DOCUMENT INFORMATION PAGE

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Application #(s):	NDA 213026
Communication Type:	Correspondence
Communication Group:	NDA Action
Communication Name:	Accelerated Approval
Communication ID:	COR-NDAACTION-04
Drafted by:	Michael Matthews
Clearance History:	Sally Yasuda 02/16/2021
Finalized:	Eric B 25Feb21
Filename:	
Signatory Authority:	NMEs and 351(a) BLAs must be signed by the Office Director or Deputy Office Director. Person who is covering for the signatory authority can sign on their behalf (i.e., the signature block on the letter will not change).
Use Statement:	Use when approving an NDA under 21 CFR 314.510 (approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity).
Notes:	**Note:** Remember to check for acceptability of facility **prior to issuing approval letter**. **Labeling:** Before attaching labeling, ensure that the following items have been addressed (see "Final Check of Labeling Format Before Attaching Documents to Approval Letter" slide presentation on *LDT's intranet site* for details): 1) Remove annotations (e.g., tracked changes, comments, content in headers/footers); however, page numbers are allowed (see #5) 2) Remove line numbers 3) Assess number of columns in three sections of labeling (two columns for Highlights and Table of Contents, and one-column for Full Prescribing Information). If incorrect, ask applicant to address. 4) Correct/update dates in Highlights (e.g., Initial U.S. Approval, Recent Major Changes, and Revision Date)

	5) If page numbers are included, ensure first page of each labeling document starts with Page #1 (e.g. Prescribing Information, Patient Package Insert, Medication Guide, and Instructions for Use all start with Page #1)
Additional Information	**TO BE COMPLETED BY CLINICAL:** Maximum Daily Dose (MDD): Enter MDD(s) for drug product being approved Instructions: 1. MDD must be provided in one of the following three units, as appropriate: milligrams (mg), milliliters (ml), grams (g) 2. MDD must be provided as a whole number

Version: 10/22/2020

END OF DOCUMENT INFORMATION PAGE

The letter begins on the next page.

FDA U.S. FOOD & DRUG ADMINISTRATION

NDA 213026

ACCELERATED APPROVAL

Sarepta Therapeutics, Inc.
Attention: Carl Denny
Executive Director, Global Regulatory Affairs
215 First Street, Suite 415
Cambridge, MA 02142

Dear Mr. Denny:

Please refer to your new drug application (NDA) dated June 25, 2020, received June 25, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Amondys 45 (casimersen) injection.

This new drug application provides for the use of Amondys 45 (casimersen) injection 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.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on November 4, 2020, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 213026**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Amondys 45 (casimersen) injection shall be 24 months from the date of manufacture when stored at 5°C ± 3°C.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA. This priority review voucher (PRV) has been assigned a tracking number, PRV NDA 213026. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(l) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher.

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application, and must include the date the sponsor intends to submit the application. This notification should be prominently marked, "Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher."

- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the priority review voucher may be transferred, but each person to whom the priority review voucher is transferred must notify

FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred, the sponsor to whom the priority review voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the priority review voucher was transferred.

- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.

- The sponsor of an approved rare pediatric disease product application who is awarded a priority review voucher must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:

  - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),

  - the estimated demand in the U.S. for the product, and

  - the actual amount of product distributed in the U.S.

You may also review the requirements related to this program by visiting FDA's Rare Pediatric Disease Priority Review Voucher Program web page.[3]

ADVISORY COMMITTEE

Your application for Amondys 45 was not referred to an FDA advisory committee because the safety profile of casimersen is acceptable, the clinical trial design is acceptable, and the findings on the surrogate marker are clear.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval. We remind you of your postmarketing requirement specified in your

[3] https://www.fda.gov/industry/developing-products-rare-diseases-conditions/rare-pediatric-disease-rpd-designation-and-voucher-programs

submission dated February 9, 2021. This requirement, along with required completion dates, is listed below.

4005-1 In order to verify the clinical benefit of casimersen, complete Study 4045-301 (Essence), A Double-Blind, Placebo-Controlled, Multicenter Study with an Open-Label Extension to Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in Patients with Duchenne Muscular Dystrophy. The study includes a randomized, double-blind, placebo-controlled period of 96-weeks and concludes after an open label extension period to 144 weeks. The primary endpoint will be the 6-minute walk test.

Draft Protocol Submission: 11/2015 (submitted)
Final Protocol Submission: 03/2019 (submitted)
Trial Completion: 04/2024
Final Report Submission: 10/2024

Submit clinical protocols to your IND 118086 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

REQUIRED PEDIATRIC ASSESSMENTS

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 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 this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify unexpected serious risks of QT prolongation on the ECG, carcinogenicity, or immunogenicity, or an unexpected serious risk of particle formation.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

4005-2 Submit ECG data from Study 4045-301 to support a request to waive a thorough QT study. If these data do not support a thorough QT study waiver, you will need to evaluate the effect of casimersen on the QTc interval in a dedicated study, as per the ICH E14 guideline.

The timetable you submitted on February 9, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 11/2015 (submitted)
Final Protocol Submission: 03/2019 (submitted)
Study Completion: 04/2024
Final Report Submission: 10/2024

4005-3 A two-year carcinogenicity study of intravenously administered casimersen in rat.

The timetable you submitted on February 9, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 04/2021
Final Protocol Submission: 06/2021
Study Completion: 07/2024
Final Report Submission: 10/2024

4005-4 A 26-week carcinogenicity study of casimersen, administered by a clinically relevant route, in an appropriate transgenic mouse model.

The timetable you submitted on February 9, 2021, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 04/2021
Final Protocol Submission: 06/2021
Study Completion: 08/2022
Final Report Submission: 11/2022

4005-5 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.

The timetable you submitted on February 9, 2021, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/2021
Study Completion:	07/2021
Final Report Submission:	09/2021

4005-6 Evaluate patient immune responses to dystrophin in patients from Study 4045-301. Test collected samples 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. The final report submission should include the final clinical study report and the 96-week immunogenicity evaluation. The Final Immunogenicity Report should include the 144-week data.

The timetable you submitted on February 9, 2021, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	08/2020 (submitted)
Study Completion:	04/2024
Final Report Submission:	10/2024
Final Immunogenicity Report Submission:	04/2025

4005-7 Develop and validate assays to measure antibodies to casimersen. The assays should measure IgM, IgG and IgE antibody isotypes. Evaluate the samples from patients in Study 4045-101 and Study 4045-301 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. The final report submission should include the final clinical study report and the 96-week immunogenicity evaluation. The Final Immunogenicity Report should include the 144-week data.

The timetable you submitted on February 9, 2021, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	9/2021
Assay Validation Report Submission:	9/2021
Study Completion:	04/2024
Final Report Submission:	10/2024
Final Immunogenicity Report Submission:	04/2025

4005-8 We note a recent change in the analytical method for particulate matter characterization from USP <788> Microscopy (Method 2) to USP <788> Light Obscuration (Method 1) for release and stability testing. Submit interim particulate matter stability data using the revised analytical method (i.e., Method 1) as soon as the data are available per the proposed schedule outlined in the table entitled “Table 1: Estimated Timing for Casimersen Stability Data Using USP <788> Method 1” in the document entitled “qualinfo-amend.pdf” in Section 1.11.1 of the amendment submitted on October 06, 2020.

The timetable you submitted on February 9, 2021, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	05/2021
Study Completion:	10/2023
Final Report Submission:	12/2023

4005-9 The freeze/thaw and in-use stability data provided in the original submission used USP <788> Microscopy (Method 2) for particulate matter characterization. Repeat both studies using the USP <788> Light Obscuration (Method 1) and submit the results in a supplement. These repeat studies should be performed using one batch of to-be-marketed (TBM) drug product manufactured at the commercial site.

The timetable you submitted on February 9, 2021, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/2021
Study Completion:	08/2021
Final Report Submission:	10/2021

4005-10 Per the document entitled “qual-info.pdf” in the amendment submitted on September 14, 2020, you plan to evaluate the use of surfactants as an approach to reduce the level of API-related subvisible and visible particles in the drug product, using eteplirsen drug product as a model system.

Independently perform these surfactant studies using casimersen drug product as well.

The timetable you submitted on February 9, 2021, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	05/2021
Study Completion:	12/2023
Final Report Submission:	03/2024

4005-11 Per the submission, the leachable study was performed using Lot 94EY-DT01 after 54 months of storage in the inverted position at 5 ± 3 °C. Repeat the leachable study using one batch of to-be-marketed (TBM) drug product manufactured at the commercial site during stability, where the data is collected at multiple stability time-points per the testing frequency recommended in ICH Q1A(R2).

The timetable you submitted on February 9, 2021, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	05/2021
Study Completion:	12/2024
Final Report Submission:	03/2025

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Submit clinical protocol(s) to your IND 118086 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).** Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

REQUESTED PHARMACOVIGILANCE

We request that you perform postmarketing surveillance for serious renal toxicity events. Provide expedited reporting of serious renal toxicity events, and provide comprehensive summaries and analyses of these events as part of your required postmarketing safety reports [e.g., periodic safety update reports (PSURs)]. In the analysis of each case, provide an assessment of causality, with documentation of risk factors and results of all assessments that support the diagnosis or the causality, along with duration of Amondys 45 therapy, the time from first Amondys 45 dose to adverse event onset, the time from last Amondys 45 dose prior to the event onset, concomitant therapies, treatment given for the event, and outcome. Include a comparison of the rates of renal failure and glomerulonephritis to background rates of those events in the general population (overall and stratified by age), as well as background rates (if available) for patients with Duchenne muscular dystrophy (DMD) (overall and stratified by age).

PROMOTIONAL MATERIALS

Under 21 CFR 314.55, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.55, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, contact Michael Matthews, Regulatory Project Manager, at Michael.Matthews@fda.hhs.gov, or at (301) 796-3047.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AMONDYS 45 safely and effectively. See full prescribing information for AMONDYS 45.

AMONDYS 45 (casimersen) injection, for intravenous use
Initial U.S. Approval: 2021

INDICATIONS AND USAGE

AMONDYS 45 is an antisense oligonucleotide indicated 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. This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with AMONDYS 45 *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials. (1)

DOSAGE AND ADMINISTRATION

- Serum cystatin C, urine dipstick, and urine protein-to-creatinine ratio should be measured before starting AMONDYS 45 (2.1)
- 30 milligrams per kilogram of body weight once weekly (2.2)
- Administer as an intravenous (IV) infusion over 35 to 60 minutes via an in-line 0.2 micron filter (2.2, 2.4)
- Dilution required prior to administration (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/2 mL in a single-dose vial (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Kidney Toxicity: Based on animal data, may cause kidney toxicity. Kidney function should be monitored; creatinine may not be a reliable measure of renal function in DMD patients. (5.1, 13.2)

ADVERSE REACTIONS

The most common adverse reactions (incidence >20% and at least 5% higher than placebo) were upper respiratory tract infection, cough, pyrexia, headache, arthralgia, and oropharyngeal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Sarepta Therapeutics, Inc. at 1-888-SAREPTA (1-888-727-3782) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 2/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

AMONDYS 45 is indicated 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. This indication is approved under accelerated approval based on an increase in dystrophin production in skeletal muscle observed in patients treated with AMONDYS 45 *[see Clinical Studies (14)]*. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Monitoring to Assess Safety

Serum cystatin C, urine dipstick, and urine protein-to-creatinine ratio (UPCR) should be measured before starting AMONDYS 45. Consider measurement of glomerular filtration rate prior to initiation of AMONDYS 45. Monitoring for kidney toxicity during treatment is recommended. Obtain the urine sample prior to infusion of AMONDYS 45 or at least 48 hours after infusion *[see Warnings and Precautions (5.1)]*.

2.2 Dosing Information

The recommended dosage of AMONDYS 45 is 30 milligrams per kilogram administered once weekly as a 35 to 60-minute intravenous infusion via an in-line 0.2 micron filter.

If a dose of AMONDYS 45 is missed, it may be administered as soon as possible after the scheduled dose.

2.3 Preparation Instructions

AMONDYS 45 is supplied in single-dose vials as a preservative-free concentrated solution that requires dilution prior to administration. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Use aseptic technique.

a. Calculate the total dose of AMONDYS 45 to be administered based on the patient's weight and the recommended dose of 30 milligrams per kilogram. Determine the volume of AMONDYS 45 needed and the correct number of vials to supply the full calculated dose.

b. Allow the vials to warm to room temperature. Mix the contents of each vial by gently inverting 2 or 3 times. Do not shake.

c. Visually inspect each vial of AMONDYS 45. The solution is a clear to slightly opalescent, colorless liquid, and may contain trace amounts of small, white to off-white amorphous particles. Do not use if the solution in the vials is cloudy, discolored or

contains extraneous particulate matter other than trace amounts of small, white to off-white amorphous particles.

d. With a syringe fitted with a 21-gauge or smaller bore non-coring needle, withdraw the calculated volume of AMONDYS 45 from the appropriate number of vials. To avoid dulling the needle and fragmenting the stoppers, replace the needle periodically during preparation.

e. Dilute the withdrawn AMONDYS 45 in 0.9% Sodium Chloride Injection, USP, to make a total volume of 100 to 150 mL. Gently invert 2 to 3 times to mix. Do not shake. Visually inspect the diluted solution. Do not use if the solution is cloudy, discolored or contains extraneous particulate matter other than trace amounts of small, white to off-white amorphous particles.

f. Administer the diluted solution via an in-line 0.2 micron filter.

g. AMONDYS 45 contains no preservatives and should be administered immediately after dilution. Complete infusion of diluted AMONDYS 45 within 4 hours of dilution. If immediate use is not possible the diluted product may be stored for up to 24 hours at 2 °C to 8 °C (36 °F to 46 °F). Do not freeze. Discard unused AMONDYS 45.

2.4 Administration Instructions

Application of a topical anesthetic cream to the infusion site prior to administration of AMONDYS 45 may be considered.

AMONDYS 45 is administered via intravenous infusion. Flush the intravenous access line with 0.9% Sodium Chloride Injection, USP, prior to and after infusion.

Infuse the diluted AMONDYS 45 over 35 to 60 minutes via an in-line 0.2 micron filter. Do not mix other medication with AMONDYS 45 or infuse other medications concomitantly via the same intravenous access with AMONDYS 45.

3 DOSAGE FORMS AND STRENGTHS

AMONDYS 45 is a clear to slightly opalescent, colorless liquid and may contain trace amounts of small, white to off-white amorphous particles and is available as:

- Injection: 100 mg/2 mL (50 mg/ mL) solution in a single-dose vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Kidney Toxicity

Kidney toxicity was observed in animals who received casimersen *[see Use in Specific Populations (8.4) and Nonclinical Toxicology (13.2)]*. Although kidney toxicity was not observed in the clinical studies with AMONDYS 45, kidney toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides. Kidney function should be monitored in patients taking AMONDYS 45. Because of the effect of reduced skeletal muscle mass on creatinine measurements, creatinine may not be a reliable measure of kidney function in DMD patients. Serum cystatin C, urine dipstick, and urine protein-to-creatinine ratio should be measured before starting AMONDYS 45. Consider also measuring glomerular filtration rate using an exogenous filtration marker before starting AMONDYS 45. During treatment, monitor urine dipstick every month, and serum cystatin C and urine protein-to-creatinine ratio (UPCR) every three months. Only urine expected to be free of excreted AMONDYS 45 should be used for monitoring of urine protein. Urine obtained on the day of AMONDYS 45 infusion prior to the infusion, or urine obtained at least 48 hours after the most recent infusion, may be used. Alternatively, use a laboratory test that does not use the reagent pyrogallol red, as this reagent has the potential to cross react with any AMONDYS 45 that is excreted in the urine and thus lead to a false positive result for urine protein.

If a persistent increase in serum cystatin C or proteinuria is detected, refer to a pediatric nephrologist for further evaluation.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the AMONDYS 45 clinical development program, 76 patients received at least one intravenous dose of AMONDYS 45 (30 mg/kg). All patients were male and had genetically confirmed Duchenne muscular dystrophy. Age at study entry was 7 to 20 years (mean 9.9 years). Most (88%) patients were White, and 9% were Asian.

AMONDYS 45 was studied in a double-blind, placebo-controlled study (Study 1).

Patients in ongoing Study 1 received AMONDYS 45 (n=57) 30 mg/kg or placebo (n=31) intravenously once weekly for up to 96 weeks, after which all patients received or will receive AMONDYS 45 30 mg/kg for up to 48 weeks.

Adverse reactions observed in ≥20% of patients treated with AMONDYS 45 and 5% more frequently than in the placebo group in Study 1 are shown in Table 1.

Table 1. Adverse Reactions Occurring in at Least 20% of Patients Treated with AMONDYS 45 and at a Rate at Least 5% More Frequently than in the Placebo Group in Study 1

Adverse Reaction	AMONDYS 45 30 mg/kg Once Weekly (n = 57) %	Placebo (n = 31) %
Upper Respiratory Tract Infections*	65	55
Cough	33	26
Pyrexia	33	23
Headache	32	19
Arthralgia	21	10
Oropharyngeal Pain	21	7

*Includes upper respiratory infection, pharyngitis, nasopharyngitis, and rhinitis.

Other adverse reactions that occurred in at least 10% of patients treated with AMONDYS 45, and that were reported at a rate at least 5% more frequently in the AMONDYS 45 group than in the placebo group, were: ear pain, nausea, ear infection, post-traumatic pain, and dizziness and light-headedness.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no human or animal data available to assess the use of AMONDYS 45 during pregnancy. In the U.S. general population, major birth defects occur in 2% to 4% and miscarriage occurs in 15% to 20% of clinically recognized pregnancies.

8.2 Lactation

Risk Summary

There are no human or animal data to assess the effect of AMONDYS 45 on milk production, the presence of casimersen in milk, or the effects of AMONDYS 45 on the breastfed infant.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AMONDYS 45 and any potential adverse effects on the breastfed infant from AMONDYS 45 or from the underlying maternal condition.

8.4 Pediatric Use

AMONDYS 45 is indicated for the treatment of DMD in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 45 skipping, including pediatric patients *[see Clinical Studies (14)]*.

Juvenile Animal Toxicity Data

Intravenous administration of casimersen (0, 100, 300, and 900 mg/kg) to juvenile male rats once weekly for 10 weeks (postnatal days 14 to 77) resulted in renal tubular degeneration/necrosis at the highest dose tested. No effects were observed on the male reproductive system, neurobehavioral development, or immune function. At the overall no-effect dose (300 mg/kg), plasma exposure (AUC) was 4 times that in humans at the recommended human dose of 30 mg/kg/week.

8.5 Geriatric Use

DMD is largely a disease of children and young adults; therefore, there is no experience with AMONDYS 45 in geriatric DMD patients.

8.6 Patients with Renal Impairment

Renal clearance of casimersen is decreased in non-DMD adults with renal impairment based on estimated glomerular filtration rate (calculated using the Modification of Diet and Renal Disease (MDRD) equation) *[see Clinical Pharmacology (12.3)]*. However, because of the effect of reduced skeletal muscle mass on creatinine measurements in DMD patients, no specific dosage adjustment can be recommended for DMD patients with renal impairment based on estimated glomerular filtration rate. Patients with known renal function impairment should be closely monitored during treatment with AMONDYS 45.

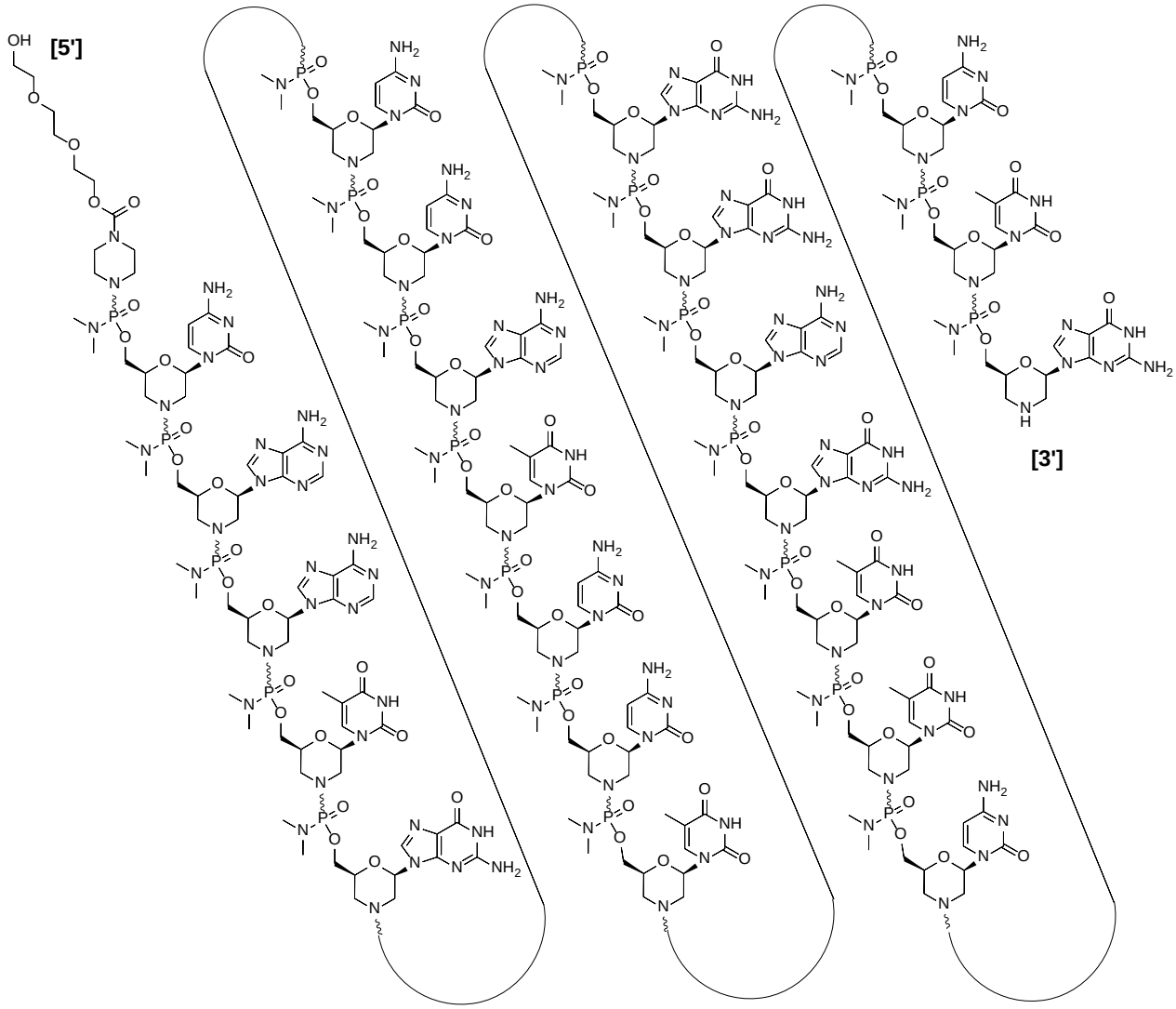
11 DESCRIPTION

AMONDYS 45 (casimersen) injection is a sterile, aqueous, preservative-free, concentrated solution for dilution prior to intravenous administration. AMONDYS 45 is a clear to slightly opalescent, colorless liquid and may contain trace amounts of small, white to off-white amorphous particles. AMONDYS 45 is supplied in single-dose vials containing 100 mg casimersen (50 mg/mL). AMONDYS 45 is formulated as an isotonic phosphate buffered saline solution with an osmolality of 260 to 320 mOSM and a pH of 7.5. Each milliliter of AMONDYS 45 contains: 50 mg casimersen; 0.2 mg potassium chloride; 0.2 mg potassium phosphate monobasic; 8 mg sodium chloride; and 1.14 mg sodium phosphate dibasic, anhydrous, in water for injection. The product may contain hydrochloric acid or sodium hydroxide to adjust pH.

Casimersen is an antisense oligonucleotide of the phosphorodiamidate morpholino oligomer (PMO) subclass. PMOs are synthetic molecules in which the five-membered ribofuranosyl rings

found in natural DNA and RNA are replaced by a six-membered morpholino ring. Each morpholino ring is linked through an uncharged phosphorodiamidate moiety rather than the negatively charged phosphate linkage that is present in natural DNA and RNA. Each phosphorodiamidate morpholino subunit contains one of the heterocyclic bases found in DNA (adenine, cytosine, guanine, or thymine). Casimersen contains 22 linked subunits. The sequence of bases from the 5' end to 3' end is CAATGCCATCCTGGAGTTCCTG. The molecular formula of casimersen is $C_{268}H_{424}N_{124}O_{95}P_{22}$ and the molecular weight is 7584.5 daltons.

The structure of casimersen is:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Casimersen is designed to bind to exon 45 of dystrophin pre-mRNA resulting in exclusion of this exon during mRNA processing in patients with genetic mutations that are amenable to exon 45

skipping. Exon 45 skipping is intended to allow for production of an internally truncated dystrophin protein in patients with genetic mutations that are amenable to exon 45 skipping *[see Clinical Studies (14)]*.

12.2 Pharmacodynamics

In the interim analysis of muscle biopsy tissue obtained at baseline and at Week 48 from patients in Study 1, patients who received AMONDYS 45 (n=27) demonstrated a significant increase in skipping of exon 45 ($p<0.001$) compared to baseline, demonstrated by reverse transcription digital droplet polymerase chain reaction (RT-ddPCR). Patients who received placebo (n=16) did not demonstrate a significant increase in exon 45 skipping ($p=0.808$). The level of exon skipping is positively correlated with dystrophin protein expression *[see Clinical Studies (14)]*.

In Study 1 *[see Clinical Studies (14)]*, dystrophin levels as assessed by the Sarepta Western blot assay increased from 0.93% (SD 1.67) of normal at baseline to 1.74% (SD 1.97) of normal after 48 weeks of treatment with AMONDYS 45. The mean change from baseline in dystrophin after 48 weeks of treatment with AMONDYS 45 was 0.81% (SD 0.70) of normal levels ($p<0.001$). This increase in dystrophin protein expression after treatment with AMONDYS 45 positively correlated with the level of exon skipping. The mean change from baseline in dystrophin after 48 weeks of treatment with placebo was 0.22% (SD 0.49). Patients who received AMONDYS 45 showed a significantly greater increase in dystrophin protein levels from baseline to Week 48 compared to those who received placebo (mean difference of 0.59%; $p = 0.004$). Dystrophin levels assessed by Western blot can be meaningfully influenced by differences in sample processing, analytical technique, reference materials, and quantitation methodologies. Therefore, comparing dystrophin results from different assay protocols will require a standardized reference material and additional bridging studies.

Correct localization of dystrophin to the sarcolemma in patients treated with AMONDYS 45 was demonstrated by immunofluorescence staining.

12.3 Pharmacokinetics

The pharmacokinetics of casimersen was evaluated in DMD patients following administration of intravenous (IV) doses ranging from 4 mg/kg/week to 30 mg/kg/week (i.e., recommended dosage). Following a single IV dose of casimersen, C_{max} was reached at the end of infusion. Casimersen exposure increased in a proportional manner with dose increment. No accumulation of casimersen was observed in plasma following once weekly dosing. Inter-subject variability (as %CV) for casimersen C_{max} and AUC ranged from 12% to 34% and 16% to 34%, respectively.

Distribution

Binding of casimersen to human plasma protein was not concentration-dependent and ranged from 8.4% to 31.6%. The mean apparent volume of distribution at steady state (V_{ss}) was 367 mL/kg (%CV = 28.9) following a 30 mg/kg dose of casimersen administered intravenously.

Elimination

The plasma clearance (CL) of casimersen was 180 mL/hr/kg at the 30 mg/kg dose. The elimination half-life ($t_{1/2}$) was 3.5 hours (SD 0.4 hours).

Metabolism

Casimersen is metabolically stable in human hepatic microsomal incubations. No metabolites were detected in plasma or urine.

Excretion

Casimersen is mostly excreted unchanged in the urine. In a clinical study with radiolabeled casimersen, more than 90% of the drug was excreted in urine, with negligible fecal excretion.

Specific Populations

Age, Sex & Race

The pharmacokinetics of AMONDYS 45 have been evaluated in male DMD patients 9 to 20 years of age. There is no experience with the use of AMONDYS 45 in DMD patients 65 years of age or older. AMONDYS 45 has not been studied in female patients. The potential impact of race on the pharmacokinetics of casimersen is unknown.

Patients with Renal Impairment

The effect of renal impairment on the pharmacokinetics of casimersen was evaluated in non-DMD subjects aged 35 to 65 years with Stage 2 chronic kidney disease (CKD) (n=8, estimated glomerular filtration rate [eGFR] ≥60 and <90 mL/min/1.73 m^2) or Stage 3 CKD (n=8, eGFR ≥30 and <60 mL/min/1.73 m^2) and matched healthy subjects (n=9, eGFR ≥90 mL/min/1.73 m^2). Subjects received a single 30 mg/kg intravenous dose of casimersen.

In subjects with Stage 2 or Stage 3 CKD, exposure (AUC) increased approximately 1.2-fold and 1.8-fold, respectively, compared with subjects with normal renal function. The C_{max} in subjects with Stage 2 CKD was similar to C_{max} in subjects with normal renal function; in subjects with Stage 3 CKD, there was a 1.2-fold increase in C_{max} compared with subjects with normal renal function. The effect of Stage 4 or Stage 5 CKD on casimersen pharmacokinetics and safety has not been studied.

Estimated GFR values derived from MDRD equations and the threshold definitions for various CKD stages in otherwise healthy adults would not be generalizable to pediatric patients with DMD. Therefore, no specific dosage adjustment can be recommended for patients with renal impairment *[see Use in Specific Populations (8.6)]*.

Patients with Hepatic Impairment

AMONDYS 45 has not been studied in patients with hepatic impairment. However, casimersen does not undergo hepatic metabolism, and the systemic clearance of casimersen is not expected to be affected by hepatic impairment.

Drug Interaction Studies

Based on *in vitro* data, casimersen has a low potential for clinically relevant drug-drug interactions with major CYP enzymes and transporters.

Casimersen did not inhibit CYP1A2, CYP2B6, CYP2C8, or CYP2D6 *in vitro*. Casimersen was a potential inhibitor of CYP3A4/5, CYP2C9, and CYP2C19 *in vitro;* however, considering its short plasma half-life and lack of plasma accumulation with the weekly dosing regimen, clinical drug interaction with substrates for these enzymes is unlikely. Casimersen did not induce

CYP1A2, CYP2B6, or CYP3A4 either at the mRNA or protein (activity) level. Casimersen was not metabolized by human hepatic microsomes and was not a substrate or strong inhibitor of the key human drug transporters tested (OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE1, MATE2-K, P-gp, BCRP, and MRP2).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies have not been conducted with casimersen.

Mutagenesis

Casimersen was negative in in vitro (bacterial reverse mutation assay and chromosomal aberration assay in CHO cells) and in vivo (mouse bone marrow micronucleus) assays.

Impairment of Fertility

Fertility studies in animals were not conducted with casimersen. No effects of casimersen were observed on the male reproductive system following weekly administration to male mice at subcutaneous doses up to 960 mg/kg for 26 weeks or to male monkeys at intravenous doses up to 640 mg/kg for 39 weeks. Plasma exposures at the highest doses tested in mouse and monkey were approximately 9 and 35 times, respectively, that in humans at the recommended human dose of 30 mg/kg/week.

13.2 Animal Toxicology and/or Pharmacology

Kidney toxicity was observed in studies in male mice and rats *[see Warnings and Precautions (5.1)]*.

In male mice, casimersen was administered weekly for 12 weeks (0, 12, 120, or 960 mg/kg) or 22 weeks (0, 300, 960, or 2000 mg/kg) by intravenous injection or for 26 weeks by subcutaneous injection (0, 300, 600, or 960 mg/kg). In the 12-week study, microscopic findings in kidney (cytoplasmic basophilia and microvacuolation) were observed at the highest dose tested. In the 22- and 26-week studies, renal tubular degeneration was observed at all doses. A no-effect dose for adverse effects on kidney was not identified. Plasma exposure (AUC) at the lowest dose tested in the 26-week study (300 mg/kg) was approximately 2 times that in humans at the recommended human dose (RHD) of 30 mg/kg/week.

In male rats, intravenous administration of casimersen (0, 250, 500, 1000, or 2000 mg/kg) weekly for 13 weeks resulted in renal tubular degeneration at all doses tested; at the highest dose, the microscopic changes were accompanied by increases in blood urea nitrogen. A no-effect dose for adverse effects on kidney was not identified. Plasma exposure (AUC) at the lowest dose tested were approximately 4 times that in humans at the RHD.

14 CLINICAL STUDIES

The effect of AMONDYS 45 on dystrophin production was evaluated in one study in male DMD patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 45 skipping (Study 1; NCT02500381).

Study 1 is an ongoing, double-blind, placebo-controlled, multicenter study designed to evaluate the safety and efficacy of AMONDYS 45 in ambulatory patients. The study is planned to enroll a total of 111 patients, age 7 to 13 years, randomized to AMONDYS 45 or placebo in a 2 to 1 ratio. Patients were required to have been on a stable dose of oral corticosteroids for at least 24 weeks prior to dosing with AMONDYS 45 or placebo. Following the 96-week double-blind period, all patients began or are to begin an additional 48 week open-label treatment period. Interim efficacy was assessed based on change from baseline in the dystrophin protein level (measured as % of the dystrophin level in healthy subjects, i.e., % of normal) at Week 48 of Study 1. Interim results from 43 evaluable patients (n = 27, AMONDYS 45; n = 16, placebo) who had a muscle biopsy at Week 48 of the double-blind period are presented in Table 2. Patients who provided muscle biopsy data had a median age of 9 years and were 86% White.

Table 2. Dystrophin Levels (% of Normal) at Baseline and at Week 48 from Muscle Biopsy Interim Results in Study 1

	Placebo	AMONDYS 45 30 mg/kg/week IV
Dystrophin by Sarepta Western blot	n=16	n=27
Baseline Mean (SD)	0.54 (0.79)	0.93 (1.67)
Week 48 Mean (SD)	0.76 (1.15)	1.74 (1.97)
Change from Baseline Mean (SD)	0.22 (0.49)	0.81 (0.70)
p-value Change from Baseline to Week 48	0.09	<0.001
Between group mean difference	0.59	
p-value between groups	p=0.004	

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

AMONDYS 45 injection is supplied in single dose vials. The solution is a clear to slightly opalescent, colorless liquid, and may contain trace amounts of small, white to off-white amorphous particles.

- Single-dose vials containing 100 mg/2 mL (50 mg/mL) NDC 60923-227-02

16.2 Storage and Handling

Store AMONDYS 45 at 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.

17 PATIENT COUNSELING INFORMATION

Kidney Toxicity

Inform patients nephrotoxicity has occurred with drugs similar to AMONDYS 45. Advise patients of the importance of monitoring for kidney toxicity by their healthcare providers during treatment with AMONDYS 45 *[see Warnings and Precautions (5.1)]*.

Manufactured for:
Sarepta Therapeutics, Inc.
Cambridge, MA 02142 USA

AMONDYS 45
(casimersen)

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/

ERIC P BASTINGS
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