects population up to Week 12 was similar to the periods after Week 12 up to Week 24 and beyond Week 24. Over the entire study duration, there were 6 infections reported as SAEs (4 of them with severe intensity). One of them occurred during the initial 12 weeks (rotavirus infection; onset: Day 10).

There were no adverse events of hypertension or blood pressure increased recorded in the All Subject analysis. Mean changes in blood pressures during the first 12 weeks after infusion do not reveal any changes considered relevant.

There were no adverse effects suggestive of steroid associated body weight. There were 8 subjects reporting AEs of weight increased. The latency was 25, 60, 189, 323, 328, 348, 423, or 557 days. The subject with onset on Day 25 did not have an ALI event reported and no additional steroid for AEs was given around or before Day 25. The subject with an AE of weight increased on Day 60, had increases in ALT, AST, and GGT from Days 43 to 141; oral prednisolone was given with 1.98 mg/kg/day as the highest dose. The subject with an onset date of Day 189, reported no AE of ALI around this time window and there was no increase in steroid dose at that time.

There were no adverse events of diabetes of glucose increased reported. Mean glucose levels during the first 12 weeks after infusion do not show changes considered relevant.

Cushingoid was reported as adverse event in 14 subjects of the All Subjects population and resolved in 6 subjects. The time to onset for all cushingoid events was in between Days 2 and 1400. In 7 subjects the onset was within the first 12 weeks after infusion (mild in 5 cases and moderate in 2; in 3 subjects the event had resolved, in 4 it had not). All cases in the 7 subjects with cushingoid beyond 12 weeks were of mild intensity. No event of cushingoid reported in the All Subjects population was serious.

ALP has been used as a rather non-specific bone marker. During the first 12 weeks after infusion, mean values of ALP in the All Subjects population showed a decrease relative to baseline that was most apparent at Week 3 with a mean (SD) decrease of 32 (21) U/L (baseline mean [SD]: 104 [37] U/L). Values returned to baseline values between Weeks 12 and 24.

Oncogenicity

A search of all available data in the All Subjects population with the malignancies SMQ did not reveal any events in that category.

2.5.8.4. Laboratory findings

Haematology

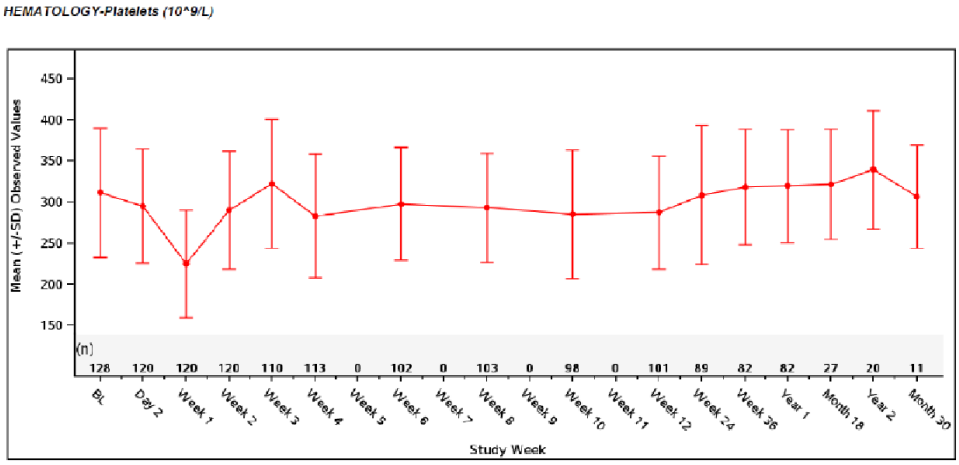
Overall, there were no trends in hematology parameters at the population level or PCS changes in individual subjects that were of clinical concern.

Changes in platelet counts over time are discussed in more detail below as they are relevant in the context of possible thrombocytopenia.

Changes in hemoglobin were assessed in the context of potential events of TMA.

Platelet Counts

The analysis of mean platelet counts over time show a decrease shortly after SRP−9001 administration, with the lowest counts at Week 1 (mean [SD] changes from baseline of −87.32 [72.79] ×109/L for the Process B 4 −8 Years or of −111.11 [83.50] $\times 10^9$/L in the All Subjects populations; baseline mean [SD]: 311.55 [78.57] $\times 10^9$/L and 317.05 [76.78] ×109/L, respectively). After this, the platelet counts rebounded and were back to baseline levels from Week 36 onwards (Figure 7).



Only subjects with baseline and postbaseline are shown in the figure.
Program: root/clinical_studies/RO7494222/CDT30328/share/pool_SCS/prod/program/g_lb_mean.sas
Date/time of run: 20JAN2024: 6:04.

Source: g_lb_sscr2_PB

Figure 7: Observed mean values in platelets over time (process B 4-8 years)

In the All Subjects population, 6 subjects experienced a Grade 2 (<75×10^9/L) reduction in platelets. Furthermore, 2 subjects showed apparent Grade 3 (<50×10^9/L) decreases on Days 43 or 74, respectively. However, the clotting observed in these samples suggests that the measurements of low platelet counts were most likely not accurate. There were no Grade 4 (<25×10^9/L) reductions. There were no Grade 3 decreases beyond Week 10.

Haemoglobin

Study 301 Part 1

Over the entire study duration in 301, 1 subject each in the SRP-9001 and in the placebo arms reported a hemoglobin level <10 g/dL. One patient in the SRP-9001 group and two subjects in the placebo group had hemoglobin below LLN within the initial 2 weeks; however, the values did not drop<10 g/dL.

Pooled analyses

Over the entire duration of the study, 2 (1%) subjects in the All subject population reported hemoglobin values< 10 g/dL and ≥ 8 g/dL. These occurred at Week 10 in one subject, and in the second subject at an unscheduled visit on Day 89. There were no subjects with hemoglobin values < 8 g/dL.

Hemoglobin levels < 10 g/dL during the first 2 weeks following administration of SRP−9001 were reviewed for signs of a potential TMA. No hemoglobin values < 10 g/dL were found up to Week 2. Thus, within the time window of 2 weeks after infusion of the AAV based gene therapy, which is a period suspected for the development of TMA, there were no instances with a drop in hemoglobin below 10 g/dL.

Chemistry

Overall, there were no trends in chemistry parameters at the population level or PCS changes in individual subjects that were of clinical concern apart from those discussed in the context of adverse events of special interest.

Changes in CK (Section 3.2.1) or cystatin (Section 3.2.2) over time are discussed in more detail below as they are relevant in the context of the possibility to develop rhabdomyolysis or TMA, respectively (Section 2.1.8.7).

Furthermore, more details about creatinine as a marker for renal function is provided in Section 3.2.3, and about LDH as an indicator for TMA in Section 3.2.4.

Changes in complement factors are described in Section 4.1 of the Integrated Summary of Immunogenicity.

Creatine kinase

Patients with DMD have grossly elevated serum creatine kinase values from birth due to leakage of the enzyme from degenerating muscle fibers. Early in the disease, between 2 and 5 years of age, creatine kinase levels in subjects with DMD are usually 50 to 300 times the upper limit of normal, and levels tend to decrease over time as muscle is lost and replaced by fibrotic tissue and fat.

Study 301 Part 1

All subjects in both the SRP-9001 and placebo groups of Study 301 showed Grade 4 CK increases at baseline. During the study, 11 subjects in the SRP-9001 group and 12 subjects on placebo had CK measurements meeting the criteria of potential clinical significance. In the SRP-9001 group values ranged from 17,624 U/L to 95,356 U/L. In the placebo group values ranged between 16,482 U/L and 64,220 U/L. Five subjects in the SRP-9001 group and three subjects in the placebo group had an increase from baseline in CK of >2× the baseline value itself.

One subject each in both treatment groups reported treatment-related adverse events with the PT of rhabdomyolysis. The subject in the SRP-9001 group had 2 SAEs of rhabdomyolysis, this individual had a baseline CK measurement of 13,959 U/L.

Pooled analyses

Categorical analyses for CK over time were performed to check for rhabdomyolysis events. Overall, the mapped visits showed that 40 subjects had CK increases >2×and ≤5×baseline, 4 subjects had increases of >5× and ≤10×baseline, and 3 subjects had CK values >10×baseline.

Of the CK increases between >2×and ≤5×baseline, 9 subjects showed an increase on Day 2. At Week 4, 6 and 8, the number of CK elevations decreased to 3 subjects each at these time points around Week 4, 6 and 8, and to 2 subjects each at Weeks 10 and 12. At Weeks 24, 36, and 52, the number of subjects with CK >2×and ≤5×baseline was 7, 10, and 11, respectively.

Two subjects had CK value 10 ×baseline increase and also met the criteria of the >5× and ≤10×baseline category. One of these subjects had an increase of 18.6×baseline at Day 2 and values remained elevated up to Day 1495. The other subject had a CK increase 44.9× baseline at Day 3 and values remained considerably above baseline at most visits up to Day 1212.

One subject had a 10 ×baseline CK increase but no other increases in the >5× and ≤10×baseline category; the peak was on Day 680 (increase of 15.2 ×baseline).

Two subjects had increases of >5×and ≤10×baseline only. One of them reached a peak of 8.61×baseline at around Day 157, and the other a peak of 6.83×baseline at Day 171.

Most of the subjects with CK elevations >2×ULN did not report treatment-related AEs in the rhabdomyolysis SMQ. Among the 13 subjects with treatment-related adverse events of rhabdomyolysis (based on the AESI definition), 4 subjects actually had an increase in CK of ≥2×baseline. Of those, the increase coincided with rhabdomyolysis SAEs in 3 subjects.

Cystatin

Cystatin levels remained overall unchanged at the population level.

Three subjects in the All Subjects population had cystatin values above the ULN, with the highest increase to 1.16 ×ULN. One of these 3 subjects had values above the ULN prior to baseline, the time to onset of the cystatin increases for the other two subjects ranged from Day 27 to Day 252). No obvious deterioration over time was observed in these 3 subjects.

The 3 subjects with abnormal cystatin values reported no relevant renal adverse events or rhabdomyolysis AEs.

Creatinine

No noteworthy changes in creatinine were observed at the population level.

Three different subjects in the All Subjects population had creatinine above the ULN on Days 56, 173 or 509, respectively.

No relevant renal adverse events nor rhabdomyolysis events were associated with the abnormal creatinine values.

Lactate dehydrogenase

Study 301 Part 1

No increases in lactate dehydrogenase (LDH) ≥ 2.0 ×baseline were seen in subjects treated with SRP-9001, while an increase was observed in 3 (4.8%) subjects in the placebo group. Of these, 2 (3.2%) subject reported an increase within 12 weeks after infusion, and 2 (3.2%) subjects reported an increase later than 12 weeks after infusion. One of the subject reported an increase in both the time windows.

Pooled analyses

An increase in LDH (U/L) of ≥ 2.0 ×baseline was overall observed in 12 (5.8%) subjects in the All Subjects population. Assessing the temporal aspect of LDH values, at Week 1, 5 subjects (2.4%) developed LDH value of ≥ 2.0 ×baseline, at Week 2 this was reported in 2 subjects (1.0%), and at Week 3 in 1 subject (0.5%). There were no subjects reported with LDH values of ≥ 2.0 ×baseline between Weeks 4 and 12. At Week 24, 1 subject (0.5%) reported an LDH value of ≥ 2.0 ×baseline. At subsequent study visits between Years 1 and 2, only 1 or 2 subjects, respectively, reported an LDH value of ≥ 2.0 ×baseline, and no subjects reported LDH values ≥ 2.0 ×baseline on subsequent visits, up to and including Year 5.

Vector shedding

Viral shedding has been monitored during the SRP-9001-103 open-label, study using commercially representative Process B material in a total of 40 subjects with DMD. Clinical shedding samples were collected from feces, urine, and saliva over up to 104 weeks. The assessment of vector shedding following SRP-9001 administration in Cohorts 1-4 is a secondary endpoint in the SRP-9001-103 study. Cohort 1 consists of 20 ambulatory patients 4 to less than 8 years of age. Cohort 2 consists of 7 ambulatory patients 8 to less than 18 years of age. Cohort 3 consists of 6 non-ambulatory patients. Cohort 4 consists of 7 ambulatory patients 3 to less than 4 years of age.

After IV administration, delandistrogene moxeparvovec vector genome undergoes rapid distribution via the systemic circulation and widely distributes into target muscle, adipose and other tissues, followed by appearance in saliva, urine and feces.

The observed serum concentration-time profile in human showed a rapid distribution phase up to Day 10 post-dose followed by the shallow and nearly flat terminal phase measured for more than three months (human: lower limit of quantification [LLOQ]) for serum was set to 45,000 copies/mL).

Importantly, consistent serum and excreta pharmacokinetic profiles and characteristics were observed across a broad pediatric and adult DMD population (aged 3 to 20 years old) and subjects with ambulatory or non-ambulatory status.

Compared to the administered dose of delandistrogene moxeparvovec (1.33×1014 vg/kg of body weight), the concentration shed is low. Viral shedding peaks on the first day post-dosing in both saliva and urine, and in the first week post-dosing in feces, and decreases rapidly to very low levels.

Table 23: Study SRP-9001 – 103 mean vector genome DNA at peak compared to week 4

Sample	Population	Mean Peak Concentration (vgc/mL)	Mean Week 4 Concentration (vgc/mL)/ (vgc/µg for feces)
Urine	All	2,750,881 (Day 1) (N=34) min-max: 1,960 - 47,000,000	1,595 (N=37) min-max: 250 - 9,790
Saliva	All	81,741,533 (Day 1) (N=30) min-max: 686,000 - 478,000,000	23,956 (N=30) min-max: 1,250 - 193,000
Feces	All	104,173,889 (Week 1) (N=9) min-max: 415,000 - 395,000,000	19,261.9 (N=26) min-max: 1,340 - 172,000

vgc=vector genome copy.
Source: Table 14.3.4.7.1 SRP-9001-103 CSR (Annex 6.4.3, Table 7)

Table 24: Summary of duration of vector shedding (weeks)

Sample/ Statistics	Cohort 1 (N=20)	Cohort 2 (N=7)	Cohort 3 (N=6)	Cohort 4 (N=7)	Total (N=40)
Urine					
n	20	6	5	6	37
Mean (SD)	17.52 (11.54)	4.83 (1.21)	20.26 (15.51)	7.19 (3.55)	14.16 (11.53)
Median	12.22	4.15	11.29	6.43	11.00
Min, Max	2.3, 36.9	4.0, 6.7	6.3, 37.1	3.1, 11.9	2.3, 37.1
Saliva					
n	20	6	5	5	36
Mean (SD)	11.43 (10.83)	7.14 (2.03)	8.06 (1.91)	9.83 (7.51)	10.02 (8.61)
Median	7.29	6.57	7.43	7.29	7.29
Min, Max	4.1, 51.1	5.0, 10.1	6.3, 11.3	5.1, 23.1	4.1, 51.1
Stool					
n	3	4	3	2	12
Mean (SD)	22.86 (0.76)	34.71 (12.78)	29.10 (7.41)	15.72 (13.33)	27.18 (11.02)
Median	23.14	30.71	27.14	15.72	25.07
Min, Max	22.0, 23.4	25.0, 52.4	22.9, 37.3	6.3, 25.1	6.3, 52.4

n=subjects who reached 3 consecutive visits that are at or below limit of detection.
The duration of vector shedding is calculated as number of weeks from infusion to the first time of three consecutive data points that are at or below the limit of detection of the shedding assay.
Source: Interim CSR Study 103 Table 14.3.4.7.2 Summary of Duration of Vector Shedding (Weeks) / SCP Section 2.2.3.2 Table 3.

Electrocardiography and echocardiography

A detailed review did not identify any cardiac signal emerging from ECG and echocardiography monitoring. AEs of cardiomyopathy related to decreases in LVEF and LFVS appeared only after a prolonged time after SRP−9001 infusion and are not considered to flag a cardiac risk relative to LVEF decline rates in the Duchenne population. James et al (2020; doi: 10.1017/S1047951119002610) report an annual decline of 1.6% per follow-up of a population of 10.8 ± 4.6 years. Placebo

comparison at 1 year after SRP-9001 infusion as available from Part 1 in Study 301 showed trend-wise less of a decrease in the SRP-9001 treated group compared to the placebo group (mean [SD]: -0.09 [5.30] and -1.48 [5.13], respectively)

Summary

Laboratory evaluations were remarkable mainly for thrombocytopenia, which is a known reaction after AAV gene-therapy administration, mediated via complement activation, and elevated liver function parameters, which are discussed in the section on AESIs.

Vector shedding is present in all investigated bodily fluids and excreta. Shedding peaks early after the IV administration of SRP-9001 and then declines rapidly, persisting at low but still measurable levels up to a year. In the PIL, advice is given on good hand hygiene, use of gloves and safe disposal of diapers and other materials for 4 weeks after the initial treatment, which is in line with other licensed AAV-base gene therapies and endorsed.

ECG and echocardiographic evaluations did not reveal unexpected declines or alterations of cardiac function in comparison to the placebo group.

2.5.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.5.8.6. Safety in special populations

Intrinsic factors

Race

The safety profile was evaluated for race. The All Subjects population included 155 White and 47 non-White subjects (information about race was missing for 5 subjects). The results have to be interpreted with caution given the relatively small size of the non-white group, but there are no obvious imbalances in the distribution of the most frequent preferred terms.

Ethnicity

The safety profile was evaluated for potential differences according to ethnicity. The All Subjects population included 35 Hispanic or Latino subjects and 169 non-Hispanic or Latino subjects (information about ethnicity was unknown or missing for 3 subjects). The results have to be interpreted with caution given the relatively small size of the non-Hispanic or Latino group, but there are no obvious imbalances in the distribution of the most frequent preferred terms.

Age/ambulation group

The safety profile was evaluated for age and ambulatory status at the time of SRP-9001 treatment. The All Subjects population included 7 ambulatory subjects <4 years, 184 ambulatory subjects 4−8 years, 8 ambulatory subjects >8 years, and 8 non-ambulatory subjects. Given the very small sample sizes of 3 of these 4 groups, the results have to be interpreted with caution. Overall, there are no obvious differences in the distribution of the most frequent preferred terms across these 4 populations.

Safety in Subjects 3 Years or ≥ 8 Years

SRP-9001 has been studied in 7 subjects aged 3 to <4 years old in Cohort 4 of Study 103. Patients ≥8 years were enrolled in different cohorts of Study 103 (N=16). Cohort 2 (ambulatory, N = 7), and Cohort 3 (non-ambulatory, N =6). Cohort 5 was split into subgroup A with 4 −8-years old ambulatory subjects (N= 6), one of them ≥ 8 years) and subgroup B with non-ambulatory subjects (N= 2), both ≥ 8 years. Please note that flat dosing applies to subjects with body weight ≤70 kg; there was 1 subject enrolled into Cohort 3 who exceeded this cut-off.

The safety profile across these cohorts as for the subjects enrolled into Part 1 of Study 103 is summarized in Table 63. Based on the available safety data from Cohorts 2, 3, 4, and 5, there is no

signal indicating a different safety profile in 3 years old patients or in patients ≥ 8 years as compared to 4 − 8 years old population.

Serious adverse avents

Two subjects (1 each in Cohorts 2 and 5A) reported SAEs of immune-mediated myositis. In another subject (Cohort 2) SAEs of vomiting and myocarditis occurred.

Hepatotoxicity

Across cohorts, all cases of hepatotoxicity were steroid responsive and, there were no subjects with an increase in total bilirubin exceeding 2 ×ULN or with an indication of liver failure. Age and higher viral load in heavier patients due the vg/kg dosing schedule have been hypothesized to be linked to the risk of hepatotoxicity. Although the number of subjects is limited, liver biochemistry monitoring in older patients following SRP-9001 infusion does not indicate a higher risk for these subjects.

Immune-mediated myositis

The occurrence of immune-mediated myositis is not considered age-related, but related to the patients' mutation in the dystrophin gene, resulting in a proposed contraindication for patients with a deletion mutation of exons 8 and/or 9.

Myocarditis

Troponin elevations exceeding 3 ×ULN or 3 ×baseline for subjects with elevated baseline values were reported in 10 out of 48 subjects enrolled in Study 103 (Table 63). Overall, the data do not indicate a higher risk of troponin elevations after SRP-9001 infusion in subjects 3 years old (1 out of 7 subjects) or in subjects ≥ 8 years old (3 out of 16 subjects). A pathophysiological hypothesis for troponin increases potentially representing"myocarditis" refers to pre-existing (sub-clinical) Duchenne cardiomyopathy. In the context of this hypothesis, the risk of myocarditis is expected to be lower in 3 years old patients than in older patients.

As the risks associated with SRP-9001 treatment are believed to be related to immunological events, these observations are considered consistent with the immune system development during the first decade of life.

Extrinsic factors

No subgroup analyses were conducted for any extrinsic factor.

2.5.8.7. Immunological events

Immunogenicity

The immunogenicity of SRP-9001 was assessed by evaluating humoral and cellular responses. Humoral response involved the determination of IgG antibody levels against AAV capsid and against the SRP-9001 micro-dystrophin protein using semi-quantitative ELISA or ECLIA assays, respectively. The cellular response was assessed in a semi-quantitative manner by detecting human interferon gamma (IFNγ) released in response to the stimulation of human peripheral blood mononuclear cells (PBMC)s with different capsid or micro-dystrophin pools (ELISPot).

Pre-existing total IgG antibodies against AAVrh74 were determined using the same ELISA assay as for ADA assessment.

Antibodies against the capsid – Anti-AAVrh74 Antibody ELISA

Antibody titer

Prior to SRP-9001 administration, anti-AAVrh74 antibody titers were determined at screening/baseline. A titer of < 1:400 for Study 301 and ≤ 1:400 for Study 103 was expected as a protocol-defined inclusion criteria at screening/baseline. The mean number of anti-AAVrh74 antibody titers increased continuously until reaching a maximum 10 weeks after SRP-9001 infusion (Figure 8).

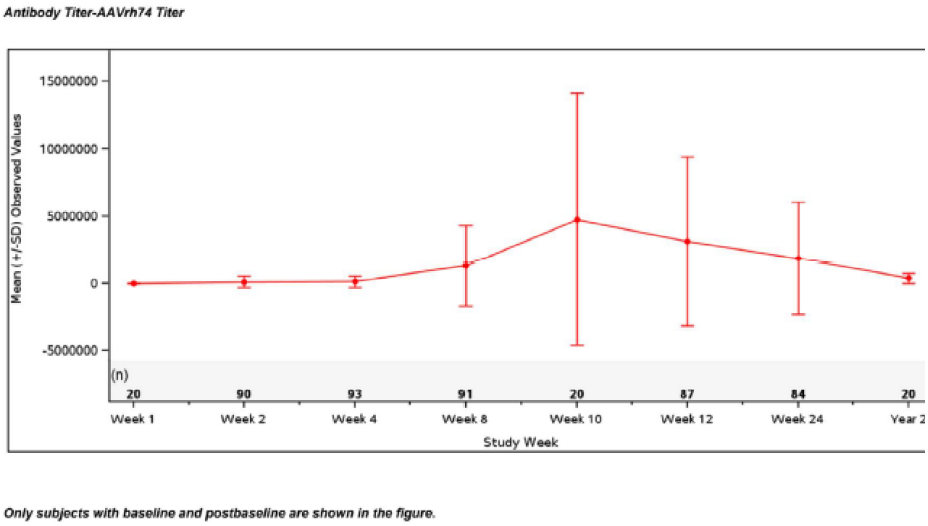


Figure 8: AAVrh74 antibody titer over time

The mean (SD) value at Week 1 was 790.0 (988.0) measured in 20 subjects, reaching 1:118279.6 (1:417335.3) measured in 93 subjects at Week 4, and the maximum of 1:4771840.0 (1:9343885.2) measured in 20 subjects at Week 10.

Afterwards, the mean (SD) number of anti-AAVrh74 antibody titers decreased to 1:1861485.7 (1:4174247.4) measured in 84 subjects at Week 24, reaching 1:353280.0 (1:392009.7) measured in 20 subjects at Year 2.

Antibody response against the AAVrh74 capsid had a similar trend in the Process B (4-8 years) analysis set and the All Subjects sets up to Year 2. For the All Subjects set, antibody titers beyond 2 years after SRP-9001 infusion is available: at Year 3, antibody titer data available for 34 subjects ranged between 1:12800 to 1:1638400 with 11 subjects having an antibody titer of 1:51200. At Year 4, antibody titer data available for 15 subjects ranged between 1:6400 and 1:819200 with 4 subjects showing an antibody titer of 1:51200. At Year 5, antibody titer data from 4 subjects ranged between 1:25600 to 1:409600.

In conclusion, antibody titers were below 1:400 at the time of enrollment for all subjects and increased rapidly until week 10 to a maximum of 1:4,771840.0. Afterwards, titres decreased but stayed elevated at a level that is considered prohibitive to another treatment attempt with the same or a related AAV vector.

Cellular immune response to the transgene product is discussed in section 3.3.7.3 of this report in conjunction with the observed AESIs of immune-mediated myositis

2.5.8.8. Safety related to drug-drug interactions and other interactions

No formal drug-drug or drug-food interaction assessments were conducted.

It is likely that no interactions are to be expected from the transgene product, i.e. the micro-dystrophin, with other medicinal products or food. However, liver toxicity following the administration of delandistrogene moxeparvovec is expected to occur in approximately 40% of recipients. The applicant was therefore requested to add information to section 4.5 of the SmPC pertaining to monitoring of concomitant medications after SRP-9001 treatment and to avoid potentially hepatotoxic medications or using other hepatotoxic agents.

2.5.8.9. Discontinuation due to adverse events

No AEs in any of the studies the SRP-9001 development program led to discontinuation of treatment or of study participation.

2.5.8.10. Post marketing experience

Since the International Birth Date (IBD, 22-Jun-2023) SRP-9001 through 2-Nov-2023, a cumulative total of 61 patients have received SRP-9001 from marketing experience, all in the USA. Based on the data obtained from the IBD through 2-Nov-2023, no new relevant information was identified regarding the safety concerns and the safety profile of SRP-9001 (PADER and PBRER).

During the first Periodic Adverse Drug Experience Report (PADER) reporting period (22−Jun-2023 to 21-Sep-2023), of the 19 patients who received SRP-9001, 1 patient experienced the non-serious adverse events of troponin I increased, lip pruritus, abdominal pain, vomiting, nausea and fatigue. The troponin I increased met the search criteria for myocarditis. This adverse event was non-serious and was assessed as related to SRP-9001. At the time of the report, the outcome of troponin I increased was reported as unknown (PADER).

Between 22-Sep-2023 and 02-Nov-2023, 42 patients received SRP-9001 gene therapy. In this period, 6 SAEs terms were reported in 2 cases (Case 1: GGT increased, AST increased, ALT increased; Case 2: vomiting, hypophagia, pyrexia) along with 7 nonserious AEs (fall, pain in extremity, asthenia, myalgia, chromaturia, ALT increased, and AST increased). Causality assessment to SRP-9001 was not provided by the reporters and the events were considered by the Sponsor to be related. The outcome of the SAEs was reported as unknown. One SAE met the search criteria for acute liver injury. There were no AEs of immune-mediated myositis, thrombotic microangiopathy, myocarditis, or seroconversion in third parties due to unintended exposure reported from post-marketing sources (PBRER).

Whilst no PBRER for the period starting 03-Nov-2023 was available at the time of finalizing this document, between 03-Nov-23 and 07-Mar-2024, 24 serious event terms were reported, compiled in 8 cases.

Late Breaking Data From Other Ongoing Studies With SRP-9001

In the ongoing Study SRP-9001-1042, on 7-Feb-2024, a SAE of urticaria was reported. The study is not part of the current submission and is an open-label, systemic gene delivery study evaluating the safety, tolerability and expression of SRP-9001 in association with imlifidase in subjects with DMD with pre-existing antibodies to rAAVrh74.

Adverse Event Information Emerging After Main Data Cut for Studies 103 and 301

On 15-Jan-24 the co-development partner Sarepta performed another data cut for Studies 103 and 301).

Study 301

In summary, analysis of safety data from an additional 4-months of follow up of Study 301 subjects, including 63 subjects who received SRP-9001 in Part 1, and 10 additional subjects who were assigned to placebo in Part 1 and received SRP-9001 in Part 2 since the 13-Sep-23 CCOD, did not show any signals that would significantly alter the safety profile of SRP-9001.

Study 103

A new data cut based on a CCOD of 15-Jan-2024 adds nearly an additional 6 months of follow up time for all the 48 subjects in that study. During the additional follow up time, 41 treatment-emergent AEs were reported, none of which was considered related to treatment (Table 58). No new SAEs were reported and none of the new AEs were severe in intensity. There were no deaths. The safety data from Study 103 during the reporting period between 24-Jul-2023 and 15-Jan-2024 is in line with the previously observed safety profile and is consistent with the overall safety profile established across all studies.

Update received with responses to D120 Questions

The **second Periodic Benefit-Risk Evaluation Report** (PBRER), which summarizes the safety data for ELEVIDYS during the reporting interval of 03 Nov 2023 to 02 May 2024 was submitted. Cumulatively in the SRP-9001 clinical trials, 363 subjects were enrolled in SRP-9001 development program and 268 subjects (265 subjects from CTs sponsored by Sarepta and 3 subjects from CT sponsored by Roche) were treated with SRP-9001 and/or placebo.

The analysis of the safety information received during this reporting interval resulted in a new important identified risk of IRRs (including Hypersensitivity) that led to the update of the core RMP (including educational materials), CCDS, and safety communications in the post-marketing and clinical trial settings. It also led to a temporary suspension of enrollment in Study 9001-104.

The **third Periodic Benefit-Risk Evaluation Report** (PBRER), which summarizes the safety data for ELEVIDYS during the reporting interval of 03 May 2024 to 02 Nov 2024 was submitted. Cumulatively in the SRP-9001 clinical trials, 417 subjects were screened in SRP-9001 development program and 296 subjects (286 subjects from CTs sponsored by Sarepta and 10 subjects from CT sponsored by Roche) were treated with SRP-9001 and/or placebo.

During the reporting period, the informed consent was revised to include IRRs (including Hypersensitivity) risk prior to the re-start of study SRP-9001-104 on 18 Sep 2024. A safety signal of Rhabdomyolysis was detected and closed during the reporting period. A safety signal of IMM in subjects with exons deletions involving the C-terminal and N-terminal parts of the DMD gene was detected during the reporting period and validated after DLP. One safety signal of Myocarditis was detected and validated after DLP on the 04 Dec 2024 and led to the reclassification of the risk of Myocarditis from important potential risk to important identified risk (late breaking information).

Safety in part 2 of pivotal trial 301

Table 25: Overview of adverse events safety population part 1 and 2

	Part1		Part2		Part 1+2	SRP-Treated
	SRP-treated in Part 1 (N=63) n (%)	Placebo-treated in Part 1 (N=62) n (%)	SRP-treated in Part 1 (N=63) n (%)	SRP-treated in Part 2 (N=60) n (%)	SRP-treated in Part 1 (N=63) n (%)	SRP-treated (N=123) n (%)
Number of AEs	689	528	352	744	1037	1781
Number of TEAEs	679	516	348	689	1027	1716
Number of SAEs	21	9	6	12	27	39
Number of Treatment-related TEAEs	235	44	34	245	269	514
Number of Treatment-related SAEs	10	0	2	11	12	23
Subjects with any AE	62 (98.4)	57 (91.9)	53 (84.1)	56 (93.3)	62 (98.4)	118 (95.9)
Subjects with any TEAE	62 (98.4)	57 (91.9)	53 (84.1)	56 (93.3)	62 (98.4)	118 (95.9)
Subjects with any SAEs	14 (22.2)	5 (8.1)	5 (7.9)	8 (13.3)	15 (23.8)	23 (18.7)
Subjects with any Treatment-related TEAE	48 (76.2)	17 (27.4)	15 (23.8)	50 (83.3)	52 (82.5)	102 (82.9)
Subjects with any Treatment-related SAEs	7 (11.1)	0	1 (1.6)	7 (11.7)	7 (11.1)	14 (11.4)
Subjects with any AEs leading to study discontinuation	0	0	0	0	0	0
Deaths	0	0	0	0	0	0

As of the CCOD (25 October 2024), a total of 109 subjects (Part 1 SRP-treated: 53; Part 2 SRP-treated: 56) reported at least one Adverse Event (AE) during Part 2. Overall, there were 1096 AEs (Part 1 SRP-treated: 352; Part 2 SRP-treated: 744) and 1037 treatment-emergent adverse events (TEAEs) recorded (Part 1 SRP-treated: 348; Part 2 SRP-treated: 689) reported during Part 2. Additionally, out of 18 serious adverse events (SAEs) reported in Part 2 (Part 1 SRP-treated: 6; Part 2 SRP-treated: 12), 13 were considered treatment-related (Part 1 SRP-treated: 2; Part 2 SRP-treated: 11).

The frequency of any AE and TEAE during the first year following treatment was similar between those treated in Part 1 (SRP-treated in Part 1) and those treated in Part 2 (SRP-treated in Part 2) of the 301 study, on average 10-12 events per patient. Numerically there were more SAEs in those treated in Part 1 compared with Part 2 (21 vs 12). There was consistency in safety in the percentage of subjects experiencing treatment-related TEAEs (Part 1: 48 subjects; 76.2%, Part 2: 50 subjects; 83.3%) and treatment-related SAEs (Part 1: 7 subjects; 11.1%, Part 2: 7 subjects; 11.7%).

A comparison of the safety reported in the placebo group in Part 1 (the year before treatment) and the second year of safety in patients treated in Part 1 is similar, and this supports the conclusion in the Summary of Clinical Safety that the majority of AEs occur within the first 90 days after SRP-9001 infusion.

No participants died during the study, and no participants experienced an AE that led to study discontinuation.

Across Parts 1 and 2, the most commonly reported TEAEs by System Organ Class (SOC) were: Gastrointestinal Disorders (82.9%), Infections and Infestations (69.9%), Investigations (56.1%), General Disorders and Administration Site Conditions (49.6%), Respiratory, Thoracic, And Mediastinal Disorders (44.7%). The most frequently reported Preferred Terms (PTs), occurring in 20% or more of patients, across Parts 1 and 2, were vomiting, nausea, pyrexia, cough, decreased appetite, upper respiratory tract infection, increased glutamate dehydrogenase, and COVID-19.

The frequencies of these PTs between the Study Parts are generally consistent, within 10%, between Part 1 treated and Part 2 treated. Exceptions include more frequent COVID-19 (27% vs 10%) in Part 1 treated whereas more frequent vomiting (75% vs 64%) and cough (19% vs 33%) in Part 2 treated. In Part 1, however, the higher number of events within the SOC Infections and Infestations reflects the ongoing COVID-19 pandemic during that period.

The death of a subject who was treated with Elevidys in 2019 was reported in the cover letter accompanying the responses to the D120 LoQ. In addition, on 18 March 2025, Sarepta reported that a an adolescent DMD patient has passed away following treatment with Elevidys, having suffered acute liver failure. More information was requested in both cases.

The applicant has provided more information on this case. Altogether, the totality of clinical data regarding the clinical course are considered to adequately substantiate the applicant´s classification of the fatal acute liver failure as being related to Elevidys.

The applicant has submitted all available information regarding the death of a young adolescent boy who was treated with SRP-9001 five years prior in study 102. Apart from increasing muscle pain and cramps no symptoms occurred before the death of the patient. The autopsy results were inconclusive, suggesting death due to natural progression of the disease as the cause of death, suggesting a lack of efficacy of treatment with SRP-9001.

Furthermore, the applicant has submitted information on two additional deaths that were reported since the last dossier submission. Limited information is available, which does not suggest a role of SRP-9001 in the cause of death. However, in-depth assessment will only be possible when comprehensive information is available in both cases. The autopsy report is expected to be submitted via the CTIS ad-hoc assessments regarding the current temporary halt of clinical trials in the EU.

During the Oral Explanation Meeting (June 2025), the CHMP were made aware of new fatalities that have emerged. These events will be further pursued in the context of clinical trials administration.

2.5.9. Discussion on clinical safety

Exposure

The clinical trial programme includes four clinical trials, in which both ambulatory and non-ambulatory patients had been enrolled, and in which SRP-9001 manufactured with two different processes has been administered. Collectively, the safety database supporting the MAA of delandistrogene moxeparvovec consists of 64 ambulatory subjects aged 4 to <8 years in Part 1 of the randomised, placebo controlled **pivotal trial 301**, who all have accrued a minimum safety follow-up of 52 weeks. 50 further subjects (3 patients were >7 years) were dosed in Part 2, but the available follow-up is limited to a mean of 8 weeks. 48 further patients are enrolled in **phase 2 trial 103**, of whom 20 are 4 to < 8 years old. 7 patients in this trial were 3 years of age, these patients were steroid-naïve and had a mean follow-up of only 1,47 year, the remainder of the treated subjects are all in older or non-ambulatory age cohorts. In addition, data from a further 45 subjects treated in **phase 1 study 101**

and **phase 2 study 102** are available. Studies 301 and 103 used the commercial Process B material, while studies 101 and 103 used Process A material, which differs from Process B in several Critical Quality Attributes. Therefore, data from the earlier studies should be considered supportive only. However, taking into account the limited sample size, the most conservative approach is to consider both safety data generated with process B material as well as pooled safety data generated with product derived from both manufacturing processes. Therefore, all three analysis sets provided with this MAA have been considered for the assessment of the safety profile of delandistrogene moxeparvovec:

1. SRP-9001-301 part 1: 63 patients treated with SRP-9001 and 62 patients treated with placebo, mean follow-up of 54.8 weeks

2. Exposure analysis set (All Subjects population): 207 patients who received SRP-9001 in any of the four clinical trials, mean follow-up of 1.66 years

3. Process B age 4-8 analysis set: 131 patients in the exposure analysis set from study 103 cohort 1 and from part 1 and 2 of study 301 aged 4-8 years at time of treatment and treated with process B material, mean follow-up 1,06 years

Regarding pooling of safety data derived from both ambulatory and non-ambulatory patients, the impact of extent of functional muscle mass on the safety profile is yet unknown.

There are no safety data to support the treatment of patients with LVEF <40%. As the myocardium is one of the target tissues, myocarditis is an important identified risk and cardiomyopathy is considered an additional important potential risk, a respective warning should be included in the SmPC.

In summary, the available safety database is small, with 64 subjects from the pivotal trial providing the main evidence, and with follow-up limited to approximately one year. 131 patients in the study programme were 4 to < 8 years at the time of treatment and 162 subjects in total received Process B material. The limited follow-up after SRP-9001 administration allow for characterisation of the short-term safety profile only, with impact on long-term safety data to be generated for a comprehensive dataset, not limited to but including particularly long-term cardiac safety. The limited sample size and limited follow-up of patients treated at 3 to <4 years of age preclude conclusion of the safety profile for this age range with impact on the indication.

Elevidys is being authorized in several non-EU countries; limited post-marketing safety data generated with the commercial process (B) have also been provided.

Regarding the quality of process B material, visible particles were detected (refer to Quality section). Depending on the outstanding characterization data on the origin and composition of particles, respective safety issues may be raised from a clinical perspective.

Adverse events, including SAEs and AESIs

The **most frequently reported AEs** in the SRP-9001 arm of the pivotal trial were vomiting (63.5%), nausea (39.7%), decreased appetite (31.7%), pyrexia (31.7%), Covid-19 (27.0%) and GLDH increased (27.0%). The majority of events (~80%) were of mild or moderate intensity. Placebo subjects reported similar AEs, but at a substantially reduced frequency. The most common adverse reactions throughout the presented clinical trials include vomiting, nausea, decreased appetite, increased transaminases, upper abdominal pain, and pyrexia. The pooled analyses showed comparable outcomes in the 4-<8 year Process B as well as in the All subjects population. The proportion of subjects with AEs considered related to treatment was higher in the SRP-9001 group of trial 301 (48 subjects, 76.2%) than in the placebo group (17 subjects, 27.4%) and similar to the All Subjects population (171 subjects, 82.6%) and the Process B 4 -<8 Years subpopulation (104 subjects, 79.4%) with a related AE.

22% of subjects in the SRP-9001 group in the pivotal trial versus 8% in the placebo group reported **SAEs**. Of these, SAEs in 11% of subjects were considered treatment-related in the SRP-9001 arm vs. 0% in the placebo arm. In the All subjects populations as well as in the Process B population, frequencies were comparable at about 15% of subjects. SAEs were considered treatment-related in

~9% of subjects in both pooled populations. Most of the SAEs that were considered treatment-related were also captured as AESIs. No deaths occurred during the complete clinical investigation programme.

In the pivotal study, the following events were defined as **AESIs**: hepatotoxicity, myositis, thrombotic microangiopathy, hypersensitivity, thrombocytopenia, rhabdomyolysis and troponin elevations. In addition, the applicant has provided analyses pertaining to nausea and vomiting, pyrexia, infusion-related reactions, side effects of additional steroid use and oncogenicity.

41.3% of subjects treated with SRP-9001 developed signs or symptoms of hepatotoxicity in the pivotal trial vs. 8.1% of patients treated with placebo. The majority of these events were reported within the first 90 days after treatment. All events could be managed with steroids and had a maximum duration of 77 days in the pivotal study. 5 of 26 subjects needed to be treated with IV steroids, while the remaining 21 subjects could be managed with oral steroids. ~10 % of subjects had severe AEs of hepatotoxicity. In the All Subjects population, the incidence, severity and time to onset of this AESI as well as the use of oral and IV steroids was comparable.

Immune-mediated myositis (IMM) is currently considered an AAV class effect in DMD patients (Boennemann et al., 2023), potentially leading to severe courses and sequelae. In trial 103, two subjects reported severe reactions, one of which was life-threatening. Symptoms of severe muscle weakness, including dysphagia, dyspnea and hypophonia, were observed. Both resolved with sequelae, with the muscle strength and function improved but reaching a level below baseline. IMM is considered to be a T-cell mediated inflammatory reaction against the microdystrophin transgene product in the sense of a "non-self" epitope, but its pathogenesis has not fully been understood to date. In the non-clinical program, no relevant T cell responses against delandistrogene moxeparvovec have been reported in non-GLP toxicity studies. Subjects with mutations in exons 1-17 of the DMD gene were excluded after the occurrence of a SUSAR of asthenia/muscle weakness in trial 103 leading to the hypothesis that these patients might have an increased risk of developing an unwanted immune reaction against the micro-dystrophin transgene (Amendment 2: 30 Aug 2021). However, the proposed contraindication for Elevidys focuses only on mutations in exon 8/9. The data provided do not substantiate the IMM-risk based mutation-specific indication/contraindication. The ELISpot and epitope mapping dataset provided is not considered supportive for the re-broadening of the indication in comparison to the previous clinical development program. High T-cell reactivity was also reported in patients with mutations in other exons, e.g. with a premature stop codon and a canonical splice site mutation and notably, also against pool 2. On the other hand, not all patients with exon 8/9 mutations developed IMM in study 102 (prior to the exclusion of patients with mutation in exon 8/9). No additional data were provided to support the restriction of the high risk of IMM to patients with mutations in exon 8/9. Instead, 3 cases of severe IMM associated with severe prolonged clinical courses were reported in the post-marketing period. All of them carried at least partial deletions in the area of the coding region of SRP-9001. To date, no IMM cases have been reported in patients with other mutation types that include a part of exons 1-17 or 59-71. Therefore, the contraindication to treatment was extended to patients with any deletion in exons 1 to 17 and/or 59 to 71 in the DMD gene.

The myocardium is a target tissue for treatment with SRP-9001, therefore an immune reaction leading to troponin increase and/ or **myocarditis** can be expected as a potential complication of treatment. In the pivotal trial 301, one subject reported an SAE of myocarditis, while one additional subject in the treatment group as well as two subjects in the placebo group were found to have increased troponin values. The incidences of troponin increase/ myocarditis-related AEs was comparable in the All subjects and Process B population, at approximately 12%. As the cardiac muscle is weakened by dystrophin deficiency cardiomyopathy develops early in life, leading to heart failure. As a safety precaution, subjects with an ejection fraction <40% or clinical signs or symptoms of cardiomyopathy were excluded from the clinical trials. However, no warning is specified in the SmPC. Furthermore, cardiac safety data only up to 52 weeks was available from the pivotal trial. In order to better characterise potential late-onset decrease of cardiac function, the applicant was asked to submit all cardiac safety data accrued in subjects treated with Process B material beyond 1 year post-treatment. The applicant has provided updated 2-year safety data from the patients treated in Part 1 of the pivotal trial 301,

with the incidence of myocarditis remaining at 1.6%. Updated data from study 103 demonstrate multiple elevations of troponin without clinical symptoms and sequelae. DMD patients have been demonstrated to have intermittent asymptomatic cTnI elevations (Sheybani et al; DOI: 10.1038/s41390-021-01682-5), thus rendering the cTnI assay of unclear relevance for safety monitoring.

Two cases of cardiomyopathy have been reported in the clinical development programme, which were classified as treatment-related. One young adolescent boy experienced cardiomyopathy and myocarditis on Day 4 and resolved on Day 254 after infusion of SRP-9001 in trial 103. One late breaking case report of an 11 year old subject treated at the age of 6 in study 102 with Process A material, who developed decreased LV function 4.5 years after the initial treatment illustrates the potential for an acceleration of the myocardiopathy inherent to DMD with symptoms only manifesting years after the treatment. This has to be considered for the benefit-risk assessment of SRP-9001. In response to the D180 LoOI, the applicant has updated the warning on 'myocarditis' to 'cardiac disorders', providing information on the occurrence of cardiomyopathy in clinical trials and recommending ECG and ECHO baseline testing prior to Elevidys administration.

No cases of **thrombotic microangiopathy** (TMA) were observed throughout the clinical study programme. A transient decrease in platelet counts has been observed in the haematology laboratory evaluation. Reassuringly, only few adverse events of thrombocytopenia were reported and the majority of those were not correlated with bleeding events. Decrease of platelets was also not correlated with decrease of complement factors or TMA events.

Only few **hypersensitivity** AEs were considered related to treatment in trials 101, 102, 103 and 301, but late-breaking data from other ongoing trials as well as post-marketing reports detailed hypersensitivity as well as anaphylaxis events. The reasons for the different rates of hypersensitiviy should be specified more in depth, also considering the use of filters and the different specification of the Process A and B drug material (e.g. amount of capsids).

Several instances of **rhabdomyolysis** were reported. While this condition is a known complication of the underlying disease, especially with increased physical activity, dehydration or certain anaesthetics, there were at least two instances of rhabdomyolysis early after treatment (day 3 and day 16. Assessment of relatedness is however confounded by dehydration and a viral infection. However, as rhabdomyolysis has been reported in multiple cases throughout the clinical development, it has to be reflected as an important potential risk in the RMP.

Nausea and **vomiting** as well as fever were frequently reported in subjects treated with SRP-9001, but most events were of mild or moderate intensity and responded to standard of care.

Infusion-related AEs were identified via a search for AEs with onset during the initial 24 hours after treatment: Decreased appetite, nausea, vomiting, fatigue, pyrexia, chills and tachycardia were the events with early onset after treatment.

As all subjects in the pivotal trial were on a baseline chronic corticosteroid scheme, it is difficult to discern potential unfavourable effects of additional corticosteroid use for hepatic adverse events. All subjects were on increased doses of steroids during the first 60 days after administration of SRP-9001. The incidence of infections, weight gain, diabetes and hypertension do not indicate a meaningfully increased risk for steroid-related adverse events.

In summary, while the most common observed adverse reactions were in line with the known class effects of AAV gene therapy, additional safety aspects were identified. Severe immunologic reactions to the transgene requiring deep immunosuppression, Troponin I increase, myocarditis and rhabdomyolysis have been reported. The information presented in section 4.8 the PI was not complete and has been amended. In addition, information on the frequency of need for additional immunosuppressants and on the specific additional immunosuppressive medicinal products used (e.g. tacrolimus) in clinical trials was included into the appropriate sections of the SmPC.

Notably, a high rate of patients required additional immunosuppression; in the All Subjects Population of n=207, additional corticosteroids for the treatment of hepatotoxicity were administered to n=14, for

the treatment of IMM to n=2 in combination with tacrolimus and for the treatment of troponin increase and myocarditis to n=1). In order to encompass the full extent of the safety aspects related to the administration of delandistrogene moxeparvovec, the risks of immunosuppression must also be considered when assessing the benefit/risk of delandistrogene moxeparvovec.

No malignancies were observed in the safety population. Due to the relatively short follow-up duration this was expected.

Immunogenicity / vector shedding

Anti-AAV antibody titres were below 1:400 at the time of enrolment for all subjects and increased rapidly until week 10 to a maximum of 1:4,771840.0. Afterwards, titres decreased but stayed elevated at a level that is considered prohibitive to another treatment attempt with the same or a related AAV vector.

Vector shedding is present in all investigated bodily fluids and excreta. Shedding peaks early after the IV administration of SRP-9001 and then declines rapidly, persisting at low but still measurable levels up to a year. In the PI, the importance of good hand hygiene, use of gloves and safe disposal of diapers and other materials for 4 weeks after the initial treatment is emphasised, which is in line with other licensed AAV-base gene therapies and endorsed.

Post-marketing data

The death of a subject who was treated with Elevidys in 2019 was reported in the cover letter accompanying the responses to the list of questions. In addition, on 18 March 2025, Sarepta reported that a teenage DMD patient has passed away following treatment with Elevidys, having suffered acute liver failure. More information was requested in both cases. Data submitted by the applicant substantiate acute liver failure related to Elevidys treatment as the cause of death. Another patient passed from progression of the disease, suggesting a lack of efficacy of treatment with SRP-9001. In the context of the late-breaking news on the fatality, the Rapporteurs' teams learned about Study SRP-9001-401, which was not included in the MAA dossier. The applicant has clarified that SRP-9001-401 (ENDURE) is an ongoing US only long-term observational study sponsored by Sarepta Therapeutics and is different from the proposed BN44090 study sponsored by F. Hoffmann La-Roche. As of 8 April 2025, 24 patients have been enrolled in the ENDURE study (18 in the treatment arm and 6 in the control arm). No additional safety concerns arise from the provided data. During the Oral Explanation Meeting (June 2025), the CHMP were made aware of new fatalities that have emerged. These events will be further pursued in the context of clinical trials administration.

Relevant safety finding outside of the clinical trial programme of SRP-9001 as presented for MAA

In May 2024, a lethal cardiac arrest in a young boy receiving Pfizer’s fordadistrogene movaparvovec was reported (https://www.reuters.com/business/healthcare-pharmaceuticals/pfizer-reports-patient-death-duchenne-gene-therapy-study-2024-05-07/). Currently, no further information on the potential cause is publicly available. As published by Boennemann et al. in June 2023, the four sponsors currently running gene-therapy trials in DMD, formed a working group to address the reported IMM cases and their safety implications (https://doi.org/10.1056/NEJMc2212912). In the Elevidys presubmission meeting, Roche confirmed that the collaboration is still ongoing. No updated information regarding the impact of the recent death case on the findings stated by the sponsor collaboration is available. No additional epitope and HLA fine-mapping data were provided by the applicant. As the contraindication was extended to any deletion in exons 1 to 17 and/or 59 to 71, this is considered acceptable.

The genetic abnormalities underlying DMD are diverse and can result in the expression of non-functional and unstable dystrophin, reduced dystrophin, or complete absence of dystrophin. In most of the DMD cases, deletions, duplications and point mutations are out-of-frame mutations that lead to the complete absence of dystrophin. However, also in-frame deletions were reported in DMD patients (https://doi.org/10.1016/j.medj.2023.02.005, https://doi.org/10.1002/mus.20586). The type and level of expression of dystrophin may have an impact on the safety and efficacy of SRP-9001 via e.g.

immunological effects and different utrophin expression patterns, but such a mutation-specific analysis set was not found in the application dossier.

The long-term follow-up (LTFU) study 9001-305 has been initiated for approximately 400 patients who were dosed with SRP-9001 in a previous clinical study. Study 305 provides up to 5 years of follow-up after infusion of SRP-9001. According to clinicaltrials.gov (18 August 2024), study 305 includes the safety endpoints incidence of TEAE, SAE and AESI. No safety data from study 305 was provided within this MAA dossier. However, recently published results indicate a significantly higher micro-dystrophin expression in cardiomyocytes compared to striated muscle cells with concomitant acceleration of cardiac disease, induced by competition between micro-dystrophin and utrophin (https://doi.org/10.1172/jci.insight.165869). Utrophin, the dystrophin homolog, is consistently upregulated in muscles of DMD patients and is believed to partially compensate for the lack of dystrophin in dystrophic muscle https://doi.org/10.1016/j.medj.2023.02.005). In a severe mouse model of DMD (D2.mdx), clinical dosing of the SRP-9001-like vector construct resulted in a dilated cardiomyopathic failure after at least 8-12 months. Long-term follow-up data after administration of SRP-9001 demonstrated the occurrence of cardiomyopathies in two patients and further risk-mitigation was required.

Taken together, there are additional safety concerns besides known class effects and safety concerns derived from the non-clinical programme. Uncertainties regarding the IMM risk factors were addressed by extending the contraindication to patients with any deletion in exons 1 to 17 and/or 59 to 71. With regard to cardiac safety, a warning in the SmPC highlighting the lack of clinical experience in subjects with an ejection fraction <40% and the recent reporting of cardiomyopathies is warranted and was introduced by the applicant in responses. Furthermore, ECG and ECHO were included as required baseline testing.

2.5.10. Conclusions on clinical safety

The safety profile of delandistrogene moxeparvovec is limited with regard to the number of treated patients as well as the duration of follow-up, allowing to detect only frequently occurring events in the short-term. This is illustrated by e.g. anaphylaxis and hypersensitivity events being observed outside EU in the post-marketing setting with a puzzling difference in incidence between clinical trials and the post marketing setting in other regions.

The most common adverse reactions include vomiting, nausea, decreased appetite, increased transaminases, upper abdominal pain, and pyrexia. SAEs occurred in about 15% of all subjects. Significant safety issues include hepatotoxicity, myocarditis and IMM. Hepatotoxicity occurred in a high rate of approximately 40% of patients in the pivotal trial and throughout the clinical development program.

Newly submitted longer-term cardiac safety data confirmed the incidence of myocarditis at 1.6% in the pivotal trial and established cardiomyopathy as an important potential risk.

Late-breaking information with regard to two deaths was not included in the dossier with the responses to the D120 list of questions and this was asked to be further elucidated. The death of the teenage patient was due to acute liver failure related to Elevidys administration, the death of the other young adolescent patient was attributed to progression of the disease, indicating a lack of efficacy of treatment with SRP-9001.

Furthermore, the applicant has submitted information on two additional deaths that were reported since the original submission. Limited information is available, which does not suggest a role of SRP-9001 in the cause of death. However, in-depth assessment will only be possible when comprehensive information is available in both cases. In addition, during the Oral Explanation Meeting (June 2025), the CHMP were made aware of new fatalities that have emerged. These events will be further pursued in the context of clinical trials administration. Taken together, 8 fatalities occurred during the review phase of this procedure.

Altogether, the provided dataset suggests a number of serious safety issues, some of which are potentially life-threatening.

2.6. Risk Management Plan

The CHMP and PRAC, having considered the data submitted in the application, were of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed.

2.7. Product information

Due to the negative benefit-risk ratio, the product information could not be agreed.

3. Benefit-risk balance

DMD is an X-linked, degenerative, and invariably fatal neuromuscular disease caused by mutations within the dystrophin gene. Although muscle damage is evident from birth, the first concern reported by parents of children with DMD is most commonly a delay in the developmental milestone of walking. As children with DMD get older, they lose the ability to rise from the floor or climb stairs typically within the first decade of life and subsequently lose ambulation at a median age of 13 years if treated with corticosteroids (McDonald et al. 2018). However, estimates of the mean and median age at loss of ambulation varied considerably across cohorts exposed to corticosteroids (range: 8.60–10.30 years) and non-exposed cohorts (range: 10.00–13.40 years) (Landfeldt et al. 2024).

Due to the progressive nature of the disease and cardiorespiratory weakness, despite the standard of care, life expectancy is severely reduced, with a median age of 28.1 years (Broomfield et al. 2021).

DMD is considered to usually affect males, but female manifesting carriers have been described.

3.1.1. Available therapies and unmet medical need

Current management of DMD has been focused on supportive care, which includes management of respiratory, cardiac, endocrinological, orthopedic, gastroenterological, and psychological issues (Birnkrant et al. 2016; Passamano et al. 2012). Although these measures do provide symptomatic relief and modestly prolong ambulation and life span, no treatments aim at treating the underlying pathobiological cause of this progressive, debilitating and ultimately fatal disease.

Corticosteroids, such as prednisolone and deflazacort, are widely used as part of the standard of care for the treatment of DMD. The exact mechanism of corticosteroids in DMD is unknown but likely includes immunomodulatory and anti-inflammatory actions. Vamorolone (Agamree) is a modified corticosteroid that selectively binds to the glucocorticoid receptor, that is authorised specifically for DMD.

Givinostat (Duvyzat) is an oral histone deacetylase inhibitor targeting pathogenic processes to reduce inflammation and loss of muscle that has received a positive opinion for CMA by CHMP.

Exon-skipping therapies (eteplirsen, golodirsen, viltolarsen, casimersen) have shown very modest increases in dystrophin and functional benefit for a minority of patients with mutations amenable to their mechanism of action. None of these therapies are authorized for use in the European Union.

Effective treatment for DMD remains a highly unmet medical need as no current treatment options address the root cause of the disease and significantly modify the universally progressive declining disease trajectory resulting in a severely shortened life expectancy in patients with DMD.

3.1.2. Main clinical studies

The benefit-risk assessment of SRP-9001 is mainly based on the results of the pivotal Phase 3 RCT SRP-9001-301 (hereafter referred to as Study 301) in ambulatory patients with DMD aged 4 to <8 years, supplemented by data from the ongoing Phase 3 Trial 103. Both trials used the commercial Process B material. Further data derive from completed Phase 1/2 studies undertaken with Process A material and an external control cohort. As analytical comparability for Process A has not been shown, data from these studies are considered of limited relevance.

Study 301 is an ongoing 1:1 randomized, double-blind, placebo-controlled, 2-part study of systemic gene delivery of SRP-9001 in 125 male ambulatory subjects with DMD, who are ≥ 4 to < 8 years of age. The total duration of each subject's participation in the study is expected to be approximately 108 weeks, inclusive of an up to 4-week pre-infusion period and a 52-week treatment and follow-up period in Part 1 and in Part 2. All eligible subjects have the opportunity to receive IV SRP-9001 (1.33×10^{14} vg/kg) in either Part 1 or Part 2. No subjects discontinued from the study prior to Part 1 completion.

Study 103 is an ongoing, single-arm, open-label, single-dose study. Results from two (of seven in total) cohorts may be considered supportive for the intended indication: Cohort 1 (20 ambulatory DMD subjects aged ≥ 4 to < 8 years) and Cohort 4 (7 ambulatory DMD subjects aged ≥ 3 and <4 years). Following administration of a single SRP-9001 dose, subjects were planned to be followed up from Day 1 through Week 12 (Part 1) and Week 12 through Week 260 (Part 2).

3.2. Favourable effects

Primary efficacy endpoint

A mean increase (improvement) from Baseline to Week 52 in NSAA total scores was observed following SRP-9001 administration.

Secondary endpoints

For a subset of the SRP-9001 group (n=17), the mean (SD) micro-dystrophin level (% control) by Western blot adjusted to muscle content at Week 12 was 34.29% (41.04%). For a subset of the placebo group (n=14), the mean micro-dystrophin level was BLOQ. Treatment with SRP-9001 showed a higher mean micro-dystrophin level compared to placebo at Week 12 (nominal $p < 0.0001$).

A mean decrease (improvement) from Baseline to Week 52 in time to rise from the floor was observed in the SRP-9001 group but not in the placebo group. The LSM change difference between SRP-9001 and placebo groups at Week 52 was -0.64 (95% CI: -1.06, -0.23; nominal $p = 0.0025$).

A mean decrease (improvement) from Baseline to Week 52 in time to ascend 4 steps was observed in both the SRP-9001 and placebo groups. The LSM change difference between SRP-9001 and placebo groups at Week 52 was -0.36 (95% CI: -0.71, -0.01; nominal $p = 0.0412$).

A mean decrease (improvement) from Baseline to Week 52 in time of 10-meter timed test was observed in the SRP-9001 group but not in the placebo group. The LSM change difference between SRP-9001 and placebo groups at Week 52 was -0.42 (95% CI: -0.71, -0.13; nominal $p = 0.0048$).

A mean increase (improvement) from Baseline to Week 52 in SV95C was observed in the SRP-9001 group but not in the placebo group. The LSM change difference between SRP-9001 and placebo groups at Week 52 was 0.10 (95% CI: 0.00, 0.19; nominal $p = 0.0402$).

3.3. Uncertainties and limitations about favourable effects

As only studies 103 and 301 used Process B, the overall number of treated patients for the intended commercial material is limited.

Primary efficacy endpoint

A mean increase (improvement) from Baseline to Week 52 in NSAA total scores was observed in SRP-9001 and placebo groups. The LSM change difference (SE) between SRP-9001 and placebo groups at Week 52 was 0.65 (0.55); 95% CI: -0.45, 1.74; p=0.2441. The magnitude of LSM change difference in the SRP-9001 group compared to placebo (raw NSAA: 0.65) was not statistically significant and below the estimated MCID of 2.3-4 points.

For non-white children placebo performed better than SRP-9001), but sample size is low, resulting in a wide CI.

Since the primary endpoint was not statistically significant, the gatekeeping procedure stopped. For subsequent secondary endpoints, nominal p values are reported, without adjustment for multiplicity. Therefore, results for secondary endpoints were tested outside of Type I error control. The probability of falsely claiming efficacy in one or more of the secondary endpoints is therefore not controlled at the nominal level of 5%, calling into question the relevance of any nominally significant differences in secondary endpoints.

Secondary endpoints

As measured by NSAA, the number of skills gained (the average item score is 0 at Baseline and > 0 at Part 1 Week 52) or improved (the average item score at Baseline is > 0 but less than the average item score at Part 1 Week 52) was positive in both the SRP-9001 and placebo groups. The LSM change difference between SRP-9001 and placebo groups at Week 52 was 0.19 (95% CI: -0.67, 1.06; nominal p = 0.6554).

Micro-dystrophin expression in the SRP-9001 group was highly variable, no correlation with clinical function has been established, and no threshold for functionality is known. Furthermore, the assessment was performed only in a subset of patients.

As for the defined key secondary endpoint of micro-dystrophin expression at week 12, for this progressive, "muscle-wasting" disease persistence of micro-dystrophin expression and function are more relevant, but considerable concerns on durability exist based on available, though limited, clinical pharmacology data, indicating high variability.

Despite nominal statistical significance, the LSM change differences for time to rise from the floor (-0.64 seconds) and 10-meter timed test (-0.42 seconds) were below the respective MCID of 3.6-3.7 seconds for TTR, and 1.4-2.3 seconds for 10MWR (McDonald et al, 2013). When converted to a velocity metric, a TTR of 0.04 rise/s would exceed the reported MCID of 0.023 rise/s, but not 10MWR (observed difference: 0.17 m/s; MCID: 0.212 m/s; Duong et al, 2021).

The short-term findings on TTR and 10MWR are considered a snapshot only, and are not suited to confirm efficacy on their own. The improvements at Week 52 are not maintained until Week 104.

In study 102, several subjects had considerably high (up to 30.18%) micro-dystrophin protein expression levels detected at baseline.

3.4. Unfavourable effects

The adverse event profile observed in the randomised, placebo controlled pivotal trial 301 shows that the most frequently reported AEs irrespective of causality were vomiting, nausea, decreased appetite, pyrexia, COVID-19 and GLDH increased in the treatment arm. These events were also reported in the placebo arm, but at substantially lower frequencies. The most frequent treatment related AEs were vomiting, nausea, decreased appetite and GLDH increased. The majority of events were of mild or moderate intensity and occurred during the first 60 days after treatment. The safety profile in the All subjects population and the Process B 4-<8 years population were comparable.

22% of subjects in the SRP-9001 group in the pivotal trial versus 8% in the placebo group reported SAEs. Of these, SAEs in 11% of subjects were considered treatment-related in the SRP-9001 arm vs. 0% in the placebo arm. Most of the SAEs that were considered treatment-related were also captured as AESIs.

In the pivotal study, the following events were defined as **AESIs**: hepatotoxicity, myositis, thrombotic microangiopathy, hypersensitivity, thrombocytopenia, rhabdomyolysis and troponin elevations.

Hepatotoxicity was the most frequently observed AESI. Approximately 40% of subjects treated with SRP-9001 developed signs or symptoms of hepatotoxicity in the pivotal trial. The majority of these events were reported within the first 90 days after treatment. All events could be managed with steroids and had a maximum duration of 77 days in the pivotal study. 5 of 26 subjects needed to be treated with IV steroids, while the remaining 21 subjects could be managed with oral steroids. Approximately 10 % of subjects had severe AEs of hepatotoxicity. In the All Subjects population, the incidence, severity and time to onset of this AESI as well as the use of oral and IV steroids was comparable.

Immune-mediated myositis, induced by an immune reaction against the transgene product, is an important unwanted effect of gene therapy for DMD. In the pivotal trial, the incidences of muscular weakness and other muscular events were comparable in the placebo and treatment group. In trial 103, two subjects reported severe reactions, one of which was life-threatening. Both resolved with sequelae, with muscle strength and function improved but reaching a level below baseline.

Troponin increase and/ or myocarditis can be expected as a potential complication of treatment with SRP-9001, as the myocardium is a target tissue for the AAV vector. In the pivotal trial 301, one subject reported an SAE of myocarditis, while one additional subject in the treatment group as well as two subjects in the placebo group were found to have increased troponin values. The incidences of troponin increase/ myocarditis-related AEs was comparable in the All subjects and Process B population, at approximately 12%.

The applicant has provided updated 2-year safety data from the patients treated in Part 1 of the pivotal trial 301, with the incidence of myocarditis remaining at 1.6%. Updated data from study 103 demonstrate multiple elevations of troponin without clinical symptoms and sequelae. DMD patients have been demonstrated to have intermittent asymptomatic cTnI elevations (Sheybani et al; DOI: 10.1038/s41390-021-01682-5), thus rendering the cTnI assay of unclear relevance for safety monitoring.

Two cases of cardiomyopathy have been reported. One 11-year-old boy experienced cardiomyopathy and myocarditis on Day 4 and resolved on Day 254 after infusion of SRP-9001 in trial 103. One late breaking case report of an 11 year old subject treated at the age of 6 in study 102 with Process A material, who developed decreased LV function 4.5 years after the initial treatment illustrates the potential for an acceleration of the myocardiopathy inherent to DMD with symptoms only manifesting years after the treatment.

No cases of **TMA** were observed throughout the clinical study programme.

Only few **hypersensitivity** AEs were considered related to treatment in trials 101, 102, 103 and 301, but late-breaking data from other ongoing trials as well as post-marketing reports reported hypersensitivity as well as anaphylaxis events.

Several instances of **rhabdomyolysis** were observed. While this condition is a known complication of the underlying disease, especially with increased physical activity, dehydration or certain anaesthetics, there were at least two instances of rhabdomyolysis early after treatment (day 3 and day 16), with one SAE considered as treatment-related. It is agreed that the criteria for an important identified risk were not met. However, as rhabdomyolysis has been reported in multiple cases throughout the clinical development, it should be listed as an important potential risk.

Two late breaking deaths occurred during the clinical development programme, and more information was requested on both cases. The death of the adolescent patient was due to acute liver failure related to Elevidys administration, the death of the young adolescent patient was attributed to progression of the disease, indicating a lack of efficacy of treatment with SRP-9001.

Furthermore, the applicant has submitted information on two additional deaths that were reported since the last dossier submission. Limited information is available, which does not suggest a role of SRP-9001 in the cause of death. However, in-depth assessment will only be possible when

comprehensive information is available in both cases. During the Oral Explanation Meeting (June 2025), the Rapporteurs were made aware of new fatalities that have emerged. These events will be further pursued in the context of clinical trials administration.

Anti-AAV antibody titres were below 1:400 at the time of enrolment for all subjects and increased rapidly until week 10 to a maximum of 1:4,771840.0. Afterwards, titres decreased but stayed elevated at a level that is considered prohibitive to another treatment attempt with the same or a related AAV vector.

3.5. Uncertainties and limitations about unfavourable effects

Due to the small size of the safety database, only AEs with a frequency of up to "frequent" can be detected.

Gene therapy is a treatment with a potential for late occurring adverse events, as the treatment is given once but cannot be stopped or reversed. With regard to that, the duration of follow-up of approximately 1 year for subjects in the pivotal trial is considered to cover short-term safety only.

Following the two events of immune-mediated myositis in trial 103, the Sponsor amended the exclusion criteria of the pivotal trial 301, leading to an exclusion of mutations in exons 1-17. In the SmPC, however, only a contraindication for any deletion in exon 8 and/or exon 9 in the DMD gene is proposed. While the investigations of cellular and humoral immunogenicity are acknowledged, the observed ex-vivo cellular immune response did not always correlate to peptides concordant with mutation sites in the dystrophin gene. Therefore, it is still considered uncertain if in fact only mutations in these two exons are likely to lead to such severe cases of myositis with a resulting permanent loss of function. In order to minimise the risk for IMM, the contraindication of treatment was extended to patients with any deletion in exons 1 to 17 and/or 59 to 71 in the DMD gene.

As the cardiac muscle is weakened by dystrophin deficiency, cardiomyopathy develops early in life, leading to heart failure. As a safety precaution, subjects with an ejection fraction <40% or clinical signs or symptoms of cardiomyopathy were excluded from the clinical trials. Furthermore, ECG and ECHO were included as required baseline testing. In addition, another important limitation of the available safety data relates to long-term cardiac safety, as it is unclear whether the replacement of utrophin by high levels of micro-dystrophin expression in cardiomyocytes may trigger premature cardiac deterioration.

Further uncertainty concerns the risk of DRG (Dorsal root ganglia) toxicity. The non-clinical program does not allow a valid evaluation of DRG toxicity. Hence, it remains unclear if DRG toxicity may be a potential risk.

No infusion related reactions were reported in the clinical trials, while several reports of such events in the post marketing setting have been reported. The assumption that the differences in the IRR rate in pre and post marketing are solely based on the rare occurrence is not considered conceivable. The applicant was asked to specify reasons for the different IRR rate more in depth, also considering the use of filters and the different specification of the Process A and B drug material (e.g. amount of capsids). In response to the D180 LoOI, the applicant has provided additional information regarding the frequency of IRRs overall and serious IRRs in clinical trials and the post marketing setting. Filters or the manufacturing process were ruled out as possible root causes. While a higher overall frequency of IRRs has been reported in the post-marketing phase, no difference in the rate of serious IRRs has been observed in either setting.

3.6. Effects table

Table 26: Effects table for SRP-9001 (clinical data cut-off: 13 September 2023)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
NSAA	17-item rating scale to measure functional motor abilities	Total score (LSM change (SE) from Baseline to Week 52)	2.57 (0.39)	1.92 (0.39)	Primary endpoint; LSM change difference not statistically significant and below the estimated MCID	Study 301
TTR	Timed function test	Seconds (LSM change (SE) from Baseline to Week 52)	-0.27 (0.15)	0.37 (0.15)	Not Type I error controlled, as primary endpoint failed	Study 301
10MWR	Timed function test	Seconds (LSM change (SE) from Baseline to Week 52)	-0.34 (0.10)	0.08 (0.10)	Not Type I error controlled, as primary endpoint failed	Study 301
Unfavourable Effects						
(original data cut, except for cardio-myopathy)	**All subjects population**		N=207		Includes Process A treated subjects; includes non-randomised trials 101 and 103	
Hepato-toxicity	Liver function tests increases		36.6		Severe events, significant number of patients requiring additive immunosuppression, one death due to hepatotoxicity in the post-marketing setting	
IMM (immune mediated myositis)	Asthenia, dysphonia, muscular weakness, myositis		5.8 Resolved with sequelae: 1.0			
Cardio-myopathy	1 case in trial 102 + 1 case in trial 103		0.9			
Myocarditis/ troponin I increase			8.2			
Post-marketing:	Estimated size of overall safety database		N=800			

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Deaths (cut-off date: May 09, 2025)			4		All reported post-marketing; 1 death due to liver failure, 1 death due to progression of the disease, 2 cases late breaking with limited data available	

Abbreviations: TTR=time to rise, 10MWR=10-meter timed test

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The NSAA is a validated tool to reliably assess clinically relevant functional motor abilities in ambulant children with DMD. However, in the single pivotal trial, the primary efficacy endpoint, change in NSAA from Baseline to Week 52, was not met. The difference to placebo (0.65) was not statistically significant (p=0.2441) and clearly below the estimated MCID of 2.3 points (Ayyar Gupta et al, 2023). Since the primary endpoint was not statistically significant, results for secondary endpoints are not Type I error controlled, and false positive results cannot be excluded.

For some clinically relevant timed function tests, results were nominally statistically significant in favour of SRP-9001: time to rise from the floor (TTR), time of 10-meter timed test (10MWR), and time to ascend 4 steps. However, the observed differences are below their respective MCID (McDonald et al, 2013), unless TTR or time to ascend 4 steps were converted to a velocity metric (Duong et al, 2021). Importantly, these results may be coincident findings rather than indication of a true treatment effect due to the lack of Type I error control. Hence, clinical benefit cannot be concluded from these data.

The available safety data of delandistrogene moxeparvovec is limited with regard to the number of treated patients as well as the duration of follow-up, allowing to detect only frequently occurring events in the short-term. The most frequent treatment related AEs were vomiting, nausea, decreased appetite and GLDH increased. The most frequently observed AESI was hepatotoxicity, which occurred in ~40% of subjects. While the majority of these events were of mild or moderate intensity and manageable with standard of care, some AESI which were also reported as SAE are considered to be of concern.

One of the major concerns is the development of IMM with a potentially life-threatening course or sequelae that could lead to a significant deterioration in clinical outcome. In order to minimise the risk for IMM, the contraindication of treatment was extended to patients with any deletion in exons 1 to 17 and/or 59 to 71 in the DMD gene. Hepatotoxicity, myocarditis and rhabdomyolysis have also been described as serious events that can result in extensive clinical intervention.

Two cases of cardiomyopathy have been reported, of which one (occurring 4.5 years after the initial treatment) illustrates the potential for an acceleration of the myocardiopathy inherent to DMD with symptoms only manifesting years after the treatment.

Notably, a high rate of patients required additional immunosuppression; in the All Subjects Population of n=207, additional corticosteroids for the treatment of hepatotoxicity were administered to n=14, for the treatment of IMM to n=2 in combination with tacrolimus and for the treatment of troponin increase and myocarditis to n=1). In order to encompass the full extent of the safety aspects related to the administration of delandistrogene moxeparvovec, the risks of immunosuppression must also be considered when assessing the benefit/risk of delandistrogene moxeparvovec.

3.7.2. Balance of benefits and risks

Clinically relevant endpoints show at best a very modest to no treatment effect at all.

The safety profile of delandistrogene moxeparvovec exceeds the risks expected from AAV class effects and observed in the non-clinical programme. Severe immune responses against the transgene have been reported; the risk factors to develop IMM still remain uncertain. Importantly, a large proportion of the patients treated with delandistrogene moxeparvovec developed hepatotoxicity, with one late breaking death due to acute serious liver injury reported. Troponin I increase, myocarditis, rhabdomyolysis and the potential acceleration of cardiomyopathy also need to be considered as significant safety concerns. Immunogenicity required additional immunosuppression in a large number of patients.

In the absence of robustly demonstrated efficacy and in the presence of considerable safety risks, the balance of benefits and risks remains unfavourable.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

While it is agreed in principle that a Conditional Marketing Authorisation could be an appropriate regulatory pathway for a gene therapy medicinal product in the treatment of a life-threatening orphan disease, the prerequisites for such an approval are considered not to be met by the dossier for Elevidys:

- The benefit-risk balance is positive.

  The benefit-risk balance is considered to be negative, as the burden of treatment and the observed as well as the potential risks are not outweighed by clinically relevant and sustained improvements in efficacy.

- It is likely that the applicant will be able to provide comprehensive data.

  Despite amendments to the outline of the proposed sub-study of Study 305, it is not deemed suitable to robustly demonstrate clinical efficacy in the study population. Taking into account the failed pivotal RCT it is doubtful that the proposed sub-study will provide more comprehensive clinical data.

- Unmet medical needs will be addressed.

  The considerable unmet medical need for a disease-modifying treatment in DMD is acknowledged, but Elevidys has not demonstrated a clinical benefit in the failed pivotal trial 301. The evidence provided by the totality of the submitted data is not considered to be sufficient due to its reliance mainly on the presence of micro-dystrophin in muscle biopsies. A convincing demonstration of the functionality of micro-dystrophin and its integration into biologically functional complexes is missing, as well as a correlation of observed micro-dystrophin levels and efficacy outcomes.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

  As a treatment effect has not been demonstrated and the benefit-risk is considered negative, and in view of the uncertainties remaining, an immediate availability of the product cannot be warranted.

The product is not recommended for a conditional marketing authorisation as the benefit-risk balance is negative, the applicant is unlikely to be able to provide comprehensive data after authorisation, it has not been demonstrated that the product will address an unmet medical need, and the benefits to public health of the immediate availability do not outweigh the risks inherent in the fact that additional data are still required.

Patient engagement

Input from Patient Organisation – WDO (World Duchenne Organisation)

The WDO is a global umbrella organisation of national patient organisations. They are dedicated to finding a cure and viable treatments for DMD, to promoting good standards of care, and to inform parents and people living with the condition around the globe.

WDO emphasised the considerable burden of care for caregivers of individuals with Duchenne, which is shouldered mainly by parents and negatively influences their quality of life. The unmet medical need for disease-modifying treatments persists despite decades of preclinical and clinical research.

The main concerns expressed by WDO pertained to the unknown durability of the effect of a gene therapy, the optimal age for dosing and the lack of long-term safety and efficacy data. In addition, measures to protect patients receiving treatment in clinical practice from serious complications observed in clinical trials were considered important. Follow-up data on the current status of individuals who suffered from immune-mediated myositis/ myocarditis post gene therapy were requested.

Specific concerns regarding efficacy overall reflect the Rapporteurs' concerns, which include the limitations of supportive studies using Process A material (not intended for commercial use), the exclusion of patients <4 years of age, and substantial concerns on the attributability of the (short-term) treatment effect to SRP-9001 versus the effects of immunosuppression, as well as on durability based on patients' families' experiences.

3.8. Conclusions

The overall benefit /risk balance of Elevidys is negative.

The CHMP endorse the CAT conclusion on Benefit Risk balance as described above.

4. Recommendations

Based on the CAT review of data on quality, safety and efficacy for Elevidys in the treatment of Duchenne Muscular Dystrophy, the CHMP considers by consensus that the efficacy of the above-mentioned medicinal product is not sufficiently demonstrated, and therefore recommends the refusal of the granting of the conditional marketing authorisation for the above-mentioned medicinal product. The CHMP considers that:

Whereas

- Efficacy of Elevidys has not been established in the pivotal trial. This study did not meet its primary objective and post-hoc subgroup analyses can be considered hypothesis-generating only.

- Requirements for a conditional marketing authorisation as set out in Article 4 of Commission Regulation (EC) No 507/2006 are not fulfilled.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and post authorisation measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

Furthermore, following review of the available data in the context of the applicant's claim of new active substance status, the CAT position at the time of this report is reflected in the appendix. However, in light of the negative recommendation, the CAT is of the opinion that it is not appropriate to conclude on the new active substance status.