CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213026Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 118086

MEETING MINUTES

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

Dear Mr. O'Malley:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for casimersen (SRP-4045).

We also refer to the meeting between representatives of your firm and the FDA on June 5, 2019. The purpose of the meeting was to discuss the content and format of your planned New Drug Application (NDA).

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

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

Sincerely,

{See appended electronic signature page}

Eric Bastings, M.D.
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	June 5, 2019, 3:00 – 4:00 p.m. EDT
Meeting Location:	FDA White Oak Building 22, Conference Room 1315
Application Number:	IND 118086
Product Name:	Casimersen (SRP-4045)
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
Sponsor Name:	Sarepta Therapeutics, Inc.
Meeting Chair:	Billy Dunn, M.D.
Meeting Recorder:	Fannie Choy, R.Ph.

FDA ATTENDEES

Office of Drug Evaluation I
Ellis Unger, MD, Director

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

Office of New Drug Products
Martha Heimann, PhD, Neurology CMC Lead

Office of Biotechnology Products
Ashutosh Rao, PhD, Chief, Laboratory of Applied Biochemistry, Division of Biotechnology Review and Research III (DBRR III)
Thomas Biel, PhD, Biologist, DBRR III
Baikuntha Aryal, PhD, Biologist, DBRR III
Daniela Verthelyi, MD, Laboratory Chief, DBRR III
Seth Thacker, PhD, Immunogenicity Reviewer, DBRR III

Division of Biometrics I
Xiang Ling, PhD, Statistical Reviewer

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

Office of Surveillance and Epidemiology
Ingrid Chapman, PharmD, BCPS, Risk Management Analyst, DRISK

SPONSOR ATTENDEES

Sarepta Therapeutics, Inc.
Gilmore O'Neill, MD, Executive Vice President and Chief Medical Officer
Deb Steiner, MD, Executive Medical Director, Clinical Development
Helen Eliopoulos, MD, Executive Director, Regulatory Affairs
Fubao Wang, PhD, Vice President, CMC Regulatory Affairs
Shawn Harriman, PhD, Vice President, Pre-Clinical and Translational Development
Patrick O'Malley, Executive Director, Regulatory Strategy
Xiaodong Wang, Senior Director, Clinical Pharmacology
Diane Frank, PhD, Senior Director, Translational Development
Vinay Jayakumar, Associate Director, Statistical Programming, Biometrics
Mark Vivien, PharmD, Associate Director, Safety Scientist
Lixin Han, PhD, Senior Director, Biometrics

1.0 BACKGROUND

Sarepta Therapeutics, Inc., is developing casimersen (SRP-4045), a phosphorodiamidate morpholino oligomer, 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 and the Division met in a June 2013 PIND meeting to discuss the development plan for casimersen. On November 18, 2014, a Type A meeting was held to discuss the protocol design for Study 4045-301 (ESSENCE). On August 1, 2018, a type C meeting was held to discuss the acceptability of adding an interim analysis for Week 48 dystrophin expression for the casimersen portion of Study 4045-301. The sponsor is planning a New Drug Application (NDA) submission based on interim analysis of dystrophin data to be considered for accelerated approval under subpart H.

On February 8, 2019, the Agency provided written responses to the sponsor's questions related to CMC pre-submission strategy.

Sarepta has requested this pre-submission meeting to discuss the content and format of the casimersen NDA. The sponsor is planning to submit the NDA in 2019.

The Agency granted fast track designation for casimersen for the treatment of DMD patients with mutations amenable to exon 45 skipping in July 2014.

FDA sent Preliminary Comments to Sarepta Therapeutics on May 31, 2019.

2. DISCUSSION

Question 1:

The NDA for accelerated approval of casimersen will be based on an interim analysis of the de novo dystrophin protein data at Week 48 for the first 43 enrolled patients with exon 45 skip amenable mutations and evaluable dystrophin data in Phase 3 double-blind placebo-controlled Study 4045-301; functional data from 4045-301 will not be presented in the NDA. Does the Division agree with this approach?

FDA Response to Question 1:
We agree that functional data may not need to be presented in your planned NDA submission if Study 4045-301 is still ongoing at the time of submission. See response to Question 2 regarding the analysis of dystrophin data.

Meeting Discussion: There was no meeting discussion.

Question 2:

To support an accelerated approval, dystrophin protein expression as measured by Western blot and exon skipping data will be described in Module 2.7.3 (Summary of Clinical Efficacy). Additionally, percent dystrophin-positive fibers and mean dystrophin fiber intensity will be described in Module 2.7.3 with the supporting detailed information provided in analytical reports included in Module 5. Does the Division agree with the proposed approach?

FDA Response to Question 2:
Your proposed approach for submitting the dystrophin data in modules 2 and 5 is acceptable. The referenced golodirsen NDA and related protocols for the analysis of dystrophin in muscle biopsy tissue for protein expression and exon skipping are still under review. In general, your approach for using Western blot and exon skipping bioassays for measuring dystrophin protein expression is acceptable. See additional comments below.

1. Regarding your Western blot bioassay, we reference a bioanalytical inspection of your Cambridge, Massachusetts facility under NDA 211970 (golodirsen) on April 15-17, 2019. As discussed with you at the close-out, (b) (4) We further note that you submitted an amendment under IND 118086 (SD 71) to address our concern (b) (4) ; however, in the submission, you did not address the issue (b) (4) To address this concern, revise your western blot protocol and acceptance criteria (b) (4) Provide your timeline for validating and implementing this revised protocol for western blot analyses for casimersen, as well as for all your ongoing and future drug development programs.

2. In the western blot v3 method (IND 118086/SD 71, DOC-02392), your proposed acceptance criteria for accuracy and precision at percent difference (b) (4) % are wider than the FDA recommended guidance on bioanalytical method validation (2018) and are not consistent with your method validation results of (b) (4) %. Please tighten the acceptance criteria for western blot method validation parameters based on the agency recommendations and reflective of your method validation results.

3. Please see additional comments regarding the proposed immunohistochemistry bioassay below and in response to questions 4 and 12.

In this meeting package, you propose the validation (b) (4) Refer to Question 4 for comments on the proposed validation (b) (4) The items listed below require additional information to determine if these methods are appropriate for (b) (4) method validation.

i) You state (b) (4) You should clearly state these specifications, acceptance criteria, with accompanying justifications. Additionally, numerical upper and lower limits for any acceptance criteria for quantitative attributes.

(b) (4)

Meeting Discussion:

The sponsor stated that it proposes to use (b) (4) in western blot analyses. FDA agreed (b) (4) but asked the sponsor to submit data to confirm the suitability of the feature for its intended purpose and submit revised validation studies and updated western blot protocols to reflect the changes supported by its validation (b) (4) FDA further clarified that the sponsor should evaluate the parameters (b) (4) and set predetermined acceptance criteria for any quantitative parameters (b) (4) The sponsor was advised to incorporate a manual confirmation into the protocol (b) (4)

FDA corrected that the (b) (4) % stated in the original comment regarding acceptance criteria for accuracy and precision should state (b) (4) % as observed for the (b) (4) sample.

The sponsor agreed to tighten its current (b)(4)% acceptance criteria to better reflect a worst-case scenario, such as with the (b)(4) sample at (b)(4)%. The sponsor agreed to revise the western blot protocol accordingly.

FDA asked to clarify the correlation between the normal comparator samples used for the different clinical studies completed or ongoing by the sponsor. The sponsor clarified that the controls are within (b)(4)% of the previous normal control. FDA stated that this should be helpful in making cross-study comparisons between studies carried out by the sponsor.

Question 3:

The data analysis and presentation plan for the safety dataset of approximately 69 casimersen treated patients, including analysis of adverse events of interest are described below. Does the Division agree with proposed safety data analysis and presentation plan?

FDA Response to Question 3:
On face, the safety dataset appears sufficient; however, the acceptability of the final safety dataset will be a matter of review at the time of the NDA submission.

Meeting Discussion: There was no meeting discussion.

Question 4:

Sarepta plans to submit immunohistochemistry (IHC) dystrophin data for fiber intensity and Percent Dystrophin Positive Fibers (PDPF) obtained from (b)(4) analysis. (b)(4)

oes the Division agree with this approach?

FDA Response to Question 4:
We disagree for the following reasons:

(b)(4)

(b) (4)

Meeting Discussion:

The sponsor gave a presentation (b) (4)

FDA and the sponsor discussed caveats regarding the sponsor's IHC data towards making quantitative claims of dystrophin expression considering the many limitations of this inherently qualitative method. The sponsor stated that the purpose of the IHC data was to confirm localization of the truncated dystrophin protein. FDA noted that given the consensus that IHC was not useful for quantitative assessments and that each of the images used in the analysis would require significant documentation to authenticate the findings, the sponsor may consider not providing quantitative IHC data to support its NDA submission. IHC data may still be informative to qualitatively support the localization of truncated dystrophin.

FDA asked the sponsor if it plans to collect and submit (b) (4) The sponsor stated that it does plan to collect and submit this data as an exploratory endpoint.

FDA advised the sponsor to include an exon 45 mutated DMD and another, non-exon 45 mutation DMD mutated sample in its validation run to capture the differences in baseline dystrophin expression in exon 45 DMD samples as claimed by the sponsor. Both these samples could be reported as on-run controls in the analysis. FDA further clarified that inclusion of these controls would also allow the sponsor to confirm the ability of its method to distinguish differences in baseline expression based on mutation status and allow comparison with other studies of non-exon 45 mutated DMD samples. The sponsor agreed with the proposal.

The sponsor stated that it is developing (b) (4) that could be used as reference material. FDA encouraged the sponsor to submit data and description of this reference material to allow further discussion on potential application in future studies.

Post-meeting Note:

The sponsor requested the following clarification by email on June 9, 2019:

"(The sponsor) would like to get confirmation of FDA's position related to the submission of casimersen immunohistochemistry data with the proposed NDA, as it was significantly different from our assumption prior to the meeting. Can you confirm the following are appropriate conclusions from our pre-NDA meeting:

1. Dystrophin quantification using immunohistochemistry, by (b) (4) or manual pathology scoring, is not required for a complete NDA submission.
2. The absence of supportive quantitative immunohistochemistry would not impact the approvability of the NDA.
3. Representative samples of immunohistochemistry images, to support proper localization of dystrophin in the sarcolemma, would not need to be accompanied by quantitative datasets."

The Division provided the following response by email on June 10, 2019:

"We confirm that your conclusions regarding the discussion of the IHC data discussed at the casimersen pre-NDA meeting on June 5, 2019, are correct with the following edits and clarifications noted in red:

1. Dystrophin quantification using immunohistochemistry, by (b) (4) or manual pathology scoring, is not required for a complete NDA submission.
2. The absence of supportive quantitative immunohistochemistry would not impact the potential approvability of the NDA.

3. Representative samples of immunohistochemistry images, to support proper localization of dystrophin in the sarcolemma, would not need to be accompanied by quantitative datasets.

Please note that if you plan to use any of your IHC data to make quantitative claims in your NDA or use the IHC to support quantitative claims of your WB findings, we will expect to see the IHC quantitative datasets you use to make those direct or confirmatory claims. Also, be advised that this comment is specific to your casimersen development plan in exon 45 mutated DMD patients."

Question 5:

Hepatic metabolism does not appear to be a major elimination pathway for casimersen thus, Sarepta will be requesting a waiver for the conduct of a hepatic impairment study. Does the Division agree with this approach?

FDA Response to Question 5:
We agree with your proposal.

Meeting Discussion: There was no meeting discussion.

Question 6:

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

FDA Response to Question 6:
We agree that an integrated nonclinical and clinical approach may support a TQT study waiver for this antisense oligonucleotide that has a large hERG safety margin. You should submit the following data to support a TQT study waiver:

1) For IC50 estimation of drug inhibition on ion channel currents, we currently accept room temperature data, as described in the voltage protocol document available at http://cipaproject.org/ion-channel-protocols/. Patch clamp studies of drug effects on cardiac ion channels at 37C are routinely performed at the agency.
2) To facilitate the review of the hERG assay study reports, please submit the following information for each experiment:
    a. Raw and unaltered electrophysiology records (e.g., no baseline subtraction or zeroing of baseline). The file format for the raw electrophysiology records should be in xls, xlsx or xpt format, and contain

at a minimum information about time, voltage and current signals (note specific units for these signals). For current clamp experiments, time and voltage as well as stimulus characteristics.

b. An overview file, e.g., in xls, xlsx, xpt or txt, describing the experimental conditions for each of the raw electrophysiology records. The description should include at a minimum the name of the file, temperature of the recording, when drugs and at what concentrations were added, and other information relevant to interpret the results.

3) Clinical ECG data from Study 4045-301. Without appropriate controls, Study 4045-301 is not designed to exclude small mean increases (i.e., 10 ms) in the QTc interval. As per ICH E14 Q&A 6.1, the clinical ECG data from this study can used to exclude large mean increases (i.e., 20 ms) in QTc.

Meeting Discussion:

The sponsor asked if the ECG data from clinical studies excludes large mean increases (i.e., 20 ms) in QTc, does the agency agree that the integrated nonclinical and clinical approach can support the TQT waiver. FDA stated that if the ECG data from clinical studies excludes a large mean effect, and if a review of the nonclinical cardiac safety data supports a large safety margin, FDA would not request a separate thorough QT study in healthy subjects.

Question 7:

Antidrug antibody and antidystrophin antibody assays are being developed for immunogenicity assessments. It is Sarepta's intent to submit the antidystrophin antibody data from the completed Study 4045-101 at the time of the 120-day safety update. Sarepta requests a deferral for the anti-casimersen antibody data package and agrees to a postmarketing requirement for providing these data. Does the Division agree with the approach?

FDA Response to Question 7:

You have proposed to submit the anti-dystrophin antibody data upon completion of Study 4045-101 at the time of the 120-day safety update. The data on anti-dystrophin antibodies should be submitted with the NDA application to facilitate the review. We note that the assays to detect IgG, IgM, and IgE anti-dystrophin antibodies were provided to the agency as part of IND 077429 (eteplirsen) and were found to be adequate. Please note that the cut-point calculations and matrix interference will need to be confirmed using samples from treatment-naïve patients of the target population. Regarding the assessment of anti-casimersen antibodies, the data can be supplied as a PMR.

Meeting Discussion:

FDA noted the potential importance of the immunogenicity data considering that hypersensitivity events were observed in the golodirsen and eteplirsen data and that in the latter, the issue had risen to a Warning placed in labeling. FDA also expressed concern over the need to assess a large amount of data in a very compressed timeline. FDA indicated that there would need to be further internal discussions regarding the submission of the immunogenicity data to the NDA and would follow-up with the sponsor.

Post-Meeting Note:

In a post-meeting communication dated June 6, 2019, the sponsor committed to submit the casimersen anti-dystrophin results from the completed clinical Study 4045-101 within 90 days of the NDA submission date.

2.1. Nonclinical

Question 8:

Sarepta intends to request a deferral for the 26-week mouse and 2-year rat carcinogenicity studies which will be conducted as a post-marketing commitment, does the Division agree with this approach?

FDA Response to Question 8:
Considering the seriousness of the indication, studies to assess the carcinogenic potential of casimersen would not be needed at the time of NDA submission.

Meeting Discussion: There was no meeting discussion.

2.2. Administrative

Question 9:

Sarepta will submit standardized study data for Studies 4045-101, 4045-301, 4045-302, 4045-102, 4045-103 and the ISS using standards, formats, and terminologies described in the FDA Data Standards Catalog. The details of standards, formats, and terminologies used for each study will be provided in the briefing book. Does the Division agree with this proposal?

FDA Response to Question 9:
We agree with your proposal. You may also consider submission of samples of key datasets (Study and ISS ADSL, ADEG, ADAE, Analysis biopsy related, and AEVS) prior to submitting the application so that we may verify the format.

Meeting Discussion: There was no meeting discussion.

Question 10:

Sarepta will provide the below-listed information for the purposes of BIMO inspections. Does the Division agree with this proposal?

FDA Response to Question 10:
Please submit blinded subject-level data line listings for Study 4045-301. The other data and documents you propose to provide for BIMO inspections are acceptable.

Meeting Discussion: The sponsor queried whether blinded listings of the casimersen Western blot data could be submitted for the inspection because of their concern about unblinding. FDA acknowledged the importance of data integrity for the study and agreed with the proposal.

Question 11:

Investigation of casimersen (SRP-4045) for DMD was designated by the Division as a Fast Track development program on 24 July 2014, as such Sarepta proposes the option to submit portions of the application for rolling review. Does the Division agree with the plan?

FDA Response to Question 11:
You have been granted Fast Track designation and Rolling Review is a part of this program. In a rolling review, your application is considered complete once the final component is submitted.

You should submit a formal request to your IND about the acceptability of submitting the application as a rolling submission. The request should identify the planned submission dates and describe the specific application modules that will be submitted on each date. Upon receipt, FDA will make a formal determination regarding the acceptability of the proposal and will communicated the determination in an official communication.

We also refer you to the response to Question 13.

Meeting Discussion: There was no meeting discussion.

Question 12:

As agreed to in the 11 September 2018 pre-NDA meeting for golodirsen, Sarepta intends to provide representative bioassay sample images to support dystrophin conclusions in Module 5 of the electronic common technical document (eCTD). Does the Division agree with this proposal?

FDA Response to Question 12:
We agree that you can provide representative IHC images in Module 5. Please include all full-length western blot images, including those for dystrophin and loading controls, in Module 5. As with NDA 211970 (golodirsen), you should plan to submit all IHC images acquired from each specimen on an external hard drive. As advised during the September 11, 2018 meeting, you should provide the IHC images in all three file types (TIFF, SVS, PDF) on the external hard drive. You should include raw images and images that were adjusted or annotated.

Meeting Discussion: There was no meeting discussion.

2.3. Quality

Question 13:

Sarepta plans to submit primary stability data from 3 drug product batches manufactured at [redacted] (b) (4) with 24, 12, and 6 months of available data at the time of filing.

The 3 batches that represent the primary stability batches for drug product are SEE001, SEE002, and SEE004 manufactured at [redacted] (b) (4) The drug product SEE001 and SEE002 were manufactured from drug substance manufactured at [redacted] (b) (4) (commercial and clinical drug substance manufacturer) (drug substance batches 7002071, 7002188, and 7003101, 7003103, respectively), and SEE004 from drug substance batch 7700441 manufactured at [redacted] (b) (4) (commercial drug substance manufacturer).

Does the FDA agree with our proposal?

FDA Response to Question 13:
We do not agree. Per ICH Q1A(R2), the Agency recommends that an initial NDA submission include a minimum of 12 months long-term (25°C/60% R. H.) stability data, plus 6 months accelerated (40°C/75% R. H.) data for three primary batches per strength of the same formulation as the to-be-marketed product in the proposed commercial packaging. The Office of New Drug Products (ONDP) may recommend that the Agency refuse to file an NDA that does not include the recommended stability data package. We acknowledge the severity of the indication; ONDP will exercise flexibility with respect to filing if the clinical division determines that earlier submission of an NDA is

appropriate. We note that the date on stability for drug product batch SEE004 is listed in the briefing package as April 11, 2018. Therefore, it is unclear why only 6 months of data would be available at filing.

We remind you that the expiration dating period assigned during the review will be commensurate with the extent and quality of the available stability data. Refer to ICH guidance "Q1E Evaluation of Stability Data."

Meeting Discussion: The sponsor confirmed that initial NDA submission would include the recommended 12-months long-term stability data for the primary batches. The sponsor may submit additional data during the review cycle; however, whether the data are reviewed will depend on the timing of the amendment and Agency resources.

2.0 ADDITIONAL COMMENTS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- A preliminary discussion was held on the need for a risk evaluation and mitigation strategy (REMS) and other risk mitigation. It was concluded that there is insufficient information to determine whether a REMS or other risk mitigation is necessary at this time. The need for a REMS will be determined during review of the application.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.
- In addition, we note that the FDA provided written responses in a chemistry pre-submission meeting in February 2019. We refer you to the FDA written responses of February 8, 2019, for any additional agreements that may have been reached.

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[3] and Pregnancy and Lactation Labeling Final Rule[4] websites, which include:

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

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

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

ABUSE POTENTIAL ASSESSMENT

1. After a review of the summary materials in IND 118086, CSS concludes that casimersen does not have the profile of a drug with abuse potential because it:
   - Does not produce central nervous system behaviors in either animals or humans
   - Has a mechanism of action that is limited to effects on mRNA
   - Does not distribute into the brain after intravenous administration

2. Thus, CSS concludes that an abuse potential assessment for casimersen is unnecessary.

MANUFACTURING FACILITIES

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

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

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

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[3] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm08 4159.htm

[4] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm09 3307.htm

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

Corresponding names and titles of onsite contact:

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[5]

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

1. Sarepta's handout received via e-mail on June 4, 2019, in response to FDA preliminary comments dated May 31, 2019.
2. Sarepta's slides presented at the June 5, 2019, meeting.

2.1. Clinical

Question 1:
The NDA for accelerated approval of casimersen will be based on an interim analysis of the de novo dystrophin protein data at Week 48 for the first 43 enrolled patients with exon 45 skip amenable mutations and evaluable dystrophin data in Phase 3 doubleblind placebo-controlled Study 4045-301; functional data from 4045-301 will not be presented in the NDA. Does the Division agree with this approach?

FDA Response to Question 1:
We agree that functional data may not need to be presented in your planned NDA submission if Study 4045-301 is still ongoing at the time of submission. See response to Question 2 regarding the analysis of dystrophin data.

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

Question 2:
To support an accelerated approval, dystrophin protein expression as measured by Western blot and exon skipping data will be described in Module 2.7.3 (Summary of Clinical Efficacy). Additionally, percent dystrophin-positive fibers and mean dystrophin fiber intensity will be described in Module 2.7.3 with the supporting detailed information provided in analytical reports included in Module 5. Does the Division agree with the proposed approach?

FDA Response to Question 2:
Your proposed approach for submitting the dystrophin data in modules 2 and 5 is acceptable. The referenced golodirsen NDA and related protocols for the analysis of dystrophin in muscle biopsy tissue for protein expression and exon skipping are still under review. In general, your approach for using Western blot and exon skipping bioassays for measuring dystrophin protein expression is acceptable. See additional comments below.

1. Regarding your Western blot bioassay, we reference a bioanalytical inspection of your Cambridge, Massachusetts facility under NDA 211970 (golodirsen) on April 15-17, 2019. As discussed with you at the close-out, (b) (4) (b) (4) (b) (4) We further note that you submitted an amendment under IND 118086 (SD 71) to address our concern (b) (4) (b) (4) (b) (4) however, in the submission, you did not address the issue (b) (4) (b) (4) To address this concern, revise your western blot protocol and acceptance criteria (b) (4)

Provide your timeline for validating and implementing this revised protocol for western blot analyses for casimersen, as well as for all your ongoing and future drug development programs.

2. In the western blot v3 method (IND 118086/SD 71, DOC-02392), your proposed acceptance criteria for accuracy and precision at percent difference (b) (4)% are wider than the FDA recommended guidance on bioanalytical method validation (2018) and are not consistent with your method validation results of (b) (4)%. Please tighten the acceptance criteria for western blot method validation parameters based on the agency recommendations and reflective of your method validation results.
3. Please see additional comments regarding the proposed immunohistochemistry bioassay below and in response to questions 4 and 12.

In this meeting package, you propose the validation (b) (4)- (b) (4) using an anti-dystrophin antibody and muscle biopsies. Refer to Question 4 for comments on the proposed validation (b) (4) The items listed below require additional information to determine if these methods are appropriate for (b) (4) method validation.

i) You state (b) (4) You should clearly state these specifications, acceptance criteria, with accompanying justifications. Additionally, numerical upper and lower limits for any acceptance criteria for quantitative attributes.

(b) (4)

(b) (4)

Sarepta's response:
Sarepta acknowledges the FDA feedback and submits the below preliminary response to support further discussion during the pre-NDA meeting.

(b) (4)

Given the above clarifications, will the agency accept the Western blot data generated from the current methodology?

Question 3:
The data analysis and presentation plan for the safety dataset of approximately 69

casimersen treated patients, including analysis of adverse events of interest are described below. Does the Division agree with proposed safety data analysis and presentation plan?

FDA Response to Question 3:

On face, the safety dataset appears sufficient; however, the acceptability of the final safety dataset will be a matter of review at the time of the NDA submission.

Sarepta's response:

Sarepta acknowledges the feedback; propose no discussion at the meeting.

Question 4:

Sarepta plans to submit immunohistochemistry (IHC) dystrophin data for fiber intensity and Percent Dystrophin Positive Fibers (PDPF) obtained from (b) (4) analysis. (b) (4) (b) (4) (b) (4) Does the Division agree with this approach?

FDA Response to Question 4:

We disagree for the following reasons:

(b) (4)

(b) (4)

Sarepta's response:

Sarepta acknowledges the FDA feedback and submits the below preliminary response to support further discussion during the pre-NDA meeting.

Study 4045-301 Dystrophin Expression Determined by (b) (4)

Prior recommendations from the Division highlighted the desire to move away from manual pathologist scoring due to the inherent bias and encouraged Sarepta to continue to develop digital image analysis solutions such as (b) (4) *(31 July 2018 FDA teleconference). Although technical difficulties* (b) (4) *were observed* (b) (4) (b) (4)

We will provide all requested information regarding validation (b) (4) (b) (4) *Here, we present the summary data from analysis of both fiber intensity and PDPF* (b) (4) *for the interim Study 4045-301 biopsy set (response section 1, below).*

Resolution of the technical issue (b) (4) *has been demonstrated* (b) (4) *using the* (b) (4) *method.* (b) (4)

Section 1. Results from (b) (4) ***analysis of Study 4045-301 muscle biopsy set***

(b) (4)

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(b) (4)

Question 5:

Hepatic metabolism does not appear to be a major elimination pathway for casimersen thus, Sarepta will be requesting a waiver for the conduct of a hepatic impairment study. Does the Division agree with this approach?

FDA Response to Question 5:

We agree with your proposal.

Sarepta's response:

Sarepta acknowledges the feedback; propose no discussion at the meeting.

Question 6:

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

FDA Response to Question 6:

We agree that an integrated nonclinical and clinical approach may support a TQT study waiver for this antisense oligonucleotide that has a large hERG safety margin. You should submit the following data to support a TQT study waiver:

1) For IC50 estimation of drug inhibition on ion channel currents, we currently accept room temperature data, as described in the voltage protocol document available at http://cipaproject.org/ion-channel-protocols/. Patch clamp studies of drug effects on cardiac ion channels at 37C are routinely performed at the agency.

2) To facilitate the review of the hERG assay study reports, please submit the following information for each experiment:

   a. Raw and unaltered electrophysiology records (e.g., no baseline subtraction or zero'ing of baseline). The file format for the raw electrophysiology records should be in xls, xlsx or xpt format, and contain at a minimum information about time, voltage and current signals (note specific units for these signals). For current clamp experiments, time and voltage as well as stimulus characteristics.
   b. An overview file, e.g., in xls, xlsx, xpt or txt, describing the experimental conditions for each of the raw electrophysiology records. The description should include at a minimum the name of the file, temperature of the recording, when drugs and at what concentrations were added, and other information relevant to interpret the results.

3) Clinical ECG data from Study 4045-301. Without appropriate controls, Study 4045-301 is not designed to exclude small mean increases (i.e., 10 ms) in the QTc interval. As per ICH E14 Q&A 6.1, the clinical ECG data from this study can used to exclude large mean increases (i.e., 20 ms) in QTc.

Sarepta's response:

Sarepta acknowledges the FDA feedback and submits the below preliminary response to support further discussion during the pre-NDA meeting.

Sarepta will provide an IC50 estimation at room temperature in accordance with FDA request and confirms hERG assay study reports submitted with the NDA will include all information requested by FDA.

Sarepta recognizes the Agency's concern regarding the lack of appropriate controls and ability to only exclude large mean increases in QTc (20ms) based on the current study design. The data for casimersen treated patients will be similar to the data for golodirsen patients. As outlined in Amendment 9 of Study 4045-301 and consistent with the QTc waiver request for golodirsen,

Sarepta intends to submit all clinical ECG data for review upon the completion of Study 301, which will include triplicate PK-time matched ECG data for both casimersen and golodirsen.

If the ECG data from clinical studies excludes large mean increases (i.e., 20 ms) in QTc, given the lack of interaction of casimersen with the cardiac channel encoded by hERG, as evidenced by the results of the nonclinical study, and the lack of adverse effects on cardiac conduction for eteplirsen in clinical and post-marketing use, does the agency agree that the integrated nonclinical and clinical approach can support the TQT waiver?

Question 7:

Antidrug antibody and antidystrophin antibody assays are being developed for immunogenicity assessments. It is Sarepta's intent to submit the antidystrophin antibody data from the completed Study 4045-101 at the time of the 120-day safety update. Sarepta requests a deferral for the anti-casimersen antibody data package and agrees to a postmarketing requirement for providing these data. Does the Division agree with the approach?

FDA Response to Question 7:

You have proposed to submit the anti-dystrophin antibody data upon completion of Study 4045-101 at the time of the 120-day safety update. The data on anti-dystrophin antibodies should be submitted with the NDA application to facilitate the review. We note that the assays to detect IgG, IgM, and IgE anti-dystrophin antibodies were provided to the agency as part of IND 077429 (eteplirsen) and were found to be adequate. Please note that the cut-point calculations and matrix interference will need to be confirmed using samples from treatment-naïve patients of the target population. Regarding the assessment of anti-casimersen antibodies, the data can be supplied as a PMR.

Sarepta's response:

Sarepta acknowledges the FDA feedback and submits the below preliminary response to support further discussion during the pre-NDA meeting.

Sarepta acknowledges the final review and approval of the assays to detect IgG, IgM and IgE anti-dystrophin antibodies, including the information request on April 8, 2019 requesting additional information to support the validation of the assays. We also acknowledge the conclusions from the golodirsen NDA Mid-Cycle review meeting confirming FDA's expectation that, if our product is approved, the anti-dystrophin antibody clinical data should be made available soon after approval as part of an immunogenicity PMR. Table 1 provides current estimates of timelines for critical steps necessary for anti-dystrophin reporting of clinical results across the PMO platform of eteplirsen, golodirsen and casimersen.

Table 1: Current estimated PMO anti-dystrophin analysis timelines

Program/Study	*Studies*	*Anti-dystrophin Analyte*	*Samples Available*	*Sample Analysis*	*Projected Data Transfer*	*Estimated TFLs*	*Target report date*
Eteplirsen	*4658-203, 4658-204, 4658-301*	*IgG*	*Yes*	*Completed*	*Completed*	*Completed*	*16Dec*
		IgE	*Yes*	*In progress*	*31 Jul*	*09 Aug*	
		IgM	*Yes*	*31 Jul*	*30 Aug*	*10 Sep*	
Golodirsen	*4053-101*	*IgG*	*Yes*	*Completed*	*Completed*	*Completed*	*30Sep*

		IgE	*Yes*	*In progress*	*29 Jul*	*07 Aug*	
		IgM	*Yes*	*15 Jul*	*29 Jul*	*07 Aug*	
Casimersen	*4045-101*	*IgG*	*31 Jul*	*21 Aug*	*4 Sep*	*13 Sep*	*15Nov*
		IgE	*31 Jul*	*21 Aug*	*4 Sep*	*13 Sep*	
		IgM	*31 Jul*	*21 Aug*	*4 Sep*	*13 Sep*	

In order to pursue the opportunity for a treatment option for the exon 45 skip amenable DMD patients as soon as possible, Sarepta is working toward a potential NDA submission in July of 2019. Based on an assessment of resources and vendor capabilities and considering the established commitment to eteplirsen and golodirsen reporting, the requirement for casimersen anti-dystrophin clinical data to be submitted with the NDA would likely be rate limiting for submission (by as much as 4 months).

Furthermore, preliminary data from golodirsen IgG testing indicates no evidence of immunogenicity with respect to dystrophin. To-date we have reviewed golodirsen clinical results for the IgG antibody which were completed prior to FDA's final approval of the assay. In Study 4053-101, there were 25 patients treated with golodirsen who were assessed for immunogenicity based on IgG to anti-dystrophin. Of these, 2 (8%) patients were found to have had a positive anti-dystrophin IgG status at 2 timepoints, non-consecutive, and treatment-emergent. Adverse event data for the 2 patients (b) (6) *with low-positive anti-dystrophin IgG results were reviewed for AEs occurring within 30 days prior to or after the confirmed positive results. Neither patient experienced any serious AEs during the trial and no AEs were documented within 30 days following the positive IgG results. Only 1 event, mild vomiting, was documented within 30 days prior to a positive IgG result (for Patient* (b) (6) *).*

In light of the comprehensive ongoing activity associated with the assessment of anti-dystrophin immunogenicity for PMOs, Sarepta would like to further discuss the option of submitting the casimersen anti-dystrophin clinical results with the 120 Day safety update.

2.2. Nonclinical

Question 8:

Sarepta intends to request a deferral for the 26-week mouse and 2-year rat carcinogenicity studies which will be conducted as a post-marketing commitment, does the Division agree with this approach?

FDA Response to Question 8:

Considering the seriousness of the indication, studies to assess the carcinogenic potential of casimersen would not be needed at the time of NDA submission.

Sarepta's response:

Sarepta acknowledges the feedback; propose no discussion at the meeting.

2.3. Administrative

Question 9:

Sarepta will submit standardized study data for Studies 4045-101, 4045-301, 4045-302, 4045-102, 4045-103 and the ISS using standards, formats, and terminologies described in the FDA Data Standards Catalog. The details of standards, formats, and terminologies used for each study will be provided in the briefing book. Does the Division agree with this proposal?

FDA Response to Question 9:
We agree with your proposal. You may also consider submission of samples of key datasets (Study and ISS ADSL, ADEG, ADAE, Analysis biopsy related, and AEVS) prior to submitting the application so that we may verify the format.

Sarepta's response:
Sarepta acknowledges the feedback and will submit samples of key datasets prior to the submission to verify the formats; propose no discussion at the meeting.

Question 10:

Sarepta will provide the below-listed information for the purposes of BIMO inspections. Does the Division agree with this proposal?

FDA Response to Question 10:
Please submit blinded subject-level data line listings for Study 4045-301. The other data and documents you propose to provide for BIMO inspections are acceptable.

Sarepta's response:
Sarepta acknowledges the feedback and is providing the following preliminary response for discussion at the pre-NDA meeting.

Sarepta agrees to submit blinded subject-level data listings by site for Study 4045-301, however, we counter propose to specifically exclude muscle biopsy data. The current trial integrity process for Study 4045-301 employs sham patient ID's for muscle biopsy endpoints because changes in dystrophin values from Baseline for real patient IDs would potentially be attributable to treatment groups even in the absence of the treatment group information. The exclusion of muscle biopsy data from the blinded subject-level data listings by site will ensure trial integrity and prevent any potential accidental unblinding for Study 4045-301.

Question 11:

Investigation of casimersen (SRP-4045) for DMD was designated by the Division as a Fast Track development program on 24 July 2014, as such Sarepta proposes the option to submit portions of the application for rolling review. Does the Division agree with the plan?

FDA Response to Question 11:
You have been granted Fast Track designation and Rolling Review is a part of this program. In a rolling review, your application is considered complete once the final component is submitted.

You should submit a formal request to your IND about the acceptability of submitting the application as a rolling submission. The request should identify the planned submission dates and describe the specific application modules that will be submitted on each date.

Upon receipt, FDA will make a formal determination regarding the acceptability of the proposal and will communicated the determination in an official communication.

We also refer you to the response to Question 13.

Sarepta's response:
Sarepta acknowledges the feedback and will submit a formal request for a rolling submission per FDA advice should we decide to pursue this option; propose no discussion at the meeting.

Question 12:

As agreed to in the 11 September 2018 pre-NDA meeting for golodirsen, Sarepta intends to provide representative bioassay sample images to support dystrophin conclusions in Module 5 of the electronic common technical document (eCTD). Does the Division agree with this proposal?

FDA Response to Question 12:

We agree that you can provide representative IHC images in Module 5. Please include all full-length western blot images, including those for dystrophin and loading controls, in Module 5. As with NDA 211970 (golodirsen), you should plan to submit all IHC images acquired from each specimen on an external hard drive. As advised during the September 11, 2018 meeting, you should provide the IHC images in all three file types (TIFF, SVS, PDF) on the external hard drive. You should include raw images and
images that were adjusted or annotated.

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

2.4. Quality

Question 13:

Sarepta plans to submit primary stability data from 3 drug product batches manufactured at (b) (4) with 24, 12, and 6 months of available data at the time of filing.

The 3 batches that represent the primary stability batches for drug product are SEE001, SEE002, and SEE004 manufactured at (b) (4). The drug product SEE001 and SEE002 were manufactured from drug substance manufactured at (b) (4) (commercial and clinical drug substance manufacturer) (drug substance batches 7002071, 7002188, and 7003101, 7003103, respectively), and SEE004 from drug substance batch 7700441 manufactured at (b) (4) (commercial drug substance manufacturer).

Does the FDA agree with our proposal?

FDA Response to Question 13:

We do not agree. Per ICH Q1A(R2), the Agency recommends that an initial NDA submission include a minimum of 12 months long-term (25°C/60% R. H.) stability data, plus 6 months accelerated (40°C/75% R. H.) data for three primary batches per strength of the same formulation as the to-be-marketed product in the proposed commercial packaging. The Office of New Drug Products (ONDP) may recommend that the Agency refuse to file an NDA that does not include the recommended stability data package.

We acknowledge the severity of the indication; ONDP will exercise flexibility with respect to filing if the clinical division determines that earlier submission of an NDA is appropriate. We note that the date on stability for drug product batch SEE004 is listed in the briefing package as April 11, 2018. Therefore, it is unclear why only 6 months of data would be available at filing.

We remind you that the expiration dating period assigned during the review will be commensurate with the extent and quality of the available stability data. Refer to ICH guidance "Q1E Evaluation of Stability Data."

Sarepta's response:
Updated stability data will ensure that the initial NDA submission will satisfy the requirements of a minimum of 12 months long term stability data plus 6 months accelerated data for the 3 primary batches and is provided below (Table 1, blue font). Updated data was not available at the time of the previously submitted briefing document. In addition, the following stability data will be included in the NDA submission: [1]. Up to 36 months real-time stability data for 7 supportive stability lots; [2]. 6 months accelerated stability data for all 9 lots. So far, all available data met specifications for both real-time and accelerated conditions.

We plan to request agency's permission to provide additional stability data during review. In the NDA submission, we intend to propose the initial shelf-life of 24 months to be supported by the real-time stability data of 18 months for 3 primary stability lots and 18-36 months for 6 supportive lots and the accelerated stability data of 6 months for all 9 lots.

Table 1: Availability of DP Stability data

DP Lot*	*Role*	*DS Manufacturing Site**	*By Submission (Months)*	*During Review (Months)*	*Accelerated Stability by Submission (Months)*
SEE001	*Primary*	(b) (4)	*24*	*24*	*6*
SEE002	*Primary*		*12*	*18*	*6*
SEE004	*Primary*		*12*	*18*	*6*
80EY-DT01	*Supportive*		*36*	*36*	*6*
94EY-DT01	*Supportive*		*36*	*36*	*6*

97EY-DT01	*Supportive*	(b) (4)	*36*	*36*	*6*
107EY-DT01	*Supportive*		*36*	*36*	*6*
118EY-DT01	*Supportive*		*36*	*36*	*6*
SEE003	*Supportive*		*12*	*18*	*6*

* (b) (4) *All DP lots are manufactured at* (b) (4)

We are further confirming your awareness of our proposal to manufacture the casimersen DS at two sites (b) (4) *of one CMO* (b) (4) *In addition to the release data, comparability studies were conducted to demonstrate that the product manufactured at both* (b) (4) *are comparable (see the briefing document). Drug substance from both* (b) (4) (b) (4) *are used to manufacture the DP* (b) (4)

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/s/

NICHOLAS A KOZAUER
06/27/2019 09:20:04 AM
Signing for Eric Bastings, MD