CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 211970

APPEAL GRANTED

Sarepta Therapeutics, Inc.
Attention: Patrick O'Malley
Executive Director, Regulatory Affairs
215 First Street, Suite 415
Cambridge, MA 02142

Dear Mr. O'Malley:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for golodirsen.

I also refer to your September 13, 2019, request for formal dispute resolution received on September 13, 2019. The appeal concerned the August 19, 2019 Complete Response (CR) letter issued by Ellis Unger, MD, Director, Office of Drug Evaluation (ODE) I.

I also refer to the meeting held between FDA and Sarepta on October 17, 2019, where the issues raised in your request for formal dispute resolution were discussed.

I also acknowledge receipt of the requested additional clarifying information on October 24, 2019.

I have carefully reviewed the materials you submitted in support of your appeal, as well as reviews, meeting minutes, and the CR letter.

I have completed my review of your request for formal dispute resolution and grant your appeal. I describe below the basis for my decision.

I will not discuss the background on Duchenne's muscular dystrophy (DMD) or golodirsen's mechanism of action in any detail, as these are both discussed in numerous prior FDA reviews; briefly, DMD is a rare X-linked neuromuscular disease that results in progressive weakness, and respiratory compromise, and is ultimately and nearly uniformly fatal. The deficiency in dystrophin in patients with DMD is caused by frameshifting deletions, duplications, or nonsense mutations that cause complete or nearly complete loss of dystrophin or non-functional versions of dystrophin proteins. Golodirsen is an exon-skipping antisense oligonucleotide (ASO) that can treat a series of amenable mutations in Exon 53. The Company conducted a study (Study 4053-101), submitted in the NDA, that evaluated the pharmacodynamic activity of golodirsen based upon dystrophin levels in patients with DMD with amenable mutations.

Regarding the increase in dystrophin seen in Study 4053-101, the CR letter from the ODE I concludes that "if there is indeed a clinical effect of golodirsen, the effect size is small." The

letter acknowledges that the prior accelerated approval of eteplirsen establishes a precedent for the use of increased dystrophin levels as a "reasonably likely" surrogate endpoint to predict benefit in patients with DMD. However, the letter notes that "…if a mean increase in dystrophin of 9 parts per thousand is construed to be reasonably likely to predict clinical benefit, the clinical benefit would surely be, at most, very small." With regard to the approval decision for eteplirsen, the letter observes that eteplirsen had a very benign safety profile, with minimal risks identified. As a result, according to the CR letter "…eteplirsen's benefit – no matter how tiny and unverified – was weighed against essentially no risk." In contrast, ODE I determined that there were relevant safety concerns for golodirsen, discussed further below, with no expectation of greater benefit than was observed for eteplirsen, resulting in an unfavorable benefit risk balance.

ODE I raised two safety issues pertinent to golodirsen, renal toxicity and indwelling intravascular port infections; neither of these were considered as risks for eteplirsen at the time of that drug's approval. I will discuss both of these issues in more detail later in this document. In addition to these safety concerns, the CR letter notes that the post-approval confirmatory trial for eteplirsen has not been initiated, pointing out that demonstration of benefit of eteplirsen may not, therefore, occur in the foreseeable future. I will return to the issue of the timeline for the post-approval confirmatory trial, as it is an important consideration in my assessment of the benefit risk balance of golodirsen.

The CR letter concludes that "because of the risks of serious infection and renal toxicity, the most expeditious route to approval would be to provide substantial evidence of a clinical benefit on physical function/performance…through completion of the placebo-controlled study. It would also be necessary to develop a practicable renal monitoring paradigm to allow mitigation of the renal risk. Finally, if the drug could be administered without implantation of an indwelling port, the benefit-risk profile could be improved."

In summary, with safety concerns identified for golodirsen, and an expectation of a "small" benefit, ODE I concluded that the benefit risk balance for golodirsen was unfavorable, and therefore determined that a CR action was appropriate.

The company's appeal letter responds to the issues raised in the CR, describing four points of disagreement: first, the company argues that it is not correct to conclude that the small increase in dystrophin would result in only a "commensurately small" clinical benefit, and suggesting the potential for a more substantive benefit to be obtained; second, the company argues that the CR letter overstates the risk associated with the use of implanted intravenous infusion ports; third, the company argues that renal risk is also overstated, that a large margin exists between the exposure leading to the non-clinical findings and the clinical exposure, and also that effective renal monitoring can be implemented; and fourth, the company argues that the CR letter does not recognize "the therapeutic context" in which the drug would be used; that is, that the patients who would receive golodirsen are in dire need of additional treatments. Based upon these arguments, the Company requests that the ODE I decision to take a CR action for the golodirsen NDA be reversed and the drug approved.

I will address the issues raised in the CR and the responses to these issues in the Company's FDRR letter in some detail, and then discuss my assessment of the benefit risk balance of golodirsen. I will begin by reviewing the potential for clinical benefit, then discuss the two safety concerns raised in the CR letter, and finally discuss my benefit risk assessment considering both the "therapeutic context", as the company refers to the setting for this drug, and also the role of the confirmatory study in contributing to the benefit risk balance of golodirsen.

First, with regard to the potential for clinical benefit, it seems evident that golodirsen treatment will not provide marked improvements in strength and survival given the extent of dystrophin increase observed, described below. However, I do not agree that the magnitude of benefit to be obtained would necessarily be "very small" if by that is meant providing only minimal improvement in muscle function of only marginal clinical importance to patients with DMD. I will approach my assessment of this issue from both a regulatory policy perspective, and, importantly, from a scientific perspective.

As a regulatory matter, an approval using a surrogate endpoint indicates that a clinical benefit is considered reasonably likely. A clinical benefit is a positive therapeutic effect that is *clinically meaningful* in the context of a given disease, meaning that a non-clinically meaningful therapeutic effect would not support an approval decision. An approval determination, even for a drug with no apparent safety risks, requires that clinical benefit is either demonstrated (for traditional approval) *or* is considered reasonably likely (for accelerated approval). A trivial or "very small" benefit, one that is of minimal relevance to patients, would not be sufficient for either accelerated or full approval, regardless of the safety profile of the drug. Thus, the implication of the accelerated approval of eteplirsen is that the increment in dystrophin observed was considered reasonably likely to predict a clinical benefit. The potential benefit of golodirsen must be considered in light of the prior approval of eteplirsen. I recognize that the approval determination for eteplirsen was highly controversial, with many reasonable scientists not supportive of the decision. Nonetheless, from a regulatory perspective, this precedent establishes that FDA considered the change in dystrophin to be reasonably likely to provide a clinical benefit for a serious and life-limiting disease with substantial unmet need. And, it is against such a benefit that any risks of the drug under consideration must be weighed.

From a scientific perspective, I also do not concur with ODE I's assessment that the extent of benefit would be, necessarily, "very small". As I will review below, the complicated biological role of dystrophin in muscle and our limited knowledge of what "threshold" increase in dystrophin increases muscle strength, as well as the uncertainties related to the biopsy estimation of the increase in dystrophin, makes predicting the magnitude of improvement in function from the increase in dystrophin observed with golodirsen challenging. My conclusion is that although it has been convincingly demonstrated that golodirsen increases muscle dystrophin levels, the clinical impact of the observed increase is not readily predictable and cannot be concluded to be only minimal.

Further, it is important to consider whether meaningful benefit is likely to accrue across the entire treated population (reflected by the study population mean response) or might be observed in a subset of patients, perhaps related to particular genotypes or to other susceptibility factors,

who may obtain a larger dystrophin and clinical response to this drug. If golodirsen does provide benefit in a subset of patients, a biomarker or clinical measure may ultimately be able to identify such responders and allow the drug to be used in a more targeted manner, thereby avoiding long-term treatment in non-responders. The confirmatory trial may shed light on this issue (for example by correlating responses to genotype or other baseline characteristics), which could further enhance the benefit risk balance for this drug.

With regard to interpreting the impact of the observed increase in dystrophin, although a generally linear relationship between increased dystrophin and improved muscle function has been observed in animal models and in the clinical setting, as noted above, the *threshold* for the level of dystrophin above which meaningful improvement in muscle function may be seen is not predictable. There are also uncertainties regarding the interpretation of results observed from the single on-treatment biopsy conducted in Study 4053-101 at 48 weeks, which further limit the interpretation of the dystrophin results.

To consider the extent of benefit that may result from an increase in dystrophin, some background on the role of this protein in muscle function is relevant. Skeletal muscle is a highly organized tissue with actin-containing fine filaments and myosin-containing thick filaments arranged longitudinally as myofibrils. The myofibrils are connected to the sarcolemma by subsarcolemmal complexes called costameres that transmit contractile forces from sarcomeres of one myofiber to another—thereby preventing sarcolemmal rupture by synchronizing contraction of the myofibers. Dystrophin is a 427-kD submembrane rod-shaped protein with four functional domains incorporated into a large macromolecular complex of proteins (the dystrophin-glycoprotein complex [DGC]). This protein complex localizes to the inner surface of the sarcolemma where there is a high abundance of costameres. One domain of dystrophin connects with F-actin, and other domains interact with other proteins of the DGC. In addition to dystrophin, this protein complex includes syntropins, dystrobrevin, neuronal nitric oxide synthase (NOS; activation of which produces NO, which, in turn, increases vascular flow during contraction), transmembrane proteins (dystroglycan, sarcoglycan, and sarcospan), and extracellular proteins (dystroglycan and laminin-2). The DGC connects the intracellular cytoskeleton, including the myofibrils, to the sarcolemma and to the basement membrane. The integrity of this complex is essential for myofibers to withstand mechanical stress from the contracting actin-myosin complex fibrils and prevent sarcolemma damage and resulting cellular degeneration (Rahimov F, Kunkel LM. Journal of Cell Biology 201(4):499-510, 2013; Batchelor CL, Winder SJ. Trends in Cell Biology 16:198-205, 2006; Wallace GQ, McNally EM. Ann Rev of Physiol 71:37-57, 2009).

As noted, DGC also serves in an integrative and signaling role. Loss of dystrophin results in decreased activation of neuronal NOS resulting in diminished NO generation and reduced vasodilation during contraction. In turn this renders cells more susceptible to ischemia and injury. Dystrophin deficiency also leads to microtubular disorganization and dysregulation of calcium homeostasis resulting in sustained calcium influx from the sarcolemma likely contributing to myofibril damage. Further, the DGC is associated with multiple signaling pathways including CaM kinase II, PI-3 kinase, and MAP kinase. The role of these various signaling cascades is less well defined, but they appear to regulate intracellular homeostasis.

Since the DGC serves both structural and homeostatic functions, the relationship between dystrophin and muscle function may be complicated, with both dystrophin level and proportion of fibers with dystrophin expression relevant.

Severe DMD is usually associated with nearly complete loss of dystrophin (reported as < 3% and usually < 1%). Given the deficiency in this protein, many therapeutic strategies, as is the case with golodirsen, have been focused on increasing muscle dystrophin content. A number of studies have attempted to provide insight on the relationship between dystrophin content and disease severity. I will briefly review some of this literature, as it relates to the potential for clinical benefit from relatively low dystrophin levels.

I will start with information derived from studies in animal models with a genetically determined dystrophin deficiency. In a study of a mouse strain with low (~5%) dystrophin, investigators reported increased muscle strength and improved survival relative to mice with no dystrophin expression (Li D, Yue Y, Dongsheng D. Amer J of Pathology 172: 133201341, 2008; Li D, Yue Y, Duan D. PLoS 5: e15286, 2010). Another study (van Putten M, Hulskar M, et al. The FASEB J. 27: 2484-2495, 2013) examined mice with variable expression of dystrophin, attempting to relate the extent of dystrophin with survival and muscle strength. These investigators compared mice with absent dystrophin to animals on the same background strain with variable dystrophin levels (ranging from 3 to 16.2%). Notably, even animals with < 4% dystrophin had prolonged survival relative to mice that expressed no dystrophin. In addition, animals with low but measurable dystrophin expression (< 4%) had substantially greater strength (hanging time) on the 2-limb and 4-limb hanging test than mice with no dystrophin expression, but less than animals with higher dystrophin expression: 298 s, 71 s, and 404 s, respectively, for 2-limb hang time. A similar pattern was reported for the 4-limb hanging wire test and for a forelimb grip strength test. In a study of exon-skipping ASOs in a rodent model of muscular dystrophy, the mdx mouse (Sharp PS, et al. Mol Therapy 19:165-171, 2011), a generally linear reduction in contraction-induced injury was observed with a threshold of approximately 20% percent positive dystrophin fibers; however, there was no clear relationship seen between the improvement in dystrophin and improvement in specific force. Another study of the ASO administration in dystrophin deficient mice showed improvements in muscle resistance to eccentric contractions with dystrophin expression in approximately 25% of muscles (Malerba A, Sharp PS, et al. Mol Therapy 19: 345-354, 2011).

How these rodent models of genetic deficiency and of application of an ASO (with dystrophin assays of unknown accuracy) translate to the clinical setting with golodirsen treatment is not clear. Nonetheless, the studies in knock-out animals suggest that low levels of dystrophin (<4%) relative to complete dystrophin deficiency may improve function and survival, and the ASO studies suggest that modestly increased proportion of fibers staining with dystrophin can provide improved muscle function.

Clinical data addressing this question are limited. Neri et al (2007) examined 4 patients with X-linked dilated cardiomyopathy, a disorder associated with reduced dystrophin production in skeletal muscle and predominant loss of dystrophin protein in the heart. The 4 patients had dystrophin content in their skeletal muscle ranging from 29 to 40% of control muscles. All four

patients had normal neuromuscular examinations, with muscle biopsies that showed minimal to mild myopathic changes. Consistent with this observation, patients with Becker's muscular dystrophy (BMD), a milder form of muscular dystrophy with later onset and longer survival, have dystrophin levels that are often in the 30% range, with dystrophin both quantitatively abnormally low and abnormally truncated. Hoffman et al (Ann Neuro, 1989) characterized disease progression and muscle function in patients with DMD or BMD, and noted that patients could be placed into several categories: DMD patients who have < 3% dystrophin and typically become wheelchair bound by about 11 years of age; severe BMD patients who have dystrophin levels in the 3-10% range and typically require a wheelchair in the 13-20 year age range; moderate to mild BMD patients who have dystrophin levels of ≥ 20% and typically require a wheelchair only after age 20 years. Finally, in a study looking at the natural history of DMD patients with different specific mutations, a mutation that has been associated with slight expression of dystrophin was observed to have a longer time to loss of ambulation (Bello et al. Neurology 87:1-9, 2016).

Whether increased dystrophin levels and increased percentage of fibers expressing dystrophin with ASO treatment provide the same (or less or more) muscle function relative to the same pattern of dystrophin present in the context of genetic deficiency states is unknown. Another variable is the nature of the truncated protein expressed with exon-skipping ASOs. I will not go into this in detail, except to note that there is evidence both from preclinical animal models and clinical settings (e.g., BMD), that truncated dystrophin can be functional. Nonetheless, the impact of the various truncated dystrophins that may be seen with golodirsen (based upon the specific genotype of the patient treated) may differ in functional outcomes. In summary, there appears to be a generally linear relationship between dystrophin content in muscle (amount and percentage of fibers) and muscle strength. Studies examining what "threshold" level of dystrophin is required suggest that even low expression and distribution across fibers may lead to detectable increases in muscle strength, but the threshold for such increases in strength in humans is unknown.

With this background, I will briefly review the results of the clinical study of golodirsen intended to support the accelerated approval and discuss some of the uncertainties associated with the muscle biopsy results from this study.

Study 4053-101 is a Phase 1/2 trial in patients with DMD age 6 to 15 years, with a genetic defect amendable to exon 53 skipping (patients with a range of deletions were eligible to participate). Patients had to have a baseline 6-minute walk test distance achieved of ≥ 250 meters, a North Star Ambulatory Assessment score of > 17 or a rise time of < 7 seconds, and be on a stable dose of corticosteroids. In Part 1, 12 patients were randomized (1:2) to placebo or to rising doses of golodirsen, with weekly intravenous administration of golodirsen starting at 4 mg/kg and increasing to 30 mg/kg. In Part 2, patients from Part 1 continued on their randomized treatment (so those on golodirsen continued at 30 mg/kg) and 13 additional patients were entered (overall 17 patients received golodirsen and 8 patients received placebo). All patients underwent a muscle biopsy pre-randomization and again at Week 48 to assess dystrophin levels and distribution in muscle; a range of other procedures to assess strength, respiratory and cardiac function were performed at intervals during the treatment period.

The results of the muscle biopsy showed a marked *relative* increase in dystrophin, but a small *absolute* increase, rising from a mean value of 0.095% at baseline to 1.019% at Week 48. There was, however, a relatively wide distribution of increases in dystrophin observed, with some patients having no discernible or a minimal increase and others (approximately 25%) having increases to the 1.5-2% or higher range, with the highest responses in the range of 3.5-4.5%. An assessment of the proportion of fibers with positive dystrophin was performed using intensity of dystrophin staining of slices of muscle tissue. This assessment was confounded by technical issues, limiting the accuracy of the results. The company attempted to make corrections to provide an estimate of percent dystrophin positive fibers (PDPF) but results from these analyses must be viewed as only estimates of the response. The sponsor reports that baseline PDPF was 2.6% and the Week 48 response was 15.1%. Similar to the results of dystrophin levels, a subset of patients had PDPF in the 20-40% or greater range. As ODE I points out, in the 4053-101 study, there was no associated clinical improvements observed (e.g., in 6-minute walk test), nor a relationship between change in walk test distance and change in dystrophin. However, the study was underpowered to detect improvements or even a relationship between these endpoints, especially given the high variability in change from baseline in the 6-minute walk test. Although this study does not provide direct support for clinical benefit of golodirsen, the lack of such a finding suggests that improvements in muscle strength, if eventually demonstrated with golodirsen treatment, are unlikely to be marked (and therefore would not be expected to be detectable in a small number of patients as in Study 4053-101).

There are a number of limitations that must be considered in interpreting the biopsy results. The biopsy reflects the response from a single muscle type at one timepoint. In animal studies of ASO treatment, there were substantial differences in dystrophin response in different muscles (Alter J, Lou F et al. Nature Medicine 12: 175-178, 2005). Such differences would seem likely to be present in the clinical response to ASO treatment related to differences in ASO uptake or response to ASO based upon such factors as muscle size, vascularization, and fiber type, among other factors. Further, the biopsy was taken in a two-week window period after the dose was administered; the time course of increased translation of the truncated dystrophin is unknown, so whether biopsies performed earlier post-dosing may have had different dystrophin responses is unknown, although dystrophin, once expressed, would not be expected to turnover rapidly.

As noted above, the critical question that remains unanswered is the “threshold” of dystrophin above which a clinical response would be observed and below which no discernible response would be detected. Although golodirsen increases dystrophin levels and increases the proportion of muscles expressing dystrophin, the magnitude of muscle strength improvement that will be observed with these changes is not predictable. However, despite the uncertainties regarding threshold and interpretation of biopsy results, I do not agree that the improvements in muscle strength would be minimal or “very small”. Even if large changes in muscle strength are unlikely, modest improvements in hand or leg muscle strength, or diaphragmatic strength that lead to improvements (or delay losses) in hand coordination or grip strength, or in ambulation, or in respiratory function, or in other important muscle functions, would be meaningful to patients, and are reasonably likely to be seen with golodirsen, consistent with evidence on the effects of low levels of dystrophin (vs complete absence), discussed above.

As is evident from the above discussion, there remains uncertainty regarding the increment in dystrophin that would translate to increased muscle strength resulting in clinical benefit in patients with DMD. As I have indicated, my assessment is that the animal model and human data support a conclusion that modest increases in dystrophin are reasonably likely to provide a meaningful benefit with regard to increasing muscle strength in patients with DMD, although this benefit may largely accrue to patients with the greater increases in dystrophin. Therefore, I have concluded, and consistent with the regulatory precedent from eteplirsen, that the increase in dystrophin observed in Study 4053-101 with golodirsen treatment is reasonably likely to predict clinical benefit.

Since I agree with ODE I that a marked increase in strength would be unexpected, important safety risks with golodirsen treatment could still result in an unfavorable benefit to risk balance. In the next sections, I will discuss in detail the renal risk, and approach to monitoring renal function, and the risks related to indwelling ports.

As noted in the CR letter, the preclinical toxicology studies of golodirsen show that this drug is associated with kidney injury with a no observed adverse effect level (NOAEL) that is only several-fold above the clinical exposure in the most sensitive species. The CR letter states that monitoring renal function is not practicable in patients with DMD, with no established methods to assure appropriate detection of injury, raising the risk of progressive, undetected renal impairment during use of golodirsen. As I will discuss below, I do not agree with this conclusion.

Preclinical toxicology studies were conducted in mice, rats (mature and juvenile) and in cynomolgus monkeys. In rodent models, prominent renal toxicity was observed that was dose-related, with tubular degeneration observed, and renal failure leading to death, particularly noted in mouse and juvenile rate toxicology studies. Histopathology at the low dose showed mild tubular degeneration in 1/32 animals and mild vacuolation in 18/32, with notably more severe renal injury seen at the higher doses. At this low dose, C_{max} was 595 µg/mL and AUC was 338 µg-hr/mL, and 2260 µg/mL and 1080 µg-hr/mL at the mid-dose, relative to a C_{max} of 56.6 µg/mL and an AUC of 94.8 µg-hr/mL at the 30 mg/kg dose in clinical study 4053-101, described above. Thus, there was evidence of slight renal toxicity (at the low dose) at an exposure of about 3 to 4-fold above the clinical AUC (and about 10-fold above the C_{max}), and marked renal toxicity at approximately 10-fold above the AUC and 20-fold above the C_{max}. Studies in the mouse showed generally similar patterns of renal injury (largely tubular degeneration and regeneration) and at similar exposures.

In cynomolgus monkeys, renal toxicity was similar in pattern but was observed only at higher exposures than in rodent models. Doses of 80, 200, and 400 mg/kg were evaluated in a 9-month cynomolgus monkey toxicology study. The low dose was considered the NOAEL based upon renal toxicity, with a C_{max} of 571 µg/mL and an AUC of 836 µg-hr/mL, exposures that were 8 to 10-fold above clinical exposures at the planned dose (30 mg/kg). Findings related to potential tubular injury (tubular dilation, vacuolation) were assessed as minimal at 200 mg/kg and mild at 400 mg/kg, a dose also associated with renal mononuclear cell infiltration. At 200 mg/kg dose,

the C_{max} was 1250 µg/mL and the AUC was 1620 µg-hr/mL; thus, approximately 20-fold above the clinical exposures at the 30 mg/kg dose in the clinical study 4053-101.

Notably, in rodents and cynomolgus monkey toxicology studies, increases in urea nitrogen, creatinine, and the urinary protein/creatinine ratio correlated with the extent of histological renal injury.

The toxicology review concluded that "the pivotal nonclinical studies indicate that severe renal impairment (including irreversible renal damage in the juvenile animals) can result from chronic exposure to golodirsen, with only a small margin based upon exposure. However, because kidney function is monitorable, the nonclinical data are considered adequate to support approval of golodirsen for the treatment of patients with DMD…." It is notable that although the pattern of injury (tubular) was similar, the primate species (cynomolgus monkeys) was several-fold less sensitive to the toxicity than seen in the rodent studies. Nonetheless, since it is not established which species better predicts human risk, the appropriate approach is to consider the NOAEL based upon the most sensitive species.

As noted, the CR letter raised the concern that kidney function is not readily monitorable in patients with DMD based upon their reduced muscle mass and resulting low serum creatinine. The CR letter goes on to state that "cystatin C, kidney injury molecule-1 (KIM-1), and the urinary protein/creatinine ratio have been mentioned as monitorable parameters; however, none of the details have actually been worked out, and accordingly, no practicable proposals for renal monitoring have been proposed." The review comments, appropriately, that the draft labeling from the Company noted the limitations of serum creatinine but failed to advise physicians of appropriate means to monitor renal function. The CR letter concludes that "because there is no established way of monitoring renal function in this patient population, practitioners could be blind to worsening renal function, leaving these patients vulnerable. At this juncture, therefore, there is no way to provide adequate instructions for use in labeling."

There are several issues relevant to monitoring for renal injury in patients with DMD that I will review in the paragraphs below. However, it is worth noting that the clinical studies have not, to date, observed a signal for renal injury associated with golodirsen, nor has a signal been observed in IND safety reports from the ongoing confirmatory trial of golodirsen.

Although serum creatinine levels are lower in patients with DMD, serum creatinine remains measurable, as seen from the baseline levels in the 4053-101 study. Serum creatinine-based eGFR overestimates direct measurements of GFR in individuals with low muscle mass, such as patients with DMD. However, since monitoring of renal function focuses on *changes* from baseline in serum creatinine (or eGFR), rather than the absolute creatinine value, assessing serum creatinine changes over time should still prove useful to monitor renal function in DMD patients. Usual laboratory assay variability in serum creatinine (+/- 0. 2 mg/dL in most laboratories) will create more "false positive" rises in creatinine, given the low baseline values. Nonetheless, repeat determinations and observations over time should still permit this to be a useful measurement to detect renal injury when combined with urine protein/creatinine ratio and cystatin C, discussed below. Another issue is the loss of muscle mass, and therefore creatinine

production, over time in patients with DMD. This raises the possibility of failing to detect progressive renal impairment due to the "opposing" trends of reduced creatinine production—that would lower serum creatinine—and falling GFR—that would increase serum creatinine. Although I would expect decreases in muscle mass to be very gradual, over many years, this emphasizes the importance of using a panel of available renal status measures to monitor renal function in these patients.

Turning to cystatin C, there are a number of studies that have reported on the utility of this measure in patients with DMD. I will briefly review this literature below, as well as the current recommendations on settings where cystatin C may be useful for renal monitoring.

Cystatin C is a small (13.3 kDa) basic protein produced by all nucleated cells, not affected by lean tissue or muscle mass. The accuracy of cystatin C in estimating GFR in DMD patients was assessed by Braat et al (Braat E et al. Neuromuscular Disorders 25: 381-387, 2015) who showed that serum creatinine markedly overestimated eGFR, while, in contrast, cystatin C correlated well with directly measured GFR. Kimura et al (Kimura K et al. Int Heart J. 57: 386-388, 2016) also studied cystatin C-based estimations of GFR in two patients with moderate renal dysfunction and muscular dystrophy, compared to inulin clearance, and found good agreement in both patients (<20% difference with directly measured GFR using inulin clearance). Motoki (Motoki T, et al. Neuromuscular Disorders 25: 754-757, 2015) reported using cystatin C in 4 patients with DMD who had renal insufficiency all showing increases in serum creatinine that remained in the normal range (but with substantial increases above their baseline levels) and who had elevated cystatin C levels consistent with their degree of renal insufficiency. In a study of DMD patients (n=35) (Viollet L, Gailey S, et al. Muscle Nerve 49: 438-442, 2009), the cystatin C levels were comparable to non-DMD volunteers: 0.67 +/- 0.11 mg/L vs 0.69 +/-0.09 mg/L, respectively. Notably, in this study, corticosteroids did not alter the levels of cystatin C in patients receiving corticosteroids (0.69 vs 0.63 mg/L).

There is an extensive literature on the use of cystatin C to monitor renal function in non-DMD populations which should be directly applicable to patients with DMD requiring such monitoring. The literature suggests that cystatin C-based eGFR is generally comparable to serum creatinine-based measurements. Numerous studies have compared cystatin C to serum creatinine in detection of acute kidney injury in different settings such as during cardiac surgery, after radiological procedures with contrast dye, in acute emergency settings, and drug-associated nephrotoxicity. In addition, several trials have used cystatin C to monitor renal function in patients with DMD (Kirschner J et al. Lancet 9:1053-59, 2010; Raman SV et al. J Am Heart Assoc. 8:e103501, 2019). In Study 4035-101, baseline levels of cystatin C had a mean and distribution similar to that reported in the literature.

A recent review stated that "routine outpatient monitoring of cystatin C is not justified because measurement of serum creatinine is far less expensive and is recommended for following GFR in most cases. Thus, use of cystatin C has largely evolved to a "…role in instances where it is known that serum creatinine-based eGFRs are likely to be suboptimal." (Seegmiller JC, Eckfeldt JH, Lieske JC. Adv Chronic Kid Dis. 25: 84-92, 2018). Notably, in the 2012 KDIGO Clinical

Practice Guideline for the Evaluation and Management of Chronic Kidney Disease, the following recommendation is provided:

"4.4.2: Where precision is required for dosing….and/or estimates may be unreliable (e.g., due to *low muscle mass*), we recommend methods based upon cystatin C or direct measurement of GFR. (1C)." (italics added)

Thus, standard recommendations for the monitoring of patients guide physicians to the use of cystatin C in patients with low muscle mass, such as those with DMD. There is nothing about DMD that would suggest that cystatin C could not be applied to renal monitoring; there is no reason to believe that the literature on the use of cystatin C is not relevant to DMD: the KDIGO guideline recommendation is applicable in this setting.

Although serial serum creatinine and cystatin C measurements should provide effective monitoring of renal function, both measures have limitations in patients with DMD. For this reason, labeling should indicate that a baseline direct measurement of renal function (GFR) should be performed prior to initiation of golodirsen therapy. This will be important if there are uncertainties in the interpretation of renal function changes during treatment.

As noted above, in the non-clinical toxicology studies, in both rodent and NHP species, the urine protein to creatinine ratio correlated with histological renal injury. Thus, this may be another appropriate measure to employ in screening for kidney injury in patients treated with golodirsen. However, given the potential for low urine creatinine in DMD patients, additional efforts are needed by the company to determine if this test, or a timed collection of urine for protein (such as a 24-hour urine collection), would be appropriate to detect evidence of increased protein that would occur from tubular renal injury.

In addition to the measures I have outlined above to monitor renal function, I note that markers of tubular injury (e.g., urinary beta$_2$-microglobulin) have been clinically used, and are commercially available, to detect tubular injury in the setting of drugs with this risk and labeling should note that such measures may be useful during golodirsen treatment when uncertainty regarding renal injury is present.

In summary, I conclude that monitoring of renal function monitoring in DMD patients treated with golodirsen in clinical practice using a panel of standard, commercially-available measures of renal function (serum creatinine, cystatin C, and an assessment of urine protein) should appropriately detect events of renal injury. The use of renal tubular injury markers may also be advised when there is uncertainty regarding renal effects of golodirsen. All patients should have a baseline direct GFR measured prior to initiation of therapy with golodirsen.

The second safety issue raised in the CR letter relates to the risk of infections in indwelling intravascular ports. The letter noted that there were 11 FAERS reports of port infections among the 469 patients who have received eteplirsen, based upon the most recent PADER (7/17/2019). In reviewing these cases, among the 7 patients with a medical history provided, 4 of 7 had extensive, complicated medical histories (including respiratory failure, gastrointestinal tube placement, and concurrent cardiac disease); in 5 of 11, the port was considered as the primary

source of infection, and the source was confounded in the others. However, regardless of the exact incidence of port infections in patients treated with eteplirsen, it is clear that such infections will occur in patients who have an indwelling port for administration of golodirsen, if it is approved because there is no reason to expect that the incidence seen with the administration of golodirsen would be substantively different from other clinical settings where chronic intravenous therapy is used, except in patients with specific risk factors for infection (such as in chemotherapy induced neutropenia) where the incidence may be higher.

Based upon a response to my information request, the Company states that about half of patients using eteplirsen have chosen to use an indwelling port for drug administration. It may be possible to minimize, but not eliminate, the occurrence of these infections using several approaches. First, given the chronicity of drug administration (which may be over years), it may be reasonable to advise physicians to use peripheral intravenous administration of golodirsen as the preferred route, limiting use of ports to circumstances where peripheral administration is challenging, such as in patients distant from a physician's office receiving home-based drug dosing, or where peripheral venous access is difficult. Second, since health care providers administering golodirsen may not be versed in the use of indwelling intravascular ports (most often used by oncologists or infectious disease specialists), educational measures for both HCPs and for patients and families intended to enhance care and monitoring may reduce the risk of serious port infections.

Despite efforts to minimize use of ports and improve care of ports to reduce the risk of infection, such infections will occur, and must be considered related to the use of this drug; hence, this risk must be considered in the benefit risk balance for golodirsen.

For a rare, serious, life-threatening, and ultimately fatal disease such as DMD with no treatment, approving a drug several years in advance of when clinical benefit is demonstrated is consistent with the intent of accelerated approval. Moreover, as I discussed above, in such a progressive, ultimately fatal disease, a greater degree of uncertainty regarding the robustness of the "reasonably likely" surrogate endpoint may be acceptable. For a patient diagnosed with DMD, golodirsen could potentially be administered for many years or even decades. Such long-term treatment increases a patient's drug-related risks, including both the risk renal injury (since cumulative exposure may be relevant to renal risk, if such a risk exists) and the risk of port infection, since for any individual patient, the risk of experiencing such an infection is cumulative over time. For this reason, timely completion of a *robust* confirmatory trial mitigates a patient's risks by limiting the duration of exposure and thereby the cumulative exposure-related risks of the drug if it does not show an effect. A prolonged delay in *definitively* assessing the clinical benefit of golodirsen results in a less favorable benefit risk balance for patients using this drug, since it would mean the possibility of life-long exposure to an ineffective drug, with its attendant cumulative risks, and no clinical benefit.

Based upon the above considerations, at the face to face meeting with the Company, I raised the status of the proposed post-approval confirmatory study as a key issue. I asked the company the following questions: 1) what differences in endpoints assessing strength or ambulation or other important functions are considered clinically meaningful and how are these assessed? 2) how

well is the study powered to detect these meaningful differences? and, 3) if golodirsen were approved, would this study provide a definitive determination of whether clinical benefit was confirmed? I also requested an update on when the study would read out.

The company stated that the study was designed with extensive guidance from FDA (Division of Neurology Products) and included endpoints that were sufficiently powered (~90%) to detect relevant clinical benefits. The company also noted that the study was making good progress on recruitment, with 153 of the planned 222 subjects already randomized, and with a rate of enrollment of about 4 to 6 patients per month. The company noted that all US patients would complete participation in the study prior to US launch, if the drug is approved based upon this appeal response. The company expects completion of the study with read out of results in 2023. Even if the rate of patient accrual is half that anticipated, the estimate of trial completion in 2023-2024 is still achievable. Thus, if golodirsen is made available to patients in 2020, no patient would be on this drug for longer than about 3-4 years prior to the availability of the results of the confirmatory study.

In summary, my assessment is that study 4053-101 convincingly demonstrates that golodirsen increases skeletal muscle dystrophin levels and the percentage of muscle fibers with positive dystrophin staining. Patients with DMD are looking for improvement in muscle strength, even if only a modest increase in handgrip or arm strength, or respiratory muscle strength that might allow them some improvement in their ability to perform daily tasks, such as dressing or typing, or even reduce their time on mechanical ventilation. As I discussed above, the extent of increase in dystrophin varied in Study 4053-101, which suggests that clinically meaningful benefits may not be obtained in all treated patients, but may be seen in a subset of higher responders. Although the preclinical toxicology studies show a lower fold-margin from the NOAEL to clinical exposures for renal injury for golodirsen relative to eteplirsen, my assessment is that this is monitorable in the clinical practice setting. For patients who utilize indwelling ports for golodirsen administration, there is a risk of infection that is cumulative over time. However, since the occurrence of such infections can be reduced with appropriate management (including avoiding use of such ports, if possible), and managed with early detection and port removal, my assessment is that the benefit of meaningful improvement in muscle strength and function that may be obtained with golodirsen outweighs this manageable risk, such that the benefit risk balance of golodirsen is positive—with the understanding that a robust confirmatory study will be completed in a timely fashion so as to provide confirmation of benefit, or lead to withdrawal of this drug from the market.

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.

The company has committed to putting all reasonable efforts into the completion of the confirmatory study. In advance of the face to face meeting regarding this FDRR, I posed the question to the company: "if golodirsen was approved, would this study inform a definitive determination of whether clinical benefit was confirmed?" Their answer was in the affirmative, arguing persuasively that the study was designed and powered to identify a clinical benefit. Based upon this, 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.

This constitutes the final decision at the Office of New Drugs level. Any questions concerning your appeal should be addressed to Melissa Sage at 301-796-6449.

Sincerely,

{See appended electronic signature page}

Peter Stein, MD
Director
Office of New Drugs
Center for Drug Evaluation and Research

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/

PETER P STEIN
11/22/2019 03:15:47 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 119982

MEETING MINUTES

Sarepta Therapeutics, Inc.
Attention: Parnian Zia-Amirhosseini, Ph.D.
Executive Director, Regulatory Affairs
215 First Street, Suite 415
Cambridge, MA 02142

Dear Dr. Zia-Amirhosseini:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SRP-4053 (golodirsen).

We also refer to the meeting between representatives of your firm and the FDA on September 11, 2018. The purpose of the meeting was to discuss the format and content of your planned New Drug Application (NDA) for SRP-4053.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Fannie Choy, Regulatory Project Manager, at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Billy Dunn, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	September 11, 2018, 11:00 a.m. – 12:00 p.m.
Meeting Location:	FDA White Oak Building 22, Conference Room 1311
Application Number:	IND 119982
Product Name:	SRP-4053 (golodirsen)
Proposed Indication:	Treatment of Duchenne muscular dystrophy (DMD) in patients who have a mutation of the DMD gene that is amenable to exon 53 skipping
Sponsor/Applicant Name:	Sarepta Therapeutics, Inc.
Meeting Chair:	Billy Dunn, M.D.
Meeting Recorder:	Fannie Choy, R.Ph.

FDA ATTENDEES

Office of Drug Evaluation I
Ellis Unger, MD, Director

Division of Neurology Products
Billy Dunn, MD, Director
Nick Kozauer, MD, Associate Director
Teresa Buracchio, MD, Clinical Team Leader
Christopher Breder, MD, PhD, Clinical Reviewer
Annie Nguyen, RPh, Regulatory Project Manager
Fannie Choy, RPh, Regulatory Project Manager

Office of Biotechnology Products
Ashutosh Rao, PhD, Chief, Laboratory of Applied Biochemistry, Division of Biotechnology Review and Research III (DBRR III)
Baikuntha Aryal, PhD, Bioassay Reviewer, DBRR III
Zhenzhen Liu, PhD, Product Quality and Immunogenicity Reviewer, DBRR III

Division of Biometrics I
Kun Jin, PhD, Biometrics Team Leader
Xiang Ling, PhD, Statistical Reviewer

Office of Clinical Pharmacology
Hobart Rogers, PharmD, PhD, Genomics and Targeted Therapy Reviewer
Nan Zheng, PhD, QT-Interdisciplinary Review Team

Office of Surveillance and Epidemiology
Charlotte Jones, MD, PhD, MSPH, Reviewer, Division of Risk Management

SPONSOR ATTENDEES

Sarepta Therapeutics, Inc.
Gilmore O'Neill, MB, MMSc, Senior Vice President, Chief Medical Officer
Gary Charbonneau, MS, Senior Vice President, Regulatory Affairs
Paul Korner, MD, Vice President, Medical Strategy & Clinical Development
Parnian Zia-Amirhosseini, PhD, Executive Director, Regulatory Affairs
Lixin Han, PhD, Senior Director, Biometrics
Xiaodong Wang, Senior Director, Clinical Pharmacology
Diane Frank, PhD, Senior Director, Translational Development
Joseph Rutkowski, PhD, Senior Director, Nonclinical Development
Geno Clemenzi, Senior Director, Regulatory Affairs Operations
Vineet Sharma, Director, Statistical Programming

1.0 BACKGROUND

Sarepta Therapeutics, Inc., is developing golodirsen (SRP-4053), a phosphorodiamidate morpholino oligomer, for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a mutation of the DMD gene that is amenable to exon 53 skipping.

The Division provided written responses to the sponsor's pre-IND questions in March 2014. On February 6, 2018, a type C meeting was held to discuss the preliminary nonclinical and clinical pharmacodynamic data of golodirsen. The sponsor requested the Division's feedback regarding the appropriateness of a New Drug Application (NDA) submission for golodirsen to be considered under the accelerated approval pathway and the acceptability of Study 4045-301 (ESSENCE) as a confirmatory clinical study to support accelerated approval.

A CMC pre-submission meeting was scheduled on May 3, 2018. The sponsor requested to cancel the May 3, 2018, meeting after reviewing the Agency's preliminary responses issued on April 24, 2018. On August 27, 2018, the sponsor submitted the first portion of its NDA under rolling review granted by the Agency on July 23, 2018.

Sarepta has requested this pre-submission meeting to discuss the clinical and nonclinical content of its NDA submission as well as the data submission plan and format. The sponsor is targeting to submit the final portion of the NDA in December 2018.

The Agency granted fast track designation and orphan drug designation for golodirsen for the treatment of DMD in patients who have a confirmed mutation of DMD gene that is amenable to exon 53 skipping in December 2014 and May 2018 respectively.

FDA sent Preliminary Comments to Sarepta on September 7, 2018.

2.0 DISCUSSION

2.1. Clinical Questions

Question 1:

As discussed at the Type C Meeting held on 06 February 2018, the NDA for accelerated approval of golodirsen will be based on the de novo dystrophin protein data obtained from Week 48 of Part 2 in comparison to pretreatment (baseline) of Phase 1/2 Study 4053-101. Dystrophin protein expression by Western blot, percent dystrophin-positive fibers, mean dystrophin fiber intensity, and exon-skipping data will be described in Module 2.7.3 (Summary of Clinical Efficacy) with the supporting interim CSR for Study 4053-101 and detailed information included in Module 5.

Does the Agency agree with this plan?

FDA Response to Question 1:

In general, your proposal appears acceptable. We have had extensive conversation with you in preparation for your submission. Please ensure that all components of the dystrophin bioassays and supporting information, including protocols and validation reports previously discussed with you, are also incorporated.

We remind you of our recent teleconference on July 31, 2018, where you proposed submitting immunohistochemistry data in your NDA from both the MuscleMap analysis for mean dystrophin fiber intensity and percent dystrophin-positive fibers and by manual scoring for percent dystrophin positive fibers.

With regard to the sample image data files you submitted on August 17, 2018, please provide all raw image files in each of the three file formats you provided as samples (TIFF, PDF, and SVS). Please include the SVS files because they contain the source image and meta data.

Meeting Discussion:

The sponsor confirmed that it will provide all three image types for the MuscleMap-based analysis. The sponsor clarified that for the manual scoring of dystrophin-positive fibers, only TIFF files will be provided. The Agency agreed and requested that the TIFF images with and without annotation be provided. The sponsor agreed to this request.

The Agency asked if the raw data files will be hyperlinked from the eCTD submission. The sponsor clarified that it was not planning to insert hyperlinks but instead plans to state the location and identity of the files in the reviewer guide. The Agency then recommended that the sponsor include representative images from each patient in the submission to aid the reviewer.

Question 2:

As agreed at the Type C Meeting held on 06 February 2018, the safety database for the NDA will contain data from approximately 50 patients amenable to exon 53 skipping treated with 30 mg/kg IV golodirsen once weekly, including 20 patients exposed for ≥ 120 weeks. The data analysis and presentation plan for the safety dataset are provided below.

Does the Agency agree with proposed safety data analysis and presentation plan?

FDA Response to Question 2:

As previously noted in the final Type C meeting minutes dated March 2, 2018, assuming no specific safety issues of concern evolve that might influence our current thinking, the proposed safety database appears to have the potential to support the clinical portion of your NDA submission, pending review at the time of any such submission. The data analysis and presentation plan appear to be acceptable. We also refer you to Attachment 1 regarding DNP's standard requests for safety analyses for NDA submissions.

Meeting Discussion:

The Division clarified that the standard requests for safety analyses in Attachment 1 were intended for general guidance and acknowledged that not all requests would be appropriate for the golodirsen safety database. The sponsor should try to address the requests that are appropriate for this program.

The sponsor was encouraged to send sample databases and the Define file so that the acceptability of their format could be evaluated before their submission in the NDA. The sponsor agreed to send these materials following the meeting.

Post-Meeting Note: The sponsor submitted examples of several sample ADaM SAS transport files and Define files of various formats. The following issues should be addressed prior to submission of the datasets in the NDA:

1. Columns with the planned treatment (e.g., in the ADSL file) have a "<"; please provide the exact amount planned.
2. Columns with the actual treatment (e.g., ADAE and ADSL) have a "<"; please provide the exact amount administered, particularly for the ADAE file where this should correspond to the amount given at the time of the event or just prior to the event if they were not at the same time.
3. Separate the echocardiogram data from the ECG data.
4. Additional information to include with your NDA:
    a. Send a file containing copies of the original ECGs and echocardiogram reports
    b. Indicate if the interpretations and intervals for the ECG were centrally read or the source of these data and interpretations.

At this time, there are no questions regarding the other datasets or the Define files, although there may be questions after they are evaluated in the NDA review.

Question 3:

Sarepta plans to include available data from an ongoing radiolabeled absorption, metabolism, excretion study (4053-103) in healthy volunteers in the NDA. The metabolite profiling piece of the data package will not be available until post-NDA submission. Thus, Sarepta proposes to provide this segment of the study results within the first 30 days after the submission of NDA.

Does the Agency agree with this proposal?

FDA Response to Question 3:
At the time of completing your NDA submission, all necessary data required for evaluation of the NDA need to be included in your submission.

Meeting Discussion: There was no meeting discussion.

Question 4:

As discussed herein, hepatic metabolism does not appear to be a major elimination pathway for golodirsen. Thus, Sarepta will be requesting a waiver for the conduct of a hepatic impairment study.

Does the Agency agree with this approach?

FDA Response to Question 4:
This approach is acceptable.

Meeting Discussion: There was no meeting discussion.

Question 5:

Based on its size and cumulative nonclinical and clinical data on its pharmacology and its mechanism of action, golodirsen is not expected to interact with the cardiac channel encoded by the human ether-a-go-go related gene (hERG), or adversely affect cardiac conduction. Thus, Sarepta will be requesting a waiver for a thorough QT (tQT) study.

Does the Agency agree with this approach?

FDA Response to Question 5:
Available data on golodirsen is not adequate to support a waiver for a TQT study. We have the following recommendations for you to consider:

1) We recommend that you conduct in vitro evaluation (i.e., hERG assay) with golodirsen using the FDA-recommended voltage protocol (see http://cipaproject.org/wp-content/uploads/sites/24/2018/06/CiPA-protocol-061318.pdf; use hERG current protocol to assess IC50 only).
2) We recommend that you collect additional ECG data to capture potential QT effects at the end of infusion after the first dose, in your ongoing or future clinical trials. If ECG data in Study 4053-101 and Study 4045-301 were collected around Tmax of golodirsen, please provide details of the ECG sampling schedule and submit ECG data for review.

Meeting Discussion:
The sponsor has proposed to submit hERG assay data, in vivo non-human primate data, and available QTc data from study 4053-101 to support a waiver of TQT study.

The sponsor confirmed that available QTc data in study 4053-101 were obtained from 14 unique subjects, and time-matching PK samples were not available for the ECG data at end of infusion from 7 patients. FDA suggested that available QTc data from study 4053-101 would not be adequate due to its small sample size and a lack of information on systemic exposure in these patients. The sponsor agreed to collect additional ECG data to capture potential QT effects at the end of infusion after the first dose, in the ongoing or future clinical trials.

The sponsor agreed to provide an estimate of the safety margin based on systemic exposure in the in vivo non-human primate study.

FDA agreed with the sponsor's proposal to submit hERG assay data, in vivo non-human data, and QTc data around Tmax after the first dose from ongoing and future studies, to support a request for waiving the need for a TQT study.

Question 6:

With regard to immunogenicity (antidrug antibody and antidystrophin antibody), assays are being developed for immunogenicity assessments. It is Sarepta's intent to submit the antidystrophin antibody data with the 120-day safety update. Sarepta requests a deferral for the antigolodirsen antibody data package and agrees to a postmarketing commitment for providing these data.

Does the Agency agree with this approach?

FDA Response to Question 6:
We do not agree with the proposed submission strategy for anti-golodirsen antibody data as a post-marketing commitment. However, it may be possible to agree to you submitting the assay validation reports and the clinical data from Study 4053-101 obtained using the validated assays as a post-marketing requirement. We recommend that the assay validation reports be provided prior to testing your pivotal trial samples. Refer to FDA Draft Guidance for Industry Assay Development and Validation for Immunogenicity Testing of Therapeutic Proteins: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM192750

Meeting Discussion: There was no meeting discussion.

2.2. Data Format Questions

Question 7:

Sarepta will submit standardized study data for Studies 4053-101, 4045-301, 4053-103, 4053-104 and the Integrated Summary of Safety using standards, formats, and terminologies described in the FDA Data Standards Catalog. The details of standards, formats, and terminologies used for each study will be provided below.

Does the Agency agree with this proposal?

FDA Response to Question 7:
In general, your proposal is acceptable. Please also ensure each study has a demography dataset with one row per subject and the treatment as a column variable. All datasets must include a Define document in PDF with all variable codes listed.

Meeting Discussion: There was no meeting discussion.

Question 8:

Sarepta will provide the below-listed information for the purpose of biomedical Bioresearch Monitoring (BIMO) inspections.

Does the Agency agree with this proposal?

FDA Response to Question 8:
The data and documents you propose to provide for BIMO inspections are acceptable. Additionally, please provide a tentative schedule for your clinical study 4053-101 biopsy acquisition, sample processing, sample blinding/unblinding, and each dystrophin analyses, including the site(s) where they will occur.

Meeting Discussion: There was no meeting discussion.

3.0 ADDITIONAL COMMENTS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. In addition, the rolling submission schedule for the complete NDA application was referenced.

  POST-MEETING NOTE: For an application granted rolling review, the NDA review generally will not begin until the complete application has been submitted to the FDA.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion was held on the need for a risk evaluation and mitigation strategy (REMS) or other risk management actions. At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a REMS will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application, and therefore, there are no agreements for late submission of application components.

- In addition, we note that a CMC pre-submission meeting was scheduled on May 3, 2018. You requested to cancel the May 3, 2018, meeting after reviewing the FDA preliminary

responses issued on April 24, 2018. We refer you to the FDA responses of April 24, 2018, for any additional agreements that may have been reached.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the Guidance for Industry, *Assessment of Abuse Potential of Drugs*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

Based on information submitted to date under the IND, it appears that golodirsen does not have the profile of a drug with abuse potential because it:

- Has a mechanism of action that is limited to effects on mRNA
- Does not distribute into the brain after intravenous administration
- Does not produce central nervous system behaviors in either animals or humans

Thus, further abuse potential assessment for golodirsen will not be necessary prior to NDA submission.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator

and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

1. DNP Pre-NDA Meetings: General Clinical Safety Requests.

2. Sarepta's handout received via e-mail on September 10, 2018, in response to FDA preliminary comments dated September 7, 2018.

Attachment 1.

DNP Pre-NDA Meetings
General Clinical Safety Requests

Datasets:

1. Each individual subject should be assigned a single unique subject identifier across the entire application (e.g., including open label extensions of the trials). Include the unique subject identifier in the ISS and individual studies' datasets.
2. Submit datasets for all Phase 1, Phase 2, Phase 3 studies (including open label extension studies), including the Phase 2 and 3 studies performed for indications other than the one proposed for this application.

For additional guidance refer to the FDA webpage on Study Data Standards Resources.

General Submission Contents:

1. Follow the requirements noted in 21CFR 314.50 (d)(5)(vi), Summary of Safety Information and the Guideline for the Format and Content of the Clinical and Statistical Sections of an Application
2. Provide an assessment of safety as per the FDA Guidance for Industry: Premarketing Risk Assessment
3. Include a copy of each clinical study protocol as well as each amended protocol. Provide a list of the inclusion and exclusion criteria for each of the studies, including those introduced as part of protocol amendments. Please submit all versions of the protocols (and Statistical Analysis Plan) and the date when changes were implemented. Please ensure that a Summary of Changes for each version is included.
4. In addition to the comprehensive analyses performed for the pivotal trials, the ISS should also comprehensively integrate safety analyses for all other study group pools for treatment-emergent adverse events (TEAEs), deaths, serious adverse events, discontinuations for TEAEs, TEAEs of special interest, subgroups, and vital sign/laboratory/ECG measurements.
5. Submit a table detailing all of the tables and figures featured in the clinical efficacy and safety sections of the application. The table should contain the following:
   a. Title of the table or figure in the application
   b. A hyperlink to the location of the table or figure with page number
   c. A hyperlink to the SAS code used to create the table or figure (including information regarding the datasets that were used)
6. Format the tables of the ISS according to examples in FDA's Reviewer Guidance – Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review.
7. Include active hyperlinks from the lists of references to the referenced article.
8. Provide DSMB meeting minutes (including any data/slides presented). For those meetings that were cancelled or meetings where no minutes were taken, please include a place holder

for that meeting noting such and signed by a member of the clinical team. Please also ensure that these packages come with a table of contents and are bookmarked by date.
9. Include information regarding important regulatory actions in other countries and foreign labeling (translated, if applicable).
10. Submit an annotated version of the pre-BLA meeting minutes that include hyperlinks, when applicable, to the analysis and/or documents requested.

Adverse events:

1. Follow the coding rules for MedDRA in the ICH-endorsed "MedDRA Term Selection: Points to Consider" document accessible at MedDRA
2. For each of the studies, the submitted datasets should contain both the verbatim terms and the MedDRA coding with all levels of the MedDRA hierarchy. For each adverse event, MedDRA coding should be provided for the primary MedDRA path as well as the alternative MedDRA coding paths.
3. Provide a summary table of the original AE coding dictionaries that were used in each of the trials.
4. The preparation of the adverse event dataset for the ISS should include MedDRA Preferred Terms from a single version of MedDRA.
5. Ensure that all adverse events are presented, and not only events deemed "drug-related."
6. Provide a table of treatment-emergent adverse events reported in ≥ 2% of subjects (after rounding) in any drug treated dose group (and greater than placebo) sorted by MedDRA SOC (in alphabetical order) and then by MedDRA Preferred Term.
7. Provide a table which summarizes the outcomes of all pregnancies. Provide a table which summarizes all known adverse events in subject offspring.

Narratives and Case Report Forms (CRFs):

1. Provide narratives and case report forms for deaths, adverse events leading to drug discontinuation, SAEs, pregnancies, and AEs of special interest. You should be prepared to supply any additional CRFs or narratives with a rapid turnaround upon request. Narratives should be integrated. For subjects who had more than one event requiring a narrative (whether in the same trial or in the core study and an extension) present a single narrative (rather than separate narratives for the various events).
2. Include a word file (and excel spreadsheet) that indicates those subjects for whom you submitted a case report form and/or narrative. This file should include an indicator for whether each item was submitted and the reason why it was submitted along with hyperlinks to the narrative and CRF.
3. Provide reports for any autopsies conducted during any of the studies.
4. Provide a line listing, narrative, and case report form for all subjects who fit the Hy's Law laboratory criteria.

5. Note that CRFs should include all clinical documents collected about the patient regardless of whether you label them "CRFs", e.g., MedWatch/CIOMS forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc.
6. Provide a tabular listing of all subjects with all discontinuations, sorted by reason. The table should include columns for study number, treatment group, unique subject ID, primary reason for drug or study discontinuation. For reasons including Lost to follow-up, Other, Physician/investigator decision, Withdrew consent, and Patient decision, provide more specific information regarding the discontinuation. The Division may want to request selected narratives/CRFs from some of these patients, but they do not need to be submitted at the time of the initial NDA/BLA submission.
7. Narrative summaries should provide a complete synthesis of all available clinical data and an informed discussion of the case. The narratives should be comprehensive enough for the reader to come to a reasonable conclusion regarding the subject and the adverse event. The following items should be included (but not limited to):
    a) Patient age and gender
    b) Adverse event onset and stop dates (presented as relative Study Day number)
    c) Signs and symptoms related to the adverse event being discussed
    d) An assessment of the relationship of exposure duration to the development of the adverse event
    e) Pertinent medical history
    f) Concomitant medications with start dates relative to the adverse event
    g) Pertinent physical exam findings
    h) Any abnormal vital sign measurements
    i) Pertinent test results (e.g., lab data, ECG data, procedures, biopsy data, autopsy results)
    j) Discussion of the diagnosis as supported by available clinical data
    k) For events without a definitive diagnosis, a list of the differential diagnoses
    l) Treatment provided
    m) Re-challenge results (if performed)
    n) Outcomes and follow-up information

Laboratory and Vital Sign Measurements:

1. Refer to the following FDA webpage for the CDER position on use of SI units for lab tests: SI Units.
2. Provide the normal reference ranges for every laboratory value. Please ensure that appropriate pediatric reference values are used for pediatric patients.
3. Clearly list the normal values, as well as the thresholds for analysis of outliers, for outlier analyses of laboratory data, vital signs, and ECG data.
4. When possible, use the latest version of the National Institutes of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE) for toxicity grades and shift analyses.
5. Report the number and percentage of subjects with at least one post-treatment vital sign measurement meeting any of these criteria:
    • Systolic Blood Pressure: <90 mmHg, >140 mmHg, >160 mmHg

- Diastolic Blood Pressure: <50 mmHg, >90 mmHg, >100 mmHg
- Pulse Rate: <60 bpm, >100 bpm
- Body Weight: decrease of ≥7% from baseline and increase of ≥7% from baseline
- Temperature: >38.0 °C, <36.0 °C
- Respiratory rate: <12 breaths/min, > 20 breaths/min

6. Summarize the protocols for collecting ECG data. Summarize the frequency of post-treatment QTc >450 ms, >480 ms, and >500 ms.

Other requests:

1. Patient profiles
   Submit individual patient profiles containing all laboratory and other study results in a single place for each patient. Provide this information for patients who died, had a serious adverse event, discontinued from the trial due to an adverse event, or had a medically significant event for which a narrative is submitted. Include all the information recorded for that patient, including but not limited to:
   a) Age
   b) Sex
   c) Dates of screening, randomization and starting therapy
   d) Whether the patient completed or did not complete the study, with dates and reason for withdrawal
   e) Adverse events (reported term, preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not and action taken with drug)
   f) Prior medications and concomitant medications with dates of start and end
   g) Vital signs and laboratories, sorted by date, with reference ranges *
   h) Autopsy reports for all deaths. (If an autopsy report is not available, explicitly state this.)
   i) Full reports for radiologic studies, ECG, MRI, pathology results, special studies and procedures with dates and reference ranges
   j) Provide relevant results obtained outside of clinical trial visits, including those obtained during hospitalization or emergency room visits, in each patient file. Also include baseline study results.
   k) For patients who had IND safety report(s), include dates when the initial and follow up safety reports were submitted.

   Create a PDF file for each patient and a table of contents with links to each assessment for each patient.

2. Please submit for Division comments an example narrative from a patient who had more than one serious adverse event and participated in the controlled and extension studies prior to submitting your NDA.
3. We request that you submit a sample integrated summary of safety datasets (with data definition file) for Division comments prior to submitting the NDA. This process could help

to identify and resolve any potential issues of navigability or interpretability that could impact the review of your application.

GOLODIRSEN (SRP-4053) INJECTION

Pre-NDA Meeting

Purpose of Meeting: The primary purpose of this meeting is to discuss and obtain Agency's concurrence regarding the nonclinical and clinical content of the planned New Drug Application (NDA) submission as well as the data submission plan and format.

Sarepta acknowledges Agency's preliminary comments, and would like to discuss questions 1, 2 and 5; no discussion of questions 3, 4, 6, 7 and 8 are needed.

Question 1.

As discussed at the Type C Meeting held on 06 February 2018, the NDA for accelerated approval of golodirsen will be based on the de novo dystrophin protein data obtained from Week 48 of Part 2 in comparison to pretreatment (baseline) of Phase 1/2 Study 4053-101. Dystrophin protein expression by Western blot, percent dystrophin-positive fibers, mean dystrophin fiber intensity, and exon-skipping data will be described in Module 2.7.3 (Summary of Clinical Efficacy) with the supporting interim CSR for Study 4053-101 and detailed information included in Module 5.

Does the Agency agree with this plan?

FDA Response to Question 1:

In general, your proposal appears acceptable. We have had extensive conversation with you in preparation for your submission. Please ensure that all components of the dystrophin bioassays and supporting information, including protocols and validation reports previously discussed with you, are also incorporated.

We remind you of our recent teleconference on July 31, 2018, where you proposed submitting immunohistochemistry data in your NDA from both the MuscleMap analysis for mean dystrophin fiber intensity and percent dystrophin-positive fibers and by manual scoring for percent dystrophin positive fibers.

With regard to the sample image data files you submitted on August 17, 2018, please provide all raw image files in each of the three file formats you provided as samples (TIFF, PDF, and SVS). Please include the SVS files because they contain the source image and meta data.

Sarepta's Response:

We confirm that Sarepta will be supplying the .svs, .TIFF and .pdf file format for MuscleMap™ analysis on an external hard drive as communicated previously.

For manual scoring as defined in the protocol and based on the response submitted to the Agency last week, the original source images for the high powered fields are in the .TIFF file

format, thus, there are no .svs files for the manual scoring. We would like to confirm that we are providing only .TIFF files for source and annotated images used for manual scoring.

Question 2.

As agreed at the Type C Meeting held on 06 February 2018, the safety database for the NDA will contain data from approximately 50 patients amenable to exon 53 skipping treated with 30 mg/kg IV golodirsen once weekly, including 20 patients exposed for ≥ 120 weeks. The data analysis and presentation plan for the safety dataset are provided below.

Does the Agency agree with proposed safety data analysis and presentation plan?

FDA Response to Question 2:

As previously noted in the final Type C meeting minutes dated March 2, 2018, assuming no specific safety issues of concern evolve that might influence our current thinking, the proposed safety database appears to have the potential to support the clinical portion of your NDA submission, pending review at the time of any such submission. The data analysis and presentation plan appear to be acceptable. We also refer you to Attachment 1 regarding DNP's standard requests for safety analyses for NDA submissions.

Sarepta's Response:

Sarepta acknowledges the Division's feedback. We also acknowledge the receipt of general guidance provided in Attachment 1; we would like to confirm this is a general guidance and in some cases not applicable to our patient population and accelerated program. A few examples are provided below.

Regarding request 1 under the section entitled Narratives and Case Report Forms (CRFs) in Attachment 1, we would like to clarify that for study 4045-301 patient narratives will be submitted using sham IDs; however, these will not be accompanied by CRFs in order to maintain the blind and integrity of the study. Applicable CRFs for study 4053-101 will be included in the NDA.

Regarding request number 5 under Laboratory and Vital Sign in Attachment 1, we have established criteria for blood pressure and heart rate that are appropriate for the range of the pediatric male DMD population being studied and will report these parameters according to these criteria. With regards to body weight, Sarepta will report the number and percentage of subjects with a decrease of ≥7% from baseline. However, considering the growing pediatric population and the long term nature of these studies, we do not plan to report the number and percentage of subjects with an increase of ≥7% increase in weight from baseline.

In regards to your suggestion (item 3) under Other requests in Attachment 1 to submit a sample integrated summary of safety datasets (with the definition file) for review, we were not planning on submitting a sample dataset or data definition file. We have designed our ISS datasets and data definition file in accordance with FDA data standards requirements (Study Data Standards Resources). Does FDA have any specific concerns?

Question 3.

Sarepta plans to include available data from an ongoing radiolabeled absorption, metabolism, excretion study (4053-103) in healthy volunteers in the NDA. The metabolite profiling piece of the data package will not be available until post-NDA submission. Thus, Sarepta proposes to provide this segment of the study results within the first 30 days after the submission of NDA.

Does the Agency agree with this proposal?

FDA Response to Question 3:
At the time of completing your NDA submission, all necessary data required for evaluation of the NDA need to be included in your submission.

Sarepta's response:
Sarepta acknowledges the feedback; no discussion at the meeting.

Question 4.

As discussed herein, hepatic metabolism does not appear to be a major elimination pathway for golodirsen. Thus, Sarepta will be requesting a waiver for the conduct of a hepatic impairment study.

Does the Agency agree with this approach?

FDA Response to Question 4:
This approach is acceptable.

Sarepta's response:
No discussion at the meeting.

Question 5.

Based on its size and cumulative nonclinical and clinical data on its pharmacology and its mechanism of action, golodirsen is not expected to interact with the cardiac channel encoded by the human ether-a-go-go related gene (hERG), or adversely affect cardiac conduction. Thus, Sarepta will be requesting a waiver for a thorough QT (tQT) study.

Does the Agency agree with this approach?

FDA Response to Question 5:
Available data on golodirsen is not adequate to support a waiver for a TQT study. We have the following recommendations for you to consider:

1) We recommend that you conduct in vitro evaluation (i.e., hERG assay) with golodirsen using the FDA-recommended voltage protocol (see http://cipaproject.org/wpcontent/uploads/sites/24/2018/06/CiPA-protocol-061318.pdf; use hERG current protocol to assess IC50 only).
2) We recommend that you collect additional ECG data to capture potential QT effects at the end of infusion after the first dose, in your ongoing or future clinical trials. If ECG data in Study 4053-101 and Study 4045-301 were collected around Tmax of golodirsen, please provide details of the ECG sampling schedule and submit ECG data for review.

Sarepta's response:

To address this waiver request, Sarepta accepts the Division's recommendation to conduct in-vitro evaluation of hERG assay for golodirsen. In addition, in-vivo non-human primate data as well as available QTC data from study 4053-101 will provide support for this waiver request.

Non-human primate data:

There was no observed QT prolongation following administration of golodirsen in the single-dose safety pharmacology study evaluating the effects on cardiovascular, respiratory, and neurological function and the 12-week toxicology study, both completed in cynomolgus monkeys.

In the cardiovascular safety pharmacology assessment study, SRP-4053 was evaluated at dose levels of 5, 40 and 320 mg/kg, in telemetered male cynomolgus monkeys (Study 4053-sph-001). SRP-4053 was administered by intravenous injection via the left and right tail vein, using a dose rate of approximately 6 mL/min. For each dose, ECG data collection commenced at least 1 hour prior to the start of dosing and ended at least 24 hours following the start of dosing. Data were analyzed at nominal time points of 45 and 30 minutes prior to the start of administration and at 0.25, 0.5, 1, 2, 4, 6, 8, 12, 16, 20 and 24 h following the start of administration.

In the 12-week nonhuman primate toxicology study, SRP-4053 was administered once weekly at dose levels of 5, 40 and 320 mg/kg, infused via either tail vein over approximately 3 minutes. ECGs were obtained predose and at 1-hour post dose during Week 11 (Day 71) (Study 4053-tox-001).

Clinical Study 4053-101:

ECG evaluation was conducted at pre-specified visits during the dosing period of Study 4053-101 at the 30 mg/kg once weekly dose. The below table outlines the available post-infusion ECGs from 14 unique treated patients according to the time relative to the end of infusion, as of the cutoff date of 2 February 2018.

Study 4053-101	*0-30 minutes post-end of infusion*	*30-60 minutes post-end of infusion*	*>60 minutes*
Number of ECGs	*12 (7 patients)*	*9 (7 patients)*	*11 (7 patients)*

Would provision of the hERG assay data, the above non-human primate and updated clinical QTC data be adequate for a TQT waiver?

Question 6.

With regard to immunogenicity (antidrug antibody and antidystrophin antibody), assays are being developed for immunogenicity assessments. It is Sarepta's intent to submit the antidystrophin antibody data with the 120-day safety update. Sarepta requests a deferral for the antigolodirsen antibody data package and agrees to a postmarketing commitment for providing these data.

Does the Agency agree with this approach?

FDA Response to Question 6:
We do not agree with the proposed submission strategy for anti-golodirsen antibody data as a post-marketing commitment. However, it may be possible to agree to you submitting the assay validation reports and the clinical data from Study 4053-101 obtained using the validated assays as a post-marketing requirement. We recommend that the assay validation reports be provided prior to testing your pivotal trial samples. Refer to FDA Draft Guidance for Industry Assay Development and Validation for Immunogenicity Testing of Therapeutic Proteins: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM192750

Sarepta's response:
Sarepta will be submitting assay validation reports for the anti-golodirsen antibody assay prior to analysis of 4053-101 and pivotal study 4045-301. We agree this commitment would be a post-marketing requirement. No discussion needed at the meeting.

Question 7.

Sarepta will submit standardized study data for Studies 4053-101, 4045-301, 4053-103, 4053-104 and the Integrated Summary of Safety using standards, formats, and terminologies described in the FDA Data Standards Catalog. The details of standards, formats, and terminologies used for each study will be provided below.

Does the Agency agree with this proposal?

FDA Response to Question 7:
In general, your proposal is acceptable. Please also ensure each study has a demography dataset with one row per subject and the treatment as a column variable. All datasets must include a Define document in PDF with all variable codes listed.

Sarepta's response:
We acknowledge the Division's response with no discussion needed at the meeting.

Question 8.

Sarepta will provide the below-listed information for the purpose of biomedical Bioresearch Monitoring (BIMO) inspections.

Does the Agency agree with this proposal?

FDA Response to Question 8:

The data and documents you propose to provide for BIMO inspections are acceptable. Additionally, please provide a tentative schedule for your clinical study 4053-101 biopsy acquisition, sample processing, sample blinding/unblinding, and each dystrophin analyses, including the site(s) where they will occur.

Sarepta's response:

Sarepta confirms this information will be provided for Study 4053-101 for which the interim muscle biopsy analysis has been completed. No discussion needed at the meeting.

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/

WILLIAM H Dunn
10/10/2018