



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Office of Biostatistics and Pharmacovigilance (OBPV)
Division of Pharmacovigilance (DPV)**

PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM

From: Brendan Day, MD, MPH
Medical Officer, Pharmacovigilance Branch 2
(PB2), DPV, OBPV, CBER, FDA

To: Emmanuel Adu-Gyamfi, PhD
Chair of the Review Committee
Office of Tissues and Advanced Therapies

Through: Christopher Jason, MD
Branch Chief, PB2

Meghna Alimchandani, MD
Deputy Director, DPV
OBPV, CBER, FDA

Subject: Review of Pharmacovigilance Plan

Sponsor: Sarepta Therapeutics, Inc.

Product: ELEVIDYS (Delandistrogene moxeparvovec)¹

Application Type / Number BLA 125781/0

Proposed Indication Treatment of ambulatory patients with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the DMD gene

Submission Date: September 28, 2022

Action Due Date: May 29, 2023 (original PDUFA ADD); June 22, 2023 (modified)

¹ The product was referred to as SRP-9001 during product development.

1 OBJECTIVE

The purpose of this review is to assess the adequacy of the sponsor's pharmacovigilance plan (PVP) submitted under the original BLA 125781/0 based on the safety profile of Delandistrogene moxeparvovec (also referred to in this memo by the name used during product development: SRP-9001). Our review will determine whether any safety-related studies such as Post-Marketing Requirements (PMRs) and/or Post-Marketing Commitments (PMCs) are warranted, or if Risk Evaluation and Mitigation Strategies (REMS) are required for SRP-9001, should this product be approved. Please refer to Appendix A1 for the complete list of materials reviewed for this memorandum.

2 BACKGROUND

Duchenne muscular dystrophy (DMD) is a severe, progressive muscle-wasting disease caused by mutations in the *DMD* gene, which encodes dystrophin, a large cytoskeletal protein that is necessary for normal muscle fiber structure and function (1, 2). Although primarily expressed in skeletal and cardiac muscle, dystrophin is also found in the brain and retina. Because DMD is an X-linked recessive defect, most individuals with DMD are male, although female carriers can rarely display symptoms (2). The estimated birth prevalence of DMD ranges from 15.9 to 19.5 per 100,000 live male births whereas estimated the point prevalence of DMD ranges from 1.9 to 10.9 per 100,000 males (3).

DMD typically presents around 2-3 years of age with difficulty climbing stairs, walking, or frequent falls. Due to ongoing muscle damage, laboratory testing shows abnormally high levels of creatinine kinase (CK), alanine aminotransferase (ALT), and aspartate aminotransferase (AST). Individuals with DMD experience progressively worsening muscle weakness, with most individuals becoming wheelchair-bound by 10-12 years of age and requiring ventilation assistance around 20 years of age (1). Intellectual impairment, including learning and behavioral difficulties, and DMD-associated cardiomyopathy are common in individuals with DMD (2). Although life expectancy has improved in recent decades, most individuals with DMD die between ages 20 and 40 years from cardiac or respiratory complications (1). Treatment of DMD requires a multidisciplinary approach to address both the physical and psychosocial aspects of the disease (1, 4). From a pharmacologic standpoint, glucocorticoids are the cornerstone of therapy, although other therapies are emerging (e.g., mutation-specific therapies are now available for certain patients) (4).

The goal of SRP-9001 is to compensate for the deficiency in functional dystrophin in DMD patients by introducing expression of a functional shortened SRP-9001 dystrophin protein (also called "micro-dystrophin") in muscle cells. This micro-dystrophin is expected to increase and preserve strength and protect muscles from contraction-induced injury. SRP-9001 is a recombinant adeno-associated virus (AAV) gene therapy product comprised of three components: 1) vector: a non-replicating, recombinant, AAV serotype rh74 (AAVrh74) vector, 2) promoter: a MHCK7 gene regulatory component comprising a creatine kinase 7 promoter and an α -myosin heavy chain enhancer, 3) transgene, contained in the ELEVIDYS micro-dystrophin protein expression cassette. Therefore, the proposed mechanism of action for SRP-9001 is the transduction and

subsequent expression of a micro-dystrophin encoding transgene in skeletal and cardiac muscle cells.

3 PRODUCT INFORMATION

3.1 Product Description

ELEVIDYS (delandistrogene moxeparvovec-rokl) is a recombinant gene therapy designed to deliver the gene encoding the ELEVIDYS micro-dystrophin protein. It is a non-replicating, recombinant, adeno-associated virus serotype rh74 (AAVrh74) based vector containing the ELEVIDYS micro-dystrophin transgene under the control of the MHCK7 promoter. The genome within the ELEVIDYS AAVrh74 vector contains no viral genes and is consequently incapable of replication or reversion to a replicating form.

ELEVIDYS is a preservative-free, sterile, clear, colorless liquid that may have some opalescence and may contain white to off-white particles. ELEVIDYS is a solution for intravenous infusion with a concentration of 1.33×10^{13} vg/mL and supplied in a single-use 10 mL vial. Each vial contains an extractable volume of 10 mL and the following excipients: 200 mM sodium chloride, 13 mM tromethamine HCl, 7 mM tromethamine, 1 mM magnesium chloride, 0.001% poloxamer 188.

3.2 Proposed Indication

The sponsor's proposed indication statement as submitted to the original BLA 125781/0 is:

"ELEVIDYS is indicated for the treatment of ambulatory patients with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the *DMD* gene. This indication is approved under accelerated approval based on an increase of ELEVIDYS micro-dystrophin protein expression reasonably likely to predict clinical benefit observed in patients treated with ELEVIDYS [see *Clinical Studies* (14)]. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials."

Reviewer comment: OBPV defers to the product office on the final language for the indication statement. Should this product be approved, please refer to the final version of the Package Insert submitted by the sponsor for any final agreed-upon language regarding indication after FDA review and the approval letter for description of the confirmatory trial postmarketing requirement under Accelerated Approval. Furthermore, OBPV defers to product office with regards to (b) (4)

4 PERTINENT REGULATORY HISTORY

4.1 SRP-9001

The Sponsor submitted a Biologics License Application (BLA) for accelerated approval of Delandistrogene moxeparvovec (SRP-9001), including a request for Priority Review, on September 28, 2022. Development of SRP-9001 was designated as a Fast Track development program on June 3, 2020, and SRP-9001 received orphan drug status on June 21, 2018. On November 18, 2022, in a meeting with the Center Director, the

clinical reviewer recommended that the FDA refuse to file (RTF) the application citing concerns about a lack of demonstrated efficacy and inadequacy of the submitted clinical studies. However, this recommendation was overruled and on November 25, 2022, the application was filed and classified as a Priority review. On May 12, 2023, the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) convened to discuss the application. The committee members voted 8-6 in support of Accelerated Approval of SRP-9001—using as a surrogate endpoint, expression of Sarepta’s micro-dystrophin at Week 12 after administration of SRP-9001—for the treatment of ambulatory patients with Duchenne muscular dystrophy with a confirmed mutation in the DMD gene. SRP-9001 has not been approved by any foreign regulatory agencies.

4.2 Class Safety Concerns for AAV Gene Therapy

On September 2-3, 2021, the FDA’s CTGTAC convened to discuss “Toxicity Risks of Adeno-associated Virus (AAV) Vectors for Gene Therapy.” The CTGTAC discussed serious and life-threatening risks associated with AAV gene therapy including hepatotoxicity (the most common adverse event associated with systemic AAV therapy), thrombotic microangiopathy (including cases of atypical hemolytic uremic syndrome in DMD subjects), neurotoxicity (including dorsal root ganglion toxicity) and oncogenicity (a potential risk of integration and insertional mutagenesis based on findings from animal studies) (5, 6). Given the potential for delayed adverse events (such as oncogenicity), the FDA recommends up to five years duration for any long-term follow up studies for AAV vectors (7).

Four AAV gene therapy products have been approved by the FDA since 2017 (Table 1). Like SRP-9001, two of these products (Zolgensma and Hemgenix) are systemically administered in a single dose; both products have voluntary registry-based postmarketing safety studies. Zolgensma, which is indicated for the treatment of Spinal Muscular Atrophy (Type I), is the systemic AAV gene therapy product with the most postmarketing experience to date. Since initial approval in 2019, FDA has issued two Section 921 postings for Zolgensma: one for “thrombotic microangiopathy (TMA)” based on four postmarketing cases of TMA and one for “fatal hepatotoxicity” based on two postmarketing cases of fatal hepatotoxicity. The Section 921 posting for “thrombotic microangiopathy” resulted in Package Insert updates to ‘Warnings and Precautions’ and ‘Postmarketing Experience.’ The Section 921 posting for “fatal hepatotoxicity” resulted in Package Insert updates to ‘Boxed Warning,’ ‘Warnings and Precautions,’ and ‘Postmarketing Experience.’ The postmarketing findings of “fatal hepatotoxicity” also prompted a dear healthcare provider letter (DHCP), submitted on July 27, 2022, which mentions that over 2000 patients had been treated worldwide “across clinical trials, managed access programs, and in the commercial setting” (STN 125694/335). (b) (4)




Table 1. FDA-approved AAV gene therapy products

Product Name	Initial FDA Approval	Route of Administration
Luxturna (voretigene neparvovec-rzyl)	12/19/2017	Intraocular
Zolgensma (onasemnogene abeparvovec-xioi)	5/24/2019	Intravenous
Hemgenix (etranacogene dezaparvovec-drlb)	11/22/2022	Intravenous
Adstiladrin (nadofaragene firadenovect-vncg)	12/16/2022	Intravesical

Abbreviations: Adeno-associated virus (AAV)

5 DESCRIPTION OF SRP-9001 CLINICAL TRIAL SAFETY DATABASE

5.1 Clinical studies

The clinical study safety data reviewed are from the Summary of Clinical Safety (Module 2.7.4) and the interim Clinical Study Reports for Studies SRP-9001-101, SRP-9001-102 (Parts 1 and 2), and SRP-9001-103 (Module 5.3.5) submitted to BLA 125781/0. Late-breaking clinical safety data were also reviewed from the 120-Day Safety Update Report (BLA 125781/0.17). OBPV defers to the product office on final review of the clinical database, including safety and efficacy outcomes, which will inform the final language in the USPI. Below is our *focused* review of the sponsor data initially submitted to the BLA, to inform decisions pertaining to pharmacovigilance planning, should this BLA 125781/0 be approved. Please refer to the Package Insert for the final clinical safety data.

Four ongoing clinical studies are evaluating the use of SRP-9001 in individuals with DMD (Table 2). Two different manufacturing processes were used for the product used in these studies, with the earlier development process referred to as Process A and the intended commercial process referred to as Process B. Two ongoing clinical studies are evaluating use of the “to-be-marketed” Process B material (SRP-9001-103 and SRP-9001-301). The Sponsor submitted safety data from three of the four ongoing clinical studies, excluding their largest study (SRP-9001-301), which is a Phase 3, randomized, double-blind, placebo-controlled study using Process B material.

Reviewer comment: The clinical studies submitted in support of this BLA have a number of limitations with regards to safety: 1) they use two different process materials, we defer to CMC and clinical reviews regarding the comparability of the two processes, 2) they are of limited size and duration of follow up, 3) two studies are single arm, open-label, which introduces bias, 4) only select AEs were reported from the largest Phase 3 randomized controlled study (SRP-9001-301), and 5) none of the submitted clinical studies are completed (interim safety data submitted for review). Having limited safety data from Phase 3 randomized controlled studies leads to greater uncertainty regarding the safety of the product. The duration of follow up from these studies is not sufficient to rule out long-term AEs.

Table 2. Summary of clinical studies supporting the safety of SRP-9001*

Study	N	Description
SRP-9001-101 <i>Process A material</i>	4	Phase 1/2a, first-in-human, open-label, single-arm, proof-of-concept study conducted at a single site in the US to evaluate safety, micro-dystrophin expression, and physical function after a single dose of Process A material SRP-9001 (1.33×10^{14} vg/kg) in ambulatory subjects aged 4 to <8 years with DMD.
SRP-9001-102 <i>Process A material</i>	41	Phase 2, randomized, three-part, double-blind, placebo-controlled (part 1), crossover (part 2) then open-label (part 3) study conducted at two sites in the US to evaluate safety, micro-dystrophin expression, and physical function after a single dose of Process A material SRP-9001 in ambulatory subjects aged 4 to <8 years with DMD. Three dose levels were administered in part 1: <ul style="list-style-type: none"> • 6.29×10^{13} vg/kg (6 subjects) • 8.94×10^{13} vg/kg (6 subjects) • 1.33×10^{14} vg/kg (8 subjects) All subjects in Part 2 who received SRP-9001 received 1.33×10^{14} vg/kg (21 subjects).
SRP-9001-103 <i>Process B material</i>	39	Phase 1b, open-label, single-arm study conducted at five sites in the US to evaluate safety, micro-dystrophin expression, vector shedding, and immunogenicity after a single dose of Process B (to-be-marketed) material SRP-9001 (1.33×10^{14} vg/kg for subjects < 70 kg; 9.31×10^{15} vg for subjects ≥ 70 kg) in subjects with DMD in four cohorts: <ul style="list-style-type: none"> • Cohort 1: 20 male DMD ambulatory subjects (≥ 4 to < 8 years of age at Screening); • Cohort 2: 7 male DMD ambulatory subjects (≥ 8 to < 18 years of age at Screening); • Cohort 3: 6 male DMD non-ambulatory subjects (no age restriction); and • Cohort 4: 6 male DMD ambulatory subjects (≥ 3 to < 4 years of age at Screening).
SRP-9001-301† <i>Process B material</i>	88‡	Phase 3, multinational, randomized, double-blind, placebo-controlled, crossover study to evaluate safety and immunogenicity after a single dose of either Process B material SRP-9001 (1.33×10^{14} vg/kg) or placebo (1:1 randomization) in ambulatory male subjects with DMD aged 4 to <8 years.

Abbreviations: Duchenne muscular dystrophy (DMD), vector genome (vg)

*Adapted from: Table 1 “Listing of SRP-9001 Clinical Studies” (module 5.2 Tabular Listing of All Clinical Studies) and Table 1 “Clinical Studies Supporting the Safety of SRP-9001” (module 2.7.4 Summary of Clinical Safety)

†Aggregate safety data from this study was not submitted for FDA review. However, it is included in this table because select AEs were included in safety data submitted for review.

‡Number of subjects dosed (SRP-9001 or placebo) up to August 12, 2022.

5.2 Adverse events

5.2.1 Integrated Safety Data

Because the study populations in the submitted clinical studies were of limited size, this reviewer included a review of pooled data from the “Integrated safety data” submitted by the Sponsor. Integrated safety data from three clinical studies (SRP-9001-101, SRP-9001-102, and SRP-9001-103) was evaluated in the Summary of Clinical Safety (Module 2.7.4). Two analysis sets were used: 1) a Primary Analysis Set (comprised of 20 subjects treated with SRP-9001 in Study SRP-9001-102 and 20 placebo controls) and 2) an Exposure Analysis Set (comprised of 84 subjects across the three studies who were treated with SRP-9001). Unless otherwise stated, the safety results discussed in this subsection refer to the Exposure Analysis Set.

Most common AEs

The five most common adverse events (AEs) experienced by recipients of SRP-9001 were vomiting (n=52; 61.9%), decreased appetite (n=40; 47.6%), upper respiratory tract infection (n=34; 40.5%), nausea (n=34; 40.5%) and pain in extremity (n=24; 28.6%) (Table 3). Temporal patterns for gastrointestinal and hepatotoxicity events were observed, with vomiting typically occurring within two weeks and hepatotoxicity typically occurring within 60 days. Lastly, the Sponsor performed an analysis of exposure-adjusted incidence rates (EAIR) and found the following systemic PTs to have an “elevated risk” (more than double risk compared to placebo): vomiting, nausea, abdominal pain, pyrexia, arthralgia, rhabdomyolysis, irritability, and sleep disorder. Local PTs with an “elevated risk” included vessel puncture site hemorrhage, skin abrasion, limb injury and ecchymosis. When restricting to only events considered “treatment-related” by the study investigator, the following PTs still had an “elevated risk”: vomiting, nausea, abdominal pain, and rhabdomyolysis.

Table 3. Twenty most common adverse events following SRP-9001 (Exposure Analysis Set)*

Rank	Preferred Term	n	%
1	Vomiting	52	61.9
2	Decreased appetite	40	47.6
3	Nausea	34	40.5
4	Upper respiratory tract infection	34	40.5
5	Pain in extremity	24	28.6
6	Abdominal pain upper	23	27.7
7	Irritability	23	27.4
8	Procedural pain	22	26.2
9	Pyrexia	19	22.6
10	Cough	18	21.4
11	Headache	18	21.4
12	Fatigue	17	20.2
13	Gamma-glutamyltransferase increased	15	17.9
14	COVID-19	14	16.7

15	Glutamate dehydrogenase decreased	14	16.7
16	Diarrhea	13	15.5
17	Incision site hemorrhage	13	15.5
18	Rhinorrhoea	13	15.5
19	Viral infection	13	15.5
20	Constipation	11	13.1

*Table adapted from Table 2.2.1.2, Integrated Summary of Safety Tables (Module 5.3.5.3)

Reviewer comment: In addition to the common AEs in Table 3, the AE “Liver function test increased” (an aggregate of several PTs: AST increased, ALT increased, GGT increased, GLDH increased, hepatic enzyme increased, transaminases increased, and blood bilirubin increased) is identified in the PVP as “very common” (n=30; 35.7%). Thrombocytopenia is also highlighted in the PVP as being “very common” (n=10; 11.9%).

SAEs

A total of 14 serious adverse events (SAEs) were reported by 12 (14.3%) recipients of SRP-9001 (two subjects reported two SAEs each). According to the study investigator’s assessment, 10 of these SAEs were treatment related (Table 4). All participants who experienced SAEs recovered without sequelae, except for two participants: 1) subject (b) (6) recovered from immune-mediated myositis with residual weakness, and 2) subject (b) (6) recovered from myocarditis with the addition of two cardiac medications.

Table 4. Serious adverse events following SRP-9001 (Exposure Analysis Set)*

#	Study; Treatment	Subject	PT	Relatedness
1	SRP-9001-102 (Part 1); Placebo	(b) (6)	Rhabdomyolysis	Yes
2	SRP-9001-102 (Part 1); Placebo	(b) (6)	Humerus fracture	No
3	SRP-9001-102 (Part 1); SRP-9001	(b) (6) **	Rhabdomyolysis	Yes
4	SRP-9001-102 (Part 1); SRP-9001	(b) (6)	Liver injury	Yes
5	SRP-9001-102 (Part 1); SRP-9001	(b) (6)	Rhabdomyolysis	Yes
6	SRP-9001-102 (Part 1); SRP-9001	(b) (6)	Transaminases increased	Yes
7	SRP-9001-102 (Part 2); SRP-9001	(b) (6)	Appendicitis	No
8	SRP-9001-102 (Part 2); Placebo	(b) (6)	Femur fracture	No
9	SRP-9001-102 (Part 2); Placebo	(b) (6) **	Femur fracture	No
10	SRP-9001-103; SRP-9001	(b) (6)	Transaminases increased	Yes

11	SRP-9001-103; SRP-9001	(b) (6)		Vomiting	Yes
12	SRP-9001-103; SRP-9001	(b) (6)	***	Immune-mediated myositis	Yes
13	SRP-9001-103; SRP-9001	(b) (6)		Vomiting	Yes
14	SRP-9001-103; SRP-9001	(b) (6)	***	Myocarditis	Yes

*Adapted from Table 13 in Summary of Clinical Safety (page 39-40), Table 31 in interim Clinical Study Report for Study SRP-9001-102 (Part 1) (page 84), Table 25 in interim Clinical Study Report for Study SRP-9001-102 (Part 2) (page 71)

**Treated with SRP-9001 in Part 1 of Study SRP-9001-102 but did not receive treatment in Part 2

***Recovered with sequelae

Reviewer comment: Although Study SRP-9001-301 was not included in the Summary of Clinical Safety, the Sponsor also noted a single Suspected Unexpected Serious Adverse Reaction (SUSAR) case of rhabdomyolysis in from this study.

Deaths

No deaths were reported as of the data cutoff dates for each study in the Summary of Clinical Safety.

AESIs

Acute liver injury (ALI)

Because individuals with DMD may have elevated transaminases at baseline, the Sponsor defined acute liver injury (ALI) as follows: gamma-glutamyl transferase (GGT) > 3 × upper limit of normal (ULN), glutamate dehydrogenase (GLDH) > 2.5 × ULN, alkaline phosphatase (ALP) > 2 × ULN, or alanine aminotransferase (ALT) > 3 × baseline excluding ALT elevation from muscle. Using this definition, ALI was observed in 31 (36.9%) of subjects treated with SRP-9001. Severity was mild or moderate in 26 (83.9%) subjects and severe in 5 (16.1%) subjects. Three subjects experienced an SAE of ALI, but none of these resulted in clinically significant liver dysfunction (e.g., coagulopathy) or subsequent liver failure. The two most severe cases (Subjects (b) (6) involved an elevated bilirubin (one subject experienced jaundice), but these cases had confounding by concurrent infection (*H. pylori* and Parvovirus, respectively). Both cases were treated with corticosteroids and recovered.

Aside from a single case of stomach pain, which the Sponsor attributed to concurrent *H. pylori* infection, all cases were asymptomatic with regards to symptoms of hepatic inflammation. In addition, all cases resolved spontaneously or with corticosteroids. The mean time to onset of hepatotoxicity cases was 51 days with a mean time to peak of 8 days and a mean time to resolution of 35 days.

Immune-mediated myositis

One SAE of “immune-mediated myositis” was reported in Study SRP-9001-103. Approximately one month after SRP-9001 treatment, Subject (b) (6) experienced

muscle weakness, dysphagia, dysphonia, and difficulty sitting/walking. A muscle biopsy indicated an immune reaction to the transgene protein. He was diagnosed with severe, life-threatening, immune-mediated myositis without cardiac involvement. He was treated with plasmapheresis and an unspecified immunomodulatory treatment. He recovered but his strength did not return to baseline. The Sponsor attributed this patient's increased risk of immune-mediated myositis to his specific dystrophin mutation (involving exons 3-43). The Sponsor assessed eight other subjects with mutations in exons 1-17 (exons that are in both the SRP-9001-micro-dystrophin transgene and the naturally occurring full-length dystrophin gene) and did not find any other cases of immune-mediated myositis. Based on this clinical assessment, as well as results from ex vivo epitope mapping for the index subject, the Sponsor proposed a contraindication for patients with any deletion that fully includes exons 9-13.

Reviewer comment: The Sponsor attributed this patient's immunogenic risk to his specific DMD gene mutation (involving exons 3-43). Because SRP-9001-micro-dystrophin transgene contains exons 1-17 of the naturally occurring full-length dystrophin gene, the Sponsor hypothesized that mutations in exons 1-17 may impart higher immunogenic risk. They evaluated subjects with mutations involving any part of exons 1-17 (n=9) and the aforementioned subject was the only individual who experienced immune-mediated myositis. Therefore, the Sponsor proposed a contraindication for patients "with any deletion that fully includes exons 9-13 in the DMD gene." In the 120-Day Safety Update Report (BLA 125781/0.21), the Sponsor added the 59-71 regions (exons) in the C-terminus of the SRP-9001 construct as also being areas where mutations may confer risk. This reviewer defers to the clinical reviewer and review team regarding the appropriateness of the proposed contraindication in the Package Insert.

Thrombocytopenia

Thrombocytopenia was observed in the clinical studies both as a treatment-emergent adverse event (TEAE) and a laboratory parameter. Thrombocytopenia was typically mild, observed within the first two weeks after treatment, resolved without treatment within one week, and was not associated with bleeding complications.

Ten (11.9%) subjects experienced one or more TEAEs of thrombocytopenia, all of which were considered by the investigator to be treatment related. The Sponsor separately assessed TEAEs of ecchymosis, which was reported in 10 (11.9%) subjects. However, only two (4.4%) subjects experienced ecchymosis during the thrombocytopenia risk window (0-2 weeks).

Laboratory parameters showed that 51 (60.7%) subjects experienced a platelet count ($10^9/L$) of <150 or <200 with a decrease of at least 100.

Thrombotic microangiopathy was not observed in these clinical studies.

Troponin increased

Troponin increased was observed in each of the clinical studies as a TEAE and in Study SRP-9001-103 as a laboratory parameter.

Eight (9.5%) subjects had a TEAE of troponin increased, including one subject in Study SRP-9001-103 (Subject (b) (6)) with pre-existing cardiomyopathy who experienced SAEs of vomiting and myocarditis. This subject developed vomiting the day after his infusion which led to hospitalization on Day 3. Prior to a planned discharge, an incidentally increased troponin lab test returned, prolonging his hospitalization. The subject was asymptomatic “except for a brief, self-limited episode of non-specific chest pain” and on Day 6 his troponin I peaked at > 40 ng/mL. Cardiac workup included electrocardiogram, an assessment of his ejection fraction, and a cardiac MRI. These studies were unremarkable, except for the cardiac MRI which showed residual changes. As a result of these events, the subject was prescribed two additional cardiac medications for his chronic cardiomyopathy (aldosterone and carvedilol). The Sponsor identified “Troponin increased” as a safety signal based on this subject’s reported AEs.

The Sponsor defined troponin elevation based on laboratory data as troponin I > 3 x ULN (or 3 x baseline for subjects with elevated baseline values). Three (3.8%) subjects had troponin elevation based on laboratory data, including the aforementioned subject with the SAEs of vomiting and myocarditis.

Reviewer comment: “Troponin increased” was classified as an Important Potential Risk in the originally submitted PVP (BLA 125781/0.0). However, as discussed later in this memorandum, this was subsequently changed to “Myocarditis” in submission BLA 125781/0.17.

Rhabdomyolysis

The Sponsor assessed subjects with TEAEs included in the SMQ rhabdomyolysis/myopathy. Of the 14 (16.7%) subjects treated with SRP-9001 who met the search criteria, two subjects (Subjects (b) (6)) met the Sponsor’s case definition for “possible rhabdomyolysis.”² One subject was hospitalized and received intravenous (IV) fluid before recovering. A second subject was not hospitalized and spontaneously recovered. Neither subject experienced a complication (cardiac, renal, or electrolyte). The Sponsor suspected that increased physical activity caused these two cases of “possible rhabdomyolysis.”

Reviewer comment: Although rhabdomyolysis is an adverse event associated with DMD, the Primary Analysis Set revealed an imbalance in the number of subjects with the TEAE PT ‘Rhabdomyolysis’: three (15%) subjects in the SRP-9001-treated group vs. one (4.8%) subject in the placebo group. The Sponsor’s assessment of EAIR also showed an “increased risk” of rhabdomyolysis among SRP-9001-treated subjects compared to placebo: the EAIR (SE) was 0.18 (0.10) among SRP-9001-treated subjects and 0.05 (0.05) among placebo subjects. Although the number of subjects is too small to draw any firm conclusions, these findings at least raise the possibility that the risk of

² Two of three signs/symptoms (myalgia or muscle pain; weakness or inability to walk; dark urine or myoglobinuria) and acute CPK elevation (at least 2 x baseline).

rhabdomyolysis may be increased beyond what is expected at baseline in subjects with DMD. In addition to the cases described above, the Sponsor also reported a SUSAR case from Study SRP-9001-301 in a blinded subject who was hospitalized for Grade 3 rhabdomyolysis two days after study treatment (placebo or SRP-9001).

5.2.2 Clinical study SRP-9001-101

Study description

Study SRP-9001-101 is an ongoing phase 1/2a, first-in-human, open-label, single-arm, proof-of-concept study evaluating the safety of Process A material SRP-9001 in ambulatory DMD subjects aged 4 to <8 years (Table 2). Investigators originally designed this study to enroll a total of 12 subjects in two separate cohorts (Cohort A for subjects aged 3 months to 3 years; Cohort B for subjects aged 4 to 7 years), but enrollment stopped after four subjects enrolled in Cohort B, to allow for enrollment of subjects in this age range for Study SRP-9001-102, which was being conducted at the same study center. All four subjects were followed for three years following treatment as of the data cutoff date for this interim Clinical Study Report. Safety follow-up for this study is ongoing for a planned total of five years.

Demographics

All four subjects were male, and the median age was 4.5 years (range 4 to 6 years). All subjects were not Hispanic or Latino; three subjects were white, and one subject reported a race of 'Other.'

Most common AEs

All four subjects experienced multiple AEs. All AEs were non-serious and were mild or moderate in severity. The most common AEs reported were vomiting (15 AEs) and upper respiratory tract infections (11 AEs), which were reported by all four subjects. Three of four subjects experienced Hepatic enzyme increased and Procedural pain. The most common treatment-related AEs included vomiting (9 AEs), Hepatic enzyme increased (4 AEs), and decreased appetite (2 AEs). Other treatment-related AEs included nausea (1 AE), fatigue (1 AE), and asthenia (1 AE).

Reviewer comment: Although not reported as an AE in this study, all four subjects experienced transient decreases in their platelet counts within two weeks of treatment. No cases were associated with an AE (e.g., bleeding) and all four subjects spontaneously recovered by Week 2 or 3. The lowest reported platelet count at Week 1 was $109 \times 10^9/L$ (Subject 1). There were no cases of atypical hemolytic uremic syndrome and no mention of thrombotic microangiopathy.

SAEs

There were no SAEs as of the data cutoff for the interim clinical study report.

Deaths

There were no deaths as of the data cutoff for the interim clinical study report.

AESIs

Acute Liver Injury (ALI)

Three of the four subjects met the study definition for acute liver injury with onset between Day 47-61 and resolution by Day 53-82. All cases were related, serious, and mild or moderate in severity. All cases resolved with corticosteroid treatment and there were no associated clinical signs of liver failure reported.

Thrombocytopenia

All four subjects experienced transient decreases in platelet count not associated with bleeding.

Reviewer comment: There were no cases of immune-mediated myositis, troponin increased, or rhabdomyolysis reported in this study. However, troponin data were not collected in Studies SRP-9001-101 and -102.

5.2.3 Clinical study SRP-9001-102 (Parts 1 and 2)

Study description

Study SRP-9001-102 is an ongoing phase 2 randomized, three-part, double-blind, placebo-controlled (Part 1), crossover (Part 2) then open-label (Part 3) study evaluating the safety of Process A material SRP-9001 in ambulatory DMD subjects aged 4 to <8 years (Table 2). In Part 1, 20 subjects received SRP-9001 (eight subjects received a dose of 1.33×10^{14} vg/kg). In Part 2, 21 subjects received SRP-9001 (all 21 subjects received a dose of 1.33×10^{14} vg/kg). Blinded safety follow-up of subjects was 48 weeks for Part 1 and 48 weeks for Part 2. Safety data from Part 3 (open-label) were not submitted for review but will be included in the final study report.

Demographics

All 41 treated subjects were male. Twenty subjects received SRP-9001 in Part 1 ("initial SRP-9001 group") and 21 subjects received placebo in Part 1 ("initial placebo group"). Of the 20 subjects assigned to receive placebo in Part 2 ("crossover to placebo group"), 18 received placebo (two subjects who were treated with SRP-9001 in Part 1 were not treated with placebo in Part 2). Of the 21 subjects assigned to receive SRP-9001 in Part 2 ("crossover to SRP-9001 group"), all 21 received SRP-9001. The mean age was 6.27 years (range 4.34 to 7.98 years) with 16 subjects aged 4-5 years and 25 subjects aged 6-7 years. The majority of participants were White (73.2%) and not Hispanic or Latino (85.4%).

Most common AEs

In Part 1, the most common AEs in the initial SRP-9001 group were upper respiratory tract infection (13 subjects; 65%), vomiting (13 subjects; 65%), cough (9 subjects; 45%), and ecchymosis (9 subjects; 45%). The most common AEs in the initial placebo group were upper respiratory tract infection (13 subjects; 61.9%), viral infection (9 subjects; 42.9%), vomiting (7 subjects; 33.3%), and procedural pain (7 subjects; 33.3%).

In Part 2, the most common AEs in the crossover to SRP-9001 group were vomiting (16 subjects; 76.2%), decreased appetite (15 subjects; 71.4%), nausea (1 subject; 52.4%), and procedural pain (9 subjects; 42.9%). The most common AEs in the crossover to placebo group were upper respiratory tract infection (8 subjects; 40%), procedural pain (6 subjects; 30%), and pain in extremity (6 subjects; 30%).

Most AEs in both Parts 1 and 2 were mild or moderate in severity.

Reviewer comment: Vomiting was the most common treatment-related AE in both Parts 1 and 2. The imbalance between groups for vomiting was observed within two weeks after treatment and there were no SAEs for vomiting. Temporal associations with treatment were observed for gastrointestinal events (nausea/vomiting) and hepatobiliary investigation events (acute liver injury).

SAEs

In Part 1, five subjects experienced a total of six SAEs (Table 4): 3 (15%) subjects in the initial SRP-9001 group, 2 (9.5%) subjects in the initial placebo group. All SAEs in the initial SRP-9001 group were considered related and included rhabdomyolysis (2 SAEs), liver injury (1 SAE), and transaminases increased (1 SAE).

In Part 2, three subjects experienced a total of three SAEs (Table 4): 1 (4.8%) subject in the crossover to SRP-9001 group and 2 (10%) subjects in the crossover to placebo group. None of the SAEs in Part 2 were considered related (1 SAE of appendicitis, 2 SAEs of femur fracture).

Deaths

There were no deaths as of the data cutoff for the interim clinical study reports.

AESIs

Acute liver injury (ALI)

In Part 1, hepatotoxicity AEs were more common in the initial SRP-9001 group (7 subjects; 35%) than in the initial placebo group (0 subjects). Two subjects in the initial SRP-9001 group experienced severe hepatotoxicity events, which were also treatment-related SAEs. Subject (b) (6) experienced severe liver injury. Subject (b) (6) experienced severe transaminases increased and severe blood bilirubin increased. Clinically significant hepatic laboratory abnormalities were also more common in the initial SRP-9001 group (14 subjects; 70%) than in the initial placebo group (7 subjects; 33.3%). All seven subjects who met the study definition of acute liver injury were in the initial SRP-9001 group.

In Part 2, hepatotoxicity AEs were only observed in the crossover to SRP-9001 group (7 subjects; 33.3%). No hepatotoxicity SAEs were observed in Part 2. Clinically significant hepatic laboratory abnormalities were also more common in the crossover to SRP-9001 group (20 subjects; 95.2%) than in the crossover to placebo group (12 subjects; 60%).

All eight subjects who met the study definition of acute liver injury were in the crossover to SRP-9001 group.

In both Parts, all clinically significant cases resolved with additional corticosteroid treatment.

Thrombocytopenia

In Part 1, there were no thrombocytopenia AEs. Laboratory studies showed a decrease in platelet count at Week 1 for subjects in the initial SRP-9001 group, which was largely recovered by Week 2 and not associated with bleeding events. Subjects in the initial SRP-9001 group also experienced a decrease in complement levels at Week 1, which was largely recovered by Week 2 and not associated with signs or symptoms of atypical hemolytic uremic syndrome.

In Part 2, five AEs of thrombocytopenia were reported among subjects in the crossover to SRP-9001 group. All were non-serious, related, mild to moderate in severity, resolved within a week, and were not associated with bleeding. Three subjects had a platelet count less than 75,000/mm³. Subjects in the crossover to SRP-9001 group also experienced a decrease in total complement at Week 1 which was largely recovered by Week 2 and not associated with signs or symptoms of atypical hemolytic uremic syndrome.

Troponin increased

Troponin data were not collected in Studies SRP-9001-102. Cardiac assessments with electrocardiogram (ECG) and echocardiogram were performed. In Part 1, two subjects in the initial SRP-9001 group experienced a decrease in left ventricular ejection fraction (LVEF) from baseline to less than 55%, although there were no associated AEs. In Part 2, one subject in the crossover to SRP-9001 group and three subjects in the crossover to placebo group experienced a decrease in LVEF from baseline to less than 55%. In Part 2, two subjects (9.5%) in the crossover to placebo group had non-serious AEs of cardiomyopathy.

Reviewer comment: There does not appear to be a clear pattern or trend suggestive of a cardiac safety signal in the limited cardiac assessment data from this study.

Cardiomyopathy is a known complication of DMD.

Rhabdomyolysis

In Part 1, three (15%) of subjects in the crossover to SRP-9001 group experienced AEs relevant to rhabdomyolysis (2 AEs of rhabdomyolysis, 1 AE of myalgia) compared to one (4.8%) in the crossover to placebo group. When evaluated against a case definition, one case in each treatment group was considered possible or probably rhabdomyolysis and each case resolved without complication. In Part 2, two subjects in the crossover to SRP-9001 group and two subjects in the crossover to placebo group experienced rhabdomyolysis AEs; none met the case definition for possible or probably rhabdomyolysis.

Reviewer comment: There is no clear trend of a safety signal for rhabdomyolysis in this study.

5.2.4 Clinical study SRP-9001-103

Study description

Study SRP-9001-103 is an ongoing phase 1b, open-label, single-arm study evaluating the safety of Process B material SRP-9001 in DMD subjects among four cohorts (Table 2). Thirty-nine subjects overall were treated with SRP-9001. Safety results for all four cohorts were reported in the interim clinical study report, with results for Cohort 1 (n=20) up to Week 52 and results for the remaining cohorts (n=19) up to data cutoff date April 6, 2022. The median duration of follow up for all participants was 50.29 weeks (range 5 to 71.4 weeks). Safety follow up for all subjects is ongoing for a planned total of five years.

Reviewer comment: This small, open-label, single-arm study is the only study submitted for review that uses the to-be-marketed Process B material SRP-9001.

Demographics

All 39 treated subjects were male. Most subjects were White (79.5%) and not Hispanic or Latino (84.6%). The median age overall was 6.19 years (range 3.24 to 20.23 years). There were 20 subjects in Cohort 1, seven subjects in Cohort 2, six subjects in Cohort 3, and six subjects in Cohort 4.

Most common AEs

Most subjects (37 subjects; 94.9%) experienced at least one adverse event. The most common AEs were vomiting (19 subjects; 48.7%), decreased appetite (15 subjects; 38.5%), nausea (15 subjects; 38.5%), and glutamate dehydrogenase increased (11 subjects; 28.2%). Most AEs were mild or moderate in intensity.

Reviewer comment: Vomiting generally occurred within the first two weeks after treatment and was mild or moderate in intensity. However, two vomiting AEs were SAEs (discussed more below).

SAEs

Four subjects (10.3%) experienced a total of five SAEs (Table 4): transaminases increased (1 SAE), vomiting (2 SAEs), immune-mediated myositis (1 SAE), and myocarditis (1 SAE). The investigator considered each SAE to be related to study treatment. Two subjects experienced SAEs resulting in sequelae: 1) Subject (b) (6) experienced immune-mediated myositis and recovered but without return to baseline strength, 2) Subject (b) (6) experienced vomiting and myocarditis and recovered but with the addition of two new cardiac medications. Lastly, the two subjects that had SAEs of vomiting each required hospitalization to managed dehydration (both recovered).

Deaths

There were no deaths as of the data cutoff for the interim clinical study report.

AESIs

Acute liver injury (ALI)

Fifteen subjects met the protocol-defined laboratory criteria for acute liver injury. None of these subjects had elevations of bilirubin or abnormal international normalized ratios (INRs). All cases resolved with additional corticosteroid dosing.

Immune-mediated myositis

One (2.6%) subject experienced immune-mediated myositis after receiving SRP-9001 (see above section 5.2.1 'Integrated Safety Data' regarding Subject (b) (6)).

Reviewer comment: A subgroup analysis of subjects with mutations in exons 1-17 (n=9) did not reveal any additional safety signals beyond immune-mediated myositis.

Thrombocytopenia

Five (12.8) subjects reported an AE of thrombocytopenia. All were non-serious, mild or moderate in intensity, resolved without intervention, and were not associated with bleeding.

Laboratory data showed transient decreases in platelet count and transient complement activation (specifically, decreases in complement factor 4 and complement factor 3) within the first two weeks after treatment. There were no associated clinical AEs. Two subjects experienced a platelet count less than 75,000/microL: one patient had a platelet count of 51,000/microL on Week 2 which returned to normal by week 3; another patient had a platelet count of 71,000 on Day 7 which returned to normal by Day 9.

Troponin increased

Three (7.7%) subjects reported an AE of troponin increased. All were nonserious, mild in intensity, and not associated with cardiac AEs. (Note: The one SUSAR case of myocarditis was initially coded as troponin increased and later re-coded to myocarditis.) One subject with normal baseline value had an LVEF <55% (54.3) at Week 52, not associated with any cardiac AEs.

Rhabdomyolysis

Five subjects (12.8%) experienced 7 AEs that were relevant to rhabdomyolysis, five of which were reported within 2 weeks of infusion. All events were non-serious, mild to moderate in intensity, and resolved. Most (6 AEs) were considered treatment-related by the investigator. No AEs were associated with renal dysfunction.

Reviewer comment: As with Study SRP-9001-101, the small study population size and lack of a blinded comparator group are major limitations of the clinical safety database I.

5.3 120-Day Safety Update

After the external mid-cycle meeting (and after review of the above originally submitted clinical safety data), the Sponsor submitted updated safety information for SRP-9001 in a 120-Day Safety Update report (STN 125781/0.17, received January 30, 2023). This report replaced and updated the prior Summary of Clinical Safety (Module 2.7.4). In

addition, the Sponsor submitted a revised pharmacovigilance plan (PVP), with changes related to findings from the 120-Day Safety Update report.

The 120-Day Safety Update report provided updated clinical safety data (with later data lock dates) for the three clinical studies submitted in support of the original BLA (Study SRP-9001-101, Study SRP-9001-102, and Study SRP-9001-103). (The Sponsor did not submit updated interim Clinical Study Reports with the 120-Day Safety Update report.) In addition, the Sponsor also provided a description of all treatment-related serious adverse events reported in Study SRP-9001-301 (until data lock date December 22, 2022).

5.3.1 Exposure Analysis Set Update

The safety analysis sets and analyses are analogous to those of the original Summary of Clinical Safety (SCS). One additional subject was included in the Exposure Analysis Set (n=85 compared to n=84 in the original SCS), while the number of subjects in the Primary Analysis Set remained unchanged. Observation time for the Exposure Analysis Set increased to a median 1.82 subject-years (from a prior 1.34 subject-years).

No new treatment-related SAEs were reported from Study SRP-9001-101, Study SRP-9001-102, or Study SRP-9001-103, compared to the original SCS. A subject in Study SRP-9001-102 (Subject (b) (6)) experienced an additional SAE (femur fracture), which was considered not related. This increased the total number of SAEs in the Exposure Analysis Set to 15 SAEs among 12 subjects. No deaths were reported (as of December 22, 2022).

Reviewer comment: Findings from the updated Exposure Analysis Set were largely comparable compared to the original SCS. Although the observation time and absolute number of AEs increased, there was only one additional SAE, which was considered not related to treatment.

5.3.2 Study SRP-9001-301 Update

For Study SRP-9001-301, the 120-Day Safety Update report included reports of treatment-related SAEs for seven blinded subjects (Table 5), while the original SCS included only one SUSAR case from Study SRP-9001-301 (rhabdomyolysis).

Table 5. Treatment-related serious adverse events in blinded Study SRP-9001-301 (as of December 22, 2022)

#	Study; Treatment	Subject	PT	Outcome
1	SRP-9001-301; Blinded	(b) (6)	Rhabdomyolysis	Recovered
2	SRP-9001-301; Blinded	(b) (6)	Transaminases increased	Recovered
3	SRP-9001-301; Blinded	(b) (6)	Myocarditis	Recovered
4	SRP-9001-301; Blinded	(b) (6)	GGT increased	Recovered
5	SRP-9001-301; Blinded	(b) (6)	Hypertransaminasaemia	Recovered
6	SRP-9001-301; Blinded	(b) (6)	Hepatotoxicity	Ongoing, Improving
7	SRP-9001-301; Blinded	(b) (6)	Hepatic enzymes increased	Recovered

Among these treatment-related SAEs, this reviewer found the following cases to be notable:

- Subject (b) (6) (Myocarditis): A (b) (4) year-old male with DMD received SRP-9001 or placebo and six hours later developed fever and seizure-like activity. He was taken to the emergency room and admitted to the pediatric intensive care unit. Laboratory workup revealed an elevated troponin I of 6,283.38 pg/mL (reference range: ≤ 45.00 pg/mL). EKG and echocardiogram results were normal. He was treated with IV fluids for hypotension. Additional steroids were not administered since his troponin levels were down-trending and his echocardiogram was normal. He was monitored closely and by Day 20 the event had resolved (normal troponin, EKG, and echocardiogram). Although this case did not include imaging findings consistent with myocarditis, an external expert confirmed this case of myocarditis as [probably] treatment-related given the close temporal relationship to gene therapy and the inability to rule out pyrexia, seizure-like activity, and vomiting as non-specific symptoms of myocarditis.
- Subject (b) (6) (Hypertransaminasaemia): A (b) (4) year-old male with DMD and no known pre-existing liver disease received SRP-9001 or placebo and on Day 35 experienced abnormal laboratory tests suggestive of hepatic inflammation. Later he experienced a significant increase in AST (1,878 U/L), ALT (2,897 U/L), and GGT, as well as an elevation in bilirubin. He was hospitalized and treated with IV corticosteroids. Laboratory testing was also notable for alpha-1 antitrypsin carrier status (M1Z phenotype). After being discharged, he was admitted a second time due to increasing liver enzymes. A liver biopsy was performed which revealed “chronic hepatitis with neutrophilic and lymphocytic portal infiltrate interface hepatitis and bile ductular proliferation, as well as bridging fibrosis with focal nodule formation (grade 3, stage 3 Batt-Ludwig grading and staging system).” The pathologist noted that cryptogenic cirrhosis has been reported with increased frequency in patients with M1Z alpha-1 antitrypsin phenotype. The subject remained asymptomatic throughout the event.
- Subject (b) (6) (Hepatotoxicity): A (b) (4) year-old male with DMD received SRP-9001 or placebo and on Day 29 experienced nausea, right-sided abdominal pain, scleral icterus, and abnormal liver function tests (including AST of 2,667 U/L, ALT of 1,868 U/L, and total bilirubin of 2.3 mg/dL). He also experienced bloody, clay-colored stools. He was hospitalized and treated with IV corticosteroids. Clinicians suspected drug-induced liver injury from the gene therapy. The subject was discharged, and the SAE was ongoing but clinically improving at the time of last follow up.

Reviewer comment: The myocarditis case (Subject (b) (6)) was notable because this is the second case of myocarditis reported (and confirmed by an external expert) in the clinical studies for SRP-9001. This second case prompted the Sponsor to change the Important Potential Risk of “Troponin increased” to “Myocarditis.” The two cases of acute liver injury were notable for the severity of their clinical presentation (both had transaminase levels in the thousands and one experienced multiple hepatotoxicity symptoms) and the associated care (both required hospitalization for administration of

IV steroids and one required a liver biopsy). Neither case of acute liver injury progressed to fulminant liver failure, although the second case was not yet resolved at the time of reporting.

6 SUMMARY OF FOREIGN POSTMARKETING EXPERIENCE

SRP-9001 is not commercially available in any countries. Therefore, there are no postmarketing data available for SRP-9001.

7 SPONSOR'S PHARMACOVIGILANCE PLAN

A summary of the Sponsor's Pharmacovigilance Plan (PVP) is provided in Table 6 below.

Table 6. Sponsor's Pharmacovigilance Plan

Type of Concern	Safety Concern	Proposed Action
Important Identified Risk	Acute liver injury	<p><i>Clinical studies</i></p> <ul style="list-style-type: none"> • Safety monitoring in ongoing studies <p><i>Enhanced pharmacovigilance</i></p> <ul style="list-style-type: none"> • Follow up of cases • Targeted questionnaire • Monthly review of cases and analysis in aggregate reports • Expedited reporting (regardless of seriousness or expectedness) of cases to FDA within 15 calendar days
Important Identified Risk	Immune-mediated myositis	<p><i>Clinical studies</i></p> <ul style="list-style-type: none"> • Safety monitoring in ongoing studies <p><i>Enhanced pharmacovigilance</i></p> <ul style="list-style-type: none"> • Follow up of cases • Targeted questionnaire • Monthly review of cases and analysis in aggregate reports • Expedited reporting (regardless of seriousness or expectedness) of cases to FDA within 15 calendar days
Important Identified Risk	Thrombocytopenia	<p><i>Clinical studies</i></p> <ul style="list-style-type: none"> • Safety monitoring in ongoing studies <p><i>Enhanced pharmacovigilance</i></p> <ul style="list-style-type: none"> • Follow up of cases • Targeted questionnaire • Monthly review of cases and analysis in aggregate reports

Important Potential Risk	Myocarditis	<p><i>Clinical studies</i></p> <ul style="list-style-type: none"> • Safety monitoring in ongoing studies <p><i>Enhanced pharmacovigilance</i></p> <ul style="list-style-type: none"> • Follow up of cases • Targeted questionnaire • Monthly review of cases and analysis in aggregate reports • Expedited reporting (regardless of seriousness or expectedness) of cases to FDA within 15 calendar days (includes cases of both 'Myocarditis' and 'Troponin increased')
Important Potential Risk	Thrombotic microangiopathy	<p><i>Clinical studies</i></p> <ul style="list-style-type: none"> • Safety monitoring in ongoing studies <p><i>Enhanced pharmacovigilance</i></p> <ul style="list-style-type: none"> • Follow up of cases • Targeted questionnaire • Monthly review of cases and analysis in aggregate reports • Expedited reporting (regardless of seriousness or expectedness) of cases to FDA within 15 calendar days
Missing Information	Long-term safety	<p><i>Clinical studies</i></p> <ul style="list-style-type: none"> • SRP-9001-305: planned phase 3, open-label, long-term extension study for subjects who received SRP-9001 in another study (minimum follow-up time: 5 years) <p><i>Postmarketing safety study</i></p> <ul style="list-style-type: none"> • SRP-9001-401: planned phase 4, observational study of safety and efficacy of SRP-9001 in postmarketing setting
Missing Information	Rhabdomyolysis	<p><i>Clinical studies</i></p> <ul style="list-style-type: none"> • Safety monitoring in ongoing studies <p><i>Enhanced pharmacovigilance</i></p> <ul style="list-style-type: none"> • Follow up of cases • Targeted questionnaire • Monthly review of cases and analysis in aggregate reports

Missing Information	Oncogenicity due to integration and insertional mutagenesis	<p><i>Clinical studies</i></p> <ul style="list-style-type: none"> • Safety monitoring in ongoing studies • SRP-9001-305: planned phase 3, open-label, long-term extension study for subjects who received SRP-9001 in another study (minimum follow-up time: 5 years) <p><i>Postmarketing safety study</i></p> <ul style="list-style-type: none"> • SRP-9001-401: planned phase 4, observational study of safety and efficacy of SRP-9001 in postmarketing setting
---------------------	---	---

*Adapted from Table 8 in “SRP-9001 Risk Management Plan” STN 125781/0.25, Module 1.16.1

Reviewer comment: The Sponsor’s original PVP listed “Acute liver injury” and “Immune-mediated myositis” as Important Identified Risks and “Troponin increased” as an Important Potential Risk.

On December 21, 2022, FDA sent the Sponsor an Information Request (DPV IR #1) asking them to include “Long-term safety” as Missing Information in the PVP and propose a postmarketing long-term follow up (LTFU) safety study. On January 9, 2023, the Sponsor responded (BLA 125781/0.11) and included an updated PVP as well as study outline for a postmarketing LTFU safety study (Study SRP-9001-401). On January 30, 2023 (BLA 125781/0.17), the Sponsor provided results from their 120-Day Safety Update Report, including an updated PVP in which they changed the Important Potential Risk “Troponin increased” to “Myocarditis” due to an additional clinical trial case of myocarditis and external expert assessment of both reported myocarditis cases.

On February 13, 2023, FDA sent the Sponsor an Information Request (DPV IR #2) asking them to include “Transient thrombocytopenia” as an Important Identified Risk and “Rhabdomyolysis,” “Thrombotic microangiopathy,” and “Oncogenicity due to integration and insertional mutagenesis” as Important Potential Risks. On February 21, 2023, the Sponsor responded (BLA 125781/0.21) and included an updated PVP in which they agreed to classify “Thrombocytopenia” as an Important Identified Risk and “Thrombotic microangiopathy” as an Important Potential Risk. However, the Sponsor felt that “Rhabdomyolysis” and “Oncogenicity due to integration and insertional mutagenesis” would be better classified as Missing Information. For “Rhabdomyolysis,” the Sponsor argued that the causality between SRP-9001 and rhabdomyolysis is less clear than for myocarditis (an Important Potential Risk). For “Oncogenicity due to integration and insertional mutagenesis,” the Sponsor argued that this is a low theoretical risk. This reviewer agrees with the rationale and reclassification of “Rhabdomyolysis” and “Oncogenicity due to integration and insertional mutagenesis” as proposed by the Sponsor.

On February 23, 2023, FDA sent the Sponsor an Information Request (DPV IR #3) asking them to make minor corrections to Table 8 in the PVP. On March 2, 2023, the Sponsor responded (BLA 125781/0.25) and submitted a corrected PVP.

On May 30, 2023, FDA sent the Sponsor an Information Request (DPV IR #4) asking them to make the following revisions to their PVP: 1) specify the timeframe for expedited reporting as “for three years post-licensure,” 2) include expedited reporting for all acute liver injury events, regardless of bilirubin elevation, 3) include a table of MedDRA search terms that will be used for each safety concern requiring enhanced pharmacovigilance, and 4) include version number and date for updated PVPs. On June 2, 2023, the Sponsor responded (BLA 125781/0.62) and submitted a revised PVP (Version 6) that addressed these requests.

7.1 Routine Pharmacovigilance

The Sponsor plans to employ routine pharmacovigilance practices in compliance with FDA (in accordance with 21 CFR 600.80) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines. Routine pharmacovigilance activities will include review of spontaneous reports, clinical trial reports, literature searches, data mining, and signal detection. Additional planned risk mitigation activities include product labeling, targeted education and outreach (for sites and prescribers administering SRP-9001), treatment guides (for patients/caregivers and prescribers), continuing medical education, and a toll-free phone number to answer questions and report adverse events.

7.2 Enhanced Pharmacovigilance

In addition to the routine pharmacovigilance activities described above, the Sponsor proposed enhanced pharmacovigilance in the form of targeted questionnaires and expedited reporting for each of the following safety concerns: acute liver injury, immune-mediated myositis, myocarditis (and troponin increased), and thrombotic microangiopathy.

Reviewer comment: Based on FDA review of available safety data, FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is not necessary at this time.

7.3 Clinical extension study

To evaluate long-term safety of SRP-9001 in clinical study participants, the Sponsor plans a phase 3, open-label extension study (Study SRP-9001-305). Approximately 126 subjects from ongoing Study SRP-9001-301 and 148 subjects from planned study SRP-9001-303 will be enrolled. Duration of follow up will be a minimum of five years post-SRP-9001 infusion. Proposed milestones are as follows:

- Final protocol submission: July 31, 2023
- Study completion date: January 31, 2031
- Final study report completion: June 30, 2031

7.4 Safety-related Postmarketing Study (voluntary sponsor study)

The Sponsor submitted a study synopsis for a planned phase 4, observational study of safety and efficacy of SRP-9001 in the postmarketing setting (Study SRP-9001-401). The study is primarily powered for an efficacy outcome but is also designed to evaluate safety outcomes. The study design is a prospective cohort study involving two cohorts: 1) an exposed group (subjects who were first recruited then received commercial SRP-9001) and 2) an unexposed or standard of care group (subjects who were receiving or prescribed chronic glucocorticoid treatment at the time of recruitment). The Sponsor plans to recruit 227 subjects with DMD to each group with both groups recruited by the same treating physicians. Subjects in each group will be followed every six months for a total of 10 years. The Sponsor plans to submit a full protocol for this study after approval of the original BLA. Proposed milestones are as follows:

- Final protocol submission: July 31, 2023
- Study completion date: December 31, 2037
- Final study report completion: June 30, 2038

Reviewer comment: The proposed study synopsis is acceptable. On February 13, 2023, FDA sent the Sponsor an Information Request (DPV IR #2) providing feedback on the study synopsis. On February 21, 2023, the Sponsor responded (BLA 125781/0.21), addressing our feedback in the IR response, and stating that the feedback will be considered for inclusion into the final submitted protocol. The Sponsor plans to include all safety concerns in the PVP as safety outcomes in the Study SRP-9001-401. Based on the available safety data, there are no postmarketing requirement or postmarketing commitment safety studies at this time. Note that Study SRP-9001-401 will be conducted as a voluntary sponsor study.

8 ANALYSIS OF SPONSOR'S PHARMACOVIGILANCE PLAN

8.1 Important Identified Risks

8.1.1 Acute liver injury

Hepatotoxicity is the most common adverse event associated with intravenous administration of systemic AAV vectors (6). In addition to recognition as a class effect for AAV vectors, hepatotoxicity has also been observed in clinical trial subjects after receipt of SRP-9001. The Sponsor referred to hepatotoxicity in the clinical studies as "acute liver injury (ALI)" and defined the term according to laboratory parameters that considered baseline elevations observed within the DMD population. ALI was commonly observed among recipients of SRP-9001, with most cases observed within 60 days of the infusion and resolving within several weeks, either spontaneously or with increased dosage of corticosteroids. Although there were no cases of clinically significant liver dysfunction or subsequent liver failure, observed cases did include severe cases involving hospitalization and IV corticosteroids. In addition, postmarketing cases of fatal hepatotoxicity have been reported following administration of another AAV vector gene therapy (onasemnogene abeparvovec; Zolgensma) resulting in FDA regulatory action (Section 921 Posting, safety-related labeling changes, enhanced pharmacovigilance).

Sponsor-proposed mitigation strategies for ALI (beyond labeling and routine pharmacovigilance activities) include active follow-up of postmarketing cases, use of a targeted questionnaire, monthly review of cases and analysis in aggregate reports, and expedited (15-day) reporting. In addition, in the proposed Package Insert, the Sponsor recommends laboratory monitoring of liver function at baseline and weekly for the first three months (with continued monitoring if clinically indicated).

Reviewer comments: The Sponsor's proposed mitigation strategies for ALI are acceptable.

8.1.2 Immune-mediated myositis

As described in section 5.2.1 above, a subject in Study SRP-9001-103 experienced a serious adverse event of severe, life-threatening immune-mediated myositis with subsequent sequelae of residual weakness. The Sponsor hypothesized that this subject was at increased risk for this event due to his specific DMD mutation. Therefore, the Sponsor plans to mitigate this risk mainly through labeling (restricting use in patients with certain mutations). In addition, the Sponsor proposed enhanced pharmacovigilance for this AE (active follow up of cases, targeted questionnaire, monthly review of cases and analysis in aggregate reports, and expedited [15-day] reporting).

Reviewer comments: The Sponsor's proposed mitigation strategies for immune-mediated myositis are acceptable.

8.1.3 Thrombocytopenia

In the submitted clinical studies, thrombocytopenia was observed as both a treatment-emergent adverse event and as a laboratory parameter. Recipients of SRP-9001 typically experienced mild, transient thrombocytopenia within the first two weeks of treatment, that resolved within one week, and was not associated with bleeding complications. Thrombocytopenia was common in the submitted clinical studies, affecting 11.8% of subjects in the Exposure Analysis Set.

The Sponsor proposed enhanced pharmacovigilance for this AE (active follow up of cases, targeted questionnaire, and monthly review of cases and analysis in aggregate reports). In addition, in the proposed Package Insert, the Sponsor recommends laboratory monitoring of platelets at baseline and weekly for the first two weeks (with continued monitoring if clinically indicated).

Reviewer comment: The Sponsor's proposed mitigation strategies for thrombocytopenia are acceptable. Expedited reporting for thrombocytopenia is not necessary since the Sponsor has agreed to expedited reporting of thrombotic microangiopathy.

8.2 Important Potential Risks

8.2.1 Myocarditis

Individuals with DMD are at increased risk for cardiovascular complications (e.g., cardiomyopathy) due to dystrophin deficiency in heart muscle (8). In the submitted clinical studies, two subjects experienced myocarditis after SRP-9001 infusion. Both cases presented with serious (requiring hospitalization) vomiting and were incidentally

noted to have elevated troponin-I levels. Despite potential confounding by underlying condition, both cases were confirmed by external expert review. In addition to these two cases of myocarditis, cases of troponin increased not associated with a diagnosis of myocarditis were also observed among SRP-9001 recipients.

The Sponsor proposed enhanced pharmacovigilance for this AE (active follow up of cases, targeted questionnaire, monthly review of cases and analysis in aggregate reports, and expedited [15-day] reporting). In addition, in the proposed Package Insert, the Sponsor recommends laboratory monitoring of troponin-I at baseline and weekly for the first month (with continued monitoring if clinically indicated).

Reviewer comment: The classification of this AE as a “potential” risk is appropriate given the potential confounding by underlying condition. The Sponsor’s proposed mitigation strategies for myocarditis are acceptable.

8.2.2 Thrombotic microangiopathy

Thrombotic microangiopathy (TMA) is a potentially life-threatening clinical syndrome characterized by microangiopathic hemolytic anemia, thrombocytopenia, and end organ involvement (9). TMA has been reported following receipt of adeno-associated virus (AAV) gene therapy in both the clinical trial and postmarketing settings (5, 10). Clinical trial cases include aHUS-like events among DMD subjects treated with AAV gene therapy (5). In the postmarketing setting, TMA cases have been reported following receipt of Zolgensma (onasemnogene abeparvovec), an AAV gene therapy indicated for pediatric patients with spinal muscular atrophy (SMA) (10). These postmarketing reports resulted in a Section 921 posting, a “Dear Doctor” letter, and updates to the Package Insert for Zolgensma (“Warnings and Precautions” and “Postmarketing Experience” sections) (11-13). Lastly, postmarketing cases of TMA, including a fatal case, have been reported in the literature for Zolgensma (14, 15). Although TMA was not observed among SRP-9001 recipients, as noted above, thrombocytopenia was commonly observed. In addition, laboratory monitoring of complement levels in Study SRP-9001-102 and Study SRP-9001-103 showed evidence of complement activation following SRP-9001 infusion, which paralleled the same time frame observed for thrombocytopenia. These findings raise concern that TMA could be observed in the postmarketing setting, once the product is used in a larger, more diverse patient population.

The Sponsor proposed enhanced pharmacovigilance for this AE (active follow up of cases, targeted questionnaire, monthly review of cases and analysis in aggregate reports, and expedited [15-day] reporting). As noted above in the proposed Package Insert, the Sponsor recommends platelet monitoring.

Reviewer comments: The Sponsor’s proposed mitigation strategies for TMA are acceptable.

8.3 Important Missing Information

8.3.1 Long-term safety

Due to the limited clinical study population size and duration of safety follow up, DPV asked the Sponsor to include “long-term safety” as Missing Information in the PVP (DPV IR #1). In addition, DPV requested that the Sponsor’s PVP include a proposed postmarketing long-term follow up (LTFU) safety study. The Sponsor agreed to both of these requests. Lastly, the Sponsor also plans a long-term extension study for follow up of subjects who received SRP-9001 in clinical trials.

Reviewer comment: The Sponsor’s plan to address Missing Information “long-term safety” is acceptable.

8.3.2 Rhabdomyolysis

Rhabdomyolysis is a potentially life-threatening and known complication of muscular dystrophies, including Duchenne Muscular Dystrophy (16). Rhabdomyolysis has also been reported in clinical studies among subjects with DMD following SRP-9001 infusion. Based on an observed imbalance in exposure-adjusted incidence rate (EAIR) among SRP-9001 recipients in the submitted clinical studies, DPV asked the Sponsor to classify this AE as an Important Potential Risk. However, given the paucity of additional clinical data to support a causal relationship, DPV agreed with the Sponsor’s proposal to classify “Rhabdomyolysis” as Missing Information.

The Sponsor proposed enhanced pharmacovigilance for this AE (active follow up of cases, targeted questionnaire, and monthly review of cases and analysis in aggregate reports).

Reviewer comment: The Sponsor’s plan to address Missing Information “Rhabdomyolysis” is acceptable.

8.3.3 Oncogenicity due to integration and insertional mutagenesis

Although AAVs do not have a propensity to integrate into host genomic DNA, animal studies of AAV vectors have shown evidence of vector-mediated insertional mutagenesis, suggesting the potential for oncogenicity due to AAV integration (5, 7). However, this risk is considered lower for AAV vectors compared to other gene therapy products (e.g., retroviral vectors) (7). Sponsor-submitted clinical data do not demonstrate any long-term safety concerns (including oncogenicity). However, the study population and duration of safety follow up were limited. Therefore, the Sponsor considered this theoretical risk as Missing Information.

The Sponsor plans to evaluate for this safety concern in their planned clinical trial extension study (SRP-9001-305) and the proposed postmarketing safety study (SRP-9001-401).

Reviewer comment: The Sponsor’s plan to address Missing Information “Oncogenicity due to integration and insertional mutagenesis” is acceptable.

9 DPV ASSESSMENT

Given the review of safety data submitted for this original BLA, the Sponsor's plan for surveillance and pharmacovigilance activities for SRP-9001 is acceptable. After several communications with the Sponsor, the most recently revised PVP (BLA 125781/0.62) now adequately captures the important safety concerns represented in the submitted clinical safety data. In addition to labeling and routine pharmacovigilance, the Sponsor will be required to conduct enhanced pharmacovigilance with expedited reporting for acute liver injury, immune-mediated myositis, myocarditis, and thrombotic microangiopathy, and the sponsor will conduct a long-term follow up study of SRP-9001 recipients. Should this product be approved, the above surveillance activities are adequate for postmarketing safety monitoring and will further characterize the safety profile during the post-licensure period. Lastly, FDA has determined that a REMS is not needed at this time. As with other FDA-approved AAV gene therapy products, this reviewer anticipates that use of this product will be limited to subspecialists familiar with treating DMD patients. In addition, the Sponsor plans to offer training and education to clinicians and sites of care; note that these educational materials are to be provided voluntarily by the sponsor.

Reviewer comment: We defer to the product office on the final decision regarding the regulatory action for this original BLA, and efficacy study as a postmarketing requirement (PMR) under Accelerated Approval, (b) (4)

Please see clinical review memorandum and the Summary Basis for Regulatory Action (SBRA). DPV will review future submissions of updated clinical safety data when available.

10 DPV RECOMMENDATIONS

Should this product be approved, DPV recommends the following surveillance activities for postmarketing safety monitoring of SRP-9001:

1. Routine pharmacovigilance, which includes adverse event reporting in accordance with 21 CFR 600.80.
2. Enhanced pharmacovigilance:
 - a. Follow up of spontaneously reported cases, targeted questionnaires, review of cases and analysis of aggregate data in periodic safety reports for the following safety concerns: acute liver injury, immune-mediated myositis, myocarditis (including troponin increased), thrombocytopenia, thrombotic microangiopathy, and rhabdomyolysis.
 - b. Expedited (15-day) reporting (regardless of seriousness or expectedness) to FAERS for three years following approval for the following safety concerns: acute liver injury, immune-mediated myositis, myocarditis, and thrombotic microangiopathy.
3. A voluntary long-term follow up postmarketing safety study (Study SRP-9001-401) will be conducted by the sponsor to provide 10-year safety and effectiveness follow-up for SRP-9001. This is a prospective cohort study, that will include a comparator group, and plans to enroll 454 subjects with DMD (227 subjects exposed to SRP-9001 and 227 subjects unexposed to SRP-9001).

The available safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS) or a postmarketing requirement (PMR) safety study. There is no postmarketing commitment (PMC) for a safety study for this product.

REFERENCES

1. Duan D, Goemans N, Takeda Si, Mercuri E, Aartsma-Rus A. Duchenne muscular dystrophy. *Nature Reviews Disease Primers*. 2021;7(1):13. doi: 10.1038/s41572-021-00248-3.
2. Venugopal V, Pavlakis S. StatPearls [Internet]: Duchenne Muscular Dystrophy. Treasure Island (FL): StatPearls Publishing; 2022.
3. Ryder S, Leadley RM, Armstrong N, Westwood M, de Kock S, Butt T, et al. The burden, epidemiology, costs and treatment for Duchenne muscular dystrophy: an evidence review. *Orphanet Journal of Rare Diseases*. 2017;12(1):79. doi: 10.1186/s13023-017-0631-3. PubMed Central PMCID: PMC5405509.
4. Birnkrant DJ, Bushby K, Bann CM, Apkon SD, Blackwell A, Brumbaugh D, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. *Lancet Neurol*. 2018;17(3):251-67. Epub 2018 Feb 3. doi: [https://doi.org/10.1016/S1474-4422\(18\)30024-3](https://doi.org/10.1016/S1474-4422(18)30024-3).
5. U.S. Food and Drug Administration. Briefing Document: Toxicity Risks of Adeno-associated Virus (AAV) Vectors for Gene Therapy (GT) 2021 [December 21, 2022]. Available from: <https://www.fda.gov/media/151599/download>.
6. U.S. Food and Drug Administration. Meeting Presentation: Toxicity Risks of Adeno-associated Virus (AAV) Vectors for Gene Therapy (GT) 2021 [December 21, 2022]. Available from: <https://www.fda.gov/media/151969/download>.
7. U.S. Food and Drug Administration. Long Term Follow-Up After Administration of Human Gene Therapy Products: Guidance for Industry 2020 [December 21, 2022]. Available from: <https://www.fda.gov/media/113768/download>.
8. Birnkrant DJ, Bushby K, Bann CM, Alman BA, Apkon SD, Blackwell A, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. *Lancet Neurol*. 2018;17(4):347-61. Epub 2018 Apr. doi: 10.1016/S1474-4422(18)30025-5.
9. Palma LMP, Vaisbich-Guimarães MH, Sridharan M, Tran CL, Sethi S. Thrombotic microangiopathy in children. *Pediatr Nephrol*. 2022;37(9):1967-80. Epub 2022 Jan 18. doi: 10.1007/s00467-021-05370-8.
10. Chand DH. CTGTAC 09.03.2021 Meeting Presentation: Clinical Findings of Thrombotic Microangiopathy (TMA) [February 8, 2023]. Available from: <https://www.fda.gov/media/151999/download>.
11. U.S. Food and Drug Administration. April - June 2020 | Potential Signals of Serious Risks/New Safety Information Identified by the FDA Adverse Event Reporting System (FAERS) 2020. Available from: <https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/april-june-2020-potential-signals-serious-risksnew-safety-information-identified-fda-adverse-event>.

12. U.S. Food and Drug Administration. Package Insert - ZOLGENSMA 2022. Available from: <https://www.fda.gov/media/126109/download>.
13. U.S. Food and Drug Administration. CTGTAC 09.02.21 Meeting Transcript Day 1: Toxicity Risks of Adeno-associated Virus (AAV) Vectors for Gene Therapy (GT) 2021. Available from: <https://www.fda.gov/media/154120/download>.
14. Guillou J, de Pellegars A, Porcheret F, Frémeaux-Bacchi V, Allain-Launay E, Debord C, et al. Fatal thrombotic microangiopathy case following adeno-associated viral SMN gene therapy. *Blood Adv.* 2022;6(14):4266-70. doi: 10.1182/bloodadvances.2021006419.
15. Chand DH, Zaidman C, Arya K, Millner R, Farrar MA, Mackie FE, et al. Thrombotic Microangiopathy Following Onasemnogene Apeparvovec for Spinal Muscular Atrophy: A Case Series. *J Pediatr.* 2021;231:265-8. Epub 2020 Nov 28. doi: <https://doi.org/10.1016/j.jpeds.2020.11.054>.
16. Lahoria R, Milone M. Rhabdomyolysis featuring muscular dystrophies. *J Neurol Sci.* 2016;361:29-33. Epub 2015 Dec 10. doi: 10.1016/j.jns.2015.12.013.

APPENDIX

Materials Reviewed

Table A1: Materials reviewed in support of this assessment

Date	Source	Document Type	Document(s) Reviewed
28-Sept-2022	Sponsor	BLA 125781/0.0	Module 1.16.1, Risk Management (Non-REMS) Module 2.4, Nonclinical Overview Module 2.5, Clinical Overview Module 2.7.4, Summary of Clinical Safety Module 5.3.5, Interim Clinical Study Reports for Studies SRP-9001-101, -102, -103 and Integrated Summary of Safety (ISS)
30-Jan-2023	Sponsor	BLA 125781/0.17	Module 1.16.1, Risk Management (Non-REMS) Module 2.7.4, 120 Day Safety Update Report
21-Feb-2023	Sponsor	BLA 125781/0.21	Module 1.11.3 Clinical Information Amendment Module 1.16.1, Risk Management (Non-REMS)
02-Mar-2023	Sponsor	BLA 125781/0.25	Module 1.2 Cover Letter Module 1.16.1 Risk Management (Non-REMS)
02-Jun-2023	Sponsor	BLA 125781/0.62	Module 1.2 Cover Letter Module 1.11.3 Clinical Information Amendment Module 1.16.1 Risk Management (Non-REMS)

Table A2: DPV Information Requests and Sponsor Responses

IR #	IR sent	Description of IR	Sponsor response received	STN
DPV IR #1	21-Dec-2022	Request for postmarketing safety study and updated PVP	09-Jan-2023	BLA 125781/0.11
DPV IR #2	13-Feb-2023	Revised PVP feedback, study synopsis feedback	21-Feb-2023	BLA 125781/0.21
DPV IR #3	23-Feb-2023	Revised PVP feedback	02-Mar-2023	BLA 125781/0.25
DPV IR #4	30-May-2023	Revised PVP feedback	02-Jun-2023	BLA 125781/0.62

Abbreviations: Division of Pharmacovigilance (DPV), Information Request (IR), submission tracking number (STN)