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Population pharmacokinetics-based recommendations for a single delayed or missed dose of nusinersen

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Abstract

Nusinersen is an antisense oligonucleotide approved for the treatment of spinal muscular atrophy. The drug is given intrathecally at 12 mg, beginning with 3 loading doses at 2-week intervals, a fourth loading dose 30 days thereafter, and maintenance doses at 4-month intervals. This population pharmacokinetic model was developed to clarify how to maintain targeted nusinersen exposure after an unforeseen one-time delay or missed dose. Simulations demonstrated that the impact of a one-time delay in dosing or a missed dose on median cerebrospinal fluid exposures depended on duration of interruption and the regimen phase in which it occurred. Delays in loading doses delayed reaching the peak trough concentration by approximately the duration of the interruption. Resumption of the regimen as soon as possible resulted in achieving steady state trough concentration upon completion of the loading phase. A short delay (30–90 days) during the maintenance phase led to prolonged lower median cerebrospinal fluid concentration if all subsequent doses were shifted by the same 4-month interval. However, administration of the delayed dose, followed by the subsequent dose as originally scheduled, rapidly restored trough concentration. If a dose must be delayed, patients should return to the original dosing schedule as soon as possible.

Keywords: Nusinersen; Dosing; Delayed treatment; Pharmacokinetics; Spinal muscular atrophy.

1. Introduction

Spinal muscular atrophy (SMA) is a progressive neuromuscular disease affecting infants, children, and adults. It is a leading genetic cause of death in infants and children [1,2]. SMA is caused by deletions or mutations in the survival motor neuron 1 (*SMN1*) gene, which encodes for SMN protein [3]. Deficiency of SMN protein leads principally to degeneration of spinal cord alpha motor neurons and progressive muscular atrophy, particularly in the trunk and proximal limb muscles. The paralogous *SMN2* gene differs from *SMN1* and produces mostly truncated protein that is dysfunctional and rapidly degraded. It also produces a small amount of normal SMN protein that rescues individuals from an otherwise lethal condition but is insufficient for normal motor development and function [4].

SMA is classified into four types, based on age at symptom onset and highest motor milestone achieved [5,6]. Generally, a higher *SMN2* gene copy number is associated with less severe

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disease. SMA Type I has the highest birth prevalence and is the most severe form of the disease [1,5]. Respiratory failure typically occurs at <2 years of age. In a natural history study published in 2017, median survival for infants with SMA Type I was 8 months (95% confidence interval, 6–17) [7]. SMA Types II, III, and IV begin at later infancy, childhood, and adulthood, respectively [5]. Symptoms are less severe but still debilitating and progressive.

Nusinersen is an antisense oligonucleotide approved in the United States [8], Europe [9], and elsewhere for the treatment of SMA in infants, children, and adults. It modifies pre-messenger RNA splicing of *SMN2* to increase production of full-length SMN protein. Results from clinical trials demonstrate clinically meaningful efficacy and a favorable risk-benefit profile across a broad range of individuals with SMA [10–15].

Preclinical pharmacokinetic (PK) data suggest that cerebrospinal fluid (CSF) nusinersen concentrations may be used as a surrogate of spinal cord tissue concentration (Biogen data on file). The half-life of CSF elimination is 102–111 days, and a central nervous system tissue concentration range of 2–10 μg/g is appropriate to increase SMN protein and improve survival and motor function (Biogen data on file).

In clinical practice, nusinersen is given intrathecally at doses of 12 mg. The most common approved regimen begins with three loading doses at 2-week intervals, a fourth loading dose 30 days thereafter, and maintenance doses at 4-month intervals. Unforeseen circumstances, such as the COVID-19 pandemic and other intercurrent illnesses (especially among severely affected infants), have the potential to cause delayed or missed doses. Clinical trials with nusinersen reported no instances of significant delays or missed doses [10–15], so information on potential therapeutic interruptions is not available.

The objective of this report is to describe a PK modeling and simulation approach for nusinersen that provides data on how to best maintain the targeted nusinersen CSF exposure in individuals with SMA following a one-time delay in dosing or a missed dose. In a population PK approach, means for the population are calculated. Then a parameter set is calculated for each patient individually, and appropriate distribution is calculated for each parameter. As such, the model integrates all PK data from all patients.

2. Materials and methods

This population PK analysis utilized plasma and CSF concentration data from participants in 10 clinical trials with variable dose and dosing regimens of intrathecally administered nusinersen [10-15]. These participants included children and adolescents with later-onset SMA, infants with infantile-onset SMA, and presymptomatic infants who were genetically diagnosed with SMA at study start. The trials were conducted in compliance with the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice guidelines, and local regulatory requirements. Brief descriptions of the studies are provided in *Supplementary Material 1*.

Plasma and CSF concentration measurements, as well as the dose and time at which those measurements were taken, were integrated into a single dataset incorporating all PK data from all trials. Eighteen models were considered and evaluated (Supplemental Table 1) based on: (1) the changes in the objective function value for comparing hierarchical models and the Akaike information criterion for comparing non-hierarchical models; (2) visual inspection of goodness-of-fit plots and prediction-corrected visual predictive check plots; (3) evaluation of parameter estimates and their relative standard errors, *P*-values for mean empirical Bayes estimates, inter-individual variability shrinkage, and condition number; and (4) whether the correlation test was passed with all off-diagonal elements of the correlation matrix of estimate having an absolute value < 0.95. A model associated with no large correlations was considered preferable to one with highly correlated parameters.

A nonparametric bootstrap approach was used to calculate the distribution of parameter estimates. The bootstrap generated 200 sets of new datasets by sampling individuals (i.e., using the individual subject as the sampling unit) with replacement from the original dataset, and fitting the model to each new dataset. Stratification by population was done in the resampling procedure. Any runs with failed minimization were terminated and runs with estimates near a boundary were skipped when calculating the bootstrap results. The distribution of parameter estimates from the bootstrap was also graphically compared with the parameter estimates from the model outputs. Concentration data were logarithmic.

2.1. Covariate analysis

The covariate analysis was done by a combination of the stepwise covariate model approach and the visual inspection of the trends of inter-individual variability versus covariates. The covariates, population (later-onset SMA, infantile-onset SMA, and presymptomatic SMA) and time-varying weight were assessed first. Additional analysis was done using time-varying age as a covariate via a maturation model.

2.2. Simulation of dosing interruption

The Fisher information matrix and the interindividual variability measures of all relevant parameters were sampled to produce an ensemble of 10,000 unique parameter sets. Each parameter set was subjected to a different dosing regimen that deviated from the accepted label regimen in several distinct ways.

The duration of dosing interruption and the phase at which that interruption occurred were immediately identified as critically impactful on nusinersen exposure in CSF. Therefore, variations on the approved label dosing regimen (Table 1) were selected to interrogate delays in dosing of variable duration during both the maintenance phase and loading phase of treatment. Delays of 30, 60, and 90 days on a single dose

Table 1
Simulated dosing regimens.

Scenario	PK model
Control dosing regimen	12 mg on Days 1, 15, 29, and 59, and subsequently every 120 days
Delays during loading phase	Second or third loading dose delayed by 30, 60, and 90 days
One-time delay in dosing during the maintenance phase	Only the fifth maintenance dose* is delayed by 30, 60, and 90 days from the control dosing regimen; all subsequent doses were administered per the control dosing regimen
Delay in all subsequent doses during the maintenance phase	The fifth maintenance dose and all subsequent doses are delayed by 30, 60, and 90 days from the control dosing regimen
Missed dose	The fifth maintenance dose is excluded; all other doses are administered per the control dosing regimen
Additional dose after missed dose	An additional 12-mg dose is administered 14 days after the resumption of dosing in the missed-dose scenario

* The population PK model predicts that patients will have reached steady-state CSF concentration before the fifth maintenance dose.

during the maintenance phase were investigated, as was the time taken for CSF C_{trough} (the lowest CSF concentration before the next dose) to achieve a value commensurate with that of the control dosing regimen as described in Table 1. We further investigated the question of whether an additional loading dose would be necessary should the duration of interruption exceed a full maintenance dosing interval (missed dose). In addition, we investigated the effect on CSF PK of delaying all subsequent maintenance doses. Finally, we investigated the effect of a delay in administering the second and third loading doses (nominally administered on days 15 and 29, respectively) on CSF PK. Delays in administering each loading dose of 30, 60, and 90 days were simulated.

2.3. Data analysis methods and software

NONMEM® Version 7.3 and Perl-speaks-NONMEM Version 4.6.0 (ICON Development Solutions, Ellicott City, MD) were used for the nusinersen population PK analysis. R software (R version 3.3.1, R Foundation for Statistical Computing, Vienna, Austria) was used for data handling and plotting. Covariate analysis used a combination of the stepwise covariate model approach and a visual inspection of the trends. An additional analysis was done using time-varying age as a covariate via a maturation model. A nonparametric bootstrap approach was used to generate the distribution of parameter estimates.

3. Results

3.1. Population PK model method and evaluation

We generated a four-compartment model with first-order processes for clearance and mass transfer between different

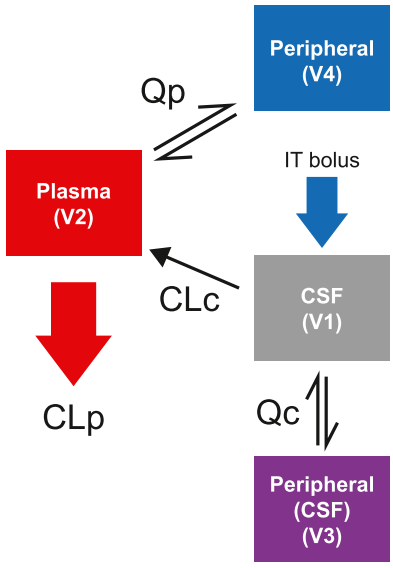

Fig. 1. Four-compartment pharmacokinetic model used for dosing simulations. CLc = clearance from cerebrospinal fluid to plasma; CLp = clearance from plasma; CSF = cerebrospinal fluid; IT = intrathecal; Qc = intercompartmental clearance between V1 and V4; Qp = intercompartmental clearance between V2 and V3; V1 = volume of distribution of central CSF compartment; V2 = volume of distribution of central plasma compartment; V3 = volume of distribution of peripheral CSF compartment (spinal or other tissues surrounding the CSF); V4 = volume of distribution of peripheral plasma compartment (muscle, bone, fatty tissues).

compartments. The four compartments determined clearance from central cerebrospinal fluid (CSF), peripheral CSF, central plasma, and peripheral plasma. This PK model calculated the volume of distribution for four different compartments: CSF, plasma, and adjacent tissues into which the drug can diffuse from either (Fig. 1). Exponential error models were used to describe the inter-individual variability of different PK parameters. A proportional error model was used to describe the residual error. Akaike lognormal distribution for interindividual variability was calculated for the four parameters describing the CSF, and plasma volumes, as well as the clearance from those two compartments. For all models, a first-order conditional estimation with interaction method was applied.

Development of the population PK model utilized measurements of 3812 samples collected from CSF and 5185 samples from plasma taken from 370 participants in 10 clinical trials. Parameter estimates and relative standard errors derived from the final model are presented in Table 2. A 4-compartment model with exponential errors for inter-individual variability on CLP, V2, V1 and CLC, correlation between CLP and V2, correlation between V2 and V1, a proportional residual error for both sample matrices, and fitting the natural log-transformed concentration data was able to capture the trends of observed nusinersen CSF and plasma concentrations as the pediatric patients grew over time. The final model had an objective function value OFV of 90.0.

The simulations presented here are based on the ENDEAR study regimen of maintenance doses every 4 months,

Table 2
Parameter estimates from the final population pharmacokinetics model of nusinersen.

Parameter description (unit)	Parameter	Final model (NONMEM)		Final model (bootstrap)	
		Estimate (%RSE)	95% CI[c]	Estimate[c]	95% CI[c]
QP (L/hour)	TH1	0.240 (8.96)	0.197, 0.283	0.243	0.174, 0.313
QC (L/hour)	TH2	0.0783 (7.96)	0.0658, 0.0908	0.0782	0.0507, 0.105
CLP (L/hour)	TH3	2.78 (3.91)	2.56, 3.00	2.78	2.57, 2.98
%CV for CLP IIV	OM1:1	22.3%[a] (13[b])	—	22.0%[d]	17.0%, 28.1%[d]
CLC (L/hour)	TH4	0.158 (5.71)	0.140, 0.176	0.158	0.133, 0.181
%CV for CLC IIV	OM4:4	25.8%[a] (13[b])	—	25.7%[d]	21.8%, 28.8%[d]
V1 (L)	TH5	0.391 (15.2)	0.272, 0.510	0.382	0.266, 0.561
%CV for V1 IIV	OM3:3	88.3%[a] (27[b])	—	89.9%[d]	72.1%, 108%[d]
V2 (L)	TH6	39.3 (6.48)	34.2, 44.4	39.3	34.8, 44.3
%CV for V2 IIV	OM2:2	31.4%[a] (26[b])	—	31.5%[d]	23.2%, 38.8%[d]
V3 (L)	TH7	166 (22.0)	93.0, 239	170	106, 256
V4 (L)	TH8	324 (5.82)	286, 362	322	239, 400
Residual proportional error	TH9	0.548 (0.661)	0.541, 0.555	0.549	0.508, 0.581
Fractional difference in CLC comparing POP=2 to POP=1	TH10	0.159 (36.3)	0.0438, 0.274	0.158	0.0694, 0.267
Fractional difference in CLC comparing POP=3 to POP=1	TH11	−0.577 (5.65)	−0.642, −0.512	−0.581	−0.682, −0.446
Fractional difference in CLP comparing POP=3 to (POP=1 & 2)	TH12	0.694 (26.1)	0.332, 1.06	0.690	0.331, 1.02
Linear slope for CLP_WT relationship when WT ≤ 20 kg (1/kg)	TH13	0.0483 (3.07)	0.0453, 0.0513	0.0483	0.0449, 0.0505
Linear slope for CLP_WT relationship when WT > 20 kg (1/kg)	TH14	0.0206 (18.8)	0.0129, 0.0283	0.0201	0.0131, 0.0280
Fractional diff. in V2 comparing POP=3 to (POP=1 & 2)	TH15	−0.494 (48.5)	−0.974, −0.014	−0.454	−0.712, 0.280
Linear slope for V2_WT relationship when WT ≤ 20 kg (1/kg)	TH16	0.0546 (2.58)	0.0518, 0.0574	0.0546	0.0511, 0.0570
Linear slope for V2_WT relationship when WT > 20 kg (1/kg)	TH17	0.0281 (28.8)	0.0119, 0.0443	0.0309	0.00956, 0.0526
Linear slope for V1_WT relationship (1/kg)	TH18	0.0303 (23.0)	0.0163, 0.0443	0.0298	0.0110, 0.0430
Correlation between CLP & V2	OM2:1	0.893[a] (17[b])	—	0.889[e]	—
Correlation between V2 & V1	OM3:2	0.446[a] (58[b])	—	0.403[e]	—

[a] Final parameter estimate from OMEGA - CORR MATRIX FOR RANDOM EFFECTS.
[b] RSE based on final parameter estimate and standard error of estimate from OMEGA − COV MATRIX FOR RANDOM EFFECTS. Out of 200 bootstrap replicates, 46 runs with minimization terminated and one run with estimates near a boundary were skipped when calculating the bootstrap results.
[c] Based on medians and percentile CIs.
[d] %CV = sqrt(OMEGA2) × 100, where OMEGA2 values were from median, 2.5%, and 97.5% of percentile CIs.
[e] Correlation between CLP and V2 = OMEGA(2,1) / (OMEGA(1) × OMEGA(2)), and correlation between V2 and V1 = OMEGA(3,2) / (OMEGA(2) × OMEGA(3)).CI, confidence interval; CLC = (drainage) clearance from the CSF to the plasma; CLP: clearance from the plasma; CSF = cerebrospinal fluid; IIV = inter-individual variability; NONMEM = non-linear mixed effects modeling; POP (patient population): 1 for later-onset SMA, 2 for infantile SMA, and 3 for pre-symptomatic SMA; QC = intercompartmental clearance between V1 and V4; QP = intercompartmental clearance between V2 and V3; RSE = relative standard error of the parameter estimate (%RSE = standard error × 100/parameter estimate); SMA = spinal muscular atrophy; V1 = volume of distribution of the central CSF compartment; V2 = volume of distribution of the plasma compartment; V3 = volume of distribution of the peripheral CSF compartment; V4 = volume of distribution of the peripheral plasma compartment; WT = weight.

and simulations for other dosing regimens are generally consistent with these. Simulations using the model predict an approximate nusinersen half-life of 4 months. All C_{trough} values presented below are medians. Goodness-of-fit plots are presented in Supplemental Figs. 1 and 2.

3.2. Simulation of delayed dosing

Delays in administering second and third loading dose delayed the peak C_{trough} by approximately the duration of the interruption (Fig. 2). Resumption of the dosing regimen as soon as feasible resulted in achieving C_{trough} concentrations similar to those predicted in the control dosing regimen upon completion of the delayed loading phase. Neither maximum concentration (C_{max}) nor maximum C_{trough} are predicted to exceed values obtained during the loading phase of the label regimen. These results apply only to a short-duration interruption (30–90 days) in dosing.

Delayed dosing during the maintenance phase was found to result in an approximate 10% reduction in median CSF trough concentration per 30 days of interruption in dosing (Fig. 3). Maximum C_{trough} drop of approximately 12%, 21%, and 32% occurred after 30-day, 60-day, and 90-day delay, respectively.

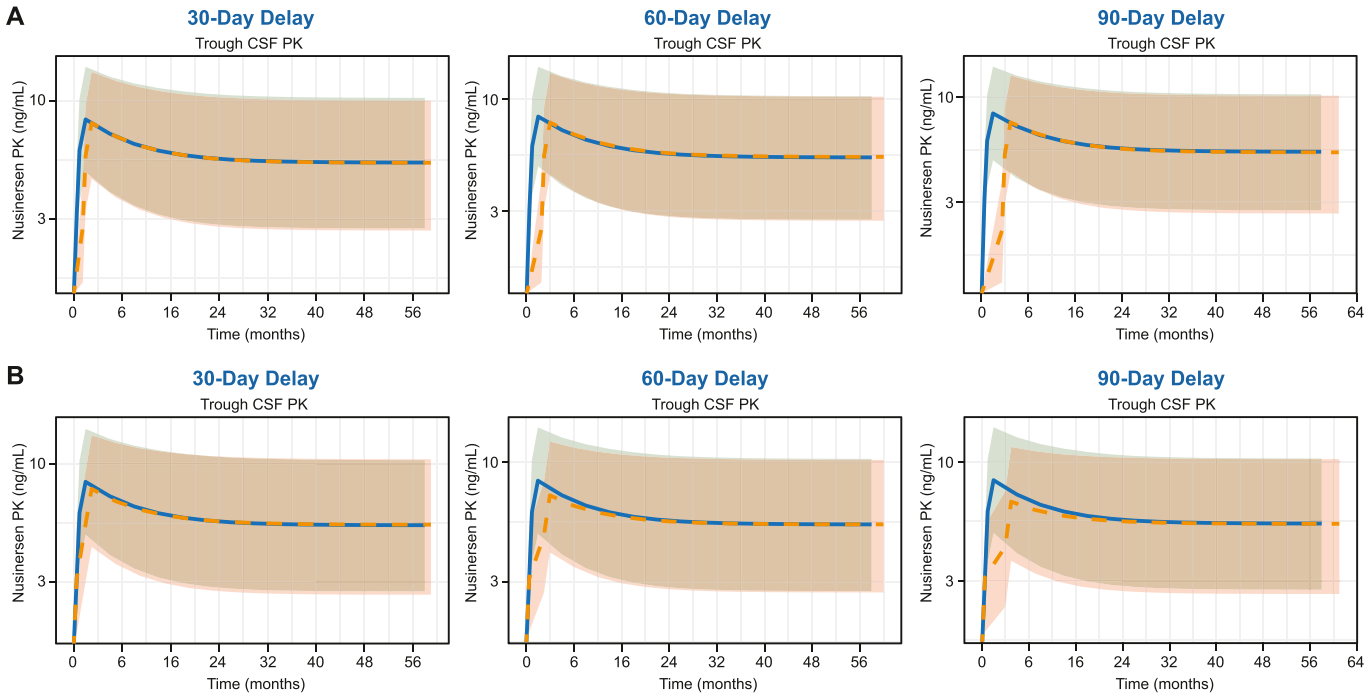

Fig. 2. Nusinersen CSF steady state (C_{trough}) "restored" after delayed (A) second or (B) third loading dose. See Table 1 for description of dose-delay scenarios. Lines represent median C_{trough} values for planned (solid blue) and delayed (dashed orange) doses. Shaded areas are 95% confidence intervals. CSF = cerebrospinal fluid; C_{trough} = minimum concentration; PK = pharmacokinetics.

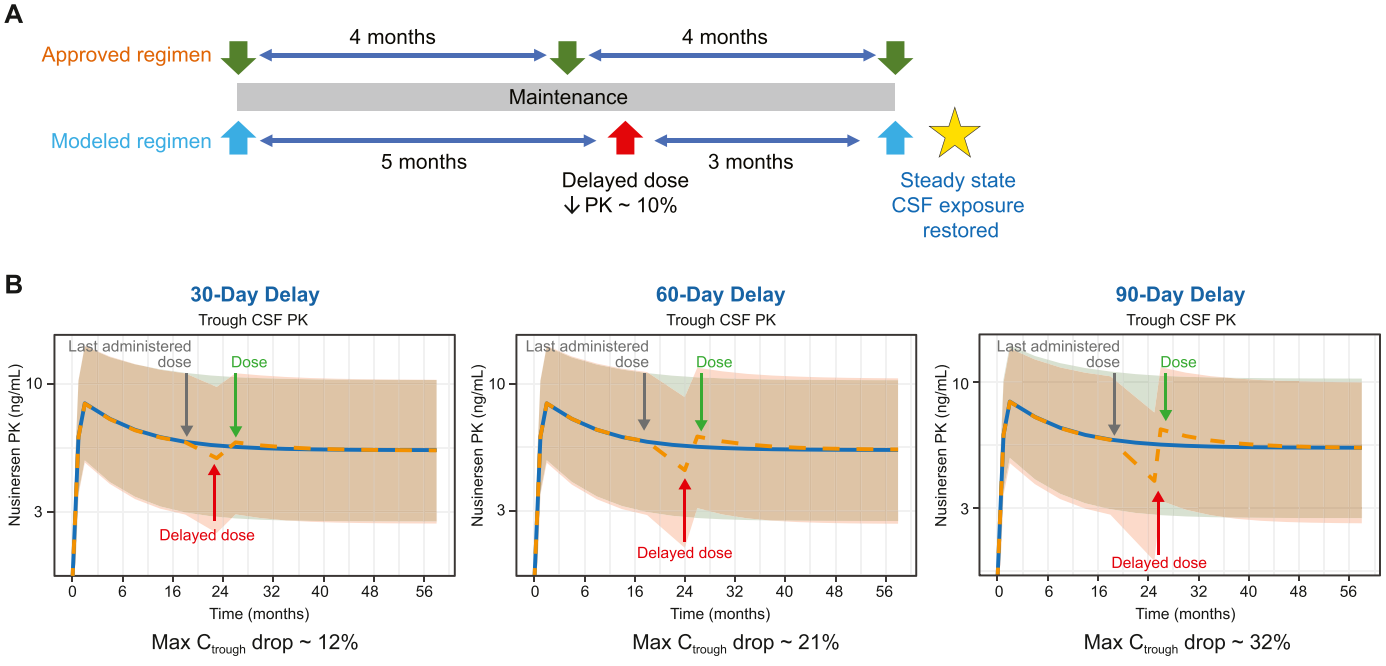

Fig. 3. Administering a maintenance dose on the modeled control dosing regimen after (A) a delayed dose (B) quickly restores C_{trough} to steady state. Delayed dosing resulted in an approximately 10% reduction in C_{trough} per month delay. Doses were administered on days 689 (~24 months, 30-day delay), 719 (~25 months, 60-day delay) or 749 (~26 months, 90-day delay), compared with the control schedule of administration on day 659 (~23 months). However, if subsequent doses of nusinersen are administered as originally planned (day 779 [~28 months], and every 4 months thereafter), C_{trough} is made consistent with control upon administration of the first scheduled dose on day 779. Lines represent median C_{trough} values for planned (solid blue) and delayed (dashed orange) doses. Shaded areas are 95% confidence intervals. CSF = cerebrospinal fluid; C_{trough} = minimum concentration; PK = pharmacokinetics.

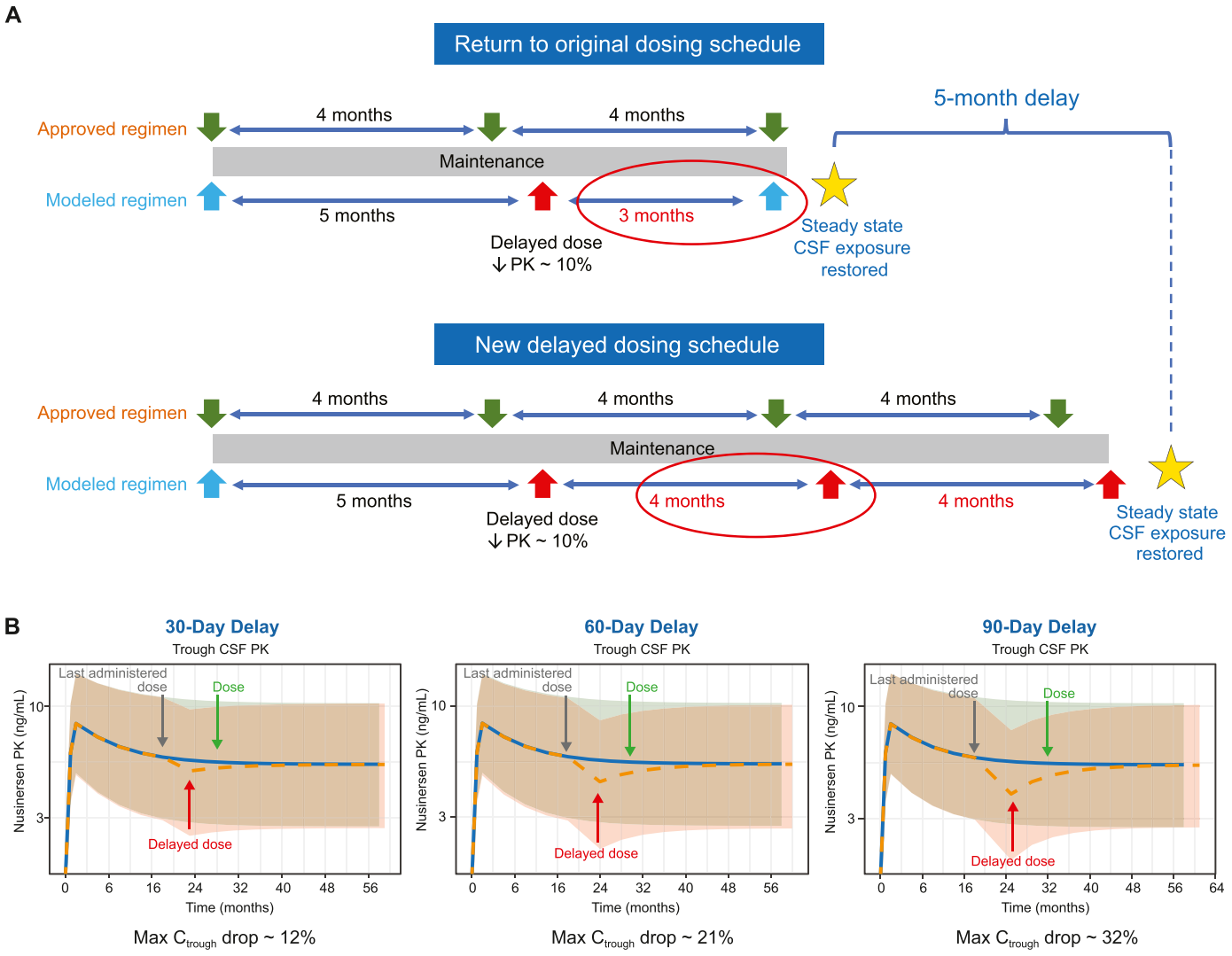

Fig. 4. Administering maintenance dose 4 months after a delayed dose (A) significantly delays restoring C_{trough} to steady state (B) compared with modeled control dosing regimen. For every 30 days delay in dose administration, the C_{trough} was reduced by ~10%. Administering nusinersen on a 4-month schedule after days 689 (~24 months, 30-day delay), 719 (~25 months, 60-day delay) or 749 (~26 months, 90-day delay) resulted in restoration of PK consistent with the control regimen (Table 1) on day 809 (~28 months, 30-day delay in dosing), 1199 (~42 months, 60-day delay) or day 1349 (~48 months, 90-day delay). Lines represent median C_{trough} values for planned (solid blue) and delayed (dashed orange) doses. Shaded areas are 95% confidence intervals. CSF = cerebrospinal fluid; C_{trough} = minimum concentration; PK = pharmacokinetics.

Administration of a dose followed by a subsequent dose as originally scheduled rapidly restored median CSF C_{trough} with up to a 90-day delay in dosing (Fig. 3). Despite the shortened dosing interval, neither C_{max} nor maximum C_{trough} is predicted to exceed values obtained during loading phase of label regimen.

However, even a short delay (30–90 days) during the maintenance phase led to a prolonged period of lower median CSF concentration (5–19 months, depending on the duration of interruption) if all subsequent doses were shifted by the same duration (Fig. 4). A 30-day delay resulted in CSF levels being restored about 5 months later than if the original maintenance dosing schedule was used after resuming dosing (Fig. 3). A 60-day and 90-day dosing delay resulted in CSF being restored about 10 months and 19 months later, respectively, than if the original maintenance dosing schedule was used after resuming dosing as in Fig. 3.

3.3. Simulation of missed dose

Simulation of a single missed dose resulted in a 39% decrease in C_{trough}. If no additional loading doses are administered, C_{trough} remains suboptimal for approximately 20 months after resumption of dosing (Fig. 5). However, administration of an additional dose 14 days subsequent to resumption of dosing resulted in rapid restoration of desired concentrations, leading to restoration of C_{trough} 19.5 months earlier than if this additional dose was not administered.

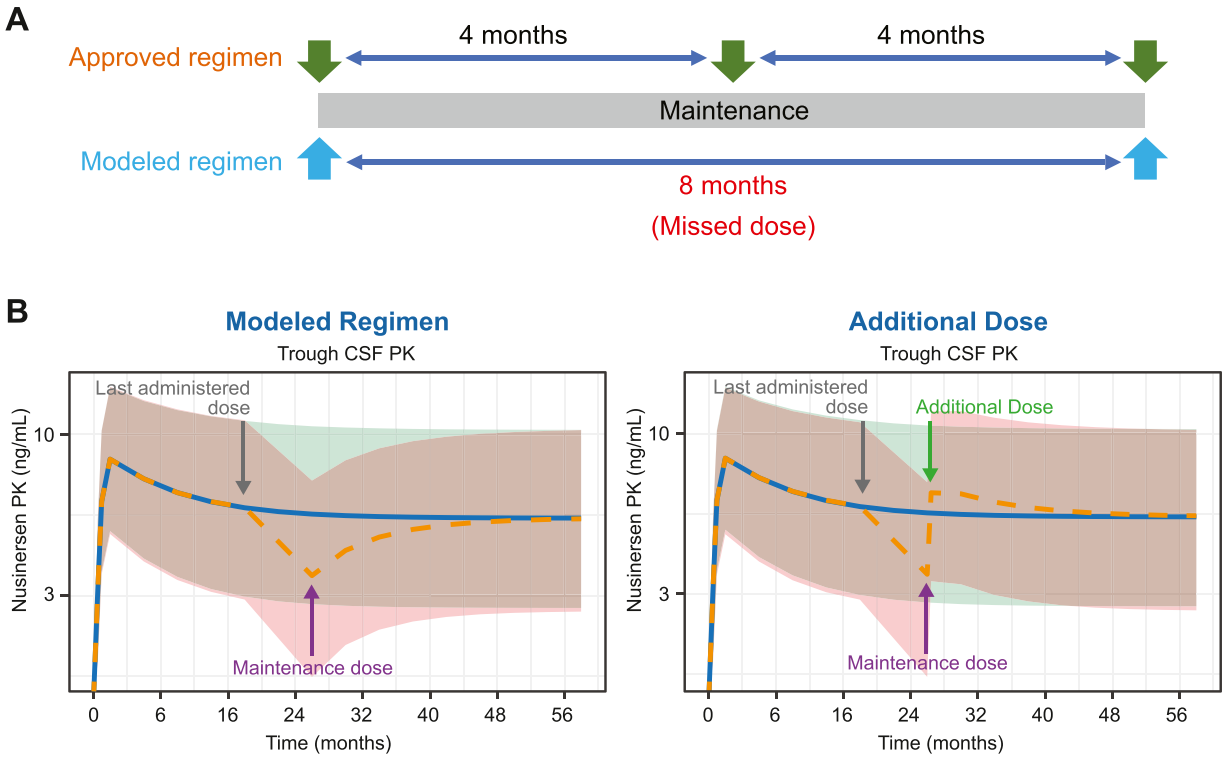

Fig. 5. Missing one maintenance dose leads to suboptimal C_{trough} for ~20 months after resuming dosing (A). Administering an additional dose 2 weeks after resuming dosing will restore desired concentrations 19.5 months earlier (B). Resumption dosing occurs on Day 899 in both A and B. Additional dose in B occurs on Day 913. Lines represent median C_{trough} values for planned (solid blue) and missed (dashed orange) doses. Shaded areas are 95% confidence intervals. CSF = cerebrospinal fluid; C_{trough} = minimum concentration; PK = pharmacokinetics.

Although C_{trough} and C_{max} are predicted to temporarily exceed that of the control dosing regimen during maintenance dosing, they are not predicted to exceed the levels observed during the loading phase, and they are predicted to return to the control maintenance concentration within 8 months.

4. Discussion

Using this population PK model, the impact of a one-time delay in dosing or a missed dose on median nusinersen CSF exposures was found to be strongly dependent on both the duration of dosing interruption and the phase in the accepted dosing regimen when the interruption occurred. In situations where the delay is in administering the second and third loading doses, resumption of the dosing regimen as soon as possible results in achieving concentrations commensurate with the control regimen upon completion of the delayed loading phase. In cases where the dosing delay occurs during the maintenance phase, administration of the delayed dose when possible, followed by the subsequent dose as originally scheduled, is expected to restore targeted exposure levels. Periods of interrupted dosing longer than 4 months may require administration of additional loading doses in order to restore steady state concentrations more rapidly. Determinations from the dosing simulations presented here would be applicable to other established dosing regimens for nusinersen.

This analysis also demonstrated linear clearance of nusinersen from the CSF compartment, resulting in a terminal half-life within the CSF of approximately 4 months. A previous population PK analysis of nusinersen by Luu et al. [16] showed a median terminal half-life of 163 days in the CSF of pediatric patients, supporting dosing at once every 4–6 months. In Phase 3 clinical trials, nusinersen maintenance doses have been given at 6 months [12] and 4 months [11]. The ongoing SHINE extension study (NCT02594124) provides maintenance doses every 4 months.

Data from this population PK analysis enhance our understanding of nusinersen as a therapy for patients with SMA. Further clinical evaluations of nusinersen are ongoing and will provide additional PK information. Data from current studies in pre-symptomatic infants and at higher doses in both children and adults will allow further evaluation of the relationship between dose and exposure in these patient populations. In addition, real-world studies in infants, children, and adults with SMA receiving nusinersen have recently been published [17–20].

Despite being based on plasma and CSF measurements from clinical trials, this PK analysis has some limitations. These results represent median values from the population of individuals and do not reflect results for any particular

individual. Individual results may vary. Although preclinical studies have shown linearity in the pharmacokinetics of nusinersen at concentrations above those described here, the clinical dataset is very sparse at CSF trough concentrations above 10 ng/mL, and therefore this model may not accurately reflect the PK of nusinersen above this level. Finally, the model applies only to a one-time delayed or missed dose, not repeated delays.

5. Conclusions

Delays in administering second and third loading doses resulted in a delay in achieving C_{trough} consistent with the control regimen by approximately the duration of the dosing interruption. Resumption of the dose loading regimen as soon as possible resulted in achieving desired C_{trough} upon completion of the delayed loading phase. Even a short delay (30–90 days) during the maintenance phase led to a prolonged period of lower median CSF concentration if all subsequent doses were shifted by the same duration. However, administration of the dose, followed by the subsequent dose as originally scheduled, rapidly restored median CSF C_{trough}. We do not expect that the safety profile of nusinersen was altered in this scenario, which is especially relevant for patients treated in the real-world setting.

Based on data from the nusinersen clinical development program, 4 loading doses of nusinersen should occur in the first 2 months, followed by a maintenance dose every 4 months thereafter. If a dose must be delayed, patients should return to the original dosing schedule as soon as possible.

Declaration of Competing Interest

D. MacCannell reports being an employee of and holding stock/stock options in Biogen.

Z. Berger reports being an employee of and holding stock/stock options in Biogen.

L. East was an employee of Biogen at the time the studies were conducted and reports being a former employee of and holding stock/stock options in Biogen.

E. Mercuri reports serving on advisory boards for SMA studies for AveXis, Biogen, Ionis, Novartis, and Roche; acting as principal investigator for ongoing Biogen/Ionis and Roche clinical trials; and receiving funding from Famiglie SMA Italy, Italian Telethon, and SMA Europe.

J. Kirschner reports receiving funding for consultancy/educational/research activities concerning SMA from AveXis, Biogen, Roche, and Scholar Rock.

F. Muntoni reports serving on advisory boards for Biogen and Pfizer Rare Diseases; acting as a consultant for AveXis, Biogen, Roche, Santhera, and Sarepta; receiving honoraria from AveXis, Biogen, Roche, Santhera, and Sarepta; receiving grants from European Commission, MDA USA, MDUK, and MRC; receiving investigator grants from Biogen and Sarepta; and acting as principal investigator for Biogen nusinersen trials and Roche olesoxime and risdiplam trials in SMA.

M.A. Farrar reports acting as a consultant and serving on advisory boards for AveXis, Biogen, and Roche; acting as principal investigator for ongoing AveXis, Biogen, and Roche clinical trials; and receiving an investigator grant from Biogen.

J. Peng reports being an employee of Nuventra, which performed contract research for Biogen.

J. Zhou reports being an employee of Nuventra, which performed contract research for Biogen.

I. Nestorov reports being an employee of and holding stock/stock options in Biogen.

W. Farwell reports being an employee of and holding stock/stock options in Biogen.

R.S. Finkel reports serving on advisory boards for AveXis, Biogen, and Roche; acting as a consultant for AveXis, Biogen, Neurogene, Novartis, and Roche/Genentech; receiving research support from AveXis, Biogen, Cytokinetics, Roche, and Scholar Rock; serving on a data safety monitoring board for the AveXis AVXS-101 Phase 1 gene transfer study and Roche Moonfish Phase 1b study; acting in an advisory capacity for nonprofit organizations CureSMA, SMA Europe, SMA Foundation, and SMA Reach (UK); and receiving royalty payments from Children's Hospital of Philadelphia for licensing fees obtained for use of the CHOP INTEND motor function scale and from Elsevier for co-editing a textbook.

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Data availability

Requests for data supporting this manuscript should be submitted to the Biogen Clinical Data Request Portal (www.biogenclinicaldatarequest.com).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2021.02.014.

References

[1] Lunn MR, Wang CH. Spinal muscular atrophy. Lancet 2008;371:2120–33. doi:10.1016/S0140-6736(08)60921-6.

[2] Monani UR, Lorson CL, Parsons DW, Prior TW, Androphy EJ, Burghes AH, et al. A single nucleotide difference that alters splicing patterns distinguishes the SMA gene *SMN1* from the copy gene *SMN2*. Hum Mol Genet 1999;8:1177–83. doi:10.1093/hmg/8.7.1177.

[3] Darras BT. Spinal muscular atrophies. Pediatr Clin North Am 2015;62:743–66. doi:10.1016/j.pcl.2015.03.010.

[4] Singh RN, Howell MD, Ottesen EW, Singh NN. Diverse role of survival motor neuron protein. Biochim Biophys Acta Gene Regul Mech 2017;1860:299–315. doi:10.1016/j.bbagrm.2016.12.008.

[5] Finkel R, Bertini E, Muntoni F, Mercuri E, ENMC SMA Workshop Study Group. 209th ENMC International Workshop: Outcome Measures and Clinical Trial Readiness in Spinal Muscular Atrophy 7–9 November 2014, Heemskerk, The Netherlands. Neuromuscul Disord 2015;25:593–602. doi:10.1016/j.nmd.2015.04.009.

[6] Darras BT, Markowitz J, Monani U, De Vivo DC. Spinal muscular atrophies. In: Darras BT, Royden Jones Jr H, Ryan MM, De Vivo DC, editors. Neuromuscular disorders of infancy, childhood, and adolescence. San Diego, CA: Academic Press; 2015. p. 117–45.

[7] Kolb SJ, Coffey CS, Yankey JW, Krosschell K, Arnold WD, Rutkove SB, et al. NeuroNEXT Clinical Trial Network on behalf of the NN101 SMA Biomarker Investigators. Natural history of infantile-onset spinal muscular atrophy. Ann Neurol 2017;82:883–91. doi:10.1002/ana.25101.

[8] Biogen SPINRAZA (nusinersen) injection, for intrathecal use; 2020. www.spinraza.com/content/dam/commercial/specialty/spinraza/caregiver/en_us/pdf/spinraza-prescribing-information.pdf [accessed June 25, 2020].

[9] European Medicines Agency Spinraza 12 mg solution for injection; 2017. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004312/WC500229704.pdf [accessed June 25, 2020].

[10] Finkel RS, Chiriboga CA, Vajsar J, Day JW, Montes J, De Vivo DC, et al. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a Phase 2, open-label, dose-escalation study. Lancet 2016;388:3017–26. doi:10.1016/S0140-6736(16)31408-8.

[11] Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. ENDEAR Study Group. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. N Engl J Med 2017;377:1723–32. doi:10.1056/NEJMoa1702752.

[12] Mercuri E, Darras BT, Chiriboga CA, Day JW, Campbell C, Connolly AM, et al., CHERISH Study Group. Nusinersen versus sham control in later-onset spinal muscular atrophy. N Engl J Med 2018;378:625–35. doi:10.1056/NEJMoa1710504.

[13] Darras BT, Chiriboga CA, Iannaccone ST, Swoboda KJ, Montes J, Mignon L, et al. ISIS-396443-CS2/ISIS-396443-CS12 Study Groups. Nusinersen in later-onset spinal muscular atrophy: long-term results from the Phase 1/2 studies. Neurology 2019;92:e2492–506. doi:10.1212/WNL.0000000000007527.

[14] De Vivo DC, Bertini E, Swoboda KJ, Hwu WL, Crawford TO, Finkel RS, et al., NURTURE Study Group. Nusinersen initiated in infants during the presymptomatic stage of spinal muscular atrophy: interim efficacy and safety results from the Phase 2 NURTURE study. Neuromuscul Disord 2019;29:842–56. doi:10.1016/j.nmd.2019.09.007.

[15] Darras BT, Farrar MA, Mercuri E, Finkel RS, Foster R, Hughes SG, et al. An integrated safety analysis of infants and children with symptomatic spinal muscular atrophy (SMA) treated with nusinersen in seven clinical trials. CNS Drugs 2019;33:919–32. doi:10.1007/s40263-019-00656-w.

[16] Luu KT, Norris DA, Gunawan R, Henry S, Geary R, Wang Y. Population pharmacokinetics of nusinersen in the cerebral spinal fluid and plasma of pediatric patients with spinal muscular atrophy following intrathecal administrations. J Clin Pharmacol 2017;57:1031–41. doi:10.1002/jcph.884.

[17] Szabó L, Gergely A, Jakus R, Fogarasi A, Grosz Z, Molnár MJ, et al. Efficacy of nusinersen in Type 1, 2 and 3 spinal muscular atrophy: real world data from Hungarian patients. Eur J Paediatr Neurol 2020 [*epub ahead of print*]. doi:10.1016/j.ejpn.2020.05.002.

[18] Veerapandiyan A, Eichinger K, Guntrum D, Kwon J, Baker L, Collins E, et al. Nusinersen for older patients with spinal muscular atrophy: a real-world clinical setting experience. Muscle Nerve 2020;61:222–6. doi:10.1002/mus.26769.

[19] Hagenacker T, Wurster CD, Günther R, Schreiber-Katz O, Osmanovic A, Petri S, et al. Nusinersen in adults with 5q spinal muscular atrophy: a non-interventional, multicentre, observational cohort study. Lancet Neurol 2020;19:317–25. doi:10.1016/S1474-4422(20)30037-5.

[20] Pane M, Coratti G, Sansone VA, Messina S, Bruno C, Catteruccia M, et al. Italian Expanded Access Program Working Group. Nusinersen in Type 1 spinal muscular atrophy: twelve-month real-world data. Ann Neurol 2019;86:443–51. doi:10.1002/ana.25533.