CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211970Orig1s000

SUMMARY REVIEW

Summary Memorandum

Date	December 9, 2019
From	Teresa Buracchio, M.D. Eric Bastings, M.D. Billy Dunn, M.D.
Subject	Summary Memorandum
NDA/BLA # and Supplement#	211970; Resubmission to Complete Response
Applicant	Sarepta
Date of Submission	November 27, 2019
PDUFA Goal Date	January 27, 2020
Proprietary Name	Vyondys 53
Established or Proper Name	Golodirsen
Dosage Form(s)	Intravenous solution
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.
Applicant Proposed Dosing Regimen(s)	30 mg/week
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	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.
Recommended Dosing Regimen(s) (if applicable)	30 mg/week

1. Introduction

This is a resubmission of NDA 211970 for golodirsen, proposed 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 submission is in response to the Complete Response (CR) letter issued by the Office of Drug Evaluation I (ODE I) on August 19, 2019, and to the Appeal Granted letter issued by the Office of New Drugs (OND) on November 22, 2019.

This submission contains proposed prescribing information, previously submitted, negotiated, and agreed upon with the Division of Neurology Products during the original review of the application, that includes updates to the Warnings and Precautions section for monitoring of renal function. Additionally, the submission contains the following information.

- Safety update
- Summary description of proposed activities related to education regarding indwelling ports
- Confirmatory study commitment letter
- Resubmission of previously negotiated PMRs
- Consumer and healthcare professional materials amended to reflect renal monitoring recommendations and education for line infections
- Resubmission of previously negotiated carton and container labeling
- Proprietary name resubmission

2. Background

The applicant initially submitted a new drug application for golodirsen for the treatment of Duchenne muscular dystrophy (DMD) in patients with a confirmed DMD mutation amenable to exon 53 skipping on December 19, 2018. The submission contained biomarker and safety data from Study 4053-101, a first-in-human, multicenter, dose-titration study to assess the safety, tolerability, efficacy, and pharmacokinetics of once-weekly intravenous infusions of golodirsen in 25 patients with a mutation in the DMD gene amenable to exon 53 skipping. Additional safety data were provided by an interim analysis of unblinded safety data from an ongoing randomized, double-blind, placebo-controlled Phase 3 study (4045-301).

Review of the data in Study 4053-101 showed that there was a mean increase in truncated dystrophin quantification by western blot relative dystrophin levels from 0.10% of normal at baseline to 1.02% after 48-59 weeks of treatment with golodirsen, with a mean change from baseline of 0.92%. The change in dystrophin level, albeit small, has a high level of statistical persuasiveness ($p<0.001$). The most frequent adverse events observed with golodirsen were mild and included headache, pyrexia, and gastrointestinal symptoms. Based on these data, the Division recommended approval of the application.

A CR letter was issued by Dr. Ellis Unger, Director, ODE I, on August 19, 2019. In the CR letter, Dr. Unger cited two safety issues as the basis for the CR: 1) infections related to vascular access; and 2) renal toxicity. The renal toxicity concerns were based on findings in nonclinical studies. Glomerulonephritis has also been reported with other antisense oligonucleotides. Although Dr. Unger noted that there was no clear evidence of renal toxicity in the clinical development program, there were only a small number of DMD patients exposed to golodirsen in the program and it may not have been adequate to detect a signal. Additionally, Dr. Unger noted that because creatinine levels may not be a reliable measure of renal function in DMD patients, "there is no proven way to monitor renal function in these patients, there is no way to provide adequate instructions for use in labeling." The risk for infections related to vascular access was predominantly identified in the eteplirsen program, a drug with a mechanism of action similar to golodirsen that is approved for the treatment of DMD in patients with an exon-51 skippable mutation. Dr. Unger states in the CR letter that given the small change in dystrophin of 0.9%, "this small benefit, which has not been verified, does not outweigh its risks."

The applicant submitted a Formal Dispute Resolution Request on September 13, 2019.

An Appeal Granted letter was issued by Dr. Peter Stein, Director, OND, on November 22, 2019. In the Appeal Granted letter, Dr. Stein concluded that clinically meaningful benefits "are reasonably likely to be seen with golodirsen, consistent with evidence on the effects of low levels of dystrophin (vs. complete absence)." Dr. Stein concluded that monitoring of renal function in DMD patients was feasible with serial monitoring of measures of renal function. He noted that all patients should have a baseline direct GFR measured prior to initiation of therapy with golodirsen. Regarding the use of ports for vascular access, Dr. Stein felt that this must be considered related to the use of the drug and should be considered in the risk-benefit balance for golodirsen.

Dr. Stein concluded that the applicant should resubmit the application for golodirsen and that it could be approved, provided the following requirements were met:

"Based upon the above considerations, the company should re-submit their application as a complete response to the FDA August 19, 2019 CR letter, including updated labeling that contains recommendations for renal monitoring, considering the points I have raised above (including further consideration as to how best to monitor urine protein, the need for a baseline direct GFR measurement, and reference in labeling to use of renal tubular injury markers if appropriate). In order to address the deficiencies outlined in the CR letter, the company may reference this FDR decision letter. Once labeling language and post-marketing requirements are discussed with and agreed upon by the Division, the FDA will approve the application for golodirsen. In addition, given the important risks associated with indwelling intravascular port infections, minimizing this risk is important in assuring a positive benefit risk balance. Therefore, the company should provide support and education for patients receiving golodirsen to minimize the use of indwelling intravascular ports, and, where needed, assure appropriate

management… I request that the company provide a written commitment, prior to approval of golodirsen, that if the results of the confirmatory study do not support a clinical benefit (i.e., no relevant analyses finds sufficient evidence of such a benefit), that they will voluntarily withdraw golodirsen from the market".

3. Review of Submission

3.1 Safety Update

The applicant provided an update of clinical safety findings since the last data lock point (DLP) for the NDA 120-day safety update on October 26, 2018. Since that time, three additional patients have been treated, with an approximate additional 59 patient-years of observation since the DLP. There were 5 reports of serious adverse events that did not appear to be related to golodirsen (influenza, fracture, hypoxia). There was one report of proteinuria on urinalysis that was still blinded; the event was reported as trace proteinuria that was transient. There were no line-related infections. Other adverse events were consistent with those already described in the prescribing information.

No new safety issues have been identified since the initial NDA review.

3.2 Renal Monitoring

The applicant has added a proposal for renal monitoring to Section 5.2 Warnings and Precautions for Renal Toxicity. The applicant proposes the measurement of glomerular filtration rate (GFR) by 24-hour urine collection prior to initiation of therapy, consistent with Dr. Stein's recommendation. Routine monitoring with a monthly urinalysis and measurement of serum cystatin C is recommended, with follow-up of any positive assessments, defined as 2+ proteinuria or elevated serum cystatin C, with a 24-hour urine collection to quantify proteinuria and assess GFR. The applicant proposes that these assessments are the most reliable for the DMD population, since they do not rely on measurement of creatinine, and the use of other biomarkers in the DMD population have not been established. The applicant maintains that this monitoring is adequate for screening for glomerulonephritis or decline in renal function.

The applicant's proposal for renal monitoring appears to be adequate.

3.3 Study Commitment Letter

The applicant has provided a letter with the following commitment, consistent with Dr. Stein's request:

"If it is concluded that the results of the confirmatory study do not support a clinical benefit (i. e., no relevant analyses find sufficient evidence of such a benefit), Sarepta Therapeutics will voluntarily withdraw golodirsen from the market."

3.4 Educational materials

The applicant has submitted a proposal to educate patients/caregivers about the care of ports through the SareptaAssist program. The applicant submitted a copy of the patient brochure "Getting Started" and has included a section on the use of ports. The applicant also proposes to educate healthcare providers regarding ports through its team of Educations Support Managers (ESM). The ESMs utilize the Dosing and Administration Guide (the Guide) to facilitate their in-service education for healthcare providers. This document has been revised to state that it is important to follow that manufacturer's instructions for infusions devices to minimize the potential for infection.

The applicant's proposed education plan is adequate to address the risk of line infections.

4. Labeling

See the final negotiated product label. Labeling negotiations with the applicant have been completed and the applicant has accepted all recommended changes.

5. Postmarketing Recommendations

The post-marketing requirements (PMRs) and timelines had previously been negotiated with the applicant during the original review of the application. The PMRs and timelines were confirmed with the applicant.

The Division of Risk Management (DRISK) concluded that a risk evaluation and mitigation strategy (REMS) is not necessary for golodirsen.

6. Risk-Benefit Assessment

As discussed in the Division's original summary memorandum, the dystrophin biomarker data are proposed by the applicant as a surrogate endpoint that is reasonably likely to predict a clinical benefit, in support of the approval of golodirsen under the accelerated approval pathway. Golodirsen has a novel mechanism of action that has a well-understood relationship to the disease pathophysiology, and is the first drug that has been shown to increase dystrophin levels in DMD patients with a genetic mutation amenable to exon 53 skipping. 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. A confirmatory study intended to confirm clinical benefit is ongoing.

Safety concerns regarding the potential for renal toxicity and line/port infections were raised during the ODE I review. Although renal toxicity has not been observed in the clinical development program, monitoring of renal function is prudent given the nonclinical findings with golodirsen and findings of glomerulonephritis seen with other antisense oligonucleotides. The applicant has proposed an acceptable renal monitoring plan for DMD patients, given the limitations of using creatinine measurements and the lack of established renal biomarkers in this population. The risk of line/port infections cannot be entirely avoided, but the applicant's proposed educational plan may help to minimize the risk of infections. Overall, the risk minimization efforts appear adequate and support an acceptable risk/benefit profile of golodirsen for the treatment of DMD patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping.

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/s/

TERESA J BURACCHIO
12/12/2019 04:36:22 PM

ERIC P BASTINGS
12/12/2019 04:42:49 PM

WILLIAM H Dunn
12/12/2019 04:43:14 PM

Summary Memorandum

Date	August 16, 2019
From	Teresa Buracchio, M.D. Eric Bastings, M.D.
Subject	Summary Memorandum
NDA/BLA # and Supplement#	211970
Applicant	Sarepta
Date of Submission	December 19, 2018
PDUFA Goal Date	August 19, 2019
Proprietary Name	Vyondys 53
Established or Proper Name	Golodirsen
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1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Duchenne muscular dystrophy (DMD) is a rare progressive X-linked neuromuscular disorder caused by mutations in the dystrophin gene. Lack of dystrophin results in degeneration of muscle fibers, inflammation, and ultimately replacement of muscle by fibrotic and adipose tissue. The disease causes progressive and profound muscle weakness and degeneration. Muscle weakness typically begins between ages 3 to 5 years, with loss of ambulation usually occurring by 12 years of age. Death typically occurs before age 30 years, generally from respiratory and/or cardiac muscle involvement. The disease prevalence is estimated to be 1.4 per 10,000 males ages 5 to 24 years.

Golodirsen is an antisense oligonucleotide (ASO) of the phosphorodiamidate morpholino oligomer (PMO) subclass that was designed to target premessenger ribonucleic acid (mRNA) in the nucleus of a cell to alter the splicing process that creates a mature mRNA. Golodirsen targets 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 35-60 minutes.

There are two FDA-approved treatments for DMD. Deflazacort (Emflaza) 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 (Exondys 51) received a biomarker-based accelerated approval in September 2016, for the treatment of a subset of DMD patients with mutations in the dystrophin gene that are amenable to exon 51 skipping. This approval was based on the demonstration of increases in truncated dystrophin protein; the clinical benefit of these changes has not been established.

This submission contains biomarker and safety data from Study 4053-101, a first-in-human, multicenter, dose-titration study to assess the safety, tolerability, efficacy, and pharmacokinetics of once-weekly intravenous infusions of golodirsen in 25 patients with a mutation in the DMD gene amenable to exon 53 skipping. Additional safety data is provided by an interim analysis of unblinded safety data from an ongoing randomized, double-blind, placebo-controlled Phase 3 study (4045-301).

Truncated dystrophin quantification by western blot in Study 4053-101 showed a mean increase in relative dystrophin levels from 0.10% of normal at baseline to 1.02% after 48-59 weeks of treatment with golodirsen, with a mean change from baseline of 0.92%. The change in dystrophin level, albeit small, has a high level of statistical persuasiveness ($p<0.001$). Performance on the 6-minute walk test and pulmonary function tests, with at least 144 weeks of follow-up, showed a decrease from baseline; however, these results are not interpretable in the absence of a control group.

The dystrophin biomarker data are proposed by the applicant as a surrogate endpoint that is reasonably likely to predict a clinical benefit, in support of the approval of golodirsen under the accelerated approval pathway. The accelerated approval pathway is appropriate for golodirsen because DMD is clearly a serious and life-threatening disease, and golodirsen has the potential to address an unmet medical need and provide an advantage over available therapy (deflazacort) in some patients. Deflazacort has a modest response rate, and there is evidence that a substantial proportion of DMD patients are not using steroids, in part because of their safety profile. Golodirsen has a novel mechanism of action that has a well-understood relationship to the disease

pathophysiology, and is the first drug that has been shown to increase dystrophin levels in DMD patients with a genetic mutation amenable to exon 53 skipping, thereby potentially improving muscle function. 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. A confirmatory study intended to confirm clinical benefit is ongoing.

Although limited in size, the safety database is adequate to support the safety of golodirsen for a rare condition such as DMD. Overall, the most frequent adverse events observed with golodirsen were mild, and included headache, pyrexia, and gastrointestinal symptoms. Kidney is a well-known target organ for ASOs, and golodirsen is primarily distributed to the kidney. Renal toxicity was the primary toxicity observed in nonclinical studies, and nonclinical data suggest the potential for serious renal toxicity in humans. No serious renal adverse reaction, however, was reported in golodirsen clinical studies. The seriousness of the indication along with the unmet medical need make the risk for renal toxicity acceptable, and manageable through labeling and enhanced pharmacovigilance. Hypersensitivity reactions have been identified and should be described as a warning/precaution in the label. PMRs should be issued for assessments of QT prolongation (see Section 5) and immunogenicity.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• DMD is a rare progressive X-linked neuromuscular disorder caused by mutations in the dystrophin gene. Lack of dystrophin results in degeneration of muscle fibers, inflammation, and ultimately replacement of muscle by fibrotic and adipose tissue. • The disease causes progressive and profound muscle weakness and degeneration. Muscle weakness typically begins between ages 3 to 5 years, with loss of ambulation usually occurring by 12 years of age. Death typically occurs before age 30 years, generally from respiratory and/or cardiac muscle involvement. The disease prevalence is estimated to be 1.4 per 10,000 males ages 5 to 24 years.	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	• 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 DMD gene that is amenable to exon 51 skipping.	Deflazacort, the only drug with full approval for the treatment of DMD, has a modest response rate, and there is evidence that a substantial proportion of DMD patients are not using steroids, in part because of their safety profile. There are no therapies targeted to mutations amenable to exon-53 skipping.
Benefit	• Truncated dystrophin quantification by western blot showed a mean increase in dystrophin levels from 0.10% of normal at baseline to 1.02% after 48-59 weeks of treatment with golodirsen. The mean change from baseline in dystrophin level, 0.92%, is highly statistically significant ($p<0.001$). The median change from baseline in dystrophin level was 0.88%. • Exon 53 skipping was confirmed by measurement and sequence verification of exon 53 skipped mRNA. There was an increase in exon 53 skipping in all patient samples, with individual increase from baseline ranging from 2.5% to 37.3% (mean 16.4%; nominal $p<0.001$). • Performance on the 6-minute walk test and pulmonary function tests, with at least 144 weeks of follow-up, showed a decline from baseline; however, these results are not interpretable in the absence of a control group.	The applicant has demonstrated a small, but statistically significant increase in de novo (truncated) dystrophin protein in DMD patients with a genetic mutation amenable to exon 53 skipping. 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.
Risk and Risk Management	• At the time of the NDA submission, there were 58 patients exposed to golodirsen, with 35 patients with >48 weeks of exposure, and 23 patients with >120 weeks of exposure. • The most common adverse reactions (incidence ≥25% and higher than	Overall, the most frequent adverse events observed with golodirsen were mild; none caused substantial or permanent harm to patients. Headache, pyrexia, gastrointestinal symptoms are

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	placebo) were headache, pyrexia, cough, vomiting, abdominal pain, nasopharyngitis, and nausea. • Hypersensitivity reactions, including rash, pyrexia, pruritus, urticaria, dermatitis, and skin exfoliation have occurred in patients treated with golodirsen. • Renal toxicity was the primary toxicity observed in nonclinical studies, and nonclinical data suggest the potential for serious renal toxicity in humans. However, no serious renal adverse reaction or worrisome renal abnormalities were observed in clinical studies. • There is also a risk of infection and other complications related to the indwelling catheters that may be used to administer golodirsen, but this risk is not specific to golodirsen. • There is inadequate data to assess the potential for QT prolongation and immunogenicity.	the most common adverse events. Nonclinical studies indicate a potential for serious renal toxicity in humans, but no serious renal adverse reaction have been observed in human. The seriousness of the indication, along with the unmet medical need, make the risk for serious renal toxicity acceptable. It will be important to inform patients and prescribers about the risk, and a warning regarding the potential for renal toxicity will be included in labeling. Enhanced pharmacovigilance for renal toxicity should also be requested. Hypersensitivity reactions have occurred in patients who were treated in patients treated with golodirsen, and the risk of hypersensitivity reactions should be described in section 5 of labeling (Warnings and Precautions). Because of limitations due to the small number of patients exposed and duration of exposure in the clinical trials, it is likely that adverse reactions not identified to date, or of a magnitude not observed to date, will occur in the postmarketing setting. Risk management can be achieved through clear product labeling and routine postmarketing surveillance, plus enhanced pharmacovigilance for renal toxicity and rhabdomyolysis. The applicant should be required to assess the immunogenicity of golodirsen and evaluate the potential for QT prolongation as post-marketing requirements.

2. Background

This application provides dystrophin biomarker data proposed as a surrogate endpoint that is reasonably likely to predict clinical benefit in support of the accelerated approval of golodirsen for the treatment of Duchenne muscular dystrophy (DMD) in patients with a confirmed DMD mutation amenable to exon 53 skipping. Golodirsen is a new molecular entity (NME) and has not previously been the subject of any marketing application.

Golodirsen (also referred to as SRP-4053 in this memorandum) is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) subclass that was designed to target premessenger ribonucleic acid (mRNA) in the nucleus of a cell to alter the splicing process that creates a mature mRNA. Golodirsen targets 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 35-60 minutes.

There are two FDA-approved treatments for DMD. Deflazacort (Emflaza) received full approval in February 2017 for the treatment of DMD. Deflazacort is a glucocorticoid, a member of the corticosteroid class of medications, that is purported to have anti-inflammatory and immunosuppressive properties and has been shown to improve muscle strength in DMD patients. Eteplirsen (Exondys 51) received a biomarker-based accelerated approval in September 2016 for the treatment of a subset of DMD patients with mutations in the dystrophin gene that are amenable to exon 51 skipping. This approval was based on the demonstration of increases in truncated dystrophin protein; the clinical benefit of these changes has not been established and must be confirmed by a clinical study.

DMD is a rare progressive X-linked neuromuscular disorder caused by mutations in the dystrophin gene. Lack of dystrophin results in degeneration of muscle fibers, inflammation, and ultimately replacement of muscle by fibrotic and adipose tissue. The disease causes progressive and profound muscle weakness and degeneration. Muscle weakness typically begins between ages 3 to 5 years, with loss of ambulation usually occurring by 12 years of age. Death typically occurs before age 30 years, generally from respiratory and/or cardiac muscle involvement. The disease prevalence is estimated to be 1.4 per 10,000 males ages 5 to 24 years.[1]

This submission contains biomarker and safety data from Study 4053-101, a 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 4 to 30 mg/kg in 25 patients with a mutation in the DMD gene amenable to exon 53 skipping. Additional safety data are provided by an unblinded interim analysis from an ongoing randomized, double-blind, placebo-controlled Phase 3 study (4045-301).

[1] Romitti et al. Pediatrics. 2015; 135. https://pediatrics.aappublications.org/content/135/3/513

A detailed summary of the regulatory history of golodirsen is provided in the combined clinical and statistical review.

3. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Martha Heimann. Dr. Heimann's review lists the entire OPQ team that was involved with the review of this application.

Golodirsen injection is a sterile, preservative-free solution for intravenous infusion. It is supplied as single-dose vials containing 100 mg golodirsen per 2 mL phosphate-buffered saline. The proposed dose of golodirsen is 30 mg/kg administered by IV infusion once per week. The product must be diluted in saline prior to use.

The OPQ team has determined that golodirsen drug substance is adequately characterized by standard analytical methods (UV, HRMS, Molecular Sequencing, HPLC, 1H, 13C and 31P NMR) that are used for oligonucleotide-based therapeutics. The specifications for golodirsen drug substance include appropriate tests and acceptance criteria for critical quality attributes (CQAs) that include appearance, identification (monotopic mass and sequencing), assay, purity, and related substances (IP-HPLC), residual solvents, water content, residue on ignition, pH, bacterial endotoxins and microbial limits. Process impurities are adequately characterized and their limits in the drug substance specifications are qualified in nonclinical studies.

The manufacturing process and in-process controls are adequately described and deemed suitable for commercial production. The analytical procedures are adequately validated and suitable for their intended use.

There were no outstanding issues identified in the OPQ review, and all manufacturing facilities for this product were found to be acceptable. OPQ recommends approval of this NDA. Please refer to the OPQ review for details of the product quality assessment.

4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer for this application was Dr. Barbara Wilcox, with Dr. Lois Freed performing a secondary review.

Dr. Wilcox concludes that the application is approvable from a pharmacology/toxicology standpoint. Dr. Freed notes a few notable differences between golodirsen and eteplirsen, an antisense oligonucleotide (ASO) that received accelerated approval for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. Dr. Freed emphasizes that any comparison between golodirsen and eteplirsen is limited by several factors: they were not tested in the same studies, a 26-week toxicity study in mouse was not conducted for eteplirsen, and there were differences in the dosing regimen used for golodirsen and eteplirsen. Dr. Freed however observes that in monkey, eteplirsen (for 12 or

39 weeks) resulted in tubular basophilia, vacuolation, and basophilic granules at the highest dose tested; renal tubular basophilia, dilatation, degeneration (minimal-slight), and mononuclear inflammation were observed in the high-dose recovery group in the 39-week study. Therefore, the pattern of microscopic renal changes in monkey differed between golodirsen and eteplirsen (e.g., golodirsen resulted in a wider distribution of toxicity in kidney, and only eteplirsen resulted in degeneration) but were generally of similar severity. Dr. Freed also observes that the most notable difference between golodirsen and eteplirsen was in the juvenile rat study. 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 (300 mg/kg) and high doses. When eteplirsen was administered at the same doses (0, 100, 300, or 900 mg/kg) weekly by IV injection during the same postnatal period, there were no deaths or drug-related clinical signs. Dr. Freed notes that microscopic changes in kidney were observed, which were correlated with changes in clinical pathology markers of renal function (e.g., increased BUN, creatinine, and Pi). However, eteplirsen had no effect on urinary bladder/ureter, and no instance of the severe renal impairment or renal failure that was observed with golodirsen.

Based on the available data in juvenile rat, Dr. Freed estimates 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, which need to be taken into consideration, Dr. Freed notes that rat is considered a relevant species for human. Dr. Freed adds that at the recommended human dose of 30 mg/kg, plasma exposure is only 2.6-fold lower than that at the no-adverse-effect-level in the most sensitive species (juvenile rat).

Dr. Freed concludes that 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. Dr. Freed notes that as previously agreed to by the division, carcinogenicity studies in two species may be conducted post-approval (as PMRs), based on the seriousness of the indication.

5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) review was written by Drs. Bilal AbuAsal (the primary reviewer), Hobart Rogers, Atul Bhattaram, Christian Grimstein, and Sreedharan Sabarinath (the clinical pharmacology team lead). The final signatory for the OCP review was Dr. Ramana Uppoor.

Table 1 below summarizes the key findings of the OCP review with respect to the pharmacologic and clinical pharmacokinetic (PK) properties of golodirsen.

Table 1: Summary of OCP Review Findings

Mechanism of Action	Golodirsen is designed 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 truncated dystrophin protein.
Absorption	Golodirsen is administered intravenously and bioavailability is assumed to be 100%. Median Tmax was approximately 1 hour (end of infusion).
Distribution	The mean golodirsen steady-state volume of distribution was 668 mL/kg at a dose of 30 mg/kg. Golodirsen plasma protein binding ranged from 33% to 39% and is not concentration dependent.
Metabolism and Elimination	Data from in vitro metabolism and ADME studies indicate that golodirsen is metabolically stable and is mostly excreted unchanged in urine. No metabolites were detected in plasma or urine. Golodirsen elimination half-life (SD) was 3.5 (0.6) hours, and plasma clearance was 346 mL/hr/kg at the 30 mg/kg dose.
Renal Impairment	In non-DMD subjects with stage 2 chronic kidney disease (CKD) (creatinine clearance ≥ 60 and < 90 mL/min/1.73 m2), golodirsen AUC increased approximately 1.2-fold and Cmax was unchanged. In subjects with stage 3 CKD (creatinine clearance ≥ 30 and < 60 mL/min/1.73/m2), the AUC and Cmax increased approximately 1.9-fold and 1.2-fold, respectively. Creatinine clearance is not considered as a reliable metric to characterize renal function in the DMD population because the disease affects muscle tissue. Therefore, no dose-adjustment recommendations based on creatinine clearance can be provided for golodirsen. However, patients with known renal function impairment should be closely monitored during treatment with golodirsen.
Hepatic Impairment	Golodirsen is primarily excreted in urine unchanged. Hepatic metabolism is not expected to affect the exposure of golodirsen. Therefore, no dose adjustment is needed in patients with hepatic impairment.
Drug Interactions	In vitro assessments suggest that golodirsen has low potential for drug-drug interactions with CYP enzymes and drug transporters.
QT Prolongation	There is insufficient information to assess the effects of golodirsen on QT prolongation.

Dosing Regimen:
The recommended dose of golodirsen is 30 milligrams per kg administered by IV infusion once weekly over 35 to 60 minutes.

Genetic mutations:
Of the eight deletion mutations (42-52, 45-52, 47-52, 48-52, 49-52, 50-52, 52, 54-58) amenable to exon 53 skipping, only five (45-52, 48-52, 49-52, 50-52, 52) were enrolled in the clinical studies with golodirsen. It is reasonable to conclude that the restoration of the reading frame by golodirsen should be beneficial for all DMD mutations amenable to exon 53 skipping. Hence, the OCP team recommends that golodirsen should be indicated for patients with any of the mutations amenable to exon 53 skipping.

QT prolongation:
The applicant submitted a request for a waiver for a QT study. The QT-IRT determined that there is not adequate information to assess the effects of golodirsen on QT prolongation. The ongoing confirmatory trial (Study 4045-301) is collecting additional ECG assessments. The QT-IRT team recommends that a new request for QT waiver be submitted once these data are available.

OCP recommends approval of this application.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical - Efficacy

Dr. Chris Breder was the clinical reviewer for this application. Dr. Xiang Ling was the biometrics reviewer, and Dr. Kun Jin was the biometrics team lead. Dr. Baikuntha Aryal and Dr. Ashutosh Rao (lead) from the Office of Biotechnology Products (OBP) reviewed the dystrophin assays.

Study 4053-101 was a first-in-human clinical trial and was conducted in Europe and the United States to assess the safety, tolerability, efficacy, and PK of once-weekly 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. Part 1 was a double-blind, placebo-controlled, dose-finding study. Patients were randomized to receive either a weekly IV infusion of placebo (n=4) or golodirsen (n=8) 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, which is still ongoing, is a 168-week open-label study to assess biomarker and clinical outcomes. All 12 treated patients from Part 1 continued in Part 2. Part 2 also enrolled 13 new patients with a deletion amenable to exon 53 skipping for open-label treatment with golodirsen. Additionally, Part 2 enrolled 14 untreated subjects with DMD not amenable to exon 53 skipping but who otherwise met study enrollment criteria. The applicant indicated that the untreated population was intended to provide natural history data for patients who were not amenable to exon 53 skipping and was not intended to serve as a control group for golodirsen; therefore, this untreated cohort will not be discussed further in this memorandum.

The study enrolled male patients aged 6 to 15 years, inclusive, with an 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), taking a stable dose of corticosteroids for at least 24 weeks, stable cardiac and pulmonary status, and the ability to walk a mean distance of ≥250 meters at both the Screening and Baseline visits. Patients also had to have either a North Star Ambulatory Assessment (NSAA) total score >17 or rise (Gowers') time <7 seconds.

The primary biological endpoint for Part 2 of the study was the change from Baseline to Week 48 of Part 2 in dystrophin levels (in biceps muscle biopsy samples) determined by western blot. For patients enrolled in Part 1 and continuing into Part 2, muscle biopsies were collected at the Baseline visit (pretreatment) of Part 1 and at Week 48 of Part 2. For de novo Part 2 patients, muscle biopsies were collected at the Baseline (pretreatment) visit of Part 2 and at Week 48 of Part 2. 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 (exon skipping assessments, western blot, and immunohistochemistry [IHC] analysis). All samples were analyzed at once, as they were allocated. Personnel performing the assays were blinded to treatment status (pre-treatment vs. on-treatment).

Secondary biological endpoints for Part 2 of the study include the change from Baseline to Week 48 for the following:

- Dystrophin intensity levels determined by IHC
- Percent dystrophin-positive fibers as determined by IHC
- Exon 53 skipping determined by measurement and sequence verification of exon 53 skipped mRNA

Several additional assessments were collected as secondary endpoints, including the 6MWT, forced vital capacity percent predicted (FVC%p), maximum inspiratory pressure percent predicted, maximum expiratory pressure percent predicted, NSAA, muscle magnetic resonance imaging (MRI), and assessments of upper limb function.

Data Quality and Integrity

OBP reviewed the assays used to analyze the muscle biopsies and determined that the western blot method was appropriately validated and conducted to reliably measure relative dystrophin content in the patient samples. The IHC analysis using MuscleMap algorithm had significant problems due to high fluctuations in background staining that resulted in inconsistent values for dystrophin intensity. No significant issues were identified with the RT-PCR method. Both western blot and RT-PCR method are semi-quantitative in nature, but combined information from both methods may be used to measure and compare dystrophin patient responses to treatment with golodirsen.

Statistical Analysis

For each time point (Baseline vs. Week 48 of Part 2), replicate gel runs were performed to determine dystrophin level (% normal) by western blot. The average of replicate values from

available gel runs were used in the analyses. In the case of only one available gel result, that value was used in the analyses. Imputation methods were specified for assay results outside of the limits of quantification.

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

No adjustment was made for the testing of multiple endpoints.

Patient Demographics
The golodirsen-treated population (n=25) had the following characteristics: mean age of 8.4 years (range 6 to 13), 92% White, mean duration of disease of 56 months (range 16 to 122), mean duration of corticosteroid use of 35 months (range 9 to 98), with 48% taking deflazacort and 52% taking prednisone.

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 safety review was conducted by an independent DSMB, these 12 patients were rolled into Part 2 of the study. In Part 2, these 12 patients, and 13 new patients amenable to exon 53 skipping, received open-label treatment with golodirsen. The total golodirsen group (n=25) was defined as patients who received golodirsen in any part of the study. As of the submission cutoff date of June 29, 2018, 23 of the 25 patients (92%) in the total golodirsen group were ongoing in the study. Two patients (8%) withdrew from the study during Part 2, with "patient decision" as the reported reason.

Results

Primary endpoint
A statistically significant increase in dystrophin was observed with once-weekly IV golodirsen, from a baseline of 0.10% of normal dystrophin levels to 1.02% of normal at Part 2 Week 48, based on western blot (Table 2). The average increase in dystrophin level was 0.92% of normal, and the median increase was 0.88% of normal. The level of dystrophin protein at Week 48 of Part 2 ranged from 0.09% to 4.30% of normal, including 18 patients with values above the lower limit of quantification (LLOQ) of 0.25%. The distribution of changes in dystrophin from baseline is shown in Figure 1. An analysis of dystrophin levels versus duration of golodirsen treatment showed minimal correlation. These results were verified by the FDA biometrics and clinical reviewers.

Table 2: Dystrophin Levels Determined by Western Blot in Study 4053-101

	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.

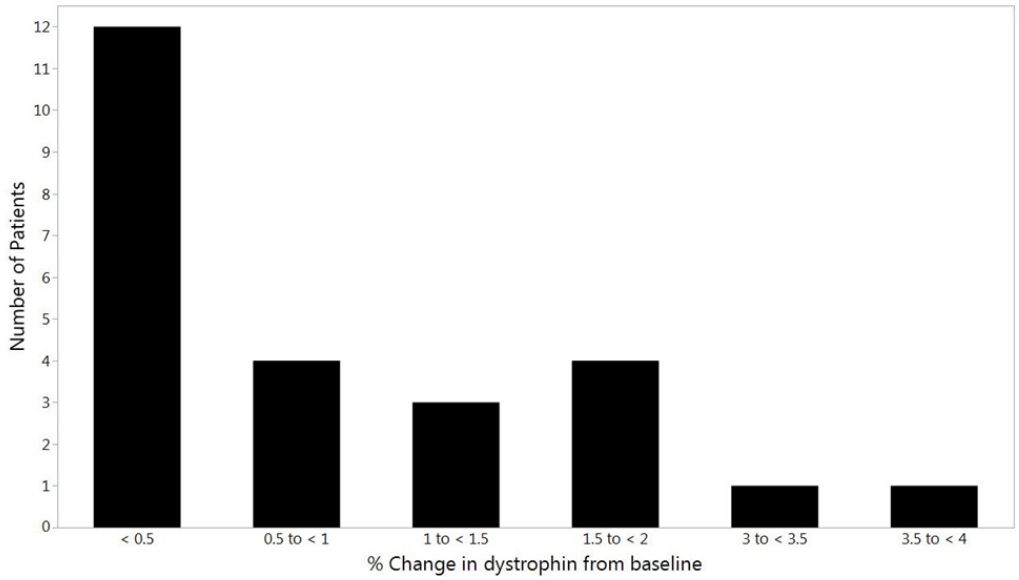
[c] Exclusion of 2 samples with discrepant protein concentration values resulted in a mean of 0.996% (SR-17-044 DEV-0023).

[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, page 78.

Figure 1. Distribution of Change from Baseline to Week 48 in Percent Dystrophin in Study 4053-101



Source: Analysis by clinical reviewer, Dr. Breder.

Secondary endpoints

- Dystrophin intensity levels determined by IHC
- Percent dystrophin-positive fibers as determined by IHC

As discussed above, the IHC analysis using the MuscleMap algorithm had significant problems due to high fluctuations in background staining. While the data provide qualitative confirmation of dystrophin localization at the sarcolemmal boundary, OBP does not recommend that the IHC datasets be used to draw any quantitative conclusions regarding drug effect. release

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

The analytical results provided by the applicant show an increase in exon 53 skipping in all patient samples, with individual percent increase from baseline in exon 53 skipping ranging from 2.5% to 37.3%. The mean percent increase from baseline for all 25 patients was 16.4% ($p<0.001$). Based on Dr. Breder's analysis of the data, the median change from baseline in percent skipping is 13.5%.

- Clinical outcomes

There were observed declines on the 6MWT and the FVC%p. Changes in these outcomes cannot be interpreted in the absence of a control group.

Efficacy Conclusions

There is no disagreement among the review team that a statistically significant increase in dystrophin after golodirsen treatment has been rigorously established. Dr. Breder, however, recommends a complete response action. Dr. Breder notes that "there is not sufficient knowledge to know how much "dystrophin" would be needed to represent a meaningful benefit". Further, Dr. Breder notes that "the product resulting from golodirsen treatment is not the natural protein, so it is not known if it functions to the same degree". Dr. Breder acknowledges a comment made to the applicant during the development program that [*…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.*] Dr. Breder further states that [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.] There is, however, no clear relationship between the statement from Dr. Fleming and the quoted statement from the review division to the applicant, as the division's comment related to the number of studies needed to support approval (i.e., single-study approval vs. independent substantiation from more than one study), and not to the type of endpoint used (surrogate or other). The statistical persuasiveness of the study results, and support from secondary endpoints (e.g., RT-PCR) make reliance on a single study entirely appropriate, and replication in a new study unnecessary. Dr. Breder also bases his recommendation on the fact 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." That argument is not valid, as the timing of clinical studies is not relevant in the scientific judgment as to whether a surrogate marker is reasonably likely - or not- to predict clinical benefit.

The accelerated approval provisions of FDASIA in section 506(c) of the FD&C Act provide that FDA may grant accelerated approval to: . . . a product for a serious or life-threatening disease or condition . . . upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. We will review the efficacy results in the context of these criteria for accelerated approval.

DMD clearly meets the criteria of a serious and life-threatening condition.

There are currently two drugs approved for the treatment of DMD: eteplirsen, and deflazacort. The indication for eteplirsen is for patients who have a confirmed mutation of the DMD gene

that is amenable to exon 51 skipping, i.e., a population distinct from that proposed for golodirsen. Deflazacort is indicated for a broad DMD population, irrespective of genetic mutation. However, deflazacort has a modest response rate, and there is evidence that a substantial proportion of DMD patients are not using steroids, in part because of their safety profile. As described in the Guidance for Industry: Expedited Programs for Serious Conditions Drugs and Biologics,[2] a drug may address an unmet need where there is available therapy, if "a drug with a novel mechanism of action (but comparable safety and effectiveness) could have the potential to provide an advantage over available therapy in some patients. In such a case, the novel mechanism of action should have a well-understood relationship to the disease pathophysiology. In addition, there should be a reasonable basis for concluding that a significant number of patients may respond differently to the new drug compared with available therapy." The role of dystrophin is well-characterized in the pathophysiology of DMD. Golodirsen has a novel mechanism of action of skipping exon 53 in the dystrophin gene, leading to increased production of truncated dystrophin, with the potential to improve muscle function. While a clinical benefit remains to be confirmed, the safety of golodirsen does not appear worse than that of steroids.

Additionally, the expedited programs guidance describes that benefit compared to existing therapy can be demonstrated when a drug is used "in combination with available therapy (i.e., as demonstrated in an add-on study)". In the clinical study, all patients were taking background therapy with steroids, including deflazacort. Therefore, golodirsen offers the potential to provide a benefit additional to that of steroids.

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.

The confirmatory randomized, double-blind, placebo-controlled study (Study 4045-301 - ESSENCE) intended to confirm clinical benefit is ongoing.

[2] https://www.fda.gov/media/86377/download

8. Safety

Dr. Breder conducted the safety review of this application.

Study 4053-101 and 4045-301 are the primary sources of safety data. Study 4053-101 was described in Section 7. Study 4045-301 is an ongoing randomized, double-blind, 3-arm placebo-controlled efficacy and safety study in DMD patients with genotypically confirmed out-of-frame deletions amenable to exon 45 or 53 skipping. In that study, patients with mutations amenable to exon 53 skipping are randomized to golodirsen or placebo, and patients with mutations amenable to exon 45 skipping are randomized to casimersen (an investigational PMO) or placebo. The applicant submitted interim unblinded safety data from 50 patients enrolled in Study 301 (33 treated with golodirsen and 17 treated with placebo) to support the safety analyses in the application.

Dr. Breders's review indicates that a total of 58 DMD patients were exposed to golodirsen at the time of the NDA submission, and 60 DMD patients were exposed at the time of the 120-day safety update. At the time of the NDA submission, there were 52 patients with >24 weeks months of exposure, 35 patients with >48 weeks of exposure, and 23 patients with >120 weeks of exposure. All patients were exposed to the 30 mg/kg dose of golodirsen that is proposed for marketing. The safety database is adequate in the context of a rare disease such as DMD.

Dr. Breder reviewed the coding of the adverse event terms in the submission and aggregated similar terms for the safety analyses. Please refer to Dr. Breder's review for a description of his aggregation and disaggregation methods.

The following are the principal conclusions of Dr. Breders's safety review of the application:

Deaths. No deaths occurred in the golodirsen clinical development program.

Discontinuations. No patient in the golodirsen clinical development program discontinued study treatment due to a treatment-emergent adverse event (TEAE).

Serious Adverse Events. Ten patients experienced a serious adverse event in the golodirsen clinical development program. Pyrexia and fracture were the only adverse events that occurred in more than one patient.

All Adverse Events (serious plus non-serious). For the analysis of incidence of TEAEs, Dr. Breder analyzed the pooled controlled study populations from Part 1 of Study 4053-101 and from Study 4045-301 (interim data). The most frequently occurring adverse events (>5% and greater than placebo) are presented in Table 3 below.

Table 3: Treatment-Emergent Adverse Events with an Incidence Greater Than Placebo and Risk Difference Greater than or Equal to Five Percent from Part 1 of Study 4053-101 and Study 4045-301 (interim data)

Adverse Reaction	Golodirsen (N = 41) %	Placebo (N = 21) %
Headache	41	10
Pyrexia	41	14
Abdominal pain	27	10
Administration site pain	17	0
Nasopharyngitis	27	14
Back pain	17	5
Pain	17	5
Fall	29	19
Nausea	20	10
Dizziness	15	5
Cough	27	19
Vomiting	27	19
Ligament sprain	12	5
Ear infection	7	0
Seasonal allergy	7	0
Tachycardia	7	0

Source: Analysis by clinical reviewer, Dr. Breder.

Laboratory and clinical assessments and vital signs. Dr. Breder evaluated the clinical laboratory assessments for mean change and for outliers by treatment and visit. Analyses of markers of renal injury are discussed below under adverse events of interest. No other findings regarding laboratory values, vital signs, or electrocardiograms (ECGs) were identified as being of clinical concern. See Section 5 for a discussion of the QT assessment.

Adverse Events of Interest

Infusion related reactions/Hypersensitivity Reactions. The applicant defined infusion-related reactions as adverse events occurring within 24 hours after infusion start times. Dr. Breder reviewed adverse events under this criterion with incidence 2% greater than placebo and with more than one event reported, and identified events of headache, back pain, hyperhidrosis, and nausea. Dr. Breder also reviewed broader standard MEDDRA queries (SMQs) for hypersensitivity and other hypersensitivity-related reactions. With this analysis, Dr. Breder identified additional hypersensitivity-related adverse events, such as pyrexia, cough, myalgia, and dermatitis. These events were generally mild, but some did require clinical intervention. Dr. Breder feels that the infusion-related events are more appropriately grouped with other hypersensitivity-related terms and he recommends that they be included as a warning in the label for “hypersensitivity reactions.”

Renal adverse events. Kidney is a well-known target organ for ASOs, and golodirsen is primarily distributed to the kidney and excreted intact in urine following parenteral administration. As renal toxicity was identified as a potential risk in nonclinical studies, Dr. Breder reviewed SMQs for renal events. Three cases of transient proteinuria were identified in the review in the controlled studies and open-label extension. All were reported to be mild, transient, and not leading to study drug discontinuation. There were no adverse events reported related to renal impairment.

Because creatinine values may not be informative in DMD patients due to muscle pathology, Dr. Breder performed an analysis of other renal biomarkers (e.g., BUN, Cystatin C, and Kim-1). Transient increases in BUN were noted but there were no values higher than the upper limit of normal. As nonclinical studies identified a risk for serious renal toxicity in human, that risk should be described as a warning in labeling, and renal adverse events should be monitored with enhanced pharmacovigilance.

Rhabdomyolysis. A serious event of rhabdomyolysis was identified during the review. The case occurred in a 7-year-old patient who received golodirsen for 11 days prior to the event. The patient was reported to be more active than usual and had several falls prior to the onset of the event. Golodirsen treatment was interrupted and the event resolved. The patient had subsequent transient events of increased blood creatine phosphokinase (Day 32) and myalgia (Day 83), but golodirsen dosing was not changed.

As rhabdomyolysis is not uncommon in DMD patients, it is challenging to attribute this case to golodirsen. Given the seriousness of the case, rhabdomyolysis should be monitored with enhanced pharmacovigilance.

Immunogenicity
At the pre-NDA meeting, it was agreed that the applicant would provide anti-dystrophin antibody data with the 120-day safety update and anti-golodirsen antibody data as a PMR. Due to ongoing assay validation issues, the applicant was not able to provide anti-dystrophin antibody data during the review cycle. The immunogenicity review team provided feedback to the applicant on assay validation during the review. Immunogenicity assessments should be required as a PMR.

Safety conclusions
The safety experience with golodirsen supports an acceptable risk/benefit profile. Overall, the most frequent adverse events observed with golodirsen were mild, including headache, pyrexia, and gastrointestinal symptoms. Hypersensitivity reactions have been identified and will be described as a warning/precaution in the label. Renal toxicity was the primary toxicity observed in nonclinical studies, and nonclinical data suggest the potential for serious renal toxicity in humans. No serious renal adverse reaction, however, was reported in golodirsen clinical studies. The seriousness of the indication along with the unmet medical need make the risk for renal toxicity acceptable, and manageable through labeling (as a warning) and enhanced pharmacovigilance. Additionally, although not observed in the safety database for this submission, it is noted that there is also a possible risk of infection and other

complications related to the indwelling catheters that may be used to administer golodirsen. This risk, however, is not specific to golodirsen.

PMRs should be issued for assessments of QT prolongation (see Section 5) and immunogenicity.

9. Advisory Committee Meeting

This application was not referred for review to an advisory committee because the safety profile of golodirsen is acceptable for the intended population, the clinical trial designs were acceptable, and the findings on the surrogate marker were clear.

10. Pediatrics

This application contains pediatric data described in Sections 7 and 8. Pediatric Research Equity Act (PREA) requirements were not triggered for this orphan indication.

11. Other Relevant Regulatory Issues

No Good Clinical Practice (GCP) issues were identified in Dr. Breder's review.

Dr. Breder concludes that the applicant has adequately disclosed financial interests and arrangements with clinical investigators.

Inspections were performed by the Office of Scientific Investigations (OSI) for clinical sites and the Office of Study Integrity and Surveillance (OSIS) for bioanalytical issues. OSI noted that there were inspectional observations at the clinical investigator sites and applicant's site; however, these findings were felt to be unlikely to have a significant impact on overall study results. OSI determined that the study data generated are acceptable and may be used in support of this NDA. OSIS determined that bioanalytical data are reliable to support a regulatory decision.

The Controlled Substance Staff (CSS) determined that there was no abuse potential of golodirsen prior to the NDA submission.

12. Labeling

Please refer to the final negotiated product label. Labeling negotiations with the applicant have been completed and the applicant has accepted all recommended changes.

13. Postmarketing Recommendations

The Division of Risk Management (DRISK) reviewer for the application was Lindsey Crist, who concluded that a risk evaluation and mitigation strategy (REMS) is not necessary for golodirsen.

The following will be postmarketing requirements:

- In order to verify the clinical benefit of golodirsen, complete Study 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.
- Submit ECG data from Study 4045-301 to support your request to waive a thorough QT study. If these data do not support a TQT study waiver, you will need to evaluate the effect of golodirsen on the QTc interval in a dedicated study as per the ICH E14 guideline.
- A study to evaluate patient immune responses, including IgM and IgG isotypes to dystrophin among patients treated with golodirsen in Study 4053-101 of the clinical development program.
- A study to evaluate patient immune responses, to golodirsen among patients treated with golodirsen in Study 4053-101 of the clinical development program.
- Evaluate the immunogenicity of golodirsen-induced truncated dystrophin protein.
- A 26-week carcinogenicity study of golodirsen, administered by a clinically relevant route, in an appropriate transgenic mouse model.
- A two-year carcinogenicity study of intravenously administered golodirsen in rat.

14. Recommended Comments to the Applicant

None.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TERESA J BURACCHIO
08/19/2019 09:17:52 AM

ERIC P BASTINGS
08/19/2019 09:25:10 AM