CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211970Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	211970
Goal Action Date	December 11, 2019
OSE RCM #	2018-2784
Reviewer Name(s)	Lindsey W. Crist, PharmD, BCPS
Team Leader	Donella Fitzgerald, PharmD
Deputy Division Director	Jamie Wilkins, PharmD
Review Completion Date	December 9, 2019
Subject	Evaluation of Need for a REMS: Resubmission after Complete Response
Established Name	Golodirsen
Trade Name	Vyondys 53
Name of Applicant	Sarepta Therapeutics, Inc.
Therapeutic Class	Antisense oligonucleotide
Formulation(s)	Solution for injection
Dosing Regimen	30 mg/kg administered by intravenous infusion once weekly

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1 Introduction

This document is an addendum to the Division of Risk Management (DRISK) review of the new molecular entity (NME) Vyondys 53 (golodirsen), New Drug Application (NDA) 211970, dated August 19, 2019. Sarepta Therapeutics, Inc (Sarepta) submitted the original NDA 211970 for golodirsen, on December 19, 2018, with the proposed indication 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. A Complete Response (CR) was issued on August 19, 2019 due to the Agency's conclusion that the benefit/risk balance for golodirsen was not favorable.[1] Sarepta submitted a formal dispute resolution request for which an Appeal Granted Letter was issued on November 22, 2019.[2] A Class 1 Resubmission was subsequently submitted on November 27, 2019 and is the subject of this addendum review.[3] The resubmission includes the following: a safety update, revised labeling, postmarketing requirements (PMRs), a confirmatory study commitment letter, and a summary of the proposed education activities to educate and enhance awareness of the proper care and monitoring for indwelling ports to help reduce the risk of serious infections.

2 Background

2.1 Product Information

Golodirsen, a new molecular entity (NME), is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) subclass proposed for the treatment of DMD in pediatric and adult patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. Golodirsen binds to pre-mRNA of the DMD gene to induce skipping of exon 53. Skipping exon 53 can restore the mRNA reading frame for translation resulting in production of an internally shortened, but potentially functional dystrophin protein. Golodirsen is proposed to be supplied as a solution in a single-dose vial containing 100 mg/2 mL that requires further dilution before administration via intravenous infusion. The proposed dose of golodirsen is 30 mg/kg once-weekly by intravenous infusion for the lifetime of the patient. Golodirsen is not approved in any jurisdiction at this time.

2.2 Regulatory History

The following is a summary of the regulatory history for golodirsen, NDA 211970, relevant to this review:

- 08/19/2019: The Agency issued Sarepta a Complete Response (CR) due to an unfavorable benefit/risk balance for golodirsen.[1]
- 09/12/2019: A Type A Post Action (End of Review) meeting was held between the Office of Drug Evaluation (ODE) I, Division of Neurology Products, and the Applicant to discuss the deficiencies cited in the CR letter. Sarepta requested reconsideration of the CR action. The Applicant was informed that in order for reconsideration, the application would need to be resubmitted addressing the deficiencies. Alternatively, the Applicant may submit a formal dispute resolution request.

- 09/13/2019: Sarepta submitted a formal dispute resolution request concerning the August 19, 2019 CR action.
- 10/17/2019: A Type A Formal Dispute Meeting held between the Agency and the Applicant to discuss the formal dispute resolution request.
- 10/21/2019: The Agency issued Sarepta a Dispute Appeal Interim Response Letter requesting further clarifying information to make a decision for the formal dispute resolution request.
- 11/22/2019: The Agency issued Sarepta an Appeal Granted Letter.[2]
- 11/27/2019: Sarepta submitted a Class 1 Resubmission for golodirsen, NDA 211970 for the treatment of DMD in pediatric and adult patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping.[3]

3 Benefit Assessment

The clinical benefit of golodirsen was summarized in the original DRISK review dated August 19, 2019.[4] For additional details regarding the development program, see the Clinical Review of NDA 211970 dated August 15, 2019[5], the Cross-Disciplinary Team Leader (CDTL) Summary Memorandum dated August 19, 2019[6], and the Office Director Decisional Memo dated August 19, 2019.[7] The ODE I Director concluded that "if one accepts that the small change in dystrophin level is reasonably likely to predict clinical benefit, it seems reasonable to assume that the clinical benefit would be commensurately small".[7]

Upon review of the formal dispute resolution request and data from the submission, the Office of New Drugs (OND) Director concluded that the pivotal study demonstrates that golodirsen increases dystrophin levels.[2] Changes in the surrogate endpoint of dystrophin levels have been determined by the Agency to be reasonably likely to predict clinical benefit based on the approval for eteplirsen, another antisense oligonucleotide agent approved for DMD. He did not concur with the assessment that the extent of benefit for golodirsen would be "commensurately small" as it is not known what threshold of changes in dystrophin levels will result in clinical benefits. He concludes that the current efficacy data supports approval under the Accelerated Approval Pathway, however, completion of the confirmatory study is necessary to confirm the clinical benefit and uphold the benefit/risk balance.[2]

Sarepta did not include new efficacy data in the resubmission. The resubmission included a commitment statement that if the results of the ongoing confirmatory study do not support clinical benefit, Sarepta will voluntarily withdraw golodirsen from the market.[3]

4 Risk Assessment & Safe-Use Conditions

The Applicant's resubmission included an update of the safety database for the reporting interval September 10, 2018 through September 9, 2019.[a] The clinical development program includes 80 male patients with an estimated cumulative exposure total of 197 patient-years. There were no deaths in the current reporting interval or in the clinical development program. There were 5 additional reports of serious adverse events[b] during the reporting interval including influenza (N=2), fracture (N=2), and hypoxia (N=1). No patients have discontinued golodirsen therapy due to adverse events. The safety profile was similar to the original submission data.

4.1 ADVERSE EVENTS OF SPECIAL INTEREST

4.1.1 Renal Toxicity

Renal toxicity was identified as a risk associated with golodirsen in the first review cycle. Renal toxicity was the primary toxicity observed in nonclinical studies and the data suggest the potential for renal toxicity in humans.[8] There were no cases of serious renal toxicity in the clinical studies, however, the safety database was small. Another concern was the challenge of monitoring renal function in this patient population since creatinine may not be a reliable marker. The CR Letter cited "because there is no established way to monitor renal function in this patient population, practitioners could be blind to worsening renal function, leaving these patients vulnerable" and that there is no way to provide adequate instructions in the label.

In response to the safety concerns addressed in the CR Letter, the OND Director concluded that there are other available measures of renal function that may be used for monitoring for renal toxicity in golodirsen-treated patients. He recommended labeling revisions to include specific recommendations on the optimal strategies for renal function monitoring.[2]

Sarepta submitted updated information about renal toxicity in the safety database. There was 1 case of proteinuria during the reporting interval resulting in a total of 4 cases in the clinical development program. All cases were mild and nonserious per the Applicant. Sarepta revised the proposed label to include recommendations for renal monitoring in Section 5, Warnings and Precautions which aligned with the recommendations described by the OND Director.

[a] Three trials were ongoing during this reporting time period including 4045-301 (double-blind placebo controlled study with open label extension), 4045-302 (long-term open-label extension), and 4053-101 randomized double-blind placebo controlled dose titration study with an open label extension).

[b] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

4.1.2 Infections due to indwelling intravascular ports

In the first review cycle, the risk of infections due to indwelling intravascular ports for administration was identified in the CDTL and Office Director Decisional Memo based on post-marketing data for eteplirsen, another antisense oligonucleotide approved for DMD patients with a different mutation.[6,7] These reports included serious and life-threatening infections, including sepsis. Since golodirsen dosing and administration is similar to eteplirsen, the risk of infections due to chronic indwelling intravascular ports is applicable to golodirsen. The CR letter noted that the benefit/risk profile may be improved if indwelling intravascular ports were avoided for administration of golodirsen.

In response to this risk, the OND Director concluded that although there is an increased risk for infections when administration occurs via an indwelling intravascular port that this risk is likely similar to other chronic intravenous therapies. He concluded that the risk of infections can be mitigated through appropriate patient selection for use of ports, port care, early detection, and appropriate management. He recommended the Applicant provide support and education for patients receiving golodirsen to minimize the use of indwelling ports and provide guidance for appropriate monitoring for infections and management.

In the safety report included in the resubmission, no serious blood stream infections or port-related events were reported. Sarepta included a proposal for port education for patients and healthcare providers (See Section 5 for details).

5 Risk Management Activities Proposed by the Applicant

The resubmission proposed pharmacovigilance and labeling for risk management. In response to the Appeal Granted Letter recommendations, Sarepta included a summary of proposed educational activities to increase awareness and educate patients and providers on appropriate management of indwelling intravascular ports. Sarepta proposes patient education through their patient support program SareptaAssist which will include information on special considerations for using ports in the "Getting Started" Brochure. Sarepta proposes healthcare provider education through in-service education sessions by Educational Support Managers.

6 Discussion of Need for a REMS

DMD is a rare, incurable X-linked recessive, neuromuscular disorder caused by mutations in the gene encoding dystrophin, a protein important for the structural stability of myofibers. The absence of dystrophin results in muscle degeneration that progresses through childhood and adolescence with eventual loss of ambulation and wheelchair dependence, decreased respiratory function and ventilator dependence, cardiomyopathy, and death. Treatment options are limited resulting in an unmet need for new therapies. Golodirsen is the first agent to increase dystrophin in patients with a genetic mutation amenable to exon 53 skipping.

The evidence for efficacy for the accelerated approval of golodirsen is based on a single study. There was a statistically significant increase in the primary biologic endpoint of change from Baseline to Part 2 Week 48 in dystrophin protein levels. The OND Director concluded that the increase in dystrophin observed with golodirsen is reasonably likely to predict clinical benefit.

The risk of renal toxicity observed in the nonclinical studies will be communicated through labeling. The proposed golodirsen label recommends measurement of glomerular filtration rate prior to patients initiating therapy. Further information on the risk of renal toxicity and options for monitoring are included in Section 5, Warnings and Precautions. Creatinine may not be a reliable method of monitoring renal function DMD patients as they have profoundly reduced muscle mass. Therefore, the proposed labeling includes recommendations for routine monitoring through urinalysis. If there is a positive assessment, then the label recommends the use of a 24-hour urine collection to quantify proteinuria and assess GFR. The proposed recommendations for renal monitoring aligned with the recommendations by the OND Director. The use of indwelling intravascular ports for administration of golodirsen may increase the risk of infections, including serious infections such as sepsis over time. The risk of these infections is likely to be similar to other chronic intravenous therapies. Prescribers may be familiar with port-related infections since eteplirsen, another antisense oligonucleotide which is approved for DMD, has the same risk. However, since eteplirsen has not been on the market for a long period of time and this risk is not included in labeling, education for providers was recommended by the Agency for this risk. Sarepta proposed education for healthcare providers and treatment sites that prescribe and administer golodirsen therapy as outlined in the Appeal Granted Letter. The proposal includes education on port care, early detection, and management for infections. Patients may also receive education via Sarepta's patient support program for this risk.

7 Conclusion & Recommendations

The initial CR action for golodirsen was based upon an unfavorable benefit/risk profile, primarily due to the risks of renal toxicity and infections due to indwelling intravascular ports. These safety risks can be adequately addressed through labeling and an education proposal, respectively, per the conclusions outlined by the OND Director in the the Appeal Granted Letter. At the time of this review, labeling is ongoing.

Should the Division of Neurology 1 have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

8 Appendices

8.1 References

1. Unger E. Complete Response Letter for Vyondys 53 (golodirsen), NDA 211970. August 19, 2019.
2. Stein P. Formal Dispute Resolution Appeal. Appeal Granted Letter for Vyondys 53 (golodirsen), NDA 211970. November 22, 2019.
3. Sarepta Therapeutics. Resubmission Vyondys 53 (golodirsen), NDA 211970. November 27, 2019.

4. Crist L. Division of Risk Management. REMS Determination Review for Vyondys 53 (golodirsen), NDA 211970. August 19, 2019.
5. Breder CR, A; Aryal B, Ling, X. Division of Neurology Products. Combined Review (Clinical/Biotechnology Products/Biometrics) for Vyondys 53 (golodirsen), NDA 211970. August 15, 2019.
6. Buracchio T, Bastings E. Division of Neurology Products. Summary Memorandum for Vyondys 53 (golodirsen), NDA 211970. August 19, 2019.
7. Unger E. Office of Drug Evaluation I. Office Director Decisional Memo for Vyondys 53 (golodirsen), NDA 211970. August 19, 2019.
8. Wilcox BJ. Division of Neurology Products. Nonclinical Review for golodirsen, NDA 211970. July 3, 2019.

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/s/

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Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	211970
PDUFA Goal Date	August 19, 2019
OSE RCM #	2018-2784
Reviewer Name(s)	Lindsey W. Crist, PharmD, BCPS
Team Leader	Donella Fitzgerald, PharmD
Deputy Division Director	Jamie Wilkins, PharmD
Review Completion Date	August 19, 2019
Subject	Evaluation of Need for a REMS
Established Name	Golodirsen
Trade Name	Vyondys 53
Name of Applicant	Sarepta Therapeutics, Inc.
Therapeutic Class	Antisense oligonucleotide
Formulation(s)	Solution for injection
Dosing Regimen	30 mg/kg administered by intravenous infusion once weekly

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Vyondys 53 (golodirsen) is necessary to ensure the benefits outweigh its risks. Sarepta Therapeutics, Inc (Sarepta) submitted a New Drug Application (NDA) 211970 for golodirsen with the proposed indication 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. The risks associated with golodirsen include hypersensitivity reactions and renal toxicity. The applicant did not submit a proposed REMS or risk management plan with this application.

The Agency recommends a Complete Response as there continue to be concerns regarding the overall benefit/risk balance with this product, although there are no safety risks which would require a REMS at this time.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[a] Vyondys 53, (golodirsen) is necessary to ensure the benefits outweigh its risks. Sarepta Therapeutics, Inc (Sarepta) submitted a New Drug Application (NDA) 211970 for golodirsen with the proposed indication 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 application is under review in the Division of Neurology Products (DNP). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Golodirsen, a new molecular entity (NME), is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) subclass proposed for the treatment of DMD in pediatric and adult patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. Golodirsen was granted orphan-drug and Fast Track designation. Golodirsen binds to pre-mRNA of the DMD gene to induce skipping of exon 53. Skipping exon 53 can restore the mRNA reading frame for translation resulting in production of an internally shortened, but potentially functional dystrophin protein. Golodirsen is proposed to be supplied as a solution in a single-dose vial containing 100 mg/2 mL that requires further dilution before administration via intravenous infusion. The proposed dose of golodirsen is 30 mg/kg once-weekly by intravenous infusion for the lifetime of the patient.[b] Golodirsen is not approved in any jurisdiction at this time.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for golodirsen, NDA 211970, relevant to this review:

- 12/11/2014: Fast Track designation granted for the treatment of DMD

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity*.

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug*.

- 05/22/2018: Orphan drug designation granted for the treatment of DMD
- 07/23/2018: Rolling review request granted
- 12/19/2018: The final portion of a rolling original NDA was received for golodirsen (NDA 211970)
- 02/12/2019: Priority Review granted.
- 04/11/2019: A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for golodirsen.
- 06/18/2019: A Late Cycle meeting was held between the Agency and the Applicant via teleconference. No issues related to risk management were discussed.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

DMD is a rare, incurable X-linked recessive, neuromuscular disorder affecting approximately 1 in every 3500 to 5000 male births worldwide.[1,2,c] DMD is caused by mutations in the gene encoding dystrophin, a protein critical to the structural stability of myofibers in skeletal and cardiac muscle. The majority of the mutations are deletions that cause a disruption in the mRNA reading frame and prevent the production of functional dystrophin. The absence of dystrophin causes degeneration of muscle fibers, inflammation, and replacement of muscle by fibrotic and adipose tissue. The clinical course is characterized by progressive muscle weakness that is typically diagnosed by the age of five years. Muscle degeneration worsens throughout childhood and adolescence resulting in the loss of ambulation and wheelchair dependence, decreased respiratory function and ventilator dependence, cardiomyopathy, and death.[d] Patients often die in their late teens to twenties, usually due to cardiac or respiratory failure.

Targeted skipping of selected exons may result in restoration of the mRNA reading frame and result in a truncated, but possibly functional dystrophin. It is theorized that increases in dystrophin levels in patients with DMD may be of clinical benefit, however, trials with clinical endpoints are ongoing. About 8% of males with DMD have deletion mutations that are amenable to exon 53 skipping.[3]

3.2 Description of Current Treatment Options

There are limited treatment options for DMD. Eteplirsen (Exondys 51) is an antisense oligonucleotide indicated for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

amenable to exon 51 skipping. It was approved by the FDA in September 2016 using the accelerated approval pathway based on the demonstration of a small increase in dystrophin in clinical trials.[4] It is the only approved agent that targets the absence of dystrophin, however, it is only an option for a small subpopulation who have mutations amenable to exon 51 skipping. Risks associated with eteplirsen include hypersensitivity reactions including pyrexia, flushing, cough, dyspnea, bronchospasm, rash, urticaria, and hypotension. There are no approved agents for patients with mutations amenable to exon 53 skipping.

Glucocorticoid therapy is the mainstay of treatment for most patients with DMD and is associated with an increase in strength, muscle function, and pulmonary function, although the duration of benefit is uncertain. Deflazacort (Emflaza) was approved in February 2017 and is the only systemic corticosteroid with an FDA-approved indication for DMD. It is currently indicated for the treatment of DMD in patients 2 years of age and older.[5] Treatment with corticosteroids is complicated by a wide variety of common side effects, such as weight gain, Cushingoid appearance, cataracts, gastrointestinal symptoms, behavioral changes, acne, and excessive hair growth.[6]

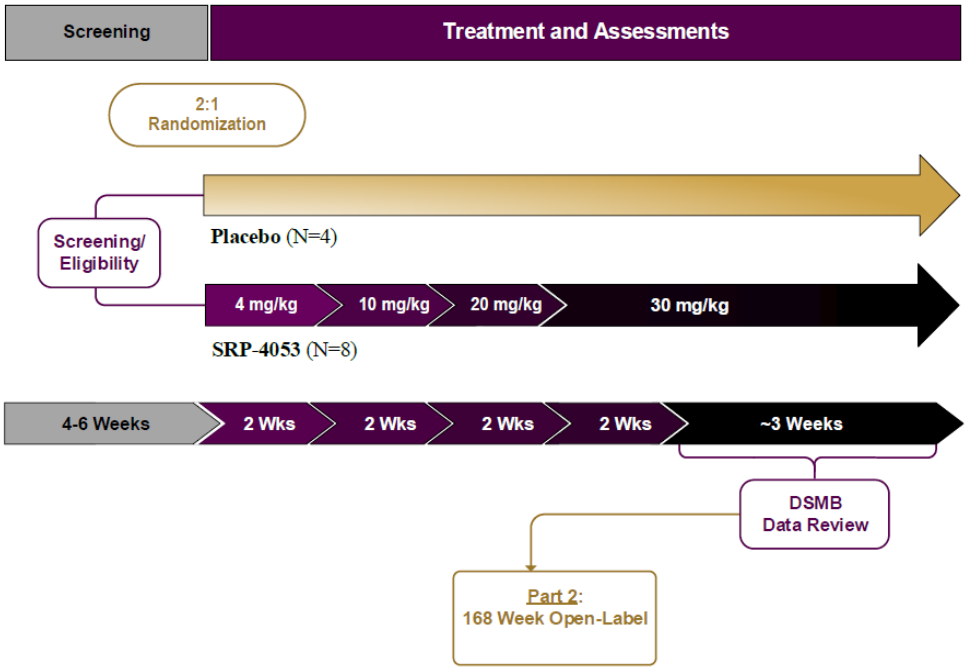
Other options for treatment include supportive therapies including physical therapy and use of assistive devices (e.g. braces or wheelchairs), surgery, and respiratory and cardiac support. The current treatments delay but do not prevent mortality.

4 Benefit Assessment

The clinical development program for golodirsen consists of a two-part Phase 1/2 study (Study 4053-101, NCT02310906) and an ongoing, multicenter, randomized, double-blind, placebo-controlled Phase 3 study (Study 4045-301, NCT02500381, also known as ESSENCE). The ESSENCE trial is evaluating the efficacy and safety of treatment with golodirsen in patients with deletion mutations amenable to skipping exon 53 and a treatment arm with another investigational antisense oligonucleotide for deletion mutations amenable to skipping exon 45. Efficacy results are not currently available and were not used to support the efficacy determination for this application.

The pivotal study supporting efficacy at the time of submission of this application is Study 4053-101. Part 1 of Study 4053-101 consisted of a randomized, double-blind, placebo-controlled study which evaluated the pharmacokinetics and safety of escalating weekly doses (4 mg/kg to 30 mg/kg) of golodirsen compared to placebo in 12 patients over 12 weeks (golodirsen group=8, placebo group=4). Eligible subjects were required to be on stable doses of corticosteroids for at least 6 months. Figure 1 depicts the study schematic for Part 1.

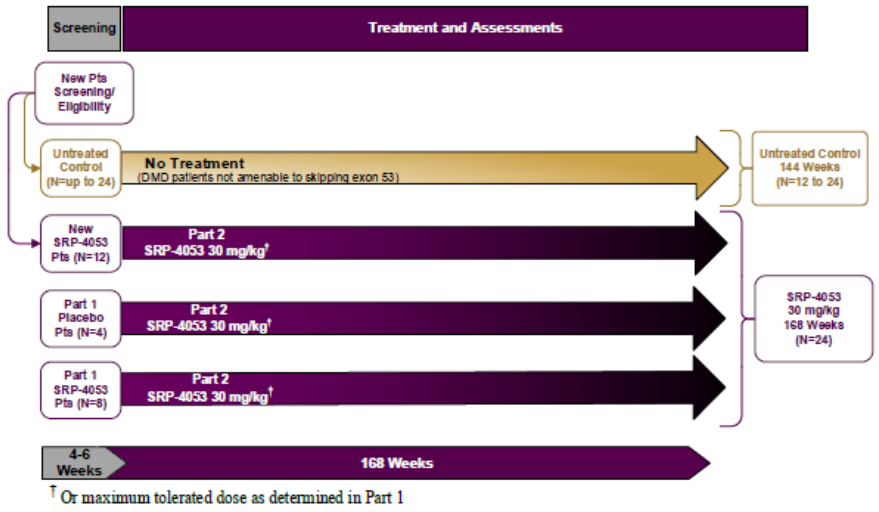
Figure 1. Study 4053-101 – Study Schematic for Part 1, Double-Blind Dose Titration[7]



Source: Sarepta Therapeutics. Summary of Clinical Efficacy

Part 2 is an ongoing, long-term, open-label study evaluating golodirsen in 25 patients with DMD. The patient population consisted of the 12 patients who completed Part 1, and 13 newly enrolled patients with DMD and mutations amenable to exon 53 skipping. All patients received golodirsen 30 mg/kg IV weekly (or the maximum tolerated dose if already treated in Part 1). A cohort of 14 DMD patients with mutations not amenable to exon 53 skipping were enrolled to evaluate the natural disease course. No comparison analyses were performed. Figure 2 depicts the study schematic for Part 2. The primary endpoint was the change from baseline at Part 2 Week 48 in dystrophin protein levels in muscle biopsy samples measured by Western Blot. A descriptive analysis is planned for clinical endpoints from baseline to Part 2 Week 144 for the 6-minute walk test and forced vital capacity percent predicted, however, evaluation of these endpoints is ongoing.

Figure 2. Study 4053-101 – Study Schematic for Part 2, Open-Label and Untreated patients[7]



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: Sarepta Therapeutics. Summary of Clinical Efficacy

Results:

Treatment with weekly golodirsen in the 25 patients enrolled in Part 2 resulted in increased dystrophin levels from baseline. Results for the primary endpoint are summarized in Table 1 below. Definitions for populations analyzed:

- Group 1 consisted of the 17 subjects that were untreated prior to the start of Part 2 (4 patients assigned to placebo in Part 1 and 13 new patients enrolled in Part 2).
- Group 2 consisted of 8 patients that received golodirsen in Part 1 who continued into Part 2.
- Total Golodirsen consisted of all patients who received treatment during any part of Study 4053-101

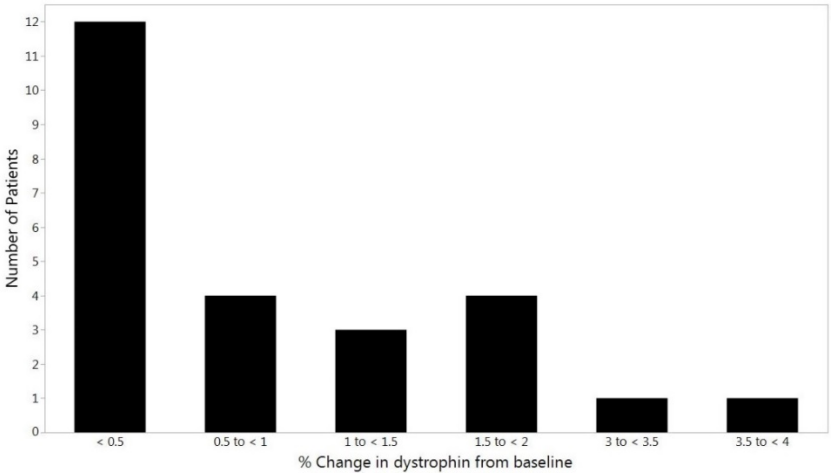
Table 1. Primary Endpoint Results, Percent Dystrophin Levels vs. Normal in Study 4053-101 Part 2[7]

		Group 1 (N=17)	Group 2 (N=8)	Total Golodirsen (N=25)
Baseline	Mean (SD) Median Min, Max	0.091 (0.0567) 0.065 0.03, 0.22	0.104 (0.0914) 0.104 0.02, 0.31	0.095 (0.0136) 0.068 0.02, 0.31
Part 2 Week 48	Mean (SD) Median Min, Max	0.840 (0.6429) 0.908 0.09, 1.91	1.398 (1.5719) 0.739 0.11, 4.30	1.019 (1.0328) 0.908 0.09, 4.3
Change to Part 2 Week 48	Mean (SD) Median Min, Max P-value	0.750 (0.6660) 0.875 0.01, 1.84 <0.001	1.294 (1.5079) 0.659 0.01, 3.99 0.008	0.924 (1.0129) 0.875 0.01, 3.99 0.001
Fold Change from Baseline to Part 2 Week 48	Mean (SD) Median Min, Max	13.960 (14.1889) 9.551 1.01, 53	20.208 (29.6874) 8.919 1.07, 89.7	15.959 (20.0031) 9.551 1.04, 89.71

Source: Adapted from Sarepta Therapeutics. Summary of Clinical Efficacy

The review team concluded that the Applicant's methodology for Western blot was adequate.[8] The median change from baseline in dystrophin after 48 weeks of treatment was 0.88% (interquartile range: 0.08 – 1.5%), and the mean change from baseline was 0.92% (Standard Error 0.20). The distribution of change in percent dystrophin from baseline to Week 48 by number of patients is shown in Figure 3.

Figure 3. Distribution of Change from Baseline to Week 48 in Percent Dystrophin[8]



Source: Clinical Reviewer Analysis

Data on functional endpoints was limited as the study is ongoing. Decreases in the six-minute walk test were observed in the total golodirsen group at the timepoints analyzed. The mean decrease in the 16 patients that reached Part 2 Week 144 was 92.5 meters. Pulmonary function was evaluated by measuring change in FVC percent predicted from baseline. Pulmonary function decreased over time and for the 18 patients that reached Part 2 Week 144, the mean decrease was 5.349%.

The clinical reviewer concluded that the amount of dystrophin produced is small and resultant clinical benefits do not seem reasonably likely and recommends a complete response.[8,e]

5 Risk Assessment & Safe-Use Conditions[f]

The primary safety analysis for golodirsen in patients with DMD is based on data from the ongoing, clinical trials, Study 4053-101 and Study 4045-301. At the time of submission, safety data was available through the data lock date of June 29, 2018.[9] Sarepta submitted a 120-Day Safety update that included additional safety data through a data lock date of October 26, 2018. Interim safety data from the long-term extension Study 4045-302[g] was included. A total of 60 subjects with DMD treated with golodirsen (116.91 patient-years) and 21 subjects treated with placebo (21.09 patient years) comprised the safety population. The median treatment duration based on the 120-day Safety Update is around 89 weeks.[10]

Three populations were used for safety analysis in DMD patients and are defined in Table 2. Population 2 served as the largest pooled double-blind safety data and was used by the clinical reviewer for most analyses.[8] Population 3 (All Golodirsen) included safety data with the longest duration of treatment for golodirsen.

Table 2. Safety Population Definitions[10]

Population	Treatment group	Time period
Population 1 (Study 4045-301)	**Placebo (N=17)** **Golodirsen 30 mg/kg (N=33)**	All weeks in Study 4045-301 double-blind period up to lock date
Population 2 (pooled data from Study 4053-101, Part 1 and 4045-301)	**Placebo (N=21)** - Pooled data of placebo patients from Study 4053-101, part 1 (N=4) and Study 4045-301 (N=17) **Golodirsen (N=41)** - Pooled data from Study 4053-101 (N=8), part 1 and Study 4045-301 (N=33)	Part 1 weeks of Study 4053-101 and all weeks of double-blind period of Study 4045-301 up to lock date
Population 3 (pooled data for all golodirsen)	**All Golodirsen (N=60)** - Includes patients treated with golodirsen in Study 4053-101, part 2 (N=25), Study 4045-301 (N=35) plus data from the open-label period and extension trial (4045-302)	All golodirsen weeks throughout double-blind and open label periods of Study 4053-101, 4045-301, and 4045-302 up to lock date

Source: Adapted from Sarepta. 120-Day Clinical Safety Update

Most subjects studied, regardless of assigned treatment, experienced at least one treatment-emergent adverse event (TEAE). In Population 2, 95.1% of patients (39/41) treated with golodirsen and 95.2% of patients treated with placebo (20/21) reported at least 1 treatment emergent adverse event (TEAE). No patients discontinued study treatment due to a TEAE.[9] Common AEs with an incidence greater than

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

[g] Study 4045-302 is an ongoing, Phase 3 long-term, open-label extension trial of Study 4045-301.

placebo and frequency of at least 20% in golodirsen treated patients included headache, pyrexia, fall, cough, abdominal pain, nasopharyngitis, cough, vomiting, and nausea.[8]

5.1 SERIOUS ADVERSE EVENTS[h]

No deaths were reported in the clinical trials based on the submitted application data. Nine patients treated with golodirsen reported a total of 15 serious adverse events (SAEs) compared to one patient treated with placebo who reported 2 SAEs. None of the SAEs led to treatment discontinuation.

SAEs reported in golodirsen-treated patients included hyperhidrosis, hypoaesthesia, myoglobinuria, rhabdomyolysis, increased blood creatinine phosphokinase, spinal compression fracture, lymphadenitis, pyrexia (2 events), vomiting, hypocalcemia, viral gastroenteritis, hematemesis, tonsillar hypertrophy, and convulsion. A 7 year old who experienced myoglobinuria, rhabdomyolysis, and increased blood creatinine phosphokinase required hospitalization and interruption of therapy, but he recovered and restarted treatment. Although rhabdomyolysis may be expected in the natural history of DMD, the clinical reviewer noted that this event was severe in intensity and there was a similar case identified in the eteplirsen trials.[8]

One patient on placebo reported two SAEs, a femoral neck fracture and later in the trial a femur fracture, both classified as severe. Both events led to hospitalization, but the patient continued assigned treatment and recovered.

5.2 SEVERE ADVERSE EVENTS

A total of 10 events were classified as severe with 8 events occurring in 5 subjects on golodirsen and two events occurring in 1 subject on placebo. The severe events that occurred with golodirsen treatment not already discussed above included osteoporosis and bone decalcification (N=1), fibula fracture (N=1), abasia (N=1), and humerus fracture (N=1). The two severe events in the subject on placebo were the fractures discussed above.

5.3 ADVERSE EVENTS OF SPECIAL INTEREST

5.3.1 Hypersensitivity Reactions

The clinical reviewer completed additional analyses for hypersensitivity-related adverse reactions as the Applicant analysis was too limited for case identification. The most frequent related preferred terms (with incidence greater in golodirsen group than placebo and percent difference of 5% or greater) in the clinical reviewer's analysis of Population 2 are summarized in the table below.[8]

[h] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Table 3. Incidence of Hypersensitivity-related Preferred Terms (Population 2)[8]

Hypersensitivity Preferred term	Golodirsen (N=41) N (%)	Placebo (N=21) N (%)
Pyrexia	20 (41%)	3 (14%)
Cough	11 (27%)	4 (19%)
Seasonal allergy	3 (7%)	0
Erythema	2 (5%)	0
Multiple allergies	2 (5%)	0
Myalgia	2 (5%)	0

Source: Adapted from Clinical Reviewer analysis

Additional hypersensitivity reactions that occurred during the trials at a rate higher than placebo included rash, dermatitis, pruritis, urticaria, and skin exfoliation. Some of the reactions were not self-limiting and required treatment.

5.3.2 Renal Toxicity

Renal toxicity was observed in nonclinical studies with golodirsen.[11] Renal toxicity was a major adverse effect seen in in mice, monkeys, and rats. Renal impairment was observed in male mice primarily at the highest dose studied (960 mg/kg). Microscopic findings in the kidney (tubular dilatation, basophilic or eosinophilic casts, vacuolation) and increases in serum markers of renal function (e.g., urea nitrogen, creatinine) were observed. Treatment with golodirsen in male monkeys also resulted in renal impairment. Dose dependent increases of serum markers of renal function increased along with microscopic kidney findings described as dilation and microvesicular vacuolation of the dilation convoluted tubules and collecting ducts were observed. Severe renal toxicity, including glomerulonephritis resulting in deaths of juvenile rat pups, occurred in a juvenile animal toxicology study in the high dose group (900 mg/kg/week). In surviving pups, there was a dose-dependent increase in the incidence and severity of renal tubular effects (including degeneration/regeneration, fibrosis, vacuolation, and dilatation.

6 Expected Postmarket Use

Golodirsen is likely to be prescribed by neurologists who specialize in the treatment of DMD and are familiar with the risks of eteplirsen and other treatments for DMD. Golodirsen is to be administered as an intravenous infusion. It may be administered in settings that can accommodate the administration and monitoring for intravenous infusions such as infusion centers, provider clinics/office, or home infusion services. Patients often have caregivers since it is a largely pediatric population and affected patients have significant physical disability.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for golodirsen beyond routine pharmacovigilance and labeling. Although no risk management activities were proposed by the Applicant, the clinical reviewer recommends enhanced pharmacovigilance for the risks of renal toxicity and rhabdomyolysis if golodirsen were approved.

8 Discussion of Need for a REMS

DMD is a rare, incurable X-linked recessive, neuromuscular disorder caused by mutations in the gene encoding dystrophin, a protein important for the structural stability of myofibers. The absence of dystrophin results in muscle degeneration that progresses through childhood and adolescence with eventual loss of ambulation and wheelchair dependence, decreased respiratory function and ventilator dependence, cardiomyopathy, and death. Treatment options are limited resulting in an unmet need for new therapies. Golodirsen is the first agent to increase dystrophin in patients with a genetic mutation amenable to exon 53 skipping.

The evidence for efficacy for the accelerated approval of golodirsen is based on a single study. There was a statistically significant increase in the primary biologic endpoint of change from Baseline to Part 2 Week 48 in dystrophin protein levels. The clinical review team has concluded that the increase was small and that increases in dystrophin are not reasonably likely to result in clinical benefit. The safety database for golodirsen was small but acceptable for this serious disease. The risk of hypersensitivity and rhabdomyolysis were observed in the clinical studies, and renal toxicity was observed in the nonclinical studies. Most treatment-emergent adverse events in the clinical studies were mild to moderate in intensity. Additional data will be available once the trials are complete. Additionally, the clinical reviewer recommended enhanced pharmacovigilance for the risk of renal toxicity and rhabdomyolysis.

The likely prescribers of golodirsen if it were to be approved will be neurologists who have detailed knowledge of the disease and are likely to have familiarity with treatment options. Risks associated with golodirsen include hypersensitivity and renal toxicity. These risks could be communicated with labeling if approval were to be considered. If golodirsen were approved, the clinical reviewer also recommends enhanced pharmacovigilance for renal toxicity and rhabdomyolysis.

9 Conclusion & Recommendations

The Agency recommends a Complete Response as there continue to be concerns regarding the overall benefit/risk balance with this product, although there are no safety risks which would require a REMS at this time.

Should DNP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

10 Appendices

10.1 References

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