CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213026Orig1s000

OTHER REVIEW(S)

IMMUNOGENICITY ASSESSMENT

Application Type	NDA
Application Number	213026
Submit Date	01/10/2020
Received Date	01/10/2020
Division/Office	CDER/OND/ON/DNI
Review Completion Date	01/10/2021
Product Name	Casimersen
Proposed Proprietary Name Error! Bookmark not defined.	AMONDYS 45
Pharmacologic Class	PMO exon Skipping
Applicant	Sarepta Therapeutics, Inc.
Applicant Proposed Indication(s)	Duchenne muscular dystrophy (DMD) in (b) (4) patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping.

Immunogenicity Assessors

Primary Assessor(s)	Seth Thacker PhD
Secondary Assessor(s)	Daniela Verthelyi PhD MD

Assessor Recommendation:
The sponsor has submitted data for anti-dystrophin antibodies in the casimersen trials. These data were generated using assays that were developed for assessing anti-dystrophin antibodies in patients treated with eteplirsen and golodirsen and have already been deemed fit for use. The sponsor submitted anti-dystrophin ADA data for Study 4045-101, which had 12 patients enrolled No positive samples were found. The FPR for these assays in Study 4045-101 were 1.3%(IgG), 7.9% (IgE), and 39% (IgM) as calculated by the assessor.

The sponsors has not submitted an assay for the detection of Casimersen-specific ADAs or provided a plan on how they assess the risk associated with the generation of novel epitopes in the dystrophin formed by exon 45 skipping. PMRs will be issued to the sponsor to develop and validate the assays and to assess the patients in study 4045-101 and 4045-301 for Abs to the product and to the peptide generated through the exon skipping strategy.

Suggested language for the PMRs

1) Anti-dystrophin response:

Evaluate patient immune responses to dystrophin in patients from Study 4045-301 (b) (4) (b) (4) Test samples collected using fully validated anti-dystrophin assays that detect IgM, IgG and IgE antibodies. Provide antibody titers for samples that are positive for antibodies to dystrophin. Assess the impact of immune responses on product pharmacokinetics and clinical efficacy and safety.

2) Anti-casimersen response:
   a. Develop and validate assays to measure antibodies to Casimersen. The assays should measure IgM, IgG and IgE antibody isotypes.

   b. Evaluate the samples from patients in Study 4045-101 and Study 4045-301 (b) (4) (b) (4) for antibodies to casimersen. Test samples that are positive for antibodies to casimersen for titer and neutralizing activity using fully validated assays. Until these assays have been fully validated and reviewed by FDA, sufficient samples should be banked and stored under appropriate conditions to allow for retesting as needed. Determine the impact of immune responses on product pharmacokinetics and clinical efficacy and safety.

3) Immunogenicity of novel epitopes induced by exon skipping:
Evaluate the immunogenicity of casimersen-induced truncated dystrophin protein. Assess the immunogenicity risk of any novel epitopes that will be present in the casimersen-induced truncated dystrophin protein. This can be done using clinical data, in silico or in vitro assays. If there are novel epitopes that could increase the immunogenicity risk, evaluate the immunogenicity of casimersen-induced truncated dystrophin protein in the corresponding patients treated with casimersen in Study 4045-301 (b) (4)

2. Review

Document Reviewed	Link to Document	Submission Date
5.3.5.3 Study SR-19-008, SR-19-010, and SR-18-074	Study SR-19-008 SR-19-010 SR-18-074	08/19/2020
5.3.3.2 Study 4045-101	\\CDSESUB1\evsprod\nda213026\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5332-patient-pk-init-tol-stud-rep\4045-101\4045-101-immuno-rep.pdf	1/10/2020
5.3.3.2 Study 4045-101	\\CDSESUB1\evsprod\nda213026\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5332-patient-pk-init-tol-stud-rep\4045-101\4045-immuno-tables-list.pdf	1/10/2020

Immunogenicity Risk Assessment:
This immunogenicity risk associated with this product is low. The DP targets an endogenous protein to induce exon skipping and allow a truncated protein to be produced. The exon skipping can create novel epitopes which

could induced an immune response to the newly generated protein. Any immune response that is generated to dystopian would have the potential to induce further muscle damage and reverse any benefit the patient would have received, but there is scientific evidence this occurs naturally in these patatients. The rare disease nature of DMD also means there is a small population of patients making the studies small and the assessment of the immunogenicity risk challenging.

Review:

The sponsor has submitted three assays in their NDA package for the assessment of anti-dystrophin IgA, IgG, and IgE. These assays have been submitted previously under the NDA 211970 (golodirsen) and they were deemed fit for use. The sponsor also submitted data from Study 4045-101 in which the samples collected from the twelve patients in the study were tested using the anti-dystophin assays. The sponsor reported no positive samples in their study, but due to the small number of patients tested it is difficult to assess if the cut point established in the validation assay is appropriate for this patient population. The sponsor does have a larger study ongoing (4045-301) which will provide more information regarding the potential immunogenicity risk of the product. There is no expectation that the cut points should be different between eteplirsen and golodirsen treated patients and the established cut point should be appropriate for this population as well, but the cut point will need to be confirmed in the study population.

The sponsor has not provided any information regarding their plans to address the potential immunogenicity risk of the novel epitopes that could be formed following exon 45 skipping induced by their drug product.

The sponsor has not provided any information regarding their plans to address the potential development of anti-Casimersen antibody development, but in the clinical protocol they have detailed the days they will collect serum for immunogenicity testing.

Background:

Dystrophin: Dystrophin is localized to the inner part of the sarcolemma of muscle fibers where it is associated with other proteins as part of the dystrophin-associated protein complex. Dystrophin is a large protein with three distinct domains. It's C and N terminal domains play an important role in the interaction with other proteins in the dystrophin associated complex with the middle stalk region is made up of many spectrin repeats.

Dystrophin plays an important role in stabilizing the muscle fibre against the mechanical forces of muscle contraction by providing a shock-absorbing connection between the cytoskeleton and the extracellular matrix and is also believed to have a role in signaling. The absence of dystrophin is thought to render muscle cells susceptible to stretch-induced damage and necrosis.

Duchenne and Becker's muscular dystrophy is a fatal X-linked neuromuscular disorder caused by mutations in the *DMD* gene that disrupt the open reading frame and prevent the full translation of its protein product, dystrophin. Patients develop muscle weakness in the early years of life and lose the ability to walk by their early teens; unless appropriate respiratory and cardiac treatment is initiated, affected individuals typically die before reaching their twenties.

The majority of *DMD* gene mutations are deletions (~65%) although duplications (~10%), small mutations (~22%) and deep intronic mutations (~2–3%) are also documented. Restoration of the open reading frame and dystrophin production can be achieved by exon skipping using antisense oligonucleotides targeted to splicing elements. This truncated form will contain a shorten stalk region but will still contain the C and N terminal domains. This approach aims to transform the Duchenne muscular dystrophy phenotype to that of the milder disorder, Becker muscular dystrophy, typically caused by in-frame dystrophin deletions that allow the production of an internally deleted but partially functional dystrophin. There is ongoing debate regarding the

functional properties of the different internally deleted dystrophins produced by exon skipping for different mutations; more insight would be valuable to improve and better predict the outcome of exon skipping clinical trials.

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DANIELA I VERTHELYI
02/24/2021 11:20:21 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: February 5, 2021

To: Teresa Buracchio, M.D.
Division of Neurology 1 (DN1)

Michael Matthews, MS, RAC, Regulatory Project Manager, (DN1)

Tracy Peters, PharmD, Associate Director for Labeling, (DN1)

From: Sapna Shah, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for AMONDYS 45 (casimersen) injection, for intravenous use

NDA: 213026

In response to DN1 consult request dated August 18, 2020, OPDP has reviewed the proposed product labeling (PI), and carton and container labeling for the original NDA submission for AMONDYS 45 (casimersen) injection, for intravenous use (Amondys 45).

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DN1 (Tracy Peters) on January 22, 2021 and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on November 4, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Sapna Shah at (240) 402-6068 or Sapna.Shah@fda.hhs.gov.

15 Pages of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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SAPNA P SHAH
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum:	December 8, 2020
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 213026
Product Name and Strength:	Amondys 45 (casimersen) Injection, 100 mg/2 mL (50 mg/mL)
Applicant/Sponsor Name:	Sarepta Therapeutics, Inc.
OSE RCM #:	2020-1342-1
DMEPA Safety Evaluator:	Vandna Kishore, R.Ph., CPH, RAC-US
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on November 4, 2020 for Amondys 45. The Division of Neurology 1 (DN 1) requested that we review the revised container label and carton labeling for Amondys 45 (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Kishore V. Label and Labeling Review for Amondys 45 (NDA 213026). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 October 16. RCM No.: 2020-1342.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON NOVEMBER 4, 2020

Container labels[b]

[b] The November 4, 2020 submission contained two versions of the draft vial label that are identical except for the barcode/part number and location of the lot number and expiration date. In response to the Agency's email correspondence dated November 27,2020, Sarepta provided the following rationale for the two vial labels: Vials of AMONDYS 45 may be labeled using different labeling equipment. The vial label layouts provided with two different part numbers allows the lot and expiration date to be printed in the correct location for each piece of equipment. Sarepta has identified an additional packaging vendor that will require a different vial label layout that will submitted as an annual reportable change. All of the vial labels submitted to FDA will be used.

Carton labeling

(b) (4)

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/s/

VANDNA N KISHORE
12/08/2020 02:33:01 PM

BRIANA B RIDER
12/08/2020 02:39:29 PM

Clinical Inspection Summary

Date	12/3/2020
From	Cara Alfaro, Pharm.D.; Clinical Analyst Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Michael Matthews, Regulatory Project Manager David Hosford, M.D.; Medical Officer Teresa Buracchio, M.D.; Team Leader Division of Neurology 1 Office of Neuroscience
NDA #	213026
Applicant	Sarepta Therapeutics, Inc.
Drug	Casimersen
NME	Yes
Proposed Indication	Treatment of Duchenne muscular dystrophy (DMD) in (b) (4) patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping
Consultation Request Date	8/14/2020
Summary Goal Date	12/18/2020
Priority/Standard Review	Priority
Action Goal Date	2/25/2021
PDUFA Date	2/25/2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Iannaccone, Mathews, and Mendell were inspected in support of this NDA and covered Protocol 4045-301. The study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication.

For Protocol 4045-301, the primary efficacy endpoint supporting accelerated approval was dystrophin expression (a biological endpoint) at baseline and Week 48. With regard to this endpoint, the inspections focused on verifying whether the protocol was followed with respect to obtaining muscle biopsy samples. No significant issues were identified with regard to muscle biopsy collection, preparation, and processing.

II. BACKGROUND

Casimersen injection is being developed under NDA 213026 (IND 118086) for the treatment of Duchenne Muscular Dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping.

The sponsor has submitted interim results of an ongoing Phase 3 study, Protocol 4045-301, to support the accelerated approval of casimersen for the treatment of DMD amenable to exon 45 skipping. Accelerated approval is based on the change from baseline to Week 48 of the biological endpoint, dystrophin expression.

Protocol 4045-301

Title: "A double-blind, placebo-controlled, multicenter study with an open-label extension to evaluate the efficacy and safety of SRP-4045 [casimersen] and SRP-4053 [golodirsen] in patients with Duchenne Muscular Dystrophy"

Subjects: 90 (enrollment continuing)

Sites: 39 sites; North America 20 [United States 19, Canada 1], Western Europe (17), Eastern Europe (1), Middle East/Central Asia (1)

Study Initiation and Completion Dates: 9/7/2016 - study is ongoing

Database Cut-off Date: 5/31/2019

This is an ongoing, double-blind, placebo-controlled study of two investigational drugs, casimersen and golodirsen, in subjects with genetically confirmed DMD with deletion mutations amenable to skipping exon 45 or 53. Additional eligibility criteria included males, 7 to 13 years of age (inclusive), mean 6-Minute Walking Test (6MWT) distance of $\geq$300 and $\leq$450 meters at screening and baseline visits, and receiving a stable dose of oral corticosteroids for at least 24 weeks prior to Week 1 and dose is expected to remain constant throughout the study.

The study is comprised of three phases:
Screening phase - up to 8 weeks
Double-blind phase - 96-weeks

Subjects with DMD amenable to exon 45 skipping were randomized (2:1) to:

- Casimersen 30 mg/kg/week for 96 weeks
- Placebo for 96 weeks

Subjects with DMD amenable to exon 53 skipping were randomized (2:1) to:

- Golodirsen 30 mg/kg/week for 96 weeks
- Placebo for 96 weeks

Randomization was stratified by genotype and age. Study drug was administered as weekly IV infusions.

All subjects were to have a muscle biopsy at Baseline. A second muscle biopsy was to be collected at either Week 48 or 96:

- The first 45 subjects amenable to exon 45 skipping were to undergo muscle biopsy at Week 48 and all subsequent subjects amenable to exon 45 skipping were to undergo muscle biopsy at Week 96.
- Subjects amenable to exon 53 skipping who had completed the Week 48 muscle biopsy prior to reconsenting for Amendment 6 did not undergo a further muscle biopsy.
- Subjects amenable to exon 53 skipping who had not completed the Week 48 muscle biopsy prior to reconsenting for Amendment 6 were to undergo a muscle biopsy only at Week 96.

Open-label phase – up to 48 weeks
Following completion of the 96-week double-blind period, all subjects began the open label phase and received active treatment according to their genotype.

The primary efficacy endpoint for this study, per protocol, was the change from baseline to Week 96 on the 6-minute walk test (6MWT) comparing casimersen and golodirsen to placebo. However, the sponsor is proposing accelerated approval of casimersen based on an interim analysis (n = 43) of the biological endpoint, change from baseline to Week 48 of dystrophin expression, comparing casimersen to placebo**.** The final results of this study, with the protocol-specified primary efficacy endpoint (6MWT), will be submitted when the study is completed and will be considered confirmatory.

Rationale for Site Selection

The clinical sites were chosen primarily based on risk ranking in the site selection tool, numbers of enrolled subjects, whether the site was a surgical unit site, and prior inspectional history.

III. RESULTS

1. Susan Iannaccone, M.D.
Site #204
Children's Medical Center Dallas
2350 Stemmons Freeway, Suite 5074
Dallas, TX 75207-2700
Inspection Dates: 9/15/2020 – 9/17/2020

At this site for Protocol 4045-301, 26 subjects were screened, 9 subjects were enrolled and have completed or are continuing in this ongoing study.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of all enrolled subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, training (protocol, muscle biopsies), financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, and protocol deviations.

The inspection focused on verifying whether the protocol was followed with respect to obtaining muscle biopsies as well as the preparation and processing of the samples at the clinical site per applicable manuals. For this site, procedures outlined in the Muscle Biopsy Laboratory Manual were followed. Additionally, it was confirmed that muscle biopsies were obtained after clinical evaluation and at least 48 hours after the most recent study drug infusion, as specified by protocol.

There was no evidence of underreporting of adverse events.

2. Katherine Mathews, M.D.
Site #202
University of Iowa Department of Pediatrics
200 Hawkins Drive
Iowa City, IA 52242
Inspection Dates: 9/14/2020 – 9/16/2020

At this site for Protocol 4045-301, 4 subjects were screened, 3 subjects were enrolled and are continuing in this ongoing study.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records all enrolled subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, training (protocol, muscle biopsies), financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event

reports, laboratory results, concomitant medications, and protocol deviations.

The inspection focused on verifying whether the protocol was followed with respect to obtaining muscle biopsies as well as the preparation and processing of the samples at the clinical site per applicable manuals. Site #202, located at the University of Iowa, was one of three surgical biopsy unit sites for Protocol 4045-301. All muscle biopsy samples for Protocol 4045-301 were sent from the surgical units to the (b) (4) (b) (4) for biopsy processing. Thereafter, processed samples were sent to the sponsor, Sarepta, for analysis.

Laboratory staff were to be trained on the Muscle Biopsy Laboratory Manual which required Good Clinical Practice (GCP) training, completion of a Site Personnel Training Form, and a Certificate of Biopsy Processing Proficiency Training. The FDA field investigator verified documentation for GCP training, but the Site Personnel Training Forms and Certificate of Biopsy Processing Proficiency Training documents were not completed. The director of neuropathology was interviewed and stated that all laboratory staff who processed samples were trained on the procedures while they were developing the Biopsy Laboratory Manual with the sponsor. The FDA field investigator reviewed other documents (correspondence records and other training records) verifying that the laboratory staff were qualified and adequately trained to process the muscle biopsy samples.

In addition to the three subjects enrolled at this site, the FDA field investigator reviewed 23 biopsy reports and records for subjects enrolled at other sites who had muscle biopsies performed at this surgical hub. The FDA field investigator verified that procedures outlined in the Muscle Biopsy Laboratory Manual were followed. Additionally, it was confirmed that muscle biopsies were obtained after clinical evaluation and at least 48 hours after the most recent study drug infusion, as specified by protocol.

There was no evidence of underreporting of adverse events.

3. Jerry Mendell, M.D
Site #201
The Research Institute at Nationwide Children's Hospital
700 Children's Drive
Columbus, OH 43205
Inspection Dates: 10/21/2020 - 10/28/2020

At this site for Protocol 4045-301, 15 subjects were screened, 7 subjects were enrolled and have completed or are continuing in this ongoing study. The inspection focused on the three enrolled subjects with DMD mutations amenable to exon 45 skipping who were randomized to placebo or casimersen (data still blinded).

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records of the three enrolled subjects with DMD mutations amenable to exon 45 skipping was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB/sponsor communications, training (protocol, muscle biopsies), financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, and protocol deviations.

The inspection focused on verifying whether the protocol was followed with respect to obtaining muscle biopsies as well as the preparation and processing of the samples at the clinical site per applicable manuals. In addition to enrolling subjects, Site #201 was also one of three surgical biopsy unit sites for Protocol 4045-301. All muscle biopsy samples for Protocol 4045-301 were sent from the surgical units to the (b) (4) (b) (4) for biopsy processing. Thereafter, processed samples were sent to the sponsor, Sarepta, for analysis.

Laboratory staff were to be trained on the Muscle Biopsy Laboratory Manual, which required Good Clinical Practice (GCP) training, completion of a Site Personnel Training Form, and a Certificate of Biopsy Processing Proficiency Training. The Certificate of Biopsy Processing Proficiency Training form was available for only one of three laboratory technicians who processed samples. A Note to File from the sponsor, dated 11/1/2016, stated that this site received training on the Sarepta Muscle Biopsy Manual, the Surgical Protocol, and the Muscle Biopsy Freezing Process. This Note to File specifically mentions the other two laboratory staff that did not have documentation of training via the certificate.

In addition to the subjects enrolled at this site, the FDA field investigator reviewed biopsy collection, processing, and shipping records for 10 subjects enrolled at other sites who had muscle biopsies performed at this surgical hub. The FDA field investigator verified that procedures outlined in the Muscle Biopsy Laboratory Manual were followed.

There was no evidence of underreporting of adverse events.

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Cara Alfaro, Pharm.D.
Clinical Analyst
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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Central Document Room/NDA #213026
Division of Neurology 1/Division Director/Eric Bastings
Division of Neurology 1/Medical Team Leader/Teresa Buracchio
Division of Neurology 1/Medical Officer/David Hosford
Division of Neurology 1/Project Manager/Michael Matthews
OSI/Office Director/David Burrow
OSI/Office Deputy Director/Laurie Muldowney
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein
OSI/DCCE/GCPAB/Reviewer/Cara Alfaro
OSI/GCPAB Program Analyst/Yolanda Patague

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/s/

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LABEL AND LABELING REVIEW

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

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 16, 2020
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 213026
Product Name, Dosage Form, and Strength:	Amondys 45 (casimersen), Injection 100 mg/2 mL (50 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Sarepta Therapeutics, Inc.
FDA Received Date:	June 25, 2020
OSE RCM #:	2020-1342
DMEPA Safety Evaluator:	Vandna Kishore, R.Ph., CPH, RAC-US
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 REASON FOR REVIEW

Sarepta Therapeutics, Inc. (Sarepta) submitted a New Drug Application (NDA) for accelerated approval of casimersen. As part of the review process, the Division of Neurology 1 (DN1) requested that we review the proposed container label, and carton and Prescribing Information (PI) labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Information Request	E (N/A)
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted Prescribing Information (PI), container label and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Neurology Products (DNP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	Once a proprietary name is found conditionally acceptable, the placeholder "Tradename" should be replaced with the proprietary name throughout the	We reference our March 26, 2020 Proprietary Name Request Conditionally Acceptable letter informing the Applicant that the proprietary name, Amondys 45, was found conditionally acceptable.	Replace the placeholder "Tradename" with the conditionally acceptable proprietary name, Amondys 45, throughout the PI.

Table 2. Identified Issues and Recommendations for Division of Neurology Products (DNP)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
	prescribing information (PI).		
Section 2 Dosage and Administration - Full Prescribing Information (FPI) and Highlights of Prescribing Information (HPI)			
1.	The Dosage and Administration section of the HPI and FPI contains the abbreviation 'IV'.	Abbreviations may create the potential for prescribing or administration errors.	The abbreviation 'IV' is not used in subsequent text in the Dosage and Administration Section of the HPI or FPI (2.2). Thus, inclusion of the abbreviation is unnecessary and should be deleted.

Table 3. Identified Issues and Recommendations for Sarepta Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
ALL Carton Labeling and Container Labels			
1.	The labels and labeling contain the placeholder, "Tradename."	Once a proprietary name is found conditionally acceptable, the placeholder "Tradename" should be replaced with the proprietary name on all labels and labeling. We reference our March 26, 2020 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Amondys 45, was found conditionally acceptable.	Revise the labels and labeling to include the conditionally acceptable proprietary name, Amondys 45.
Container Label			

Table 3. Identified Issues and Recommendations for Sarepta Therapeutics, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
1.	The total drug content per total volume of the product vial is not prominently displayed.	Lack of readability may contribute to wrong dose errors.	Consider increasing the prominence of the total drug content per total volume. For example, consider swapping the position of 'Single Dose' with '(50mg/mL)' on the vial label. Such as: **100 mg/2 mL** Single Dose (50 mg/mL) Rx Only
Carton Labeling			
1.	The strength of 100 mg/2 mL is difficult to read due to the lack of contrast between the (b) (4) font and (b) (4) color banner on the carton.	Color combinations that do not afford maximum legibility of text should be avoided.	Improve the color contrast between the text and the banner for better readability.
2.	The usual dosage statement can be improved.	To ensure consistency with the physician labeling rule (PLR) formatted Prescribing Information.	Revise the statement (b) (4) to read as follows: "Dosage: See prescribing information."
3.	The product requires a specific diluent (that is, 0.9% Sodium Chloride Injection, USP) which is not stated on the carton labeling.	To emphasize the correct preparation and help avoid errors associated with using a wrong solution for dilution.	Consider adding the following statement to the side panel of the carton labeling: "Must be diluted with 0.9% Sodium Chloride Injection, USP." To accommodate this change, consider minimizing the trademark information.

4 CONCLUSION

Our evaluation of the proposed Amondys 45 Prescribing Information (PI), container label and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Sarepta Therapeutics, Inc. so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Amondys 45 that Sarepta Therapeutics, Inc. submitted on June 25, 2020.

Table 4. Relevant Product Information for Amondys 45	
Initial Approval Date	N/A
Active Ingredient	casimersen
Indication	For the treatment of relapsing Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping.
Route of Administration	Intravenous infusion
Dosage Form	Injectable
Strength	100 mg/2mL (50 mg/mL)
Dose and Frequency	30 milligrams per kilogram administered once weekly as a 35 to 60-minute intravenous (IV) infusion
How Supplied	Single-dose vials containing 100 mg/2 mL (50 mg/mL)
Storage	2 °C to 8 °C (36 °F to 46 °F). Do not freeze. Store in original carton until ready for use to protect from light.
Container Closure	(b) (4) clear glass vial, with a 13-mm opening. The vials are closed with 13mm grey (b) (4) l rubber stoppers (b) (4) and further capped with an aluminum flip-off seal.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 5, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Amondys 45 (casimersen), NDA 213026. Our search identified zero previous reviews.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Amondys 45 labels and labeling submitted on June 25, 2020 by Sarepta Therapeutics, Inc.

- Container label received on June 25, 2020.
- Carton labeling received on June 25, 2020.
- Prescribing Information (Image not shown) received on June 25, 2020, available from \\CDSESUB1\evsprod\nda213026\0006\m1\us\114-labeling\draft\labeling\proposed.docx

F.2 Label and Labeling Images

Container Label

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Carton Labeling

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: June 17, 2019

From: CDER DCRP QT Interdisciplinary Review Team

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiovascular and Renal Products /CDER

To: Yuet L Choy (Fannie), RPM
DNP

Subject: QT-IRT Consult to IND 119982 / IND 118086 / NDA 211970 (SDN 088)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 5/29/2019 regarding the sponsor's revised QT study protocol. The QT-IRT reviewed the following materials:

- Sponsor's revised protocol and summary of changes (Submission 0072, IND 119982); and
- Previous QT-IRT reviews for IND 118806 dated 05/28/2019, for IND 119982 dated 09/04/2018, for NDA 211970 dated 04/23/2019 in DARRTS.

1 QT-IRT Responses

The revised protocol is generally consistent with what has been proposed to support the QT assessment plan for golodirsen and casimersen at the time of previous QT-IRT reviews. Therefore, we find the revised protocol acceptable.

The revised protocol does not specify the number of subjects to be included in the protocol addendum. The sponsor should include sufficient number of subjects to characterize the effects of these products on the QTc interval.

2 BACKGROUND

Previously the QT-IRT concluded that an integrated approach based on in vitro hERG assay data and clinical ECG data from the Phase 3 study 4045-301, could potentially serve as a substitute of the conventional thorough QT study to characterize the QT prolongation risks of golodirsen and casimersen. The conclusions were made based on the sponsor's description of proposed protocol

amendment to study 4045-301 protocol. Specifically, the sponsor proposed to collect triplicate 12-lead ECG and matching PK samples predose, at the end of infusion, and at 3-hr (for golodirsen) or 1-3 hr (for casimersen) post the end of infusion in newly enrolled patients. The ECG data will be centrally read and the primary endpoint, QTcF will be analyzed using central tendency analysis. At the time of previous reviews, 60 patients amenable to exon 53 skipping were to be enrolled with 2:1 randomization to receive golodirsen or placebo treatment (Sponsor's waiver request, Submission 0004 under NDA 211970), and approximately 14-18 patients amenable to exon 45 skipping will be available to provide predose and postdose ECG data while on casimersen treatment (Sponsor's briefing material, Submission 0081 under IND 118086). Note that the timepoint at the end of infusion is most relevant for QT assessment given the short half-life of these oligonucleotides.

In the revised protocol, the sponsor proposes to include triplicate ECG and matching PK samples at predose (baseline), at the end of infusion, and at 1 to 3 hours after the end of infusion, after the first dose and at Week 96 visit during the double-blinded phase, and on Week 1 of the open-label treatment phase. The sampling schedule covers the most important timepoint (i.e. the end of infusion) and is generally consistent with what was proposed at the time of previous QT-IRT reviews. ECG acquisition method is consistent with previously discussed (i.e. collected in replicate and immediate before PK sampling; centrally read). Therefore, we find the revised protocol acceptable for QT assessment purposes.

The revised protocol does not specify the number of subjects to be affected by the protocol addendum. Whether a sufficient number of subjects could be enrolled to power the QT assessment is the sponsor's risk.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

NAN ZHENG
06/17/2019 11:57:58 AM

LARS JOHANNESEN
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CHRISTINE E GARNETT
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VANDNA N KISHORE
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BRIANA B RIDER
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