ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS
ADVISORY COMMITTEE

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ETEPLIRSEN BRIEFING DOCUMENT ADDENDUM

NDA 206488

Sarepta Therapeutics, Inc.
215 First Street
Cambridge, MA 02142 USA

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INTRODUCTION

Sarepta and the FDA have no more critical challenge than to reliably bridge and extend the benefits of medical innovation to patients. Eteplirsen has been developed as an innovative therapy, customized to treat a unique set of DMD genetic mutations, those which are amenable to skipping exon 51.

This addendum provides updated efficacy data as requested by FDA. It will also address Sarepta's position on the FDA's existing authority and mandate to exercise flexibility in the evaluation of data for a rare disease such as DMD. Finally, Sarepta will provide clarification of comments in the FDA briefing document that we believe are key inaccuracies.

UPDATED ETEPLIRSEN CLINICAL EFFICACY DATA: WEEK 216 LOSS OF AMBULATION AND 6-MINUTE WALK TEST RESULTS

Summary of Year 4 Loss of Ambulation (LOA) Status by Kaplan-Meier Analysis

A summary of the Kaplan-Meier analysis results comparing Year 4 LOA rates of eteplirsen-treated subjects and external controls is provided below.

Study 201/202 (n=12): 2 LOAs, 10 ambulatory, %LOA = 16.7%.

External control (n=13): 10 LOAs, 1 ambulatory, 2 missing data at year 4; %LOA = 89.7% by Kaplan-Meier analysis taking into account missing data cases; p=0.004 by log-rank test.

Six-Minute Walk Test

The eteplirsen NDA was based on a large significant advantage of over 100 meters on the 6MWT for the eteplirsen-treated boys compared to external control boys at Year 3. This magnitude of effect was consistent and verified by several sensitivity analyses including those adjusting for covariates of baseline age and 6MWT **(Section 6.5.1.1 of Sarepta's briefing document)**.

Subsequent to the NDA submission, the FDA requested additional Study 201/202 data through Week 216; the requested 6MWT data are provided in Table 1. All 10 of the eteplirsen boys who were ambulant at time of NDA submission remain able to walk at Week 216. Their ages at this point in the study range from 11.8 years to 15.2 years, with 4 of the boys aged 14 or older. This is in contrast to what was stated in the FDA Briefing Document for drisapersen, *"by age 10-14, DMD patients become wheel chair bound"* (Peripheral and Central Nervous System Drugs Advisory Committee Meeting November 24, 2015; NDA 206031 Briefing Document for Drisapersen, page 28).

In addition, Year 4 data for the external control patients amenable to exon 51 skipping have recently become available, are is provided in Table 2.

Table 1: Study 201/202 Subjects (n=12) with Results of 6MWT at Year 4

Dose Group	Subject Number	Baseline 6MWT	Year 3 6MWT	Year 4 6MWT	Age at Year 4
Placebo to 30 mg/kg	007	374	312	197	11.7
	008	346	100	55	14.2
Placebo to 50 mg/kg	005	374	247	143	11.7
	013	400	301	230	14.3
30 mg/kg	002	416	378	349	12.7
	006	355	359	332	14.2
	009	330	0	0	13.9
	010	256	0	0	13.9
50 mg/kg	003	366	324	192	11.0
	004	389	355	221	12.5
	012	351	298	237	14.6
	015	401	483	400	13.3

Table 2: External Control Subjects (n=13) with Results of 6MWT at Year 4

Subject Number	Baseline 6MWT	Year 3 6MWT	Year 4 6MWT	Age at Year 4
(b) (6)	380	195	*Missing	12.6
	295	35	0	13.3
	380	0	0	12.0
	329	218	0	12.8
	388	0	0	12.1
	388	0	0	14.1
	325	0	0	11.3
	458	362	300	14.2
	200	0	0	15.5
	373	273	0	13.0
	327	0	0	15.5
	451	240	0	15.2
	355	*Missing	*Missing	12.3

* External control patients with missing 6MWT data at Year 4.

** Of note, patients (b) (6) and (b) (6) were subsequently reported to have loss of ambulation with "0" meters on the 6MWT at ~4.5 years. In addition, external control patient (b) (6) was known to have lost ambulation with a 6MWT of "0" at 4.8 years.

Table 3: Summary of Year 4 6MWT Difference in Mean Change from Baseline between Study 201/202 Subjects and External Controls by Model (estimated mean difference, *p*-value)

Model	**MMRM** **N= 12/13**	**ANCOVA** **N=12/11**
Covariate: Baseline 6MWT	146.5, *p*=0.003	150.3, *p*=0.002
Covariates: Baseline 6MWT, Age	143.1, *p*=0.004	156.1, *p*=0.002
Rank transformed data analyzed Covariate: Baseline 6MWT	8.4, *p*=0.004	8.7, *p*=0.001

Conclusion

Based on available data for LOA and 6MWT status at 4 years, Study 201/202 patients performed better than EC patients in a statistically significant and clinically meaningful manner.

FLEXIBILITY REGARDING EVIDENCE REQUIRED TO MEET THE SUBSTANTIAL EVIDENCE STANDARD

FDA's existing authority allows for the use of scientifically-driven flexibility in the application of the statutory standards for approval, in particular through the accelerated approval pathway for serious or life-threatening diseases as codified in the Food and Drug Administration Safety and Innovation Act (FDASIA), signed into law on 09 July 2012. While application of regulatory flexibility has been most prevalent in the areas of oncology and HIV/AIDS, nowhere is the use of such flexibility more impactful than in the case of new therapies for the treatment of serious and life-threatening rare diseases. The need for innovative and flexible approaches to FDA review across divisions increases as more rare disease therapies are being developed, where the contextual knowledge of patients and their diseases often evolves in parallel with clinical development.

Authority for such flexibility is borne directly from federal regulations which state in part "[w]hile the statutory [substantial evidence of effectiveness] standards apply to all drugs, the many kinds of drugs that are subject to the statutory standards and the wide range of uses for those drugs demand flexibility in applying the standards." The regulations go on to empower use of this flexibility by requiring the FDA "*to exercise its scientific judgment to determine the kind and quantity of data and information… required to provide for a particular drug to meet the statutory standards*" (21 CFR 314.105(c)). More recently, FDA affirmed in draft guidance that *"[t]here is no specific minimum number of patients that should be studied to establish effectiveness and safety of a treatment for any rare disease."* (Guidance for Industry - *Rare*

Diseases: Common Issues in Drug Development, August 2015). Utilizing this authority, FDA allows for the broadest application of flexibility for new therapies intended to treat persons with life-threatening and severely-debilitating illnesses, especially where no satisfactory alternative therapy exists (21 CFR §312.80).

Congress embraced this flexible approach to drug evaluation in enacting Title IX of FDASIA in 2012. That law provided both the Findings and Sense of Congress with respect to FDA's authority to grant accelerated approval for drugs for serious and life-threatening diseases where the effect on a surrogate endpoint or intermediate clinical endpoint is reasonably likely to predict clinical benefit. Uncertainty about whether clinical benefit would be verified and the possibility of undiscovered risks are the reasons that accelerated approval is reserved for drugs intended to treat serious conditions, such as the use of eteplirsen in the treatment of Duchenne muscular dystrophy. Importantly, FDA acknowledged that approval under such a pathway may involve *"fewer, smaller, or shorter clinical trials than is typical for a traditional approval…"* ((FDASIA Section 901(a)(1)(C)) and that "*trials using external controls, such as historically controlled trials, may be considered adequate and well-controlled, and may provide or contribute to evidence of efficacy to support approval*." (FDA Guidance for Industry: *Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment*, June 2015). There are numerous examples where FDA's flexibility has established regulatory precedent in rare diseases, including those described in the Sarepta briefing document and:

- Carbaglu® (carglumic acid): approved in March 2010 for treatment of N-acetylglutamate synthase (NAGS) deficiency based on a case series from fewer than 20 patients and comparison to a historical control group.
- Ceptrotin® (human plasma derived protein C concentrate): approved in March 2007 for the treatment of severe congenital Protein C deficiency based on a study of 18 patients using a comparison to historical control data.

Such variation in the type and quantity of evidence used by the FDA to assess the efficacy of novel therapeutic agents underscores the Agency's flexible approach to meeting standards for drug approval. It is clear in the context of the review of drugs for rare diseases FDA has the authority—and specific direction from Congress—to exercise flexibility in considering all of the available data.

CLARIFICATION OF KEY INACCURACIES IN THE FDA BRIEFING DOCUMENT

Dystrophin Analytical Methodology:

FDA Statement	Sarepta Clarification
"It is important to note that the applicant digitally processed dystrophin images in their background material (images in Appendix 12) in such a way that low intensity values were preferentially increased to produce a higher intensity and higher contrast image." (FDA BD page 29 of PDF)	The digitally processed images referenced by FDA in this statement were included in Sarepta's briefing document for demonstration purposes only, and it is far more important to note that the referenced images were not used in the analysis of fiber intensity, nor to score dystrophin-positive fibers.
"Biomarker studies on the 4th biopsy obtained at Week 180 were conducted by the applicant with technical advice from FDA. However, the reliability of results remains questionable for a number of reasons, including the lack of independent confirmation." (FDA BD page 30 of PDF)	Methodology for dystrophin analyses of the fourth biopsy tissue samples, including confirmatory assessments of percent dystrophin-positive fibers (PDPF) analysis performed by 3 independent pathologists, were agreed with FDA prior to conducting any analyses of the fourth biopsy tissue samples. In accordance with the mutually agreed-upon protocols for the assessment of dystrophin-positive fibers in DMD muscle biopsy samples from the fourth biopsy obtained at Week 180, 3 independent pathologists performed a blinded assessment of the randomized muscle fiber microscopy images, which independently confirmed the results obtained by the pathologist at Nationwide Children's Hospital (NCH). Assessment of PDPF at NCH indicated a significant increase in PDPF score ($p<0.001$) relative to untreated control samples. This increase in PDPF score was confirmed by the 3 independent pathologists ($p<0.001$).
"Random measurement error can be large in comparison to the estimated amount of dystrophin." (FDA BD page 31 of PDF)	The random measurement error of our Western blot protocol for measurement of dystrophin levels was well below the observed difference between untreated and treated Week 180 biopsy samples. A rigorous validation of the Western blot method was reviewed by the FDA prior to Week 180 biopsy analysis. Validation data demonstrated a %CV of +/- 50% and a linear range ($R^2>0.9$) of sensitivity extending as low as 0.25% of normal.
"There is no simple or reliable way to compare estimates of dystrophin amount derived from immunofluorescence with estimates derived from Western blot." (FDA BD page 35 PDF).	Correlation between dystrophin quantification by Western blot and IHC methods has been demonstrated by multiple laboratories (Taylor, 2012; Anthony, 2011; Anthony, 2014; Hathout, 2015 FDA Workshop on Measuring Dystrophin).

FDA Statement	Sarepta Clarification
"In this context, the applicant selected three BMD patients as comparators for the Week 180 dystrophin studies, one of whom had low dystrophin level of about 2% of normal. However, the BMD patients selected by the applicant do not appear representative, and this patient may correspond to one of the rare BMD patients with very low dystrophin levels." (FDA BD page 34 of PDF)	BMD patient samples were not chosen to be representative; rather, they were selected in response to an FDA request to assess the relationship between dystrophin as measured by Western blot and immunofluorescence fiber intensity. Therefore, BMD samples were obtained that represented low, middle, and higher ranges of dystrophin expression. A comparable Western blot analysis-IHC correlation was presented by Hathout, et al. (MDA 2015 Scientific Conference poster, FDA-NIH workshop on measuring dystrophin, 2015), where BMD biopsies were chosen to represent low- and mid-level dystrophin expression. Consistently, their BMD low patient biopsy was 2% of normal.

Potential Clinical Impact:

FDA Statement	Sarepta Clarification
"With these two comparisons of eteplirsen to placebo, there was a positive finding for only the lower dose (30 mg/kg) and for just one of the two time points (the later time point). The lack of an effect with the higher dose group tends to undermine the finding in the lower dose group and the lack of even a positive trend at the earlier time point (with a higher dose) sheds doubt on the finding at a later time point." (FDA BD page 7 of PDF)	The study was designed to see whether dose (50 mg/kg vs. 30 mg/kg) or duration was the most important criterion to enable consistent dystrophin production. • Duration of therapy was observed to be the critical variable when interpreting dystrophin levels. 12 weeks does not represent a clinically relevant duration of therapy (FDA BD page 26 of PDF). • Significant dystrophin levels were by measured at Week 24 for the 30 mg/kg dose, and, importantly, at Weeks 48 and 180 for both the 30 and 50 mg/kg doses by all dystrophin assay methods.
"Arguably, placebo-treated patients who were blinded to treatment assignment from other controlled trials are more appropriate as matched controls than registry patients, as they may receive special care and attention as trial participants, and may be more highly motivated." (FDA BD page 13 of PDF)	The placebo patients from another study as referenced by the FDA are not appropriate for comparison with the eteplirsen-treated patients (FDA BD pages 8, 9, 40-44, and 50 of the PDF): Baseline characteristics are not comparable between eteplirsen and the proposed placebo group: • Placebo group included boys <7 years old • Placebo group included many patients with baseline 6MWT >440 meters which is outside the eteplirsen trial's inclusion criteria Placebo patients were followed for only one year, whereas eteplirsen-treated patients were followed for 3 or more years:

FDA Statement	Sarepta Clarification
	• By virtue of the ambulatory requirement at study entry, older placebo patients (e.g. ≥11 years) were a group of pre-selected, better performing subjects. • The first year of an 11-year-old-at-baseline placebo patient (i.e. 11-12 years old) to the third year of a 9-year-old boy with 3 years of eteplirsen treatment (i.e. 11-12 years old) is not a valid comparison due to the difference in duration of observation, as well as the biased selection of the 11-year -old ambulatory placebo boy, irrespective of both patients having the same age at last assessment. • Comparison of eteplirsen-treated patients to the appropriately matched external control shows that more than one year is required to observe a divergence in disease progression between the two groups.
"The robustness of the study result is a concern since a single patient could change the results substantially." (FDA BD page 69 of PDF)	This statement is inaccurate. A comprehensive sensitivity analysis was performed in order to address any potential issue regarding robustness of the data. Specifically: • Two patients were removed: the best performing eteplirsen and the worst performing external control patient. • Results demonstrated a robust 6MWT treatment advantage of >100 meters with nominal significance.
"Finally, as the sponsor's natural history study proceeded, some patients left to enter interventional clinical trials, further decreasing the similarity of the natural history cohort to the eteplirsen patients." (FDA BD page 47 of PDF)	The 2 external control patients who entered interventional trials did not diminish the comparability of the natural history cohort. Two types of sensitivity analyses were performed to confirm the magnitude of difference remained over 100 meters and maintained nominal significance: • MMRM using all available data • Last Observation Carried Forward imputation (conservative analysis assuming that the 2 control patients did not decline)

Regulatory Feedback:

FDA Statement	Sarepta Clarification
"As the duration of exposure in Study 202 increased, the applicant proposed comparing the clinical course of treated patients to historical controls." (FDA BD page 38 of PDF)	The proposal to compare with historical control patients originated from the FDA. Specifically, a requirement to compare the clinical course of treated patients in Study 202 to matched patient-level historical control data was made by the FDA at the March 2014 guidance meeting, and reiterated at the September 2014 pre-NDA meeting. Sarepta had proposed an open-label confirmatory study comparing treated patients to

FDA Statement	Sarepta Clarification
	concurrent (not historical) untreated patients with exon deletions not amenable to skipping exon 51 (i.e. the PROMOVI study).