CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211970Orig1s000

CLINICAL REVIEW(S)

Office of Drug Evaluation-I: Decisional Memo

Date	August 19, 2019
From	Ellis F. Unger, MD Director Office of Drug Evaluation-I Office of New Drugs Center for Drug Evaluation and Research (CDER)
Subject	Office Director Decisional Memo
New Drug Application (NDA) #	211970
Applicant Name	Sarepta Therapeutics
Date of Submission	December 19, 2018
PDUFA Goal Date	August 19, 2019
Proprietary Name/ Established (USAN) Name	Vyondys 53 Golodirsen intravenous solution
Dosage Forms/Strengths	100 mg/2mL solution in a single-use vial 30 mg/kg administered weekly as IV infusion over 35-60 minutes
Indication originally sought by applicant (see page 29 for final)	Treatment of Duchenne muscular dystrophy (DMD) in pediatric and adult patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping.
Action:	*Complete response*

Material Reviewed/Consulted - Action Package, including:	
Regulatory Project Manager	Yuet (Fannie) Choy
Medical Officer/Clinical	Christopher Breder
Clinical Pharmacology/Pharmacometrics	Bilal AbuAsal, Hobart Rogers, Atul Bhattaram, Christian Grimstein, Sabarinath Sreedharan, Ramana Uppoor
Biometrics (Statistical)	Xiang Ling
Nonclinical (Pharmacology Toxicology)	Barbara Wilcox, Lois Freed, Paul Brown
Office of Biotechnology Products	Ashutosh Rao, Amy Rosenberg
Office of New Drug Quality Assessment	Rohit Tiwari, Su Tran, Rao Kambhampati, Wendy Wilson-Lee, Erin Kim, Nallaperumal Chidambaram, Jennifer Patro, Jesse Wells, Ying Zhang, Martha Heimann
Office of Scientific Investigations	Cara Alfaro, Phillip Kronstein, Kassa Ayalew
Microbiology	Jennifer Patro, Jesse Wells, Martha Heimann
Office of Study Integrity and Surveillance	Arindam Dasgupta, Charles Bonapace
Immunogenicity Review (OPQ)	Seth Thacker, Daniela Verthelyi
Office of Prescription Drug Promotion	Sapna Shah, Aline Moukhtara
Division of Medication Error Prevention and Analysis	Chad Morris, Briana Rider, Lolita White, Danielle Harris
Associate Director for Labeling	Tracy Peters
Cross-Discipline Team Leader	Teresa Buracchio
Director (acting) Division of Neurology Products	Eric Bastings

1. Introduction

Sarepta Therapeutics is seeking accelerated approval for golodirsen for the proposed indication:

> "[redacted] (b) (4) is indicated for the treatment of Duchenne muscular dystrophy (DMD) in pediatric and adult patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 53 skipping. This indication is approved under accelerated approval based on an increase in dystrophin production *[see Clinical Studies (14)]*. [redacted] (b) (4) Continued approval for this indication may be contingent upon further verification of a clinical benefit in confirmatory trials."

2. Background

Description:

Golodirsen is an antisense oligonucleotide (ASO) of the phosphorodiamidate morpholino oligomer (PMO) subclass that was designed to target premessenger ribonucleic acid (mRNA) in the cell nucleus to alter the splicing process that creates a mature mRNA. Golodirsen's putative mechanism of action is to target a region in exon 53 to restore the mRNA reading frame and induce the production of *de novo* truncated dystrophin protein. Golodirsen has been developed as once-weekly intravenous (IV) infusions at a dose of 30 mg/kg infused over 35 to 60 minutes. Development of golodirsen proceeded under IND 119982.

Disease Background:

Duchenne muscular dystrophy is an X-linked recessive neuromuscular disorder caused by mutations of the dystrophin gene located on the short arm of the X chromosome. These mutations disrupt the mRNA reading frame, leading to the absence or near-absence of dystrophin protein in muscle cells. The disorder affects 1 in ~3,600 boys (~1 in 10,000 to 14,000 males). Patients who are amenable to skipping exon 53 constitute ~8% of the DMD patient population.

Dystrophin is thought to maintain the structural integrity of the muscle cell membrane by connecting the cytoskeleton to the underlying extracellular matrix and by acting as a scaffold for several molecules that also contribute to normal muscle physiology. Absence of dystrophin leads to mitochondrial dysfunction and damage, with inflammatory processes also appearing to contribute to muscle pathology. Muscle fibers ultimately undergo necrosis with replacement by adipose and connective tissue. Principal disease manifestations include progressive degeneration of skeletal and cardiac muscle, leading to loss of physical function in childhood and adolescence with premature death from respiratory and/or cardiac failure in the second to fourth decade.

There are two FDA-approved treatments for DMD. Deflazacort is a glucocorticoid approved for treatment of DMD in patients 2 years of age and older. Deflazacort is purported to have anti-inflammatory and immunosuppressive properties and has been shown to improve muscle strength in DMD patients. Eteplirsen was given accelerated approval by the Center for Drug Development and Research (CDER) on September 19, 2016, for the treatment of a subset of DMD patients with mutations in the dystrophin gene that are amenable to exon 51 skipping.

CDER's approval was based on the demonstration of a small increase in truncated dystrophin protein in 12 boys with DMD. The clinical benefit of this increase has not been established. The required confirmatory study, to verify and describe the clinical benefit, has not yet been initiated by Sarepta.

3. Product Quality

The Office of Product Quality (OPQ) recommends approval of this NDA. Please refer to the OPQ review for details of their assessment.

4. Nonclinical Pharmacology/Toxicology:

The following is based on the primary and supervisory reviews by Drs. Barbara Wilcox and Lois Freed, respectively:

The kidney was the 1° target organ in all species and strains tested (C57BL/6NCrl mouse, CByB6F1-Tg(HRAS)2Jic WT mouse, Sprague Dawley rat, and cynomolgus monkey), and kidney is a well-known target organ of ASOs. Golodirsen, a PMO ASO, is primarily distributed to the kidney and excreted intact in urine (~75% of dose) following parenteral administration.

The applicant states that golodirsen's nonclinical safety profile is similar to (or consistent with) that of eteplirsen; however, any comparisons between golodirsen and eteplirsen are limited by several factors. The two drugs were not tested in the same studies: a 26-week toxicity study in mouse, conducted for golodirsen, was not conducted for eteplirsen, and there were differences in the dosing regimen used for golodirsen and eteplirsen in the 39-week IV toxicity studies in cynomolgus monkey (30-minute infusion vs bolus injection, respectively, and higher doses were tested for golodirsen [0, 8, 200, and 400 mg/kg] than for eteplirsen [0, 5, 40, and 320 mg/kg]). The notable observations are summarized below.

In the monkey, the pattern of microscopic renal changes differed between golodirsen and eteplirsen (e.g., golodirsen resulted in a wider distribution of toxicity in kidney, and only eteplirsen resulted in degeneration), but the findings were generally similar in severity. Findings in the femorotibial joint and heart were observed with golodirsen but not with eteplirsen – differences that may reflect differences in C_0/C_{max} (higher with eteplirsen) and area under the concentration-time curve (AUC, higher with golodirsen).

The most notable difference between golodirsen and eteplirsen was observed in the juvenile rat. Following administration of golodirsen at a high dose of 900 mg/kg, there were multiple premature deaths due to renal toxicity/failure; tubular degeneration/regeneration was observed at the mid-dose (300 mg/kg) and high-dose (900 mg/kg). When eteplirsen was administered to male Sprague Dawley rats during the same postnatal period (postnatal days 14 to 77) at the same weekly doses (0, 100, 300, or 900 mg/kg IV) there were no deaths or drug-related clinical signs. Microscopic changes in kidney were observed, which were correlated with changes in clinical pathology markers of renal function (e.g., increased blood urea nitrogen [BUN], creatinine, and Pi). However, eteplirsen had no effect on urinary bladder/ureter, and no instances of the severe renal impairment or renal failure were reported, unlike golodirsen.

Based on the available data in juvenile rat, it appears that golodirsen has a greater risk for renal toxicity than does eteplirsen; renal failure leading to death was observed only with golodirsen.

While there are interspecies differences in the anatomical and functional development of the kidney that need to be taken into consideration, rat is considered a relevant species for human. At the recommended human dose of 30 mg/kg, plasma exposure (AUC of ~90 µg*hr/mL) is only 2.6-fold lower than that at the no-adverse-effect-level in the most sensitive species (juvenile rat). The human relevance of the femorotibial joint synovial hyperplasia observed in monkey with golodirsen (but not eteplirsen) is uncertain. Based on the available information, it does not appear to be a toxicity typically observed with ASOs.

Dr. Wilcox concluded: "The pivotal nonclinical studies indicate that severe renal impairment (including irreversible renal damage in the juvenile animals) can result from chronic exposure to golodirsen, with only a small safety margin based on exposure. However, because kidney function is monitorable, the nonclinical data are considered adequate to support approval of golodirsen for the treatment of DMD in patients with mutations amenable to exon 53 skipping therapies."

Dr. Freed concluded: "The nonclinical studies of golodirsen are adequate to support approval for the proposed indication, although the data suggest the potential for serious renal toxicity in humans."

5. Clinical Pharmacology

Golodirsen is metabolically stable and excreted mostly unchanged in the urine. Findings of a dedicated renal impairment study in adult non-DMD subjects indicate that kidney function impacts the exposure of golodirsen. In subjects with Stage 2 CKD (creatinine clearance ≥ 60 and < 90 mL/min/1.73 m^2), golodirsen's AUC increased approximately 1.2-fold and C_{max} was unchanged. In subjects with Stage 3 CKD (creatinine clearance ≥ 30 and < 60 mL/min/1.73/m2), the AUC and C_{max} increased approximately 1.9-fold and 1.2-fold, respectively. Subjects with Stage 3 CKD were not studied. *However, dose adjustment for golodirsen based on creatinine clearance is not feasible because creatinine clearance is not considered as a reliable metric to characterize renal function in DMD population.* This is because of the DMD disease characteristics predominantly affecting muscles. Estimated creatinine clearance values derived from the Cockcroft-Gault equation and the threshold definitions for mild, moderate, and severe renal impairment in otherwise healthy adults would not be generalizable to DMD patients. *Monitoring of changes in renal function in DMD patients is an issue that needs further scientific research.*

The clinical pharmacology review team recommends labeling communicating that golodirsen exposure will be increased in patients with impaired renal function, and patients with known renal impairment should be closely monitored during treatment.

6. Clinical Microbiology

Not applicable.

7. Clinical/Efficacy

Indication Sought:

As above, Sarepta is seeking accelerated approval of golodirsen for the proposed indication:

"[redacted] (b) (4) is indicated for the treatment of Duchenne muscular dystrophy (DMD) in pediatric and adult patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 53 skipping. This indication is approved under accelerated approval based on an increase in dystrophin production *[see Clinical Studies (14)]*. [redacted] (b) (4) Continued approval for this indication may be contingent upon further verification of a clinical benefit in confirmatory trials."

The Eteplirsen Review:

The basis for consideration of accelerated approval of golodirsen is CDER's September 19, 2016, accelerated approval of eteplirsen, a related Sarepta ASO indicated for the treatment of DMD in patients with a confirmed mutation of the DMD gene amenable to exon 51 skipping. The eteplirsen review and regulatory decision are germane to the golodirsen NDA.

The accelerated approval of eteplirsen was contentious;[1,2] the history is well documented and only the salient points are summarized herein. The original focus of the 2015-16 eteplirsen review was on clinical data, specifically subjects' physical performance as assessed by the 6-minute walk test and the North Star Ambulatory Assessment (NSAA). As the May 26, 2016 goal date was approaching, the Office of New Drugs (OND) and CDER could not reach agreement on the regulatory action for this NDA – OND favored issuance of a *Complete Response* whereas CDER favored *Approval*. The Center Director made the decision to advise the applicant to pursue accelerated approval based on a surrogate endpoint. The applicant was informed:

> "If you are successful in showing, to FDA's satisfaction, a meaningful increase in dystrophin by Western blot analysis between the paired pre-and post-treatment samples, we expect to be able to grant an accelerated approval within four business days of receiving the data (assuming all other aspects of the application are approvable)."

There was agreement on the potential utility of dystrophin as a surrogate marker to support accelerated approval, although all recognized that the specific threshold for an increase in dystrophin that was "reasonably likely" to predict clinical benefit was a matter of judgment. Of note, the above advice called for a "meaningful increase in dystrophin," without further clarification. At the time, there was little consensus on the actual magnitude of increase needed, although some experts in the scientific community had opined that 10% was a reasonable objective. (Of note, an inherent difficulty germane to the question of "reasonably likely" is the reality that the dystrophin produced by these drugs is truncated, and the functionality of this abnormal dystrophin cannot be tested. Accelerated approval therefore depended on the untestable assumption that the truncated dystrophin was functional. For the sake of simplicity, however, I will not consider this further.)

[1] https://www.accessdata fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_Redacted.pdf, accessed 8/14/2019

[2] https://www.accessdata fda.gov/drugsatfda_docs/nda/2017/SeifeProduction_2017_07_24.pdf, accessed 8/14/2019

In the study that ultimately supported eteplirsen's accelerated approval, 13 patients underwent baseline muscle biopsies, followed by treatment with weekly open-label eteplirsen (30 mg/kg) for 48 weeks, after which dystrophin levels were reassessed by Western blot. In the 12 patients with evaluable results, the dystrophin level increased, on average, from 0.16% ± 0.12% (mean ± SD of normal) to 0.44% ± 0.43% ($p < 0.05$). The median increase after 48 weeks was 0.1% of normal, i.e., one part in 1000.

No one on the review team in the Division of Neurology Products, no one in the Office of Drug Evaluation-I, and no one in the Office of New Drugs opined that this small level of dystrophin was "reasonably likely" to predict clinical benefit, and no one supported accelerated approval. Subsequently, the European Committee for Medicinal Products for Human Use (CHMP) provided a similar opinion: "efficacy and safety of the above mentioned medicinal product is not properly or sufficiently demonstrated. Therefore, the CHMP has recommended the refusal of the granting of the conditional marketing authorisation for Exondys."[3]

The Eteplirsen Approval:

Before I had completed my memorandum outlining the reasons for ODE-I's *Complete Response* action, regulatory authority for the NDA was taken by the CDER Center Director, who wrote a memorandum and letter (9/19/2016) in support of accelerated approval.

Disagreeing with the action of the Center Director, I appealed CDER's decision to FDA's Office of Scientific Integrity. The Office of the Chief Scientist convened the Agency Scientific Dispute Process Review Board (the SDR Board) to consider the appeal. The SDR Board was chaired by the acting Chief Scientist (Dr. Luciana Borio). After their investigation, she concluded:

> "By any meaningful objective standard, however, the overall evidence derived from eteplirsen's limited clinical development program does not support that the levels of dystrophin produced by eteplirsen at the doses studied are reasonably likely to provide clinical benefit."

Ultimately, however, the appeal was decided by the Commissioner, who deferred "…to Dr. Woodcock in her role as Center Director to make the decision to approve eteplirsen under the accelerated approval provisions."

For drugs granted accelerated approval, postmarketing confirmatory trials are required to verify and describe the anticipated clinical benefit. As outlined in the letter of approval, the applicant is required to conduct a 2-year randomized, double-blind, controlled trial of eteplirsen in patients with a confirmed DMD gene mutation amenable to exon 51 skipping. Patients are to be randomized to the approved dosage of eteplirsen (30 mg/kg weekly) or to a dosage that would provide significantly higher exposure, e.g., 30 mg/kg daily. This design obviated the need for a placebo control group, which few patients with exon 51 mutations appeared likely to accept. The primary endpoint is the North Star Ambulatory Assessment. The goal is to verify and describe the clinical benefit through a comparison of clinical effect(s) of the to-be-marketed dose with a dose that was 7-fold higher than the to-be-marketed dose. Demonstration of a dose-response would verify the clinical benefit. Moreover, because the to-be-marketed dose

[3] https://www.ema.europa.eu/en/documents/assessment-report/exondys-epar-refusal-public-assessment-report_en.pdf, accessed 8/14/2019

produced only a small amount of dystrophin in the absence of apparent toxicity, the study could provide valuable information by showing more robust dystrophin production at a higher dose.

The draft study protocol was to have been submitted by 10/2016, with trial completion by 11/2020. Given that completion of the 2-year study was required by 11/2020, the last patient should have been enrolled by 11/2018. In fact, the study has not been initiated.

Development of Golodirsen:

The development of other antisense oligonucleotides was proceeding at the time of eteplirsen's approval, and Sarepta was keenly interested in their pathways to approval.

In preparation for a 2/6/2018, Type C Guidance meeting, Sarepta questioned:

> "Does the Agency agree that the de novo dystrophin protein produced by the 25 patients treated with golodirsen at Week 48 in Study 4053-101 is an appropriate surrogate endpoint which is reasonably likely to predict clinical benefit and to support accelerated approval?"

Recognizing the Center Director's prior decision on the accelerated approval of eteplirsen, the Division of Neurology Products and ODE-I addressed their question with this preliminary response:

> "Eteplirsen was approved based on minimal increases in dystrophin, a surrogate marker, that led to a conclusion at the CDER level that such increases were reasonably likely to predict clinical benefit. Based on this precedent, and barring any evidence to suggest otherwise, a statistically significant increase in de novo (truncated) dystrophin protein in Study 4053-101 based on a scientifically sound experimental design and rigorous analytical methods potentially could serve as a basis for accelerated approval of golodirsen for the treatment of Duchenne muscular dystrophy."

Data Submitted in this NDA in Support of Accelerated Approval of Golodirsen:

Study Design:

One study (Study 4053-101) was submitted to provide evidence of the biological activity of golodirsen in support of accelerated approval. This is an ongoing, Phase 1/2, first-in-human, multicenter, dose-titration study to assess the safety, tolerability, efficacy, and pharmacokinetics of once-weekly intravenous infusions of golodirsen in patients with DMD and a confirmed mutation in the DMD gene amenable to exon 53 skipping. This study is being conducted in 2 parts: Part 1 is complete; Part 2 is ongoing.

Part 1 was a randomized, double-blind, placebo-controlled, dose-titration evaluation to assess the safety, tolerability, and pharmacokinetics of golodirsen. Twelve (12) patients were randomized to golodirsen (n=8) or placebo (n=4), and baseline biopsies of the biceps brachii muscle were collected in all patients. Test drugs were infused weekly, and the dose was escalated over approximately 12 weeks (i.e., 4, 10, and 20 mg/kg, each for 2 weeks, followed by 30 mg/kg beginning at Week 7).

Part 2 is an ongoing, long-term, open-label evaluation of the efficacy and safety of 30 mg/kg golodirsen in patients amenable to exon 53 skipping. All 12 patients from Part 1 continued into Part 2, with 13 new patients added (total number of patients in Part 2 = 25). Thus, 8 of 25 patients received golodirsen in both Parts 1 and 2 of the study, and 17 of 25 patients received golodirsen exclusively in Part 2.

Patients in Part 2 also had biopsies of the biceps brachii before institution of treatment. Treated patients from Parts 1 and 2 had a second muscle biopsy from the contralateral biceps muscle at Week 48 of Part 2. Because the 8 patients who were randomized to golodirsen in Part 1 had received ~12 weeks of treatment prior to entering Part 2, the duration of golodirsen exposure prior to the Week 48 biopsy varied. Functional data are also being collected, i.e., 6-minute walk distance and pulmonary function tests.

An additional cohort of 14 untreated patients, not amenable to exon 53 skipping, was enrolled into Part 2 and participated in scheduled assessments for 144 weeks, but at a lower frequency than the treated patients. The untreated patient group was intended to evaluate the natural history of the disease for patients who were not amenable to exon 53 skipping. With different mutations, these patients are not considered to constitute a valid control group for golodirsen-treated patients. Untreated patients did not undergo muscle biopsies.

Results:

For the 25 patients in Part 1/2, the baseline dystrophin level was 0.10 ± 0.07 (mean ± SD). At Week 48, the mean dystrophin level was 1.02 ± 1.03 (mean ± SD) for a mean increase of 0.92 ± 1.01.

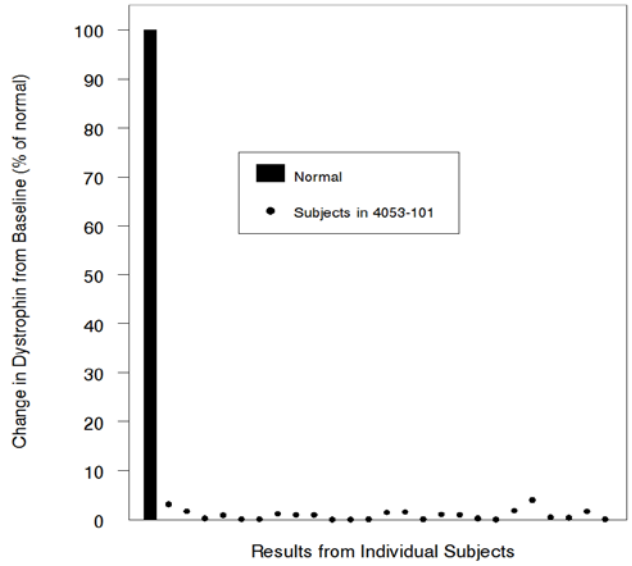
As shown by the applicant (Table 1), the mean increases in truncated dystrophin are similar in response to golodirsen and eteplirsen in patients with mutations amenable to exon 53 and exon 51 skipping, respectively – with absolute mean increases of 0.9%, i.e., 9 parts in a thousand. We agree.

Table 1: Dystrophin by Western Blot: Comparison of Eteplirsen and Golodirsen

	Western Blot Percent of Normal	
	Eteplirsen Week 180	**Golodirsen Part 2 Week 48**
Mean (Baseline/Untreated)	0.08	0.095
Mean (Treated-Week 180)	0.93	1.019
Absolute Increase	0.85	0.924
P-value	0.007	<0.001

Figure 1 shows the individual changes in dystrophin for the 25 patients in Study 4053-101. These are shown on a normal (100%) scale to place the data in proper perspective and avoid exaggeration of the effect size.

Figure 1: Study 4053-101 – Change in Dystrophin Relative to Normal Levels



With respect to clinical data, Figure 2 shows progressive loss of mean (± SD) 6-minute walk distance by visit for the 25 patients in Study 4053-101, with individual responses shown by chronological age in Figure 3.

Figure 2: Study 4053-101 – 6-minute Walk Distance by Visit (mean ± SD)

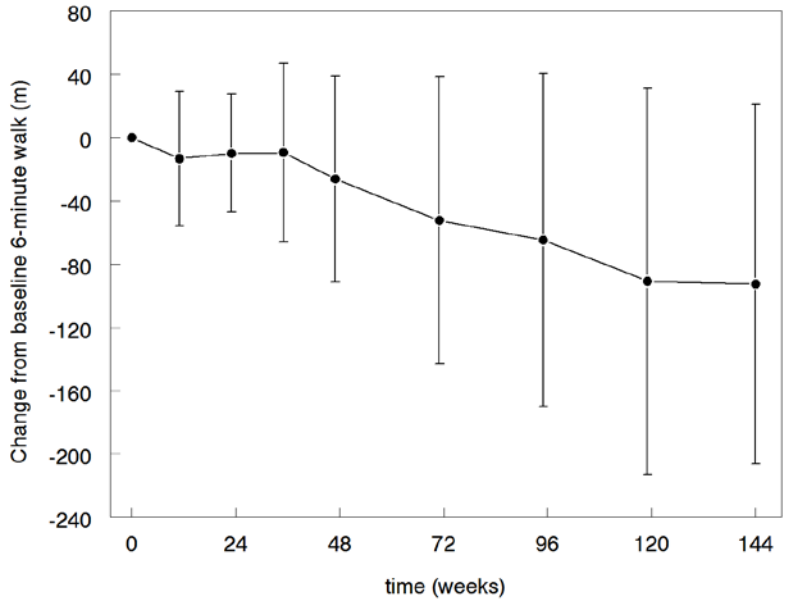
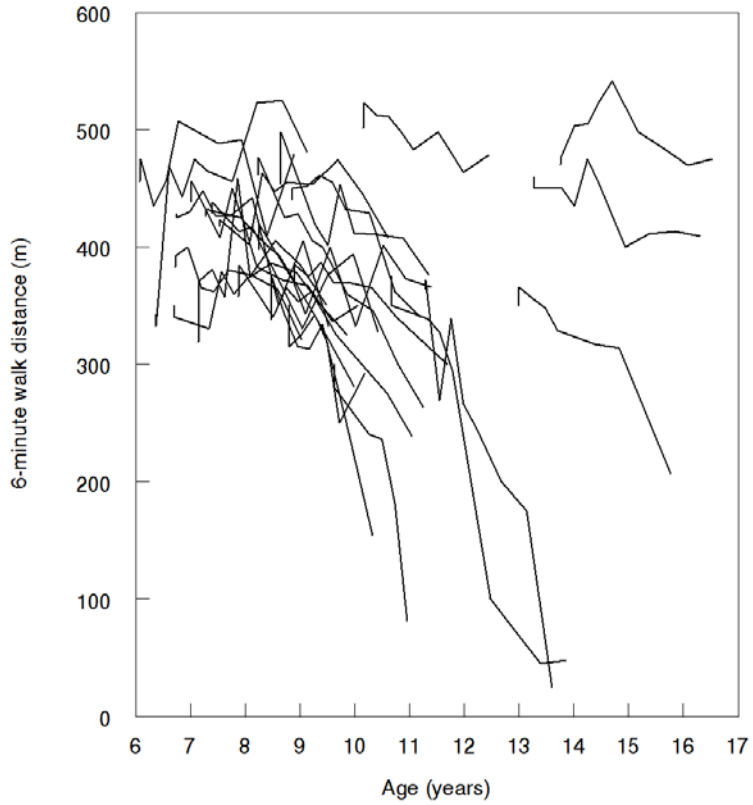


Figure 3: Study 4053-101 – Individuals' 6-minute Walk Distances by Actual Age

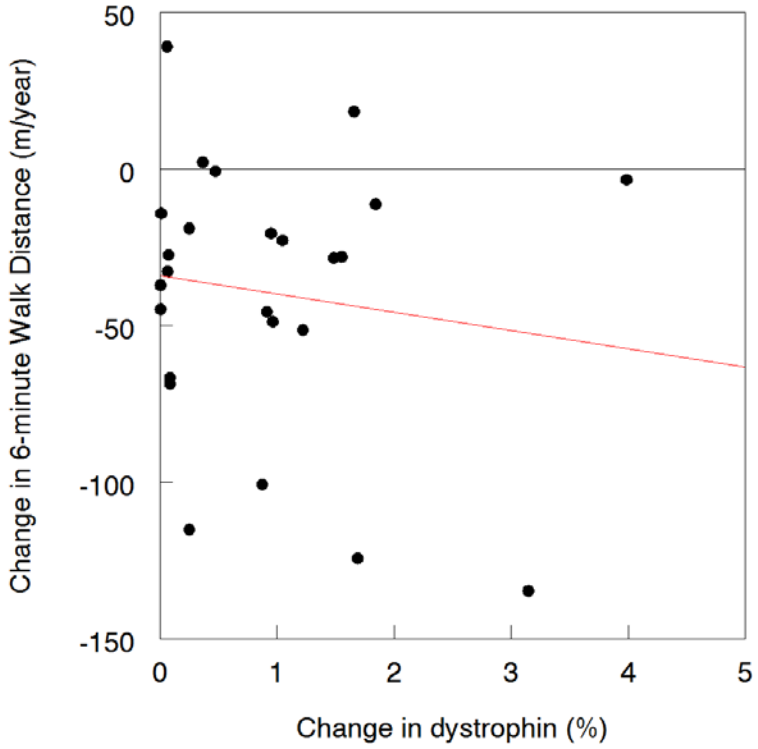


Note that the 6-minute walk provides a direct measure of patients' function and would be an acceptable clinical endpoint in DMD studies. The data from Study 4053-101 are uncontrolled and difficult to interpret but do not appear to be different than natural history data reviewed as part of the eteplirsen NDA. Certainly, they do not show the kind of dramatic effect that could be acceptable for approval based on a comparison with natural history data (see FDA's Guidance for Industry: E 10 Choice of Control Group and Related Issues in Clinical Trials).

Importantly, Study 4053-101 recorded longitudinal changes in 6-minute distance and changes in dystrophin concentration in 25 patients – certainly not an inconsequential amount of data. If changes in dystrophin concentration of the magnitude observed in the study are reasonably likely to predict clinical efficacy, one might expect a positive correlation between changes in the pharmacodynamic marker (dystrophin) and the clinical effect (6-minute walk distance).

For each of the 25 patients in Study 4053-101, the change in their 6-minute walk distance was calculated as a function of time in meters (m) per year using linear regression, i.e., a slope, during their time of observation. A positive value indicates improvement in performance with respect to time; a negative value indicates worsening of performance. (Data were obtained from \0004\m5\datasets\4053-101\analysis\adam\datasets\adbi.xpt and adeff.xpt.) Figure 4 shows the correlation between change in dystrophin (x-axis) and change in 6-minute walk distance (y-axis).

Figure 4: Correlation Between Change in Pharmacodynamic Marker (Change in Dystrophin) and Clinical Effect (Change in 6-minute Walk Distance). R = 0.14



The correlation between the change in 6-minute walk distance/year and change in dystrophin is quite poor (R=0.14). Moreover, to the extent that one can interpret the slope of this regression line, it is not positive, as would be expected if changes in dystrophin of this magnitude predicted efficacy. *With no correlation between change in dystrophin and change in physical performance, the data from these 25 patients provide no evidence to support the concept that the change in the surrogate is reasonably likely to predict clinical benefit.*

Assessment of the Division of Neurology Products:

The primary clinical reviewer recommends a *Complete Response* action for this application. He considers the production of a small amount of truncated dystrophin, with evidence of exon skipping as demonstrated by reverse transcription polymerase chain reaction (RT-PCR), to constitute proof of concept. The reviewer does not believe that the applicant has provided substantial evidence of a treatment effect that is reasonably likely to predict clinical benefit:

> "The amount of dystrophin produced in response to golodirsen treatment is very small. While it is somewhat possible that the amount of dystrophin produced may lead to a modest clinical benefit, such a benefit does not appear reasonably likely."

In contrast, the management of the Division of Neurology Products endorses *Accelerated Approval*, stating:

> "The applicant has demonstrated a statistically persuasive, albeit small, increase in de novo (truncated) dystrophin protein in DMD patients with a genetic mutation amenable to exon 53 skipping with weekly intravenous administration of golodirsen 30 mg/kg, in a

> study with a scientifically-sound design, and using rigorous analytical methods. Although there remains uncertainty regarding the level of dystrophin that would be likely to confer clinical benefit, the increase in dystrophin levels demonstrated for golodirsen is similar in size to that established for eteplirsen, a drug that received accelerated approval based on a conclusion by CDER that the increase in dystrophin level was reasonably likely to predict clinical benefit. Based on this precedent, and barring any evidence to suggest otherwise, the statistically significant increase in de novo (truncated) dystrophin protein demonstrated in Study 4053-101 supports accelerated approval of golodirsen for the treatment of DMD in patients with a genetic mutation amenable to exon 53 skipping."

In the context of the Center's 2016 accelerated approval of eteplirsen, based on production of a small quantity of dystrophin (mean <1% of normal), the Division appears to consider this a "settled matter." Their memorandum, written by subject matter experts in neurology, never states the belief that the quantity of dystrophin produced by golodirsen is reasonably likely to predict clinical benefit. The memo doesn't address the quantity of truncated dystrophin that would be reasonably likely to predict clinical benefit. In short, the memo supports accelerated approval based solely on precedent, the Center Director's 2016 accelerated approval of eteplirsen.

Finally, if one accepts that a small, 0.9%, mean change in dystrophin is reasonably likely to predict clinical benefit, it seems likely that the clinical benefit associated with this change would be commensurately small. The clinical results of Study 4053-101 further suggest that if there is indeed an effect of golodirsen, the effect is small.

8. Safety

There are two important safety issues: 1) infections related to vascular access; and 2) renal toxicity. Both are potentially life-threatening, and the latter is difficult or impossible to monitor.

Infections Related to Vascular Access:

In 2016, in my assessment of the eteplirsen NDA, I cautioned:

> "Of note, many patients in these studies are now receiving infusions through chronic indwelling catheters. Although we are not aware of any serious adverse events caused by infections, with approval of this drug there would undoubtedly be serious infections and possibly rare deaths eventually. The risk of an indwelling IV line in patients on chronic corticosteroids should be mentioned in labeling if the drug is approved."

Since the 2016 approval of eteplirsen, Sarepta has been submitting quarterly Periodic Adverse Drug Experience Reports (PADERs). The most recent PADER (7/17/2019) states that a total of 469 patients have been exposed to commercial eteplirsen through 3/18/2019.

Importantly, late in the review cycle I learned that reports of significant device infections, bacteremia, sepsis, septic shock, and deaths have been submitted through quarterly PADERs. Some cases have been reported spontaneously to FDA's Adverse Event Reporting System (FAERS). These cases, as summarized by the Division, are shown in Table 2. I found no mention of these cases in the golodirsen NDA.

Table 2: Eteplirsen's Postmarketing Reports of Device Infections, Bacteremia, and Sepsis

FAERS#	Date	Medical History	Preferred Terms	Narrative	Comments
13122403	1/2017	Atrial fibrillation, Cachexia, Cardiomyopathy, Decubitus ulcer, Duchenne muscular dystrophy, Gastrostomy tube site complication, Muscle contracture, Respiratory failure, Tracheostomy, Vascular device user	**Septic shock, Sepsis,** Respiratory distress, Ischaemic hepatitis, Cardiac arrest	Patient with ventilator-dependence, g-tube, **port**. Also with chronic decubitis ulcers. Admitted to hospital with respiratory distress, cardiac arrest, **sepsis**. Death from cardiac arrest. Death was attributed to "end-stage DMD."	confounded by ventilator, decub ulcers
13268695	2/2017	Autism spectrum disorder, Colonoscopy, Dialysis, Duchenne muscular dystrophy, Joint contracture, Obesity, Respiratory failure, Scoliosis, Tenotomy, Tooth disorder, Tracheostomy, Ventricular dyssynchrony	Tachycardia, **Pseudomonal bacteraemia,** Pneumonia, Pain in extremity, Malaise, Hypertension, Chest pain, Anxiety	Patient with ventilator-dependence and **port**. Developed bilateral leg pain and chest pain after port de-accessed. Taken to ED for tachycardia and hypertension. Diagnosed with pneumonia and ***pseudomonas*** **bacteremia**. **Port + for pseudomonas and removed. Exondys discontinued as family did not want port replaced.**	confounded by ventilator
14077329	7/2017	**Central venous catheterisation**, Pericardial effusion	Pyrexia, Dehydration, **Bacteraemia,** Abdominal pain	Patient with **port**. The patient presented with a fever of 103F and abdominal pain and was hospitalised for dehydration and **bacteremia. Bacterial culture grew *Klebsiella* and treatment included IV antibiotics.**	**port** likely source of infection
14284355	11/2017	Not reported	**Device related infection**	Patient became ill, went to ED, **treated with antibiotics for presumed port infection; port culture reported to be positive but organism not identified;** (b) (6)**: admitted to hospital for "port issues."**	**port** likely source of infection
14484983	1/2019	Not reported	**Device related infection**	Patient noticed **discharge from port and went to hospital where port was removed.**	**port** likely source of infection
14828296	3/2018	Abdominal pain, Central venous catheterisation, Chills, Gastrointestinal tube insertion, Leukopenia, Pyrexia, Thrombocytopenia	**Sepsis,** Respiratory failure, Gallbladder disorder	Patient taken to ED with fever and decreased oral intake, received IV fluids: (b) (6): taken to ED with **septic shock (fever, abdominal pain, tachycardia, decreased urine) presumed secondary to line infection. Line culture with *Strep pyogenes*.**	**port** likely source of infection
15143119	3/2018	Central venous catheterisation, Device related infection	**Injection site infection,** Infusion site swelling	Patient noticed **port infection and went to ED where port was removed.** Had Exondys infusion administered by peripheral IV on the same day and experienced swelling.	**port** likely source of infection
15182648	7/2018	Anaemia, Cardiomyopathy, Dependence on respirator, Gastrostomy, Inflammatory bowel disease, Muscle contracture, Respiratory failure	**Sepsis**, Oedema peripheral, Cardiac failure congestive	Patient with ventilator dependence, g-tube, **port**. (b) (6) patient hospitalized for peripheral edema and **sepsis**. (b) (6): patient **died** of "congestive heart failure."	death - multiple factors
15590967	UNK	Not reported	**Sepsis**	Patient went to ER for **possible sepsis**.	insufficient information
15699217	11/2018	Cardiomyopathy, Chronic respiratory failure, Depression, Hospitalisation, Hypotonia, Hypoxic-ischaemic encephalopathy, Implantable defibrillator insertion, Joint contracture , Mechanical ventilation, Obesity, Pneumonia, Seizure, Sinus arrest, Sleep apnoea syndrome, Spinal operation, Tracheostomy	**Septic shock, Sepsis**, Pneumonia, Multiple organ dysfunction syndrome, Cardio-respiratory arrest, Brain injury	Patient with pacemaker/AICD, ventilator, **port**. (b) (6): patient found pulseless at home; resuscitated for 10 minutes; cardiac arrest again in ED with 2 minutes of resuscitation; CT suggestive of aspiration pneumonia; diagnosed with **septic shock** secondary to pneumonia; patient comatose; CT head c/w diffuse anoxic injury. Removed from life support.	confounded by ventilator, aspiration pneumonia
16084969	UNK	Not reported	**Sepsis**	Patient's family member stated that the patient had **sepsis on an unknown date.**	insufficient information

Thus, we are aware of 11 cases reported with 469 patients exposed – a frequency of 2.3%. Because reporting in FAERS is voluntary for health care professionals, patients, and their advocates, we recognize that substantial underreporting is possible (conversely, the raw data may contain duplicate reports). In any case, it seems likely that the rate of serious infusion device-related infections with eteplirsen has been *at least* 2.3%.

Some may characterize these infections as device-related rather than drug-related and downplay their significance. This is a weak argument: these individuals would have had no reason to undergo implantation of a central intravenous infusion port other than to receive eteplirsen; many of these infections would not have occurred if the patients had not been receiving eteplirsen. *If these devices are necessary to deliver the drug, then these infections must be construed to be drug-related.*

Although the aforementioned information was obtained from the eteplirsen postmarketing experience, such information is directly applicable to the potential marketing of golodirsen, which too would be administered through implanted infusion ports in many patients.

We must also consider the data submitted from the golodirsen development program. Study drugs were administered via a central venous access port in approximately half of the patients in the golodirsen development program (~30 of 60). Some 30% of such patients (i.e., ~9) had device-related adverse events. These adverse events were primarily procedural pain, catheter site pain, catheter site bruises, and rash; the applicant noted that these adverse events did not lead to discontinuation or interruption of investigational product. I found no serious or severe adverse events of infection in the applicant's database (adae.xpt), and there were no reports of bacteremia or sepsis in the applicant's Summary of Clinical Safety. Accordingly, neither bacteremia nor sepsis are mentioned in the Division's review documents.

Some may cite the lack of reported device-related infections in the golodirsen development program as generally reassuring. Importantly however, only ~30 patients have received the drug through a central venous access port, and such patients were enrolled at highly specialized centers. With no infections reported in ~30 patients with infusion ports through a median exposure of ~1.5 years, based on the rule of 3, the estimated upper limit of the 95% confidence interval for the risk of a serious infections through 1.5 years is 1/(30/3), or about 10%.

We well recognize that, no matter the level of expertise of healthcare providers involved in inserting and managing central access ports, infections *will occur*, and the DMD patient population is at heightened risk in light of their chronic corticosteroid use and generally debilitated condition. Thus, the 2.3% or greater risk of serious infections reported in the eteplirsen postmarketing period is directly applicable to future patients who might receive commercially available golodirsen.

Renal Toxicity:

As noted in Section 4, above, the nonclinical reviews found significant risk of renal toxicity. Dr. Wilcox noted that severe renal impairment can result from chronic exposure to golodirsen, and cited irreversible renal damage in juvenile animals with only a small safety margin. Dr. Freed also found the potential for serious renal toxicity in humans. Based on the juvenile rat data, Dr. Freed estimates that golodirsen has a greater risk for renal toxicity than does eteplirsen. She

notes that renal failure leading to death was observed in the golodirsen juvenile rate study, but not in a similar eteplirsen juvenile rat study. Moreover, renal toxicity, including potentially fatal glomerulonephritis, has occurred with administration of other antisense oligonucleotides.

With golodirsen, the potential for clinical renal toxicity is magnified by two important factors:

1) As noted in Section 5, above, golodirsen is metabolically stable and excreted mostly unchanged in the urine; therefore, renal dysfunction increases golodirsen exposure. In subjects with reduced creatinine clearance (between 30 and 60 mL/min/1.73/m^2), exposure (area under the concentration-time curve) increased approximately 2-fold. Thus, renal toxicity leading to a decrease in renal function could be self-perpetuating, with the potential to occur rapidly.

2) Because patients with DMD have reduced muscle mass with attenuated creatinine production, serum creatinine cannot be used as the basis to monitor renal function or to adjust the dose of medications. (I calculated a mean serum creatinine of 0.25 mg/dL across all patients in the development program.)

The clinical pharmacology review team notes that "monitoring of changes in renal function in DMD patients is an issue that needs further scientific research." Cystatin C, kidney injury molecule-1 (KIM-1), and the urinary protein/creatinine ratio have been mentioned as monitorable parameters; however, none of the details have actually been worked out, and, accordingly, there are no practicable proposals for renal monitoring in the draft label. The Division's plan is to inform patients and prescribers about the risk, provide a warning about increased exposure with impaired renal function, and request enhanced pharmacovigilance.

The current working draft version of the Package Insert includes this language in Section 5.2 of WARNINGS AND PRECAUTIONS:

> "Renal function should be monitored in patients taking VYONDYS 53. Because of the effect of reduced skeletal muscle mass on creatinine measurements, creatinine may not be a reliable measure of renal function in DMD patients."

Obviously, this language leaves much to be desired, in that it does not provide actionable advice on monitoring of renal function.

Ordinarily, where harm is anticipated, there are adequate means available to monitor patients to avoid risk, and appropriate advice can be recommended in labeling. The present situation is unique, however, in that standard monitoring of serum creatinine would not be sufficient for these patients. Because there is no established way of monitoring renal function in this patient population, practitioners could be blind to worsening renal function, leaving these patients vulnerable. At this juncture, there is no way to provide adequate instructions for use in labeling.

I will note that there was no clear evidence of renal toxicity in the clinical development program; however, the size of the exposed patient population was quite small, such that the development program would be unlikely to detect adverse events that occur infrequently.

9. Benefit-risk

Benefit:

Sarepta's intent has consistently been to seek accelerated approval through a change in the dystrophin biomarker, following the pathway that led to eteplirsen's accelerated approval. In that sense, they have been successful. The amount of dystrophin produced be golodirsen is similar to the quantity produced by eteplirsen (9 parts per thousand, Table 1), and it is because of the Center Director's precedent that the Division's management supports golodirsen's accelerated approval.

Accelerated Approval:

The relevant statutory and regulatory framework (section 506(c) of the FD&C Act and 21 CFR part 314, subpart H) state that a drug can receive accelerated approval if 3 factors are satisfied:

1. If the drug treats a serious or life-threatening disease or condition;
2. if the drug provides a meaningful therapeutic benefit over existing treatments; and
3. if the drug demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit. I consider Factor 3 to have 3 subparts; all of which must be satisfied:

    (a) whether the surrogate endpoint is appropriate for the disease;
    (b) whether there is substantial evidence of an effect on the surrogate endpoint, and;
    (c) whether the magnitude of the effect size meets the test of being "reasonably likely" to predict clinical benefit.

In terms of the prospect for accelerated approval for golodirsen, factor 1 is satisfied because DMD is both serious and life-threatening. With respect to factor 2, deflazacort was approved for all patients with DMD including patients with mutations amenable to exon 53 skipping. Deflazacort is not curative, however, and its mechanism of action is distinct from that of golodirsen. Clearly, if a drug ameliorated the fundamental genetic defect of the disease and produced a significant quantity of functional dystrophin, it would offer a meaningful therapeutic advantage over deflazacort, satisfying factor 2.

The critical question is whether factor 3 is satisfied, the question of "reasonably likely."

For subpart (a) of factor 3, the Division and ODE-I have agreed that the near-lack of dystrophin is the proximal cause of DMD, and that the level of dystrophin in skeletal muscle is an appropriate surrogate endpoint that could predict efficacy of a drug.

Subpart (b) of factor 3 questions whether there is substantial evidence of the effect on the surrogate endpoint. For this application, the biologists and statisticians on the review team are satisfied that there is substantial evidence of an effect on the surrogate (dystrophin).

Subpart (c) of factor 3, the determination that the magnitude of the effect size is "reasonably likely" to predict clinical benefit, is a matter of judgment, and there have been strong differences of opinion across the Center.

To place these small quantities of Becker-type dystrophin into perspective, various investigators have attempted to correlate specific levels of dystrophin with clinical course, e.g., maintenance of physical function, age at loss of ambulation. Some have cited nonclinical data to relate dystrophin levels to maintenance of physical function. It is important to recognize, however, that many methodological factors affect these assays, and comparisons of values across laboratories could lead to erroneous conclusions.

Van den Bergen *et al* studied the relation between dystrophin levels (quantified by Western blot) and clinical severity in 33 patients with Becker muscular dystrophy (van den Bergen JC, et al. *J Neurol Neurosurg Psychiatry* 2014;85:747). Although the authors did not find a linear relationship between dystrophin levels and disease severity, patients with dystrophin levels <10% all showed a severe disease course. This study led to the general perception that a dystrophin level that is 10% of normal would constitute a meaningful goal.

Anthony K *et al* (*Neurology* 2014;83;2062) compared results of Western blot analyses from 6 patients (3 with DMD; 3 with Becker Muscular Dystrophy) across 5 experienced laboratories, finding marked variability that was particularly pronounced at low levels of dystrophin.

Suffice it to say that low levels of dystrophin are difficult to quantify, and significant variability is expected. There is no evidence that dystrophin increases in the range of 0.9% provide a clinical benefit. Simply put, no one can name the critical dystrophin threshold. Thus, if all other things were equal, it could be reasonable to follow the precedent set by the accelerated approval of eteplirsen and similarly grant accelerated approval to golodirsen, based on the change in dystrophin protein as quantified by Western blot.

If one accepts, based by the Center Director's 2016 precedent, that a small change in dystrophin (mean = 9 parts per thousand) is reasonably likely to predict clinical benefit, it seems reasonable to assume that the clinical benefit would be commensurately small.

Risk: Golodirsen's Risks Differ Importantly from Eteplirsen's Known Risks at the Time of its Approval:

Infections:

When eteplirsen was approved in 2016, I raised the theoretical possibility of infections related to indwelling ports; however, no serious infections had been reported in the development program. *Importantly, the possibility of infections did not figure into eteplirsen's risk-benefit calculus at the time of its approval.*

Three years later, with some 469 patients having been exposed to commercial eteplirsen, we have incontrovertible evidence of a significant likelihood of serious infections, including sepsis, septic shock, and possibly death. Thus, the risk of serious and life-threatening infections is no longer theoretical. Moreover, the infection risk is a function of the patient population and the delivery system – not the drug. Accordingly, the risk is fully applicable to golodirsen, and the 2.3% frequency from eteplirsen's voluntary postmarketing reporting probably represents a

conservative estimate of the risk, given the typical under-reporting of spontaneous adverse events.

Again – to emphasize – the risk of serious and life-threatening infections, including sepsis, was not known in 2016 when eteplirsen gained accelerated approval; however, this risk is known now.

Renal toxicity:

As noted above, based on nonclinical studies, golodirsen has a greater risk for renal toxicity than does eteplirsen; renal failure leading to death was observed in the golodirsen juvenile rat study, but not in a similar eteplirsen juvenile rat study

The eteplirsen package insert has never included any information on renal toxicity in its "Warnings and Precautions" or "Adverse Reactions" sections.

In contrast, the current draft golodirsen package insert being negotiated with the Division includes language in "Warnings and Precautions:"

> 5.2 Renal Toxicity
>
> Renal toxicity was observed in animals who received golodirsen *[see Use in Specific Populations (8.4)]*. Although renal toxicity was not observed in the clinical studies with VYONDYS 53, renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides. Renal function should be monitored in patients taking VYONDYS 53. Because of the effect of reduced skeletal muscle mass on creatinine measurements, creatinine may not be a reliable measure of renal function in DMD patients.

Again, because there is no proven way to monitor renal function in these patients, there is no way to provide adequate instructions for use in labeling.

When eteplirsen was granted accelerated approval in 2016, Sarepta was required to perform a study to verify eteplirsen's clinical benefit. As noted previously, patients were to be randomized to the approved dosage of eteplirsen (30 mg/kg weekly) or to a dosage that would provide 7-fold higher exposure, e.g., 30 mg/kg daily. We believed that it was entirely appropriate to increase the eteplirsen dose by a factor of 7 because we were not aware of any significant toxicity related to the drug. The same cannot be said of golodirsen, where nonclinical data have demonstrated considerable risk of renal toxicity. *This contrast serves as a further indication of the difference in safety between the two drugs, providing the rationale for not following the Center Director's 2016 precedent on accelerated approval of eteplirsen.*

Risk Summary – Differential Risks of Eteplirsen and Golodirsen:

In summary, therefore, at the time of eteplirsen's approval, there were no adverse events of note in the clinical data, and no nonclinical concerns, in short, the drug had no known toxicities. *The approval weighed a small potential benefit against essentially zero risk.* The lack of toxicity allowed us to require a confirmatory trial studying a dose that was 7-fold higher than the to-be-marketed dose. Golodirsen, on the other hand, has concerns with respect to renal toxicity, and

no proven way to monitor patients to recognize toxicity early when it might be reversible. We now also have proof that patients with DMD who undergo implantation of intravenous infusion ports will have serious and life-threatening infections, with the risk exacerbated by chronic corticosteroid use and general debilitation. Neither of these risks were considerations in the approval of eteplirsen: the renal risk did not exist, and the risk of infections was only theoretical. *For golodirsen, its benefit, similar to that of eteplirsen, must be weighed against these risks.*

10. Decision

In the Commissioner's September 16, 2016, decision with respect to "Scientific Dispute Regarding Accelerated Approval of Sarepta Therapeutics' Eteplirsen (NDA 206488),"[4] under "Opportunities for Process Improvement," it was explicitly noted (in bold lettering):

> **"Thus, I am confident that this unique situation will not set a general precedent for drug approvals under the accelerated approval pathway, as the statute and regulations are clear that each situation must be evaluated on its own merits based on the totality of data and information."**

The Commissioner's opinion was prescient, given the present circumstances. Golodirsen must be evaluated on its own merits based on the totality of the data and available information.

First, considering the Center Director's' 2016 decision on the accelerated approval of eteplirsen, one could take the Division's approach and grant accelerated approval of golodirsen – assuming all other aspects of the two drugs were equal. Unfortunately, golodirsen's risk profile differs considerably from the risk profile of eteplirsen as it was known at the time of approval. At the time eteplirsen was approved, essentially no risks had been identified, albeit there was limited clinical experience. *Importantly therefore, eteplirsen's benefit – no matter how tiny and unverified – was weighed against zero risk.* In contrast, golodirsen's risk of renal toxicity poses a significant concern, leading to a warning in the draft labeling with which the applicant agrees. As noted above, the renal risk could be self-perpetuating because the drug is primarily eliminated through excretion. Moreover, because serum creatinine cannot be used to monitor renal function in patients with DMD, there is no practicable and proven paradigm for renal monitoring for this drug in this patient population. The problem is laid bare by statements in section 5.2 of the current draft labeling with respect to renal monitoring; these statements are neither comprehensible nor actionable:

> "Renal function should be monitored in patients taking VYONDYS 53. Because of the effect of reduced skeletal muscle mass on creatinine measurements, creatinine may not be a reliable measure of renal function in DMD patients."

Having recently become aware of postmarketing reports of serious and life-threatening infections with eteplirsen, we now recognize that administration of <u>both</u> drugs via implanted intravenous ports poses considerable risk of serious and life-threatening infections.[5] Though we well recognize that the risk is similar for both drugs, the risk was only theoretical when eteplirsen was approved in 2016; *the risk was not considered in the Center's approval of eteplirsen.* For

[4] Downloaded 8/12/2019 from https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488Orig1s000SumR.pdf

[5] (b) (5)

the present evaluation of golodirsen, we are acutely aware of this risk, and it must be weighed when considering accelerated approval. The important point here is that the benefit-risk balance with golodirsen differs from the benefit-risk balance that was known for eteplirsen at the time of its accelerated approval.

As noted, if a mean increase in dystrophin of 9 parts per thousand is construed to be reasonably likely to predict clinical benefit (and none of the subject matter experts in the Division have stated that it is), the clinical benefit would surely be, at most, very small. I have reached the conclusion that this small benefit, which has not been verified, does not outweigh its risks. One risk (serious and life-threatening infections) is proven; the other (renal toxicity) has been identified in nonclinical studies, and significant glomerulonephritis has occurred with other antisense oligonucleotides. Though renal toxicity has not been detected in the small number of patients exposed in the golodirsen development program, the risk is nevertheless concerning and unmonitorable. *The risk-benefit profile for eteplirsen was quite different when it was given accelerated approval in 2016, as no risks were evident.*

Confirming the Clinical Benefit of Small Changes in Dystrophin:

As noted above, Sarepta was to begin their confirmatory trial for eteplirsen some time ago – ideally at or near the time of its 2016 approval. Now, almost 3 years after approval, the company has not initiated the required confirmatory trial. Given that the company has established a standard paradigm and design for these types of studies, given that the company has relationships with a number of DMD referral centers, and given that some 469 patients have received commercial eteplirsen, it will be important to ask the company why they have not initiated their required confirmatory study. We possess no more knowledge about the clinical efficacy of eteplirsen than we did three years ago, yet patients are being subjected to the risk of serious and life-threatening infections. (b) (5)

Other Information to be Communicated to Sarepta:

1. The failure to initiate eteplirsen's confirmatory study is very concerning to FDA, and of concern to the public.

2. The company has continued to perform open muscle biopsies on patients to obtain immunohistochemistry data. Such information can be useful to show the localization of dystrophin in skeletal muscle samples, however, samples from a small number of patients would suffice for this purpose. The immunohistochemistry data are not quantitative; they can be, in fact, quite deceptive. We should discourage the company from pursuing open muscle biopsies in these boys, which can be painful and invasive. Adequate tissue can be collected for Western blot using less invasive needle biopsy methods.

11. Path Forward

Because of the risks of serious infections and renal toxicity, the most expeditious route to approval would be to provide substantial evidence of a clinical benefit on physical

function/performance (e.g., NSAA, 6-minute walk distance, other measures of physical performance) through completion of the placebo-controlled study. It would also be necessary to develop a practicable renal monitoring paradigm to allow mitigation of the renal risk. Finally, if the drug could be administered without implantation of an indwelling port, the benefit-risk profile could be improved.

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/s/

ELLIS F UNGER
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CLINICAL REVIEW

Application Type	Original NDA
Application Number(s)	NDA 211970 (IND 119982)
Priority or Standard	Priority
Submit Date(s)	12/19/18
Received Date(s)	12/19/18
PDUFA Goal Date	8/19/19
Division/Office	OND/ODE1/DNP
Reviewer Name(s)	Breder, C [Clinical]; Rao, A and Aryal, B [Office of Biotechnology Products]; Ling, X [Biometrics]
Review Completion Date	8/15/19
Established/Proper Name	Golodirsen
(Proposed) Trade Name	Vyondys 53
Applicant	Sarepta
Dosage Form(s)	Intravenous solution
Applicant Proposed Dosing Regimen(s)	30 mg/Week
Applicant Proposed Indication(s)/Population(s)	Treatment of Duchenne muscular dystrophy (DMD) in pediatric and adult patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping.
Recommendation on Regulatory Action	[Clinical Reviewer] Complete Response
Recommended Indication(s)/Population(s) (if applicable)	Not Applicable

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology

OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Golodirsen injection is supplied in single-use, 2-mL clear (b) (4) glass vials containing 100 mg golodirsen. Golodirsen injection is diluted to 100-150 mL with normal saline prior to administration via intravenous (IV) infusion. Golodirsen at 30 mg/kg will be administered chronically (i.e., lifetime dosing) by once-weekly IV infusions between 35 to 60 minutes in duration.

Golodirsen is designed as an exon skipping phosphorodiamidate morpholino oligomer (PMO), to bind to exon 53 of dystrophin pre-mRNA, resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 53 skipping. Exon skipping is intended to allow for production of an internally shortened dystrophin protein.

1.2. Conclusions on the Substantial Evidence of Effectiveness

[Note: this Section reflects the opinion of only Dr. Christopher D. Breder]

The evidence submitted for accelerated approval of NDA 211970 was comprised of Western blot data from a single study 4053-101. The methodology of this study for the Western blot and supporting exon-skipping blots were deemed as adequate. However, the immunohistochemistry-based data were not deemed adequate for consideration as evidence. release

The Western blot data demonstrated a median increase of 0.88 (interquartile range – 0.08 – 1.5%) from baseline. There is not sufficient knowledge to know how much "dystrophin" would be needed to represent a meaningful benefit. Historical estimates based on levels of normal dystrophin in Becker's Muscular Dystrophy patients were not performed with enough rigor to rely on these data. Further, the product resulting from golodirsen treatment is not the natural protein, so it is not known if it functions to the same degree.

A primary issue faced in this review is whether my decision should be based on my independent scientific analysis or whether because of the previous approval of eteplirsen, any production of the truncated dystrophin would be enough to support an approval. I appreciate the regulatory precedent set by the eteplirsen NDA and all the issues raised in the Center Director's memo. I also acknowledge the comment from the February 6th meeting minutes that a *"…statistically significant increase in de novo (truncated) dystrophin protein in Study 4053-101 based on a scientifically sound experimental design and rigorous analytical methods potentially could serve as a basis for accelerated approval of golodirsen for the treatment of Duchenne muscular dystrophy."* The Minutes go on to state that the Applicant *"…should explain why you believe that submission of a single study, lacking concurrent controls, provides substantial evidence of the effect on dystrophin."* This is particularly important, as Thomas Fleming (Fleming, 2005) noted "…unfortunately, demonstrating treatment effects on these biological "surrogate"

endpoints, while clearly establishing biological activity, may not provide reliable evidence about effects of the intervention on clinical efficacy measures."

I do not find the Applicant's argument compelling because it is essentially the same as that posed for eteplirsen but with no clinical data (though eteplirsen's was negative) and these arguments were rejected by several supervisory levels in the Division and Office where I review. I base this opinion on the scientific evidence described in the review and that despite having submitted an IND more than twelve years ago for the original oligonucleotide, eteplirsen, the Applicant has not demonstrated even a proof of concept that the truncated dystrophin produced by this mechanism of treatment would lead to a clinical benefit. This deficiency is reflected in the Commissioner's Summary Review (p. 6/126) *"Because of the uncertainties in this situation with a surrogate that has not been validated…"*[1] . The applicant has not only provided no evidence of a treatment effect, but in my review of the NDA (206488), I demonstrated a negative correlation between the protein level on Western blot and the clinical endpoints. While I appreciate that the accelerated pathway of approval is to allow treatment for situations where demonstration of clinical benefit will be intolerably long, I also believe that use of therapies that do not offer real chances of benefit may preclude patients from taking those under current development that may provide a benefit or at least a reasonable chance.

1.3. Benefit-Risk Assessment

[Note: this Section reflects the opinion of only Dr. Christopher D. Breder]

[1] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_Redacted.pdf

Benefit-Risk Integrated Assessment

Golodirsen, is a phosphorodiamidate morpholino oligomer with a sequence designed to bind to exon 53 of the human dystrophin pre-mRNA. It is intended to cause the skipping of exon 53 and generate an internally truncated dystrophin.

Duchenne Muscular Dystrophy (DMD) is a fatal, degenerative, X-linked recessive genetic disorder associated with mutations in the dystrophin gene diagnosed between the ages of 3 to 5 years, when toddlers develop a waddling gait and inability to jump which progresses to loss of ambulation. While pulmonary and cardiac function are generally normal during early childhood, muscles of the heart and diaphragm progressively weaken during adolescence, and patients often die from cardiac or respiratory failure in their early 20s.

Currently there are no drugs approved for the treatment of this mutation of DMD. However, EXONDYD51 is approved for lesions amenable to Exon 51 skipping and deflazacort is a corticosteroid approved for the treatment of DMD that is used to lessen the inflammation and slow disease progression. Central to the care of children with DMD is a rigorous program of respiratory therapy, adjunctive drug therapy (e.g., ace-inhibitors to decrease afterload), and non-medical therapy such as orthoses and physical therapy.

With respect to the evaluation of ***Benefit***, the conclusion of this review is that there is no substantial evidence that any effect on the biomarker as evaluated by the Applicant is reasonably likely to predict clinical benefit. An expanded executive summary of the analysis of efficacy is found in **Section 7.**

With respect to the evaluation of ***Risk***, the extent of patient exposure to golodirsen was small and the studies were not designed to control for evaluating long-term safety. To date there have not been deaths in the program and a few serious adverse events and severe AEs that are consistent with DMD however they seem to occur more in the active treatment arms, which may reflect the trial design as noted above. Hypersensitivity reactions will be included in Warnings and Precautions.

Benefit-Risk Dimensions

Table 1 Benefit Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Duchenne Muscular Dystrophy (DMD) is a degenerative X-linked recessive genetic disorder associated with mutations in the dystrophin that result in the absence or near absence of functional dystrophin protein. Lack of dystrophin results in degeneration of muscle fibers, inflammation, and ultimately replacement of muscle by fibrotic and adipose tissue. • Exon 53 skip-amenable DMD, a subgroup of DMD, is defined by the presence of exon 53 in the dystrophin gene and the deletion of one or more exons contiguous with exon 53, resulting in an out-of-frame deletion in which the reading frame is potentially restorable by the skipping (removing) of exon-53. Mutations that are potentially amenable by skipping exon 53 are thought to comprise about 8% of the DMD population, resulting in a prevalence of about 1200 boys in the US. • Loss of muscle strength is progressive, typically beginning with a waddling gait and inability to jump in young boys, progressing to a loss of ability to ambulate. The loss of ambulation is generally considered to occur between ages 8 to 16 years, but about 25% of patients may still be ambulatory at age 16. While pulmonary and cardiac function are generally normal during childhood, muscles of the heart and diaphragm progressively weaken during adolescence, and patients often die from cardiac or respiratory failure in their early 20s.	• DMD is a serious and life-threatening disease. The loss of muscle strength in DMD is progressive, leading to loss of ambulation in the teens, followed by decline in respiratory and cardiac function, resulting in death typically in the third decade.
Current Treatment Options	• There is no FDA-approved treatment specific for exon 53 skipping amenable DMD. • Emflaza (deflazacort) is a glucocorticoid approved for treatment of Duchenne muscular dystrophy (DMD) in patients 2 years of age and older. • Exondys 51 is approved for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the	• There is a substantial unmet need for therapies in DMD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	DMD gene that is amenable to exon 51 skipping. • The current standard of care is glucocorticoids, which are thought to provide a modest beneficial effect on function and survival. In addition, supportive care, such as assisted ventilation and physiotherapy, is modestly effective in prolonging function and survival.	
Benefit	• The applicant seeks an accelerated approval based on the results of Western blots from the truncated dystrophin protein in Study 4053-101. The median protein change from baseline is 0.88%. • While not submitted as part of the NDA, performance on the Six-minute Walk test and pulmonary function tests with at least 144 Weeks of followup showed a decrease from baseline. These data were not controlled and so the efficacy cannot be evaluated.	• The applicant has provided proof of concept through Western blots and exon skipping as demonstrated in RT-PCR. • The amount of dystrophin produced in response to golodirsen treatment is very small. While it is somewhat possible that the amount of dystrophin produced may lead to a modest clinical benefit, such a benefit does not appear reasonably likely.
Risk and Risk Management	• At the time of the 120-day Safety update, 60 patients were included in the All-golodirsen treated population. Eleven for six months to one year, twenty-three (23) were treated for about one to 2 years, and twenty-three for more than two years. • Renal toxicity was observed in nonclinical studies. • Most adverse events in human were of a frequency and severity that description in the Table of common Adverse Events in labeling and usual pharmacovigilance is adequate. AEs of proteinuria, rhabdomyolysis, as well as falls and fractures, while not always occurring with a frequency that would rise to inclusion in the is part of labeling, were occasionally severe in intensity with serious sequelae. Hypersensitivity reactions should be included in the Warnings and	The safety database for patients exposed at the intended dose is small, but enough to assess frequent adverse events, and acceptable for this serious disease with great unmet medical need.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	precautions section.	

1.4. Patient Experience Data

Table 2 Patient Experience Data Relevant to this Application

X	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	X Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
X	Patient experience data that were not submitted in the application, but were considered in this review:	
	X Input informed from participation in meetings with patient stakeholders	
	X Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

DMD is a rare, recessive, X-linked, degenerative neuromuscular disorder with a worldwide incidence of approximately 1 in 3500 neonatal boys, irrespective of geographical region, race, or population density. DMD is characterized by an absence of the protein dystrophin. Dystrophin is a rod-shaped cytoplasmic protein that connects the cytoskeleton of a muscle fiber the surrounding extracellular matrix through the cell membrane. Functionally, dystrophin acts to stabilize the sarcolemma membrane against the stress imposed by muscle contraction. The lack

of dystrophin in DMD results in a severe disease observed in the first years of life with patients typically losing ambulation around the age of 12 years and the need for mechanical ventilation around 18 years of age. Another related genetic disease is Becker Muscular Dystrophy (BMD), where an internally-deleted dystrophin is produced. BMD results in a much milder phenotype with many patients remaining ambulant throughout life or even asymptomatic.

The stark contrast between DMD and BMD phenotype is the presence of dystrophin. In DMD the reading-frame of the mRNA is disrupted and little to no dystrophin is produced, whereas in BMD, the reading frame is intact and an internally-deleted, but somewhat functional dystrophin protein is produced.

There are a large variety of mutations that can cause DMD, with one out of three mutations occurring *de novo*. Over 4500 pathogenic mutations are known to cause DMD. Large deletions are present in about 60% of patients, large duplications in about 10%, and point mutations (confined mostly to coding exons) in about 30% of patients (Lim et al., 2011). Of the deletion mutations, approximately 66% of patients carry a deletion of one or more exons, of which 70% cluster between exon 45 and 55 (Aartsma-Rus et al., 2009). There are eight DMD deletion mutations (42-52, 45-52, 47-52, 48-52, 49-52, 50-52, 52, 54-58) that are thought to be amenable to treatment with golodirsen.

2.2. Analysis of Current Treatment Options

There are no therapies approved for this specific DMD mutation; however, Emflaza (deflazacort; NDA 208684,208685) is a corticosteroid indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients 2 years of age and older. The effectiveness of Emflaza for the treatment of DMD was established in Study 1, a multicenter, randomized, double-blind, placebo-controlled, 52-week study conducted in the US and Canada. The study population consisted of 196 male pediatric patients 5 to 15 years of age with documented mutation of the dystrophin gene, onset of weakness before 5 years of age, and serum creatinine kinase activity at least 10 times the upper limit of normal (ULN) at some stage in their illness. Patients were randomized to therapy with deflazacort (0.9 or 1.2 mg/kg/day), an active comparator, or placebo. A comparison to placebo was made after 12 weeks of treatment. After 12 weeks, placebo patients were re-randomized to receive either deflazacort or the active comparator; all patients continued treatment for an additional 40 weeks. Baseline characteristics were comparable between the treatment arms.

In Study 1, efficacy was evaluated by assessing the change between Baseline and Week 12 in average strength of 18 muscle groups. Individual muscle strength was graded using a modified Medical Research Council (MRC) 11-point scale, with higher scores representing greater strength.

The change in average muscle strength score between Baseline and Week 12 was significantly greater for the deflazacort 0.9 mg/kg/day dose group than for the placebo group (Table 3).

Table 3 Efficacy Results from Deflazacort Labeling

Treatment	N	Change from Baseline LS Mean (95% CI)	P-value
Deflazacort 0.9 mg/kg/day	51	0.15 (0.01, 0.28)	0.017
Placebo	50	-0.10 (-0.23, 0.03)	

Source: Deflazacort US Package Insert

Compared with the deflazacort 0.9 mg/kg/day group, the deflazacort 1.2 mg/kg/day group demonstrated a small additional benefit compared to placebo at Week 12 but had a greater incidence of adverse reactions. Although not a pre-specified statistical analysis, compared with placebo, the deflazacort 0.9 mg/kg/day dose group demonstrated at Week 52 the persistence of the treatment effect observed at Week 12 and the small advantage of the 1.2 mg/kg/day dose that was observed at Week 12 was no longer present. Also, not statistically controlled for multiple comparisons, results on several timed measures of patient function (i.e., time to stand from supine, time to climb 4 stairs, and time to walk or run 30 feet) numerically favored deflazacort 0.9 mg/kg/day at Week 12, in comparison with placebo.

An additional randomized, double-blind, placebo-controlled, 104-week clinical trial evaluated deflazacort in comparison to placebo (Study 2). The study population consisted of 29 male children 6 to 12 years of age with a DMD diagnosis confirmed by the documented presence of abnormal dystrophin or a confirmed mutation of the dystrophin gene. The results of the analysis of the primary endpoint of average muscle strength scores in Study 2 (graded on a 0-5 scale) at 2 years were not statistically significant, possibly because of a limited number of patients remaining in the placebo arm (subjects were discontinued from the trial when they lost ambulation). Although not statistically controlled for multiple comparisons, average muscle strength scores at Months 6 and 12, as well as the average time to loss of ambulation, numerically favored deflazacort in comparison with placebo.

Exondys 51 (eteplirsen; NDA 206488) is a similar antisense oligonucleotide approved for deletions in Exon 51 and associated mutations. In the 12 patients with evaluable results, the pre-treatment dystrophin level was 0.16% ± 0.12% (mean ± standard deviation) of the dystrophin level in a healthy subject and 0.44% ± 0.43% after 48 weeks of treatment with Exondys 51 ($p < 0.05$). The median increase after 48 weeks was 0.1%. While this reviewer and the supervisory staff of the Division and Office, including the Acting FDA Chief Scientist and Chair of the Agency Scientific Dispute Process Review Board, Dr Luciana Borio did not feel that there was adequate evidence for approval, a decision at the Center-Director level, that was upheld by the Commissioner, was made to grant accelerated approval.

Table 4 Summary of Treatment Armamentarium Relevant to Proposed Indication

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety Issues	Other Comments
FDA Approved Treatments [Combine by Pharmacologic Class, if relevant]						
No approved therapies for Exon 53 or associated mutations						
Deflazacort	DMD	2017	Oral	See above	Steroid-class	DMD >2yo
Other Treatments – [Combine by Pharmacologic Class, if relevant]						
Prednisone	Not approved					

Source: Clinical Reviewer

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Table 5 Key Regulatory History

Date	Interaction	Outcome
10/10/2013	pIND meeting request	Comments provided 3/20/2014; Meeting withdrawn / cancelled; Division expressed concerns on OL design of 4053-101
11/17/2014	New IND	
11/17/2014	Fast Track designation request	Granted 12/11/2014
6/24/2015	Full clinical hold	Nonclinical deaths with inadequate human margin; continued (11/06/2015) after response on 10/08/2015; Hold removed 1/28/16 after response on 12/29/2015
11/22/17	Meeting request	Meeting 11/06/2018; Discussion of primary endpoint (% dystrophin) and proposed confirmatory study (ESSENCE)
1/19/2018	[redacted] (b) (4)	
6/07/2018	Rolling review request	Granted 7/23/2018
6/18/2018	Meeting request	Meeting 8/1/2018; Minutes issues 8/28/2018 Discussion of

keep redacted

Date	Interaction	Outcome
		confirmatory trial analysis
9/11/2018	pNDA Meeting	Discussion of application content
12/19/2018	New NDA	NDA received

Source: Clinical Reviewer

3.2. Foreign Regulatory Actions and Marketing History

To the best of this reviewer's knowledge, golodirsen has not been approved in any region.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The final review of OSI findings were not available at the time of this review; however, preliminary findings under evaluation include not taking the biopsy according to protocol and under-dosing. There is a potential issue surrounding maintenance of the blind for three subjects.

4.2. Product Quality

The OPQ review team recommends APPROVAL of NDA 211970 for Golodirsen Injection for intravenous infusion. There are no recommended post-marketing commitments.

4.3. Nonclinical Pharmacology/Toxicology

The following was essentially extracted from the Primary Nonclinical review.

Pivotal nonclinical toxicology studies were conducted in mouse, rat and cynomolgus monkey. Kidney toxicity was the major adverse effect in all species. Studies up to 26-weeks duration in male mouse with IV doses up to 960 mg/kg were conducted. Renal impairment at the high dose was reflected in effects on clinical chemistry parameters including increased creatinine, increased CK, increased urea nitrogen, increased potassium and phosphorus. The clinical chemistry findings correlated with microscopic kidney findings of tubular dilatation, vacuolation of the tubular epithelium (all groups with increased severity and incidence in the HD group), and basophilic casts. Hypertrophy of the transitional epithelium of the urinary bladder and ureter was also observed in mouse studies at the MD and HD.

In monkey studies, the magnitude of the renal toxicity appeared to be somewhat less severe but effects on clinical chemistry parameters and kidney histopathology were also apparent in a 39-week monkey study in which male cynomolgus monkeys received weekly IV injections of

golodirsen at doses up to 400 mg/kg. As in the mouse, elevated urea nitrogen and creatinine were observed in HD monkeys. Urine chemistry showed increased urine creatinine, urea and elevated protein/creatinine ratio at the HD. The adverse effects on clinical chemistry in HD monkeys were correlated with microscopic kidney findings described as dilation of the distal convoluted tubules and collecting ducts in MD and HD groups, microvesicular vacuolation of the distal convoluted tubule and collecting ducts in the MD and HD groups. Synovial hyperplasia in bone was also observed at the MD and HD. The kidney findings persisted through the recovery period, but the bone findings did not.

In a juvenile developmental toxicity study, male rat pups received weekly IV injections at doses up to 900 mg/kg for 10 weeks beginning on post-natal day 14. No adverse effects on neurobehavioral or immune system development were observed. However, in this study, severe renal toxicity was observed that was lethal at the HD. There were 31 unscheduled deaths in the HD groups that was determined to be due to renal toxicity. At the end of the dosing period, microscopic findings in the kidney of surviving HD pups were like those described in previous studies (minimal to marked tubular vacuolation, minimal to marked tubular degeneration/regeneration, minimal to moderate tubular dilatation, minimal to moderate eosinophilic casts). The kidney findings in the HD were considered irreversible. In addition to the adverse findings in the kidney multiple additional findings were observed that were considered secondary to impaired renal function. These included mineralization of multiple tissues, degeneration of coronary artery tunic media, atrial thrombosis and reduced bone area and density. No effects of golodirsen were observed on male reproductive organs or in sperm evaluations.

In ADME studies, no induction of inhibition of hepatic microsomal enzymes were observed, no significant interactions with known human drug transporters, low plasma protein binding in human plasma, and no metabolism by in the presence of human hepatic microsomes. Distribution of radiolabeled golodirsen showed rapid and extensive distribution to all tissues except CNS. Excretion of golodirsen was shown to be via the urinary route and largely as unmetabolized drug.

A panel of genetic toxicology studies was conducted and golodirsen had not apparent mutagenicity or clastogenicity.

4.4. Clinical Pharmacology

No significant clinical pharmacology issues were identified at the time of this review.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

One trial (4053-101) is submitted for consideration of pharmacodynamic data, the percent dystrophin compared to normal, as measured by Western Blot. Study 4053-101 and 4045-301 contribute to the safety population. Studies 4053-103 and -104 are clinical pharmacology studies.

Table 6 Table of Studies

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. Pts Study Population	No. Centers / Countries
Controlled Studies to Support Efficacy and Safety							
4053-101	0231 0906	Baseline-controlled w intercalated placebo patients	Part 1: Ascending to 30mg/kg: 4 mg/kg in Weeks 1-2; 10 mg/kg in Weeks 3-4; 20 mg/kg in Weeks 5-6; and 30 mg/kg beginning at Week 7 (Part 2) to Week 186	% dystrophin by WB	48 Weeks	25, DMD	4 centers in France, Italy, and the United Kingdom. During the conduct of the study, 1 patient (Patient (b) (6)) moved to a 5th center in the United States
Studies to Support Safety							
4045-301	0250 0381	Double-blind, placebo-controlled, multi-center	Once weekly IV infusions of 30 mg/kg SRP-4045 or 30 mg/kg SRP-4053 respectively (combined-active group) or placebo for up to 96 weeks followed by an open label extension period for 48 weeks (up to Week 144 of study)	This study will only be evaluated for safety. The primary endpoint of the	96 Week double blind with an open label extension to Week 144	222, DMD patients, with a planned minimum target of 111 patients amenable to exon 45 skipping and 111 patients amenable to exon 53	57 centers; Currently only enrolling ex-US patients in Australia, Europe and Israel

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. Pts Study Population	No. Centers / Countries
				ongoing study is the change From Baseline in the Total Distance Walked During 6-Minute Walk Test (6MWT) at Week 96		skipping, (2:2:1 randomization)	
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)					
4053-104		Renal PK Study		ADME		24, HNV	
4053-103		Mass balance		ADME		8, HNV	

Source: Clinical Reviewer

5.2. Review Strategy

This is a combined review on the part of the Clinical, Biometrics, and Office of Biotechnology Disciplines. Dr. Breder (Clinical) will review the safety and the efficacy results, Xiang Ling, the statistics associated with the primary endpoint, and Dr. Rao, the methodology used for dystrophin mRNA and protein quantification (e.g., Western Blots, Immunohistochemistry, and PCR techniques). Dr Breder will perform the risk-benefit analysis in this review.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. SRP-4053 (Golodirsen Injection) A 2-Part, Randomized, Double-Blind, Placebo-Controlled, Dose-Titration, Safety, Tolerability, And Pharmacokinetics Study (Part 1) Followed by An Open-Label Efficacy and Safety Evaluation (Part 2) of SRP-4053 in Patients with Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping Study Design

Overview, Objective, and Trial Design

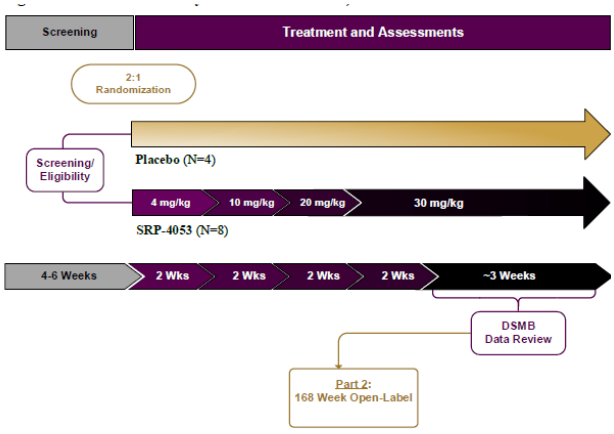
Study 4053-101 was a first-in-human clinical trial conducted in Europe and United States to assess the safety, tolerability, efficacy, and PK of once-weekly intravenous (IV) infusions of golodirsen in patients with genotypically confirmed DMD with a deletion amenable to exon 53 skipping. This study was conducted in two parts. In Part 1, patients received a weekly IV infusion of placebo or golodirsen at escalating dose levels, each for at least 2 weeks: 4 mg/kg/week in Weeks 1-2; 10 mg/kg/week in Weeks 3-4; 20 mg/kg/week in Weeks 5-6; and 30 mg/kg/week beginning at Week 7.

Part 2 is ongoing and is being conducted to assess ambulation, endurance, muscle function, the biological activity of golodirsen via dystrophin expression, safety, tolerability, the PK of golodirsen administered once weekly, and respiratory function. Part 2 included an untreated group participating in scheduled assessments for 144 weeks. All 12 treated patients from Part 1 continued in Part 2. Part 2 also enrolled 13 new patients for open-label treatment with golodirsen. These patients had a clinical diagnosis of DMD confirmed by the finding of a genomic deletion amenable to exon 53 skipping. In addition, up to 24 patients who did not receive treatment were enrolled in Part 2. The patients in the untreated group were DMD patients with a confirmed deletion of exon(s) not amenable to treatment by exon 53 skipping, but who otherwise met the same eligibility criteria as treated patients newly recruited to Part 2.

Fourteen (14) subjects with DMD not amenable to exon 53 skipping were enrolled in part 2 of the study to study the natural history of this cohort. They did not receive treatment and are not further discussed in this review. The study report notes *"…The untreated patient group was intended to evaluate the natural history of the disease for patients who were not amenable to exon 53 skipping and was not considered a control group for golodirsen-treated patients*"[2] This group is represented by the amber bar in Figure 2 below.

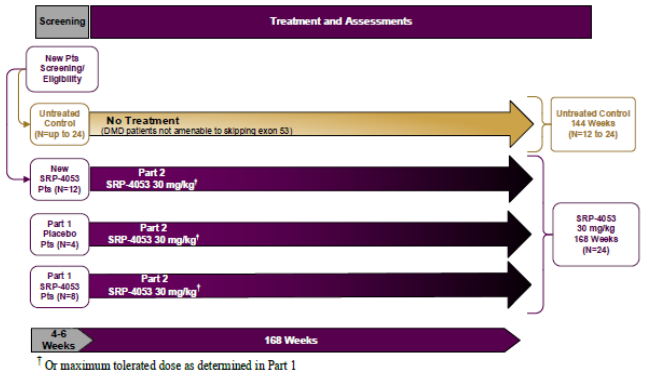
[2] P. 23 of 222 4053-101 CSR

Figure 1 Study Schematic for Part 1 (Double-blind Dose Titration)



DSMB=Data Safety Monitoring Board; SRP-4053=golodirsen; Wks=weeks

Figure 2 Study Schematic for Part 2 (Open-label and Untreated Patients)



† Or maximum tolerated dose as determined in Part 1

Note: A total of 13 new patients were enrolled in Part 2 for a total of 25 treated patients; a total of 14 untreated patients were enrolled in Part 2.
DMD=Duchenne muscular dystrophy; Pts=patients; SRP-4053=golodirsen

Source: 4053-101 Interim Study Report, pp. 22-3

Study Population

Key Inclusion Criteria

1. Males aged 6 to 15, inclusive.
2. For treated patients (all patients in Part 1 plus 13 additional treated patients in Part 2), established clinical diagnosis of DMD amenable to exon 53 skipping (e.g., deletions of exons such as 42 to 52, 45 to 52, 47 to 52, 48 to 52, 49 to 52, 50 to 52, 52, or 54 to 58) as documented by a genetic report from an accredited laboratory confirming deletion endpoints by multiplex ligation-dependent probe amplification or sequencing.
3. For Part 2 untreated patients, established clinical diagnosis of DMD with a confirmed genomic deletion of exon(s) not amenable to exon 53 skipping as documented by an accredited laboratory and genomic methodology.
4. Had intact right and left biceps muscles or an alternative upper arm muscle group.
5. Had stable cardiac and pulmonary function that, in the Investigator's opinion, was unlikely to decompensate over the duration of the study.
6. Achieved a mean 6MWT distance of ≥250 meters at both the Screening and Baseline visits (prior to Week 1). The mean 6MWT distance at the Screening and Baseline visits was the average of 2 separate assessments on 2 consecutive days at each visit. The baseline mean (average of Baseline Day 1 and 2) must have been within 15% of the screening mean (average of Screening Day 1 and 2).
7. Patients had to meet one of the following 2 criteria:
• North Star Ambulatory Assessment (NSAA) total score >17; or
• Rise (Gowers') time <7 seconds
8. Had been on a stable dose or dose equivalent of oral corticosteroids for at least 24 weeks prior to Week 1 and the dose was expected to remain constant (except for modifications to accommodate changes in weight) throughout the study. Note: patients were allowed to take other

medication (excluding other RNA antisense or gene therapy agents) including angiotensin-converting enzyme inhibitors, angiotensin receptor blocking agents, β-blockers, and potassium, provided they had been on a stable dose for at least 12 weeks prior to Week 1 and the dose was expected to remain constant throughout the study. assistive devices for ambulation was not permitted during the 6MWT.

Key Exclusion Criteria

1. Use of any pharmacologic treatment, other than corticosteroids, that might have had an effect on muscle strength or function, within 12 weeks prior to study entry (e.g., growth hormone, anabolic steroids).
2. Previous treatment with the experimental agents BMN-195 (SMT C1100) or PRO053.
3. Current or previous treatment with any other experimental treatments within 12 weeks prior to study entry. Untreated patients only could have been enrolled concurrently in other non-interventional studies, or in interventional studies in which participants were known to be treated with standard-of-care medication, provided they did not interfere with study assessments performed in Study 4053-101, and the patient met all the protocol-required entry criteria.
4. Had a left ventricular ejection fraction (LVEF) of <50% (or equivalent fractional shortening) based on the Screening ECHO and QT interval calculated using the Fridericia correction (QTcF) >450 msec.
5. Had a forced vital capacity <50% of predicted value or required nocturnal ventilation.
6. Major surgery within 3 months prior to Week 1 or planned orthopedic surgery for any time during this study, which would have interfered with the ability to perform outcome measures.
7. Use of any aminoglycoside antibiotic or statin within 12 weeks of Week 1 or need for use of an aminoglycoside antibiotic or statin during the study.
8. Presence of other clinically significant illness including significant cardiac, pulmonary, hepatic, renal, hematologic, immunologic, behavioral disease, or malignancy.
9. Loss of ≥30 degrees of plantar flexion from the normal range of movement at the ankle joint due to contracture (ie, fixed loss of >10 degrees plantar flexion from plantigrade assuming normal range of dorsiflexion of 20 degrees).
10. Change in contracture treatment such as serial casting, contracture control devices, night splints, stretching exercises (passive, active, self) within 3 months prior to enrollment, or expected need for such intervention during the study.

Endpoints

Tables of Events are included in **Section 13.1Schedules of Events**.

Part 1

The primary objectives for Part 1 are Pharmacokinetics and Safety. The full schedule of events is found in Table 34.

Part 2

Biological

The primary biological endpoint for Part 2 of the study was the change from Baseline to Part 2 Week 48 in dystrophin protein levels (in muscle biopsy samples) determined by Western blot. Secondary biological endpoints for Part 2 of the study include the change from Baseline to Part 2 Week 48 for the following:

• Dystrophin intensity levels determined by immunohistochemistry (IHC)

• Percent dystrophin-positive fibers as determined by IHC

• Exon 53 skipping determined by measurement and sequence verification of exon 53 skipped mRNA

At the clinical study site, biopsied tissue samples were mounted, frozen in isopentane, and transferred to the University College London. Mounted biopsy specimens were stored in vapor phase liquid nitrogen at University College London Dubowitz Neuromuscular Centre histology laboratory until tissue sections were allocated for analysis. Frozen biopsy blocks were allocated for exon skipping assessments, Western blot, and IHC analysis. All samples were analyzed at once, as they were allocated.

Efficacy and Pharmacodynamics

1. 6-minute walk test through Part 2 Week 144; primary efficacy endpoint was change from Baseline to Part 2 Week 144

2. Forced vital capacity percent predicted (FVC%p) through Part 2 Week 144; Forced vital capacity percent predicted, maximum inspiratory pressure percent predicted, and maximum expiratory pressure percent predicted were calculated. These secondary efficacy endpoints were analyzed as change from Baseline to Part 2 Week 144

3. Other endpoints included:

    - North Star Ambulatory Assessment

    - Leg Muscle Magnetic Resonance Imaging and Magnetic Resonance Spectroscopy

        i. fat content in lower leg muscle and skeletal muscle edema at the tibialis anterior

    - Timed 4-step test

    - MoviPlate

        i. a tool that measures the ability to produce repeated movements between 2 cylindrical target keys aligned in the sagittal plane.

    - Performance Upper Limb

    - Pinch and Hand Grip

- Pediatric Outcomes Data Collection Instrument
- Actimetry (optional participation)

Statistical Analysis Plan [per Biometrics Reviewer]

The 4053-101 Statistical Analysis Plan (SAP) is dated 30 May 2018. The original Muscle Biopsy/ Pharmacodynamic SAP is dated 10 August 2017. It was amended once with a date of 06 August 2018 to pre-specify the statistical methods for PDPF by manual scoring prior to unblinding of manual scoring PDPF data (Baseline vs Part 2 Week 48).

The primary biological endpoint is the change from baseline at Week 48 in dystrophin protein levels determined by Western blot. For patients who are enrolled in either placebo or SRP-4053 group of Part 1 and continuing in the SRP-4053 group of Part 2, muscle biopsies are collected at the Baseline visit (pretreatment) of Part 1 and at Week 48 of Part 2. For patients who are not enrolled in Part 1 and are enrolled in the SRP-4053 group of Part 2, muscle biopsies are collected at the Baseline visit (pretreatment) of Part 2 and at Week 48 of Part 2.

Personnel performing the assays were blinded to treatment status (pre-treatment vs on-treatment). Blinding was performed by dedicated personnel at (b) (4). Unblinding of muscle biopsy samples was to occur only after the assays had been completed, the SAP for muscle biopsy-based endpoints had been finalized, and final assay data had been submitted to (b) (4).

Patients in the muscle biopsy set, consisting of all patients who receive at least one dose of study drug and who have data from both Baseline (pre-treatment) and Part 2 Week 48 (on-treatment) muscle biopsy samples, were included in the analyses. Summaries are provided for the following groups:
• Total Golodirsen Treated: Patients who receive SRP-4053 in any part of the study;
• Golodirsen Group 1: Patients who receive placebo in Part 1 followed by SRP-4053 in Part 2, or patients who enroll in Part 2 and receive SRP-4053;
• Golodirsen Group 2: Patients who receive SRP-4053 in Part 1 and continue SRP-4053 in Part 2.
Note that Golodirsen Group 1 and Golodirsen Group 2 are not protocol-specified treatment groups; rather, they are subgroups of patients with different expected durations of SRP-4053 treatment at the time of Part 2 Week 48 muscle biopsy.

A one-sample permutation test was used to test the null hypothesis that the mean change from Baseline to Part 2 Week 48 in dystrophin level is 0.

For each time point (Baseline vs Part 2 Week 48), replicate gel runs are performed to determine dystrophin level (% normal) by Western blot. The average of replicate values from available gel runs will be used in the analyses. In the case of only one available gel result, then that value will be used in the analyses. For the calculation of average assay value, if there are assay results outside of the limits of quantification, different imputation

methods will be used. Values less than the lower limit of quantification (LLOQ; 0.25) will be imputed using one of 3 methods: as 0, as 0.24 (level immediately below the LLOQ), and as the actual measured value, even if those values are below the LLOQ. Values greater than the upper limit of quantification (ULOQ; 4.00) will be imputed using one of 2 methods: as 4.01 (level immediately above the ULOQ), and as the actual measured value, even if those values are above the ULOQ. If there are both values less than LLOQ and values greater than ULOQ, then there will be 6 imputation methods. Of them, the primary analysis will be based on the actual measured value for values less than LLOQ and based on the actual measured value for values greater than ULOQ. Analyses based on other imputation methods will be considered sensitivity analyses.

Secondary biological endpoints include the change from baseline at Week 48 for the following:
• Dystrophin intensity levels determined by immunohistochemistry (IHC);
• Percentage of dystrophin-positive fibers as determined by IHC;
• Exon 53 skipping determined by measurement and sequence verification of exon 53 skipped mRNA.
No adjustment will be made for the testing of multiple endpoints.

Protocol Amendments

Study 4053-101 had 8 amendments. Several reduced the assessments of the untreated group to the extent that assessment of their comparability with the treated group would not be as interpretable.

- 19 NOV 2014
  • Changed MRIs to optional at 12 weeks and 24 weeks for the untreated control group in Part 2.
  • Removed the untreated control group Part 2 Week 1 functional assessments for NSAA, 6MWT, pulmonary function tests, and the timed 4-step.
  • Removed the assessment of vital signs for the untreated control group from Weeks 5 to 7, 9 to 11, 13 to 15, 17 to 19, 21 to 23, 25 to 35, and 37 to 47.
  • Updated language for the untreated control group functional assessments in Section 10 (Study Assessments).
  • Clarified that patients in the untreated control group could have been enrolled concurrently in an observational study, unless it interfered with assessments in this study.

- 07 APR 2015

  • Reduced the frequency of assessments for the untreated control group in Part 2 of the study to reduce the burden on patients and parents in this group.

- 20 APR 2016

• Clarified that control patients were to undergo all procedures at Screening and Baseline except for skin/muscle biopsies.

In the final amendment (08Nov 2017), the protocol was amended to "…clarify[y] that the untreated control group only was used to understand the natural history of DMD patients with other mutations."

6.1.1. Study Results

Compliance with Good Clinical Practices

The study was reported to have been conducted in accordance with the ethical principles of Good Clinical Practice, according to the International Conference for Harmonisation Harmonised Tripartite Guideline.

Financial Disclosure

See Appendix 13.3

Patient Disposition

A total of 12 patients were included in Part 1 of the study; 8 patients received treatment with golodirsen and 4 patients received treatment with placebo. Once Part 1 was completed and a cumulative safety review was conducted by an independent DSMB, these 12 patients enrolled into Part 2 of the study. In Part 2, the 12 patients from Part 1 and 13 new patients amenable to exon 53 skipping were enrolled to receive open-label treatment with golodirsen (Table 8). As of the 29 June 2018 cutoff date, 23 of the 25 patients (92.0%) in the Total Golodirsen Group were ongoing in the study and 2 patients (8.0%) withdrew from the study. Both patients who withdrew from the study discontinued during Part 2 due to withdrawal by patient (ie, patient decision).

Of the 14 **untreated** patients in Part 2 (not included in table), 6 patients (42.9%) were ongoing in the study and 8 patients (57.1%) prematurely discontinued from the study. Reasons for premature discontinuation included withdrawal by patient (4 patients), lost to follow-up (1 patient), and other (3 patients [including 2 patients due to enrollment in a therapeutic study and 1 patient due to personal reasons]).

Table 7 Rationale for Discontinuation (Study 4053-101)

Patient Number	Reason for D/C	Dose at D/C	Week of D/C	Relevant info
Study 4053-101				
(b) (6)	W/D by Subject	30 mg/kg	73	No significant AEs at time of D/C
	W/D by Subject	30 mg/kg	98	No significant AEs at time of D/C
	W/D by Subject	Untreated	11	No significant AEs at time of D/C
	Personal reasons	Untreated	94	No significant AEs at time of D/C
	W/D by Subject	Untreated	76	No significant AEs at time of D/C

Patient Number	Reason for D/C	Dose at D/C	Week of D/C	Relevant info
(b) (6)	Lost to F/U	Untreated	51	No significant AEs at time of D/C
	Inclusion in a Therapeutic Study	Untreated	109	No significant AEs at time of D/C
	Inclusion in a Therapeutic Study	Untreated	121	Moderate Rhabdomyolysis @ Week 87
	W/D by Subject	Untreated	45	No significant AEs at time of D/C
	W/D by Subject	Untreated	91	No significant AEs at time of D/C
	Study 4053-301			
	Family moved	30 mg/kg	11	No significant AEs at time of D/C

Source: Clinical Reviewer

Table 8 Summary of Patient Disposition (Combined Parts 1 & 2 Analysis – All Enrolled Patients)

	Untreated (N=14) n (%)	Golodirsen Group 1[a] (N=17) n (%)	Golodirsen Group 2[b] (N=8) n (%)	Total Golodirsen Group (N=25) n (%)
Enrolled	14 (100.0)	17 (100.0)	8 (100.0)	25 (100.0)
First Enrolled in Part 1	N/A	4 (23.5)	8 (100.0)	12 (48.0)
Randomized in Part 1	N/A	4 (23.5)	8 (100.0)	12 (48.0)
First Enrolled in Part 2	14 (100.0)	13 (76.5)	0	13 (52.0)
Treated[c]	N/A	17 (100.0)	8 (100.0)	25 (100.0)
Ongoing	6 (42.9)	15 (88.2)	8 (100.0)	23 (92.0)
Discontinued	8 (57.1)	2 (11.8)	0	2 (8.0)
Lost to follow-up	1 (7.1)	0	0	0
Withdrawal by patient	4 (28.6)	2 (11.8)	0	2 (8.0)
Other	3 (21.4)[d]	0	0	0

N/A=not applicable
[a] Patients who received placebo in Part 1 followed by golodirsen in Part 2, or patients who enrolled in Part 2 and received golodirsen.
[b] Patients who received golodirsen in Part 1 and continued golodirsen in Part 2.
[c] Treated patients were those who received any study drug, including partial infusions.
[d] Reasons included enrollment in a therapeutic study (2 patients) and personal reasons (1 patient).

Source: 4053-101 Interim Study Report p. 70

Clinical Reviewer's comments
1. Neither of the two golodirsen treated patients who discontinued had significant AEs at the time of discontinuation.
2. The sparse numbers and attrition in the untreated control group diminish their utility as an unbiased, untreated control.

Protocol Violations/Deviations

- (b) (6) (10, 45.0) Accidental Unblinding Unblinded pharmacy team provided unblinded

information to blinded site team
- (b) (6) (8, 39.4) Inclusion Criteria Patient was enrolled in violation of Inclusion/Exclusion
- (b) (6) (8, 39.4) Accidental Unblinding Unblinded pharmacy team provided unblinded information to blinded site team
- (b) (6) (9, 30.3) Inclusion Criteria Patient was enrolled in violation of Inclusion/Exclusion

Demographic Characteristics

Clinical Reviewer's comments – The demographics of the study (Table 9) and other baseline characteristics (Table 10) were as expected for a study in this patient population.

Table 9 Demographic characteristics of the primary efficacy analysis

Demographic Parameters	**Total** N=25, (100%)
Sex	
Male	25 (100%)
Female	0
Age	
Mean years (SD)	8.14 (2.18)
Median (years)	8
Min, max (years)	6 - 13
Race	
White	23 (92)
Other[1]	2 (8)
Ethnicity	
Hispanic or Latino	4 (16)
Not Hispanic or Latino	9 (36)
Not Reported	12 (48)

Source: Clinical Reviewer Analysis of ADSL dataset

All the patients in Study 4053-101 were from outside of the US (Source: Information Request Application Type/Number: NDA 211970 Supporting Document Number: 31).

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)
Table 10 Demographic of Other Baseline Characteristics

Variable	Untreated (N=14)	Golodirsen Group 1[a] (N=17)	Golodirsen Group 2[b] (N=8)	Total Golodirsen Group (N=25)
Baseline BMI (kg/m^2)[c]				
Mean (standard deviation)	19.18 (3.770)	18.25 (2.779)	21.00 (4.707)	19.13 (3.651)
Median	18.18	17.92	18.31	18.16
Minimum, maximum	14.8, 27.4	15.2, 25.4	16.9, 28.8	15.2, 28.8
Baseline 6MWT Distance (meters)[d]				
Mean (standard deviation)	452.9 (49.79)	407.9 (55.22)	401.3 (58.23)	405.8 (55.06)
Median	460.1	401.0	414.5	408.5
Minimum, maximum	351, 539	333, 512	290, 469	290, 512
Mutation, n (%)				
45-52	0	5 (29.4)	3 (37.5)	8 (32.0)
48-52	0	4 (23.5)	1 (12.5)	5 (20.0)
49-52	0	3 (17.6)	2 (25.0)	5 (20.0)
50-52	0	3 (17.6)	1 (12.5)	4 (16.0)
52	0	2 (11.8)	1 (12.5)	3 (12.0)
Time Since DMD Diagnosis to Baseline (months)				
Mean (standard deviation)	53.44 (25.700)	54.02 (21.043)	59.71 (32.708)	55.84 (24.790)
Median	51.65	51.22	52.34	51.22
Minimum, maximum	17.0, 99.9	30.8, 104.9	16.1, 122.9	16.1, 122.9
Duration of Corticosteroid Use at Day 1 (months)				
Mean (standard deviation)	32.82 (17.367)	34.07 (23.526)	37.84 (27.598)	35.28 (24.379)
Median	32.38	24.90	33.46	29.77
Minimum, maximum	8.7, 72.5	11.3, 97.7	8.9, 96.9	8.9, 97.7

6MWT=6-minute walk test; BMI=body mass index; DMD=Duchenne muscular dystrophy
Note: One patient each in the untreated cohort had mutation of 1-47, 3-7, 7-17, 8-43, 10-21, 22-25, 30-43, 35-43, 45, 45-50, 46-51, 46-52, 51, and 61-62.
[a] Patients who received placebo in Part 1 followed by golodirsen in Part 2, or patients who enrolled in Part 2 and received golodirsen.
[b] Patients who received golodirsen in Part 1 and continued golodirsen in Part 2.
[c] Baseline was the last value prior to the first dose of golodirsen administration for treated patients, or the last value on or before the Day 1 date for untreated patients.
[d] Baseline was the average of Day 1 and Day 2 for the visit immediately prior to dosing when 6MWT was collected twice (Part 1 and 2 golodirsen, untreated) or the last value prior to the first dose of golodirsen when 6MWT was collected once.
Source: 4053-101 Interim Study Report p. 76

Efficacy Results – Primary Endpoint

Treatment with golodirsen once weekly was reported to result in an average increase of +0.924% in dystrophin protein from a baseline of 0.095% of normal dystrophin levels to 1.019% of normal at Part 2 Week 48. The levels of dystrophin protein at Part 2 Week 48 ranged from 0.09% to a high of 4.30% of normal, including 18 out of 25 patients with values at Part 2 Week 48 above the LLOQ of 0.25%. Analysis of Western Blot levels versus the duration of golodirsen treatment showed minimal correlation.

Table 11 Dystrophin Levels Determined by Western Blot – Values <LLOQ Analyzed as Measured and Values >ULOQ Analyzed as Measured (Muscle Biopsy Set)

	Statistic	Golodirsen Group 1[a] (N=17)	Golodirsen Group 2[b] (N=8)	Total Golodirsen Group (N=25)
Baseline	Mean	0.091	0.104	0.095
	SD (SE)	0.0567 (0.0138)	0.0914 (0.0323)	0.0680 (0.0136)
	Median	0.065	0.104	0.068
	Min, Max	0.03, 0.22	0.02, 0.31	0.02, 0.31
Part 2 Week 48	Mean	0.840	1.398	1.019[c]
	SD (SE)	0.6429 (0.1559)	1.5719 (0.5557)	1.0328 (0.2066)
	Median	0.908	0.739	0.908
	Min, Max	0.09, 1.91	0.11, 4.30	0.09, 4.30
Change to Part 2 Week 48	Mean	0.750	1.294	0.924
	SD (SE)	0.6660 (0.1615)	1.5079 (0.5331)	1.0129 (0.2026)
	Median	0.875	0.659	0.875
	Min, Max	0.01, 1.84	0.01, 3.99	0.01, 3.99
	p value[d]	<0.001	0.008	<0.001
Fold Change From Baseline to Part 2 Week 48	Mean	13.960	20.208	15.959
	SD (SE)	14.1889 (3.4413)	29.6874 (10.4961)	20.0031 (4.0006)
	Median	9.551	8.919	9.551
	Min, Max	1.04, 53.00	1.07, 89.71	1.04, 89.71
Fold Change of Mean Part 2 Week 48 Over Mean Baseline		9.274	13.432	10.733

LLOQ=lower limit of quantitation; Max=maximum; Min=minimum; SD=standard deviation; SE=standard error; ULOQ=upper limit of quantitation
Note: Baseline was the last recorded value prior to the first dose of study drug (placebo or golodirsen).
[a] Patients who received placebo in Part 1 followed by golodirsen in Part 2, or patients who enrolled in Part 2 and received golodirsen.
[b] Patients who received golodirsen in Part 1 and continued golodirsen in Part 2.
[c] Exclusion of 2 samples with discrepant protein concentration values resulted in a mean of 0.996% (SR-17-044 DEV-0023).
[d] p value was based on 1-sample permutation t-test.
Source: SR-17-068 Table 14.2.2.1

Source: 4053-101 Interim Study Report p. 78

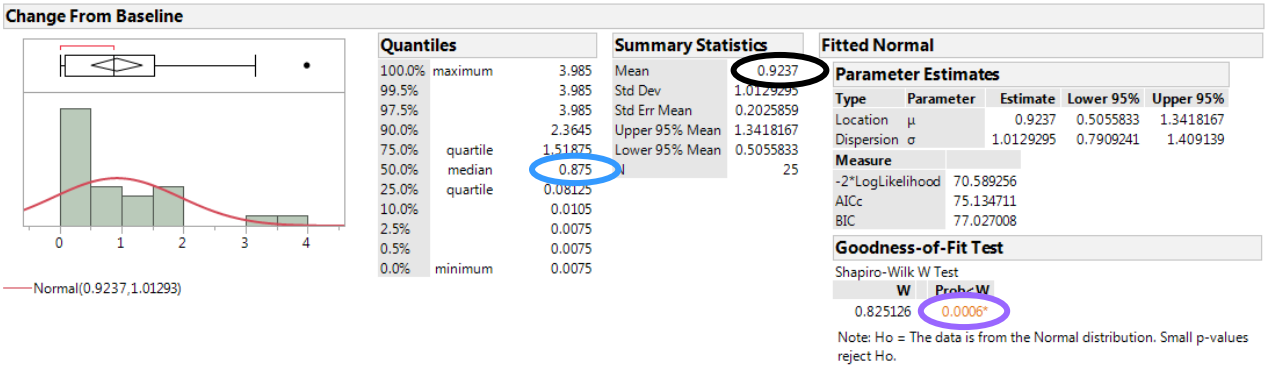
Clinical Reviewer's Comments and Analyses **[C. Breder]–**

The stated analysis for the primary biological endpoint is the change from baseline at Week 48 in dystrophin protein levels determined by Western blot. The Statistical Analysis Plan also describes, "For each time point (Baseline vs Part 2 Week 48), replicate gel runs are performed to determine dystrophin level (% normal) by Western blot. The average of replicate values from

available gel runs will be used in the analyses." No conventions are mentioned in this section of the SAP if the data is skewed.

Given the few subjects in the analysis of the primary endpoint, I reconfirmed the result with the original data (**Table 12**). In the last step, where the change from baseline for the group needed to be calculated, I first determined that the values for change from baseline were not in a normal distribution by the Shapiro-Wilk Test (Purple figure in **Figure 3**). Of note, the mean for this calculation was the same value (0.92%; black circle in **Figure 3**) reported by the Applicant. I do not believe the difference in these numbers is a point to consider for approvability but has implications in what is included in labeling.

Figure 3 Median Change from Baseline for the Percent Dystrophin Protein from Western Blot



Source: Clinical Reviewer analysis of ADBI dataset

The distribution of change in percent dystrophin from baseline to Week 48 by number of patients is shown in Figure 4.

Figure 4 Distribution of Change from Baseline to Week 48 in Percent Dystrophin

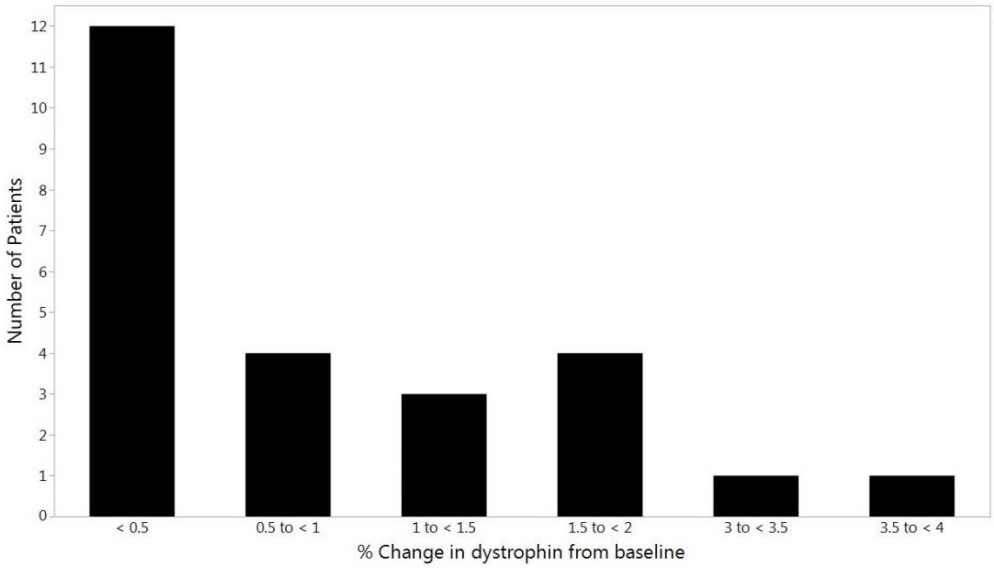


Table 12 Western Blot Calculations for Primary Analysis

USUBJID	Average Baseline, Block A	Average Baseline, Block B	Average of Baseline Block A & B	Average of Week 48, Block A	Average of Week 48, Block B	Average of Week 48, Block A & B	Change from Baseline (Avg. Week 48 minus Avg. Baseline)
(b) (6)	0.1	0.105	0.1025	2.995	3.505	3.25	3.15
	0.32	0.3	0.31	4.86	3.73	4.295	3.99
	0.015	0.02	0.0175	1.61	1.53	1.57	1.55
	0.055	0.08	0.0675	0.825	1.755	1.29	1.22
	0.04	0.025	0.0325	0.405	3.04	1.7225	1.69
	0.215	0.21	0.2125	0.185	0.255	0.22	0.01
	0.15	0.065	0.1075	0.845	1.27	1.0575	0.95
	0.145	0.295	0.22	0.375	0.19	0.2825	0.06
	0.1	0.03	0.065	1.07	0.99	1.03	0.97
	0.12	0.1	0.11	0.365	0.36	0.3625	0.25
	0.04	0.05	0.045	0.095	0.145	0.12	0.08
	0.05	0.055	0.0525	0.635	0.205	0.42	0.37

(b) (6)

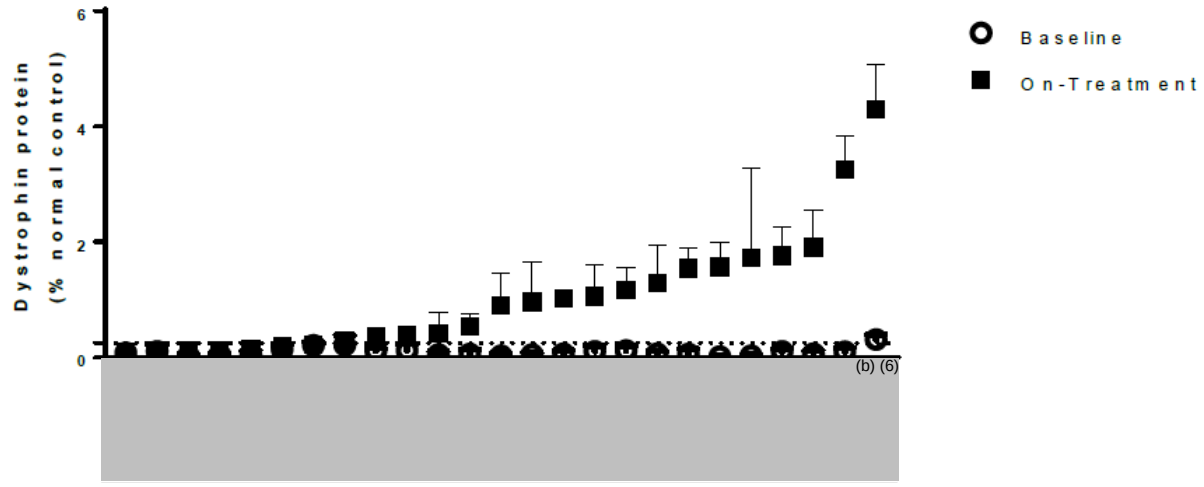
0.015	0.04	0.0275	0.215	0.015	0.115	0.09
0.03	0.1	0.065	2.41	1.405	1.9075	1.84
0.025	0.1	0.0625	0.45	0.625	0.5375	0.48
0.115	0.1	0.1075	2.15	1.385	1.7675	1.66
0.025	0.08	0.0525	0.37	1.565	0.9675	0.92
0.07	0.17	0.12	0.45	0.295	0.3725	0.25
0.01	0.055	0.0325	1.355	0.46	0.9075	0.88
0.02	0.09	0.055	0.245	0.04	0.1425	0.09
0.095	0.065	0.08	0.07	0.115	0.0925	0.01
0.195	0.015	0.105	0.055	0.17	0.1125	0.01
0.09	0.19	0.14	0.215	0.2	0.2075	0.07
0.105	0.015	0.06	1.745	1.345	1.545	1.49
0.105	0.14	0.1225	0.925	1.415	1.17	1.05

Source: Clinical Reviewer analysis of ADBI dataset

Statistical Reviewer's Comments and Analyses **[Biometrics Reviewer - Xiang Ling]**

I confirmed the sponsor's analysis result in Table 11. Biopsies of 24 out of 25 patients at the Baseline time point expressed dystrophin levels below the LLOQ of 0.25%, while 18 out of 25 patients had values at Part 2 Week 48 above the LLOQ (Figure 5). Taking the values "as measured," an increase in dystrophin levels was observed for all 25 golodirsen treated patients. The mean increase was 0.9% of normal dystrophin level, which was statistically significant by the primary analysis of one-sample permutation test. A significant increase in dystrophin protein from Baseline to Part 2 Week 48 was observed for all alternative imputation methods for values <LLOQ or >ULOQ, suggesting that the analysis result is robust to the handling of values outside the range of quantification. I also conducted a sensitivity analysis using a sign test, which is a nonparametric test with very few assumptions. The analysis showed similar results (p-value < 0.0001), supporting the primary analysis.

Figure 5 Dystrophin Levels Determined by Western Blot at Baseline and Part 2 Week 48 for Individual Patients



Source: Interim Clinical Study Report Figure 3, page 79.

Data Quality and Integrity [OBP Reviewers – B. Aryal and A. Rao (Lead)]

The following documents associated with bioassays from NDA submission were reviewed with respect to bioassay validation and fidelity of the submitted data to the validated bioassay submitted in the NDA application.

SR-17-008 WB method optimization
SR-17-009 WB method validation
SR-17-041 New normal standard for WB
SR-17-042 Tissue allocation report for clinical study
SR-17-044 WB technical report of sample analysis
SR-17-045 indirect immunofluorescence staining
SR-17-046 Image capture of cryosections obtained from clinical study 4053-101

SR-17-054 RT-PCR analysis
SR-17-058 RT-PCR method qualification
SR-17-068-Assessment of novel dystrophin expression-muscle map -internal report
SR-17-069 Muscle Biopsy report for study 4053-101
SR-17-070 Western blot validation report
SR-17-061 Assessment of novel dystrophin localization -Muscle Map
SR-17-062-Validation of MANDYS/Merosin duplex IF-tIA assay background correction
SR-17-071 Report of Manual scoring

The Sponsor summarized the method validation results in the following Table 13 from method validation report SR-17-070. Western blot method was successfully validated with all validation parameters meeting the pre-specified acceptance criteria. The Sponsor used exposure time of 5 minutes, 10 minutes, and 15 minutes for validation and results from all exposure time indicate that all validation parameters met the pre-defined acceptance criteria. The Sponsor also provided western blot method 2.0 validation protocol (SR-17-009) and raw data for method validation in validation report SR-17-070.

Table 13. Validation criteria and sumamry of results

Table 2: Validation Criteria and Results

Parameters	Acceptance Criteria	Result	Pass/Fail
Spike and Recovery	*RSD for calculated dystrophin level for each Precision Standard (2% and 0.5%) across a minimum of 3 gels for analyst 1 and 2 should be not greater than 75%*	All lanes met the *not greater than 75%* RSD	Pass
Precision	*RSD for each level precision Standard (2% and 0.5%) across a minimum 3 gels should be not greater than 50%*	The RSD for each level is less than 50%	Pass
Intermediate Precision	*RSD for each level precision Standard (2% and 0.5%) across a minimum 3 gels each for analyst 1 and 2 should be not greater than 75%*	The RSD for each level for both Analysts is less than 75%	Pass
Specificity	*The presence of a band in the 425 kD region of normal standards.*	Band is present at ~425 kDa in the standard in all blots	Pass
Linearity	*The coefficient of determination (R^2) of the linear regression must be ≥ 0.90*	$R^2 \geq 0.90$	Pass
Limit of Detection (LOD)	*The RSD of the band for LOD is not greater than 90%*	Standard levels 1.0, 0.5 and 0.25% have RSD of <50%	Pass: LOD is lower than levels tested
Limit of Quantitation (LOQ)	*The RSD for the bands for LOQ should be less than 70%*	Standard levels 1.0, 0.5 and 0.25% have RSD of <50%	Pass: LOQ is lower than levels tested

Source: SR-17-070 Study Report, Table 2, Page 8

Since a full-length purified dystrophin protein is not available to serve as a reference standard, the Sponsor used a pool of normal non-DMD, non-BMD muscle biopsies lysate as a surrogate reference standard of normal dystrophin (100% dystrophin content). Similarly, a pool of DMD tissue lysate was used as a negative control (~0% dystrophin content).

Preparation of normal control and DMD control pools
The normal control (NC) pool was generated using an equal number of tissues sections from each of the 11 normal non-DMD/non-BMD muscle biopsies. The dystrophin levels in each NC sample was compared with previously established normal control standard, NC-5, using western blot. All 11 samples showed slight variations in dystrophin content in the range of 70.0% - 116.7% compared to NC-5 reference standard (dystrophin content considered 100%) previously used to determine % dystrophin in muscle biopsies obtained from a different clinical study. The Pooled NC standard showed 83.3% dystrophin content compared to single standard NC-5. The Sponsor states that this 16.7% differences between NC pool and NC-5 is within the validated error (±20%) of western blot method; therefore, this NC pool is suitable for use as a standard to quantify dystrophin levels in the unknown samples using western blot.

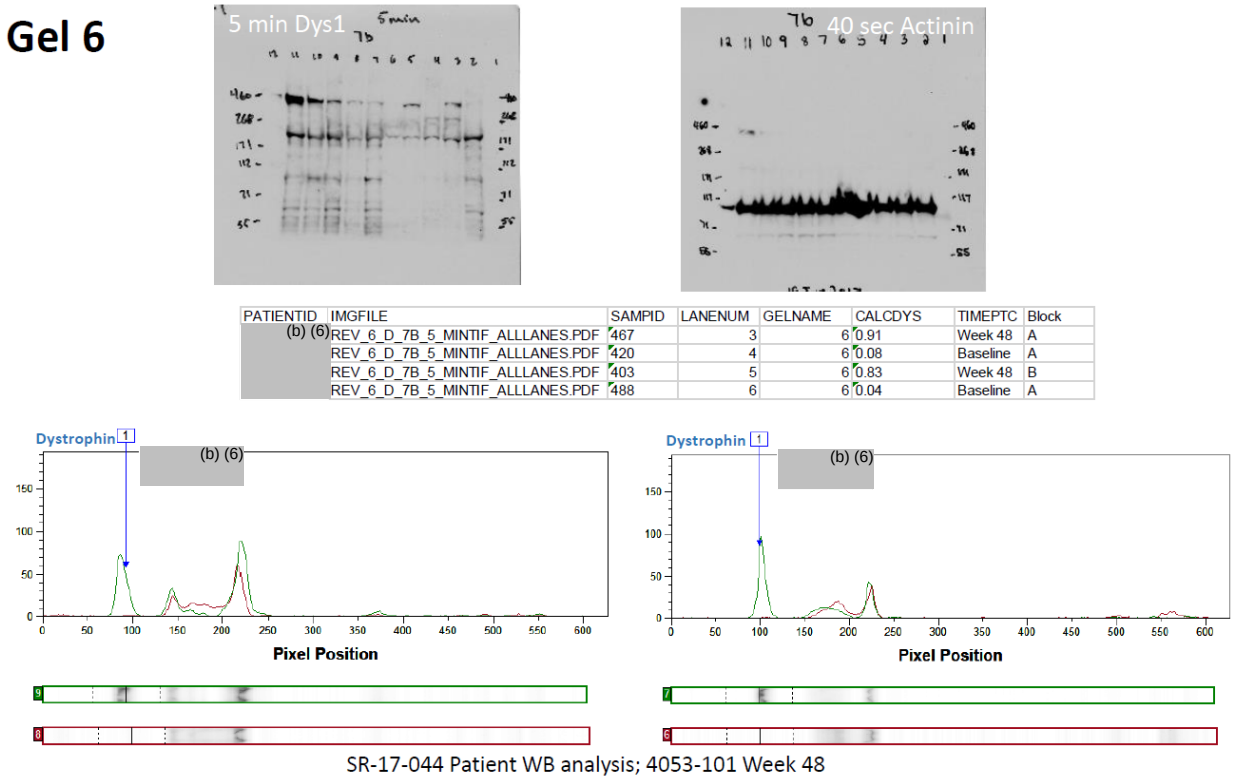
The DMD pool matrix for western blot standard curve was generated from eight DMD tissue with exon 51 amenable mutations. Each of the DMD tissue was confirmed to have dystrophin level below the lower limit of quantification (0.01 – 0.06% of NC) using 3-points standard curve included in each gel.

Reviewer comments*: The NC-5 is a normal standard prepared from a single tissue sample that was previously used to analyze dystrophin in on-treatment DMD tissue samples from a previous clinical study with eteplirsen. For the preparation of NC pool, the Sponsor has used 11 normal non-DMD/non-BMD muscle biopsies. Even though the dystrophin content in NC pool is slightly lower (83.3% of NC-5) than NC-5 single normal standard, NC pool is considered representative of normal dystrophin level in healthy individuals because dystrophin levels is known to vary among healthy personnel and it was prepared from 11 normal non-DMD/non-BMD muscle biopsies lysate with dystrophin content in the range of 70.0% - 116.7% compared to NC-5 reference standard (100%).*
The Sponsor successfully executed western blot method validation because all validation parameters met the pre-defined acceptance criteria and were consistent with FDA guidance on bioanalytical method validation. We previously reviewed the western blot method and method validation during bioassay method development under IND 119982 and provided our comments/recommendation to the Sponsor during our meetings with the Sponsor (Type C meeting held on 02/06/2018, teleconference held on 07/31/2018, and pre-NDA meeting held on 09/11/2018). The Sponsor has addressed our comments to improve method performance that includes reporting % dystrophin of all individual NC tissue samples used in generation of NC pool and selecting the normal controls that show dystrophin content closer to 100% of previously established healthy control (NC-5).

According to Sponsor, all samples were analyzed once and in a blinded manner, as they were allocated. The dystrophin protein levels in the biopsy samples were analyzed using the validated western blot method version 2.0 (Protocol SR-17-044). For western blot analysis, each patient had

biological (tissue block A and B, from same patient) and technical replicates (gel 1 and 2, from same tissue block) for both baseline and part 2 week 48 on-treatment samples. Each biopsy tissue block (block A and block B) from each patient at baseline and week 48 was analyzed separately as biological replicates in different gels; therefore, there are 8 samples for each patient ran in 4 separate gels. Each gel contains a high molecular weight protein marker (lane 1), a negative control (DMD) sample (lane 2), two pairs of blinded test samples at baseline and week 48 from two patients (lanes 3-6), a five points standard curve (lanes 7-11) and a high molecular weight protein marker (lane 12). A 28 µL sample containing 40 µg of total protein in tissue lysate was loaded in each lane. The Sponsor provided 50 raw and full-length western blot images that were used to run all samples from 25 patients. The Sponsor also provided raw data for dystrophin level (% dystrophin relative to normal 100%) at baseline and week 48 determined by ImageQuant software. The dystrophin protein level was determined from the band intensity detected at ~427 kDa. The representative image and accompanying analysis taken from study report SR-17-044 for patient samples with dystrophin expression (lanes 3 and 5) in week 48 on-treatment samples is included below in Figure 5.

Figure 6. Western blot raw data for Gel #6.



SR-17-044 Patient WB analysis; 4053-101 Week 48

Source: SR-17-044 Study Report, Gel # 6, Page 94

***Reviewer comments**: I evaluated dystrophin band intensities in all gel images and compared them with the dystrophin content reported by the Sponsor for each sample in study report SR-17-044. The percent dystrophin shown in raw data in gel images matches with the reported results. Based on raw data, 17 of 25 patients showed an increase in dystrophin expression as indicated by a*

distinct band at ~427 kDa compared to dystrophin level in the corresponding baseline sample. The increase in dystrophin level was consistent among replicates of both tissue blocks. In some cases, (e.g. (b) (6)*, gel # 17), there was a shift in dystrophin band towards low molecular weight compared to NC standard or the dystrophin band of another patient sample (* (b) (6)*) within the same gel. This shift is expected because of the expression of exon 53 skipped internally truncated version of dystrophin and variability in dystrophin mutations among DMD patients.*

All patient samples showed slight variability in baseline dystrophin levels, but the average baseline dystrophin level was below the LLOQ (0.25% of normal) except for one patient sample (b) (6)*, gel # 45-48) which showed baseline dystrophin level above the LLOQ (average value of 0.31). This patient also showed highest level of dystrophin band intensity (mean value = 4.3% of normal) in week 48 sample. Visual inspection of dystrophin bands for this patient samples also shows elevated level of dystrophin bands compared to other patient samples. Therefore, detection of dystrophin band intensity beyond currently validated ranges in the standard curve for patient* (b) (6) *may not be due to high method variability but due to lack of wider dynamic range (beyond 4%) in the current validated standard curve for percent dystrophin. This issue can be addressed in future by extending the dynamic range of percent dystrophin in the standard curve. Regardless of patient-to-patient variability in baseline dystrophin levels and percent changes after treatment, visual inspection and calculated dystrophin levels in all biological and technical replicates of 17 patient samples show an increase in dystrophin levels compared to baseline in both blocks (block A and B) of tissue biopsies. No bioassay deviations were reported that would significantly impact the interpretation of the data. Therefore, dystrophin data analyzed by currently validated western blot are considered to be reliable to assess dystrophin expression in week 48 on-treatment samples.*

The Sponsor provided raw and full-length images of all 50 blots with alpha actinin bands at 40 second exposure time but did not provide information how they evaluated the loading control (alpha actinin) to determine dystrophin expression in week 48 patient samples. Variation in loading control can impact the accuracy of % dystrophin content determined by western blot. The Sponsor also did not provide information about sample stability data. Therefore, we sent an information request on 3/26/2019 requesting raw data for loading control and sample stability information.

The Sponsor responded to our IR on 4/2/2019 and provided all requested information. The Sponsor states that for each gel to meet the acceptance criteria for dystrophin analysis, the alpha actinin variances for each lane should be <±50% in comparison to the average of all actinin band intensity value. Any gel having loading control variances in a single lane >±50% of the average of all actinin band intensity will result in failure of that gel. The Sponsor provided raw data for alpha actinin band intensity values for each lane of all 50 gels, and all values are within <±50% of the average band intensity.

The Sponsor also provided stability protocol (SR-17-049) and 18 months of stability data for frozen normal tissue lysate. The stability study was performed using normal tissue lysate prepared from frozen tissue at each time point as a reference and comparing to frozen normal tissue lysate (normal control pool) prepared at time zero. The Sponsor performed stability testing at 1, 4, 6, 9, 12, and 18 months. Stability data at each time point passed the acceptance criteria without showing any trends in % dystrophin level over time.

Reviewer comments: *The Sponsor provided all information requested in our IR regarding alpha-actinin bands and sample stability. The data provided by the Sponsor supports that the frozen tissue lysates are stable over the period of analysis based on the duration between the last biopsy taken (January 04, 2017) and date reported on signature page of western blot final report (August 08, 2017). The lane-to-lane sample loading uniformity assessed by alpha actinin band intensities was within the pre-specified acceptance criteria of 50%. Therefore, there are no current concerns based on loading uniformity or sample stability over the course of study with samples from 4053-101.*

Immunohistochemistry (IHC) method to determine dystrophin intensity and percent dystrophin-positive fibers (PDPF)

The blinded cryosections of muscle biopsies generated under protocol SR-17-042 from clinical study 4053-101 were stained by indirect immunofluorescence staining protocol at the University of Iowa Hospital (Protocol SR-17-045). Mouse monoclonal anti-dystrophin antibody (MANDYS106) and rat monoclonal anti-merosin antibody (MEROSIN) were used as primary antibodies, and Alexa Fluor 594 goat anti-mouse IgG2a (TRITC, red channel, 617 nm) and Alexa Fluor 488 rabbit anti-rat IgG (FITC, Green channel, 519 nm) were used as secondary antibodies for staining to identify dystrophin protein and sarcolemma membrane in the muscle fibers. Stained slides were shipped to Flagship Bioscience for analysis (SR-17-047) using a semi-automated image analysis algorithm MuscleMap™. A total of 200 slides (2 slides per biopsy resulting in 8 slides per patient) were labeled with MANDYS106/Merosin dual immunostaining assay. On-run controls (DMD10 and healthy control CTRL2) were included as a batch control in every batch of slide labelling and scanning under study 7273-3270. If the on-run controls failed to meet the pre-established mean membrane intensity (0.132-0.198 for sample DMD10 and 0.591-0.888 for CRTL2) then the entire batch of slides were removed from the study. All slides were scanned using 3DHISTECH Panoramic MIDI fluorescence scanner in the FITC and TRITC channels at 20x magnification and fixed exposure time.

Determination of threshold value and problems encountered with validated MuscleMap algorithm

(b) (4)

Exon 53 skipping determined by measurement and sequence verification of exon 53 skipped mRNA using RT-PCR analysis

The exon 53 skipped mRNA is shorter than native unskipped mRNA; therefore, nested endpoint RT-PCR method was utilized to differentiate and quantify the ratio of skipped to unskipped transcript as an indirect method to confirm the mechanism of action of golodirsen using paired baseline and on treatment biopsy tissue samples. A semi-quantitative, endpoint RT-PCR method V 1.0 (SR-17-054) was qualified for specificity and precision using gene-specific primers and report was provided in study report SR-17-058. The acceptance criteria for both specificity and precision were met. Three primer sets were used for system suitability and method qualification. The amplicon sizes were within 15% of the predicated sizes for all three primer sets and no amplicon was detected in water or negative control RT-PCR sample.

The Sponsor states that RNA isolation method was not qualified or validated, and RNA used for qualification study isolated under research principles found to be acceptable for use based on QC, auditing of notebook and appropriate isolation processes. The RNA isolation data were reviewed for both RNA quality score (RQS) and concentration. The Sponsor states that sample with RQS ≥3.0 are acceptable and no RNA samples were found to be RQS <3. Full report of RNA isolation data sheets was provided in study report SR-17-053 and summarized in Table 16. RT-PCR criteria for method qualificationbelow.

Table 16. RT-PCR criteria for method qualification

Parameters	Target Acceptance Criteria	Result	Pass/Fail
Precision	*RSD of unskipped band for three out of four quadruplicate reactions <50%*	Highest RSD was 32.5%	Pass
Specificity	*Amplicon is within 15% of predicted size for three out of four quadruplicate reactions* *No RT and no RNA controls contain no amplicon products*	All amplicons were within 15% of the predicted size Controls showed no amplicon products	Pass

Source: SR17-058 Study Report, Table 3, Page 6

RNA was extracted from each tissue section of muscle biopsy and analyzed by endpoint RT-PCR using patient-specific primers designed to amplify a product of specific size for exon 53 skipped and unskipped sequence as shown in the following Table 17. Patient genotype and amplicon size of mutation specific primers by RT-PCRprovided by the Sponsor.

Table 17. Patient genotype and amplicon size of mutation specific primers by RT-PCR

Number of patients	Genotype (exons deleted)	Primers Exon Location	Unskipped amplicon (bp)	Skipped amplicon (bp)
8	45-52	44-54	429	217
5	48-52	47-54	306	94
5	49-52	47-54	492	280
4	50-52	47-54	594	382
3	52	51-54	414	202

Sources: Reports SR-17-054, SR-17-058, and SR-17-088

Source: Summary of Biopharmaceutic Studies and Associated Analytical Methods, Table 4, Page 10

The PCR reactions were performed in quadruplicate for each biological sample and analyzed on a LabChip Gx Touch to quantify the molarity of skipped and unskipped bands. The band intensity data were used to calculate percent skipping using the following formula.

Percent skipping = [skipped amplicon band intensity/ (skipped + unskipped amplicon band intensities] *100

The analytical data provided by the Sponsor shows that all part 2, week 48 patient samples demonstrated an increase in exon 53 skipping with individual mean percent increase in exon skipping in the range from 2.5% to 37.32% from baseline. The mean percent increase from baseline for all 25 patients was 16.363% and data analysis shows that this increase from baseline was statistically significant ($p<0.001$).

The Sponsor states that there was a positive correlation between exon 53 skipping and dystrophin production determined by western blot (Spearman correlation coefficient of 0.50, $p=0.011$). The side-by-side comparison of RT-PCR data and western blot data provided in study report 4053-101 suggests that individual patients with larger increase in dystrophin level from baseline showing the larger increase in percent 53 exon skipping (e.g. patient (b) (6)) but there are several exceptions where increase in dystrophin level does not perfectly match with exon skipping data.

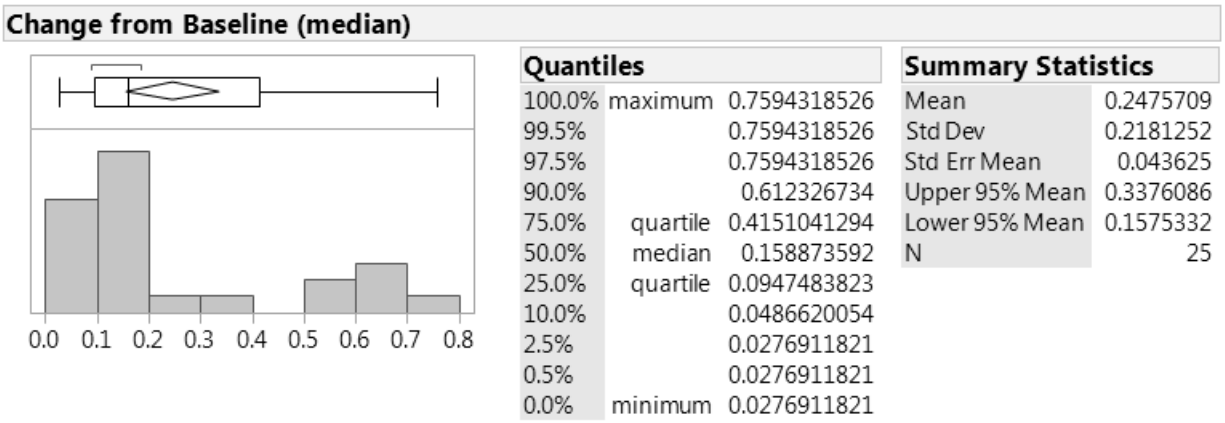
Reviewer comments*: The Sponsor used a semi-quantitative endpoint RT-PCR method to quantify exon 53 skipped dystrophin mRNA as an indirect method of mechanism of action of golodirsen. The RT-PCR method was qualified for specificity and precision using gene-specific primers. The analytical results provided by the Sponsor show an increase in exon 53 skipping in all patient samples with individual mean percent increase in exon 53 skipping ranging from 2.5% to 37.32% from baseline. The mean percent increase from baseline for all 25 patients was 16.363% ($p<0.001$). No issues were noted in the execution of the assay.*

Efficacy Results – Secondary and other relevant endpoints [Clinical Reviewer]

Exon Skipping Ratio

The Exon Skipping Ratio is a ratio of Exon 53 Skipped / Unskipped quantified by RT-PCR of mRNA and contrasted by each Visit. The Applicant reported the change in Exon Skipping ratio as ($\bar{x} = 0.25$, $\tilde{x} = 0.16$). Using the same analysis methods and conventions, I (CDB) determined the median change from baseline in Exon Skipping ratio to be 0.16 (Figure 14).

Figure 14 Median Change from Baseline in Exon Skipping Ratio

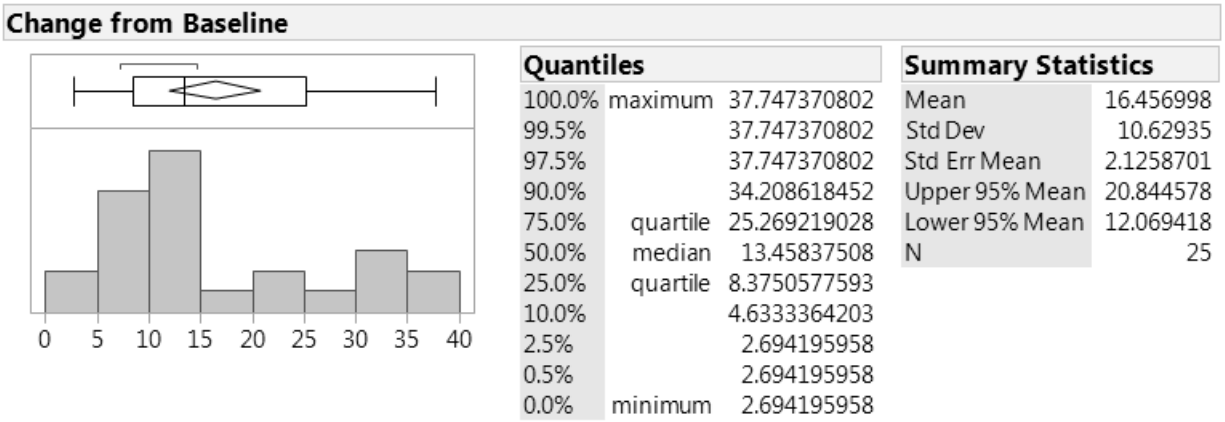


Source: Clinical Reviewer analysis of ADBI dataset

Percent Skipping

The Applicant reported the change in Percent Skipping as ($\bar{x}$ = 16.36, $\tilde{x}$ = 13.60).
Using the same analysis methods and conventions, I (CDB) determined the median change from baseline in percent skipping to be 13.46% (Figure 15).

Figure 15 Median Change from Baseline in Percent Skipping



Source: Clinical Reviewer analysis of ADBI dataset

Functional Endpoints

Six Minute Walk Test

A mean decrease in 6MWT from a Baseline of 405.8 meters was observed in the Total Golodirsen Group at Part 2 Week 48 (26.1 meters), Part 2 Week 72 (52.2 meters), Part 2 Week 96 (64.6 meters), and Part 2 Week 120 (86.1 meters). For the 16 patients who had reached Part 2 Week 144 as of the data cutoff, the mean decrease was 92.5 meters. Patients in Golodirsen Group 2,

who had longer follow-up, had a larger mean decrease from Baseline than patients in Golodirsen Group 1 at each evaluation.

Table 18 Change in 6MWT From Baseline through Week 144 (Efficacy Set)

	Statistic	Golodirsen Group 1[a] (N=17)	Golodirsen Group 2[b] (N=8)	Total Golodirsen Group (N=25)
Baseline (meters)	N	17	8	25
	Mean (SD)	407.9 (55.22)	401.3 (58.23)	405.8 (55.06)
	Median	401.0	414.5	408.5
	Min, Max	333, 512	290, 469	290, 512
Change to Part 2 Week 48 (meters)	N	16	7	23
	Mean (SD)	-17.5 (58.14)	-45.8 (80.14)	-26.1 (65.06)
	Median	-25.3	-9.0	-22.5
	Min, Max	-121, 128	-209, 35	-209, 128
Change to Part 2 Week 72 (meters)	N	17	8	25
	Mean (SD)	-23.2 (65.59)	-113.8 (109.63)	-52.2 (90.74)
	Median	-15.0	-90.0	-41.0
	Min, Max	-168, 119	-290, 33	-290, 119
Change to Part 2 Week 96 (meters)	N	16	8	24
	Mean (SD)	-45.1 (91.17)	-103.8 (125.86)	-64.6 (105.07)
	Median	-46.0	-64.3	-52.8
	Min, Max	-203, 186	-291, 54	-291, 186
Change to Part 2 Week 120 (meters)	N	13	8	21
	Mean (SD)	-64.8 (117.28)	-120.6 (126.19)	-86.1 (120.81)
	Median	-56.5	-69.0	-56.5
	Min, Max	-343, 188	-318, 25	-343, 188
Change to Part 2 Week 144 (meters)	N	8	8	16[c]
	Mean (SD)	-41.3 (91.77)	-143.6 (115.30)	-92.5 (113.69)
	Median	-77.0	-118.8	-84.0
	Min, Max	-151, 144	-315, 13	-315, 144

6MWT=6-minute walk test; Max=maximum; Min=minimum; SD=standard deviation
[a] Patients who received placebo in Part 1 followed by golodirsen in Part 2, or patients who enrolled in Part 2 and received golodirsen.
[b] Patients who received golodirsen in Part 1 and continued golodirsen in Part 2.
[c] Two patients withdrew from study before Part 2 Week 144 and 2 ongoing patients had missing 6MWT at Part 2 Week 144; other missing data were due to ongoing patients who had not reached Part 2 Week 144 as of the 29 June 2018 data cutoff (Listing 16.2.1.1).
Note: Baseline was defined as the average of Day 1 and Day 2 for the visit immediately prior to dosing when 6MWT was collected twice or the last value prior to the first dose of golodirsen when 6MWT was collected once.

Source: 4053-101 Interim Clinical Study Report, p. 105

Pulmonary Function Test

A mean decrease in FVC%p from a Baseline of 92.717% was observed in the Total Golodirsen Group at Part 2 Week 48 (0.634%), Part 2 Week 72 (2.167%), Part 2 Week 96 (0.789%), and Part 2 Week 120 (3.735%). For the 18 patients who had reached Part 2 Week 144 as of the data cutoff,

the mean decrease was 5.349%. Patients in Golodirsen Group 2, who had longer follow-up had a larger mean decrease from Baseline than patients in Golodirsen Group 1 at each evaluation.

Table 19 Change in FVC Percent Predicted from Baseline through Week 144 (Efficacy Set)

	Statistic	Golodirsen Group 1[a] (N=17)	Golodirsen Group 2[b] (N=8)	Total Golodirsen Group (N=25)
Baseline (%)	N	17	8	25
	Mean (SD)	88.433 (25.0927)	101.821 (19.7216)	92.717 (23.9547)
	Median	90.081	100.914	95.700
	Min, Max	16.43, 123.08	73.32, 137.84	16.43, 137.84
Change to Part 2 Week 48 (%)	N	16	8	24
	Mean (SD)	-0.503 (25.8032)	-0.894 (9.7143)	-0.634 (21.5169)
	Median	-7.105	2.331	-1.688
	Min, Max	-28.91, 67.03	-18.12, 11.99	-28.91, 67.03
Change to Part 2 Week 72 (%)	N	17	8	25
	Mean (SD)	4.593 (27.8301)	-2.990 (10.8985)	2.167 (23.7491)
	Median	1.615	-2.519	1.399
	Min, Max	-31.13, 85.33	-17.32, 12.81	-31.13, 85.33
Change to Part 2 Week 96 (%)	N	16	7	23
	Mean (SD)	1.479 (28.3156)	-0.787 (8.1303)	0.789 (23.7872)
	Median	-0.045	-1.548	-0.592
	Min, Max	-33.37, 79.09	-12.96, 8.11	-33.37, 79.09
Change to Part 2 Week 120 (%)	N	13	8	21
	Mean (SD)	-1.308 (30.4256)	-7.681 (11.8052)	-3.735 (24.7844)
	Median	-9.410	-6.588	-9.410
	Min, Max	-39.05, 81.72	-23.88, 5.99	-39.05, 81.72
Change to Part 2 Week 144 (%)	N	10	8	18[c]
	Mean (SD)	-3.545 (35.3841)	-7.603 (11.4320)	-5.349 (26.8507)
	Median	-14.450	-6.098	-9.436
	Min, Max	-38.95, 79.57	-28.06, 8.30	-38.95, 79.57

FVC=forced vital capacity; Max=maximum; Min=minimum; SD=standard deviation
[a] Patients who received placebo in Part 1 followed by golodirsen in Part 2, or patients who enrolled in Part 2 and received golodirsen.
[b] Patients who received golodirsen in Part 1 and continued golodirsen in Part 2.
[c] Two patients withdrew from study before Part 2 Week 144; other missing data were due to ongoing patients who had not reached Part 2 Week 144 as of the 29 June 2018 data cutoff (Listing 16.2.1.1).
Note: Baseline was defined as the last value prior to the first dose of golodirsen.

Source: 4053-101 Interim Clinical Study Report, p. 104

Additional Studies

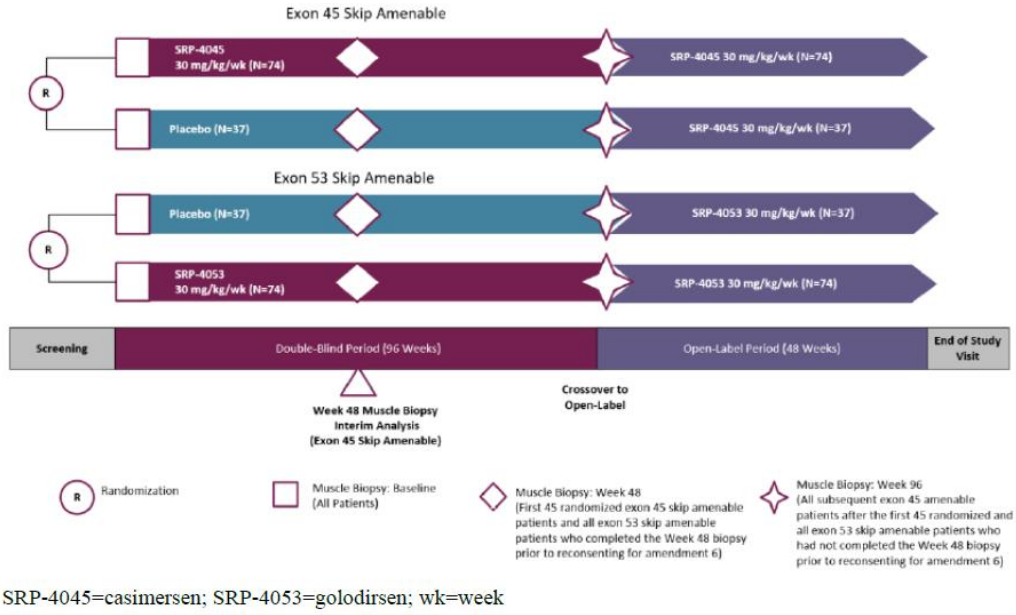
The following study was submitted in contribution to the safety database and not to contribute to the consideration of efficacy. An abbreviated description is provided below.

6.2. (4045-301) A Double-Blind, Placebo-Controlled, Multicenter Study with an Open-Label Extension to Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in Patients with Duchenne Muscular Dystrophy

6.2.1. Design

This is a double-blind, placebo-controlled, multicenter study with an open label (OL) extension that is currently ongoing.

Figure 16 Schematic Diagram of the Design of Study 4045-301 ('Essence')



SRP-4045=casimersen; SRP-4053=golodirsen; wk=week

Source: NDA Summary of Clinical Safety, p. 21

Approximately 222 DMD patients with genotypically confirmed out-of-frame deletions amenable to exon 45 or 53 skipping, respectively, will be treated in this protocol. In the double-blind treatment period, a placebo group is employed within each genotype and patients will be randomized in a 2:1 ratio to receive active treatment or matching placebo as once weekly intravenous (IV) infusion treatment. Randomization will be stratified by genotype and age (7 to 8.5 years vs >8.5 to 13 years). Following completion of the 96-week double-blind period, all patients will begin the OL period and receive active treatment according to their genotype for up to 48 weeks.

Key inclusion /exclusion criteria include:
Inclusion

1. A male with an established clinical diagnosis of DMD and an out-of-frame deletion amenable to treatment
    a. Exon 45 skipping (including but not limited to deletions of exons such as 12-44, 18-44, 44, 46-47, 46-48, 46-49, 46-51, 46-53, or 46-55) OR
    b. Exon 53 skipping (including but not limited to deletions of exons such as 42-52, 45-52, 47-52, 48-52, 49-52, 50-52, 52, or 54-58)

2. As documented prior to screening by a genetic report from an accredited laboratory defining deletion endpoints by multiplex ligation-dependent probe amplification or sequencing. The patient's amenability to exon 45 or 53 skipping must be confirmed prior to first dose using the genotyping results obtained during Screening.
2. Is between 7 and 13 years of age, inclusive, at randomization.
3. Has stable pulmonary function (FVC % of predicted ≥50% and no requirement for nocturnal ventilation) that, in the Investigator's opinion, is unlikely to decompensate over the duration of the study.
3. Has been on a stable dose or dose equivalent of oral corticosteroids for at least 24 weeks prior to Week 1 and the dose is expected to remain constant throughout the study (except for modifications to accommodate changes in weight).
4. Achieved a mean 6MWT distance of ≥300 to ≤450 meters (without assistance) at both the Screening and Baseline visits (prior to Week 1). The mean 6MWT distance at the Screening and Baseline visits is the average of 2 separate assessments on 2 consecutive business days at each visit. The Baseline mean (average of Baseline Days 1 and 2) must be within 15% of the Screening mean distance (average of Screening Days 1 and 2).

Exclusion

1. Treatment with any of the following investigational therapies according to the time frames specified:
   - At any time:
     - o Utrophin upregulating agents (except for Ezutromid)
     - o Anti-myostatin agents except for Domagrozumab (PF-06252616) (e.g., BMS-986089 or other)
     - o CRISPR/Cas9, or any other form of gene editing
     - o Gene therapy
     - o Cell-based therapy (e.g., stem cell transplantation)
     - o Any form of nucleic acid antisense therapy, except PRO045 (BMN 045) or PRO053 (BMN 053) (see below)
   - Within 24 weeks prior to Week 1:
     - o Ezutromid (SMT C1100)
     - o PRO045 (BMN 045)
     - o PRO053 (BMN 053)
     - o PRO051 (BMN 051)
     - o Domagrozumab (PF-06252616)
     - o Anti-fibrotic or anti-inflammatory agents including but not limited to: rimeporide, vamorolone (VBP-15), epigallocatechin-gallate, TAS-205, edasalonexent (CAT-1004), FG-3019, and halofuginone (HT-100)
     - o Mast cell activation inhibitor (e.g., CRD007 [pemirolast sodium])
     - o Idebenone (Raxone®)
   - Within 12 weeks prior to Week 1:
     - o Nitric oxide (NO)-active agents including, but not limited to, metformin and citrulline, isosorbide dinitrate, tadalafil, sildenafil, pentoxyfilline if taken as part of a DMD clinical trial and not for a medical indication. If taken for a medical indication, must be on a stable dose for at least 12 weeks prior to Week 1.
   - For any experimental treatment not otherwise specified in Exclusion Criterion 1, consult the medical monitor.

2. Treatment with any of the following non-investigational therapies according to the time frames
specified:
   • Within 12 weeks prior to Week 1:
      o Any pharmacologic treatment (other than corticosteroids) that may have an effect on muscle strength or function. Growth hormone for short stature and testosterone for delayed puberty are permitted if a physician has documented the diagnosis and medical necessity of treatment, and the patient started dosing at least 24 weeks prior to Week 1.
   • Within 12 weeks prior to Week 1 or anticipated need during the study:
      o Statins
      o Aminoglycoside antibiotics
3. Major surgery within 3 months prior to Week 1 or planned surgery for any time during this study, except for protocol-specified surgery, as applicable.
4. Presence of any other significant genetic disease other than DMD (e.g., dwarfism).
5. Presence of other clinically significant illness including significant cardiac, pulmonary, hepatic, renal, hematologic, immunologic, or behavioral disease, or malignancy.
6. LVEF <50% on the Screening echocardiogram (ECHO) or QTcF ≥450 msec on the Screening and Baseline electrocardiogram (ECG).
7. Dorsiflexion range of motion will be measured bilaterally and recorded as degrees from neutral (see figure). The subject will be excluded if the average loss of dorsiflexion of both extremities is > -10 degrees. For example, if the subject has -8 degrees on one side and -12 degrees on the other side, then he would still qualify because the average of the 2 sides is -10 degrees.

Efficacy, including the 6MWT, NSAA, and pulmonary function tests (PFTs), will be assessed at regularly scheduled study visits and safety will be monitored on an ongoing basis for all patients. Upon qualification for the study based on Screening and Baseline assessments and after eligibility is confirmed by both the Local Site and the Sponsor, all patients will undergo a muscle biopsy at Baseline. A second biopsy will be collected at either Week 48 or 96 as follows:

- The first 45 patients amenable to exon 45 skipping randomized into this study will undergo muscle biopsy at Week 48 and all subsequent patients amenable to exon 45 skipping randomized into this study will undergo a muscle biopsy at Week 96.
- Patients amenable to exon 53 skipping who have completed the Week 48 muscle biopsy prior to reconsenting for Amendment 6 will not undergo a further muscle biopsy.
- Patients amenable to exon 53 skipping who have not completed the Week 48 muscle biopsy prior to reconsenting for Amendment 6 will undergo a muscle biopsy only at Week 96.

The safety and tolerability of SRP-4045 and SRP-4053 will be assessed through a review and evaluation of: AEs, serious adverse events (SAEs), deaths and discontinuations due to AEs; laboratory testing including hematology, coagulation, chemistry (including serum cystatin C), and urinalysis (including urinary kidney injury molecule-1 [KIM-1]); immunogenicity assessments; ECG; vital signs; and physical examination findings.

Upon completion of the double-blind portion of this study, patients may participate in an OL treatment extension period of up to 48 weeks in which they will receive weekly treatment with 30 mg/kg SRP-4045 or SRP-4053, according to genotype. This Extension was termed 4045-302/303 and is summarized in the table below.

Table 20 Description of Study 4045-302/303

4045-302/ 3	1: Evaluate the safety and tolerability of long-term treatment with casimersen or golodirsen in patients with Duchenne muscular dystrophy. 2: Evaluate changes in physical function with long-term treatment with 30 mg/kg of casimersen or golodirsen. 3: Evaluate changes in pulmonary function with long-term treatment with 30 mg/kg of casimersen or golodirsen. 4: Evaluate immunogenicity of long-term treatment with 30 mg/kg casimersen or golodirsen.	Non-randomized, long-term, OL, parallel assignment, extension study. OL: up to 144 weeks	OL: Golodirsen or casimersen (according to genotype) 30 mg/kg once weekly for up to 144 weeks; IV	Planned: 260 patients Patients with DMD who are amenable to treatment by skipping exons 45 or 53 and who have been participating in a clinical trial evaluating casimersen (SRP-4045) or golodirsen (SRP-4053) will be eligible to transfer into this LTE study.

Source: NDA 120-Day Safety Report

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

A full integrated review and assessment of efficacy was deemed not to be necessary because the submission submitted data from only one study in evidence for the accelerated approval and because the population for this study was both small and relatively homogeneous.

[Assessment from the Clinical Reviewer]

I acknowledge the prior opinion from the Exondys 51 (NDA 206488) that any increase in dystrophin Western blot levels protein constituted grounds for approval for this type of therapy in this indication. However, given the exceedingly low levels of protein in the setting of noteworthy muscle pathology, I do not believe there has been reasonable likelihood that these results would predict a clinical benefit. In the Exondys 53 review, the changes in dystrophin by Western blot demonstrated a negative correlation when contrasted with measures of clinical function (NDA206488 Clinical Review). I therefore recommend a Complete Response until the Applicant has demonstrated that the dystrophin produced has a reasonable likelihood of resulting in clinical benefit.

8. Review of Safety

8.1. Safety Review Approach

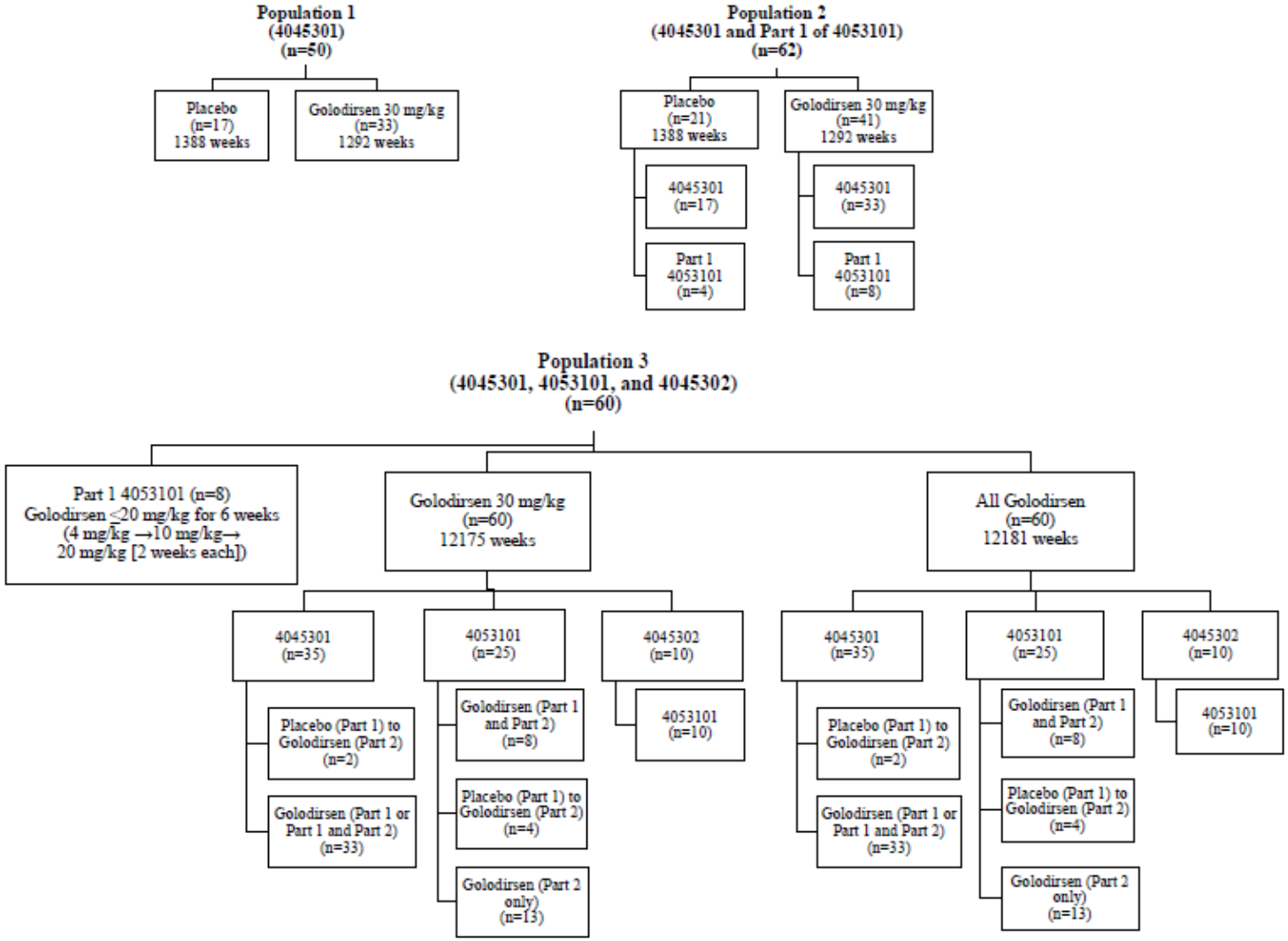
The applicant partitioned the safety population into three groups. Population 1 provided interim safety results from the placebo-controlled, double-blinded Study 4045-301. Population 2 integrated the 4045-301 data with Part 1 of Study 4053-101, thereby, thereby providing integrated golodirsen safety information, collected only during the double-blind, placebo-controlled, randomized portion of both trials. Finally, Population 3 provided a comprehensive evaluation of golodirsen safety, including safety events from both placebo-controlled and open-label experience.

The largest population that was placebo-controlled was designated by the Applicant as Population 2 (Figure 17) so this group was used for most analyses of risk, including the Table of Common Adverse Events in Section 6. The largest group of golodirsen exposed patients came from the 120-day safety update Population 3, which was reviewed for less common events, events occurring with longer delays and for sensitivity analysis of risk calculations.

Of the 25 patients enrolled in Study 101 who received treatment, all but one were from outside the US. Patients in 4045-301 in the safety population[4] are roughly evenly distributed from the US (27) and rest of world (24).

[4] Patients from Study 4045-301 were only considered in the safety analysis, not the efficacy analysis.

Figure 17 Definition of Populations for Safety Analysis



Source: NDA 120-Day Safety Update, p. 21

Planned safety assessments are presented in detail prior to reporting, analysis, and discussion of the results in Table 21.

Table 21 Safety Assessments in NDA Submission

Safety Assessment	4045-301[a]	4053-101 (Parts 1 and 2)	4045-302
Adverse events[b]	Informed consent signature through the follow-up visit	Informed consent signature through the end of study (or early termination visit)	Informed consent signature through the follow-up visit
Clinical laboratory tests			
Serum chemistry Hematology Urinalysis Coagulation	Screening, Baseline, weekly from Weeks 1 through 8, and at Weeks 12, 24, 36, 48, 60, 72, 84, and 96[cd]	Part 1: Screening, Baseline, weekly from Part 1, Weeks 1 through 9 and Week 12 Part 2: Screening (for new patients), Baseline, and Part 2, Weeks 1, 2-3, 4, 8, 12, 16, 20, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, end of study, and 4-week follow-up[cd]	Screening[g], Weeks 4, 8, 12, 24, 36, 48, 72, 96, 120, 144/ET
Vital signs	Screening, Baseline, and on infusion days within approximately 30 minutes prior to infusion and approximately 5, 30, and 60 minutes after the end of the infusion[e]	Screening, Baseline, and on infusion days within approximately 30 minutes prior to infusion and approximately 5, 30, and 60 minutes after the end of the infusion and at Screening (for new patients) and at 4-week follow-up in Part 2[e]	Weekly from Week 1 through Week 144/ET
Physical examination	Screening and Weeks 1, 4, 12, 24, 36, 48, 72, and 96 (brief examinations at Weeks 8, 16, 20, 28, 32, 40, 44, 60, and 84)	Part 1: Screening and Part 1, Weeks 1, 4, 8, and 12 Part 2: Screening (for new patients) and Part 2, Weeks 1, 4, 8, 12, 16, 20, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, end of study, and 4-week follow-up	Full physical exam[h] at Screening[g], Weeks 24, 48, 72, 96, 120, 144/ET Brief physical exam[h] at Weeks 12, 36, 60, 84, 108, 132
12-lead ECG	Screening, Baseline, Weeks 12, 24, 36, 48, 60, 72, 84, and 96	Part 1: Screening, Baseline, and Part 1, Week 12 Part 2: Screening (for new patients), Baseline, Part 2, Weeks 12, 24, 36, 48, 72, 96, 120, and 144	Screening[g], Weeks 48, 96, 144/ET
Echocardiogram	Screening and Week 96	Part 1: Screening and Part 1, Week 12 Part 2: Screening (for new patients) and Part 2, Weeks 24, 48, 72, 96, 120, and 144	Not assessed
Concomitant medications	From informed consent signature through the follow-up visit	From informed consent signature through the end of study (or early termination visit)	From informed consent signature through the follow-up visit

aPTT=activated partial thromboplastin time; ECG=electrocardiogram; ET=early termination; HEENT=head, eyes, ears, nose, and throat.
a Includes those safety assessments collected/performed during the 96-week double-blind treatment period of Study 4045-301.
b Adverse events (including serious adverse events).
c Chemistry: alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, blood urea nitrogen, calcium, chloride, creatinine, creatine phosphokinase, glucose, potassium, sodium, total bilirubin, and uric acid, with amylase, gamma glutamyl transferase, lactate dehydrogenase, and C reactive protein in 4045-301 and 4053-101 and cholesterol, iron, phosphorus, total protein, and triglycerides in 4053-103 and 4053-104. Cystatin C was analyzed in 4045-301, 4053-101, and 4053-104.
Hematology: red blood cell count, white blood cell count, hemoglobin, hematocrit, neutrophils, lymphocytes, monocytes, eosinophils, basophils, platelet count, with abnormal cells in 4045-301 and mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, red blood cell distribution width in 4053-103 and 4053-104.
Urinalysis: pH, specific gravity, glucose, ketones, occult blood/hemoglobin, and protein, with cytology, kidney injury molecule-1 in 4045-301 and 4053-101 and color and appearance, bilirubin, leukocyte esterase, nitrite, urobilinogen, and microscopic examination, including bacteria, casts, crystals, epithelial cells, red blood cells, and white blood cells (if protein, leukocyte esterase, nitrite, or blood were positive) in 4053-103 and 4053-104.
d Coagulation: Prothrombin time, aPTT, and international normalized ratio.
e Blood pressure, pulse rate, respiratory rate, and oral temperature.
f Weekly from Week 1 through Week 144/ET Temperature, supine blood pressure, respiratory rate, and supine pulse rate.
g Assessments do not need to be repeated at screening if they were performed at the End of Study visit for the original study in which the patient was enrolled.
h Full physical exam will include evaluation of general appearance, HEENT, heart, chest, abdomen, skin, lymph nodes, extremities, musculoskeletal, and neurological systems.
Brief physical exam will include evaluation of the general appearance, HEENT, heart, chest, abdomen, and skin.
Source: Study Protocols for 4045-301, 4053-101, 4053-103, and 4053-104

Source: NDA 120-Day Safety Update, pp. 16-7

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Twelve patients were treated in Part 1 of **4053-101**, 8 with active and 4 with placebo (**Table 22**). Thirteen (13) additional patients enrolled into the open label treatment of Part 2. Fourteen untreated patients, not amenable to Exon-53 Skipping were included in Part 2.

Fifty (50) of the 111 planned patients who received golodirsen or placebo have been randomized into Study 4045-301. Thirty-three (33) of the planned 74 have received golodirsen and 17 of the planned 34 have received placebo. The total number of patients exposed to golodirsen or placebo up to the cut-off date for the 120-day safety update is provided in **Table 22** and the duration of golodirsen exposure is detailed in Table 14.

Table 22 Exposure for Studies in Golodirsen Clinical Development Program Referenced in 120-Day Safety Update Report

Study Identification	Number of Patients	Patient-Years
4053-101 (ongoing)	25[a]	
Golodirsen 30 mg/kg	13	
Golodirsen ≤20 mg/kg – 30 mg/kg	8	
Placebo	4[b]	
4045-301 (ongoing)[c]	50	
Golodirsen 30 mg/kg	35[d]	
Placebo	17[d]	
4045-302 (ongoing)	10[a]	
Golodirsen 30 mg/kg	10[a]	
Total DMD Patients treated with golodirsen	**60**	**116.91**
Total DMD Patients treated with placebo	**21**	**21.09**
Total DMD Patients	**77**	
4053-103	8	
4053-104	24	
Total non-DMD Subjects	**32**	

Note: Cumulative through 26 October 2018.
a Ten patients completed Study 4053-101 and are currently enrolled in Study 4045-302; an additional 4 patients completed Study 4053-101 but have not yet rolled into Study 4045-302.
b All 4 patients subsequently received golodirsen 30 mg/kg in Part 2 of the study.
c This study also includes casimersen (SRP-4045), a separate investigational product under development by the Sponsor, intended to treat a different patient population with DMD mutations amenable to exon 45 skipping. There is no information about this product in this 120-day SU report.
d Of the 17 patients who received placebo in Part 1 of Study 4045-301, two have been treated with golodirsen 30 mg/kg in the open-label extension period of the study (Part 2). These 2 patients are counted in both treatment groups. As of 26 October 2018, the remaining 15 patients continued to receive placebo in Part 1 of Study 4045-301.
DMD=Duchenne muscular dystrophy; SU=safety update.
Source: Table 3.1.1, Table 3.1.2, and Table 3.1.3

Source: NDA 120-Day Safety Update, pp. 16-7

Table 23 Total Exposure (Safety Population of Studies 4053-101 and 4045-301)

	≤20 mg/kg (N=8)	30 mg/kg (N=58)	All Golodirsen (N=58)
Weeks on study drug			
Mean (standard deviation)	6.0 (0.08)	88.6 (58.19)	89.4 (59.39)
Median	6.0	79.1	79.1
Minimum, maximum	6, 6	12, 175	12, 181
Number of infusions			
Mean (standard deviation)	6.0 (0.00)	86.4 (58.35)	87.2 (59.55)
Median	6.0	77.5	77.5
Minimum, maximum	6, 6	12, 175	12, 181
Weeks on Study Category, n (%)			
<12 weeks	8 (100)	1 (1.7)	1 (1.7)
12 to <24 weeks	0	5 (8.6)	5 (8.6)
24 to <48 weeks	0	17 (29.3)	17 (29.3)
48 to <96 weeks	0	11 (19.0)	11 (19.0)
96 to <120 weeks	0	1 (1.7)	1 (1.7)
≥120 weeks	0	23 (39.7)	23 (39.7)
Patient-years of study drug exposure			
Mean (standard deviation)	0.115 (0.0015)	1.697 (1.1152)	1.713 (1.1382)
Median	0.115	1.515	1.515
Minimum, maximum	0.11, 0.12	0.22, 3.35	(0.22, 3.47)
Sum	0.92	98.44	99.36

Source: NDA Summary of Clinical Safety, pp. 47

8.2.2. Disposition

In study 4053-101, as of the 29 June 2018 cutoff date, 23 of the 25 patients (92.0%) in the Total Golodirsen Group were ongoing in the study and 2 patients (8.0%) withdrew from the study. Both patients who withdrew from the study discontinued during Part 2 due to withdrawal by patient (i.e., patient decision). Of the 14 untreated patients in Part 2, 6 patients (42.9%) were ongoing in the study and 8 patients (57.1%) prematurely discontinued from the study. Reasons for premature discontinuation included withdrawal by patient (4 patients), lost to follow-up (1 patient), and other (3 patients [including 2 patients due to enrollment in a therapeutic study and 1 patient due to personal reasons]).

Medical Reviewer Comment: None of the discontinued subjects appeared to have a treatment related reason for discontinuation (Table 24).

Table 24 Rationale for Discontinuation (Study 4053-101)

Patient Number	Reason for D/C	Dose at D/C	Week of D/C	Relevant info
Study 4053-101				
(b) (6)	W/D by Subject	30 mg/kg	73	No significant AEs at time of D/C
	W/D by Subject	30 mg/kg	98	No significant AEs at time of D/C
	W/D by Subject	Untreated	11	No significant AEs at time of D/C
	Personal reasons	Untreated	94	No significant AEs at time of D/C
	W/D by Subject	Untreated	76	No significant AEs at time of D/C
	Lost to F/U	Untreated	51	No significant AEs at time of D/C
	Inclusion in a Therapeutic Study	Untreated	109	No significant AEs at time of D/C
	Inclusion in a Therapeutic Study	Untreated	121	Moderate Rhabdomyolysis @ Week 87
	W/D by Subject	Untreated	45	No significant AEs at time of D/C
	W/D by Subject	Untreated	91	No significant AEs at time of D/C
	Study 4053-301			
	Family moved	30 mg/kg	11	No significant AEs at time of D/C

Source: Clinical Reviewer analysis

8.2.3. Adequacy of the safety database

The safety database was small, making interpretation of potential signals difficult; however, it was organized in a manner adequate for review.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

Overall the safety database was of adequate composition and format to be reviewable. The size of the database was small so interpretation of potential signals was difficult. As of the timing of this review, the potential unblinding mentioned in Section 4.1Office of Scientific Investigations (OSI) has not been fully evaluated, which may affect the interpretability of the safety data.

8.3.2. Categorization of Adverse Events

Adverse events were in the Summary of Clinical Safety were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1 system organ class (SOC) and preferred term (PT). Terms were checked for the accuracy of coding and new PTs assigned as described in Appendix 13.2.

8.4. Safety Results

8.4.1. Deaths

According to the Applicant (including all NDA materials), there were no deaths in the clinical program.

8.4.2. Serious Adverse Events

Serious events reported in the 120-day safety update for Population 3 are listed in Table 25 below. Events from SAEs and Common Events related to Rhabdomyolysis, Hypersensitivity and Fracture are discussed further in Section 8.4.4 Significant Adverse Events.

Table 25 Listing of Treatment-Emergent Serious Adverse Events by Patient

Study.Patient ID[a]	TEAE (Preferred Term/ System Organ Class)	Treatment Dose	Start Date (Study Day)	Stop Date (Study Day)	Severity/ Outcome	Action Taken
4045-301.999 (b) (6) (b) (6) (SRP-	Myoglobinuria/ Renal and urinary disorders	Golodirsen 30 mg/kg	(b) (6) (11)	(b) (6) (16)	Severe/ recovered/resolved	Drug interrupted, hospitalization
	Rhabdomyolysis/ Musculoskeletal and connective tissue disorders		(b) (6) (11)	(b) (6) (16)	Severe/ recovered/resolved	Dose not changed, hospitalization
	Blood creatine phosphokinase increased/ Investigations		(b) (6) (32)	(b) (6) (34)	Severe/ recovered/resolved	Drug interrupted, hospitalization
4045-301.999 (b) (6) (b) (6) (SRP	Pyrexia/ General disorders and administration site conditions	Golodirsen 30 mg/kg	(b) (6) (8)	(b) (6) (8)	Mild/ recovered/resolved	Drug interrupted, medication, hospitalization
4045-301.999 (b) (6) (b) (6) (SRP-	Hyperhidrosis/ Skin and subcutaneous tissue disorders	Golodirsen 30 mg/kg	(b) (6) (6)	(b) (6) (6)	Moderate/ recovered/resolved	Dose not changed, hospitalization
	Hypoaesthesia/ Nervous system disorders		(b) (6) (6)	(b) (6) (6)	Moderate/ recovered/resolved	Dose not changed, hospitalization
4045-301.999 (b) (6) (b) (6) (SRP-	Spinal compression fracture/ Injury, poisoning and procedural complications	Golodirsen 30 mg/kg	(b) (6) (81)	(b) (6) (139)	Mild/ recovered/resolved	Dose not changed
4045-301.999 (b) (6) (b) (6) (SRP	Lymphadenitis/ Blood and lymphatic system disorders	Golodirsen 30 mg/kg	(b) (6) (158)	(b) (6) (159)	Mild/ recovered/resolved	Dose not changed, hospitalization
4053-101 (b) (6) (b) (6) (SRP (SRP	Pyrexia/ General disorders and administration site conditions	Golodirsen 30 mg/kg	(b) (6) (1009)	(b) (6) (1012)	Moderate/ recovered/resolved	Dose not changed, medication
	Vomiting/ Gastrointestinal disorders		(b) (6) (1009)	(b) (6) (1012)	Moderate/ recovered/resolved	Dose not changed, medication
	Hypocalcaemia/ Metabolism and nutrition disorders		(b) (6) (1101)	(b) (6) (1105)	Mild/ recovered/resolved	Dose not changed, hospitalization

4053-101 (b) (6) (SRP (b) (6)	Gastroenteritis viral/ Infections and infestations	Golodirsen 30 mg/kg	(b) (6) (271)	(272)	Moderate/ recovered/resolved	Dose not changed, medication, hospitalization
	Haematemesis/ Gastrointestinal disorders		(b) (6) (271)	(272)	Moderate/ recovered/resolved	Dose not changed, hospitalization
4053-101 (b) (6) (SRP (b) (6)	Tonsillar hypertrophy/ Respiratory, thoracic and mediastinal disorders	Golodirsen 30 mg/kg	(b) (6) (444)	(446)	Moderate/ recovered/resolved	Dose not changed, medication, hospitalization
4053-101 (b) (6) (SRP (b) (6)	Convulsion/ Nervous system disorders	Golodirsen 30 mg/kg	(b) (6) (868)	(881)	Moderate/ recovered/resolved	Drug interrupted, medication, hospitalization
4045-301.99 (b) (6) (SRP (b) (6) (SRP	Femoral neck fracture/ Injury, poisoning and procedural complications	Placebo	(b) (6) (75)	(144)	Severe/ recovered/resolved	Dose not changed, medication, hospitalization
	Femur fracture/ Injury, poisoning and procedural complications		(b) (6) (432)	(468)	Severe/ recovered/resolved	Dose not changed, medication, hospitalization

Note: Cumulative through 26 October 2018.
[a] MedWatch case identification in parentheses.
ID=identification; TEAE=treatment-emergent adverse event
Source: Listing 35.1

Source: NDA 120-Day Safety Update, pp. 62-3

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

No patient in the golodirsen clinical development program discontinued study treatment due to a TEAE.

8.4.4. Significant Adverse Events

Table 26 Contains AEs that were severe in intensity. Each of these cases is considered below in the Section 8.5.1 Drug-specific events of interest within topics of Fractures and Rhabdomyolysis.

Table 26 Adverse Events of Severe Intensity (Population 2)

Period	Treatment	PTFinal	AE Start Day	AE End Day
BLINDED TREATMENT	PBO	Fracture (2 events)	75 & 432	144 & 468
	SRP-4053	Blood creatine phosphokinase increased	32	34
		Bone decalcification	301	
		Myoglobinuria	11	16
		Osteoporosis	301	
		Rhabdomyolysis	11	16
TREATMENT PHASE 5[5]	SRP-4053	Fracture	300	344
		Abasia	567	
		Fracture	544	581

Source: Clinical Reviewer Analysis of ADAE dataset

[5] 'TREATMENT PHASE 5' (30 mg/kg) = the event occurs on or after the start of part 2 of the study treatment and on or before the last dose of treatment in study 4053-101.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

In the two studies providing safety data there were a total of 1505 Adverse Events, 874 in Study 1 (Study 4053-101) and 631 in Study 2 (Study 4045-301). There were 291 unique events, 198 in Study 1 and 175 in Study 2. Adverse event terms were evaluated for potential aggregation where clinically appropriate. Events from 253 terms were either aggregated or disaggregated. Table in Appendix 13.2 **Adverse Event Term Aggregation and Disaggregation** contains the original preferred terms, and verbatim terms as well as the new preferred terms and change in Body System terms, where relevant. Table 27 lists the adverse events with an incidence greater than placebo and risk difference greater than or equal to five percent in Population 2, which combines the 101 and 301 studies. Analysis of the studies separately yields similar results.

Table 27 Table of Common Adverse Events with an Incidence Greater Than Placebo and Risk Difference Greater than or Equal to Five Percent (Population 2)

PTfinal	N(SRP-4053)	% SRP-4053	N(PBO)	% PBO	% Diff Drug - PBO
Headache	17	41	2	10	32
Pyrexia	17	41	3	14	27
Abdominal pain	11	27	2	10	17
Administration site pain	7	17	0	0	17
Nasopharyngitis	11	27	3	14	13
Back pain	7	17	1	5	12
Pain	7	17	1	5	12
Fall	12	29	4	19	10
Nausea	8	20	2	10	10
Dizziness	6	15	1	5	10
Cough	11	27	4	19	8
Vomiting	11	27	4	19	8
Ligament sprain	5	12	1	5	7
Ear infection	3	7	0	0	7
Seasonal allergy	3	7	0	0	7
Tachycardia	3	7	0	0	7

Source: Clinical Reviewer Analysis of ADAE dataset

8.4.6. Laboratory Findings

Labs were evaluated for mean change and for outliers by treatment and visit. Lab results of concern were noted in the context of the AEs of Special interest (Section 0).

8.4.7. Vital Signs

Vital signs were evaluated for mean change and for outliers by treatment and visit. Results of concern were noted in the context of the AEs of Special interest (Section 0, Cardiac Events).

8.4.8. Electrocardiograms (ECGs)

Overall there were not significant changes in EKG conduction intervals. One patient (4053-101. (b) (6) had an elevated change in QTcF of 57 msec from a baseline of 415msec to 472 (See Section 8.4.9 with QT-IRT Consult).

8.4.9. QT

The following text was extracted essentially verbatim from the QTIRT consult:

The QTiRT team noted that in the current submission, the sponsor provided raw data from the hERG assays and a plan to collect additional ECG data from Phase 3 study 4045-301. The hERG assay was done at room temperature – a deviation from GLP – though the data are adequate for interpretation. While the sponsor anticipated golodirsen would not likely affect hERG current because of its large molecular size, the data show otherwise – a reduction in hERG current within a safety margin of regulatory concern.

Golodirsen inhibited hERG current by (Mean ± SEM) 9.4 ± 0.6% at 100 μM (n = 3) and 20.1 ± 1.9% at 300 μM (n = 4), versus 6.2 ± 0.5% (n = 3) in control. hERG inhibition at 300 μM was statistically significant ($P < 0.05$) when compared to vehicle control values. The IC50 for the inhibitory effect of golodirsen on hERG potassium current was not calculated but was estimated to be greater than 300 μM. The low concentration of 100 μM (865 μg/mL), which did not produce a significant inhibition of the hERG potassium channel current, is 15- fold greater than the plasma Cmax of 56.55 μg/mL obtained with the clinical dose of 30 mg/kg (Study 4053-101). According to literature survey and current expert consensus, IC50 values are always smaller when patch clamp studies are performed at physiological temperature as opposed to room temperature if the test drug block of hERG channels were to show temperature-dependence. Since this GLP study was performed at room temperature, it is possible for IC50 to be overestimated (hence safety margin is also overestimated).

Nonclinical evaluation of the potential for golodirsen-induced QT prolongation included a single-dose and repeat-dose study of 12 weeks at doses up to 320 mg/kg, and a 39-week repeat dose study at doses up to 400 mg/kg, conducted in male cynomolgus monkeys. There was no biologically meaningful effect of golodirsen on electrocardiogram parameters.

The available clinical data do not suggest any adverse effect of golodirsen on cardiac conduction. In Study 4045-301, only 11 subjects had ECG data collected close to (i.e., collected after at least 80% drug was administered) and within 1 hour after the end of infusion; of these 11 subjects, 7 had ECG data collected within 0.5 hours after the end of infusion. In Study 4053-101, only 10 subjects had ECG data collected close to and within 1 hour after the end of infusion; of these 10 subjects, 7 had ECG data collected within 0.5 hours after the end of infusion. The sample size of clinical ECG data collected around the maximum exposure is not adequate to exclude large effects (i.e., 20 ms).

In addition, Sarepta proposes a study plan for collection of QTc data around Tmax after the first dose of golodirsen. Sarepta plans to amend the 4045-301 (ESSENCE) protocol to collect triplicate ECGs around Tmax after the first dose of golodirsen in patients that will be newly enrolled in the ESSENCE trial. As of 01 November 2018, 51 subjects amenable to exon 53 skipping have been enrolled in the golodirsen arm of the study, 60 patients remain to be enrolled. With 2:1 randomization ratio to golodirsen and placebo in ESSENCE, a total of 39 patients are required to have 80% power to detect a treatment difference of 10 msec (assuming SD 11.5 msec) in the change in QTcF from baseline (ΔQTcF) in with a one-sided alpha of 0.05. On the day of the first dose, triplicate 12-lead ECGs will be obtained at predose (baseline), at the end of infusion (around Tmax), and 3 hours post the end of infusion, along with matching PK sampling at these timepoints. The triplicate ECGs will be transmitted for centralized read and determination of QTcF. The results of the QTcF central tendency analysis will be provided to the FDA for review when the data becomes available.

8.4.10. Immunogenicity

There were no immunogenicity data included in the submission. The Office of Biological Products provided feedback on immunogenicity assays during the review. Immunogenicity assessments will be conducted as post-marketing requirements (PMRs).

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Drug-specific events of interest

- *Infusion Related Reactions*

These events were defined as:

- Adverse events with reported start times within 24 hours after infusion start time.
- Adverse events (without reported start times) that occur within a 24-hour period before, during, or after the start time of the infusion.

But not:

- Adverse event was an infusion site, application site, or other local AE not associated with IRR,

- Adverse event had a clear alternate etiology that could be ascertained based on the reported event/verbatim term (e.g., reaction to plaster, assessed as related to procedure or underlying disease by Investigator),
- Adverse event was not associated with an IRR due to the nature of the event or biological implausibility (e.g., fibula fracture, chalazion).

The Applicant identified 43 events but only 25 where they had data on start times. Of those, I applied a threshold of requiring the AE to have an incidence 2% greater than placebo and with more than one event. The following AEs were identified with these criteria.

Table 28. Adverse Events fulfilling the Criteria for Infusion-Related Reactions with Reviewer Threshold

	Population 1: 4053-101		Population 2: Part 1 of 4053-101 and 4045-301		Population 3: 4053-101, 4045-301, and -302		
Preferred Term	**Placebo (N=17) n (%)**	**30 mg/kg (N=33) n (%)**	**Placebo (N=21) n (%)**	**Golodirsen (N=41) n (%)**	**Golodirsen ≤20 mg/kg (N=8) n (%)**	**Golodirsen 30 mg/kg (N=60) n (%)**	**All Golodirsen (N=60) n (%)**
# IRR	4 (23.5)	8 (24.2)	7 (33.3)	17 (41.5)	2 (25.0)	17 (28.3)	18 (30.0)
w start time							
Headache	1 (5.9)	2 (6.1)	1 (5.9)	3 (7.3)	0	3 (5.0)	3 (5.0)
Back pain	0	1 (3.0)	0	2 (4.9)	0	2 (3.3)	2 (3.3)
Hyperhidrosis	0	1 (3.0)	0	2 (4.9)	0	2 (3.3)	2 (3.3)
Nausea	0	2 (6.1)	0	2 (4.9)	0	2 (3.3)	2 (3.3)

Source: Clinical Reviewer Analysis of ADAE dataset

Medical Reviewer comment: I would first note that event, *infusion-related reaction* is not a term appropriate for labeling as per the guidance for industry, Immunogenicity Assessment for Therapeutic Protein Products (https://www.fda.gov/media/85017/download, last accessed 02 May 2019). After a review of this topic, I believe labeling of the individual events without specific mention of the term, "infusion reaction", is warranted. There were no apparent events of reminiscent of 'cytokine-release syndrome or storm', which the preferred term suggests.

- Hypersensitivity

The clinical study database was searched using the Standardized Medical Dictionary for Regulatory Activities Query (SMQ) Hypersensitivity (broad). Using this methodology, only 3 terms were identified where the incidence on drug was greater than placebo and there was greater than one event on drug.

Erythema	Population 2: Placebo n=0; Golodirsen = 3 (7.3); (Population 3) All Golodirsen n = 5 (8.3)
Seasonal allergy	Population 2: Placebo n=0; Golodirsen = 4 (9.8); (Population 3) All Golodirsen n = 6 (10)
Rash pustular	Population 2: Placebo n=0; Golodirsen = 2 (4.9); (Population 3) All Golodirsen n = 2 (2.3)

Medical Reviewer Analysis and Comment: The method of case identification by the Applicant was much too limited. Hypersensitivity cases can be identified with several SMQs that need to be followed up at least at the PT level to verify that they are consistent with the intended case definition. Using this strategy, after consolidating and cleaning the Applicant's coding database (see Section 13.2 Adverse Event Term Aggregation and Disaggregation), I reviewed the AEs (PTFINAL) for the following MedDRA SMQs (v 21.1). The percent difference from placebo follows each in parentheses. Eosinophilic pneumonia (10), Severe cutaneous adverse reactions (7), Angioedema (3), Anaphylactic reaction (1), Hypersensitivity (1), Drug reaction with eosinophilia and systemic symptoms syndrome (SMQ) (-3). The verbatim terms and events evaluated for the *SMQ Angioedema* suggested that they were not angioedema-related events based on alternative causality or anatomical location.

Adverse events from the SMQs listed above related to hypersensitivity occurring with an incidence on Drug greater than PBO and with an % Difference ≥5 are listed below.

Table 29 Incidence of Drug and Placebo Hypersensitivity-related Preferred Terms

PTFINAL	N Rows	N(SRP-4053)	% SRP-4053	N(PBO)	% PBO	% Drug - PBO
Pyrexia	20	17	41	3	14	27
Cough	15	11	27	4	19	8
Seasonal allergy	3	3	7	0	0	7
Erythema	2	2	5	0	0	5
Multiple allergies	2	2	5	0	0	5
Myalgia	2	2	5	0	0	5

Source: Clinical Reviewer Analysis of ADAE dataset

Several of the events had a notable clinical consequence; the following events had an incidence that was greater in the treatment group than placebo (% Risk difference) and required clinical intervention:

- Events of Rash requiring medication (36%)
- Events of Pyrexia requiring medication (29%)
- Events of Pruritus requiring medication (14%)
- Events of Urticaria, classified as moderate requiring medication (10%)
- Events of Dermatitis requiring medication (5%)

See also the analysis of 120-Day Safety Update data in Section 8.7.1 for additional Hypersensitivity findings.

I recommend a Warning and Precaution for Hypersensitivity events listing the most frequent related PTs since these are clinically significant events not necessarily self-limiting without intervention.

- Renal toxicity

I reviewed the following SMQs for renal events:

- Acute renal failure
- Chronic kidney disease
- Haemodynamic oedema, effusions and fluid overload
- Proteinuria
- Rhabdomyolysis/myopathy
- Tubulointerstitial diseases
- Tumour lysis syndrome

Additionally, I performed a focused review on the following labs: bun, creatinine, all chemistries, Kim-1, Cystatin.

Analysis of Adverse events suggested further investigation of the Preferred Terms from the kidney disease related SMQs. For this investigation, I included the following SMQs (% Risk difference from placebo in parentheses): Acute Renal Failure (5), Chronic Kidney Disease (7), Haemodynamic Oedema, Effusions and Fluid Overload (5), Proteinuria (7), Rhabdomyolysis/Myopathy (15), Tubulointerstitial Diseases (0), Tumour Lysis Syndrome (2).

Adverse Events from the cases below (Table 30) were extracted from these SMQs. While rhabdomyolysis is expected in the natural history of DMD and there was only one case of rhabdomyolysis with the full constellation of clinical events one would expect in this syndrome, the Odds Ratio of rhabdomyolysis events (~8) is concerning. Further, the event was severe in intensity. I would also note that in my eteplirsen review, a similar case was identified (see Eteplirsen Primary Clinical Review, NDA 206488). Considering that this was a single event and rhabdomyolysis may be consistent with the natural history of DMD, I do not recommend it be placed in the Warning section of labeling, but I do recommend Enhanced Pharmacovigilance considering the seriousness of the disorder.

Three events of Proteinuria (in the data that included open label treatment) were identified, all on drug. All cases of proteinuria were mild and transient and there was no change to the dosing of golodirsen. Per responses to information requests from the applicant, these were not followed up with quantitative evaluations. I recommend proteinuria be placed in Section 6 of labeling.

Table 30 Adverse Events from SMQ Positive Cases (Population 2)

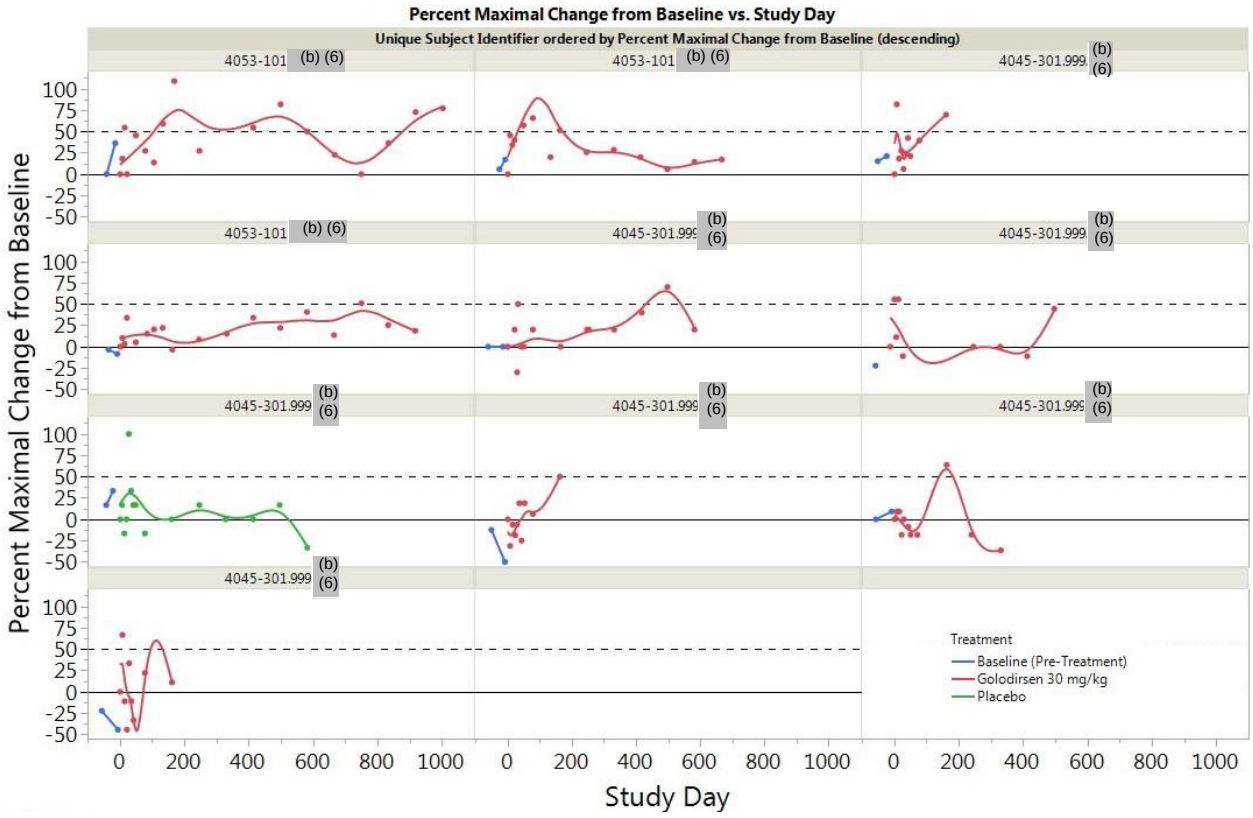
TRTA	USUBJID	PTFINAL	AESEV	AESER	AESTDY	AEENDY
PBO	4045-301.999 (b) (6)	Crystal urine present	MILD	N	162	
PBO	4045-301.999	Haematuria	MILD	N	226	227
SRP-4053	4045-301.999	Blood creatine phosphokinase increased	SEVERE	Y	32	34
SRP-4053	4045-301.999	Myalgia	MILD	N	83	83
SRP-4053	4045-301.999	Myoglobinuria	SEVERE	Y	11	16
SRP-4053	4045-301.999	Rhabdomyolysis	SEVERE	Y	11	16
SRP-4053	4045-301.999	Chromaturia	MILD	N	1	3
SRP-4053	4045-301.999	Myalgia	MILD	N	64	64
SRP-4053	4045-301.999	Proteinuria	MILD	N	31	36
SRP-4053	4045-301.999	Joint swelling	MODERATE	N	196	206

Source: Clinical Reviewer Analysis of ADAE dataset

Comparing the maximum Creatinine on Baseline versus on Treatment did not show any notable findings. This was not likely to be useful given the degree of muscle pathology and relatively low Creatinine values at Baseline in subjects.

In contrast to the Creatine results, the Maximum values for BUN appear to notably increase on treatment relative to placebo. This is particularly evident with those having higher baseline BUN values, perhaps reflecting more muscular reserve than those with low baseline BUN values. Figure 18 shows the time course of changes in BUN and demonstrates that increases were transient and remained within the normal reference range, although many of these patients started with low BUN values so the 'normal' values are not definitively reassuring.

Figure 18 Changes in the BUN lab values over time in Patients with notable Changes from Baseline.



I also evaluated the contrast between maximum baseline and maximum on treatment level of Kim-1. The proportion of subjects on treatment is slightly less than half. There is no normal Kim-1 value; however, the data suggest a higher proportion of subjects show transient elevations on this marker of renal injury. There is a balance between the proportion on treatment and placebo who show elevation of this marker of renal injury.

Evaluation of the BUN and Kim -1 over time in individual cases suggested that the elevations

were transient and there was no change to dosing with golodirsen, so I do not suggest labeling these investigations."

Adverse Reactions of other ASOs:

- Hepatotoxicity

Medical Officer Analysis and Comments: I reviewed the following SMQs for hepatic events: *Biliary disorders* (SMQ), *Biliary system related investigations, signs and symptoms* (SMQ), *Biliary tract disorders* (SMQ), *Drug related hepatic disorders - comprehensive search* (SMQ), *Hepatic disorders* (SMQ), in addition to a focused review on the following hepatic labs, Alanine Aminotransferase, Alkaline Phosphatase, Aspartate Aminotransferase, Bilirubin, Gamma Glutamyl Transferase.

Although the SMQs picked up multiple cases, an inspection of these revealed only one patient that could be identified as having a drug-induced hepatic toxicity according to the Preferred Term. USUBJID 4053-101.(b) (6), was identified as having the event of *hyperbilirubinemia* on Study Days 253 – 344. This is a 10-year-old boy, initially in the Untreated group I Study 101, who had been on chronic prednisolone for about 5 years at a dose of 20 mg/day. An inspection of his labs demonstrated baseline amino transferase levels 7 to 8-fold greater than normal, bilirubin at the high end of normal (18 vs 21 μmol/L) and normal GGT and AP. The lab that was the basis of the event was 27 μmol/L at the 36th Week of Part 2 of the 4053-101 study. The lab returned to normal by week 48. Aminotransferases remain at about the same abnormal elevations through the study. Based on these data, I do not believe hepatotoxicity requires special labeling in Sections 5 or 6 based on these data.

- Coagulation

Medical Officer Analysis and Comments: I evaluated the adverse events by reviewing the findings from all *Haemorrhage*-related *SMQs* and checking labs related to coagulation and bleeding from the Population 2 dataset. Three events were coded to Preferred Term haemorrhage following my revision of PT terms (see Section 13.2 Adverse Event Term Aggregation and Disaggregation). These did not seem to be related to a coagulopathy. While a few subjects in both treatment arms had elevated aPTT and decreased platelets, a review of the labs did not indicate an overall treatment-effect on coagulation.

I evaluated the individual maximum baseline and treatment aPTT and the minimum platelets at baseline and on treatment. While there are patient values demonstrating increase from baseline, there are about the same proportion treated with drug and placebo, considering the relative numbers exposed.

After plotting the labs of all subjects who had with the most abnormal aPTT and platelet values, I eliminated cases where there was not significant change from baseline. My analysis demonstrated that the A) aPTT values over time for patients with the most notable changes. All other hematology labs were inspected for these patients. Of those only B) the prothrombin time (PT) demonstrated a notable change. A notable finding is that while there was a patient on

placebo with similar changes the time course of the change in labs occurred early and with placebo, later. While there are patients demonstrating decrease from baseline, there are about the same proportion treated with drug and placebo, considering the relative numbers exposed.

- Severe cutaneous reactions – See review of hypersensitivity reactions in this section

❖ Other DMD-related events of interest:

- Cardiac events

I evaluated the cardiac adverse events by reviewing the findings from all cardiac-related SMQs: Cardiac arrhythmia terms (including bradyarrhythmias and tachyarrhythmias) (SMQ) and checking vital signs from the Population 2 dataset.

- Cardiac arrhythmia terms, nonspecific (SMQ)
- Cardiac arrhythmias (SMQ)
- Cardiac failure (SMQ)
- Cardiomyopathy (SMQ)
- Haemodynamic oedema, effusions and fluid overload (SMQ)
- Ischaemic heart disease (SMQ)
- Myocardial infarction (SMQ)
- Other ischaemic heart disease (SMQ)
- Pulmonary hypertension (SMQ)
- Tachyarrhythmia terms, nonspecific (SMQ)
- Torsade de pointes/QT prolongation (SMQ)

The notable findings were three subjects (with none on placebo) with events of PT Tachycardia and two with an event of PT Dyspnea (with one more on placebo). Considering the natural history of DMD and the proportion of subjects in each treatment group, I do not consider the event of dyspnea to be a signal currently. I evaluated the vital signs for the three subjects with the AE of Tachycardia, as well as the vital sign dataset. I also evaluated the heartrate in a model with factors of baseline, visit and treatment (P=0.5 for Study 101 and 0.9 for Study 301). Based on these investigations, I do not believe that the issues arise to a warning but may be included in Section 6 if the numbers warrant.

- Falls and Fractures (Analyzed separately but discussed together)

The Applicant has noted that in Populations 1 and 2, more golodirsen-treated patients (14 [42.4%] and 15 [36.6%] patients, respectively) than placebo patients (3 [17.6%] and 4 [19.0%] patients, respectively) experienced at least 1 fall-related TEAE. In the All Golodirsen Group, 27 patients (45.0%) experienced at least 1 fall-related TEAE.

Fall may be confounded by several factors, some of which are part of the natural history of the disease. One would expect the randomization process to control for this issue. Other confounders may be considered positive (increased activity); however, this was not evaluated and cannot be used in consideration of the study results to mitigate other potentially drug-related etiologies. These may include effects on balance, gait, vision, or any other modality used during one's activities to monitor or control oneself in their environment. After 'cleaning' the coding on the AE set (Section 13.2 Adverse Event Term Aggregation and Disaggregation), the analysis for the

AE PT of Fall was the following, which further substantiated the Applicant's finding of increased incidence. There are several similar sequalae of accidents (Table 31) that can be evaluated at the PT level (Table 32) such as contusion, limb injury, sprains, and ruptures that occur at a rate greater than PBO and where there are similar analytical considerations.

Table 31 Incidence and Risk of *SMQ Accidents and Injuries* (Population 2)

	SRP-4053 (N = 41)			*PBO (N = 21)*			*SRP-4053 vs. PBO*		
Level 1	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)	RD (per hundred)	RR	OR
(1) Accidents and injuries	105	23	56.1	40	9	42.86	13.24	1.309	1.704

Source: Clinical Reviewer Analysis of ADAE dataset

Table 32 Incidence of Adverse Events related to Falls and other Accidents (Population 2; N on drug>1, % Drug > PBO)

PTFINAL	N (%) SRP-4053	N (%) PBO	% (Drug - PBO)
Contusion	8 (20)	2 (10)	10
Limb injury	5 (12)	1 (5)	7
Fall	14 (34)	6 (29)	6
Fracture	4 (10)	1 (5)	5
Skin abrasion	4 (10)	1 (5)	5
Back injury	2 (5)	0 (0)	5
Ligament sprain	5 (12)	2 (10)	3

Source: Clinical Reviewer Analysis of ADAE dataset

I would recommend, at the least, including those in the Table of Adverse Events (Section 6 of Labeling), those events satisfying the threshold for inclusion.

8.6. Safety Analyses by Demographic Subgroups

Considering the small size and homogeneity (e.g., all patients were male children or adolescents and were predominantly White) of the safety database and the relatively few numbers of significant and serious events, an integrated analysis of safety is not performed. Individual cases have been described in detail, considering patient demographics.

8.7. Additional Safety Explorations

Additional safety exploration of the 120-Day Safety update revealed the following findings:

8.7.1. Additional Hypersensitivity Findings in the 120-Day safety Update

One patient (4053-101 (b) (6)) in the Population 3 group had two events of *PT Skin Exfoliation* while receiving golodirsen 30 mg/kg. The first event occurred on study day 289 and lasted 15 days and the second on day 971 and lasted 61 days. Both events were considered mild but the first required medication intervention. Both events recovered.

8.7.2. Hypertrophic Scarring/Keloid formation

In the data including open label treatment, three patients receiving golodirsen had an AE of Keloid scar or Hypertrophic scar with none on placebo. All events were mild but not all were resolved at the end of the trial, which would be clinically expected given the natural history of keloid formation. This did not rise to the level of being reported in Population 2 which was used for the determination of the recommendation for the Table of adverse events in Section 6 of labeling; however, I would recommend inclusion in this table with an incidence of 5% (3/60) or at least a description in Section 6.

Table 33 Characteristics of the Patients with an AE of Keloid/Hypertrophic Scar (Population 3)

USUBJID	AEDECOD	AE ACTION	Recovered?	AGE	RACE	ASTDY	AENDY	ADUR	# DOSES
4045-301.999.(b) (6)	Keloid scar	MED	Y	13	WHITE	62	154	93	10
4045-301.999.(b) (6)	Keloid scar	MED	Y	13	WHITE	362	Not Avail	Not Avail	51
4045-301.999.(b) (6)	Keloid scar	MED	N	7	ASIAN	120	-	-	15
4045-301.999.(b) (6)	Hypertrophic scar	NONE	N	10	WHITE	276	-	-	40

Source: Clinical Reviewer analysis of 120-Day Update ADAE dataset.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

No postmarketing experience is included in this submission.

8.8.2. Expectations on Safety in the Postmarket Setting

Because the sample size is small, it is difficult to predict the course of the safety profile of this drug; However, given the nonclinical data and few cases observed in this study, I anticipate issues of renal toxicity and rhabdomyolysis will be of greatest concern. For this reason, I believe these issues should be considered for enhanced pharmacovigilence.

8.8.3. Additional Safety Issues from Other Disciplines

See Section 4.3 Nonclinical Pharmacology/Toxicology.

8.9. Integrated Assessment of Safety

An integrated review was not performed because of the small size and homogeneity of the dataset and small number of serious or significant events.

9. Advisory Committee Meeting and Other External Consultations

An advisory committee was not felt to be necessary for consideration of issues related to substantial evidence, safety, or risk: benefit considerations for the use of this drug in the DMD population.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Recommendations for labeling are included in the text of this review. While I [cdb] am not recommending approval, the following recommendations are made if the application is approved in this cycle:

- Efficacy – Wording should be similar to the eteplirsen indication. The amount of truncated dystrophin protein should be noted as 0.9% of normal (See Section 6.1.1 Study Results).
- Warnings and precautions should include the topic of Hypersensitivity.
- Considering the paucity of safety information submitted in this application, labeling should be clear about uncertainties and deficiencies of the golodirsen clinical program.

11. Risk Evaluation and Mitigation Strategies (REMS)

No postmarketing requirements or commitments are recommended from this review.

12. Postmarketing Requirements and Commitments

- Considering that I have found several subjects' QTcF with a greater than 20 ms change from baseline, and since there appears to be a nonclinical concern raised by the hERG data, I agree with further assessment of EKGs in the ongoing 301 study.

- Although I am not recommending approval, if the drug is approved, the Essence Study should be completed as a PMR with the golodirsen arm demonstrating a significant and clinically meaningful effect.

13. Appendices

13.1. Schedules of Events

Table 34 Schedule of Events for Part 1 (Double-blind Dose Titration)

	SCRN Weeks -6 to -4	BL Weeks -2 to -1	Part 1 (Week)											
			1	2	3	4	5	6	7	8	9	10	11	12[a]
Informed consent	X													
Inclusion/exclusion criteria	X	X												
Document DMD diagnosis	X													
Confirm eligibility			X											
Randomization[b]			X											
Skin and muscle biopsy[c]		X												
Leg muscle MRI[d]		X												X
Muscle MRS[e]		X												X
6MWT[f]	X	X												X
PFTs (FVC, MIP, MEP)	X	X												X
NSAA[g]	X	X												X
Time 4-Step, MoviPlate, PUL, pinch & hand grip		X												X
PODCI		X												X
Actimetry[h]		Continuous												
Plasma/urine for PK[i]			X		X		X		X					X
Immunogenicity		X	X											X
Blood samples for potential disease-related biomarkers		X	X											X
LTBP4 and *SPP-1*		X												
12-lead ECG	X	X												X
ECHO	X													X
Clinical laboratory[j]	X	X	X	X	X	X	X	X	X	X	X			X
Vital signs[k]	X	X	Obtained in association with weekly infusions[k]											
Weight	X		X			X				X				X
Height	X													X
Physical examination	X		X			X				X				X
Dosing[l]			Weekly infusions (dose titration) beginning on Week 1											
Data Safety Monitoring Board[m]												---------X---------		
Concomitant medications	Continuous													
Adverse event monitoring	Continuous													

6MWT=6-minute walk test; BL=baseline; DMD=Duchenne muscular dystrophy; ECG=electrocardiogram; ECHO=echocardiogram; FVC=forced vital capacity; *LTBP4*=latent transforming growth factor-β binding protein-4 gene; MEP=maximum expiratory pressure; MIP=maximum inspiratory pressure; MRI=magnetic resonance imaging; MRS=magnetic resonance spectroscopy; NSAA=North Star Ambulatory Assessment; PFT=pulmonary function test; PK=pharmacokinetic; PODCI=Pediatric Outcomes Data Collection Instrument; PUL=Performance Upper Limb; SCRN=screen; *SPP-1*=secreted phosphoprotein 1

[a] Week 12 used a window of ±1 week. Beginning after the Week 12 visit and until the Data Safety Monitoring Board decision, scheduled safety assessments for all patients in Part 1 occurred every 4 weeks and functional testing occurred every 12 weeks. Patients whose efficacy assessments (6MWT, NSAA, PFTs, timed 4-step, PUL, pinch and hand grip, MoviPlate) and PODCI occurred >4 weeks before the Part 2 Week 1 visit repeated all Week 12 assessments prior to starting Part 2.

[b] Randomization (8 golodirsen and 4 placebo) occurred at Week 1 prior to the first dose.

[c] Skin and muscle biopsy procedures were performed at the same time prior to first dose once study eligibility was confirmed.

[d] MRI including 3 points Dixon and T2 sequences to measure fat content in lower leg muscle and skeletal muscle edema; MRI was performed before biopsy procedure at Baseline.

[e] At select sites with MRS capabilities, phosphorus MRS was performed before the biopsy procedure at Baseline.

[f] The 6MWT test was performed at both Screening and Baseline visits (each on 2 consecutive days), which may have required 2-night overnight stays. All other time points were performed once on 1 day.

[g] The NSAA was performed once at Screening and once at Baseline.

[h] The ActiMyo device for actimetry was distributed between Screening and Baseline. Actimetry was measured continuously with data downloaded as outlined in the ActiMyo Investigator Manual.

[i] Full plasma PK sampling (Weeks 1, 3, 5, 7) was performed at the following time points: immediately pre-infusion, at approximately 5 to 10 minutes after completion of dosing, and approximately 1, 1.5, 2, 4, 6, 8, 12, 16, and 24 hours after completion of dosing. At Week 12, samples were collected only at pre-infusion and between 5 and 10 minutes postinfusion. Urine for PK sampling was collected, on a cumulative basis, during the following time intervals: 0 to 4, 4 to 8, 8 to 12, and 12 to 24 hours after initiation of dosing.

[j] Clinical laboratory assessments included hematology, coagulation, serum chemistry, and urinalysis.

[k] Vital signs included blood pressure, pulse rate, respiration rate, and oral temperature. Patients in the treated and placebo groups had vital signs measured on infusion days within approximately 30 minutes prior to infusion and approximately 5, 30, and 60 minutes after the end of the infusion.

[l] Randomized patients in Part 1 were dose-escalated every 2 weeks to receive weekly infusions of golodirsen or placebo at: 4 mg/kg/week (Weeks 1 to 2), 10 mg/kg/week (Weeks 3 to 4), 20 mg/kg/week (Weeks 5 to 6), and 30 mg/kg (Week 7 to Data Safety Monitoring Board safety review). The initial 4 patients were staggered with a minimum of 3 days between administrations of the initial doses to each of these patients. Infusions were given according to instructions in the Pharmacy Manual. Patients were closely monitored for at least 1 hour following the completion of all infusions. Patients in Part 1 who completed Part 1 Week 12 prior to the completion of the Data Safety Monitoring Board review continued to receive weekly dosing.

[m] Data Safety Monitoring Board safety data evaluation began once the last patient at 30 mg/kg received 2 weekly doses.

Source: 4053-101 Interim Clinical Study Report

Table 35 Schedule of Events for Treated Patients in Part 2 (Screening through First 48 Weeks of Open-label Treatment)

	SCRN[a]	BL	Part 2 (Week)																
	Weeks -6 to -4	Weeks -2 to -1	1	2-3	4	5-7	8	9-11	12	13-15	16	17-19	20	21-23	24	25-35	36	37-47	48
Informed consent	X																		
Inclusion/exclusion criteria	X	X																	
Confirm eligibility[a]			X																
Document DMD diagnosis	X																		
Skin & muscle biopsy[b]		X																	X
Leg muscle MRI[c, d]		X							X[c]						X[c]				X[c]
Muscle MRS[c, e]		X							X[c]						X[c]				X[c]
6MWT[c, f]	X	X							X						X		X		X
PFT (FVC)[c]	X	X							X						X		X		X
PFTs (MIP and MEP)[c]	X	X							X						X		X		X
NSAA[c, g]	X	X							X						X		X		X
Timed 4-Step, MoviPlate, PUL, pinch & hand grip[c]		X							X						X		X		X
PODCI[c]		X													X				X
Actimetry[h]		Continuous																	
Plasma for PK[i]			X												X				X
Immunogenicity		X	X												X				X
Blood samples for potential disease-related biomarkers		X	X						X						X		X		X
LTBP4 and *SPP-1*		X																	
12-lead ECG	X	X							X						X		X		X
ECHO[c, j]	X														X				X
Clinical laboratory[k]	X	X	X	X	X		X		X		X		X		X		X		X
Weight[l]	X		X		X		X		X		X		X		X	X	X	X	X
Height	X								X						X		X		X
Vital signs[m]	X	X	Obtained in association with weekly infusions[m]																
Physical examination	X		X		X		X		X		X		X		X		X		X
Dosing[n]			Weekly infusions beginning on Week 1[n]																
Concomitant medications			Continuous																
Adverse event monitoring			Continuous																

6MWT=6-minute walk test; BL=baseline; DMD=Duchenne muscular dystrophy; ECG=electrocardiogram; ECHO=echocardiogram; FVC=forced vital capacity; *LTBP4*=latent transforming growth factor-β binding protein-4 gene; MEP=maximum expiratory pressure; MIP=maximum inspiratory pressure; MRI=magnetic resonance imaging; MRS=magnetic resonance spectroscopy; NSAA=North Star Ambulatory Assessment; PFT=pulmonary function test; PK=pharmacokinetic; PODCI=Pediatric Outcomes Data Collection Instrument; PUL=Performance Upper Limb; SCRN=screen; *SPP-1*=secreted phosphoprotein 1

[a] For new patients entering Part 2.

[b] For patients new to Part 2, skin and muscle biopsy procedures occurred at the same time prior to first dose once study eligibility was confirmed. Then, all patients in Part 2 were required to undergo a second muscle biopsy at the Week 48 visit. Biopsies at Week 48 occurred a) within 2 weeks after the Week 48 visit, b) after the clinical evaluation for Week 48, and c) at least 48 hours after the most recent infusion. After the biopsy procedure, study infusions were not to be administered until at least 24 hours post biopsy, and the Investigator medically cleared the patient.

[c] Testing used a window of ±2 weeks.

[d] MRI included 3 points Dixon and T2 sequences to measure fat content in lower leg muscle and skeletal muscle edema; MRI was performed before biopsy (as applicable) at Baseline.

[e] At select sites with MRS capabilities, phosphorus MRS was performed. Magnetic resonance spectroscopy was optional at 12- and 24-week time points.

[f] For patients new to Part 2, the 6MWT test was performed both at Screening and Baseline visits (each on 2 consecutive days), which may have required 2 night overnight stays. All other time points were performed once on 1 day.

[g] For patients new to Part 2, the NSAA was performed once at Screening and once at Baseline.

[h] The use of actimetry in Part 2 of this study was discontinued in May 2016 due to problems with the ActiMyo device.

[i] Plasma PK sampling (Weeks 1, 24, 48) was performed pre-infusion and at approximately 5 to 10 minutes postinfusion.

[j] Rollover patients from Part 1 had an ECHO every 24 weeks in Part 2. Patients new to Part 2 had an ECHO at Screening and then every 24 weeks in Part 2.

[k] Clinical laboratory assessments included hematology, coagulation, serum chemistry, and urinalysis.

[l] Weight was measured every 4 weeks.

[m] Vital signs included blood pressure, pulse rate, respiration rate, and oral temperature. Treated patients had vital signs measured on infusion days within approximately 30 minutes prior to infusion and approximately 5, 30, and 60 minutes after the end of the infusion.

[n] Treated patients in Part 2 (new and rollover patients from Part 1) received a weekly infusion of golodirsen at 30 mg/kg. Infusions were given according to instructions in the Pharmacy Manual. Patients were closely monitored for at least 1 hour following the completion of all infusions.

Note: Part 2 commenced once the Data Safety Monitoring Board had reviewed safety data from Part 1 to ensure no issues were identified that would have precluded Part 2 initiation. Only patients new to Part 2 underwent screening to determine Part 2 eligibility and baseline assessments. Rollover patients from Part 1 did not repeat Screening/Baseline and began dosing in Part 2 Week 1. Patients in Part 1 who completed Part 1 Week 12 prior to the completion of the Data Safety Monitoring Board review continued to receive weekly dosing and underwent safety laboratory testing every 4 weeks and functional testing every 12 weeks. However, Part 1 Week 12 assessments were (re)done prior to Part 2 Week 1 (rollover patients only) unless they had been completed within 4 weeks of the Part 2 Week 1 visit. A schedule of events for untreated patients is provided in Table 7.

Source: 4053-101 Interim Clinical Study Report

Table 36 Schedule of Events for Treated Patients in Part 2 (Week 49 Through End-of-Study Follow-up)

	Part 2 (Week)																						
	49-51	52	53-55	56	57-59	60	61-71	72	73-83	84	85-95	96	97-107	108	109-119	120	121-131	132	133-143	144	156	168/EOS	F/U[a]
Leg muscle MRI[b, c]												X								X		X	
Muscle MRS[b, d]												X								X		X	
6MWT[b, e]								X				X				X				X		X	
PFTs (FVC)[b]								X				X				X				X		X	
PFTs (MIP and MEP)[b]								X				X				X				X			
NSAA[b]								X				X				X				X		X	
PUL[b]								X				X				X				X		X	
Timed 4-Step, MoviPlate, pinch & hand grip[b]																				X		X	
PODCI[b]								X				X				X				X		X	
Actimetry[f]																				X			
Plasma for PK[g]												X								X			
Immunogenicity								X				X				X				X		X	
Blood samples for potential disease-related biomarkers								X				X				X				X			
12-lead ECG								X				X				X				X			
ECHO[b, c]								X				X				X				X			
Clinical laboratory[h]						X		X		X		X		X		X		X		X	X	X	X
Weight[i]						X		X		X		X		X		X		X		X	X	X	
Height								X				X				X				X		X	
Vital signs[j]			Obtained in association with weekly infusions[j] and at 4-week safety follow-up																				
Physical examination						X		X		X		X		X		X		X		X	X	X	X
Dosing[k]		Continuing weekly infusions[k]																					
Concomitant medications			Continuous																				
Adverse event monitoring			Continuous																				

6MWT=6-minute walk test; ECG=electrocardiogram; ECHO=echocardiogram; EOS=end of study; F/U=follow-up; FVC=forced vital capacity; MEP=maximum expiratory pressure; MIP=maximum inspiratory pressure; MRI=magnetic resonance imaging; MRS=magnetic resonance spectroscopy; NSAA=North Star Ambulatory Assessment; PFT=pulmonary function test; PK=pharmacokinetic; PODCI=Pediatric Outcomes Data Collection Instrument; PUL=Performance Upper Limb

[a] A safety follow-up visit occurred approximately 4 weeks after last dose (approximately Week 172).

[b] Testing used a window of ±2 weeks.

[c] Magnetic resonance imaging including 3 points Dixon and T2 sequences to measure fat content in lower leg muscle and skeletal muscle edema.

[d] At select sites with MRS capabilities, phosphorus MRS was performed.

[e] Was performed once on 1 day.

[f] Actimetry was optional at Week 144 (± 2 weeks).

[g] Plasma PK sampling (Weeks 96 and 144) was performed pre-infusion and at approximately 5 to 10 minutes post-infusion.

[h] Clinical laboratory assessments included hematology, coagulation, serum chemistry, and urinalysis.

[i] Weight was measured every 12 weeks at the clinic. Infusion took place at the clinic when weight was to be measured.

[j] Vital signs included blood pressure, pulse rate, respiration rate, and oral temperature. Treated patients had vital signs measured on infusion days within approximately 30 minutes prior to infusion and approximately 5, 30, and 60 minutes after the end of the infusion.

[k] Treated patients received a weekly infusion of golodirsen at 30 mg/kg. Infusions were given according to instructions in the Pharmacy Manual. Patients were closely monitored for at least 1 hour following the completion of all infusions. At the discretion of the Investigator, optional in-home administration of golodirsen by a visiting nurse may have been available after Part 2 Week 48 for visits that did not include functional assessments or safety, PK, or biomarker procedures such as blood/urine sample collection, ECG, ECHO, physical examinations, or MRI/MRS. For in-home dosing, additional instructions were provided in a separate manual to the visiting nurse.

Note: Part 2 commenced once the Data Safety Monitoring Board had reviewed safety data from Part 1 to ensure no issues were identified that would have precluded Part 2 initiation. Only patients new to Part 2 underwent screening to determine Part 2 eligibility and baseline assessments. Rollover patients from Part 1 did not repeat Screening/Baseline and began dosing in Part 2 on Week 1. Patients in Part 1 who completed Part 1 Week 12 prior to the completion of the Data Safety Monitoring Board review continued to receive weekly dosing and underwent safety laboratory testing every 4 weeks and functional testing every 12 weeks. However, Part 1 Week 12 assessments were (re)done prior to Part 2 Week 1 (rollover patients only) unless they had been completed within 4 weeks of the Part 2 Week 1 visit. A schedule of events for untreated patients is provided in Table 7.

Source: 4053-101 Interim Clinical Study Report

Table 37 Schedule of Events for Untreated Patients in Part 2

	SCRN	BL Days -2 to -1	Part 2 (Week) 1	12	24	36	48	72	96	120	144/EOS
Informed consent	X										
Inclusion/exclusion criteria	X	X									
Document DMD diagnosis	X										
Leg muscle MRI[a, b]		X		X[a]	X[a]		X[a]		X		X
Muscle MRS[a, c]		X		X[a, c]	X[a, c]		X[a]		X		X
6MWT[a, d]	X	X		X	X	X	X	X	X	X	X
PFTs (FVC, MIP, MEP)[a]	X	X		X	X	X	X	X	X	X	X
NSAA[a, e]	X	X		X	X	X	X	X	X	X	X
MoviPlate, Timed 4-Step, and Pinch & Hand Grip[a]		X		X	X	X	X				X
PUL[a]		X		X	X	X	X	X	X	X	X
PODCI[a]		X			X		X	X	X	X	X
Immunogenicity		X			X		X	X	X	X	X
Blood samples for potential disease-related biomarkers		X		X	X		X	X	X	X	X
Blood sample for *LTBP4* and *SPP-1*		X									
12-lead ECG	X	X		X	X	X	X	X	X	X	X
ECHO[a]	X				X		X	X	X	X	X
Clinical laboratory[f]	X	X		X	X	X	X	X	X	X	X
Height and weight	X			X	X	X	X	X	X	X	X
Physical examination	X			X	X	X	X	X	X	X	X
Vital signs[g]	X	X		X	X	X	X	X	X	X	X
Concomitant medications	Continuous										
Adverse event monitoring	Continuous										

6MWT=6-minute walk test; BL=baseline; DMD=Duchenne muscular dystrophy; ECG=electrocardiogram; ECHO=echocardiogram; EOS=end of study; FVC=forced vital capacity; *LTBP4*=latent transforming growth factor-β binding protein-4 gene; MEP=maximum expiratory pressure; MIP=maximum inspiratory pressure; MRI=magnetic resonance imaging; MRS=magnetic resonance spectroscopy; NSAA=North Star Ambulatory Assessment; PFT=pulmonary function test; PODCI=Pediatric Outcomes Data Collection Instrument; PUL=Performance Upper Limb; SCRN=screen; *SPP-1*=secreted phosphoprotein 1

[a] Testing used a window of ±2 weeks.

[b] Magnetic resonance imaging including 3 points Dixon and T2 sequences to measure fat content in lower leg muscle and skeletal muscle edema. Magnetic resonance imaging was optional at 12- and 24-week time points.

[c] At select sites with MRS capabilities, phosphorus MRS was performed. Magnetic resonance spectroscopy was optional at 12- and 24-week time points.

[d] The 6MWT test was performed at both Screening and Baseline visits (each on 2 consecutive days), which may have required 2-night overnight stays. All other time points were performed once on 1 day.

[e] The NSAA was performed once at Screening and once at Baseline.

[f] Clinical laboratory assessments included hematology, coagulation, serum chemistry, and urinalysis.

[g] Vital signs included blood pressure, pulse rate, respiration rate, and oral temperature. Untreated patients had vital signs measured one time per visit.

Source: 4053-101 Interim Clinical Study Report

13.1.1. 4045-301 ('ESSENCE Study')

13.1.2. Table 38 Schedule of Events for 4045-301 ('ESSENCE')

Study Period	Screening		Baseline 3-5 weeks after Screening	Double-Blind Treatment Period[a]																
Week	Up to 8 weeks prior to Week 1			1[b]	2	3	4	5	6	7	8	12[c]	16	20	24[c]	28	32	36[c]	40	44	48[c]
Informed Consent[t]	X	HS	SU																	
Assess Inclusion/ Exclusion Criteria	X	HS	HS																	
Confirm Eligibility[d]		HS	HS	X																
Randomization[e]			X																	
Medical History	X																			
Full Physical Examination[f]	X			X			X					X			X			X			X
Brief Physical Examination[f]											X		X	X		X	X		X	X	
Vital signs[g]	X		HS	Weekly at Local Site (pre- and post-infusion)[g]																
Weight[h]	X		HS, SU	X			X				X	X	X	X	X	X	X	X	X	X	X
Caregiver Questionnaire and Videography[r]			X									X			X			X			X
Clinical Global Impression of Change (CGIC)[s]												X			X			X			X
Safety Laboratory Assessments[t]	X		SU	X	X	X	X	X	X	X	X	X			X			X			X
Immunogenicity			SU	X			X				X	X			X			X			X
Biomarkers			SU	X			X								X						X
PK[j]				X							X		X		X		X		X		X
Whole Blood for *DMD*, *LTBP4*, and *SPP1* Genotyping[d]	X																				
Height (and ulnar length at HS visits)	X		HS									HS			HS			HS			HS
6MWT[k]		HS	HS									HS			HS			HS			HS
NSAA[k]		HS	HS									HS			HS			HS			HS
Fall Collection[l]	X		X				X				X	X			X			X			X
CWU												HS			HS			HS			HS
Timed 4-Step Test			HS									HS			HS			HS			HS
9-Hole Peg Test			HS												HS						HS
PUL			HS												HS						HS
QMT[m]			HS																		HS
PODCI			HS									HS			HS			HS			HS
PFTs[n]		HS	HS									HS			HS			HS			HS
ECG[o]		HS	HS									HS			HS			HS			HS
Triplicate 12-Lead ECGs				X[u]																	
ECHO[o]		HS																			
Muscle Biopsy[p]			SU																		SU
Study Treatment Infusion[q]				Once Weekly																	
Physiotherapy Interventions	Continuous																				
Concomitant Medications/Therapy	Continuous																				
AE Assessment	Continuous																				

Study Period	Double-blind Treatment Period (continued)			
Week	**60[c]**	**72[c]**	**84[c]**	**96[c]**
Full Physical Examination[f]		X		X
Brief Physical Examination[f]	X		X	
Vital Signs[g]	Weekly at Local Site (pre- and post-infusion)[g]			
Weight[h]	Every 4 weeks[h]			
Caregiver Questionnaire and Videography[r]	X	X	X	X
Clinical Global Impression of Change (CGIC)[s]	X	X	X	X
Safety Laboratory Assessments[i]	X	X	X	X
Immunogenicity		X		X
Biomarkers		X		X
PK[j]		X		X
Height (and ulnar length at HS visits)	HS	HS	HS	HS
6MWT[k]	HS	HS	HS	HS
NSAA[k]	HS	HS	HS	HS
Fall Collection[l]	X	X	X	X
CWU	HS	HS	HS	HS
Timed 4-Step Test	HS	HS	HS	HS
9-Hole Peg Test		HS		HS
PUL		HS		HS
QMT[m]				HS
PODCI	HS	HS	HS	HS
PFT[n]	HS	HS	HS	HS
ECG[o]	HS	HS	HS	HS
Triplicate 12-Lead ECGs				X[v]
ECHO[o]				HS
Muscle Biopsy[p]				SU
Study Treatment Infusion[q]	Once Weekly			
Physiotherapy Interventions	Continuous			
Concomitant Medications/Therapy	Continuous			
AE Assessment	Continuous			

6MWT = 6-minute walk test; AE = adverse event; CWU = continuous wheelchair use; *DMD* = Duchenne muscular dystrophy; ECG = electrocardiogram; ECHO = echocardiogram; ET = early termination; HEENT = head, ears, eyes, nose, and throat; HS = hub site; *LTBP4* = latent transforming growth factor beta binding protein 4; NSAA = North Star Ambulatory Assessment; PFT = pulmonary function test; PK = pharmacokinetics; PODCI = Pediatric Outcomes Data Collection Instrument; PUL = Performance of the Upper Limb; QMT = quantitative muscle testing *SPP1* = secreted phosphoprotein 1; SU = surgical unit; X = local site.

[a] Early termination assessments are the same as Week OL48 assessments as described in Table 2. An Early Termination visit is required if the patient discontinues more than 28 days after a Functional Assessment visit (Weeks 12, 24, 36, 48, 60, 72, 84, or 96).

[b] Week 1 should occur within 4 weeks of the Baseline Functional Assessment visit. If the Week 1 visit is >4 weeks after Baseline, the patient is required to repeat the Baseline functional assessments to reconfirm eligibility. The 2-day mean of this repeated 6MWT assessment must be within 15% of the 2-day mean for the previous Baseline assessment in order to meet eligibility.

[c] Functional assessment (Hub Site) visits may occur within ±1 week of the visit date specified in the schedule of events, with the exception of Week 96, where the functional assessment (Hub Site) visit may occur within -3 weeks of the visit date specified in the schedule of events.

[d] Eligibility will be assessed during Screening and confirmed by the local site and the Sponsor after completion of the 6MWT, PFT, and ECG at the Baseline visit. Eligibility will be reconfirmed before dosing at Week 1 based on all available data including safety laboratory assessments. This confirmation must include review of results of the Screening test for *DMD* genotyping. It is not necessary for results of the Screening tests for *LTBP4* or *SPP1* genotyping to be available for confirmation of patient eligibility.

[e] Eligible patients will be randomized using a 2:1 ratio to either the combined-active group to receive SRP-4045 or SRP-4053, according to genotype and age [7 to 8.5 vs >8.5 to 13 yrs]; approximately 74 patients per genotype), or the placebo group (approximately 37 patients per genotype). Randomization will occur at Baseline after the local site has confirmed patient eligibility after completion of the 6MWT, PFT, and ECG done at the HS Baseline visit.

[f] Full physical examination: general appearance, HEENT, heart, chest, abdomen, skin, lymph nodes, extremities, musculoskeletal, and neurological systems (refer to Section 10.4.1 for components of the neurological systems examination). Brief physical examination: general appearance, HEENT, heart, chest, abdomen, and skin.

[g] Vital signs include blood pressure, heart rate, respiration, and temperature (oral, tympanic, or axillary). Patients will have vital signs measured on infusion days within approximately 30 minutes prior to infusion and approximately 5, 30, and 60 minutes after the end of the infusion.

[h] Weight is recorded at the Hub Site on Baseline Day 1 and at the Surgical Site prior to biopsy. Starting at Week 1, weight is to be recorded every 4 weeks throughout the study. The weight obtained at the local site at Week 1 will be used to calculate the initial dose of study treatment. Subsequently, the study treatment dose will be calculated based on the most recent patient weight obtained per protocol prior to the current visit.

[i] Safety laboratory assessments include chemistry, hematology, coagulation, and urinalysis.

[j] At Weeks 1, 8, 16, 24, 32, 40, 48, 72, and 96, blood samples for assessing plasma drug concentrations will be obtained at select participating sites predose (prior to the start of the infusion), and immediately prior to the end of the infusion (expected approximate time of postdosing maximum plasma concentration for SRP-4045 and SRP-4053). Additionally, 1 blood sample will be taken during each of the following windows: approximately 1 to 3 hours and approximately 4 to 12 hours after the end of the infusion. The specific time of sample collection within each window is at the discretion of the site.

[k] The 6MWT and NSAA will be performed on 2 consecutive business days at Screening, Baseline (prior to Week 1), and every 24 weeks (at the Week 24, 48, 72, and 96 visits). This may require 2-night overnight stays. The 6MWT and NSAA will be performed on only 1 day at the Week 12, 36, 60, and 84 visits. Pulse will be obtained prior to and immediately after the 6MWT.

[l] The number of falls will be collected from the patient with the help of parents or guardians and recorded in the Patient Fall Diary as a patient-reported outcome. The Local Site is to distribute the Patient Fall Diary to the parents or guardians during the initial Screening visit and the first collection period will be 1 week prior to the start of travel to the Hub Site for the Baseline Hub visit.

[m] QMT using a hand-held myometer/dynamometer will be done for all patients. In addition, maximum voluntary isometric contraction testing (MVICT) will be done only at a subset of HS with MVICT capabilities.

[n] PFT measurements will consist of forced vital capacity (FVC), maximal inspiratory pressure (MIP), and maximal expiratory pressure (MEP), and will be performed on 2 consecutive business days at Screening, Baseline (prior to Week 1), and every 24 weeks (at the Weeks 24, 48, 72, and 96 visits). PFTs will be performed on only one day at the Week 12, 36, 60 and 84 visits.

[o] ECG and ECHO are permitted to be conducted on either Day 1 or Day 2 of the following study visits for patient convenience: Screening, Baseline (ECG only), Week 24 (ECG only), Week 48 (ECG only), Week 72 (ECG only), and Week 96.

[p] Upon qualification for the study based on Screening and Baseline assessments and after eligibility is confirmed by both the local site and the Sponsor's Medical Monitor, all patients will undergo a muscle biopsy at Baseline. A second biopsy will be collected at either Week 48 or 96 (as detailed in Section 7.1). The first 45 patients amenable to exon 45 skipping randomized into this study will undergo muscle biopsy at Week 48 and all subsequent patients amenable to exon 45 skipping randomized into this study will undergo a muscle biopsy at Week 96. Patients amenable to exon 53 skipping who have completed the Week 48 muscle biopsy prior to reconsenting for Amendment 6 will not undergo a further muscle biopsy. Patients amenable to exon 53 skipping who have not completed the Week 48 muscle biopsy prior to reconsenting for Amendment 6 will undergo a muscle biopsy only at Week 96. The biopsies at Weeks 48 (±2 weeks) or 96 (within 3 weeks prior to this visit) must occur after the clinical evaluation for Weeks 48 or 96 and at least 48 hours after the most recent infusion. For biopsies done at Week 96, biopsies must be completed prior to the transition to open-label study drug. Study infusions must not be administered until at least 24 hours post biopsy, and the Investigator must medically clear the patient before the infusion may be given.

[q] According to randomization and genotype, treatment (active treatment or placebo) will be administered by IV infusion (approximately 35-60 minutes). Patients are to be closely monitored for at least 1 hour following the completion of all infusions. It is recommended that a topical anesthetic cream (eg, lidocaine 2.5%, prilocaine 2.5%, LMX4 cream or other per Investigator's discretion) be applied prior to infusions. Patients who discontinue treatment are to have an End of Study visit 28 days after their last infusion as described in Table 2. The following guidelines for the timing of dosing are to be followed throughout the study: (1) Patients should receive study treatment once every 7 days starting at the Week 1 visit. After the first infusion, a window of ±2 days around the scheduled weekly dosing date (referenced back to the first dose at Week 1) is acceptable; (2) patients may not receive 2 separate doses of study treatment within the same 60-hour period; (3) the medical monitor is to be contacted in the event of a missed dose.

[r] Patients from select sites will participate in the Caregiver Questionnaire and Videography assessments under a separate informed consent. Patients who are already enrolled in the study and who consent to participate in the caregiver assessments will have an ad hoc first collection, per the Assessment Manual schedule. The Caregiver Questionnaire and Videography will be performed in the patient's home setting, not at the investigational site.

[s] The Clinical Global Impression of Change assessment will be required only for patients who participate in the Caregiver Questionnaire and Videography assessments and who have these assessments performed at study Baseline. To obtain the most reliable and consistent data, the Sponsor strongly recommends that the Clinical Global Impression of Change be performed by the local site study physician who knows the patient best, and the patient should be rated by the same evaluator throughout the study.

[t] An optional additional Informed Consent Form may be signed prior to the initial screening visit if needed to provide patient information for biopsy scheduling to ensure that the biopsy is performed per protocol timelines.

[u] For newly enrolled patients at select participating sites, on the day of the first dose, triplicate 12-lead ECGs will be obtained immediately prior to PK sampling at predose (Baseline), at the end of infusion, and at 1 to 3 hours after the end of infusion.

[v] For patients at select participating sites, on the day of dosing, triplicate 12-lead ECGs will be obtained immediately prior to PK sampling at predose (Baseline), at the end of infusion, and at 1 to 3 hours after the end of infusion.

13.2. Adverse Event Term Aggregation and Disaggregation

Reason for Change	AEDECOD	PTchange	N Rows
Add second PT from complex verbatim term	Arthralgia	Fall	3
	Back injury		1
	Back pain		5
	Contusion		6
	Ecchymosis		2
	Excoriation		1
	Haematoma		1
	Joint injury		2
	Laceration		1
	Ligament rupture		1
	Limb injury		3
	Lumbar vertebral fracture		1
	Muscle haemorrhage		1
	Muscular weakness		1
	Musculoskeletal pain		1
	Pain		1
	Pain in extremity		4
	Post-traumatic pain		4
	Scratch		6
	Viral infection		1
	Wound		1
Aggregated like terms	Abdominal pain upper	Abdominal pain	38
	Catheter site pain	Administration site pain	12
	Infusion site pain		4
	Vessel puncture site pain		1
	Musculoskeletal pain	Arthralgia	1
	Catheter site bruise	Catheter site related reaction	4
	Catheter site cellulitis		1
	Catheter site erythema		1
	Catheter site oedema		1
	Catheter site rash		3
	Catheter site swelling		2
	Influenza like illness	Cough	1
	Productive cough		3
	Cushing's syndrome	Cushingoid	1
	Dermatosis	Dermatitis	1

	Gastrooesophageal reflux disease	Dyspepsia	2
	Otitis externa	Ear infection	1
	Otitis media		2
	Ankle fracture	Fracture	1
	Femoral neck fracture		1
	Femur fracture		1
	Fibula fracture		2
	Foot fracture		3
	Hand fracture		1
	Humerus fracture		1
	Gastroenteritis viral	Gastroenteritis	6
	Gastrointestinal infection		3
	Viral infection		1
	Muscle haemorrhage	Haemorrhage	1
	Rectal haemorrhage		2
	Oral herpes	Herpes-type infection	5
	Keloid scar	Hypertrophic scar	3
	Incision site erythema	Incision site complication	2
	Incision site rash		1
	Incision site vesicles		1
	Influenza B virus test positive	Influenza	1
	Initial insomnia	Insomnia	2
	Mouth injury	Malocclusion	1
	Pain	Pain	1
	Pain in extremity		27
	Body temperature increased	Pyrexia	3
	Influenza like illness		1
	Rash erythematous	Rash	1
	Rash generalised		1
	Rash macular		1
	Rash papular		4
	Rash pruritic		3
	Rash pustular		7
	Rash vesicular		1
	Urticaria		1
	Lower respiratory tract infection	Respiratory tract infection	4
	Respiratory tract		1

	infection		
	Upper respiratory tract infection		12
	Viral upper respiratory tract infection		5
	Rhinitis allergic	Rhinitis	2
	Partial seizures	Seizures	1
	Heart rate increased	Tachycardia	1
	Sinus tachycardia		1
	Lumbar vertebral fracture	Vertebral fracture	2
	Spinal compression fracture		4
	Vitamin D deficiency	Vitamin D decreased	1
Term not included from multievent PT		Balance disorder	1
		Pain	1
		Pyrexia	1

13.3. Financial Disclosure Form

Covered Clinical Study (Name and/or Number): 4053-101 and 4045-301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 30		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be		

influenced by the outcome of the study: _____ Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

References

Aartsma-Rus, A., Fokkema, I., Verschuuren, J., Ginjaar, I., van Deutekom, J., van Ommen, G. J., & den Dunnen, J. T. (2009). Theoretic applicability of antisense-mediated exon skipping for Duchenne muscular dystrophy mutations. *Hum Mutat, 30*(3), 293-299. doi:10.1002/humu.20918

Fleming, T. R. (2005). Surrogate endpoints and FDA's accelerated approval process. *Health Aff (Millwood), 24*(1), 67-78. doi:10.1377/hlthaff.24.1.67

Lim, B. C., Lee, S., Shin, J. Y., Kim, J. I., Hwang, H., Kim, K. J., . . . Chae, J. H. (2011). Genetic diagnosis of Duchenne and Becker muscular dystrophy using next-generation sequencing technology: comprehensive mutational search in a single platform. *J Med Genet, 48*(11), 731-736. doi:10.1136/jmedgenet-2011-100133

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/s/

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08/15/2019 09:13:31 AM

BAIKUNTHA ARYAL
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V ASHUTOSH RAO
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XIANG LING
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I concur with the statistical review.

HSIEN MING J HUNG
08/15/2019 11:58:50 AM

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