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RESEARCH**

APPLICATION NUMBER:

209531Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Office of Clinical Pharmacology Review

NDA or BLA Number	209531
Link to EDR	Application 209531
Submission Date	09/23/2016
Submission Type	Priority
Brand Name	Spinraza™
Generic Name	Nusinersen
Dosage Form and Strength	12mg/5mL (2.4mg/mL)
Route of Administration	Intrathecal
Proposed Indication	Treatment of Spinal Muscular Atrophy
Applicant	Biogen Inc.
Associated IND	110011
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The Review Team acknowledges the input from OCP Guidance and Policy Team to this review.

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1. EXECUTIVE SUMMARY

This is an original NDA (NME) with the final part of a rolling submission submitted on 09/23/2016 seeking approval of nusinersen (SPINRAZA™) dosed intrathecally (IT) for the treatment of spinal muscular atrophy (SMA). SMA is the number one genetic cause of infant mortality and is diagnosed in approximately 1 out of every 10,000 births. SMA is caused by a homozygous deletion of the *SMN1* gene resulting in a deficiency in the production of the survival of motor neuron (SMN) protein. This deficiency leads to the death of motor neurons resulting in decreases in motor strength and function, ultimately impairing a patient's ability to reach motor milestones.

Nusinersen is a uniformly modified 2'-O-(2-methoxyethyl) [2'MOE] 18-mer antisense oligonucleotide designed to increase the splicing efficiency of the *SMN2* pre-mRNA to enhance production of full length SMN protein. This SMN protein acts as a replacement for subjects with SMA who have deletions and mutations that disable the ability of the *SMN1* gene to produce SMN protein.

The sponsor, Biogen Inc., is relying on results from a single double-blind, sham-controlled, phase 3 clinical trial (CS3B) in subjects ≤ 7 months of age with infantile-onset SMA and 2 copies of the *SMN2* gene as the basis for approval. The double-blind, sham-controlled portion of the study was stopped early after a planned interim analysis detected a statistically significant ($p < 0.0001$) greater percentage of subjects (41% to 0%) achieving a motor milestone response on the primary endpoint in the Hammersmith Infant Neurological Exam (HINE) for the nusinersen-treated group compared to the control group, respectively. In addition, the sponsor has a number of ongoing clinical trials in different types of SMA (e.g., pre-symptomatic, later onset) to support their proposed indication as well as to further evaluate the safety of nusinersen.

The primary objectives of this review are to evaluate the following: 1) the sponsor's proposed dosing regimen 2) the dose-response relationship for efficacy and safety and 3) the appropriateness of initiating therapy with nusinersen before receiving *SMN1* genotype to verify the diagnosis of SMA.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 209531. The Office recommends approval from a clinical pharmacology perspective. Key review issues with specific recommendations and comments are summarized below:

Primary evidence of effectiveness:	Primary evidence of effectiveness was established from a single pivotal efficacy study, CS3B, in infantile-onset SMA patients aged ≤ 7 months at baseline. In addition, an open label, multiple-dose, phase 2 study CS3A demonstrated an exposure-response relationship for nusinersen,
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	whereby subjects with higher exposures represented a larger percentage of motor milestone responders, CHOP-INTEND ¹ scores, and CMAP ² electrophysiological measure of motor neuron health improvements.
General dosing instructions:	<p>OCP recommends a fixed-dose of 12 mg/5 mL for all subjects with loading doses at days (b) (4), followed by the same maintenance dose every 4 months thereafter. We considered the following when recommending fixed dosing (b) (4)</p> <ul style="list-style-type: none"> • PK simulations of fixed dosing demonstrate that the mean nusinersen exposures (AUC_{inf} and C_{max}) will be ~25% higher in 0-3 month age group compared to age-based dosing. The mean difference in nusinersen exposures between dosing regimens for other age groups (>3 months to 2 years) will be less than 25%. The variability in data suggests considerable overlap in nusinersen CSF levels between age-based and fixed dosing. • Nusinersen was well-tolerated and there was no evidence for any serious adverse events (SAEs) related to exposure. • Exposure-response findings from a phase 2 study indicate higher proportion of motor milestone responders in the infantile-onset SMA population at the higher end of the dose response curve. • Fixed dosing is simpler and may reduce the potential for any dosing errors.
Dosing in patient subgroups (intrinsic and extrinsic factors):	No dose alterations recommended. Nusinersen is an oligonucleotide, administered by intrathecal route and intrinsic/extrinsic factors are not expected to impact its exposure, efficacy or safety.
Labeling:	The labeling concepts are generally adequate except for the aforementioned OCP recommendation for a fixed 12 mg/5 mL dose in all subjects. OCP also agrees that Nusinersen is to be labeled for all subjects with SMA.
Bridge between the “to-be-marketed” and clinical trial	The to-be-marketed formulation is the same as was used in the pivotal efficacy study, therefore no bridging is necessary.

¹ Children’s Hospital of Philadelphia -Infant Test of Neuromuscular Disorders

² Compound Muscle Action Potential

formulations:	
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1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Mechanism of Action: Nusinersen is an 18-mer 2'-MOE phosphorothioate antisense oligonucleotide that is intrathecally injected. Nusinersen acts as a splice-altering oligonucleotide designed to displace heterogeneous ribonucleoproteins (hnRNPs) at the intronic splice silencing site-1 (ISS-1) on the *SMN2* pre-mRNA to enhance production of full length SMN protein.

Absorption: Nusinersen is administered as an intrathecal injection.

Distribution: Nusinersen distributes rapidly to the CNS and the plasma. Plasma concentrations peak at 1-6 hours and decline rapidly due to extensive tissue distribution.

Metabolism: Nusinersen is metabolized by exonucleases primarily at the 3' end of the oligonucleotide. N-1 metabolites were found in the cerebrospinal fluid (CSF), while N-1,2,3 metabolites were found in the plasma.

Elimination: The mean terminal half-life in the CSF ranges from 135-177 days. It is mainly excreted in the urine as chain-shortened metabolites (N-1,2,3) that are not considered active. Urinary excretion of intact nusinersen represented only a small fraction of the dose (0.5%) at day 85 following a third dose of the drug.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The review team, after discussion with the sponsor, is recommending a fixed dose for all patients. This will result in nusinersen exposures that are similar, but higher than those evaluated (on an average ~25% higher in 0-3 months age group) in the clinical studies. This recommendation is supported by consideration of the projected increases in nusinersen exposures (C_{max} , AUC) in various age groups, inter-patient variability, exposure/response relationship from Phase 2, and overall safety profile of nusinersen. Additional details on age-based and fixed dose of nusinersen are provided in Section 3.3.2.

2.2.2 Therapeutic individualization

No therapeutic individualization is required for extrinsic factors regarding nusinersen because of the intrathecal route of administration and lack of its drug-drug interaction potential. Intrinsic factors like hepatic/renal impairment are not expected to affect

nusinersen exposure and such conditions are not considered prevalent in SMA patient population.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology has the following recommendations for general dosing and dose adjustment criteria based on intrinsic and extrinsic factors.



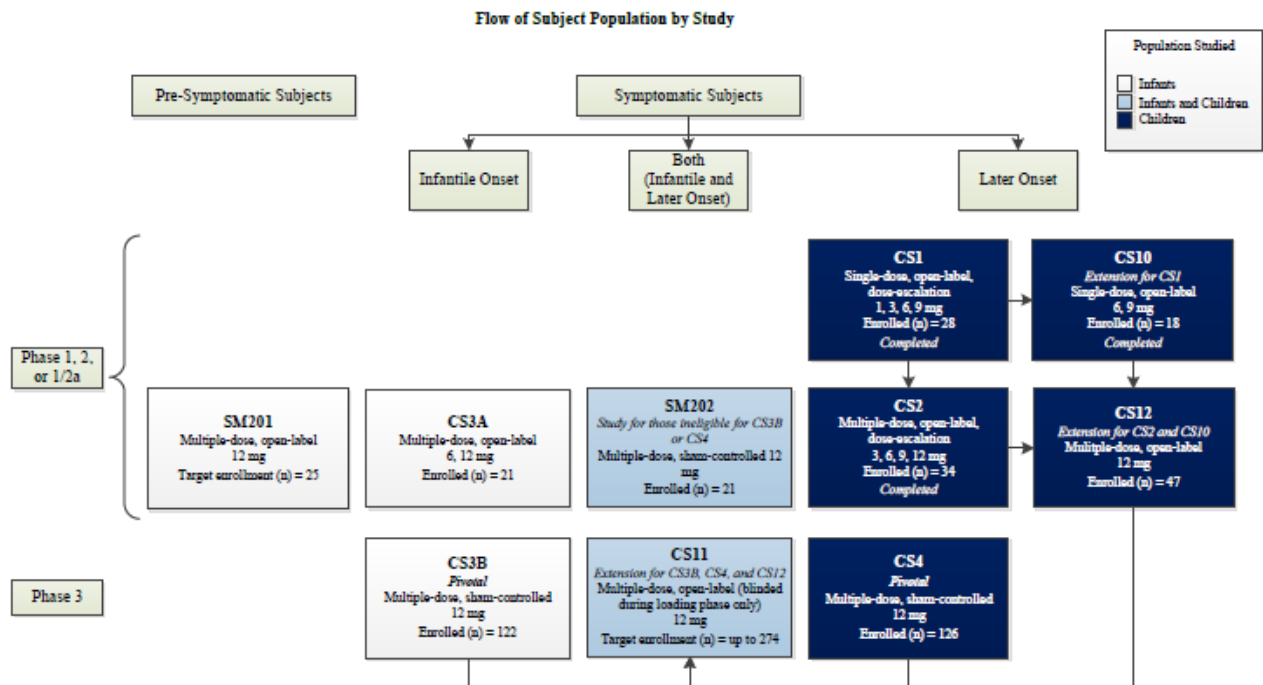
- We agree that no dose adjustments are required based on intrinsic/extrinsic factors. This is primarily because renal/hepatic impairment is not likely to occur in SMA patients. Moreover, nusinersen is an oligonucleotide administered as an intrathecal injection with low drug-drug interaction liability and no patient related factor affecting exposure is expected or identified.
- We agree that nusinersen should be labeled for the treatment of SMA. We reviewed the potential for labeling for [REDACTED] SMA, but concluded that it was not necessary.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

The clinical development program consists of 10 studies, of which, 3 are completed (a single dose escalation study CS1, its extension phase CS10 and multiple dose escalation study CS2) and 7 studies (CS11, CS12, CS3A, CS3B, CS4, SM201, SM202) are ongoing. An outline of the clinical development program is presented in **Figure 1**.

Figure 1. Study Populations in Nusinersen Development Program



Source: Page 10, Sponsor's clinical overview

A total of 173 subjects with SMA participated in the clinical studies supporting this application. These studies provide information supporting proof-of-concept, dose-finding, and the efficacy and safety of nusinersen in Type 1-3 SMA. Clinical pharmacology studies in healthy subjects were not conducted given the intrathecal route of administration of nusinersen. Drug-drug interaction studies were not conducted given the lack of any significant *in vitro* findings on nusinersen as an inducer or inhibitor of CYP enzymes or transporters. Renal and hepatic impairment studies were not conducted as concomitant renal or hepatic disease is not likely to be found in the SMA population. Nusinersen is administered by intrathecal route and is expected to exert its pharmacological effect locally in the CNS. Additionally, no patient related factors were identified that may affect nusinersen exposure.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	<p>Nusinersen acts to replace the SMN protein deficit which causes SMA, by increasing the splicing efficiency of the <i>SMN2</i> pre-mRNA. More specifically, nusinersen is an 18-mer 2'-MOE phosphorothioate antisense oligonucleotide that acts as a splice-altering oligonucleotide. Nusinersen was designed to pair with a specific target sequence on the <i>SMN2</i> pre-mRNA to displace heterogeneous ribonucleoproteins (hnRNPs) at the intronic splice silencing site-1 (ISS-1) between exons 7 and 8 to allow for more complete translation of SMN protein from the paralogous gene <i>SMN2</i>.</p> <p>Further reinforcing this concept, SMA phenotype is closely tied to <i>SMN2</i> copy number. <i>SMN2</i> serves to produce SMN protein, however at a greatly reduced rate because of differential splicing caused by the binding of the hnRNPs at the ISS-1.</p>
QT Prolongation	TQT study not conducted given no a priori concern for prolongation with antisense oligonucleotides.
General Information	
Bioanalysis	Nusinersen concentrations were measured using validated hybrid ELISA methods.
Healthy Volunteers vs. Patients	Nusinersen was not studied in healthy subjects.
Dose Proportionality	The dose-proportionality in CSF was not assessed due to sample size limitations. The PK in plasma appears to be approximately dose-proportional up to a 12 mg dose.
Variability	Inter-subject variability in pre-dose CSF (%CV) levels for nusinersen ranges from 20% to 63%.
Immunogenicity	Anti-drug antibodies (ADA) were detected in 4 subjects in the clinical development program. In 3 of these subjects, the ADA responses were transient and only detected at one time-point. There was no evidence that ADA impacted efficacy or safety of nusinersen.

Absorption	
Bioavailability	100% bioavailable in the CSF with direct intrathecal injection
T_{max}	Plasma: 1.7-6.0 hours
Distribution	
Volume of Distribution	CSF: 0.4 L Plasma: 29 L
Protein Binding	CSF: < 25% Plasma: >94%
Substrate of transporter systems	Nusinersen is not a substrate or inhibitor for BCRP, P-gp, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, and BSEP <i>in vitro</i> .
Elimination	
Mean Terminal Elimination half-life	CSF: 135-177 days, Plasma: 85 days
Metabolism	
Primary metabolic pathway(s)	Slow metabolism by exonuclease activity (N-1, 3')
Inhibitor/Inducer	Nusinersen is not an inhibitor or inducer for any of the major CYP enzymes or transporters.
Excretion	
Primary excretion pathways	Excreted by the kidney as chain-shortened oligonucleotides, which are not considered pharmacologically active.

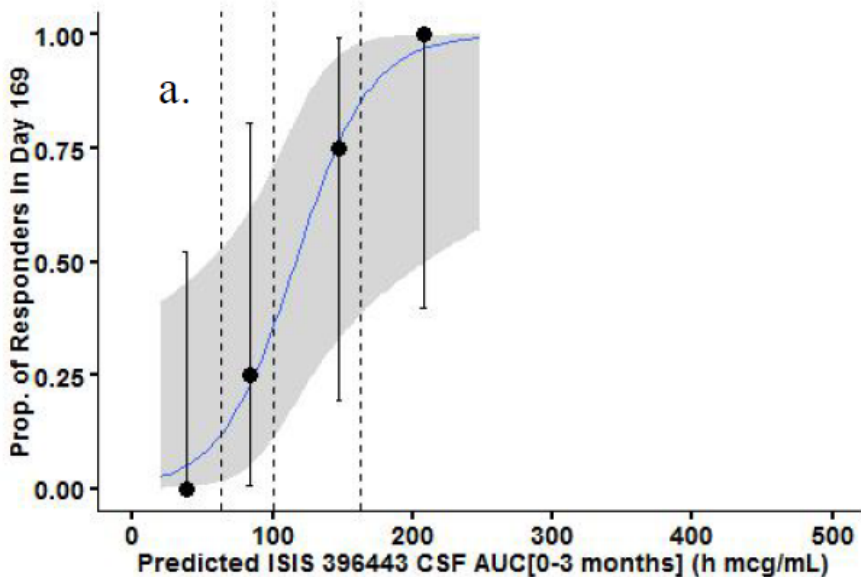
3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The evidence of effectiveness of nusinersen is supported primarily by the double-blind, sham-controlled portion of the pivotal efficacy study CS3B. The study was stopped early after a planned interim analysis detected a statistically significant ($p < 0.0001$) greater percentage of subjects achieving a motor milestone response on the primary efficacy endpoint for the nusinersen-treated group compared to the control group (41% vs. 0%

- SMN protein levels in CSF were measured in early studies that demonstrated significant increases from baseline at doses above 9 mg, however these findings were not consistent at lower doses. Moreover, SMN protein levels in CSF were highly variable.
- Dose/exposure-response analysis conducted by the sponsor for Phase 2 study CS3A also supports the selection of 12 mg as effective dose over 6 mg (**Figure 3**). The analysis showed that for each unit increase in the partial AUC_{0-3months} in CSF would result in an increase of about 4% in the odds of being a motor milestone responder in six months. Similar relationships were explored by the review team for the pivotal efficacy study CS3B. However, no definitive conclusion regarding exposure-response relationship could be derived probably because the study CS3B included only one dose level and information at Day 183 was not available from all patients due to interim cut-off. For additional details, please refer to Section 4.2.

Figure 3. Exposure-Response Relationship between the Partial CSF AUC_{0-3months} and the Overall Motor Milestones Responders in Day 169 (Phase 2 Study CS3A)



Blue line: Logistic regression line; Grey area: 95% prediction interval; Dashed line: Quartile line for the exposure; Circles: Mean response for each quartile, along with the 95% CI.

Source: Sponsor's E-R analysis from Phase 2 Study CS3A

Overall, the concepts derived from preclinical and clinical pharmacology studies supported the mechanistic rationale, proof-of-concept, and dose-response relationship that ultimately helped the sponsor demonstrate the efficacy of nusinersen in SMA patients.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, (b) (4)

[Redacted]

[Redacted] (b) (4)

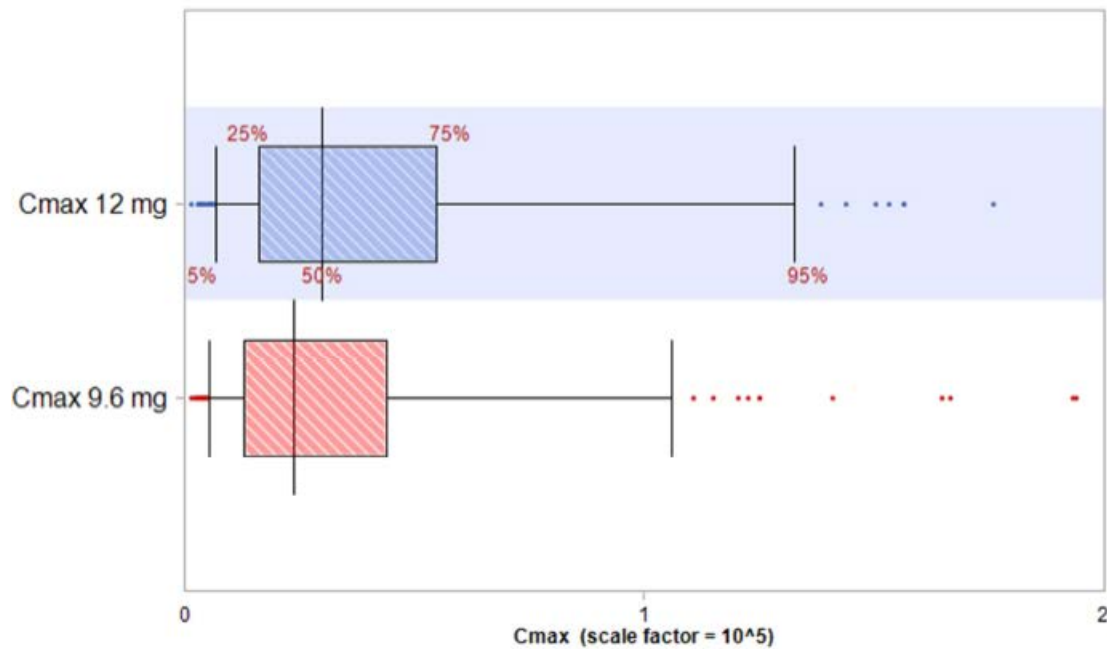
[Redacted] (b) (4)

[Redacted] (b) (4) the agency
asked the sponsor if they felt a fixed 12 mg/5 mL dose [Redacted] (b) (4) The
sponsor agreed and provided additional rationale why a fixed 12 mg/5 mL dose [Redacted] (b) (4)

[Redacted]

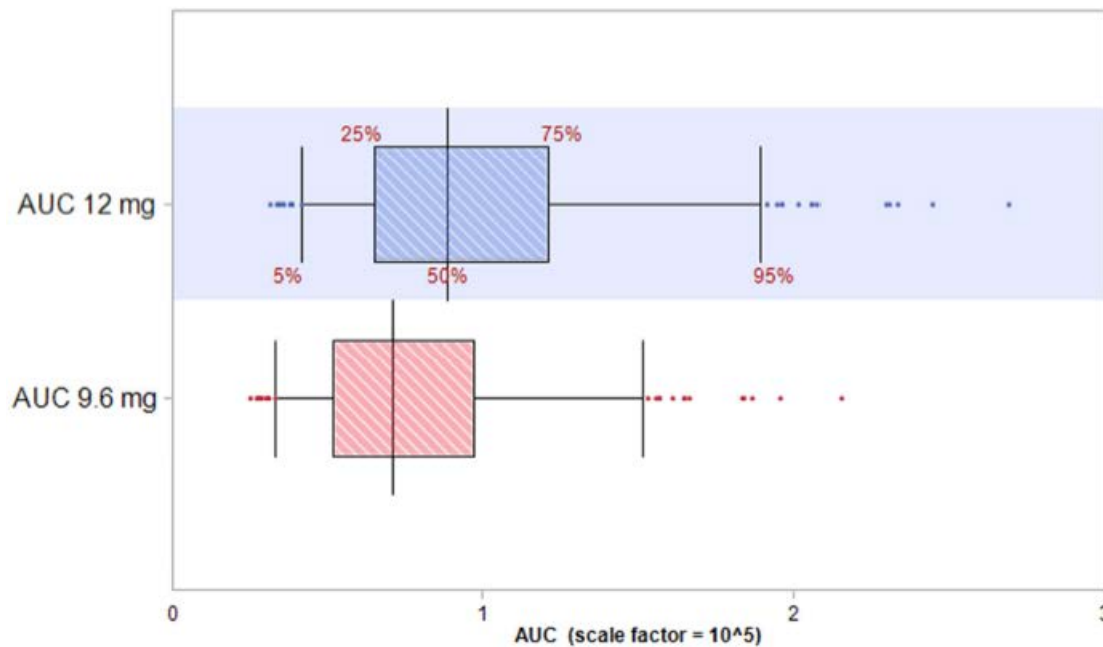
The sponsor's simulated data (See **Section 4.3** for more details) show that for C_{max} in CSF there is substantial overlap and > 90% of subjects receiving a 12 mg dose are predicted to have C_{max} values below the 95th percentile for an age based 9.6 mg dose (**Figure 5**). Moreover, CSF AUC_{inf} values shown in **Figure 6** also, demonstrate the substantial overlap, where at least 87.5% of subjects receiving the 12 mg dose are predicted to have AUC_{inf} values below the 95th percentile for the age based 9.6 mg dose. These findings are expected considering the large inter-individual variability in the volume of distribution in the CSF and moderate variability in CSF clearance.

Figure 5. Simulated C_{max} Values in CSF Illustrating the Overlap Between Nusinersen Doses of 12 mg (fixed dose) and 9.6 mg (adjusted for age) in Patients < 3 Months of Age



Source: Figure 1-A sponsor's response to IR dated 11/10/16

Figure 6. Simulated AUC_{inf} Values in the CSF Values Illustrating the Overlap Between Nusinersen Doses of 12 mg (fixed dose) and 9.6 mg (adjusted for age) in Patients < 3 Months of Age



Source: Figure 1-B sponsor's response to IR dated 11/10/16

We agree with the sponsor's assessment that a fixed dosing regimen for nusinersen in all subjects can be used. The fixed dosing may result in up to ~ 25% higher exposures in both CSF and plasma for the youngest patients (0-3 months). Given that nusinersen appears to be well tolerated and the adverse events from study CS3B do not appear to be exposure related, it is unlikely that a ~ 25% increase in exposure places these patients at an increased risk for toxicity. Moreover, the variability in nusinersen CSF concentrations (~21-63%) is such that the majority of subjects will have exposures in the range of those observed in the clinical studies. Lastly, the exposure-response findings from an open label Phase 2 study indicate a higher proportion of motor milestone responders in the infantile onset SMA population at the higher end of the dose response curve (**Figure 3**).

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

No. Dose adjustments are not necessary based on intrinsic factors such as age (see Section 3.2.2), renal or hepatic impairment. The prevalence of renal and hepatic impairment in SMA patients is considered very low. Nusinersen is an intrathecally administered oligonucleotide and is metabolized by exonucleases. Therefore, its exposure is not expected to be impacted by these intrinsic factors. Also, no patient attributes were identified from clinical studies that may affect the exposure to nusinersen.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

No. Given its intrathecal route of administration, nusinersen is not at risk for any food-drug interactions. Moreover, nusinersen is an oligonucleotide and *in vitro* studies showed that the potential for drug-drug interactions mediated by CYP enzymes or transporters are very low for nusinersen.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation

- The plasma concentrations of nusinersen were determined in human CSF and plasma by a validated hybridization enzyme linked immunosorbent assay (Hyb-ELISA) method for Study CS1 and by a validated hybridization electro-chemiluminescence assay (ELA) for all other studies. Both of these methods report the sodium salt form of nusinersen rather than the free acid form.
- SMN protein concentrations in CSF samples for pharmacodynamic measurement were determined using an Erenna[®] immunoassay.
- The immunogenicity of nusinersen was evaluated using a validated ELISA to determine the presence of anti-nusinersen antibodies in human plasma. For a more in depth review of this assay please refer to the review by the Office of Biotechnology Products.
- Nusinersen was measured in autopsy samples from 3 subjects who died during study CS3A by Hyb-ELISA. Immunohistological (IHC), immunofluorescence (IF) staining and reverse-transcription polymerase chain reaction (RT-PCR) were employed to evaluate the percentage and quantity of *SMN2* mRNA containing exon 7 in the autopsy tissue samples.
- The extent of protein binding of nusinersen was evaluated in investigational in vitro studies in human CSF and plasma using an ultrafiltration method, combined with a nuclease-dependent Hyb-ELISA detection method.

Reviewer Comment: Overall, the methods appear appropriate to adequately characterize the measured analytes. However, there was an issue with the ELISA used to measure nusinersen concentrations in studies CS1, CS2, and CS10, with some anomalously high concentrations in samples prior to dosing. Upon further evaluation using a separate ELISA assay, the concentrations were re-estimated, hence it was determined that those samples were likely mislabeled. The IHC method used for SMN protein detection is more suited for qualitative comparison and is only semi-quantitative in nature.

4.2 Clinical PK and/or PD Assessments

SMN protein levels were measured as a potential pharmacodynamic marker of nusinersen activity. SMN protein was detected in autopsy samples from thoracic spinal cord motor neurons from subjects treated with nusinersen in Study CS3A. This was only semi-quantitative due to limitations of the immunohistochemistry (IHC) method used to localize the protein. Direct measurement of SMN protein within the neuron was not feasible. Moreover, the closest concentrations that were measured were in the CSF and were quite variable. No SMN protein were available from control subjects, hence the actual change in SMN protein concentrations could not be assessed.

SMN protein concentrations were also measured in study CS2. A statistically significant increase in CSF SMN protein was observed after a single 9 mg IT dose of nusinersen, but not after one or two doses of 3 or 6 mg. Moreover, there was a trend for increased SMN protein in CSF after one or two 12 mg doses of nusinersen on days 29 and 85.

Data were available for *SMN2* mRNA containing exon 7 based on autopsy tissue samples from 3 subjects treated with nusinersen. SMA infants treated with nusinersen had higher levels of *SMN2* mRNA containing exon 7 than untreated SMA infants.

Reviewer Comment: Overall, a clear and consistent relationship between SMN protein in the CSF and nusinersen dose was not established. This may be in part due to the variability in SMN protein expression.

4.3 Population PK and/or PD Analyses

Background

The pharmacokinetics (PK) of nusinersen in the cerebrospinal fluid (CSF) and plasma of 72 infants (n=29) and children (n=43) with spinal muscular atrophy (SMA) from across five different trials (Studies 396443-CS1, ISIS 396443-CS2, ISIS 396443-CS3A, ISIS 396443-CS10, and ISIS 396443-CS12) were analyzed via population-based modeling. In these five studies, limited PK samples were obtained in the CSF and serial and sparse PK samples were obtained in the plasma of SMA patients. Brief description of the five studies is provided below:

- ISIS 396443-CS1 (completed): an open-label, single ascending-dose (SAD) Phase 1 study designed to assess the safety, tolerability and pharmacokinetics of ISIS 396443 in patients with SMA, aged 2 to 14 years of age. Patients were randomized at baseline to one of 4 independent treatment arms, and received a single IT dose of 1, 3, 6, or 9 mg.
- ISIS 396443-CS2 (completed): an open-label, multiple ascending-dose (MAD) Phase 1/2a study designed to assess the safety, tolerability and pharmacokinetics of ISIS 396443 in patients with SMA 2 to 15 years of age. Patients were randomized at baseline to one of 4 independent treatment arms, and received 2 (9-mg cohort only) or 3 IT doses of 3, 6, 9, or 12 mg on Days 1, 29 (3-, 6-, and 12-mg cohorts only), and 85.
- ISIS 396443-CS3A (ongoing): a multiple-dose study designed to assess the safety, tolerability, pharmacokinetics and efficacy of ISIS 396443 in patients with infantile-onset SMA (symptomatic SMA infants < 7 months of age at screening). Patients were randomized at baseline to one of 2 independent treatment arms, and received 3 IT doses of 6 or 12 mg during a “loading” dosing phase on Days 1, 15, and 85. All patients received multiple 12-mg IT doses every 4 months during a “maintenance” dosing phase beginning on Day 253.
- ISIS 396443-CS10 (completed): an open-label study to assess the safety and tolerability of a single IT dose (6 or 9 mg) of ISIS 396443 in patients with SMA who previously participated in ISIS 396443-CS1.

- ISIS 396443 CS12 (ongoing): an open-label study to assess the safety and tolerability of a single IT dose (12 mg) of ISIS 396443 in patients with SMA who previously participated in either ISIS 396443 CS2 or ISIS 396443-CS10. Patients received a multiple IT doses of 12 mg on Days 1, 169, 351, and 533.

The objectives of this analysis were:

- To develop a model that simultaneously describes the population PK of nusinersen in the CSF and plasma following single and multiple IT administrations to patients with SMA.
- To identify statistically significant covariates that contribute to the inter-subject variability (IIV) in the PK of nusinersen in patients with SMA and to determine if statistically significant covariates are clinically relevant through simulations.
- To explore the exposure-response relationship between partial CSF AUCs or predicted CSF nusinersen concentration and four pharmacodynamics endpoints: motor milestone response (clinical endpoint), CHOP-INTEND scores, CMAP, and SMN protein in CSF.

Data Exclusions

It was noted in the clinical trials that some pre-dose Day 1 samples (prior to the first dose) had positive CSF concentration values. The reason for this finding is potentially due to sample mis-handling (see explanation in 4.1) and this result was documented in the trial database and clinical study reports (CSRs). These values were manually removed from the NONMEM data file as they showed up for TAFD=0 with positive DVs. A total of 9 data points were removed from the programmed dataset. In addition, the total number of data points ignored from data due to outliers were 28 (not counting the excluded subjects), representing 1.9% of all data points.

Modeling Strategy

NONMEM 7.2 was used for all model estimation. The analysis was conducted using the following strategy, with each step further described below: 1) Base Model Development, 2) Random Effects Model Development, 3) Inclusion of Covariates, 4) Final Model Development, 5) Assessment of Model Adequacy (Goodness of Fit) and 6) Validation of the Final Model (also referred to as the “Full Model” as the Full Covariate Model approach was taken). FOCE INTERACTION was used for the Base Model as well as the Full Model.

The final structural components of the base model were determined based on exploratory attempts to arrive at a stable model. The simplified model consisted of two CSF compartments; this was in part supported by previous preclinical findings from monkeys which showed that there was distribution of nusinersen from CSF into brain tissues. Previous experience with the PK of anti-sense oligonucleotides (ASOs) showed that their general plasma kinetic profiles followed a two-compartment model. Thus, the potential base model would consist of at least two compartments in the plasma and two compartments in the CSF. Comparison of uni- and bidirectional flow between the CSF and plasma was also performed.

Results

The subject demographics for the pooled dataset and individual studies is shown in **Table 1**.

Table 1. Subject Demographics for the Pooled Dataset and Individual Studies

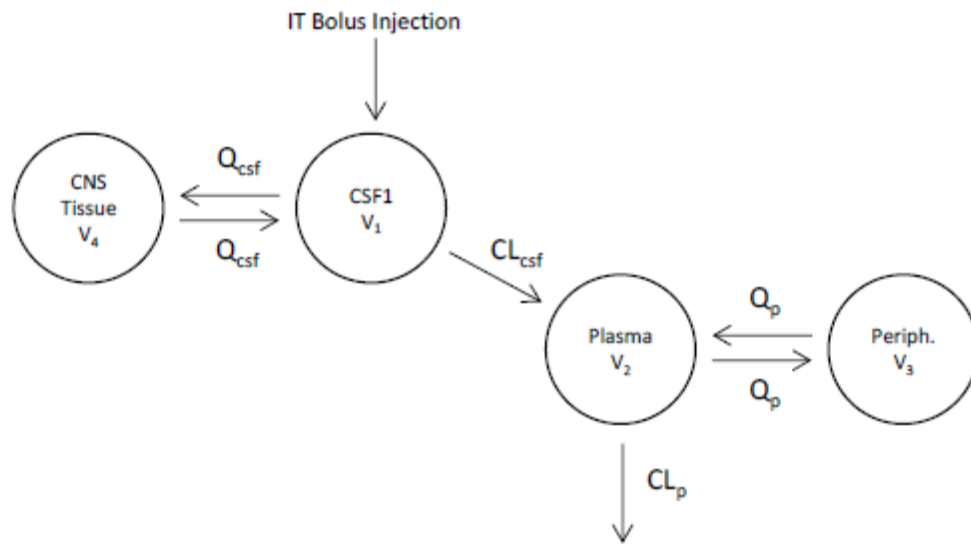
Ionis Study	Number of Subjects (N)	Age [yrs Median (Range)]	Male	Female	Weight [kg Median (Range)]	Race	CSF Data Points	Plasma Data Points
All	72 ^a	5 (0.10 to 15)	37	35	15.2 (5.1 to 83)	Caucasian: 62, Black: 4, Asian: 3, Other: 3	279	1181
CS1	24	6 (2 to 12)	9	15	18.6 (10.3 to 52.1)	Caucasian: 19, Black: 1, Asian: 2, Other: 2	15	105
CS2	32	5 (2 to 15)	19	13	21.5 (10.8 to 83.1)	Caucasian: 28, Black: 2, Asian: 1, Other: 1	53	458
CS10	16	6 (2 to 11)	5	11	18.4 (10.3 to 52.1)	Caucasian: 13, Black: 1, Asian: 1, Other: 1	16	118
CS12	43	7 (3 to 17)	22	21	16.9 (10.3 to 83.1)	Caucasian: 39, Black: 1, Asian: 2, Other: 1	100	293
CS3A	20	0.425 (0.10 to 0.57)	12	8	6.58 (5.07 to 9.25)	Caucasian: 16, Black: 1, Asian: 1, Other: 2	89	183

^a Note that many subjects continued on from one study to another (see [Section 5.1](#)); thus, the total number of unique subjects in all of the studies is less than the sum of the numbers of subjects in each study.

Source : Table 2 on page 26 in sponsor's report (is11-pop-pk-report.pdf)

The base model is shown in **Figure 7**. The model consisted of a total of four compartments, with two compartments representing the central nervous system (CNS) (a CSF compartment and a CNS tissue compartment) and two compartments representing the plasma. The model was defined in terms of the following parameters: CLp represents the plasma clearance, CLcsf represents the CSF clearance (rate of transport into the plasma), Qcsf and Qp represent the inter-compartmental clearances within the CSF and plasma, respectively, and V1, V4, V2 and V3 represent the model-estimated apparent volumes in the first CSF compartment, the CNS tissue compartment, the central plasma compartment and the peripheral plasma compartment, respectively. All clearance rate constants in the model were assumed to be linear.

Figure 7. Structural diagram of the Base Model



Source : Figure 1 on page 27 in sponsor's report (is11-pop-pk-report.pdf)

Attempts at including additional exit rate constants were not successful due to the sparse nature of the data. Preliminarily, several other alternative model structures (including one CSF compartment instead of two, bi-directional transport between CSF and plasma and nonlinear kinetics within the CSF compartments or between CSF and plasma) were attempted resulting in run failure or OFVs inferior to the chosen model.

To develop the full model, extensive graphical analysis was initially performed to assess: 1) the potential correlations between various covariates and the random effect terms, etas, and 2) the potential relationship between various covariates and each of the model parameters (CL_p , CL_{csf} , V_1 , V_2) for which the random effects (IIVs) were accounted for. In this analysis, sex (SEX), race (RACE), baseline bodyweight (BWT), baseline age (BAGE), baseline height (BHT) and baseline body surface area (BBSA) were graphically analyzed against the eta terms and model parameters prior to their selection for covariate model building. There appears to be no significant effect of SEX or RACE on any of the eta terms. Therefore, sex and race were not considered for further covariate testing.

Because BWT was considered most physiologically relevant (in comparison to BAGE, BBSA, and BHT), it was included in the full model. An allometric model was used to relate BWT to V_1 and CL_p and a linear model was used to relate BWT to V_2 as defined in the following equations:

- $V1i = V1 \left(\frac{BWT}{MBWT} \right)^{\theta V1}$
- $V2i = (1 + \theta V2)(BWT - MBWT)$
- $CLPi = CLP \left(\frac{BWT}{MBWT} \right)^{\theta CLP}$

Where V1i is the individual specific value of CSF volume, V1 is the population value of CSF volume, $\theta V1$ is the estimated exponent scaling V1i and V1 based on body weight (BWT), V2i is the individual specific value of plasma volume, $\theta V2$ is the linear parameter scaling BWT to V2, MBWT is the median body weight. CLPi is the individual plasma volume, CLP is the population volume and θCLP is the estimated exponent scaling CLPi and CLP based on cBWT.

The parameter estimates from the base model and final model are shown in **Table 2**.

Table 2. PK Model Parameters: Comparison of Base Model vs Full Model

Parameter	Base Model				Full Model				$\Delta\%IV$
	Typical Value (%RSE)	Unit	%IV	Eta Shrinkage (%)	Typical Value (%RSE)	Unit	%IV	Eta Shrinkage (%)	
Q_p	0.572 (11.3)	L/hr	NE	NA	0.568 (11.7)	L/hr	NE	NA	NA
Q_{csf}	0.069 (18.1)	L/hr	NE	NA	0.0712 (19.5)	L/hr	NE	NA	NA
CL_p	2.50 (11.2)	L/hr	58.5 (31.3)	1.78	2.36 (5.04)	L/hr	29.5 (30.2)	7.25	-29
CL_{csf}	0.133 (8.87)	L/hr	24.8 (47.9)	19.4	0.136 (9.12)	L/hr	24.4 (55.9)	20.7	-0.4
V_1	0.441 (21.7)	L	104 (>100)	15.2	0.433 (21.7)	L	88.1 (36.6)	18.0	-16
V_2	32.0 (21.7)	L	63.2 (>100)	3.66	29.0 (11.4)	L	39.0 (51.4)	10.0	-24
V_3	429 (19.2)	L	NE	NA	418 (20.9)	L	NE	NA	NA
V_4	258 (17.1)	L	NE	NA	263 (18.9)	L	NE	NA	NA
IOV OCC	NA	NA	38.1 (11.4)	4.51	NA	NA	38.1	5.21 (13.3)	0
BWT on CL_p	NA	None	NA	NA	0.494 (2.45)	None	NA	NA	NA
BWT on V_2	NA	None	NA	NA	0.689 (12.2)	None	NA	NA	NA
BWT on V_1	NA	None	NA	NA	0.047 (21.7)	None	NA	NA	NA
Epsilon (Proportional)	70.2 (2.39)	%	NA	6.94 (epsilon shrinkage)	77.2 (52.3)	%	NA	6.81 (epsilon shrinkage)	NA

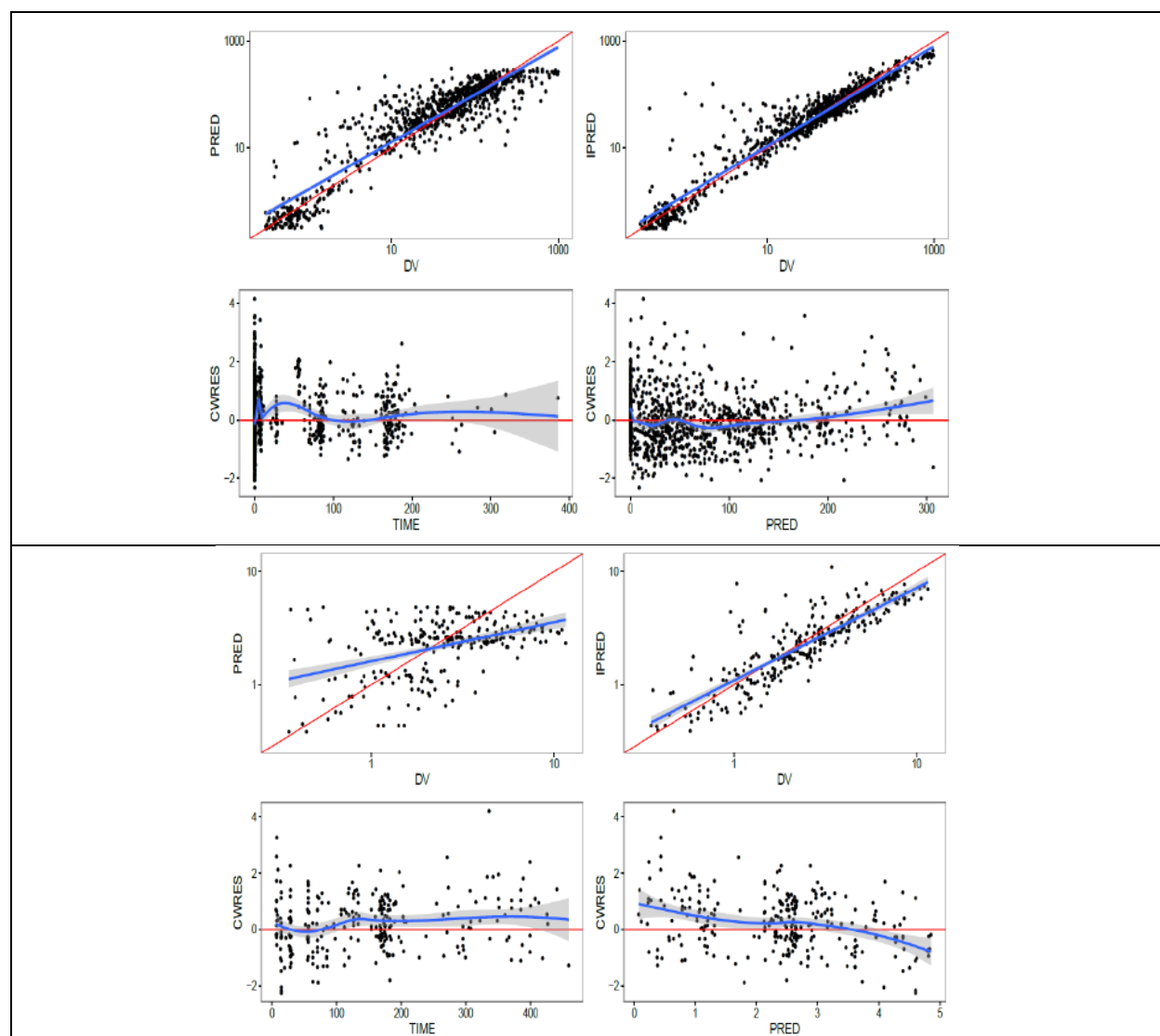
hr = Hour; %IV = Inter-subject Variability (%); IOV = inter-occasion variability; L = Liter; NA = Not Applicable; NE = Not Estimated or fixed to 0; %RSE = Relative Standard Error (%)

Source : Table 4 on page 33 in sponsor's report (is11-pop-pk-report.pdf)

Diagnostic plots for plasma and CSF data from the final model are shown in **Figure 8**. There was a noticeable systemic bias in the IPRED in terms of its prediction of the high DV values for CSF data (**Figure 8**, Bottom, IPRED vs DV); this occurs for a small cluster of data at DVs above ~7.0 ng/mL. Other unexplained variability not accounted for by the full

model may have contributed to this bias, which may include bioanalytical assay variability or variability associated with the IT route of administration and/or sampling. No such bias was observed for plasma data. The full model was used to simulate the CSF concentration-time profiles of the individual subjects in the study ISIS 396443-CS3A population and the partial CSF AUC values were calculated based on linear trapezoidal method. CSF beta half-life (terminal half-life based on the assumption of a two compartment model) values was calculated based on the Empirical Bayes Estimates (EBEs) of the microconstants of the CSF compartments. The median terminal half-life for the overall population (n=72) was 163 days. Half-life values do not seem to differ significantly between age groups.

Figure 8. Diagnostic Plots for (Top) Plasma (Bottom) CSF Data from the Full Model



Source : Figures 4, 5 on page 34-35 in sponsor's report (is11-pop-pk-report.pdf)

The sponsor also calculated the terminal half-life of nusinersen based on post-dose concentrations in Study CS1 and pre-dose concentrations in Study CS10. Study CS1 was an open-label, escalating dose study to assess the safety, tolerability and dose-range finding of a single intrathecal dose of nusinersen in patients with SMA. Study CS10 was an open-label study to evaluate the safety, tolerability, and PK of a single dose of nusinersen administered as an IT injection by lumbar puncture (LP) in subjects who previously participated in CS1. Subjects who had received 3 mg, 6 mg, or 9 mg in CS1 and had successfully completed the study were eligible for screening at 9 months (270 days) and before 15 months (450 days) after dosing in CS1.

The apparent terminal half-life in CSF was calculated estimated for each patient using the 7- or 28-day postdose concentrations observed in ISIS 396443-CS1 and the predose concentrations observed in ISIS 396443-CS10, and the following equation:

$$t_{1/2} = \frac{\ln(2)}{\left(\frac{\ln\left(\frac{\text{predose CS10 conc.}}{\text{postdose CS1 conc.}}\right)}{-t}\right)}$$

where t is the time between the postdose ISIS 396443-CS1 sample collection and the predose CS10 sample collection. Since the apparent terminal half-life was calculated using only 2 time points the values should be interpreted with caution. The mean apparent terminal half-life in CSF was estimated to be 135 to 177 days (**Table 3**), which is consistent with values observed in monkeys and suggests that a long dosing interval of 4 to 6 months could be employed to maintain CSF concentrations at a steady-state level.

Table 3. Summary Statistics of Predose CSF Concentrations and Estimated Terminal Half-Life of Nusinersen (ng/mL) in Patients Receiving Intrathecal Administration(s) of Nusinersen

			Observed CS10 Predose Concentration (ng/mL)			Observed CS1 Concentration 7 Days Post Dose (ng/mL)	Estimated Terminal Half-Life (days) ^b
CS1 Cohort	CS1 Dose	Days between CS1 Dose and CS10 Predose Collection ^a	N	Mean ± SD	Median (Range)	Mean ± SD	Mean ± SD
2	3 mg	297 to 428	6	0.372 ± 0.239	0.361 (BLQ-0.658)	2.18 ± 1.38	135 ± 14.8
3	6 mg	338 to 460	3 ^c	0.604 ± 0.223	0.681 (0.353-0.778)	3.22 ± 0.558	163 ± 26.5
4	9 mg	290 to 400	8	0.747 ± 0.441	0.671 (0.224-1.66)	3.56 ± 0.263	177 ± 41.3

CS1 = Study ISIS 396443-CS1; CS10 = Study ISIS 396443-CS10

Note: Data presented as Mean ± Standard Deviation

a Days between doses for individual patients are provided in [Listing 16.2.5.1](#).

b Half-life values were estimated on an individual patient basis, accounting for the time after the CS1 dose the CSF sample was collected. See [Listing 16.2.5.3](#) for individual half-life values and collection times.

Source : Table 10 on page 38 in report-body.pdf (Study CS 10)

Reviewer's Comments: The sponsor's structural model is based on prior experience with AONs with a phosphorothioate backbone. Although the data is limited to estimate all parameters (including interindividual variabilities), the reviewer finds the structural model acceptable. No covariates were identified that would necessitate the need for changes in dosing regimen. The estimate of half-life derived from the population pharmacokinetic analyses (163 days) is similar to that derived from model independent methods (135-177 days). The reviewer also looked at the data excluded from analysis. In some patients, for reasons not clear, on certain occasions very high CSF nusinersen levels were observed at pre-dose visit. These values are beyond the range of variability in CSF levels of nusinersen. The exclusion of these unexpected high values is reasonable.

Reviewer's Analysis

Aim

- To verify labeling statements proposed by the sponsor. This involved executing the final population pharmacokinetic model.
- What would be the changes in nusinersen CSF and plasma concentrations with the simplified fixed dosing regimen (12 mg/5 mL for all) that would administer a 25% higher dose in a 0-3 month old patient? Will it have any implications for safety?

Data

The dataset submitted by the sponsor (finalnm.xpt) was used for the analysis. The analysis was conducted using NONMEM® (Version 7).

Findings

Verification of proposed labeling statements

The reviewer was able to run the final model and derive similar estimates to those reported by the sponsor. The estimates of BWT effect on V1 (BWT on V1) and V2 (BWT on V2) in **Table 2** should be 0.596 and 0.0478 based on sponsor's report. Based on the analyses, sponsor proposed the following labeling statement in Section 12.3 Pharmacokinetics section:

Elimination

[REDACTED] (b) (4)

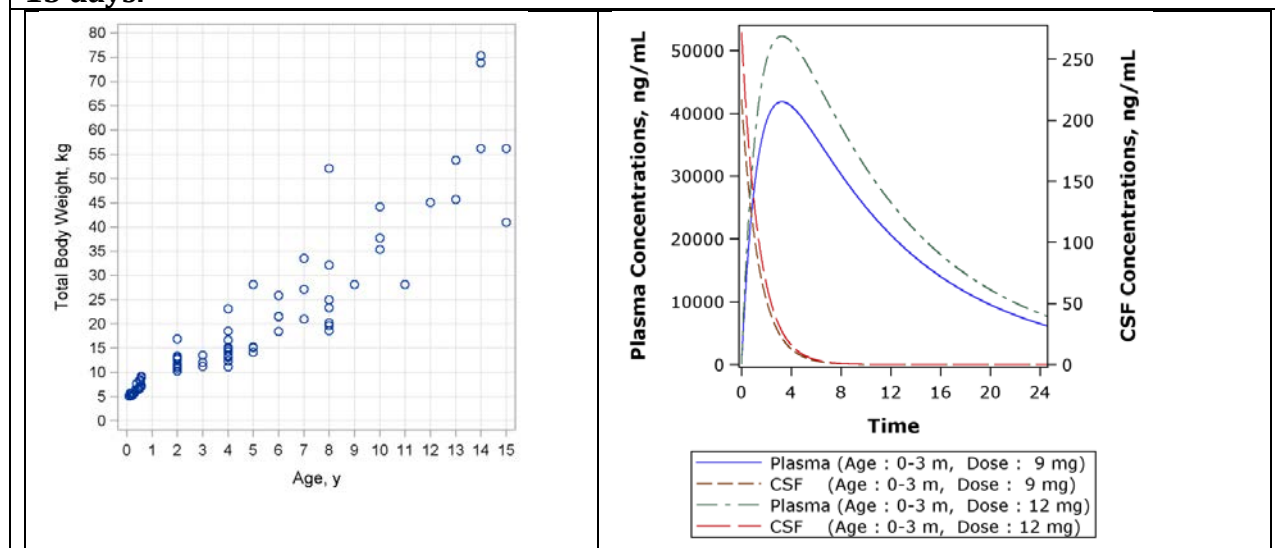
*Reviewer's Comments: The estimate of half-life derived based on population pharmacokinetic analyses or calculated as shown in **Table 3** is dependent on the amount of data. The available data (one post dose and one pre-dose across studies in the same patient) allows for*

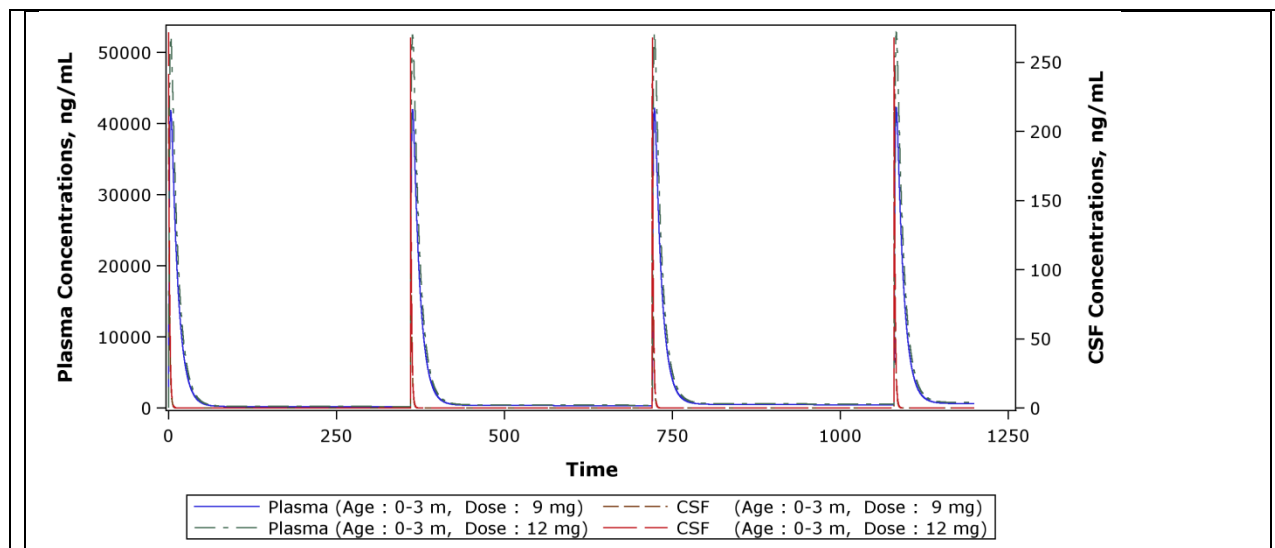
an approximate estimate of terminal elimination half-life. The proposed labeling statement is acceptable. It is also reasonable to add a sentence in the label that “The derived estimate of elimination half-life should be interpreted with caution since it is based on limited post-dose and pre-dose concentrations”.

What would be the changes in nusinersen CSF and plasma concentrations with the simplified dosing regimen that would administer 25% higher dose in a 0-3 month old patient?

The reviewer conducted simulations using the population pharmacokinetic model developed by the sponsor. Berkeley Madonna® software was used for simulation purposes. Simulations were conducted for a typical patient (Age 0-3 month and total body weight 5.5 kg). The choice of typical patient was based on the relationship between age and total body weight as shown in **Figure 9**. Simulations show that the plasma C_{max} on Day 1, in the chosen typical patient, would be 268 ng/mL after administration of 12 mg dose in comparison to 215 ng/mL after administration of 9.6 mg dose. The clinical relevance of a 25% higher nusinersen peak concentrations is not clear. The AUC would be expected to increase by a similar margin. Similar relative changes are expected for CSF nusinersen levels.

Figure 9 . (Top, Left) Relationship Between Total Body Weight and Age in SMA Patients (Top, Right) Plasma and CSF Concentrations After 9 or 12 mg Nusinersen on Day 1 (Bottom) Plasma and CSF Concentrations After 9 or 12 mg Nusinersen Every 15 days.

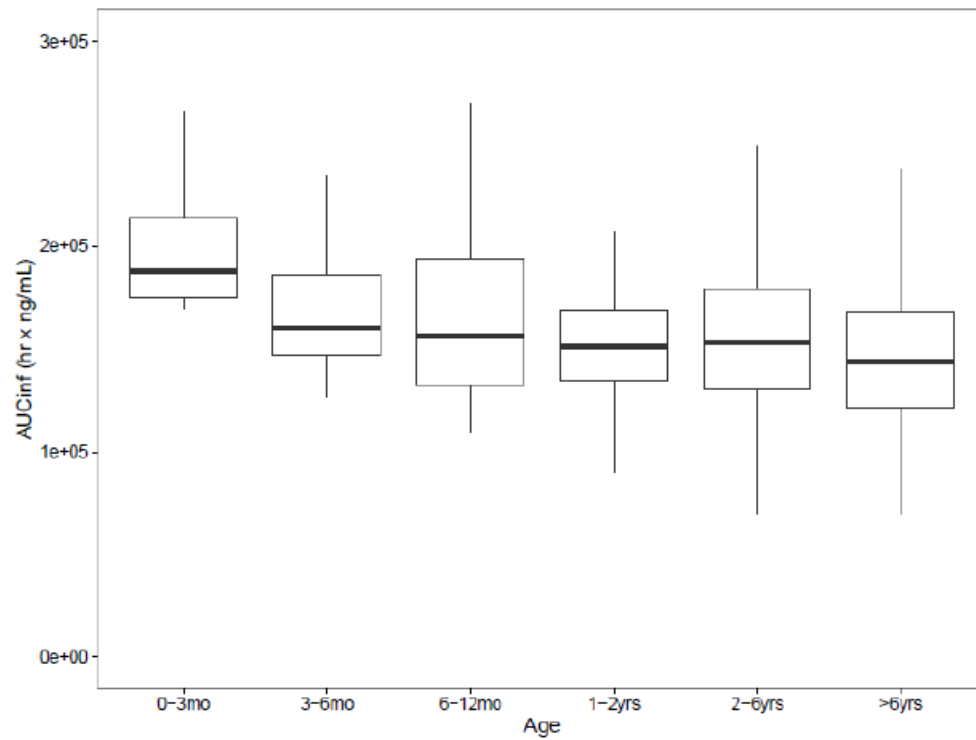




The sponsor [REDACTED] (b) (4), and provided the following supportive rationale:

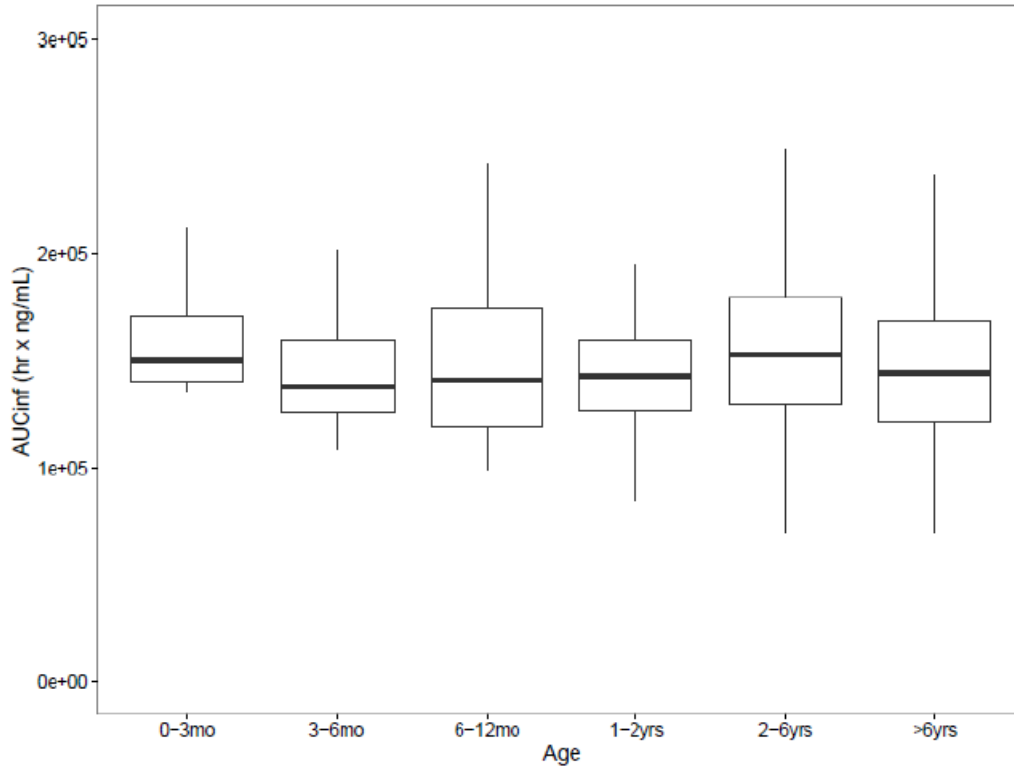
- The median simulated C_{max} and AUC_{inf} in CSF after age-based dosing (up to 2 years of age) was more comparable across all subjects than fixed dosing (Figure 19. Population Simulations Showing AUC_{inf} Relative to Age Following a Single Fixed Dose (12mg for all virtual subjects, n=1000) (Figure 10, Figure 11, Figure 12 and Figure 13).
- The range of simulated C_{max} values in CSF presented for children between birth and 2 years of age with fixed doses were similar to those in 2 to 6 years old children (Figure 12).
- The range of simulated AUC_{inf} values in CSF were generally consistent in children between 3 months and 6 years with fixed doses with higher AUC_{inf} values in those between birth and 3 months of age but the numbers of subjects simulated were very low (n=7) in that age group (Figure 10).
- The inter-individual variability (IIV) in the volume of distribution in the CSF (VCSF) was high (88.1%), while the IIV and inter-occasion variability in clearance from the CSF (CLCSF) were lower (24.4% and 38.1%, respectively), suggesting substantial overlap in exposure with varying doses.

Figure 10. Population Simulations Showing AUC_{inf} Relative to Age Following a Single Fixed Dose (12mg for all virtual subjects, n=1000)



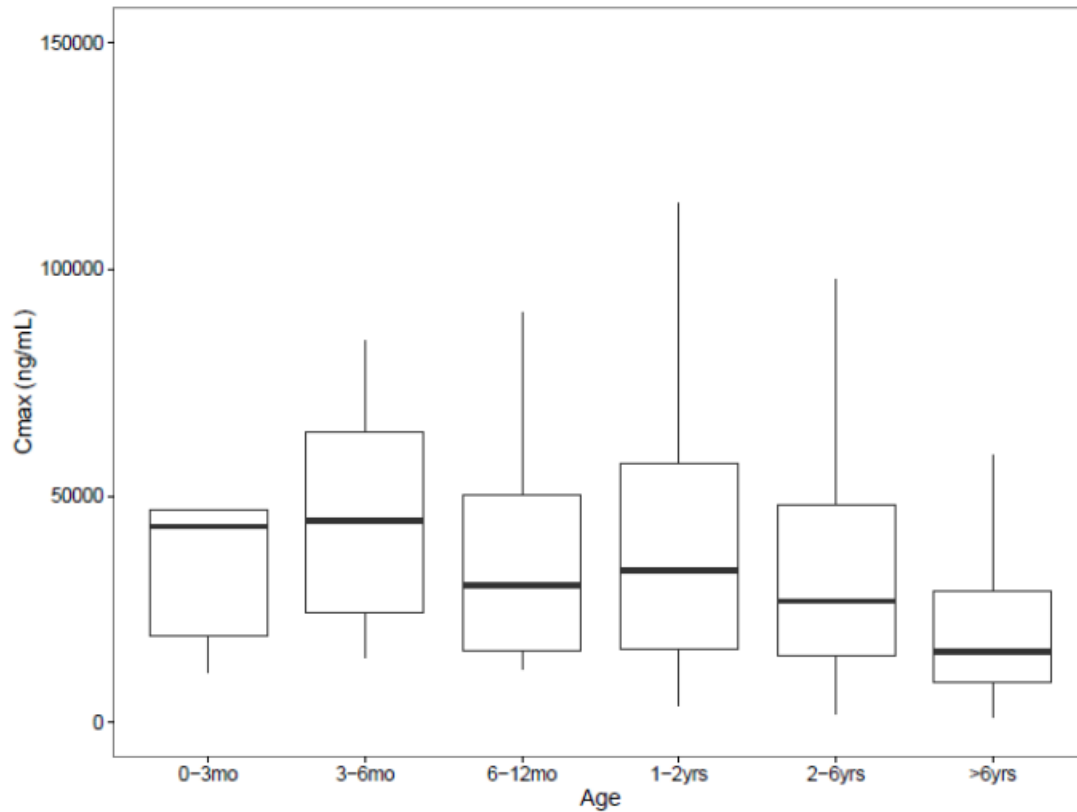
Source: Figure 8 sponsor's pop PK analysis report

Figure 11. Populations Simulations Showing AUC_{inf} Relative to Age Following an Age-based Dose (dose adjusted based on the age for each virtual subject [up to 2 years old] and Fixed Dose in Subjects Over 2 years of Age, n=1000)



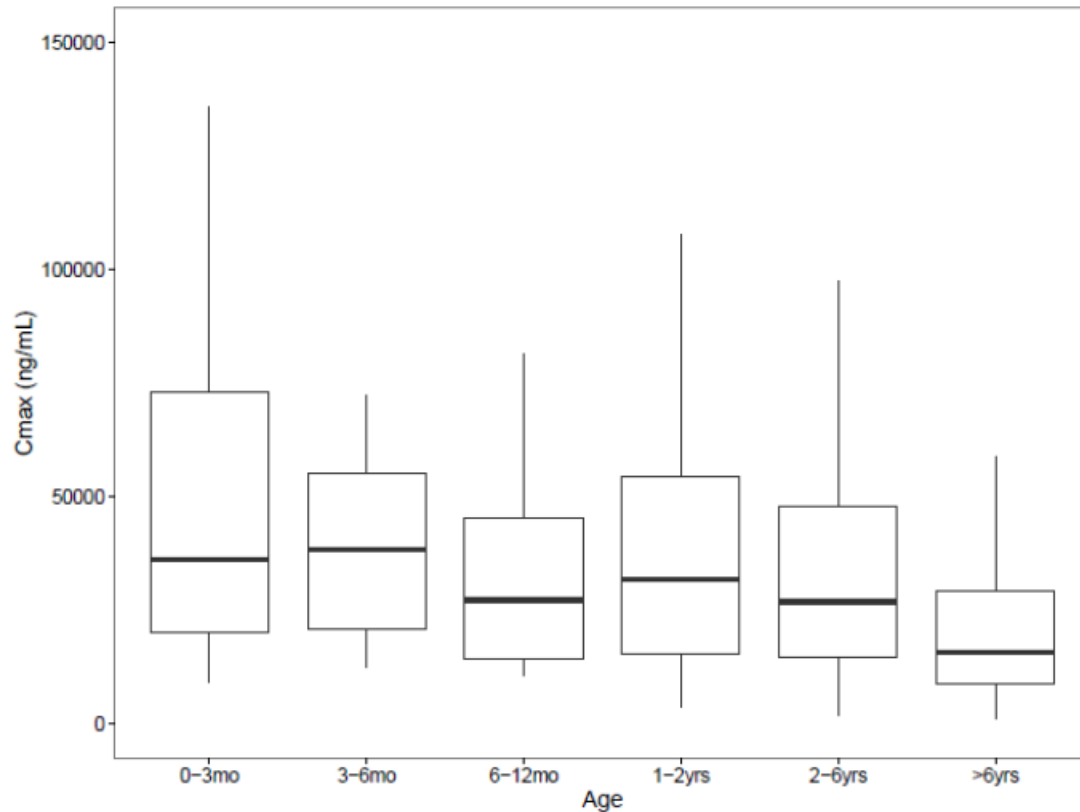
Source: Figure 9 sponsor's pop PK analysis report

Figure 12. Population Simulations Showing C_{max} Relative to Age Following a Single Fixed Dose (12 mg for all virtual subjects, n=1000)



Source: Figure 10 sponsor's pop PK analysis report

Figure 13. Population Simulations Showing C_{max} Relative to Age Following a Single Age-Based Dose (in subjects up to 2 years old) and a Fixed Dose in Subjects Over 2 Years of Age



Source: Figure 11 sponsor's pop PK analysis report

*Reviewer's Comments: The reviewer focused on understanding the impact of dose changes on C_{max} and AUC in the lower end of age group (<3 months). In this age group, the maximum impact on AUC and C_{max} due to changes in dose will be seen. The findings reported by the sponsor for the age group (<3 months) are in agreement with the findings reported by the reviewer (**Figure 9** vs **Figure 12**). In other age groups (> 3 months to 2 years), the projected mean increases in C_{max} and AUC will be less than 25% with the flat dosing compared to age-based dosing.*

4.4 Exposure-Response Analyses

Efficacy

Exposure-response analysis evaluated whether there was a relationship between nusinersen CSF concentrations or partial CSF AUC values (0-3, 0-6, and 0-12 months) and response (defined as SMN protein levels in CSF or various clinical endpoints) in Study ISIS 396443- CS3A, a study of infants under 7 months of age at screening.

Continuous Responses (CHOP-INTEND, CMAP, and SMN Protein)

Model

Response = $b_0 + b_1 \times$ PK Exposure,

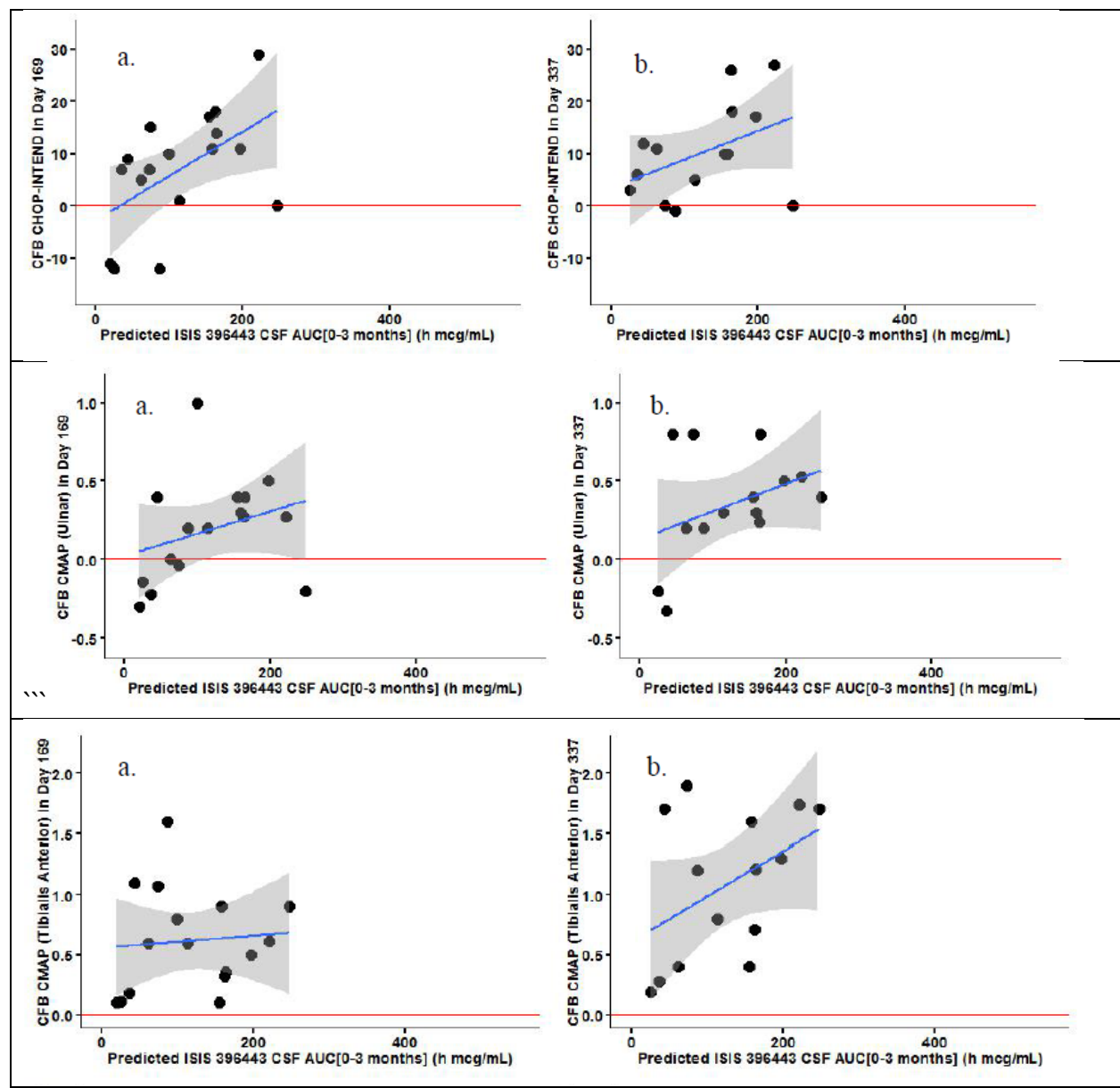
where “PK Exposure” was $AUC_{0-3\text{months}}$, $AUC_{0-6\text{months}}$, $AUC_{0-12\text{months}}$ in the CSF or the predicted CSF concentration at 253 days, “Response” was the change from baseline in the efficacy measurements (CHOP-INTEND (Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders), CMAP (Compound Muscle Action Potential), CSF SMN (Survival Motor Neuron) protein levels) at 6 or 12 months, and b_0 and b_1 were the linear regression model parameter estimates.

Findings

An increasing trend in the change from baseline CHOP-INTEND was observed in ISIS 396443-CS3A as time progressed (**Figure 14**). The linear model of the early partial AUC and the change from CHOP-INTEND baseline at six months (Day 169) and in a year (Day 337) was statistically significantly different than the “no improvement” model.

An increasing trend of change from baseline CMAP was also observed in infants in ISIS 396443-CS3A, although the increase of the change from baseline CMAP was more pronounced from the tibialis anterior CMAP data than that from the ulnar CMAP data.

Figure 14. Exposure-Response Relationship between: (Top) a.) the Partial CSF AUC_{0-3months} and the Change from Baseline in CHOP-INTEND in Day 169, b.) the Partial CSF AUC_{0-3months} and the Change from Baseline in CHOP-INTEND in Day 337. (Middle) a.) the Partial CSF AUC_{0-3months} and the Change from Baseline in CMAP (Ulnar) in Day 169, b.) the Partial CSF AUC_{0-3months} and the Change from Baseline in CMAP (Ulnar) in Day 337 (Bottom) a.) the Partial CSF AUC_{0-3months} and the Change from Baseline in CMAP (Tibialis Anterior) in Day 169, b.) the Partial CSF AUC_{0-3months} and the Change from Baseline in CMAP (Tibialis Anterior) in Day 337



Source: Figures 20, 22, 23 on page 55, 58, 60 in sponsor's report (is11-pop-pk-report.pdf)

Binary Response (Motor Milestone)

For the binary response (motor milestone response), a logistic regression model,

$$\text{logit}(p) = \ln\left(\frac{p}{1-p}\right) = b_0 + b_1 \times \text{PK Exposure},$$

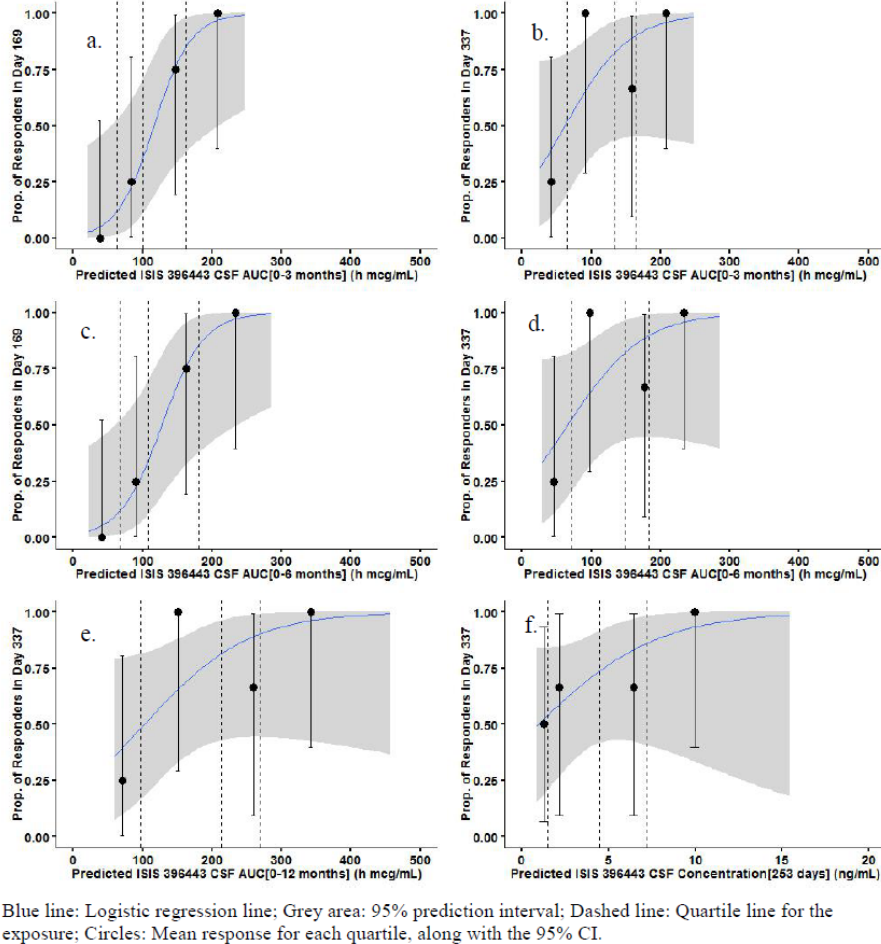
where p is the probability of achieving motor milestone, b_0 and b_1 are the intercept and slope, respectively, in the log domain was used. “PK Exposure” was CSF AUC_{0-3months}, AUC_{0-6months}, AUC_{0-12months}, or CSF concentration at 253 days,

The exposure-response relationship was concluded if the former logistic regression model, with $b_1 > 0$, was statistically different compared to the “no effect” model under the significance level of 0.05 (using χ^2 test).

A patient was classified as a responder at a given time (such as Day 169 or Day 337) if the patient achieved at least one of the motor milestones by that time. The logistic regression model of the partial AUCs or the predicted CSF concentration and the probability of being a motor milestone responder on Day 169 and Day 337 was statistically significantly different from the “no effect or constant” model (**Figure 15**).

The analysis showed that, for example, one unit increase in the partial CSF AUC_{0-3months} would result in an increase of 4% in the odds of being motor milestone responders in six months.

Figure 15. Exposure-Response Relationship between: a.) the Partial CSF AUC_{0-3months} and the Overall Motor Milestones Responders in Day 169, b.) the Partial CSF AUC_{0-3months} and the Overall Motor Milestones Responders in Day 337, c.) the Partial CSF AUC_{0-6months} and the Overall Motor Milestones Responders in Day 169, d.) the Partial CSF AUC_{0-6months} and the Overall Motor Milestones Responders in Day 337, e.) the Partial CSF AUC_{0-12months} and the Overall Motor Milestones Responders in Day 337, and f.) the Predicted CSF Concentration in Day 253 and the Overall Motor Milestones Responders in Day 337 for All Infants in ISIS 396443-CS3A



Source : Figure 18 on page 52 in sponsor's report (is11-pop-pk-report.pdf)

Reviewer's Comments: The sponsor's analysis suggests that the dose level of 12 mg would be more efficacious than 6 mg. The overall findings are reflective of dose-response. The need for loading doses is further supported by the 163 day half-life of nusinersen in CSF.

Reviewer’s Analysis

Based on interim analysis, the proportion of responders on nusinersen arm is 41% vs 0% in sham treatment arm. Will administration of nusinersen more frequently or at dose levels greater than 12 mg increase the proportion of responders?

To address this question, the reviewer conducted exposure-response analyses using data from Study CS3B. It should be noted that in Study CS3B, patients were treated with the 12 mg dose. The total motor milestone score obtained using Hammersmith Infant Neurological Examination (HINE) was used as the endpoint for analysis. The various components of total motor milestone score are provided in **Table 4**. The HINE consists of 8 motor milestone categories (head control, sitting, grasping, ability to kick in supine position, rolling, crawling, standing, and walking). Subjects can progress from complete absence of motor milestones through multiple milestones within each of the categories (2 to 4 levels in each category).

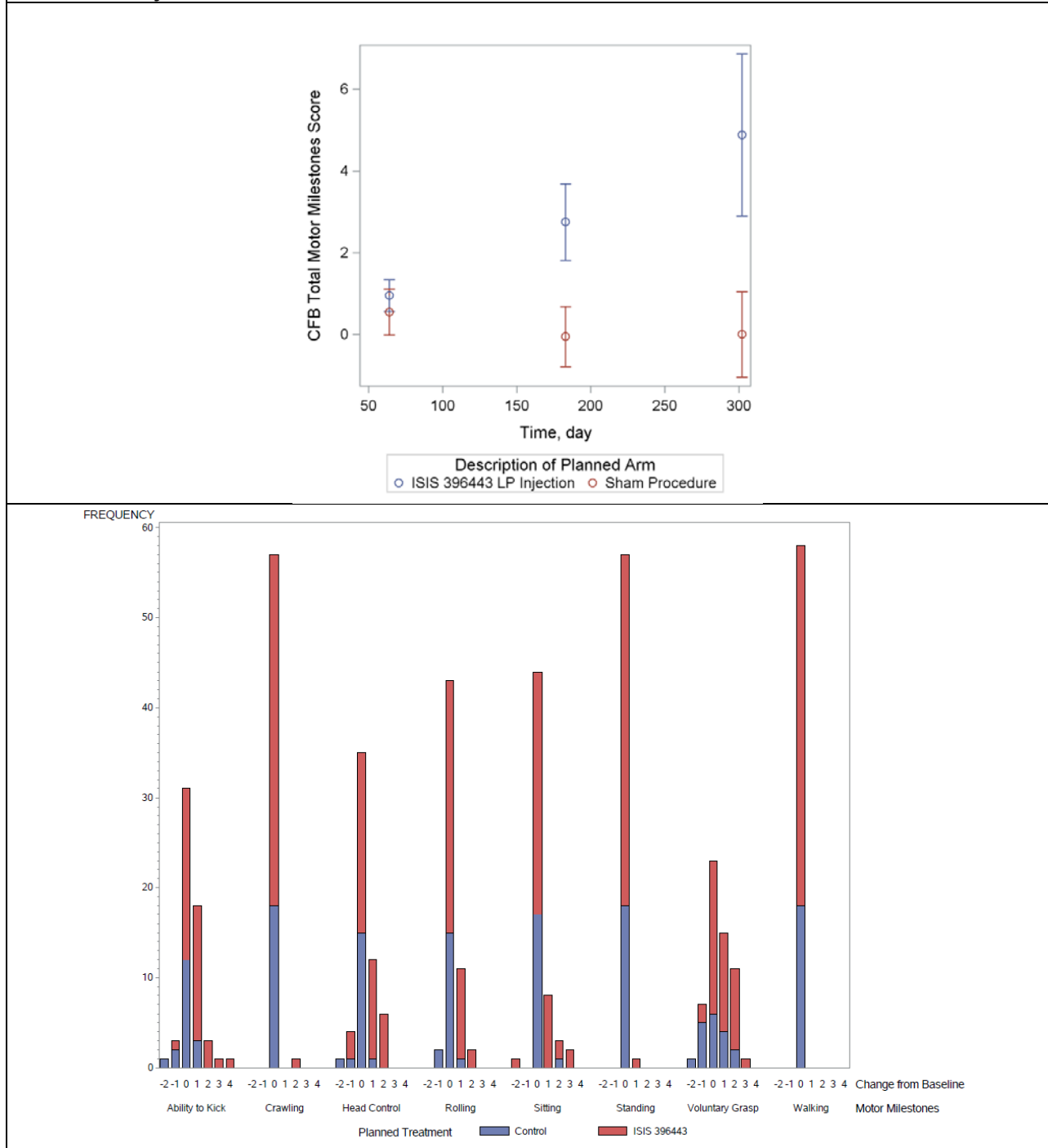
Table 4. Components of Total Motor Milestones Using Hammersmith Infant Neurological Examination (HINE)

Parameter Code	Analysis Value (C)	
Ability to Kick	No kicking	0.00
	Kick horizontally legs do not lift	1.00
	Upward (vertically)	2.00
	Touches leg	3.00
	Touches toes	4.00
	Crawling	Does not lift head
On elbow		1.00
On outstretched hand		2.00
Crawling flat on abdomen		3.00
Crawling on hands and knees		4.00
Head Control		Unable to maintain head upright
	Wobbles	1.00
	All the time maintained upright	2.00
Rolling	No rolling	0.00
	Rolling to side	1.00
	Prone to supine	2.00
	Supine to prone	3.00
Sitting	Cannot sit	0.00
	Sits with support at hips	1.00
	Props	2.00
	Stable sit	3.00
	Pivots (rotates)	4.00
Standing	Does not support weight	0.00
	Supports weight	1.00
	Stands with support	2.00
	Stands unaided	3.00
Voluntary Grasp	No grasp	0.00
	Uses whole hand	1.00
	Index finger and thumb but immature grasp	2.00
	Pincer grasp	3.00
Walking	No walking	0.00
	Bouncing	1.00
	Cruising (walks holding on)	2.00
	Walking independently	3.00

Figure 16 shows the change from baseline in total motor milestone score with time (days) in the study CS3B. Also shown in **Figure 16** are the changes in components of total motor

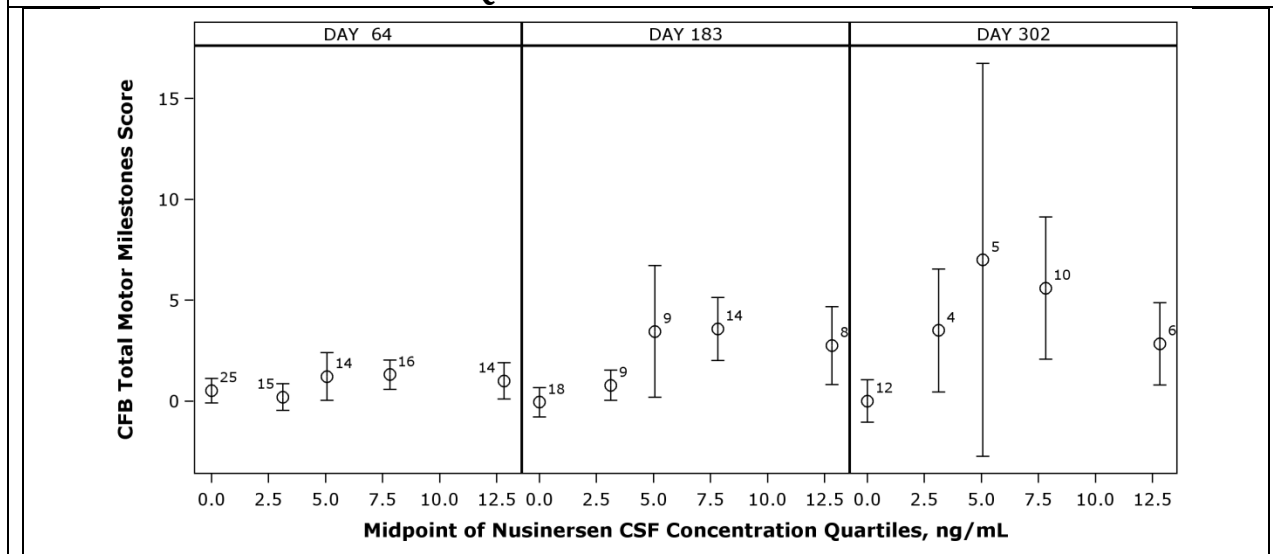
milestones score at Day 183. The data suggests improvement across many components of total milestones score in the treatment group.

Figure 16. (Top) Change From Baseline Total Motor Milestones Score With Time in Study CS3B (Bottom) Change in Components of Total Motor Milestones Score at Day 183 in Study CS3B.



To explore the relationship between nusinersen concentrations and response, the reviewer used time averaged nusinersen CSF concentrations as the exposure metric. Average of the pre-dose nusinersen CSF concentrations over all visits was taken to derive the average nusinersen CSF concentration metric. **Figure 17)** shows the relationship between CFB total motor milestone score and average nusinersen CSF concentration by visit day. A visual assessment of the observed data at Day 183 and 305 (**Figure 17)** suggests that higher doses or more frequent dosing would likely not increase the responder rate. However, these graphs should be interpreted with caution since all patients did not complete assessments at Day 183 (Refer to Dr. Tristan Massie, Reviewer, Office of Biostatistics for more details on this issue). Additionally, patients in this study were treated with only one dose (12 mg). These assessments should be re-assessed after obtaining an update on clinical response at Day 302 from all patients, if there is need for further optimization of dosing regimen. These analyses should also ensure that influential baseline factors are well adjusted.

Figure 17. CFB Total Motor Milestone Score by Study Day versus Midpoint of Nusinersen CSF Concentration Quartiles.



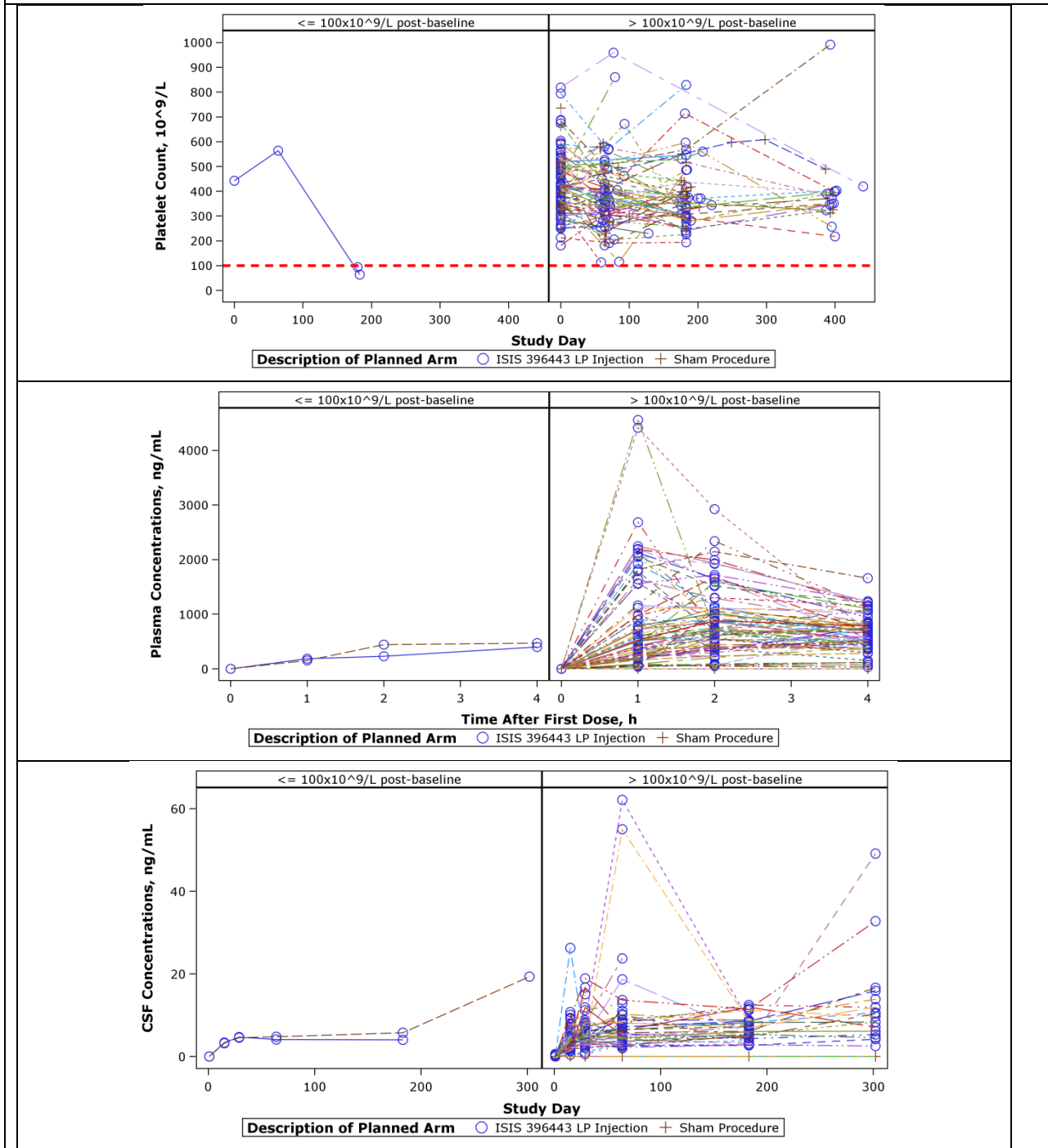
Safety

In response to a question from the review team regarding nusinersen plasma and CSF concentrations in patients with thrombocytopenia or hyponatremia, the reviewer analyzed laboratory data (platelets, sodium) from Studies CS1, CS10, CS3A and CS3B. Overall, the plasma and CSF levels of nusinersen were similar in patients with and without treatment emergent adverse events (thrombocytopenia or hyponatremia). The analyses findings, using SAS® Version 9.4, are described below:

Findings from Platelet Counts in Study CS3B

Figure 18 shows the platelet count by visit day in Study CS3B. Also, shown are the nusinersen plasma and CSF concentrations in patients with post-baseline platelet count $\leq 100 \times 10^9/L$ and $> 100 \times 10^9/L$ at any time in the study. Two patients in treatment group (IDs: 396443-CS3B/1778-5258, 396443-CS3B/1833-5261) had platelet count less than $100 \times 10^9/L$ at Day 183. The baseline platelet count for patient 396443-CS3B/1833-5261 was not available in the dataset. In the patient 396443-CS3B/1778-5258, the platelet counts increased initially at Day 64 (relative to baseline) and decreased to less than $100 \times 10^9/L$ at Day 183. Platelet count beyond Day 183 was not available in the dataset. The platelet count in this patient was measured at last loading dose visit (Day 63) prior to low levels on Day 183. It should be noted that the plasma and CSF concentrations of nusinersen in the two patients were in the range of concentrations observed in other patients.

Figure 18. (Top) Platelet Count by Day in Study CS3B (Middle) Nusinersen Plasma Concentrations in Patients With Post-Baseline Platelet Count $\leq 100 \times 10^9/L$ and $> 100 \times 10^9/L$ (Bottom) Nusinersen CSF Concentrations in Patients With Post-Baseline Platelet Count $\leq 100 \times 10^9/L$ and $> 100 \times 10^9/L$. The Threshold Value of Interest is Shown in Red Dashed Line.



Findings from Platelet Counts in Study CS1 and CS10

Figure 19 shows the platelet count by visit day in Study CS1 and Study CS10 (extension of Study CS1). Also, shown are the nusinersen plasma and CSF concentrations in patients with platelet count $\leq 100 \times 10^9/L$ and $> 100 \times 10^9/L$ at any time in the study. One patient (ID: 396443-CS1/1776-4005) had platelet count $\leq 100 \times 10^9/L$ at pre-dose visit in Study CS10. No patient in Study CS1 had platelet count $\leq 100 \times 10^9/L$. From Study CS10, only pre-dose CSF levels of nusinersen were available. It should also be noted that in patient 1776-4005, the platelet counts were $> 100 \times 10^9/L$ after the pre-dose visit in Study CS10. The plasma and CSF concentrations for patient 1776-4005 (**Figure 19**) in Studies CS1 and CS10 were in the range of concentrations observed in other patients.

Findings from Sodium Levels in Study CS3B

Figure 20 shows the sodium levels by day in Study CS3B. Also, shown are the nusinersen plasma and CSF concentrations in patients with post-baseline sodium levels ≤ 130 mmol/L and > 130 mmol/L at any time in the study. One patient (ID: 396443-CS3B/2010-5096) had sodium level ≤ 130 mmol/L at Day 183. At subsequent visit, the sodium level was > 130 mmol/L. It should be noted that the plasma and CSF concentrations of nusinersen in this patient was in the range of concentrations observed in other patients.

Figure 19. (Top) Platelet Count by Day in Study CS1 and CS10 (Middle) Nusinersen Plasma Concentrations After First Dose in Study CS1 and CS10 (Bottom, Left, Right) Nusinersen CSF Concentrations by Day in Study CS1 and CS10. The Threshold Value of Interest is Shown in Red Dashed Line. Shown in Dark Brown Dashed Line (Middle, Bottom) are the Data From Patients With Adverse Event of Interest.

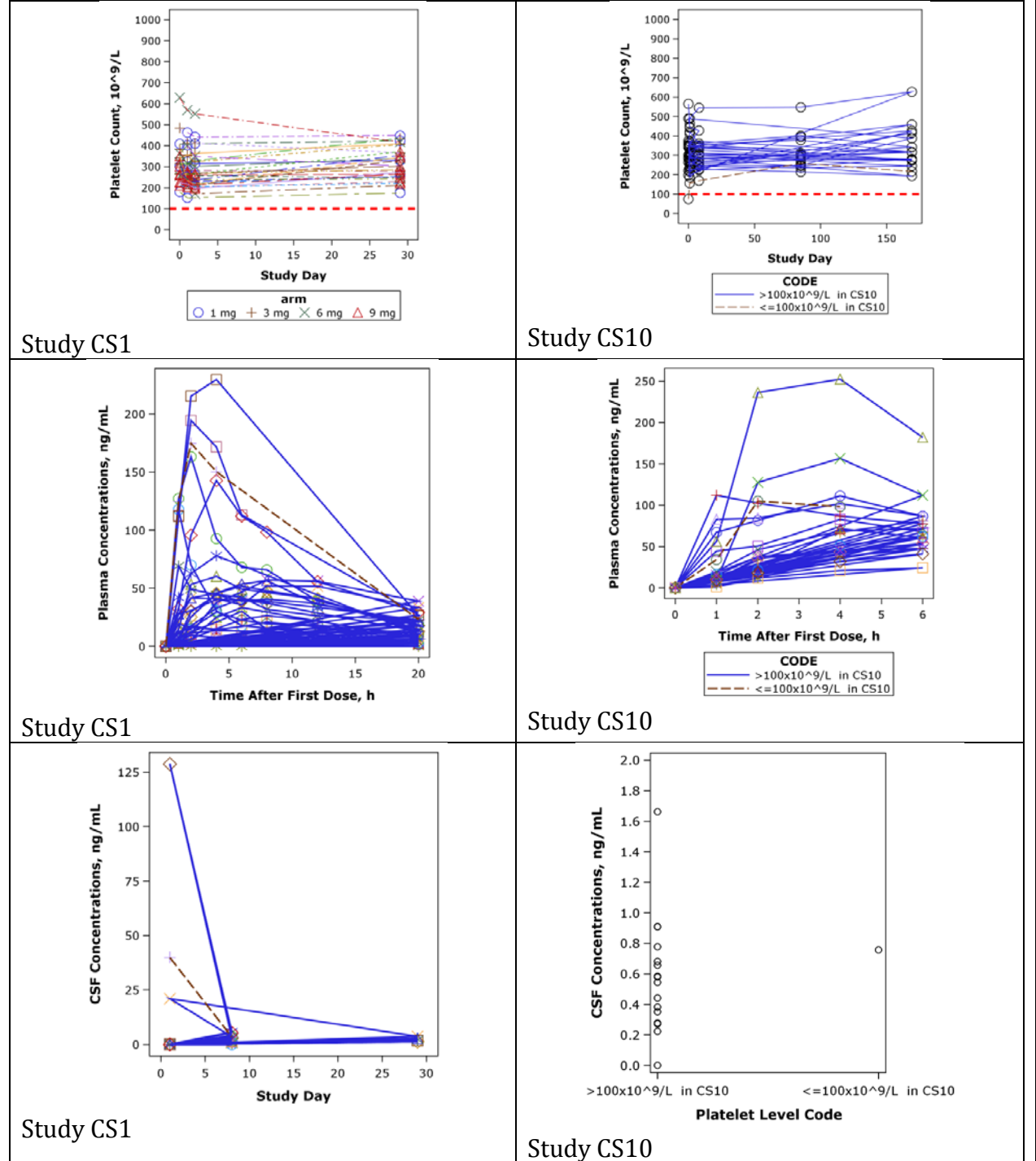
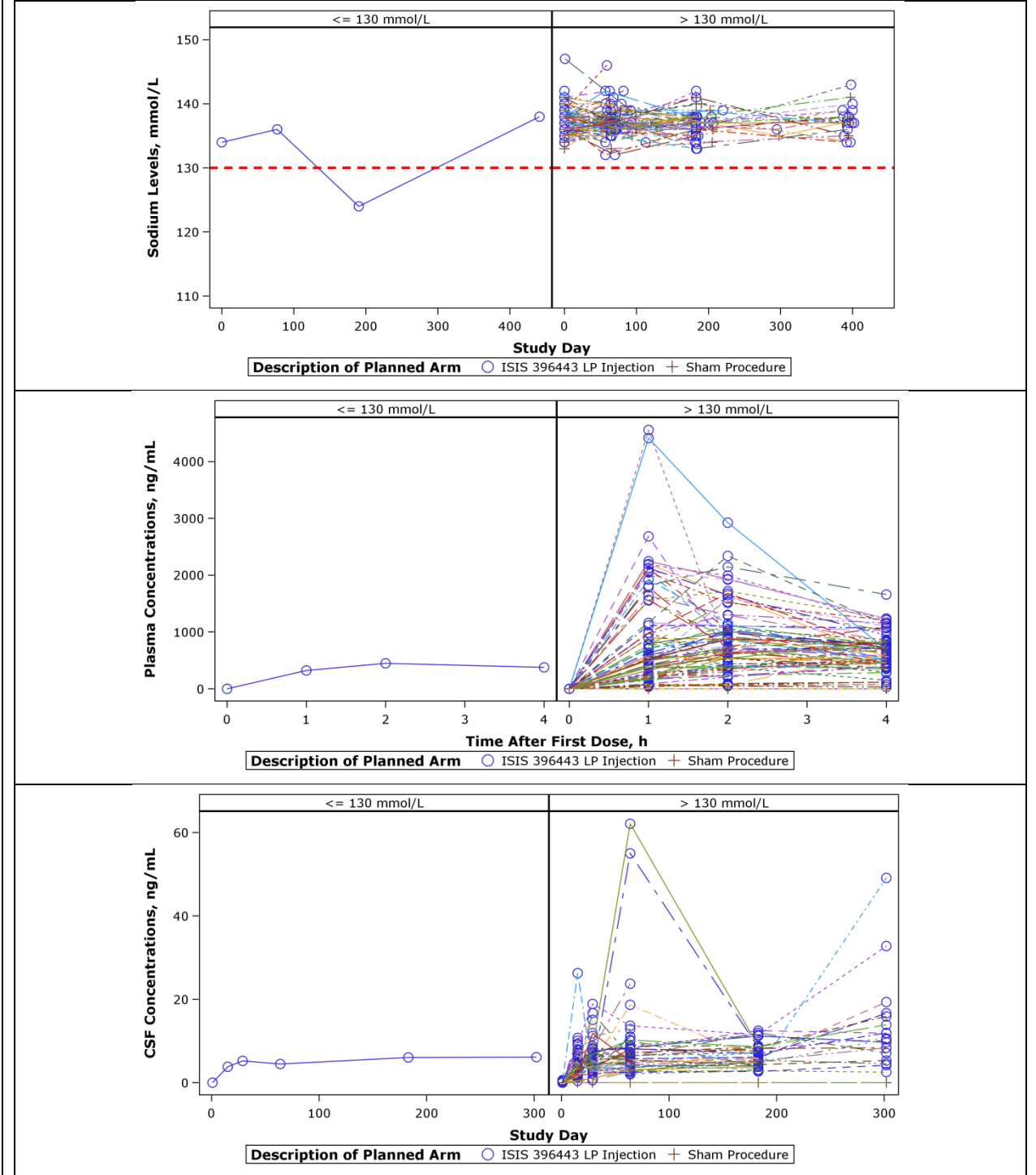


Figure 20. (Top) Sodium Levels by Day in Study CS3B (Middle) Nusinersen Plasma Concentrations in Patients With Post-Baseline Sodium Levels ≤ 130 mmol/L and > 130 mmol/L (Bottom) Nusinersen CSF Concentrations in Patients With Post-Baseline Sodium Levels ≤ 130 mmol/L and > 130 mmol/L. The Threshold Value of Interest is Shown in Red Dashed Line.



Findings from Platelet Counts and Sodium Levels in Study CS3A

Figure 21 shows the platelet count by day in Study CS3A. No patients were observed to have platelet count $\leq 100 \times 10^9/L$. Also shown in **Figure 21** are the nusinersen concentrations in plasma and CSF. Since no patient in Study CS3A had platelet count $\leq 100 \times 10^9/L$, nusinersen concentrations are being provided for informational purposes only.

Figure 22 shows the sodium levels by visit day in Study CS3A. Also, shown are the nusinersen plasma and CSF concentrations in patients with post-baseline sodium levels ≤ 130 mmol/L and >130 mmol/L at any time in the study. Three patients (IDs: 396443-CS3A/1833-1303, 396443-CS3A/1776-2305, 396443-CS3A/1776-2306) had sodium level ≤ 130 mmol/L at any time in the study. At subsequent visits in 2 patients, the sodium level was >130 mmol/L. In one patient (ID: 396443-CS3A/1833-1303), adequate follow-up information was not available in the dataset. It should be noted that the plasma and CSF concentrations of nusinersen in these patients were in the range of concentrations observed in other patients.

Figure 21. (Top) Platelet Count by Day in Study CS3A (Bottom, Left) Nusinersen Plasma Concentrations on Day 1 (Bottom, Right) Nusinersen CSF Concentrations by Study Day. The Threshold Value of Interest is Shown in Red Dashed Line.

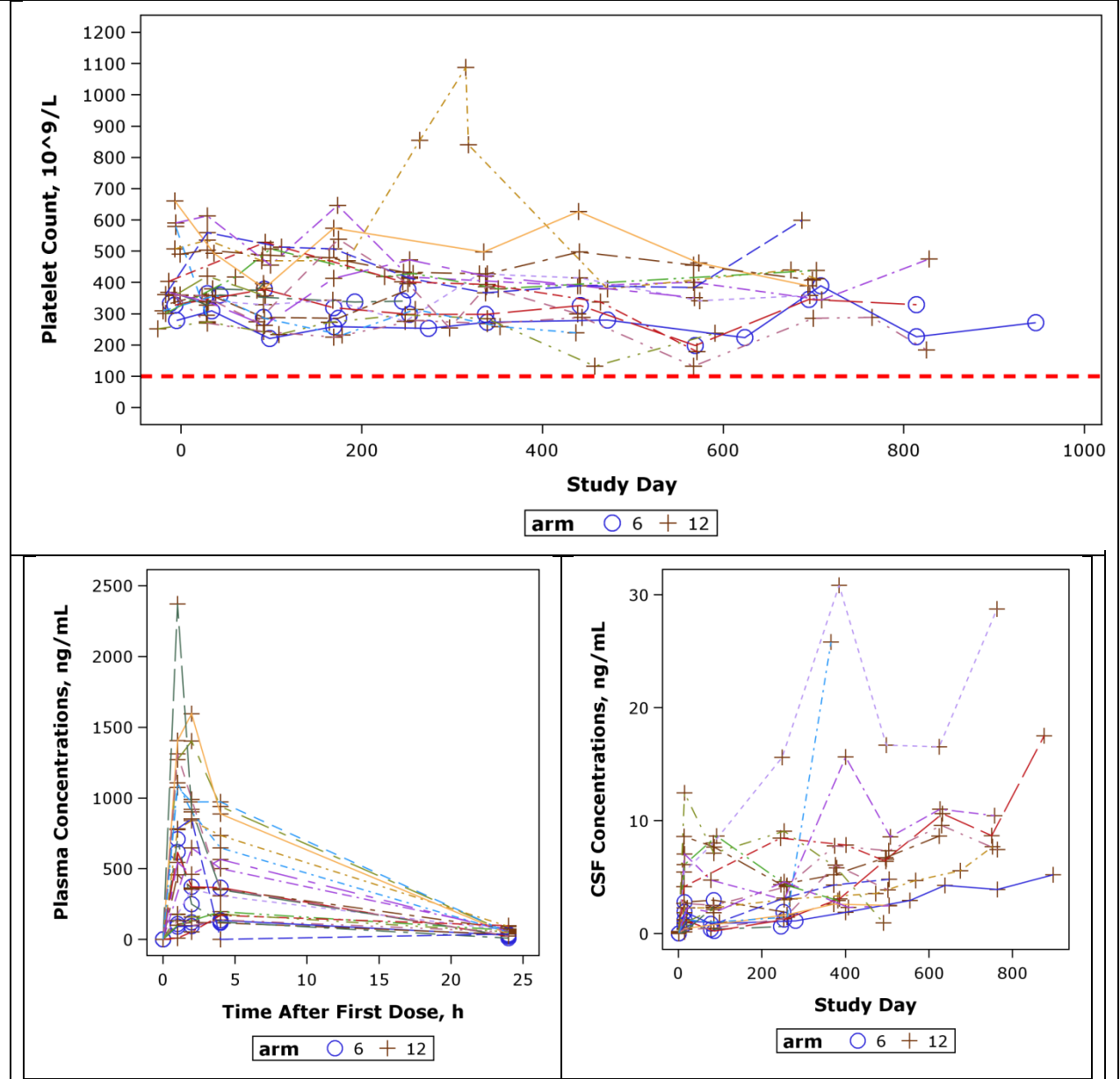
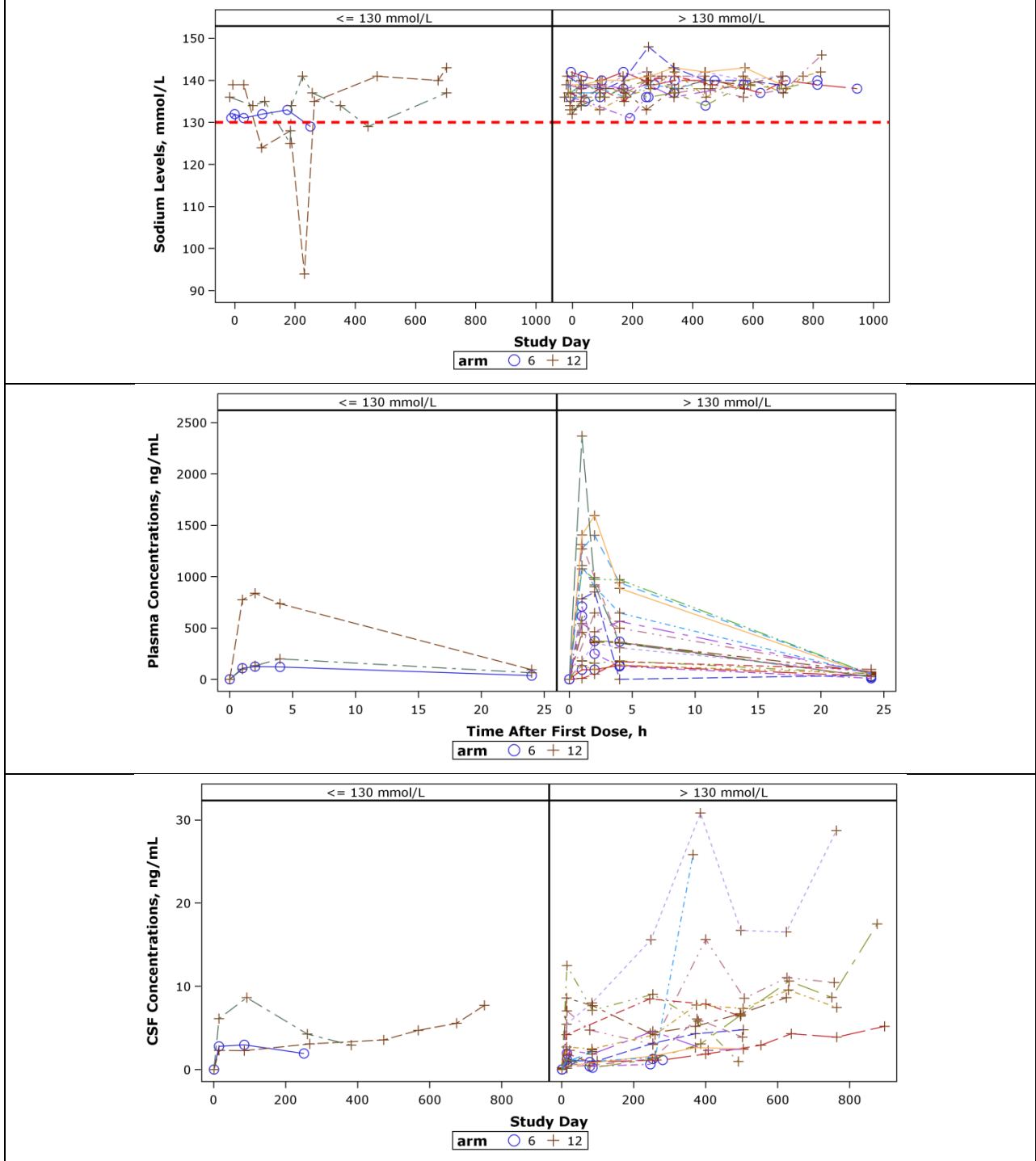


Figure 22. (Top) Sodium Levels by Day in Study CS3A (Middle) Nusinersen Plasma Concentrations in Patients With Post-Baseline Sodium Count ≤ 130 mmol/L and >130 mmol/L (Bottom) Nusinersen CSF Concentrations in Patients With Post-Baseline Sodium Count ≤ 130 mmol/L and >130 mmol/L. The Threshold Value of Interest is Shown in Red Dashed Line.



Reviewer Comment: The findings here do not demonstrate a dose response relationship for safety. Overall, the plasma and CSF levels of nusinersen were similar in patients with and without treatment emergent adverse events (thrombocytopenia or hyponatremia).

4.5 Enrichment, Stratification, and/or Biomarker-based Assessment

In order to decrease heterogeneity, the pivotal efficacy trial CS3B was enriched for subjects with 2 copies of the *SMN2* gene, however the sponsor proposes labeling nusinersen for the treatment of SMA regardless of *SMN2* copy number. Nusinersen was studied in various populations (e.g., pre-symptomatic, early onset as shown in **Figure 1**). The only subtype of disease that nusinersen was not studied in was type IV, which is the mildest (adult onset) type of SMA. Type IV patients typically do not have any motor milestone deficits, but may begin to become symptomatic (e.g. beginning to lose ambulation) in adulthood. There is no reason to believe that nusinersen will not benefit these patients. We agree with the sponsor's proposed labeling that nusinersen is intended to treat SMA.

4.6 Should the indication statement indicate that nusinersen is for the treatment of (b) (4) SMA?

(b) (4)

(b) (4)

(b) (4)

(b) (4)

- (b) (4)
- (b) (4)
- (b) (4)

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