

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**212154Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 127474

**MEETING MINUTES**

NS Pharma, Inc.  
Attention: Thomas Stover, PhD  
Senior Director, Integrated Product Development  
PharmaLex US Corp  
9302 Lee Highway, Suite 700  
Fairfax, VA 22031

Dear Dr. Stover:

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

We also refer to the meeting between representatives of your firm and the FDA on September 26, 2018. The purpose of the meeting was to discuss the content and format of a planned NDA for viltolarsen for the treatment of Duchenne muscular dystrophy (DMD) in patients amenable to exon 53 skipping.

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 Annie Nguyen, Regulatory Project Manager, by email at [Anhthu.Nguyen@fda.hhs.gov](mailto:Anhthu.Nguyen@fda.hhs.gov) or by phone at (240) 402-4460.

Sincerely,

*{See appended electronic signature page}*

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

Enclosure:  
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** September 26, 2018, 1:00 pm to 2:00pm EST  
**Meeting Location:** FDA White Oak Building 22, Room 1311

**Application Number:** IND 127474  
**Product Name:** Viltolarsen injection  
**Indication:** Treatment of Duchenne muscular dystrophy in patients amenable to exon 53 skipping  
**Sponsor/Applicant Name:** NS Pharma, Inc.

**FDA ATTENDEES**

Office of Drug Evaluation I  
Robert Temple, MD, Deputy 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  
Veneeta Tandon, PhD, Clinical Reviewer  
Lois Freed, PhD, Supervisory Pharmacologist  
Christopher Toscano, PhD, Nonclinical Reviewer  
Tracy Peters, PharmD, Associate Director of Labeling  
Sally Jo Yasuda, PharmD, Safety Team Leader  
Natalie Branagan, MD, Safety Reviewer  
Fannie Choy, RPh, Regulatory Project Manager  
Annie Nguyen, RPh, Regulatory Project Manager

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

Office of Product Quality  
Dan Berger, PhD, Chemistry Reviewer

Jason Morgan, PhD, Microbiology Reviewer  
Martha Heimann, PhD, CMC Lead for Neurology Products

Office of Clinical Pharmacology

Bilal Abuasal, PhD, Clinical Pharmacology Reviewer  
Atul Bhattaram, PhD, Pharmacometrics Reviewer  
Hobart Rogers, PharmD, PhD, Genomics and Targeted Therapy Reviewer

Office of Rare Disease

Melanie Blank, MD, Medical Officer

Office of Surveillance and Epidemiology

Ingrid Chapman, PharmD, Risk Management Analyst

**SPONSOR ATTENDEES**

Nippon Shinayku

Hiromu Nakajima, MD, PhD, Chief Medical Officer  
Tatsuya Fujii, General Manager, CMC Research & Development Dept./CMC  
Akira Saheki, PhD, Manager, Regulatory Affairs Dept./Regulatory  
Masaya Tajima, Manager, Clinical Development Dept./Clinical  
Akira Matsuura, PhD, Managing Director, Head of R&D  
Takashi Natsukawa, PhD, Manager, R&D Administration Dept./PM

NS Pharma

Yasushi Miyazawa, Vice President, R&D Department/PL  
Hironori Osaki, Senior Director, R&D Department/PM  
Tatsuya Horiguchi, Director, R&D Department/Clinical

(b) (4)

CINRG (Cooperative International Neuromuscular Research Group)

Paula Clemens, MD, CINRG Medical Director, US Study Chair

(b) (4)

**1.0 BACKGROUND**

NS Pharma Inc. is developing viltolarsen as a novel antisense oligonucleotide drug substance. Viltolarsen is being developed as a once weekly intravenous (IV) infusion for the treatment of Duchenne muscular dystrophy in patients amenable to exon 53 skipping.

The Division held a face-to-face Pre-IND meeting with the Sponsor on October 20, 2015. On July 3, 2017, the Division provided written responses to a type C meeting request regarding the clinical development of viltolarsen. On October 12, 2017, Type C written responses were provided to the Sponsor for guidance on the CMC development program. On May 15, 2018, a type C face-to-face guidance meeting was held with the Sponsor to discuss available Phase 2 clinical data and CMC plans to support a NDA for viltolarsen. A carcinogenicity special protocol assessment (SPA) was reviewed by the Agency and an agreement was sent to the Sponsor on July 12, 2018.

The Agency granted Fast Track Designation for viltolarsen injection on October 25, 2016, Orphan Drug Designation on January 12, 2017, and Rare Pediatric Disease Designation on January 24, 2017.

FDA sent Preliminary Comments to NS Pharma on September 21, 2018. NS Pharma provided responses, noted below in red, to the FDA's preliminary comments on September 25, 2018.

## **2. DISCUSSION**

### **2.1. Regulatory**

#### **Question 1:**

The Sponsor proposes to submit the NDA for this Fast Track product for a Rolling Review under Section 506(d)(1) of the Food Drug & Cosmetic Act. The following information is provided for consideration by the Division: i) Schedule of submission of each portion of the NDA, and ii) A description of each portion of the NDA that will be submitted separately. If the FDA is in agreement that this proposed Rolling Review schedule is acceptable, the Sponsor commits to provide an amendment to the open IND in accordance with the Guidance for Industry—Expedited Programs for Serious Conditions – Drugs and Biologics.

Does the FDA agree with the proposed Rolling Review plan and schedule?

#### **FDA Response to Question 1:**

Your plan for submission of Waves 1 and 2, as described in the briefing package, is acceptable.

You should identify the commercial manufacturing and testing facilities as soon as possible in your rolling submission. Since Module 3 in its entirety is expected to be submitted last (i.e., in Wave 3), these sites can be listed on the Form 356h or as an attachment to the Form 356h, preferably in Wave 1.

#### **Sponsor Response:**

The Sponsor thanks the FDA for this feedback and will identify the commercial manufacturing and testing facilities within Wave 1 of the rolling submission in accordance

with the “Manufacturing Facilities” section of the FDA Preliminary Comments to the pre-NDA meeting information package.

Nippon Shinyaku is engaged in ongoing discussion with the PMDA on the marketing authorization plan and submission schedule in Japan under the conditional early approval scheme notified in October 2017. The Sponsor is working to maintain the proposed US rolling submission plan and commits to update the Division if any changes occur following subsequent meetings with the PMDA.

The Sponsor believes no further discussion is necessary for the pre-NDA meeting.

**Discussion:**

No discussion.

**2.2. Clinical**

**Question 2:**

In comments for the 3 July 2017 Type C Meeting FDA noted that increases in dystrophin expression have the potential to serve as the basis for an accelerated approval. In comments for the Type C meeting on 15 May 2018, FDA noted that the Sponsor must still provide in the NDA evidence that dystrophin was produced by viltolarsen at levels reasonably likely to predict clinical benefit. The Sponsor plans to address FDA's request by providing epidemiological and pathophysiological evidence from the scientific literature that a milder DMD or BMD phenotype results from dystrophin levels similar to those produced by viltolarsen, and by providing preliminary clinical evidence supportive of therapeutic benefit in viltolarsen treated patients.

Does FDA agree with this approach?

**FDA Response to Question 2:**

The Division's comment from the May 15, 2018, Type C meeting was intended to highlight the need for any future NDA submission to address the accelerated approval provisions of FDASIA in Section 506(c) (i.e., that a proposed surrogate endpoint is reasonably likely to predict clinical benefit). A potentially acceptable approach to address this requirement would be to focus on the mechanistic plausibility of the reported increases in dystrophin observed with your product to predict any such future benefit.

With regard to the presentation of dystrophin data in the proposed NDA, please provide all relevant raw data for the Western blot (WB), immunohistochemistry (IHC), reverse transcription polymerase chain reaction (RT-PCR), and mass spectrometric analyses conducted in support of the NDA. Specifically, please include the following for each patient:

- Western blotting full-length and high-quality images for all dystrophin and loading control immunoblots

- IHC images, with tabulated quantitation for dystrophin-positive fibers and dystrophin intensity (normalized to both laminin and SGCA)
- Full-length and high-quality images of RT-PCR gels with confirmation of skipped band size, the E-gram gel report for each gel and quantitation for skipping efficiency
- Available mass spectrometry analysis of percent dystrophin

Additionally, please provide a listing of all current and planned sites involved in dystrophin testing, including those involved in biopsy acquisition, sample processing, sample blinding/unblinding, and each dystrophin analytical measurement.

**Sponsor Response:**

The Sponsor appreciates the FDA's preliminary comments to this question. The Sponsor would like to better understand the FDA's request to provide "all relevant raw data" related to dystrophin measurement in support of the NDA. For instance, are compressed images acceptable?

With respect to submission of all raw data, the Sponsor wishes to clarify and discuss options on how best to submit these data. As per Appendix 3 Complete Clinical Module for Rolling Review of the pre-NDA meeting package, the Sponsor plans to submit a blinded bioanalytical report ("PD Dystrophin Bioanalytical Report") prepared by (b) (4) that summarizes the WB, IF, and RT-PCR data generated from US/Canada Study NS-065/NCNP-01-201. This bioanalytical report currently includes all full Western blot and RT-PCR original images for all replicates at good resolution. The IF raw data is scans of full microscope slides for each antibody with a single section independently analyzed by two blinded analysts, and raw counts for all assessments in Tables. A representative image is included in the bioanalytical report for each biopsy. For these IF images, the Sponsor would appreciate the FDA's agreement that the current report meets expectations (please see enclosed truncated version of the blinded report with Table of Contents, List of Figures, and representative image types for each analysis). The Sponsor fully understands that the reviewers cannot conduct a full review but only asks that the reviewer focus on the raw data and particularly the IF images enclosed in this blinded report. The Sponsor will be happy to spend 10-15 minutes during the meeting to discuss the data and images contained within the full blinded report.

Please note that this bioanalytical report will be submitted blinded since the mass spectrometric analyses are ongoing using blinded patient biopsies. For NDA submission, the biopsy randomization scheme will be provided to facilitate FDA review of this blinded report.

If the FDA requires additional images following review and discussion of the report, can the FDA confirm a preference on how these images should be organized for submission? Based on the pre-NDA discussion, the Sponsor will consider how to address this request for the Japan Phase 1/2 study.

Lastly, as mentioned in the meeting information package, the Sponsor wishes to clarify that the mass spectrometric analyses of patient samples from US/Canada Study NS-

065/NCNP-01-201 remain ongoing. (b) (4) these data are not available, and the Sponsor plans to proceed with NDA submission without these data. Once the data are available, the Sponsor will prepare a separate, report to serve as an addendum to the Clinical Study Report that will be submitted in the NDA. This report can be provided to the FDA during NDA review, as soon as it is available.

### **Discussion:**

The Sponsor requested clarification on the raw immunofluorescence (IF) image files. The agency clarified that high-resolution images for each bioassay should be provided for each patient with pre- and post-samples, and asked in what format the IF files were collected. The Sponsor responded that they were not sure but would provide high-resolution images for review. The Sponsor clarified that the entire section of each slide was captured as an image and inquired whether the agency wanted the entire field or selected regions. The agency clarified that the entire field image can be submitted with and without any annotations added for analysis.

The Sponsor clarified that their mass spectrometry data will not be available for the submission of the clinical module of the NDA but will be provided before or with the final module that completes the NDA submission. The agency agreed and advised the Sponsor to update their clinical summary to reflect the additional findings of the mass spectrometry data when submitted.

The Division also clarified that the evidence that the proposed surrogate endpoint, dystrophin, is reasonably likely to predict clinical benefit can be a focused, concise rationale in the NDA submission.

### **Question 3:**

In the preliminary comments to the Type C meeting held on 15 May 2018, the FDA also noted that the Sponsor “*should also have a confirmatory trial underway at the time a marketing application is submitted as your development program intends to seek accelerated approval based on dystrophin expression. An agreement on the study design should be reached prior to the initiation of the confirmatory study. At the time of any future NDA submission, you will also need to describe how you would successfully enroll and complete the confirmatory trial, should your product receive accelerated approval.*” The Sponsor is developing a protocol synopsis for the planned confirmatory trial so that an agreement on the study design with the Agency will be reached prior to study initiation. Whereas the Sponsor will first seek marketing authorization in the US and Japan and has no definitive marketing authorization plans for other markets, a global confirmatory trial is planned. A global program allows patient enrollment in markets where the product is not available commercially. Moreover, the Sponsor intends to initiate this trial as soon as reasonably possible with the overarching goal to begin enrollment prior to US accelerated approval. A draft confirmatory trial protocol synopsis is enclosed for review by the Division.

Does the FDA agree with the proposed confirmatory study design?

**FDA Response to Question 3:**

We do not agree that [REDACTED] (b) (4) will be acceptable. We recommend that you conduct a global, randomized, double-blind, placebo-controlled study. The study should include countries where viltolarsen would not be available if it were to receive an accelerated approval in the United States (US). As described in Subpart H, CFR 314.510, such confirmatory studies should be underway at the time the marketing application is submitted. There should be an agreement with the Division on the design and the conduct of the confirmatory study. The timelines of enrollment and trial completion should be specified in the proposed protocol. Given that you intend to complete your NDA submission in February 2019, you should reach agreement with the Division as soon as possible on the design of an adequate and well-controlled confirmatory study.

**Sponsor Response:**

The Sponsor appreciates the FDA's comments on the proposed confirmatory design. The Sponsor's strong preference is to conduct a single, global confirmatory trial to meet requirements in target markets. Whereas the Sponsor is open to considering a placebo-controlled study, we would like to review the Sponsor's position to rely [REDACTED] (b) (4) as well as other considerations for a placebo arm, including impact on enrollment and approaches to powering.

[REDACTED] (b) (4)

[REDACTED] (b) (4)

In addition to discussion of the above, the Sponsor wishes to share the FDA comments with PMDA in planned meeting to understand how best to accommodate a single, global confirmatory trial. Overall, the Sponsor will share an update on the confirmatory study synopsis when PMDA feedback is provided.

**Discussion:**

The Sponsor indicated its preference to conduct a single global confirmatory trial and expressed concerns about the impact on enrolling for a placebo-controlled trial after an accelerated approval is granted in US and Japan. [REDACTED] (b) (4)

[REDACTED] Therefore, the Division reiterated their position that a placebo-controlled study would be required. The Division stressed the importance of

initiating the confirmatory placebo-controlled study as soon as possible, and strongly indicated that this study should be ongoing by the time a marketing application is submitted for review. This would enable enrollment of subjects before a potential accelerated approval, and the Division recommended that the Sponsor select sites where the drug is unlikely to be available.

(b) (4)

**Question 4:**

In accordance with the Draft Guidance for Industry on FDA's Application of Statutory Factors in Determining when a Risk Evaluation and Mitigation Strategy (REMS) is necessary and consistent with the precedent for the approval of Eteplirsen without an REMS, the Sponsor does not consider that this product will require a REMS.

Does the FDA agree that no REMS is likely to be required, pending a full review of the overview risk-benefit summary?

**FDA Response to Question 4:**

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

**Sponsor Response:**

The Sponsor thanks the FDA for this comment. Since the FDA did not express any current concerns, the Sponsor does not plan to address the need for REMS in the NDA.

No further discussion is needed during the pre-NDA meeting.

**Discussion:**

No discussion.

**Question 5:**

The clinical study population for this orphan indication is very small with 42 patients total, 32 of whom participated in Phase 2 studies. Therefore, the Sponsor believes that modules 2.7.3 Summary of Clinical Efficacy and 2.7.4 Summary of Clinical Safety will be sufficiently detailed to serve as the narrative portion of the integrated summary of efficacy (ISE) and the integrated summary of safety (ISS), respectively. Whereas the ISE and ISS narrative text will be located in Module 2, the Sponsor plans to place the data displays, other appendices, and CDISC datasets for the US/Canada and Japan studies within Module 5. The documentation will be appropriately hyperlinked in both sections. In addition, the Sponsor does not intend to pool efficacy or safety data from any of the studies in the clinical program, with the exception that safety data for

patients in Study NS-065/NCNP-01-202 will be analyzed together with safety data from the parent study (NS-065/NCNP-01-201), as reflected in the NS-065/NCNP-01-202 statistical analysis plan (Appendix 7). Therefore, no integrated analysis plan will be generated for the ISE or ISS. Results from the various studies will be presented individually or side-by-side, where appropriate, for cross-study comparisons in the ISE and ISS.

Does the FDA agree with the location of the integrated summaries of efficacy and safety?

**FDA Response to Question 5:**

We agree with the plan for the location of the integrated summaries of safety and efficacy.

We agree with pooling the safety data for patients in Study NS-065/NCNP-01-202 with safety data from the parent study (NS-065/NCNP-01-201). However, patients from Study NS065/NCNP01-P1/2 should also be pooled with these two studies in an additional pool. A separate pool should be created to include patients from the 4-week placebo-controlled portion of Study NS-065/NCNP-01-201.

Please also refer to the DNP standard safety requests attached as an appendix when you prepare your submission. We understand that not all requests will be applicable to your dataset; however, you should try to address these requests as it is feasible.

**Sponsor Response:**

The Sponsor thanks the FDA for reviewing the Study Data Standardization Plan and agreeing on the proposed location of the ISS and ISE.

Given the orphan indication and the small size of the study databases in the US/Canada and Japan Phase 2 programs, the Sponsor would like to confirm the value in pooling the safety data across these two studies. The Sponsor believes that safety data from each patient in both studies can and will be reviewed individually. Please note that the Sponsor plans to submit all patient CRFs from each study in the NDA, and the ISS will provide an integrated summary of the safety data from both US/Canada Study NS-065/NCNP-01-201 and Japan Study NS065/NCNP01-P1/2 (i.e., no integrated analysis or “pooling” under a separate Statistical Analysis Plan is proposed).

Also, the Sponsor wishes to confirm that patients from the 4-week placebo-controlled portion of Study NS-065/NCNP-01-201 (Period 1) are inherently “pooled” with the remaining 20-weeks of treatment (Period 2) as these data are entered into the same study database. Since the data will be formatted in accordance with CDISC standards (e.g. SDTM and ADaM), we believe this format should enable review of Study NS-065/NCNP-01-201 safety data by Period. The Sponsor wishes to understand the FDA’s expectation for separate pooling of data from Period 1.

Based on the above Sponsor comments and clarification, the Sponsor wishes to discuss whether the current clinical study data standardization plan is sufficient. If pooling is absolutely necessary to enable review, would pooling of adverse events only be a reasonable solution.

**Discussion:**

At the meeting, the Division clarified that these pooling strategies are the standard approaches that it takes to evaluate safety data. The “all-treated” pool may provide a better opportunity to detect a signal than separate pooling. The purpose of evaluating the placebo-controlled pool is to help evaluate causality of observed adverse events.

The Division requests pooling for all of the safety data, not just adverse events.

**Post-Meeting Follow-up Question 5 (received 9/28/2018):**

The Sponsor asks the FDA to clarify if this separate pool of Period 1 patients should include placebo patients only or all patients in Period 1 (placebo and active).

**FDA Response to Post-Meeting Follow-up Question 5:**

With regard to the question of pooling of the 4-week placebo-controlled portion of Study NS-065/NCNP-01-201, the Division requests that the data for all patients (those who received placebo and those who received active drug) during the 4-week placebo-controlled portion of the trial be submitted as a separate pool.

As a clarification regarding the 120-day safety update discussed during the meeting, the Division finds the approximately cut-off date of the end of February 2019, acceptable.

**2.3. Nonclinical**

**Question 6:**

Several nonclinical study reports and the investigator-initiated Japan Phase 1 clinical study report were previously submitted to the open IND 127474. The Sponsor intends to fully summarize all nonclinical and clinical study reports within the module 2 written and tabular summaries and proposes to cross reference the submission in the IND 127474 where the reports are located in Modules 4 and 5, respectively. The Sponsor proposes not to resubmit study reports that have been previously submitted to the IND.

Does the FDA agree with this proposal for cross-reference to the IND?

**FDA Response to Question 6:**

Your plan to reference the nonclinical and clinical information in IND 127474 by including cross-application links in the NDA, as described in your briefing package, is acceptable.

Prior to using cross application linking in an application and to ensure successful use of cross application links, it is recommended that you submit an "eCTD cross application links" sample. To submit an eCTD cross application links sample, you would need to request two sample application numbers from the ESUB team - [esub@fda.hhs.gov](mailto:esub@fda.hhs.gov). For more information on eCTD samples, please refer to the Sample Process web page which is located at

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM315023.pdf>

**Sponsor Response:**

The Sponsor thanks the FDA for this comment and can update the Division that the “eCTD cross application links” sample has been successfully completed.

No further discussion is needed during the pre-NDA meeting.

**Discussion:**

No discussion.

**2.4. Chemistry, Manufacturing and Controls**

**Question 7:**



Whereas the Sponsor will continue to monitor the batches currently on DP stability, complete data will not be available for the planned NDA submission. Nevertheless, the Sponsor plans to conduct a battery of nonclinical qualification studies using a thermally stressed drug product batch with higher percentage of impurities.

Does the FDA agree with the Sponsor’s plan to monitor such impurities?

**FDA Response to Question 7:**

It is our expectation that the NDA submission will contain information regarding characterization of impurities by SEC and HPLC analysis. Data should be presented to confirm that impurities for stability batches remain below levels observed in thermally stressed drug product. Additionally, develop and implement a control strategy for drug product elemental impurities as described in USP <232> and <233>. To establish the compatibility of the drug product formulation with the container, perform studies to demonstrate that extractables and

leachables are consistently at or below acceptable and safe levels. With regard to the plan to continue to monitor the batches on DP stability, please see the response to question 8.

Your plan to qualify potential impurities of concern in a thermally stressed batch of drug product by conducting a 13-week study in monkey, an in vitro genotoxicity assessment, and an in vitro function assessment of exon skipping activity is acceptable.

**Sponsor Response:**

The Sponsor thanks the FDA for the responses provided here. We agree with the FDA's recommendations. In the NDA, we plan to submit:

- 1) the characterization of impurities by SEC and HPLC analysis, which have been described in the information package.
- 2) the control strategy for drug product elemental impurities per USP <232> and <233>
- 3) the studies to demonstrate that extractable and leachables are below acceptable levels.

The Sponsor thanks the FDA for their comments regarding the plans for qualification of the impurities in a battery of four nonclinical studies proposed in the pre-NDA meeting package. The Sponsor would like to clarify that the study results and final audited reports will not be available for inclusion in the original NDA, as these studies are still in the planning stages (consistent with the absence of these studies in the Module 4 contents listed in Appendix 2 of the meeting information package). These reports will be submitted to the NDA once they become available.

**Discussion:**

The Division stated that if the nonclinical data are required to support qualification of impurities, it is expected that the study reports would be included in the original NDA.

**Question 8:**

In preparation for NDA submission, the Sponsor completed the manufacturing of three DP Primary Stability Batches that are currently on stability. [REDACTED] (b) (4) [REDACTED] the Sponsor intends to submit the NDA with 9 months long term stability data on the DP Primary Stability Batches in the final "complete module" wave submission of the Rolling Review (see Question 1). Within 30 days of this final wave submission to the NDA, the Sponsor proposes to provide an amendment to the pending application with a final stability report including 12 months long term stability data.

Does the Division agree that this proposed submission to the pending application?

**FDA Response to Question 8:**

We agree to the proposed submission of 12 months long term stability data within 30 days of the final wave submission to the NDA.

**Sponsor Response:**

The Sponsor thanks the FDA for this agreement. No further discussion is needed during the pre-NDA meeting.

**Discussion:**

No discussion.

**Question 9a:**

The relevant FDA guideline, “Guidance for Industry, M4Q: CTD - Quality, August 2001”, states that applicants should consult additional DS and/or DP information, such as executed batch records, to be attached in section R of the application. (b) (4)

The Sponsor proposes to provide certified English translations of the master batch records of DS process performance qualification (PPQ) batches, which well reflects manufacturing procedure of the DS commercial production, within the application because the DS PPQ batches will start but will not be completed prior to the expected date of the NDA submission (see Question 1). And the Sponsor proposes to provide the executed batch records of three DP primary batches in English because DP PPQ batches also will not start before the expected timing of the NDA submission.

Does the FDA agree with this proposal?

**FDA Response to Question 9a:**

Process Performance Qualification (PPQ) is not required for NDA approval but must be successfully completed before commercial distribution. As such, the NDA is not required to include PPQ batch information, including master or executed batch records.

The NDA should include a detailed description of the drug substance manufacturing procedures and process controls in Module 3.2.S.2. If you choose to submit an executed production record or a master batch production record, in addition to the information required in Module 3.2.S.3, you should provide a copy of the original document and an English translation, if the original is in a foreign language.

Per 21 CFR 314.50(d)(1)(ii)(a), the NDA should include the executed batch production records for the drug product stability batches. Per CFR 314.50(d)(1)(ii)(c), you may provide the proposed or actual commercial master drug product production record, or a *comparably detailed description* of the production process for a representative batch of the drug product. English translations should be provided for all original foreign language production records.

### **Sponsor Response:**

The Sponsor appreciates the FDA's comment and would like to clarify that "concurrent release" is planned for viltolarsen injection as per the May 15, 2018 Type C meeting discussion. It was discussed and agreed that in accordance with concurrent release, DS PPQ will be ongoing at the time of initial commercial distribution of DP PPQ Lots. The Sponsor committed to incorporate new knowledge gained during execution of the remaining DS PPQ plan. The Sponsor and FDA reached the following agreement as stated in the final Type C meeting minutes provided on June 6, 2018 (see Question 6 discussion):

"FDA reiterated that the concurrent release protocol should govern all material commercially released before PPQ is successfully completed for the entire drug substance process and the drug product process."

Regarding the FDA's request to submit a copy of original documentation in Japanese, as well as the English translation, the Sponsor wishes to clarify this general request. Does this only apply to Quality/CMC documentation for batch records? If so, the Sponsor agrees to comply with this request. **Please note that for nonclinical and clinical reports, the Sponsor plans to only submit English translated reports with a certificate of translation for each report.**

Finally, we want to clarify that the agency meant to state Module 3.2.S.2 and not additional section Module 3.2.S.3 as indicated in the FDA response above.

### **Discussion:**

The Agency stated that the requirement to provide original documents and translations applies to each part of the NDA that is not in English per 21 CFR 314.50(g)(2). Following further discussion regarding the requirement to provide original Japanese documentation, the Agency agreed to provide the full citation which refers to content of the summary and technical sections described in 314.50(c) and 314.50(d).

The Agency concurs with the clarification that Module 3.2.S.2 should have been referred to in the above response to Question 9a. The citation of Module 3.2.S.3 was due to a typographical error.

### **Post-Meeting Follow-up Question 9a (received 9/28/2018):**

As stated during the meeting, the Sponsor does not believe that 21 CFR 314.50 (g)(2) requires that original documentation in Japanese be submitted – the Sponsor plans to only submit complete translations of all original documents in Japanese. Regarding Modules 4 and 5, the Sponsor asks the Division to consider the listing of documents in the tables below for Japan Study NS065/NCNP01-P12 CSR and nonclinical reports of NS-065/NCNP-01. As these are a high volume and number of reports, a separate publishing team will be necessary that can publish Japanese documentation for eCTD. Moreover, Quality/CMC analytical method validation reports are also number but not list below. Do the Pharmacology/Toxicology and Clinical reviewers require these reports to review the application?

**FDA Response to Post-Meeting Follow-up Question 9a:**

See discussion comment for 9a above. A link and PDF to 21 CFR 314.50 are provided below. The Division believes that both the original and translated documents must be submitted. We are investigating this requirement from an OND policy standpoint and will follow up if more information becomes available.



21cfr314.50.pdf

Electronic Code of Federal Regulations: 21 CFR 314.50

[https://www.ecfr.gov/cgi-bin/text-](https://www.ecfr.gov/cgi-bin/text-idx?SID=9e0026e3d1135860545ac2ac33aa5c17&mc=true&node=se21.5.314_150&rgn=div8)

[idx?SID=9e0026e3d1135860545ac2ac33aa5c17&mc=true&node=se21.5.314\\_150&rgn=div8](https://www.ecfr.gov/cgi-bin/text-idx?SID=9e0026e3d1135860545ac2ac33aa5c17&mc=true&node=se21.5.314_150&rgn=div8)

**Question 9b:**

Further, the Sponsor plans to provide translators to assist with potential pre-approval inspections at each manufacturing facility. This has been common practice for the Sponsor's contract manufacturers (b)(4) when hosting FDA inspections.

If the FDA agrees with the proposal in Question 9a, is it also acceptable that the DS Primary Stability Batch executed batch records are not translated for the inspection(s), but rather the Sponsor will provide (b)(4) translators in addition to the translated master batch record of the DS Primary Stability Batches?

**FDA Response to Question 9b:**

The proposal appears acceptable. Please note that inspections sometimes require translated copies of selected documents and so the on-site translation service should be capable of creating certified translations in addition to verbal translation. The Agency cannot comment on the need for or timing of any potential pre-approval inspections.

**Sponsor Response:**

The Sponsor thanks the FDA for this comment as it prepares for pre-approval inspections.

No further discussion is needed during the pre-NDA meeting.

**Discussion:**

No discussion.

## Additional Comments

### CMC Comments:

The NDA submission should include a sterility assurance validation package that is consistent with the following guidance documents:

- “Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products”, 1994
- “Guidance for Industry Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice”, 2004

Additionally, as the drug product is an intravenous solution for injection by infusion, dilution of the concentrated drug product may be necessary prior to patient administration. If the diluted drug product holding period is greater than 4 hours at room temperature or greater than 24 hours under refrigeration, microbiological studies in support of the post-dilution storage time (as stated in the proposed product labeling) should be provided as part of the future NDA submission. Please provide a risk assessment summarizing the studies that demonstrate adventitious microbial contamination does not grow under the specified storage conditions after dilution with the specified diluent(s). Reference is made to Guidance for Industry: ICH Q8 Pharmaceutical Development, Section II.E and Guidance for Industry: ICH Q1A(R2) Stability Testing of New Drug Substances and Products, Section 2.2.7. Please include a description of the test methods and results of studies that are designed using a minimum countable inoculum (less than 100 CFU/mL) to simulate potential microbial contamination that may occur during product dilution. It is generally accepted that growth is evident when the population increases more than 0.5 log<sub>10</sub>, however other evidence of growth may be significant. Please perform the test using the storage conditions (temperature and duration) and diluents specified in product labeling. Please provide justification for the selected test conditions and/or diluents as necessary. Periodic intermediate sample times are recommended, as well as extended sample time points demonstrating that the diluted product does not support microbial growth for at least the maximum storage periods under the specified storage conditions. Challenge organisms may include strains described in USP <51> plus typical skin flora, species associated with nosocomial infection, or psychrophilic organisms. Please provide a positive control that demonstrates the viability of the organisms over the duration of the test period.

### Sponsor Response to Additional CMC Comment:

The Sponsor thanks the FDA for the additional guidance and plans to follow the recommendation to conduct microbiological studies in support of the post-dilution storage time.

No further discussion is needed during the pre-NDA meeting.

### Discussion:

No discussion.

### **Clinical Pharmacology Comments:**

- You should identify the elimination pathways for viltolarsen and evaluate whether any dose adjustments are needed based on intrinsic factors.
- Your NDA submission should include an immunogenicity assessment plan and an evaluation of the effect of immunogenicity on the pharmacokinetic (PK) and pharmacodynamic (PD) properties of viltolarsen.
- Your NDA submission should include a QT risk assessment strategy.

### **Sponsor Response to Additional Clinical Pharmacology Comment Item #3:**

The Sponsor appreciates the FDA's additional comments on Clinical Pharmacology and asks the FDA to elaborate on what information is expected to support the QT risk assessment strategy for the NDA.

### **Discussion:**

The Sponsor clarified that they have characterized QT risk using in-vitro hERG assay, in addition, the Sponsor had ECG data from Phase I and subsequent trials in patients at multiple time points. The Agency acknowledged that these data seems sufficient for filing. Evaluation of potential QT prolongation based on the submitted data will be a review issue.

### **Controlled Substance Staff (CSS) Comments:**

Viltolarsen seems not to have the profile of a drug with abuse potential. In silico, in vitro, and in vivo studies give no indication that viltolarsen has psychoactive activity. Based on the information submitted under the IND at this time, there is no need for further assessment of the abuse potential of viltolarsen.

## **3.0 ADDITIONAL INFORMATION**

### **DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

As stated in our August 1, 2018 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>.

### **PREA REQUIREMENTS**

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

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

### **PRESCRIBING INFORMATION**

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

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

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

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

## **SUBMISSION FORMAT REQUIREMENTS**

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>.

## **SECURE EMAIL COMMUNICATIONS**

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

**MANUFACTURING FACILITIES**

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

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

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

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

Corresponding names and titles of onsite contact:

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

**OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS**

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

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

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

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

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

## **PROSPECTIVE ASSESSMENTS OF SUICIDAL IDEATION AND BEHAVIOR IN CLINICAL PROTOCOLS**

Treatment-emergent suicidal ideation and behavior have been identified as a concern for a number of drugs and drug classes. For example, meta-analyses of clinical trial data for both antiepileptic drugs and antidepressants have demonstrated that these drugs increase the risk of suicidal ideation and behavior. Spontaneous reports have led to similar concerns with other drugs as well, e.g., isotretinoin and other tretinoin, beta blockers, reserpine, smoking cessation drugs, and drugs for weight loss. Because of these concerns, a prospective assessment for suicidal ideation and behavior should be included, when appropriate and feasible, in clinical trials involving all drugs and biological products for neurological indications. These assessments should generally be included in every clinical protocol, at every visit, and in every phase of development, with the exception of single-dose trials in healthy volunteers. These assessments should be conducted whether or not a particular product is known or suspected to be associated with treatment-emergent suicidal ideation and behavior. A Sponsor considering the omission of the assessment of suicidal ideation and behavior from a particular clinical protocol should prospectively discuss this omission with the Division of Neurology Products.

### **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**

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**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.**  
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/s/  
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ERIC P BASTINGS  
10/24/2018