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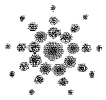
16.5 Pharmacokinetic Reports



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PHARMACOKINETICS REPORT

Title	A Randomized, Double-Blind, Placebo-Controlled, Multiple Dose Efficacy, Safety, Tolerability, and Pharmacokinetics Study of AVI-4658 (Eteplirsen), a Phosphorodiamidate Morpholino Oligomer, Administered Over 24 Weeks in the Treatment of Ambulant Subjects with Duchenne Muscular Dystrophy & Open-Label, Multiple-Dose, Efficacy, Safety, and Tolerability Study of Eteplirsen in Subjects with Duchenne Muscular Dystrophy who Participated in Study 4658-us-201
Study Number	AVI-4658-201/202
Drug Substance and Product:	AVI-4658 (Eteplirsen)
Study Design (Phase)	Phase 2
Sponsor:	Sarepta Therapeutics, Inc. 215 First Street, Suite 7 Cambridge, MA 02124
Contract Research Organization:	(b) (4)
PK Report Author:	(b) (4)
Date of Report:	Original: 17 September 2012 Amended: 26 November 2013

Confidential

The data analyses reported herein were conducted according to the principles of Good Laboratory Practice (GLP), including the archiving of essential documents.

AMENDMENTS

1. Header – all pages. Changed protocol number from 201 to 201/202.

2. Pages 1 and 3. Title Page. Changed protocol title to include title of study 202 and changed protocol number from 201 to 201/202.

3. Page 1. Updated sponsor's address

4. Page 7.Introduction. Added clarification on collection of 5 minute samples.

5. Page 7. Study Overview / Study Design. Added text describing enrollment into the rollover study 202.

6. Page 9.PK Assessments / Blood Samples / Single Draw. Added Week 1 to list of 5 minute draws.

7. Page 12. Results / Dataset. Added Week 1 to list of 5 minute draws

8. Page 13. Results / Sample and Subject Disposition for Pharmacokinetics. Added Week 1 to list of 5 minute draws.

9. Page 14. Results / Plasma Profiles. Revised numbers in text to reflect changes in Tables 4A and 4B for 5 minute samples.

10. Page 15. Conclusions. Added statement regarding dose proportionality based on 5 minute samples.

11. Page 18. Table 4A. Revised table to assign corrected study week for 5 minute sample concentration values. Added Week 36 to the table. Added 4 more ratios of week x/week y. Revised footnotes to table to explain how placebo patients in study 201 were treated in the rollover study 202.

12. Page 19. Table 4B. Revised summary table to reflect new data in table 4A. Added footnote to table to explain ratios.

SIGNATURE PAGE

Title	**A Randomized, Double-Blind, Placebo-Controlled, Multiple Dose Efficacy, Safety, Tolerability, and Pharmacokinetics Study of AVI-4658 (Eteplirsen), a Phosphorodiamidate Morpholino Oligomer, Administered Over 24 Weeks in the Treatment of Ambulant Subjects with Duchenne Muscular Dystrophy & Open-Label, Multiple-Dose, Efficacy, Safety, and Tolerability Study of Eteplirsen in Subjects with Duchenne Muscular Dystrophy who Participated in Study 4658-us-201**
Study Number	**4658-us-201/202**

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

(b) (4) & (b) (6)

27 November, 2013
Date

(b) (6)

26 November 2013
Date

Jay B. Saoud, PhD
Senior Director, Biometrics
Sarepta Therapeutics, Inc.

LIST OF ABBREVIATIONS WITH DEFINITIONS

A_e	Amount of drug excreted into the urine
AUC	Area-under-the-curve
AUMC	Area-under-the-first moment-curve
C_{max}	Maximal concentration of drug
CL_{PL}	Systemic clearance of drug
CL_R	Renal clearance of drug
Half-life ($t_{1/2}$)	Terminal half-life of drug
%Excreted	Percent of dosed drug excreted intact in the urine
%Extrap	Percent of $AUC_{0-\infty}$ extrapolated beyond the last measureable concentration
MRT	Mean residence time
R^2-adjusted	Square of the correlation coefficient for x:y regression adjusted for the number of points used in the estimation
T_{max}	Time at which maximal concentration, C_{max}, occurs
V_{ss}	Volume of distribution under steady-state conditions

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Tables

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Appendix. Listings

1. INTRODUCTION

This report summarizes the pharmacokinetics (PK) of AVI-4658 (Eteplirsen), a Phosphorodiamidate Morpholino Oligomer, which was administered over 24 Weeks in the treatment of ambulant subjects with Duchenne Muscular Dystrophy (DMD). The drug was administered in 150 mL of normal saline as an i.v. infusion over 60 minutes.

Pharmacokinetics in plasma and urine were determined from serial plasma sampling and 24 hr urine collection on Week 12.

Additionally, 5 minute post-infusion plasma samples were evaluated following (b) (4) on active drug for all subjects including placebo subjects rolled over to active drug in the rollover study (AVI-4658-us-202).

2. STUDY OBJECTIVES

This study was designed to assess the efficacy, safety, tolerability, and PK of eteplirsen in both the 30.0 mg/kg and 50.0 mg/kg doses administered over 24 weeks in subjects diagnosed with DMD.

3. STUDY OVERVIEW

3.1. Study Design

This was a randomized, single-center, double-blind, placebo-controlled, multiple-dose study to assess the efficacy, safety, tolerability, and PK of 24 once-weekly i.v. infusions of eteplirsen in subjects with genotypically confirmed DMD with an appropriate genetic lesion. Subjects were enrolled and screened to randomize 12 subjects into one of the three treatment groups:

- Treatment group 1 (n=4): 50.0 mg/kg eteplirsen once weekly x 24 weeks via a 60-minute i.v. infusion
- Treatment group 2 (n=4): 30.0 mg/kg eteplirsen once weekly x 24 weeks via a 60-minute i.v. infusion
- Treatment group 3 (total n=4): once weekly x 24 weeks via a 60-minute i.v. infusion of placebo to match 50.0 mg/kg eteplirsen (n=2; treatment group 3a) or 30.0 mg/kg eteplirsen (n=2; treatment group 3b).

Regardless of randomized treatment (including placebo subjects in treatment group 3), all subjects who completed this study at Visit 25 (Week 24) were allowed to enroll in a continuous, open-label, rollover study dependent on the finding of a safe and efficacious dose of eteplirsen. The open-label study is described under a separate protocol (AVI-4658-us-202).

3.2. Number of Study Sites

This was a single center study.

3.3. Randomization and Blinding

This was a double-blind study. All study staff were blinded as were study sponsor and contract research organization personnel with the exception of the unblinded statistician who produced the actual randomization schedule and the unblinded site person who was designated and authorized to dispense study treatment according to the randomization schedule. A second site individual who was authorized to verify the dose and assignment was also unblinded to the subject's treatment assignment.

Subjects were randomized at Visit 2. Randomization was in a 2:2:1:1 ratio to treatment groups

1. eteplirsen (50.0 mg/kg)
2. eteplirsen (30.0 mg/kg)
3. Placebo (50.0 mg/kg)
4. Placebo (30.0 mg/kg)

Randomization was based upon unstratified permuted block randomization with a block size of 6.

3.4. Administration of Study Drug: All Visits

Subjects received a 60-minute i.v. infusion of double-blind study drug.

3.5. Pharmacokinetic Assessments

3.5.1 Blood Samples

PK – Blood Collection, Single Draw: Visit 2 (Week 1, Day 1)

A single blood sample for PK determination was to be drawn at 5 ± 2 minutes after the end of study drug administration. However, this sample was either not collected or was not submitted to bioanalysis.

PK – Blood Collection, Multiple Draws: Visit 13 (Week 12)

Serial blood samples for PK determinations were drawn pre-administration ((b) (4) (b) (4)) and post-administration at 5, 15, 30, 60, and 90 minutes and 2, 4, 6, 8, 12, and 24 hours after completion of the study drug administration. See Table 1, which also describes the windows associated with each time point. The exact clock time that blood samples are drawn were recorded on the source document and entered into the eCRFs.

Table 1. Plasma and Pharmacokinetic Sample Collection Schedule After the Visit 13 (Week 12) Dose of Double-Blind Study Drug

(b) (4)

PK – Blood Collection, Single Draw: At (b) (4) on active drug

A single blood sample for PK determination was drawn at 5 ± 2 minutes after the end of study drug administration at these visits. Samples were collected from all subjects including placebo subjects rolled over to active drug. Weeks on active is not necessarily the same as Study Week.

3.5.2 Urine Samples

Visit 13 (Week 12) - A pre-infusion urine sample were collected (within 30 minutes before administration). Then all voided urine was collected from the end of dosing through 24 hours after completion of the study drug administration.

4. METHODS

4.1. PK Population

The PK population included all randomized subjects for whom there were adequate PK samples from which to estimate PK parameters. Analyses performed on the PK samples were according to treatments actually received.

4.2. PK Bioanalytical Methods

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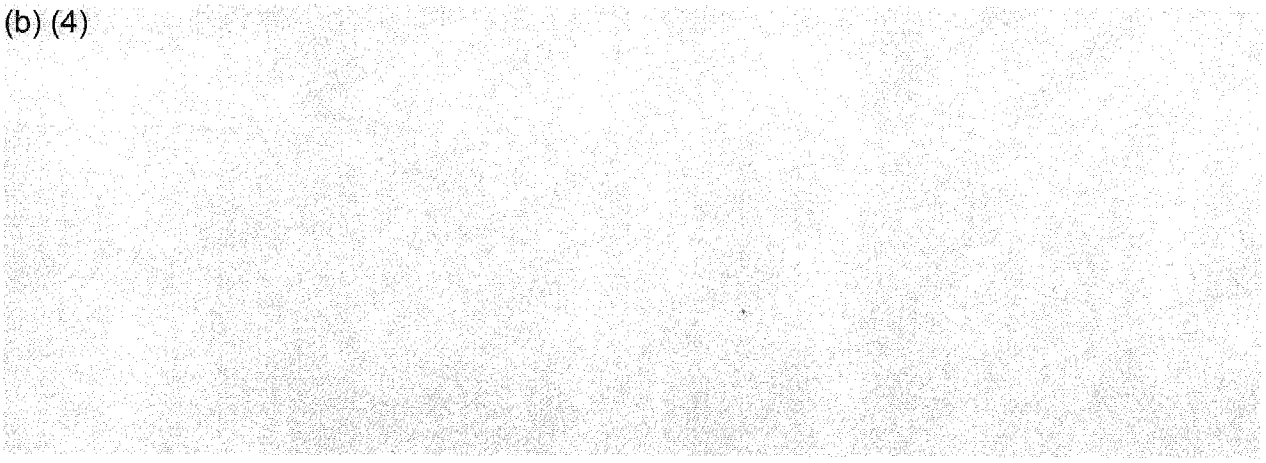

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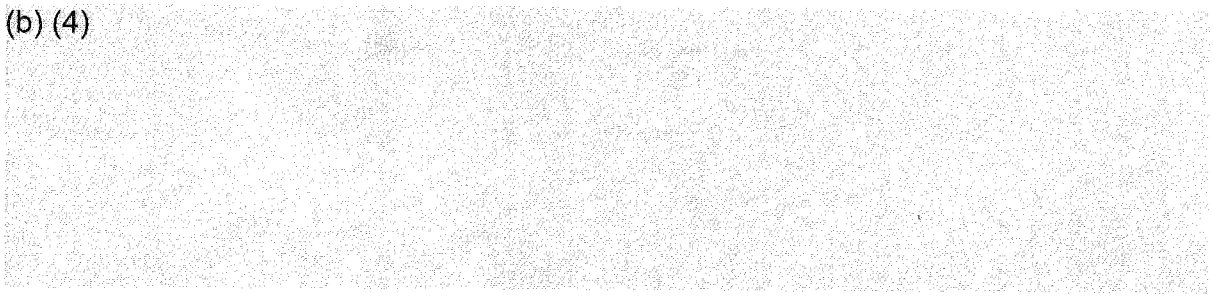


4.3. Sample Size

Twelve subjects were to be randomized with 4 subjects in each of the 3 treatment groups: eteplirsen 50.0 mg/kg, eteplirsen 30.0 mg/kg, and matching placebo. Subjects randomized to placebo were further randomized to muscle biopsy at 12 weeks (matched to 50.0 mg/kg eteplirsen; n = 2) or 24 weeks (matched to 30.0 mg/kg eteplirsen, n = 2). This sample size was selected to provide an initial assessment of the response to these doses, background variability and the proposed methods of assessing treatment effect.

4.4. Subject Disposition for PK

Subject disposition for PK was summarized by the number of subjects who received the full dose of study drug on the days on which PK samples were obtained.

4.5. PK Subject Demographics and Baseline Characteristics

Demographic characteristics including age (years), height (cm) and weight (kg) and body mass index (BMI in kg/m^2) were summarized by treatment and overall.

4.6. Pharmacokinetic Analysis

4.6.1 Pharmacokinetic Parameters

Further, the following PK parameters were calculated from multiple blood collection draws at Visit 13 (Week 12), based on the plasma concentrations of eteplirsen, according to standard noncompartmental methodology (*Gibaldi and Perrier, 1982*):

C_{max}	maximum observed concentration
T_{max}	time to maximum concentration
$AUC_{0\text{-last}}$	area under the concentration-time curve from Hour 0 to the last measurable concentration (C_{last}) at time t (T_{last}), calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations
$AUC_{0\text{-}\infty}$	area under the concentration-time curve extrapolated to infinity, calculated using the formula: $AUC_{0\text{-}\infty} = AUC_{0\text{-t}} + \frac{C_t}{\lambda_z}$

where C_t is the last measurable concentration and λ_Z is the apparent terminal phase elimination rate constant

AUC% ext — percent of $AUC_{0-\infty}$ extrapolated from time t to infinity computed as AUC% ext = 100 x ($AUC_{0-\infty}$ - AUC_{0-t}) / $AUC_{0-\infty}$. Values <10% to 15% indicate a minor dependence of $AUC_{0-\infty}$ on the log-linear regression slope.

λ_Z — apparent terminal phase elimination rate constant, where λ_Z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase

Half-Life ($t_{1/2}$) — apparent terminal elimination half-life (whenever possible), where $t_{1/2} = (\ln 2)/\lambda_Z$

CL_{PL} — plasma clearance, where $CL_{PL} = Dose/AUC_{0-\infty}$

MRT_∞ — mean residence time is the time required for 63.2% of the administered dose to be eliminated from the body.

$MRT_\infty = AUMC_{0-\infty}/AUC_{0-\infty}$

Where $AUMC_{0-\infty} = AUMC_{0-t} + (T_{last} \times C_{last})/\lambda_Z + Cl_{ast}/\lambda_Z^2$.

V_{ss} — volume distribution of drug at steady-state computed as:

$V_{ss} = CL_{PL} \times MRT_\infty$

In addition, the following PK parameters were calculated, whenever possible, for each subject based on the urine eteplirsen concentrations on Visit 13 (Week 12):

A_e — amount of drug excreted in urine

CL_R — renal clearance, where $CL_R = A_e/AUC_{0-24}$

% Excreted — the percent excreted, where % Excreted = 100*(A_e/dose)

PK analysis used actual times as recorded on the electronic case report form (eCRF). Actual elapsed time is defined as the difference between the date and clock time of sample collection and the date and clock time of start of infusion. Time zero was the start of the infusion.

Nominal elapsed times were used for mean plots and for listings and summary tables of plasma concentrations. Nominal times were based on the assumption of a 60 min infusion with time zero arbitrarily set as the end of the infusion.

4.6.2 Pharmacokinetic Analysis Data Conventions

The following PK data conventions and criteria were applied:

- Concentration values that were below the bioanalytical quantitation limit (BLQ) were assigned a numeric value of zero for summary statistics and PK parameter computation.

- $t_{1/2}$ was not reported if the log-linear regression fit was not robust. The criterion for robustness was that the regression coefficient (R2 adjusted) must be at least 0.85 or greater; otherwise $t_{1/2}$ was not reported. Also, if $t_{1/2}$ was not reported the dependent parameters, $AUC_{0-\infty}$, CL_{PL}, and V_{ss} were also not to be reported.
- Handling of Missing Data: PK analysis was based upon observed results and missing data were not included in analysis, nor was imputation performed on missing data. Descriptive statistics were based upon reported data.

4.6.3 Data Displays

Plasma concentrations, PK parameters and urinary excretion were listed and summarized by treatment group. Summary statistics included count (N), arithmetic mean (Mean), standard deviation (SD) and coefficient of variation (CV%). Group mean plots with standard deviation error bars were prepared for concentration versus nominal elapsed time. Individual subject plots were prepared for concentration versus actual elapsed times.

4.6.4 Software

Pharmacokinetic parameters were computed using the software WinNonlin 5.2 from Pharsight, a Cetara Company, St Louis, MO. USA. Plots were prepared using SigmaPlot 11.0 (Systat Software, Inc. San Jose, CA. USA) or Prism 5 (GraphPad Software, Inc. La Jolla, CA. USA). Microsoft Office 2010 Word and Excel were also used for preparing tables, listings and figures.

5. RESULTS

5.1. Dataset

These results were based on data received on 13 December 2011, 21 February 2012 and 10 May 2012. Data were for serial plasma concentrations on Visit 13 (Study Week 12), 24-hour urine data for Visit 13 (Study Week 12), and single time point plasma concentrations at 5 minutes post-infusion (b) (4) on active drug (for subjects on the original treatment randomization and rollover subjects).

5.2. Subject and Sample Disposition for Pharmacokinetics

Data were available from all subjects for pharmacokinetic analysis. Four subjects received AVI-4658 30 mg/kg, four received AVI-4658 50 mg/kg, 2 received Placebo 30 mg/kg and 2 received Placebo 50 mg/kg. Thus, there were a total of 8 subjects receiving active treatment with suitable plasma concentration profiles for pharmacokinetic analysis.

All but one subject received their assigned dose on Week 12 as a 60 minute infusion. One subject in the AVI-4658 30 mg/kg groups received a 62 minute infusion which had no impact on PK analysis because actual infusion durations and collection times were used in the analysis. Appendix Listing 1 provides the infusion times and dose amounts.

Plasma PK samples were collected as planned for all subjects. Thus, for Week 12 there were 12 serial samples per subject times 12 subjects for a total of 144 samples.

Five minute post-infusion plasma PK samples were also collected (b) (4) on active drug for active drug treated subjects, including placebo subjects rolled over to active drug. There were a total of 20 samples at these time points for the 30 and 50 mg/kg dose groups each.

Urine samples were collected as planned on Week 12 at predose and a 24-hour collection samples. Thus, there were a total of 24 urine samples.

Although the protocol specified a Visit 2, Week 1, Day 1 sample to be collected at 5 minutes post infusion, this sample was either not collected or was not submitted to bioanalysis.

5.3. Demographics for Pharmacokinetic Population

Demographics are summarized in Table 2 by treatment group and across groups. All subjects were male and were Caucasian except one Asian subject. Listings are provided in the Clinical Study Report (CSR). Age, body weight and body mass index (BMI) were similar across treatment groups and between active and placebo-treated subjects.

5.4. Exclusions from Analysis

Two concentration values for active treated subjects were excluded from PK analysis because the sample values were much higher than at the preceding time point. These excluded values were deemed to be biologically improbable.

(b) (4)

5.5. Plasma Profiles

Table 3 shows the listing and summary of AVI-4658 plasma concentrations in ng/mL at Week 12. Mean concentration-time profiles are shown in Figure 1 on both a linear and semilog plot. Time is the nominal (protocol specified) time relative to the start of infusion. Individual subject concentration-time profiles are shown in Figures 2A/B and 3A/B on linear and semilog plots. Time is actual elapsed time from the start of infusion. Appendix Listing 2 provides the plasma sampling times.

With the exception noted above of a single placebo time point concentration value of 91 ng/mL, all placebo sample values were BLQ. All predose samples for active treated subjects were BLQ.

All concentrations for active treated subjects remained quantifiable at 24 hours post-end of infusion. Concentrations at 24 hours were 0.02% to 0.07% of C_{max} and 0.31% to 13.0% of the 12 hour concentration. As shown in the mean and individual subject plots, the plasma profiles of AVI-4658 showed multi-phasic decline, possibly bi- or tri-phasic.

One subject treated at the 50 mg/kg dose level ((b) (6)) had considerably higher concentrations than for the other 3 subjects treated at this dose level.

Table 4A shows the listing and summary of AVI-4658 plasma concentrations at 5 minutes after the end of infusion on (b) (4) for subjects on active drug. This includes subjects originally on placebo who were rolled over to active drug after study week 24. The weeks in this table are weeks on active drug, not necessarily study week. Five minute concentrations across weeks were roughly similar for the 30 mg/kg dose level but somewhat more variable for the 50 mg/kg dose level, as shown by the concentration ratios.

Table 4B summarizes the 5 minute concentrations and concentration ratios across the five time points. Five minutes concentrations averaged 79,835 ± 25,092 ng/mL at the 30 mg/kg dose level and 129,210 ± 44,338 ng/mL at the 50 mg/kg dose level. Thus, 5 minute concentrations were approximately proportional to dose in that the ratio of mean concentrations at 50 versus 30 mg/kg was 1.62 which is similar to the dose ratio of 50/30 or 1.67. Concentrations compared across weeks 1 through 36 were somewhat more variable for the 50 mg/kg dose levels compared to the 30 mg/kg dose level as shown by the average of concentration ratios which were 0.950 and 1.104 for the 30 and 50 mg/kg dose levels, respectively.

5.6. Pharmacokinetic Parameters

PK parameters at Week 12 for 4 subjects at 30 mg/kg and 4 subjects at 50 mg/kg are shown in Table 5.

T_{max}, as expected, occurred at the first time point post-end of infusion. C_{max} averaged 77,200 ± 15,568 ng/mL for 30 mg/kg and 124,600 ± 54,898 ng/mL for 50 mg/kg. Variability in C_{max}, $AUC_{0-\infty}$, AUC_{0-last} and AUC_{0-24} was about 20% (CV%) for 30 mg/kg and about 50% for 50 mg/kg. C_{max} at 50 mg/kg was 1.61 times that at 30 mg/kg and $AUC_{0-\infty}$ at 50 mg/kg was 1.99 that at 30 mg/kg. Thus, between these two dose levels C_{max} appeared to increase proportional with dose increment, whereas $AUC_{0-\infty}$ increased in a greater than proportional manner with dose.

Clearance averaged 339 ± 75.8 mL/hr/kg for 30 mg/kg and 319 ± 125 mL/hr/kg for 50 mg/kg. V_{ss} averaged 601 ± 157 mL/kg for 30 mg/kg and 638 ± 224 mL/kg for 50 mg/kg. Half-life averaged 3.30 ± 0.341 hr for 30 mg/kg and 3.17 ± 0.249 hr for 50 mg/kg. MRT_{∞} averaged 1.76 ± 0.074 hr for 30 mg/kg and 2.06 ± 0.318 hr for 50 mg/kg.

(b) (6) in the 50 mg/kg group had higher Cmax and AUC values compared to other subjects in this group. CL_{PL} for this subject was lower but half-life was about the same compared to the other subjects.

5.7. Urinary Excretion and Renal Clearance

Table 6 shows urinary excretion and renal clearance for AVI-4658 in comparison to systemic clearance (CL_{PL}). Appendix Listing 3 provides the collection interval times, concentrations, volumes and dose amounts.

All pre-dose urine concentrations at Visit 13, Week 12 were BLQ with the exception of subject 1004 in the 50 mg/kg active treatment group for whom the predose concentration was 29.9 µg/mL for reasons unknown. This had no impact on the calculation of urinary PK parameters since the analysis was done only on 24-hour collections. Twenty-four hour collection concentrations for placebo treated subjects were all BLQ.

Results from analysis of the 24-hour collections in active treated subjects showed that 95.5 ± 63.9% of the dose was excreted at the 30 mg/kg dose level and 69.4 ± 24.7% at the 50 mg/kg dose level. The average percent of dose excreted at the 30 mg/kg was high due to one value of 190% of dose excreted. Obviously, this cannot be true. No reason for this anomaly is known. Without this value the percent excreted averaged 64.1 ± 13.8%. Renal clearance averaged 221 ± 53.5 mL/hr/kg (without anomalous value) and 234 ± 154 mL/hr/kg for the 30 and 50 mg/kg dose levels, respectively. Thus, renal clearance of drug accounted for about 64.1% and 69.5% of total systemic clearance (CL_{PL}). This is similar to the extent of renal excretion reported in the Phase Ib DMD study AVI-4658-28 at the higher dose levels.

6. CONCLUSIONS

- Plasma concentrations at 5 minute post end of infusion were similar between 12 and 36 weeks on active drug for each dose level and indicated dose proportionality between the 30 and 50 mg/kg dose levels.
- Between the 30 and 50 mg/kg dose levels C_{max} increased in a manner proportional with dose increase, wheareas AUC increased in a somewhat greater than proportional manner.
- CL_{PL}, V_{ss} and half-life were similar at both dose levels.
- Given the half-life of about 3 hours and the rapid decline in concentrations over 24 hours, little if any accumulation would be expected upon multiple dosing once-weekly.
- Renal clearance of intact AVI-4658 accounted for about two-thirds of total systemic clearance.
- PK of AVI-4658 given as a 1-hour IV infusion was similar to that previously reported in the DMD patient population (AVI Phase 1b study 4658-28).

7. REFERENCES

Gibaldi M. and Perrier D. Pharmacokinetics. 2nd ed. New York, NY: Marcel Dekker; 1982.

Table 2. Summary of Demographics for PK Subjects by Cohort

Treatment Group		Age	Weight (kg)	Height (cm)	BMI (kg/m^2)
AVI-4658 30mg/kg	N	4	4	4	4
	Mean	13.0	34.9	130.5	20.2
	SD	0.82	7.05	9.47	1.47
AVI-4658 50mg/kg	N	4	4	4	4
	Mean	12.5	29.1	121.0	19.6
	SD	2.08	6.38	8.00	1.79
Placebos	N	4	4	4	4
	Mean	11.5	30.7	119.3	21.5
	SD	1.73	6.03	3.40	3.98
All Groups	N	12	12	12	12
	Mean	12.3	31.5	123.6	20.5
	SD	1.61	6.41	8.47	2.54

Demographics obtained at Screening visit. Source: see Clinical Study Report.

Table 3. Plasma Concentrations of AVI-4658 in ng/mL
Visit 13 (Week 12)

		Nominal Time Point (hours)											
Treatment Group	Subject	Predose	0.083	0.25	0.5	1	1.5	2	4	6	8	12	24
AVI-4658 30mg/kg	(b) (6)	BLQ	54,400	23,900	15,300	7,980	6,000	5,490	2,340	1,030	445	**4,440**	13.8
	(b) (6)	BLQ	87,800	38,700	24,500	13,800	7,800	6,450	3,290	1,460	693	250	32.4
	(b) (6)	BLQ	80,100	44,300	22,800	14,200	10,500	6,560	2,970	1,440	704	214	21.6
	(b) (6)	BLQ	86,500	41,100	18,700	11,600	7,320	6,340	2,500	1,360	687	235	18.5
	N	4	4	4	4	4	4	4	4	4	4	3	4
	Mean	.	77,200	37,000	20,325	11,895	7,905	6,210	2,775	1,323	632	233	21.6
	SD	.	15,568	9,030	4,141	2,849	1,890	488	435	200	125	18.1	7.90
	CV%	.	20.2	24.4	20.4	24.0	23.9	7.9	15.7	15.1	19.8	7.76	36.6
AVI-4658 50mg/kg	(b) (6)	BLQ	70,400	47,000	32,100	16,400	14,100	10,500	3,700	1,580	**12,200**	244	25.8
	(b) (6)	BLQ	75,500	101,000	41,800	31,600	20,500	13,000	5,540	2,930	1,220	426	36.6
	(b) (6)	BLQ	199,000	110,000	62,300	47,300	33,400	30,200	13,900	7,930	3,960	1,250	140
	(b) (6)	BLQ	128,000	80,800	43,700	22,800	19,200	10,400	5,550	1,920	1,070	348	21.6
	N	4	4	4	4	4	4	4	4	4	3	4	4
	Mean	.	118,225	84,700	44,975	29,525	21,800	16,025	7,173	3,590	2,083	567	56.0
	SD	.	59,813	27,942	12,618	13,388	8,212	9,526	4,569	2,950	1,627	461	56.4
	CV%	.	50.6	33.0	28.1	45.3	37.7	59.4	63.7	82.2	78.1	81.4	101
Placebo 30mg/kg	(b) (6)	BLQ	BLQ	BLQ	BLQ	BLQ	**91.0**	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	(b) (6)	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
Placebo 50mg/kg	(b) (6)	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	(b) (6)	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ

Note: Suspected outliers marked in bold, excluded from PK parameter derivation and summary statistics.

Table 4A. Plasma Concentrations of AVI-4658 in ng/mL at 5 Min Post Infusion Following Week on Active Drug (Weeks 1, 12, 24, 25, 36)

			Concentration at Week on Active Drug					Concentration Ratios						
Rollover Active Treatment	Original Treatment Group	Subject	wk 01	wk 12	wk 24	wk 25	wk 36	wk 12/01	wk 24/12	wk 25/12	wk 25/24	wk 36/12	wk 36/24	wk 36/25
30mg/kg	AVI-4658 30mg/kg	(b) (6)	.	54,400	82,500	44,700	80,000	.	1.517	0.822	0.542	1.471	0.970	1.790
		(b) (6)	.	87,800	98,100	72,900	121,000	.	1.117	0.830	0.743	1.378	1.233	1.660
		(b) (6)	.	80,100	97,200	108,000	29,800	.	1.213	1.348	1.111	0.372	0.307	0.276
		(b) (6)	.	86,500	74,600	87,300	42,600	.	0.862	1.009	1.170	0.492	0.571	0.488
	Placebo 30mg/kg	(b) (6)	122,000	50,000	.	.	.	0.410	.	.	.	.	.	.
		(b) (6)	88,300	88,900	.	.	.	1.007	.	.	.	.	.	.
		N	2	6	4	4	4	2	4	4	4	4	4	4
		Mean	105,150	74,617	88,100	78,225	68,350	0.708	1.177	1.002	0.892	0.928	0.770	1.053
		SD	23,829	17,685	11,495	26,591	41,057	0.422	0.270	0.246	0.300	0.576	0.412	0.782
50mg/kg	AVI-4658 50mg/kg	(b) (6)	.	70,400	127,000	97,900	84,300	.	1.804	1.391	0.771	1.197	0.664	0.861
		(b) (6)	.	75,500	147,000	121,000	127,000	.	1.947	1.603	0.823	1.682	0.864	1.050
		(b) (6)	.	199,000	206,000	221,000	159,000	.	1.035	1.111	1.073	0.799	0.772	0.719
		(b) (6)	.	128,000	119,000	158,000	88,500	.	0.930	1.234	1.328	0.691	0.744	0.560
	Placebo 50mg/kg	(b) (6)	67,600	115,000	.	.	.	1.701	.	.	.	.	.	.
		(b) (6)	116,000	157,000	.	.	.	1.353	.	.	.	.	.	.
		N	2	6	4	4	4	2	4	4	4	4	4	4
		Mean	91,800	124,150	149,750	149,475	114,700	1.527	1.429	1.335	0.999	1.092	0.761	0.798
		SD	34,224	49,063	39,305	53,726	35,234	0.246	0.521	0.212	0.256	0.449	0.083	0.208

Note: "." designates that no sample was obtained at this time point. Placebo subjects listed were treated with placebo in study 201 and then with active drug in the rollover study 202 at the same dose level as in study 201.

Table 4B. Overall Summary of Plasma Concentrations of AVI-4658 in ng/mL at 5 Min Post Infusion Summarized Across Week on Active Drug (Weeks 1, 12, 24, 25, 36)

	Concentration		Ratios	
	30mg/kg	50mg/kg	30mg/kg	50mg/kg
N	20	20	26	26
Mean	79,835	129,210	0.950	1.104
SD	25,092	44,338	0.434	0.392
CV%	31.4	34.3	45.7	35.5
Min	29,800	67,600	0.276	0.560
Median	84,500	124,000	0.988	1.042
Max	122,000	221,000	1.790	1.947
Geometric Mean	75,383	122,148	0.841	1.041
95% CI Lower	68,092	108,459	0.775	0.946
95% CI Upper	91,578	149,961	1.126	1.263

Notes: Seven ratios for week x/week y were computed as shown in Table 4A for a total of 26 individual patient values.

Table 5. Plasma Pharmacokinetic Parameters for AVI-4658 in ng/mL
Visit 13 (Week 12)

		T_{max}	C_{max}	$AUC_{0\text{-last}}$	$AUC_{0\text{-}\infty}$	$AUC_{0\text{-}24}$	AUC% ext	CL_{PL}	V_{ss}	Half-Life ($t_{1/2}$)	R^2 adjusted	MRT_{∞}
Treatment Group	Subject	hr	ng/mL	hr*ng/mL	hr*ng/mL	hr*ng/mL	%	mL/hr/kg	mL/kg	hr		hr
AVI-4658 30mg/kg	(b) (6)	1.10	54,400	66,193	66,253	66,177	0.091	453	836	3.03	0.9878	1.85
	(b) (6)	1.08	87,800	102,101	102,278	102,061	0.173	293	519	3.79	0.9813	1.77
	(b) (6)	1.08	80,100	99,113	99,215	99,089	0.102	302	535	3.26	0.9812	1.77
	(b) (6)	1.07	86,500	96,851	96,934	96,835	0.086	309	516	3.11	0.9953	1.67
	N	4	4	4	4	4	4	4	4	4	4	4
	Mean	1.08	77,200	91,065	91,170	91,040	0.113	339	601	3.30	0.9864	1.76
	SD	0.01	15,568	16720	16,755	16,713	0.041	75.8	157	0.341	0.0067	0.074
	CV%	1.26	20.2	18.4	18.4	18.4	35.9	22.3	26.1	10.3	0.68	4.18
AVI-4658 50mg/kg	(b) (6)	1.13	70,400	107,414	107,531	107,385	0.108	465	911	3.13	0.9652	1.96
	(b) (6)	1.25	101,000	144,441	144,613	144,401	0.118	346	716	3.24	0.9912	2.07
	(b) (6)	1.08	199,000	307,758	308,453	307,582	0.226	162	401	3.44	0.9760	2.48
	(b) (6)	1.10	128,000	163,962	164,051	163,933	0.054	305	523	2.85	0.9943	1.71
	N	4	4	4	4	4	4	4	4	4	4	4
	Mean	1.14	124,600	180,894	181,162	180,825	0.127	319	638	3.17	0.9817	2.06
	SD	0.08	54,898	87,767	88,040	87,698	0.072	125	224	0.249	0.0136	0.318
	CV%	6.58	44.1	48.5	48.6	48.5	56.7	39.1	35.1	7.85	1.38	15.5

Table 6. Urinary Excretion and Renal Clearance for AVI-4658 in ng/mL
Visit 13 (Week 12)

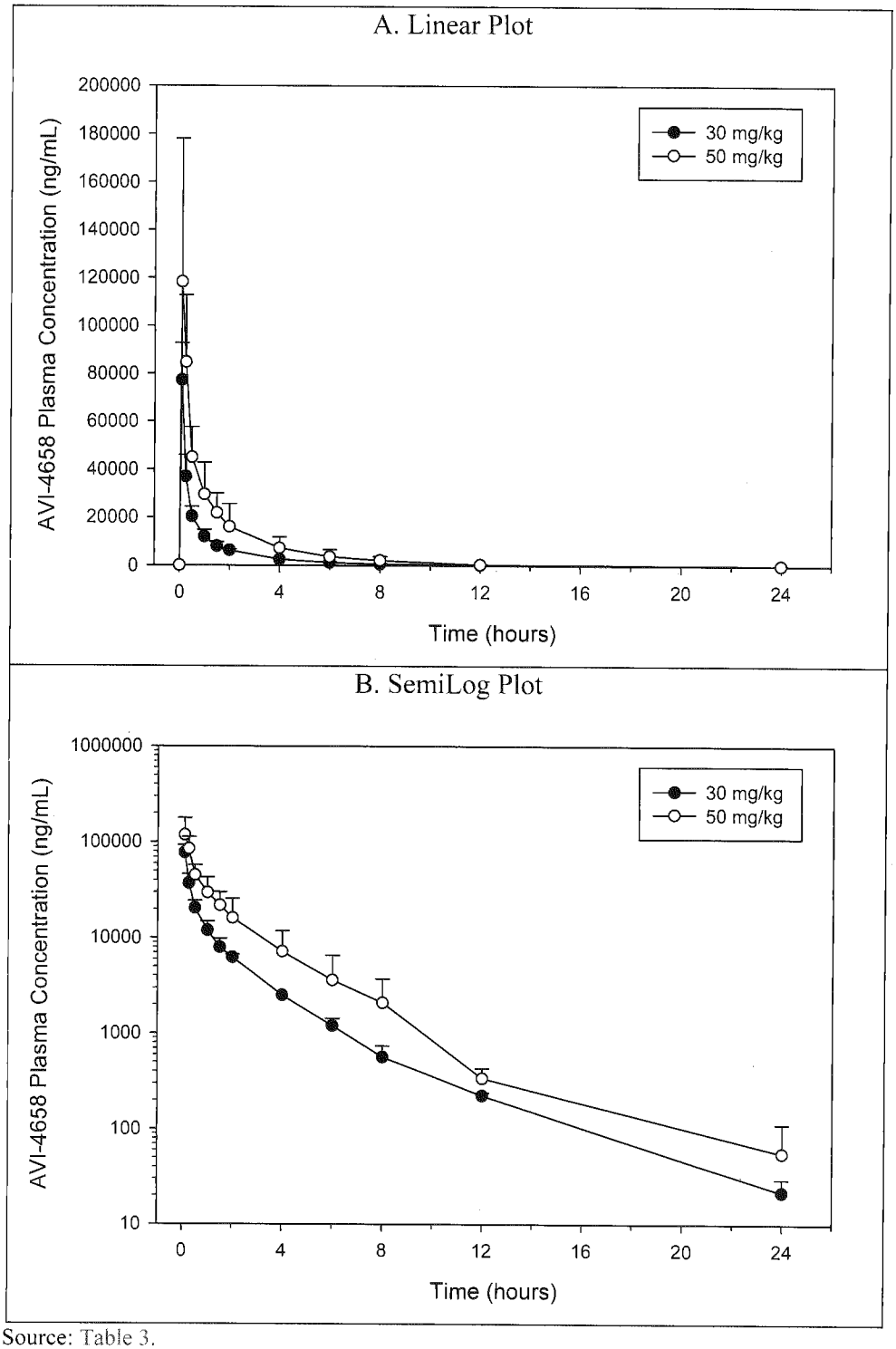
Treatment Group	Subject	Body Wt (kg) *	Urine Volume (mL)	Urine Concentration (µg/mL)	Amount Excreted (mg)	Percent of Dose Excreted	CL_R (mL/hr/kg)	CL_{PL} (mL/hr/kg)	Percent CL_R/CL_{PL}
AVI-4658 30 mg/kg	(b) (6)	25.5	1,587	278	441	57.7	261	453	57.7
	(b) (6)	36.1	1,220	485	592	54.6	161	293	54.8
	(b) (6)	44.7	1,620	661	1,071	79.9	242	302	80.0
	(b) (6)	44.2	2,555	985	**2,517**	**190**	**588**	309	**190**
	N	4	4	4	4	4	4	4	4
	Mean	37.6	1,746	602	**1,155**	**95.5**	**313**	339	**95.6**
	SD	9.0	569	299	**947**	**63.9**	**189**	75.8	**63.9**
	CV%	23.9	32.6	49.7	**81.9**	**66.9**	**60.2**	22.3	**66.9**
AVI-4658 50 mg/kg	(b) (6)	24.5	600	1,920	1,152	94.0	438	465	94.2
	(b) (6)	29.3	460	1,350	621	42.4	147	346	42.5
	(b) (6)	42.5	1,024	1,140	1,167	54.9	89.3	162	55.1
	(b) (6)	27.0	1,058	1,100	1,164	86.2	263	305	86.3
	N	4	4	4	4	4	4	4	4
	Mean	30.8	786	1,378	1,026	69.4	234	319	69.5
	SD	8.0	301	378	270	24.7	154	125	24.7
	CV%	26.0	38.3	27.4	26.3	35.6	65.7	39.1	35.5

Note: For one subject at the 30 mg/kg dose level, the amount excreted is greater than dose given and therefore percent of dose excreted and relative clearance is greater than 100%. This impacts the mean values for this dose level. The reason for this anomaly is not known.

Without the anomalously high excretion subject in the 30 mg/kg group (shown in bold), the percent of drug excreted was 64.1 ± 13.8%, the renal clearance was 221 ± 53.5 mL/hr/kg, and the percent of total systemic clearance accounted for by 24-hour renal excretion was 64.1 ± 13.8%.

* Body weight at Week 11 was used to determine infusion amount for Week 12 dose.

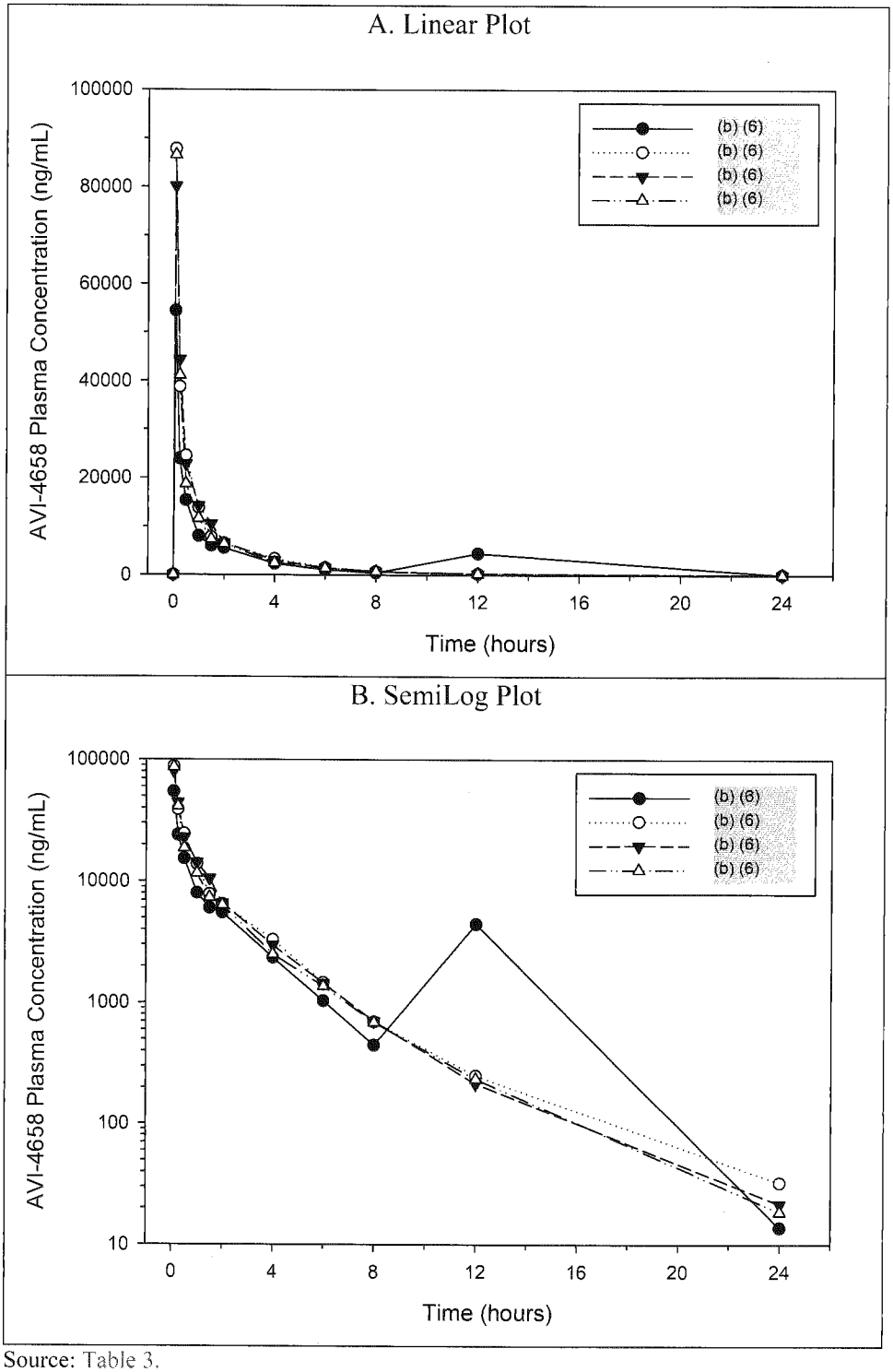
Figure 1. Mean (± SD) AVI-4658 Plasma Concentrations, Visit 13, Week 12



Source: Table 3.

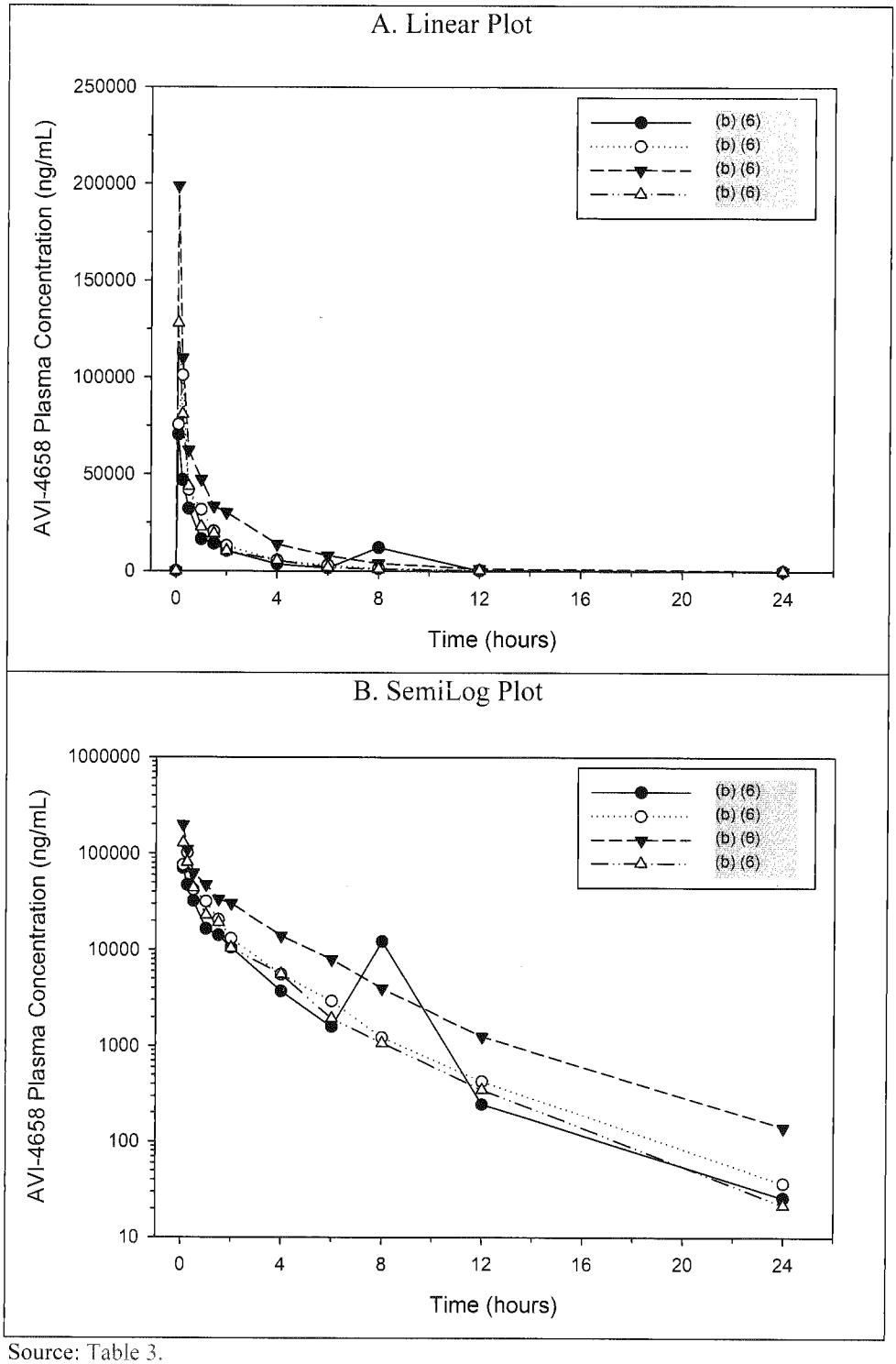
INDIVIDUAL SUBJECT PLOTS

Figure 2. Individual AVI-4658 Plasma Concentrations, Visit 13, Week 12 - 30 mg/kg -



Source: Table 3.

Figure 3. Individual AVI-4658 Plasma Concentrations, Visit 13, Week 12 - 50 mg/kg -



Source: Table 3.

APPENDIX

PK LISTINGS

Listing 1. Infusion Times and Dose Amounts for AVI-4658 for Visit 13, Week 12

Treatment Group	Subject	Date	Clock Time	Date of Body Weight Measurement	Infusion Duration (min)	Infusate Volume (mL)	Dose Amount Delivered (mg)	Body Weight (kg)	Estimated Dose (mg/kg)
AVI-4658 30mg/kg	(b) (6)	31-Oct-11	12:00	24-Oct-11	60	158.0	800	25.5	31.4
	(b) (6)	2-Nov-11	12:45	26-Oct-11	60	161.0	1100	36.1	30.5
	(b) (6)	9-Nov-11	11:50	2-Nov-11	60	163.4	1340	44.7	30.0
	(b) (6)	9-Nov-11	12:20	2-Nov-11	60	163.3	1330	44.2	30.1
AVI-4658 50mg/kg	(b) (6)	31-Oct-11	11:38	24-Oct-11	62	162.3	1230	24.5	50.2
	(b) (6)	31-Oct-11	12:30	24-Oct-11	60	164.7	1470	29.3	50.2
	(b) (6)	7-Nov-11	12:20	31-Oct-11	60	171.0	2100	42.5	49.4
	(b) (6)	9-Nov-11	13:50	2-Nov-11	60	164.0	1400	27.0	51.9
Placebo 30mg/kg	(b) (6)	7-Nov-11	12:40	31-Oct-11	60	162.0	.	40.5	.
	(b) (6)	2-Nov-11	12:00	26-Oct-11	60	160.1	.	33.6	.
Placebo 50mg/kg	(b) (6)	2-Nov-11	11:45	26-Oct-11	60	161.5	.	22.9	.
	(b) (6)	7-Nov-11	13:00	31-Oct-11	60	166.0	.	32.5	.

Notes: Body weight used to compute infusate volume was based on the weight measured at the prior visit one week earlier.
Dose amount delivered in mg = (Infusate Volume – 150) x 100.

Listing 2. Plasma Sampling Times for AVI-4658 for Visit 13, Week 12

Treatment Group	Subject	Nominal Elapsed Time (hr)	Time Point	Sample Collected	Date	Clock Time	Actual Elapsed Time (hr)
AVI-4658 30mg/kg	(b) (6)	0	PRE DOSE	YES	31-Oct-11	11:55	-0.083
		0.08	5 MIN POST DOSE	YES	31-Oct-11	13:06	1.100
		0.25	15 MIN POST DOSE	YES	31-Oct-11	13:16	1.267
		0.5	30 MIN POST DOSE	YES	31-Oct-11	13:30	1.500
		1	60 MIN POST DOSE	YES	31-Oct-11	14:00	2.000
		1.5	90 MIN POST DOSE	YES	31-Oct-11	14:30	2.500
		2	2 HOUR POST DOSE	YES	31-Oct-11	15:00	3.000
		4	4 HOUR POST DOSE	YES	31-Oct-11	16:57	4.950
		6	6 HOUR POST DOSE	YES	31-Oct-11	18:48	6.800
		8	8 HOUR POST DOSE	YES	31-Oct-11	20:55	8.917
		12	12 HOUR POST DOSE	YES	1-Nov-11	0:50	12.833
		24	24 HOUR POST DOSE	YES	1-Nov-11	13:00	25.000
	(b) (6)	0	PRE DOSE	YES	2-Nov-11	12:10	-0.583
		0.08	5 MIN POST DOSE	YES	2-Nov-11	13:50	1.083
		0.25	15 MIN POST DOSE	YES	2-Nov-11	14:01	1.267
		0.5	30 MIN POST DOSE	YES	2-Nov-11	14:15	1.500
		1	60 MIN POST DOSE	YES	2-Nov-11	14:45	2.000
		1.5	90 MIN POST DOSE	YES	2-Nov-11	15:15	2.500
		2	2 HOUR POST DOSE	YES	2-Nov-11	15:43	2.967
		4	4 HOUR POST DOSE	YES	2-Nov-11	17:38	4.883
		6	6 HOUR POST DOSE	YES	2-Nov-11	19:30	6.750
		8	8 HOUR POST DOSE	YES	2-Nov-11	21:37	8.867
		12	12 HOUR POST DOSE	YES	3-Nov-11	1:35	12.833
		24	24 HOUR POST DOSE	YES	3-Nov-11	13:53	25.133
	(b) (6)	0	PRE DOSE	YES	9-Nov-11	11:35	-0.250
		0.08	5 MIN POST DOSE	YES	9-Nov-11	12:55	1.083
		0.25	15 MIN POST DOSE	YES	9-Nov-11	13:05	1.250
		0.5	30 MIN POST DOSE	YES	9-Nov-11	13:20	1.500
		1	60 MIN POST DOSE	YES	9-Nov-11	13:50	2.000
		1.5	90 MIN POST DOSE	YES	9-Nov-11	14:20	2.500
		2	2 HOUR POST DOSE	YES	9-Nov-11	14:52	3.033
		4	4 HOUR POST DOSE	YES	9-Nov-11	16:50	5.000

Listing 2. Plasma Sampling Times for AVI-4658 for Visit 13, Week 12

Treatment Group	Subject	Nominal Elapsed Time (hr)	Time Point	Sample Collected	Date	Clock Time	Actual Elapsed Time (hr)
		6	6 HOUR POST DOSE	YES	9-Nov-11	18:47	6.950
		8	8 HOUR POST DOSE	YES	9-Nov-11	20:55	9.083
		12	12 HOUR POST DOSE	YES	10-Nov-11	0:57	13.117
		24	24 HOUR POST DOSE	YES	10-Nov-11	12:51	25.017
	(b) (6)	0	PRE DOSE	YES	9-Nov-11	12:00	-0.333
		0.08	5 MIN POST DOSE	YES	9-Nov-11	13:24	1.067
		0.25	15 MIN POST DOSE	YES	9-Nov-11	13:35	1.250
		0.5	30 MIN POST DOSE	YES	9-Nov-11	13:50	1.500
		1	60 MIN POST DOSE	YES	9-Nov-11	14:22	2.033
		1.5	90 MIN POST DOSE	YES	9-Nov-11	14:55	2.583
		2	2 HOUR POST DOSE	YES	9-Nov-11	15:20	3.000
		4	4 HOUR POST DOSE	YES	9-Nov-11	17:22	5.033
		6	6 HOUR POST DOSE	YES	9-Nov-11	19:18	6.967
		8	8 HOUR POST DOSE	YES	9-Nov-11	21:08	8.800
		12	12 HOUR POST DOSE	YES	10-Nov-11	1:10	12.833
		24	24 HOUR POST DOSE	YES	10-Nov-11	13:09	24.817
AVI-4658 50mg/kg	(b) (6)	0	PRE DOSE	YES	31-Oct-11	11:28	-0.167
		0.08	5 MIN POST DOSE	YES	31-Oct-11	12:46	1.133
		0.25	15 MIN POST DOSE	YES	31-Oct-11	12:56	1.300
		0.5	30 MIN POST DOSE	YES	31-Oct-11	13:09	1.517
		1	60 MIN POST DOSE	YES	31-Oct-11	13:40	2.033
		1.5	90 MIN POST DOSE	YES	31-Oct-11	14:10	2.533
		2	2 HOUR POST DOSE	YES	31-Oct-11	14:40	3.033
		4	4 HOUR POST DOSE	YES	31-Oct-11	16:45	5.117
		6	6 HOUR POST DOSE	YES	31-Oct-11	18:33	6.917
		8	8 HOUR POST DOSE	YES	31-Oct-11	20:43	9.083
		12	12 HOUR POST DOSE	YES	1-Nov-11	0:40	13.033
		24	24 HOUR POST DOSE	YES	1-Nov-11	12:40	25.033
	(b) (6)	0	PRE DOSE	YES	31-Oct-11	12:20	-0.167
		0.08	5 MIN POST DOSE	YES	31-Oct-11	13:35	1.083
		0.25	15 MIN POST DOSE	YES	31-Oct-11	13:45	1.250
		0.5	30 MIN POST DOSE	YES	31-Oct-11	14:00	1.500
		1	60 MIN POST DOSE	YES	31-Oct-11	14:30	2.000

Listing 2. Plasma Sampling Times for AVI-4658 for Visit 13, Week 12

Treatment Group	Subject	Nominal Elapsed Time (hr)	Time Point	Sample Collected	Date	Clock Time	Actual Elapsed Time (hr)
		1.5	90 MIN POST DOSE	YES	31-Oct-11	15:00	2.500
		2	2 HOUR POST DOSE	YES	31-Oct-11	15:31	3.017
		4	4 HOUR POST DOSE	YES	31-Oct-11	17:16	4.767
		6	6 HOUR POST DOSE	YES	31-Oct-11	19:15	6.750
		8	8 HOUR POST DOSE	YES	31-Oct-11	21:25	8.917
		12	12 HOUR POST DOSE	YES	1-Nov-11	1:15	12.750
		24	24 HOUR POST DOSE	YES	1-Nov-11	13:30	25.000
	(b) (6)	0	PRE DOSE	YES	7-Nov-11	11:57	-0.383
		0.08	5 MIN POST DOSE	YES	7-Nov-11	13:25	1.083
		0.25	15 MIN POST DOSE	YES	7-Nov-11	13:35	1.250
		0.5	30 MIN POST DOSE	YES	7-Nov-11	13:50	1.500
		1	60 MIN POST DOSE	YES	7-Nov-11	14:23	2.050
		1.5	90 MIN POST DOSE	YES	7-Nov-11	14:52	2.533
		2	2 HOUR POST DOSE	YES	7-Nov-11	15:10	2.833
		4	4 HOUR POST DOSE	YES	7-Nov-11	17:24	5.067
		6	6 HOUR POST DOSE	YES	7-Nov-11	19:27	7.117
		8	8 HOUR POST DOSE	YES	7-Nov-11	21:23	9.050
		12	12 HOUR POST DOSE	YES	8-Nov-11	1:19	12.983
		24	24 HOUR POST DOSE	YES	8-Nov-11	13:28	25.133
	(b) (6)	0	PRE DOSE	YES	9-Nov-11	12:45	-1.083
		0.08	5 MIN POST DOSE	YES	9-Nov-11	14:56	1.100
		0.25	15 MIN POST DOSE	YES	9-Nov-11	15:05	1.250
		0.5	30 MIN POST DOSE	YES	9-Nov-11	15:20	1.500
		1	60 MIN POST DOSE	YES	9-Nov-11	15:50	2.000
		1.5	90 MIN POST DOSE	YES	9-Nov-11	16:20	2.500
		2	2 HOUR POST DOSE	YES	9-Nov-11	16:51	3.017
		4	4 HOUR POST DOSE	YES	9-Nov-11	18:53	5.050
		6	6 HOUR POST DOSE	YES	9-Nov-11	20:48	6.967
		8	8 HOUR POST DOSE	YES	9-Nov-11	22:50	9.000
		12	12 HOUR POST DOSE	YES	10-Nov-11	2:40	12.833
		24	24 HOUR POST DOSE	YES	10-Nov-11	15:02	25.200
Placebo 30mg/kg	(b) (6)	0	PRE DOSE	YES	7-Nov-11	12:25	-0.250
		0.08	5 MIN POST DOSE	YES	7-Nov-11	13:45	1.083

Listing 2. Plasma Sampling Times for AVI-4658 for Visit 13, Week 12

Treatment Group	Subject	Nominal Elapsed Time (hr)	Time Point	Sample Collected	Date	Clock Time	Actual Elapsed Time (hr)
		0.25	15 MIN POST DOSE	YES	7-Nov-11	13:55	1.250
		0.5	30 MIN POST DOSE	YES	7-Nov-11	14:10	1.500
		1	60 MIN POST DOSE	YES	7-Nov-11	14:42	2.033
		1.5	90 MIN POST DOSE	YES	7-Nov-11	15:10	2.500
		2	2 HOUR POST DOSE	YES	7-Nov-11	15:40	3.000
		4	4 HOUR POST DOSE	YES	7-Nov-11	17:38	4.967
		6	6 HOUR POST DOSE	YES	7-Nov-11	19:32	6.867
		8	8 HOUR POST DOSE	YES	7-Nov-11	21:37	8.950
		12	12 HOUR POST DOSE	YES	8-Nov-11	1:30	12.833
		24	24 HOUR POST DOSE	YES	8-Nov-11	13:42	25.033
	(b) (6)	0	PRE DOSE	YES	2-Nov-11	11:25	-0.583
		0.08	5 MIN POST DOSE	YES	2-Nov-11	13:05	1.083
		0.25	15 MIN POST DOSE	YES	2-Nov-11	13:15	1.250
		0.5	30 MIN POST DOSE	YES	2-Nov-11	13:30	1.500
		1	60 MIN POST DOSE	YES	2-Nov-11	14:00	2.000
		1.5	90 MIN POST DOSE	YES	2-Nov-11	14:30	2.500
		2	2 HOUR POST DOSE	YES	2-Nov-11	14:56	2.933
		4	4 HOUR POST DOSE	YES	2-Nov-11	16:55	4.917
		6	6 HOUR POST DOSE	YES	2-Nov-11	19:00	7.000
		8	8 HOUR POST DOSE	YES	2-Nov-11	21:00	9.000
		12	12 HOUR POST DOSE	YES	3-Nov-11	1:03	13.050
		24	24 HOUR POST DOSE	YES	3-Nov-11	12:58	24.967
Placebo 50mg/kg	(b) (6)	0	PRE DOSE	YES	2-Nov-11	11:40	-0.083
		0.08	5 MIN POST DOSE	YES	2-Nov-11	12:50	1.083
		0.25	15 MIN POST DOSE	YES	2-Nov-11	13:02	1.283
		0.5	30 MIN POST DOSE	YES	2-Nov-11	13:15	1.500
		1	60 MIN POST DOSE	YES	2-Nov-11	13:45	2.000
		1.5	90 MIN POST DOSE	YES	2-Nov-11	14:15	2.500
		2	2 HOUR POST DOSE	YES	2-Nov-11	14:45	3.000
		4	4 HOUR POST DOSE	YES	2-Nov-11	16:35	4.833
		6	6 HOUR POST DOSE	YES	2-Nov-11	18:35	6.833
		8	8 HOUR POST DOSE	YES	2-Nov-11	20:55	9.167
		12	12 HOUR POST DOSE	YES	3-Nov-11	0:50	13.083

Listing 2. Plasma Sampling Times for AVI-4658 for Visit 13, Week 12

Treatment Group	Subject	Nominal Elapsed Time (hr)	Time Point	Sample Collected	Date	Clock Time	Actual Elapsed Time (hr)
		24	24 HOUR POST DOSE	YES	3-Nov-11	12:45	25.000
	(b) (6)	0	PRE DOSE	YES	7-Nov-11	12:47	-0.217
		0.08	5 MIN POST DOSE	YES	7-Nov-11	14:05	1.083
		0.25	15 MIN POST DOSE	YES	7-Nov-11	14:16	1.267
		0.5	30 MIN POST DOSE	YES	7-Nov-11	14:30	1.500
		1	60 MIN POST DOSE	YES	7-Nov-11	14:58	1.967
		1.5	90 MIN POST DOSE	YES	7-Nov-11	15:29	2.483
		2	2 HOUR POST DOSE	YES	7-Nov-11	16:00	3.000
		4	4 HOUR POST DOSE	YES	7-Nov-11	17:45	4.750
		6	6 HOUR POST DOSE	YES	7-Nov-11	19:50	6.833
		8	8 HOUR POST DOSE	YES	7-Nov-11	21:50	8.833
		12	12 HOUR POST DOSE	YES	8-Nov-11	1:50	12.833
		24	24 HOUR POST DOSE	YES	8-Nov-11	14:02	25.033

Notes: Nominal elapsed time was computed relative to the end of infusion.
Actual elapsed time was computed relative to the start date and clock time of infusion.

Listing 3. Urinary Volumes, Concentrations and Amounts by Subject and Collection Interval for AVI-4658 for Visit 13, Week 12

Treatment Group	Subject	Time Point	Start Date	End Date	Start Time	End Time	Concentration (µg/mL)	Urine Volume (mL)	Amount Excreted (mg)
AVI-4658 30mg/kg	(b) (6)	Pre Dose	31-Oct-11	31-Oct-11	11:17	11:17	BLQ<(25.0)	70	0
		0 - 24 hours	31-Oct-11	1-Nov-11	13:00	13:04	278	1587	441
	(b) (6)	Pre Dose	2-Nov-11	2-Nov-11	12:25	12:25	BLQ<(25.0)	45	0
		0 - 24 hours	2-Nov-11	3-Nov-11	13:45	13:45	485	1220	592
	(b) (6)	Pre Dose	9-Nov-11	9-Nov-11	11:30	11:30	BLQ<(25.0)	75	0
		0 - 24 hours	9-Nov-11	10-Nov-11	12:50	12:50	661	1620	1071
	(b) (6)	Pre Dose	9-Nov-11	9-Nov-11	11:45	11:45	BLQ<(25.0)	82	0
		0 - 24 hours	9-Nov-11	10-Nov-11	13:20	13:17	985	2555	2517
AVI-4658 50mg/kg	(b) (6)	Pre Dose	31-Oct-11	31-Oct-11	11:05	11:05	BLQ<(25.0)	62	0
		0 - 24 hours	31-Oct-11	1-Nov-11	12:40	12:34	1920	600	1152
	(b) (6)	Pre Dose	31-Oct-11	31-Oct-11	12:10	12:10	**29.9**	48	1
		0 - 24 hours	31-Oct-11	1-Nov-11	13:30	13:28	1350	460	621
	(b) (6)	Pre Dose	7-Nov-11	7-Nov-11	11:42	11:42	BLQ<(25.0)	67	0
		0 - 24 hours	7-Nov-11	8-Nov-11	13:20	13:20	1140	1024	1167
	(b) (6)	Pre Dose	9-Nov-11	9-Nov-11	12:10	12:10	BLQ<(25.0)	108	0
		0 - 24 hours	10-Nov-11	11-Nov-11	14:50	14:50	1100	1058	1164
Placebo 30mg/kg	(b) (6)	Pre Dose	7-Nov-11	7-Nov-11	12:10	12:10	BLQ<(25.0)	84	0
		0 - 24 hours	7-Nov-11	8-Nov-11	13:40	13:40	BLQ<(25.0)	1115	0
	(b) (6)	Pre Dose	2-Nov-11	2-Nov-11	11:00	11:00	BLQ<(25.0)	58	0
		0 - 24 hours	2-Nov-11	3-Nov-11	13:00	13:00	BLQ<(25.0)	2098	0
Placebo 50mg/kg	(b) (6)	Pre Dose	2-Nov-11	2-Nov-11	11:10	11:10	BLQ<(25.0)	130	0
		0 - 24 hours	2-Nov-11	3-Nov-11	12:45	12:45	BLQ<(25.0)	1430	0
	(b) (6)	Pre Dose	7-Nov-11	7-Nov-11	12:40	12:40	BLQ<(25.0)	58	0
		0 - 24 hours	7-Nov-11	8-Nov-11	14:00	14:00	BLQ<(25.0)	1790	0

Notes: The predose concentration for subject 1004 in the active 50 mg/kg treatment group was greater than BLQ (29.9 µg/mL) for unknown reasons.

Combs Consulting Service

PHARMACOKINETICS REPORT

Title	Open-Label, Multiple-Dose, Efficacy, Safety, and Tolerability Study of Eteplirsen in Subjects with Duchenne Muscular Dystrophy who Participated in Study 4658-us-201
Study Number	AVI-4658-202
Drug Substance and Product:	AVI-4658 (Eteplirsen)
Study Design (Phase)	Phase 2
Sponsor:	Sarepta Therapeutics, Inc. 215 First Street, Suite 7 Cambridge, MA 02124
Contract Research Organization:	(b) (4)
PK Report Author:	(b) (4)
Date of Report:	04 September 2014

SIGNATURE PAGE

Title	**Open-Label, Multiple-Dose, Efficacy, Safety, and Tolerability Study of Eteplirsen in Subjects with Duchenne Muscular Dystrophy who Participated in Study 4658-us-201**
Study Number	**4658-us-202**

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

(b) (6)

9/04/2014
Date

(b) (6)

05 September 2014
Date

Jay B. Saoud, PhD
Senior Director, Biometrics
Sarepta Therapeutics, Inc.

LIST OF ABBREVIATIONS WITH DEFINITIONS

A_e	Amount of drug excreted into the urine
AUC	Area-under-the-curve
AUMC	Area-under-the-first moment-curve
C_{max}	Maximal concentration of drug
CL_{PL}	Systemic clearance of drug
Half-life ($t½$)	Terminal half-life of drug
%Extrap	Percent of $AUC_{0-\infty}$ extrapolated beyond the last measureable concentration
MRT	Mean residence time
R^2-adjusted	Square of the correlation coefficient for x:y regression adjusted for the number of points used in the estimation
T_{max}	Time at which maximal concentration, C_{max}, occurs
V_{ss}	Volume of distribution under steady-state conditions

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2. INTRODUCTION

This report summarizes the pharmacokinetics (PK) of AVI-4658 (Eteplirsen), a Phosphorodiamidate Morpholino Oligomer, which was administered to ambulant subjects with Duchenne muscular dystrophy (DMD) who successfully completed the 28-week eteplirsen study 4658-us-201 and are being treated for an additional 164 weeks in rollover study 4658-us-202.

The drug was administered in 150 mL of normal saline as an i.v. infusion over 60 minutes.

Reported here are the pharmacokinetics in plasma determined from serial blood sampling over 24 hours at approximately study week 124 in study 4658-us-202.

3. STUDY OBJECTIVES

The primary objective of this study was to assess the ongoing efficacy, safety, and tolerability of an additional 164 weeks of treatment with eteplirsen (AVI-4658) in Duchenne muscular dystrophy (DMD) subjects who successfully completed the 28-week eteplirsen study: Study 4658-us-201.

4. STUDY OVERVIEW

4.1. Study Design

This was a continuing, open-label, multiple-dose study to assess the ongoing efficacy, safety, and tolerability of weekly IV infusions of eteplirsen (50 or 30 mg/kg) in 12 DMD subjects who successfully completed Study 4658-us-201. Subjects had the opportunity to enroll in this study during the last visit of Study 4658-us-201 (Week 28).

All 12 eligible subjects are receiving once weekly eteplirsen (50 or 30 mg/kg), currently planned for 164 weeks. In Study 4658-us-202 the a2 subjects are receiving weekly doses of eteplirsen as presented in Table 1.

Table 1. Study Design

Group	Treatment / Dose in Study 4658-us-201	Dose of Eteplirsen For Study 4658-us-202
1	50 mg/kg eteplirsen for 28 weeks	50 mg/kg eteplirsen
2	30 mg/kg eteplirsen for 28 weeks	30 mg/kg eteplirsen
3a	Placebo for 24 weeks followed by 50 mg/kg eteplirsen for 4 weeks	50 mg/kg eteplirsen
3b	Placebo for 24 weeks followed by 30 mg/kg eteplirsen for 4 weeks	30 mg/kg eteplirsen

Safety, efficacy, pharmacokinetic (PK), and biomarker assessments are performed at scheduled visits. All subjects underwent muscle biopsies for analysis of exon skipping, dystrophin expression, and inflammatory markers at Week 20; biopsies were performed within 24 to 96 hours following the completion of the eteplirsen infusion.

4.2. Pharmacokinetic Assessments

4.2.1 Blood Samples

At approximately study Week 124 of Study 4658-us-202, or approximately Week 152 from the start of Study 4658-us-201, serial blood samples for PK determinations were drawn pre-administration ((b) (4) and post-administration at 5, 15, 30, 60, and 90 minutes and 2, 4, 6, 8, 12, 16 and 24 hours after completion of the study drug administration. The exact clock time that blood samples were drawn were recorded on the source document and entered into the eCRFs.

4.2.2 Urine Samples

No urine samples were planned for study 4658-us-202.

5. METHODS

5.1. PK Population

The PK population included all subjects for whom there were adequate PK samples from which to estimate PK parameters.

5.2. PK Bioanalytical Methods

(b) (4)

5.3. Subject Disposition for PK

Subject disposition for PK was summarized by the number of subjects who received the full dose of study drug on the days on which PK samples were obtained.

5.4. PK Subject Demographics and Baseline Characteristics

Demographic characteristics including age (years), weight (kg), gender, race and ethnicity were summarized by treatment.

5.5. Pharmacokinetic Analysis

5.5.1 Pharmacokinetic Parameters

The following PK parameters were calculated from multiple blood collection draws at approximately Week 124/152, based on the plasma concentrations of eteplirsen, according to standard noncompartmental methodology (*Gibaldi and Perrier, 1982*):

C_{max} — maximum observed concentration

T_{max} — time to maximum concentration

$AUC_{0\text{-last}}$ — area under the concentration-time curve from Hour 0 to the last measurable concentration (C_{last}) at time t (T_{last}), calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations

$AUC_{0\text{-}24}$ — area under the concentration-time curve from Hour 0 to 24 hours post dose computed by interpolation or extrapolation

$AUC_{0\text{-}\infty}$ — area under the concentration-time curve extrapolated to infinity, calculated using the formula:

$$AUC_{0\text{-}\infty} = AUC_{0\text{-last}} + \frac{C_{last}}{\lambda_Z}$$

where C_{last} is the last measurable concentration and λ_Z is the apparent terminal phase elimination rate constant

AUC% ext — percent of $AUC_{0\text{-}\infty}$ extrapolated from time T_{last} to infinity computed as AUC% ext = 100 x ($AUC_{0\text{-}\infty}$ - $AUC_{0\text{-last}}$) / $AUC_{0\text{-}\infty}$. Values <10% to 15% indicate a minor dependence of $AUC_{0\text{-}\infty}$ on the log-linear regression slope.

λ_Z — apparent terminal phase elimination rate constant, where λ_Z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase

Half-Life ($t_{1/2}$) — apparent terminal elimination half-life (whenever possible), where $t_{1/2} = (\ln 2)/\lambda_Z$

CL_{PL} — plasma clearance, where $CL_{PL} = Dose/AUC_{0\text{-}\infty}$

MRT_{∞} — mean residence time is the time required for 63.2% of the administered dose to be eliminated from the body.

$MRT_{\infty} = AUMC_{0\text{-}\infty}/AUC_{0\text{-}\infty}$

Where $AUMC_{0\text{-}\infty} = AUMC_{0\text{-}t} + (T_{last} \times C_{last})/\lambda_Z + C_{last}/\lambda_Z^2$.

V_{ss} volume distribution of drug at steady-state computed as:

$V_{ss} = CL_{PL} \times MRT_{\infty}$

PK analysis used actual times as recorded on the electronic case report form (eCRF). Actual elapsed time is defined as the difference between the date and clock time of sample collection and the date and clock time of start of infusion. Time zero was the start of the infusion.

Nominal elapsed times were used for mean plots and for listings and summary tables of plasma concentrations. Nominal times were based on the assumption of a 60 min infusion with time zero arbitrarily set as the end of the infusion.

5.5.2 Pharmacokinetic Analysis Data Conventions

The following PK data conventions and criteria were applied:

- Concentration values that were below the bioanalytical limit of quantitation (reported as BLQ) were assigned a numeric value of zero for summary statistics and PK parameter computation.
- $t_{1/2}$ was not reported if the log-linear regression fit was not robust. The criterion for robustness was that the regression coefficient (R^2 adjusted) must be at least 0.85 or greater; otherwise $t_{1/2}$ was not reported. Also, if $t_{1/2}$ was not reported the dependent parameters, $AUC_{0-\infty}$, CL_{PL}, and V_{ss} were also not to be reported.
- Handling of Missing Data: PK analysis was based upon observed results and missing data were not included in analysis, nor was imputation performed on missing data. Descriptive statistics were based upon reported data.

5.5.3 Data Displays

Plasma concentrations and PK parameters were listed and summarized by treatment group. Summary statistics included count (N), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), and median. Group mean plots with standard deviation error bars were prepared for concentration versus nominal elapsed time. Individual subject plots were prepared for concentration versus actual elapsed times.

5.5.4 Software

Pharmacokinetic parameters were computed using the software Phoenix WinNonlin 6.3 from Pharsight, a Cetara LP Company, St Louis, MO. USA. Plots were prepared using SigmaPlot 11.0 (Systat Software, Inc. San Jose, CA. USA) or Prism 5 (GraphPad Software, Inc. La Jolla, CA. USA). Microsoft Office 2010 Word and Excel were also used for preparing tables, listings and figures. All analysis were performed on a computer running the 64-bit Windows 7 operating system (Microsoft Corp. Redmond, WA. USA).

6. RESULTS

6.1. Dataset

These results were based on data received on 15 August 2014. Data were for serial plasma concentrations at approximately Week 124 of Study 4658-us-202, or approximately Week 152 from the start of Study 4658-us-201

6.2. Subject and Sample Disposition for Pharmacokinetics

Data were available from all 12 subjects for pharmacokinetic analysis. Six subjects received AVI-4658 30 mg/kg and six received AVI-4658 50 mg/kg. Plasma PK samples were collected as planned for all subjects. Thus there were 13 serial samples per subject times 12 subjects for a total of 156 samples.

Subjects received their assigned dose as a 60 minute infusion approximately. (b) (4) Table 2 provides the infusion durations.

Sampling times were from -4.6% to 18.5% of nominal collection times. Deviations in infusion duration or in sampling times from nominal had no impact on PK analysis because actual infusion durations and elapsed times were used in the analysis.

6.3. Demographics for Pharmacokinetic Population

Demographic parameters race, ethnicity, age and body weight are summarized in Table 2 by treatment group. All subjects were male and were Caucasian except one Asian subject. Listings are provided in the Clinical Study Report (CSR). Age was similar across treatment groups but body weight for subjects in the 30 mg/kg group was higher than in the 50 mg/kg group (36.2 versus 29.1 kg).

6.4. Exclusions from Analysis

One concentration value was excluded from PK analysis. The predose sample for (b) (6) in the 50 mg/kg group was 10.8 ng/mL which was greater than the assay limit of quantitation (10 ng/mL). The predose values for all other subjects in the study were less than the assay limit.

6.5. Plasma Profiles

Table 3 shows the listing and summary of AVI-4658 plasma concentrations in ng/mL at Week 124/152. Mean concentration-time profiles are shown in Figure 1 on both a linear and semilog plot. Time is the nominal (protocol specified) time relative to the start of infusion. Individual subject concentration-time profiles are shown in Figures 2A/B and 3A/B on linear and semilog plots. Time is actual elapsed time from the start of infusion. Appendix Listing 1 provides the plasma sampling times.

All predose samples were below the limit of quantitation (BLQ), with the exception noted above of a single predose concentration value of 10.8 ng/mL.

All concentrations remained quantifiable at 24 hours post-end of infusion. Concentrations at 24 hours were 0.03% to 0.11% of C_{max} and 8.0% to 17.1% of the 12 hour concentration. As shown in the mean and individual subject plots, the plasma profiles of AVI-4658 showed multi-phasic decline, possibly bi- or tri-phasic.

One subject treated at the 50 mg/kg dose level ((b) (6) had considerably higher concentrations than for the other 5 subjects treated at this dose level. The maximum concentration for this subject was 1.35 times that of the next highest subject and the 24 hour concentration was 3 times that of the next highest subject.

6.6. Pharmacokinetic Parameters

PK parameters at approximately Week 124 for 6 subjects at 30 mg/kg and 6 subjects at 50 mg/kg are shown in Table 4.

T_{max}, as expected, occurred at the first time point post-end of infusion. C_{max} averaged 85,067 ± 15,913 ng/mL for 30 mg/kg and 125,750 ± 64,610 ng/mL for 50 mg/kg. Variability in C_{max}, $AUC_{0-\infty}$, AUC_{0-last} and AUC_{0-24} was about 20% (CV%) for 30 mg/kg and about 50% for 50 mg/kg.

C_{max} at 50 mg/kg was 1.48 times that at 30 mg/kg and $AUC_{0-\infty}$ at 50 mg/kg was 1.51 that at 30 mg/kg. The 5 minute concentration at 50 mg/kg was 1.48 times that at 30 mg/kg. The dose ratio was 50/30 or 1.67. Thus, between these two dose levels the 5 minute concentration and both C_{max} and $AUC_{0-\infty}$ appeared to increase in a slightly less than proportional manner with dose increment.

Clearance averaged 244 ± 54.9 mL/hr/kg for 30 mg/kg and 322 ± 150 mL/hr/kg for 50 mg/kg. V_{ss} averaged 526 ± 91.5 mL/kg for 30 mg/kg and 690 ± 340 mL/kg for 50 mg/kg. Half-life averaged 3.54 ± 0.643 hr for 30 mg/kg and 3.77 ± 0.628 hr for 50 mg/kg. MRT_{∞} averaged 2.18 ± 0.222 hr for 30 mg/kg and 2.17 ± 0.317 hr for 50 mg/kg.

(b) (6) in the 50 mg/kg group had higher Cmax and AUC values compared to other subjects in this group. CL_{PL} for this subject was lower but half-life was about the same compared to the other subjects.

7. CONCLUSIONS

- Between the 30 and 50 mg/kg dose levels both C_{max} $AUC_{0-\infty}$ appeared to increase in a slightly less than proportional manner with dose increment.
- CL_{PL} and V_{ss} were roughly similar at both dose levels but both were lower at the 30 mg/kg dose level, (b) (4) that at 50 mg/kg. Half-life was similar at both dose levels.
- Given the half-life of about 3 to 4 hours and the rapid decline in concentrations over 24 hours, little if any accumulation would be expected upon multiple dosing once-weekly.
- PK of AVI-4658 given as a 1-hour IV infusion was similar to that previously reported in the DMD patient population (Phase 1b study 4658-28 and study 4658-201).

8. REFERENCES

Gibaldi M. and Perrier D. Pharmacokinetics. 2nd ed. New York, NY: Marcel Dekker; 1982.

Table 2. Summary of Demographics and Infusion Duration by Cohort

Treatment	Subject	Race	Ethnicity	Age	Weight (kg)	Infusion Duration (min)
Eteplirsen 30.0 mg/kg	(b) (6)	Asian	Not Hispanic or Latino	9	24.8	60
	(b) (6)	White	Not Hispanic or Latino	10	35.1	72
	(b) (6)	White	Not Hispanic or Latino	7	42.0	60
	(b) (6)	White	Not Hispanic or Latino	10	35.9	60
	(b) (6)	White	Not Hispanic or Latino	9	39.8	60
	(b) (6)	White	Not Hispanic or Latino	9	39.7	60
			N	6	6	6
			Mean	9.0	36.2	62.0
			SD	1.1	6.2	4.90
			CV%	12.2	17.0	7.90
			Median	9.0	37.8	60.0
Eteplirsen 50.0 mg/kg	(b) (6)	White	Not Hispanic or Latino	7	23.7	56
	(b) (6)	White	Not Hispanic or Latino	8	27.4	60
	(b) (6)	White	Not Hispanic or Latino	7	23.6	64
	(b) (6)	White	Not Hispanic or Latino	10	38.3	60
	(b) (6)	White	Not Hispanic or Latino	10	34.5	60
	(b) (6)	White	Not Hispanic or Latino	9	26.8	68
			N	6	6	6
			Mean	8.5	29.1	61.3
			SD	1.4	6.0	4.13
			CV%	16.2	20.7	6.74
			Median	8.5	27.1	60.0

Source: see Clinical Study Report.

Table 3. Plasma Concentrations of AVI-4658 in ng/mL at Approximately Week 124

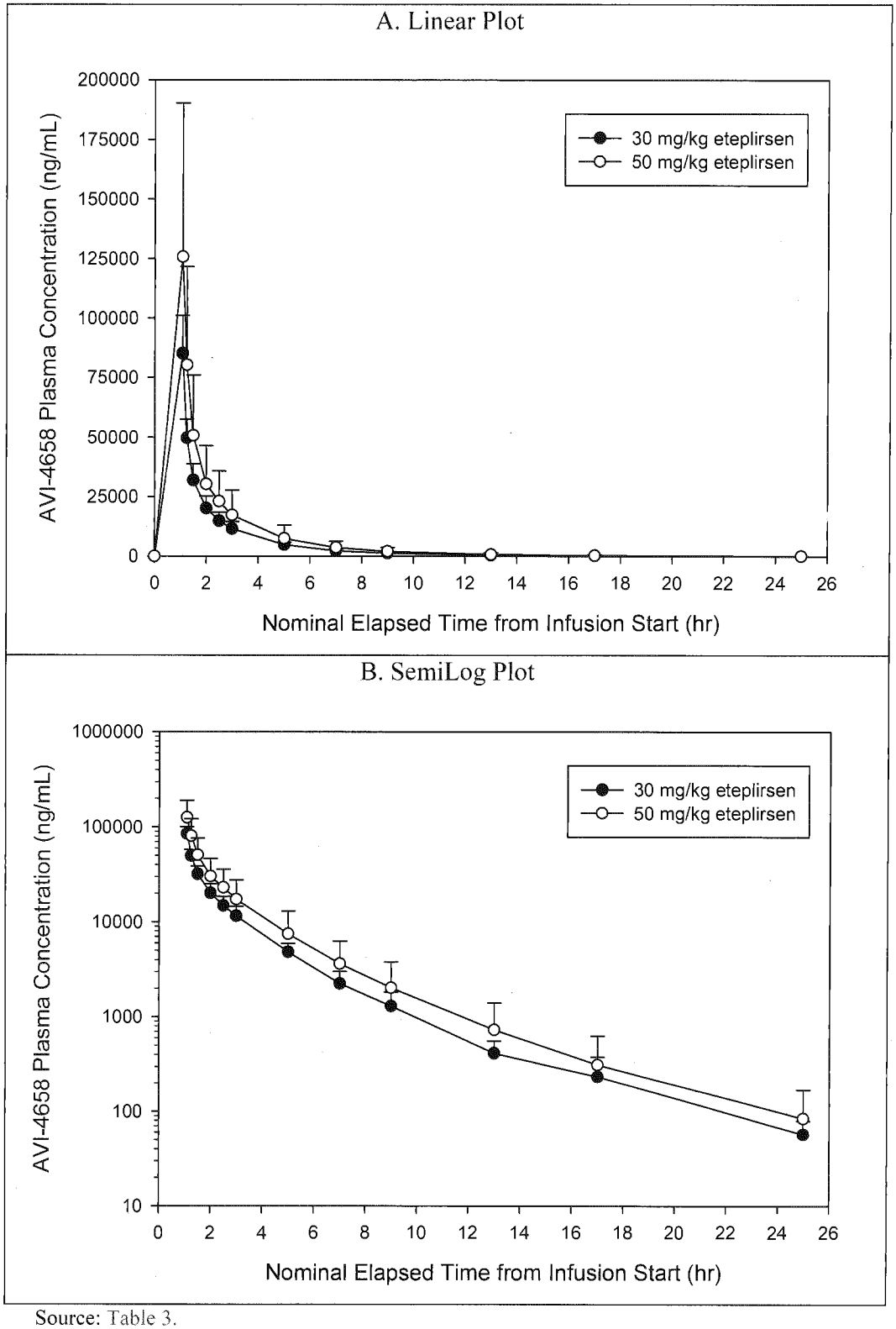
		Nominal Time in Hours (Post End of Infusion / Post Start of Infusion)												
		Predose	0.08333	0.25	0.5	1	1.5	2	4	6	8	12	16	24
Treatment Group	Subject	Predose	1.08333	1.25	1.5	2	2.5	3	5	7	9	13	17	25
30 mg/kg eteplirsen	(b) (6)	BLQ	68,900	37,800	21,600	13,400	10,300	7,560	3,470	1,460	731	239	97	21
	(b) (6)	BLQ	89,300	50,900	28,200	16,300	12,200	9,800	4,020	1,750	921	437	219	60
	(b) (6)	BLQ	63,300	42,100	28,900	17,500	12,200	9,230	4,120	1,570	931	284	156	41
	(b) (6)	BLQ	100,000	58,600	38,400	23,200	17,400	13,800	5,520	2,400	1,370	377	110	65
	(b) (6)	BLQ	102,000	54,700	37,400	24,200	18,200	14,200	5,680	2,920	1,780	587	425	80
	(b) (6)	BLQ	86,900	53,600	37,100	26,200	18,600	14,700	6,150	3,300	2,040	560	399	76
	N	6	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	0	85,067	49,617	31,933	20,133	14,817	11,548	4,827	2,233	1,296	414	234	57
	SD	0	15,913	8,002	6,757	5,093	3,648	3,045	1,091	763	527	142	144	22
	CV%	.	18.7	16.1	21.2	25.3	24.6	26.4	22.6	34.2	40.6	34.3	61.6	39.3
50 mg/kg eteplirsen	(b) (6)	BLQ	92,700	62,800	42,700	25,700	19,200	14,500	5,900	3,420	1,540	524	178	48
	(b) (6)	BLQ	165,000	105,000	59,200	31,400	22,100	15,600	6,240	3,720	1,970	661	295	83
	(b) (6)	BLQ	148,000	84,400	49,600	29,500	22,100	15,600	5,940	2,550	1,230	565	226	45
	(b) (6)	**10.8**	223,000	147,000	96,200	60,700	47,800	37,900	18,700	8,690	5,560	2,050	947	256
	(b) (6)	BLQ	76,800	47,800	28,400	16,800	13,000	9,500	3,890	1,550	810	239	101	38
	(b) (6)	BLQ	49,000	34,500	28,100	17,500	14,100	10,600	4,120	1,810	984	329	131	35
	N	6	6	6	6	6	6	6	6	6	6	6	6	6
	Mean	2	125,750	80,250	50,700	30,267	23,050	17,283	7,465	3,623	2,016	728	313	84
	SD	4	64,610	41,318	25,360	16,083	12,730	10,428	5,594	2,625	1,785	666	318	86
	CV%	.	51.4	51.5	50.0	53.1	55.2	60.3	74.9	72.5	88.5	91.5	101.6	102.2

Note: Suspected outliers marked in bold, excluded from PK parameter derivation and summary statistics.
BLQ = below limit of quantitation which is 10 ng/mL.

Table 4. Plasma Pharmacokinetic Parameters for AVI-4658 in ng/mL at Approximately Week 124

		T_{max}	C_{max}	$AUC_{0\text{-last}}$	$AUC_{0\text{-}\infty}$	$AUC_{0\text{-}24}$	AUC% ext	CL_{PL}	V_{ss}	Half-Life ($t_{1/2}$)	R^2 adjusted	MRT_{∞}
Treatment Group	Subject	hr	ng/mL	hr*ng/mL	hr*ng/mL	hr*ng/mL	%	mL/hr/kg	mL/kg	hr	.	hr
30 mg/kg eteplirsen	(b) (6)	1.08	68,900	92,146	92,253	92,123	0.116	325.2	627.5	3.469	0.9961	1.930
	(b) (6)	1.28	89,300	127,562	127,929	127,482	0.287	234.5	489.4	4.214	0.9994	2.087
	(b) (6)	1.08	63,300	100,183	100,432	100,139	0.247	298.7	645.8	4.245	0.9967	2.162
	(b) (6)	1.08	100,000	145,883	146,120	145,817	0.162	205.3	415.8	2.536	0.9252	2.025
	(b) (6)	1.08	102,000	152,489	152,904	152,400	0.271	196.2	466.5	3.576	0.9770	2.378
	(b) (6)	1.08	86,900	146,869	147,221	146,785	0.239	203.8	512.3	3.219	0.9735	2.514
	N	6	6	6	6	6	6	6	6	6	6	6
	Mean	1.12	85,067	127,522	127,810	127,457	0.220	243.9	526.2	3.543	0.9780	2.183
	SD	0.08	15,913	25,821	25,906	25,798	0.067	54.9	91.5	0.643	0.0281	0.222
	CV%	7.31	18.71	20.25	20.27	20.24	30.43	22.51	17.39	18.15	2.87	10.17
	Median	1.08	88,100	136,723	137,024	136,649	0.243	219.9	500.9	3.523	0.9866	2.125
50 mg/kg eteplirsen	(b) (6)	1.03	92,700	147,894	148,089	147,846	0.132	337.6	746.5	2.832	0.9731	2.211
	(b) (6)	1.08	165,000	219,796	220,280	219,713	0.220	227.0	445.4	4.040	0.9922	1.962
	(b) (6)	1.15	148,000	199,269	199,487	199,215	0.109	250.6	460.1	3.335	0.9990	1.836
	(b) (6)	1.08	223,000	386,723	388,212	386,445	0.383	128.8	345.4	4.031	0.9964	2.682
	(b) (6)	1.08	76,800	107,010	107,263	106,968	0.236	466.1	910.2	4.644	0.9516	1.953
	(b) (6)	1.22	49,000	95,563	95,753	95,519	0.198	522.2	1232.1	3.770	0.9849	2.360
	N	6	6	6	6	6	6	6	6	6	6	6
	Mean	1.11	125,750	192,709	193,181	192,618	0.213	322.1	690.0	3.775	0.9829	2.167
	SD	0.06	64,610	106,966	107,442	106,879	0.097	150.0	339.7	0.628	0.0179	0.317
	CV%	5.84	51.38	55.51	55.62	55.49	45.66	46.58	49.24	16.64	1.83	14.61
	Median	1.08	120,350	173,582	173,788	173,531	0.209	294.1	603.3	3.900	0.9885	2.087

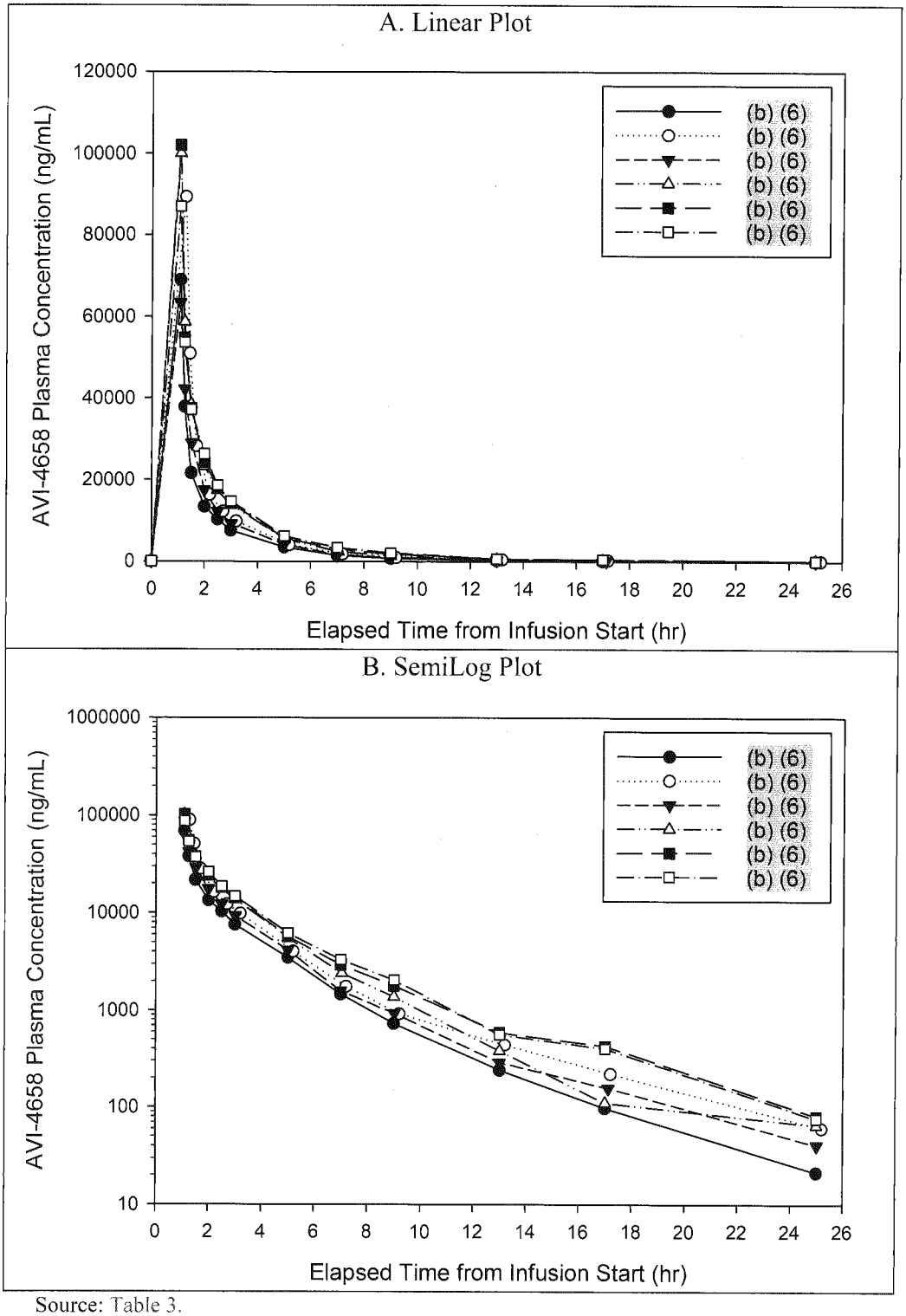
Figure 1. Mean (± SD) AVI-4658 Plasma Concentrations at Approximately Week 124



Source: Table 3.

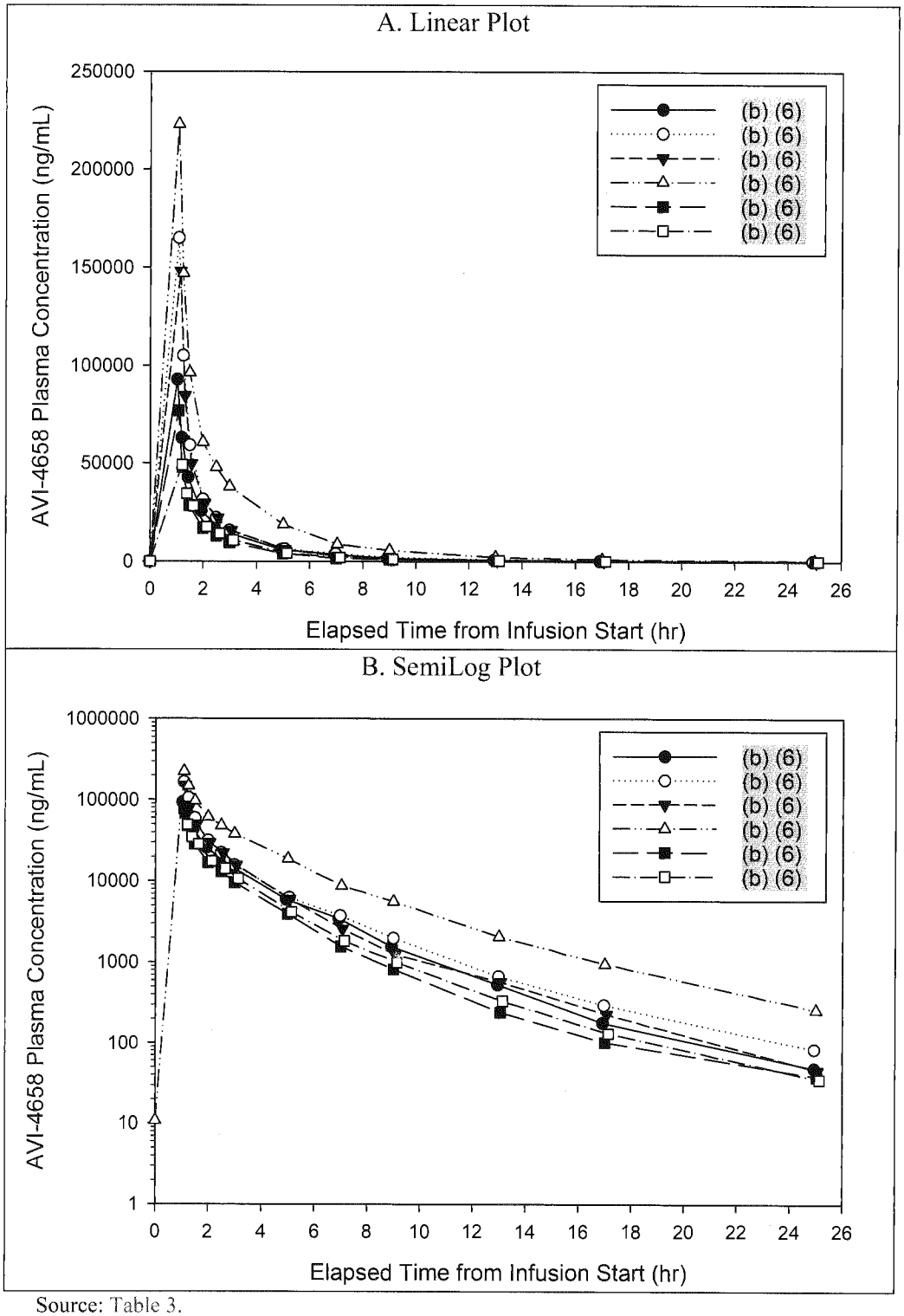
INDIVIDUAL SUBJECT PLOTS

Figure 2. Individual AVI-4658 Plasma Concentrations at Approximately Week 124 - 30 mg/kg -



Source: Table 3.

Figure 3. Individual AVI-4658 Plasma Concentrations at Approximately Week 124 - 50 mg/kg -



Source: Table 3.

APPENDIX

PK LISTINGS

Listing 1. Plasma Sampling Times for AVI-4658 at Approximately Week 124

		Nominal Time (hr)					
Treatment	Subject	From End of Infusion	From Start of Infusion	Time Point	Collection Date	Collection Time	Actual Elapsed Time (hr)
Eteplirsen 30.0 mg/kg	(b) (6)	-0.5	0	<30 min Prior to Dose	7/10/2014	10:31 AM	-0.1667
		0.12	1.0833	5 min Post Dose	7/10/2014	11:46 AM	1.0833
		0.25	1.25	15 min Post Dose	7/10/2014	11:56 AM	1.2500
		0.5	1.5	30 min Post Dose	7/10/2014	12:11 PM	1.5000
		1	2	60 min Post Dose	7/10/2014	12:41 PM	2.0000
		1.5	2.5	90 min Post Dose	7/10/2014	1:11 PM	2.5000
		2	3	2 hour Post Dose	7/10/2014	1:41 PM	3.0000
		4	5	4 hour Post Dose	7/10/2014	3:41 PM	5.0000
		6	7	6 hour Post Dose	7/10/2014	5:41 PM	7.0000
		8	9	8 hour Post Dose	7/10/2014	7:41 PM	9.0000
		12	13	12 hour Post Dose	7/10/2014	11:41 PM	13.0000
		16	17	16 hour Post Dose	7/11/2014	3:41 AM	17.0000
		24	25	24 hour Post Dose	7/11/2014	11:41 AM	25.0000
	(b) (6)	-0.5	0	<30 min Prior to Dose	7/9/2014	9:10 AM	-0.0500
		0.12	1.0833	5 min Post Dose	7/9/2014	10:30 AM	1.2833
		0.25	1.25	15 min Post Dose	7/9/2014	10:40 AM	1.4500
		0.5	1.5	30 min Post Dose	7/9/2014	10:55 AM	1.7000
		1	2	60 min Post Dose	7/9/2014	11:25 AM	2.2000
		1.5	2.5	90 min Post Dose	7/9/2014	11:55 AM	2.7000
		2	3	2 hour Post Dose	7/9/2014	12:25 PM	3.2000
		4	5	4 hour Post Dose	7/9/2014	2:25 PM	5.2000
		6	7	6 hour Post Dose	7/9/2014	4:25 PM	7.2000
		8	9	8 hour Post Dose	7/9/2014	6:25 PM	9.2000
		12	13	12 hour Post Dose	7/9/2014	10:25 PM	13.2000
		16	17	16 hour Post Dose	7/10/2014	2:25 AM	17.2000
		24	25	24 hour Post Dose	7/10/2014	10:25 AM	25.2000
	(b) (6)	-0.5	0	<30 min Prior to Dose	7/9/2014	8:59 AM	-0.1833
		0.12	1.0833	5 min Post Dose	7/9/2014	10:15 AM	1.0833
		0.25	1.25	15 min Post Dose	7/9/2014	10:25 AM	1.2500
		0.5	1.5	30 min Post Dose	7/9/2014	10:40 AM	1.5000
		1	2	60 min Post Dose	7/9/2014	11:10 AM	2.0000
		1.5	2.5	90 min Post Dose	7/9/2014	11:40 AM	2.5000

Listing 1. Plasma Sampling Times for AVI-4658 at Approximately Week 124

		Nominal Time (hr)					
Treatment	Subject	From End of Infusion	From Start of Infusion	Time Point	Collection Date	Collection Time	Actual Elapsed Time (hr)
		2	3	2 hour Post Dose	7/9/2014	12:10 PM	3.0000
		4	5	4 hour Post Dose	7/9/2014	2:10 PM	5.0000
		6	7	6 hour Post Dose	7/9/2014	4:10 PM	7.0000
		8	9	8 hour Post Dose	7/9/2014	6:10 PM	9.0000
		12	13	12 hour Post Dose	7/9/2014	10:10 PM	13.0000
		16	17	16 hour Post Dose	7/10/2014	2:10 AM	17.0000
		24	25	24 hour Post Dose	7/10/2014	10:10 AM	25.0000
	(b) (6)	-0.5	0	<30 min Prior to Dose	7/9/2014	8:47 AM	-0.2167
		0.12	1.0833	5 min Post Dose	7/9/2014	10:05 AM	1.0833
		0.25	1.25	15 min Post Dose	7/9/2014	10:15 AM	1.2500
		0.5	1.5	30 min Post Dose	7/9/2014	10:30 AM	1.5000
		1	2	60 min Post Dose	7/9/2014	11:00 AM	2.0000
		1.5	2.5	90 min Post Dose	7/9/2014	11:30 AM	2.5000
		2	3	2 hour Post Dose	7/9/2014	12:00 PM	3.0000
		4	5	4 hour Post Dose	7/9/2014	2:00 PM	5.0000
		6	7	6 hour Post Dose	7/9/2014	4:00 PM	7.0000
		8	9	8 hour Post Dose	7/9/2014	6:00 PM	9.0000
		12	13	12 hour Post Dose	7/9/2014	10:00 PM	13.0000
		16	17	16 hour Post Dose	7/10/2014	2:00 AM	17.0000
		24	25	24 hour Post Dose	7/10/2014	10:00 AM	25.0000
	(b) (6)	-0.5	0	<30 min Prior to Dose	7/15/2014	9:14 AM	-0.3500
		0.12	1.0833	5 min Post Dose	7/15/2014	10:40 AM	1.0833
		0.25	1.25	15 min Post Dose	7/15/2014	10:50 AM	1.2500
		0.5	1.5	30 min Post Dose	7/15/2014	11:06 AM	1.5167
		1	2	60 min Post Dose	7/15/2014	11:35 AM	2.0000
		1.5	2.5	90 min Post Dose	7/15/2014	12:05 PM	2.5000
		2	3	2 hour Post Dose	7/15/2014	12:36 PM	3.0167
		4	5	4 hour Post Dose	7/15/2014	2:35 PM	5.0000
		6	7	6 hour Post Dose	7/15/2014	4:35 PM	7.0000
		8	9	8 hour Post Dose	7/15/2014	6:36 PM	9.0167
		12	13	12 hour Post Dose	7/15/2014	10:35 PM	13.0000
		16	17	16 hour Post Dose	7/16/2014	2:43 AM	17.1333
		24	25	24 hour Post Dose	7/16/2014	10:36 AM	25.0167

Listing 1. Plasma Sampling Times for AVI-4658 at Approximately Week 124

		Nominal Time (hr)					
Treatment	Subject	From End of Infusion	From Start of Infusion	Time Point	Collection Date	Collection Time	Actual Elapsed Time (hr)
	(b) (6)	-0.5	0	<30 min Prior to Dose	7/7/2014	7:51 AM	-0.3167
		0.12	1.0833	5 min Post Dose	7/7/2014	9:15 AM	1.0833
		0.25	1.25	15 min Post Dose	7/7/2014	9:25 AM	1.2500
		0.5	1.5	30 min Post Dose	7/7/2014	9:40 AM	1.5000
		1	2	60 min Post Dose	7/7/2014	10:10 AM	2.0000
		1.5	2.5	90 min Post Dose	7/7/2014	10:40 AM	2.5000
		2	3	2 hour Post Dose	7/7/2014	11:10 AM	3.0000
		4	5	4 hour Post Dose	7/7/2014	1:10 PM	5.0000
		6	7	6 hour Post Dose	7/7/2014	3:12 PM	7.0333
		8	9	8 hour Post Dose	7/7/2014	5:10 PM	9.0000
		12	13	12 hour Post Dose	7/7/2014	9:10 PM	13.0000
		16	17	16 hour Post Dose	7/8/2014	1:10 AM	17.0000
		24	25	24 hour Post Dose	7/8/2014	9:10 AM	25.0000
Eteplirsen 50.0 mg/kg	(b) (6)	-0.5	0	<30 min Prior to Dose	6/23/2014	9:23 AM	-0.3167
		0.12	1.0833	5 min Post Dose	6/23/2014	10:44 AM	1.0333
		0.25	1.25	15 min Post Dose	6/23/2014	10:54 AM	1.2000
		0.5	1.5	30 min Post Dose	6/23/2014	11:08 AM	1.4333
		1	2	60 min Post Dose	6/23/2014	11:38 AM	1.9333
		1.5	2.5	90 min Post Dose	6/23/2014	12:08 PM	2.4333
		2	3	2 hour Post Dose	6/23/2014	12:38 PM	2.9333
		4	5	4 hour Post Dose	6/23/2014	2:38 PM	4.9333
		6	7	6 hour Post Dose	6/23/2014	4:38 PM	6.9333
		8	9	8 hour Post Dose	6/23/2014	6:38 PM	8.9333
		12	13	12 hour Post Dose	6/23/2014	10:39 PM	12.9500
		16	17	16 hour Post Dose	6/24/2014	2:37 AM	16.9167
		24	25	24 hour Post Dose	6/24/2014	10:38 AM	24.9333
	(b) (6)	-0.5	0	<30 min Prior to Dose	7/8/2014	9:40 AM	-0.0167
		0.12	1.0833	5 min Post Dose	7/8/2014	10:46 AM	1.0833
		0.25	1.25	15 min Post Dose	7/8/2014	10:56 AM	1.2500
		0.5	1.5	30 min Post Dose	7/8/2014	11:11 AM	1.5000
		1	2	60 min Post Dose	7/8/2014	11:41 AM	2.0000
		1.5	2.5	90 min Post Dose	7/8/2014	12:11 PM	2.5000
		2	3	2 hour Post Dose	7/8/2014	12:41 PM	3.0000

Listing 1. Plasma Sampling Times for AVI-4658 at Approximately Week 124

		Nominal Time (hr)					
Treatment	Subject	From End of Infusion	From Start of Infusion	Time Point	Collection Date	Collection Time	Actual Elapsed Time (hr)
		4	5	4 hour Post Dose	7/8/2014	2:44 PM	5.0500
		6	7	6 hour Post Dose	7/8/2014	4:40 PM	6.9833
		8	9	8 hour Post Dose	7/8/2014	6:41 PM	9.0000
		12	13	12 hour Post Dose	7/8/2014	10:40 PM	12.9833
		16	17	16 hour Post Dose	7/9/2014	2:39 AM	16.9667
		24	25	24 hour Post Dose	7/9/2014	10:37 AM	24.9333
	(b) (6)	-0.5	0	<30 min Prior to Dose	7/14/2014	7:15 AM	-1.3333
		0.12	1.0833	5 min Post Dose	7/14/2014	9:40 AM	1.0833
		0.25	1.25	15 min Post Dose	7/14/2014	9:50 AM	1.2500
		0.5	1.5	30 min Post Dose	7/14/2014	10:05 AM	1.5000
		1	2	60 min Post Dose	7/14/2014	10:35 AM	2.0000
		1.5	2.5	90 min Post Dose	7/14/2014	11:05 AM	2.5000
		2	3	2 hour Post Dose	7/14/2014	11:35 AM	3.0000
		4	5	4 hour Post Dose	7/14/2014	1:35 PM	5.0000
		6	7	6 hour Post Dose	7/14/2014	3:37 PM	7.0333
		8	9	8 hour Post Dose	7/14/2014	5:35 PM	9.0000
		12	13	12 hour Post Dose	7/14/2014	9:35 PM	13.0000
		16	17	16 hour Post Dose	7/15/2014	1:35 AM	17.0000
		24	25	24 hour Post Dose	7/15/2014	9:35 AM	25.0000
	(b) (6)	-0.5	0	<30 min Prior to Dose	7/11/2014	1:50 PM	-0.4000
		0.12	1.0833	5 min Post Dose	7/11/2014	3:27 PM	1.2167
		0.25	1.25	15 min Post Dose	7/11/2014	3:37 PM	1.3833
		0.5	1.5	30 min Post Dose	7/11/2014	3:52 PM	1.6333
		1	2	60 min Post Dose	7/11/2014	4:22 PM	2.1333
		1.5	2.5	90 min Post Dose	7/11/2014	4:52 PM	2.6333
		2	3	2 hour Post Dose	7/11/2014	5:22 PM	3.1333
		4	5	4 hour Post Dose	7/11/2014	7:22 PM	5.1333
		6	7	6 hour Post Dose	7/11/2014	9:22 PM	7.1333
		8	9	8 hour Post Dose	7/11/2014	11:22 PM	9.1333
		12	13	12 hour Post Dose	7/12/2014	3:22 AM	13.1333
		16	17	16 hour Post Dose	7/12/2014	7:22 AM	17.1333
		24	25	24 hour Post Dose	7/12/2014	3:22 PM	25.1333
	(b) (6)	-0.5	0	<30 min Prior to Dose	6/23/2014	11:46 AM	-0.5167

Listing 1. Plasma Sampling Times for AVI-4658 at Approximately Week 124

		Nominal Time (hr)					
Treatment	Subject	From End of Infusion	From Start of Infusion	Time Point	Collection Date	Collection Time	Actual Elapsed Time (hr)
		0.12	1.0833	5 min Post Dose	6/23/2014	1:26 PM	1.1500
		0.25	1.25	15 min Post Dose	6/23/2014	1:36 PM	1.3167
		0.5	1.5	30 min Post Dose	6/23/2014	1:51 PM	1.5667
		1	2	60 min Post Dose	6/23/2014	2:21 PM	2.0667
		1.5	2.5	90 min Post Dose	6/23/2014	2:51 PM	2.5667
		2	3	2 hour Post Dose	6/23/2014	3:21 PM	3.0667
		4	5	4 hour Post Dose	6/23/2014	5:21 PM	5.0667
		6	7	6 hour Post Dose	6/23/2014	7:21 PM	7.0667
		8	9	8 hour Post Dose	6/23/2014	9:21 PM	9.0667
		12	13	12 hour Post Dose	6/24/2014	1:21 AM	13.0667
		16	17	16 hour Post Dose	6/24/2014	5:21 AM	17.0667
		24	25	24 hour Post Dose	6/24/2014	1:21 PM	25.0667
	(b) (6)	-0.5	0	<30 min Prior to Dose	7/11/2014	9:02 AM	-0.1333
		0.12	1.0833	5 min Post Dose	7/11/2014	10:15 AM	1.0833
		0.25	1.25	15 min Post Dose	7/11/2014	10:23 AM	1.2167
		0.5	1.5	30 min Post Dose	7/11/2014	10:39 AM	1.4833
		1	2	60 min Post Dose	7/11/2014	11:10 AM	2.0000
		1.5	2.5	90 min Post Dose	7/11/2014	11:40 AM	2.5000
		2	3	2 hour Post Dose	7/11/2014	12:10 PM	3.0000
		4	5	4 hour Post Dose	7/11/2014	2:09 PM	4.9833
		6	7	6 hour Post Dose	7/11/2014	4:10 PM	7.0000
		8	9	8 hour Post Dose	7/11/2014	6:10 PM	9.0000
		12	13	12 hour Post Dose	7/11/2014	10:13 PM	13.0500
		16	17	16 hour Post Dose	7/12/2014	2:10 AM	17.0000
		24	25	24 hour Post Dose	7/12/2014	10:12 AM	25.0333

Notes: Nominal elapsed time was computed relative to both the end and start of infusion.
Actual elapsed time was computed relative to the start date and clock time of infusion.