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ORIGINAL PAPER

Population pharmacokinetic analysis of danvatirsen supporting flat dosing switch

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Abstract

Danvatirsen is a Generation 2.5 antisense oligonucleotide under clinical development. Population PK modelling was conducted using data from 3 available danvatirsen Phase I/II studies in oncology patients to investigate the impact of flat dosing on exposure compared to ideal body weight-based dosing. A total of 126 patients who received danvatirsen doses ranging from 1 to 4 mg/kg as monotherapy or in combination with durvalumab, most at 3 mg/kg (n = 70), was used in the danvatirsen population PK analysis. A 2-compartment model with linear elimination described the data well. Covariate analysis revealed ideal body weight was not a significant covariate on the PK of danvatirsen; nor was age, sex or race. The model-based simulation suggested that steady state weekly *AUC* and *Cmax* were very similar between 3 mg/kg and 200 mg flat dosing (geometric mean of *AUC*: 62.5 vs. 63.4 mg h/L and *Cmax*: 26.2 vs. 26.5 mg/L for two dose groups) with slightly less overall between-subject variability in the flat dosing regimen. The switch to flat dosing was approved by multiple regulatory agencies, including FDA, EMA, PMDA and ANSM. Several ongoing studies have been evaluating flat dosing. Interim analysis from an ongoing study (D5660C00016, NCT03421353) has shown the observed steady state concentration from 200 mg flat dose is in agreement with the model predictions. The population PK model could be further utilized in subsequent exposure-response efficacy and safety modelling.

Keywords Dosing strategy · Population PK · Oncology

Introduction

Danvatirsen (AZD9150, ISIS 481464) is a sixteen-nucleotide generation 2.5 antisense oligonucleotide (ASO) that targets human signal transducer and activator of transcription 3 (STAT3) mRNA which at low nanomolar concentrations decreases STAT3 mRNA levels in several cancer cell lines growing in culture. Danvatirsen is a phosphorothioate modified chimeric ASO with a 10-base central oligonucleotide core that supports mediated metabolism, flanked by 3 constrained ethyl (cEt)-modified nucleosides on both the 5′ and 3′ ends [1–3]. The novel cEt chemical modification incorporated into danvatirsen is anticipated, based on extensive preclinical studies, to confer properties similar to second generation 2′-methoxyethyl (2′-MOE) chemical modifications, but with a potential for enhanced potency. Danvatirsen is currently under clinical development in combination with durvalumab (PD-L1 antibody) in squamous cell carcinoma subtype (HNSCC), non-small cell lung cancer (NSCLC), bladder cancer and relapsed or refractory diffuse large B-cell lymphoma (DLBCL).

Second-generation ASOs following parenteral administration exhibit very similar pharmacokinetic (PK) properties [4] including multi-phasic disposition plasma profiles

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with rapid distribution half-lives (in hours) and long terminal elimination half-lives (in weeks). The ASOs with IV administration were typically administered within 1–3 h and the mean plasma clearance (CL) ranged from 1.9 and 4 L/h [4]. The clinical PK profile of danvatirsen has been characterized following two 3-h infusion studies and one 1-h infusion study. Following infusion, maximum danvatirsen plasma concentrations (*Cmax*) were observed with a median time to maximum concentration (t_{max}) occurring at the end of the infusion, as expected. After the end of the infusion, mean plasma concentrations of danvatirsen declined in a bi-phasic fashion with time, with an initial, relatively fast distribution phase (half-life of 2–3 h) that dominated the plasma clearance followed by a slower elimination phase. Mean danvatirsen plasma concentrations decreased > 90% from the *Cmax* by 24 h after the infusion. As the dose increased from 1 to 4 mg/kg, the mean *AUC* and *Cmax* values increased proportionally over the entire dose range. Overall, the interim human PK data for danvatirsen is consistent with the expected PK profile for ASOs [4].

The dose of 3 mg/kg was determined as safe and tolerable in patients with advanced solid malignancies [with the exception of hepatocellular carcinoma (HCC)] and was further evaluated in the dose expansion of the study in relapsed/metastatic squamous-cell carcinoma of head and neck (SCCHN) (data on file). Danvatirsen was dosed at 3 mg/kg ideal body weight (IBW) with three loading doses on day 1, 3 and 5 in week 1 of treatment and every week thereafter. The objective of the current analysis was to conduct population PK modelling using data from available danvatirsen studies in order to investigate the impact of flat dosing on exposure compared to IBW-based dosing.

Methods

Overview of the studies and dataset

Danvatirsen single dose and steady-state plasma concentration data from three danvatirsen Phase 1/2 studies were included in this analysis. Two of the studies completed enrolment [Study 481464-CS1 (NCT01563302) and Study D5660C00001 (NCT01839604)] and one [Study D5660C00004 (NCT02499328)] is ongoing (Table 1). The studies are referred to as diffuse large B-cell lymphoma (DLBCL), hepatocellular carcinoma (HCC) and squamous-cell carcinoma in head and neck (SCCHN), respectively thereafter.

In the DLBCL study, the doses of 2 and 4 mg/kg were administered intravenously over 3 h on day 1, 3 and 5 in week 1 and once weekly afterwards. In HCC and SCCHN studies, IV infusion of 1–3 mg/kg over 3 h and 2 and 3 mg/kg over 1 h were administered, respectively with same dosing schedule as DLBCL. The infusion time was shortened to 1 h in the later study to minimize the duration of patient's clinic stay on the study day, as the patient has other investigational drugs (tremelimumab and durvalumab) to be administered intravenously 1 h after end of danvatirsen IV infusion. Danvatirsen PK samples were taken at predose, 1, 1.5, 3 (end of infusion), 3.5, 4, 6, 8, 24 h after the start of infusion on day 1 and predose samples on other occasions. Similarly, in SCCHN study, PK samples were collected at predose and 0.5, 1 (end of infusion), 2, 4, 6 and 48 h after the start of the first dose infusion and predose and at 0.5, 1, 2, 4, and 6 h after the start of the infusion on cycle 2 day 1 (day 36 after 1st dose). Since danvatirsen is metabolized by endonucleases and exonucleases then excreted in urine, it is unlikely to have any drug-drug interaction when danvatirsen was administered in combination with durvalumab in the SCCHN study.

The institutional review boards or independent ethics committees of all investigational sites approved all clinical studies, and the studies were performed in accordance with the Declaration of Helsinki, Good Clinical Practice, and the AstraZeneca Policy on Bioethics.

PK sample analysis

Blood samples for PK sample analysis were drawn at prespecified time points following single dose administration and predose at alternate cycles. Samples were assayed by PPD (Richmond, VA, United States) using a hybridization enzyme-linked immunosorbent assay methodology. The method is applicable to the quantification of danvatirsen within a nominal range of 1.00–100 ng/mL, with the low end of the range defining the lower limit of quantification (LLOQ) and requires a 25-µL human EDTA plasma aliquot. Where appropriate, due to concentrations above the upper quantification limit, samples were diluted up to 4000-fold with blank human plasma and then quantified within the validated calibration range. In the studies included in this paper, all samples were analysed within the 1913 days demonstrated long-term storage stability in human plasma containing dipotassium EDTA at − 80 ± 10 °C and with an intra-batch and inter-batch precision, reported as coefficient of variation (CV), below the 20% (except ≤ 25% at LLOQ) acceptance criteria at all levels [5]. The overall precision for the QC samples (undiluted) at all three concentration levels was ≤ 19.1% and the overall bias ranged between − 7.2 and 1.7%. The overall precision for the dilution QC sample was 11.1% and the overall bias was − 1.5%.

Table 1 Studies included in this analysis

Study code	Study title	Dose and administration	PK sampling
ISIS 481464-CS1 (DLBCL)	A Phase 1/2 Study of ISIS 481464, an Antisense Oligonucleotide Inhibitor of STAT3, Administered to Patients with Advanced Cancers	2 and 4 mg/kg, 3 h IV infusion on day 1, 3, 5 and then once weekly	Day 1: predose, 1, 1.5, 3 (end of infusion), 3.5, 4, 6, 8, 24 h after the start of infusion Predose samples on other occasions
D5660C00001 (HCC)	A Phase I/Ib, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of danvatirsen in Patients with Advanced/Metastatic Hepatocellular Carcinoma	1, 1.5, 2, 2.5 and 3 mg/kg, 3 h IV infusion on day 1, 3, 5 and then once weekly	Day 1: predose, 1, 1.5, 3 (end of infusion), 3.5, 4, 6, 8, 24 h after the start of infusion Predose samples on other occasions
D5660C00004 (SCCHN) (ongoing)	A Phase 1b/2, Open-Label, Multicentre Study Assessing the Safety, Tolerability, Pharmacokinetics, and Preliminary Anti-tumor Activity of MEDI4736 in combination With danvatirsen or AZD5069 in Patients With Advanced Solid Malignancies and Subsequently Comparing danvatirsen and AZD5069 Both as monotherapy and in Combination With MEDI4736 as Second Line Treatment in Patients With Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck	2 and 3 mg/kg, 1 h IV infusion on day 1, 3, 5 and then once weekly	Lead-in, Day − 7: Predose and at 0.5, 1 (end of infusion), 2, 4, and 6 h after the start of the infusion Lead-in, Day − 5: At 48 h after the start of the first infusion (on Day − 7) and before the second infusion (on Day − 5) Cycle 2, Day 1: Predose and at 0.5, 1, 2, 4, and 6 h after the start of the infusion Predose samples on other occasions

Population PK model development

The characterization of danvatirsen PK started with exploration of danvatirsen plasma concentration profile. Graphical analysis of a semi-log plot suggested that the data follows a 2-compartment structure model. Both 2-compartment and 3-compartment structure model were tested in the analysis. There were 1.8% of plasma concentrations below limit of quantification (BLOQ), which were excluded from PK analysis. The inter-individual variability (IIV) of the PK parameters was incorporated using a lognormal random effect. The residual variability for danvatirsen plasma concentrations was evaluated using additive, proportional, and a combined additive and proportional model.

The potential covariate effect on danvatirsen PK was evaluated by a stepwise forward selection and backward elimination procedure using the stepwise covariate modeling (SCM) approach. The relationship between continuous covariates and the typical value of PK parameters was represented using power models:

$$\theta_{tv} = \theta_{ref} \times \left(\frac{Cov_x}{Med}\right)^{\theta_{cov}},$$

where θ_{ref} and are fixed-effect parameters and Med is the median value for covariate Cov_x.

The relationship between categorical covariates and the typical value of PK parameters was modeled as a constant proportional model:

$$\theta_{tv} = \theta_{ref} \times (1 + \theta_{cov} Cov_x)$$

The P values for forward selection was set at 0.05 and backward elimination was set at 0.001. These correspond to a decrease in the objective function value (OFV) of forward selection of 3.84 units and backward elimination of 10.83 units. Patient characteristics including age, ideal body weight, race and sex were tested on relevant danvatirsen PK parameters.

The final model was evaluated by several assessment methods, including changes in the objective function value, successful convergence, visual inspection of diagnostic plots, precision of parameter estimates, covariance estimation and plausibility of parameter estimates. The predictive performance of the final model was assessed with a visual predictive check (VPC) using simulation of 1000 new data sets [6]. The final model outcomes were also evaluated using nonparametric bootstrap approach using 1000 replicate bootstrap data sets [7].

Simulation for danvatirsen flat dosing

The impact of IBW-based dose at the danvatirsen RP2D of 3 mg/kg versus a flat dose of 200 mg was evaluated by comparing simulated steady state area under the curve (AUC) and maximum serum concentration ($Cmax$) using the population PK model. A total of 1000 patients for each dosing regimen was simulated using ideal body weight distribution of 47.2–82.7 kg based on the patients demographics from the population PK dataset.

The flat dose was later tested in an ongoing Phase Ib/II study (D5660C00016/Study 16, NCT03421353) in advanced, solid tumors and will be tested in patients with non-small-cell lung cancer (NSCLC). An interim analysis was performed to evaluate the observed concentrations in study 16 in comparison to the simulated concentrations after 200 mg dose.

Software

The nonlinear mixed-effects modelling software package (NONMEM), Version 7.3.0 (Icon Development Solutions, Ellicott City, MD, USA, 2009) was used in the population PK analysis. The first-order conditional estimation method with between and within subject random effect interaction (FOCEI) was used for NONMEM computations. R, Version 3.1.2 or greater (R-project, www.r-project.org) and the R packages Xpose (xpose.sourceforge.net), as well as Perl-speaks-NONMEM (PsN), Version 4.2.0 (www.psn.sourceforge.net) were used for the exploratory analysis, executing NONMEM runs and post-processing of NONMEM output, e.g., to assess goodness-off-it.

Results

Final population PK data set

A total of 1282 danvatirsen plasma concentrations from 123 patients was included in the population PK analysis dataset. The doses administered were 1, 1.5, 2, 3, 4 mg/kg. The summary of patient covariates from each study is shown in Table 2. Mean age of the patients was 61 years; most (75%) were male. The mean ideal body weight in 3 studies was similar, ranging from 59 to 67 kg. HCC study was in Asian population and SCCHN and DLBCL studies are in predominantly White population.

Population PK model

The final PopPK base model was a linear 2-compartment disposition model characterising by clearance (CL), volume of distribution of the central compartment (V_1), inter-compartment clearance (Q), volume of distribution of the peripheral compartment (V_2). A proportional error was also included in the model. The 2-compartment model was selected over 3-compartment model because the 3-compartment model didn't not significantly improve the objective function value (ΔOFV of − 2.1), even by adding 4 additional parameters to the model as comparing to 2-compartment model.

The IIV variability was included on PK parameters of CL, Q and V_2. Adding inter occasional variability (IOV) on V_2 significantly improved the model (ΔOFV: − 65.7). However, the variability of V_1 was negligible, adding IIV on V_1 did not significantly improve objective function value (ΔOFV of − 3.2).

The potential covariate effect was first examined by diagnostic plots of IIVs versus the potential covariates (age, sex, ideal body weight, race). No apparent trends of potential covariate effects on danvatirsen PK were observed. Specifically, the correlation between PK parameters (CL, Q, V2) and ideal body weight are shown in Fig. 1. Further evaluations of each covariate against CL,

Table 2 Summary of patient demographic data with mean, SD and range for continuous variable and N (%) for categorical variables

	Study 1 HCC	Study 4 SCCHN	Study 101 DLBCL	Total
Number of subjects	38	65	20	123
Age (years)				
Mean ± SD	59.1 ± 10.6	62.0 ± 7.93	63.9 ± 15.0	61.4 ± 10.2
Range	37–77	43–82	26–85	26–85
Ideal body weight (kg)				
Mean ± SD	62.9 ± 6.14	66.6 ± 8.93	58.5 ± 12.4	64.1 ± 9.32
Range	48.4–78.2	46.1–82.8	38.5–82.2	38.5–82.8
Sex				
Male	33 (86.8%)	49 (75.4%)	10 (50%)	92 (74.8%)
Female	5 (13.2%)	16 (24.6%)	10 (50%)	31 (25.2%)
Race				
White	0	63 (97.0%)	19 (95%)	82 (66.7%)
Black	0	1 (1.5%)	1 (5%)	2 (1.6%)
Asian	38 (100%)	1 (1.5%)	0	39 (31.7%)

HCC hepatocellular carcinoma, *SCCHN* squamous-cell carcinoma in head and neck, *DLBCL* diffuse large B-Cell lymphoma

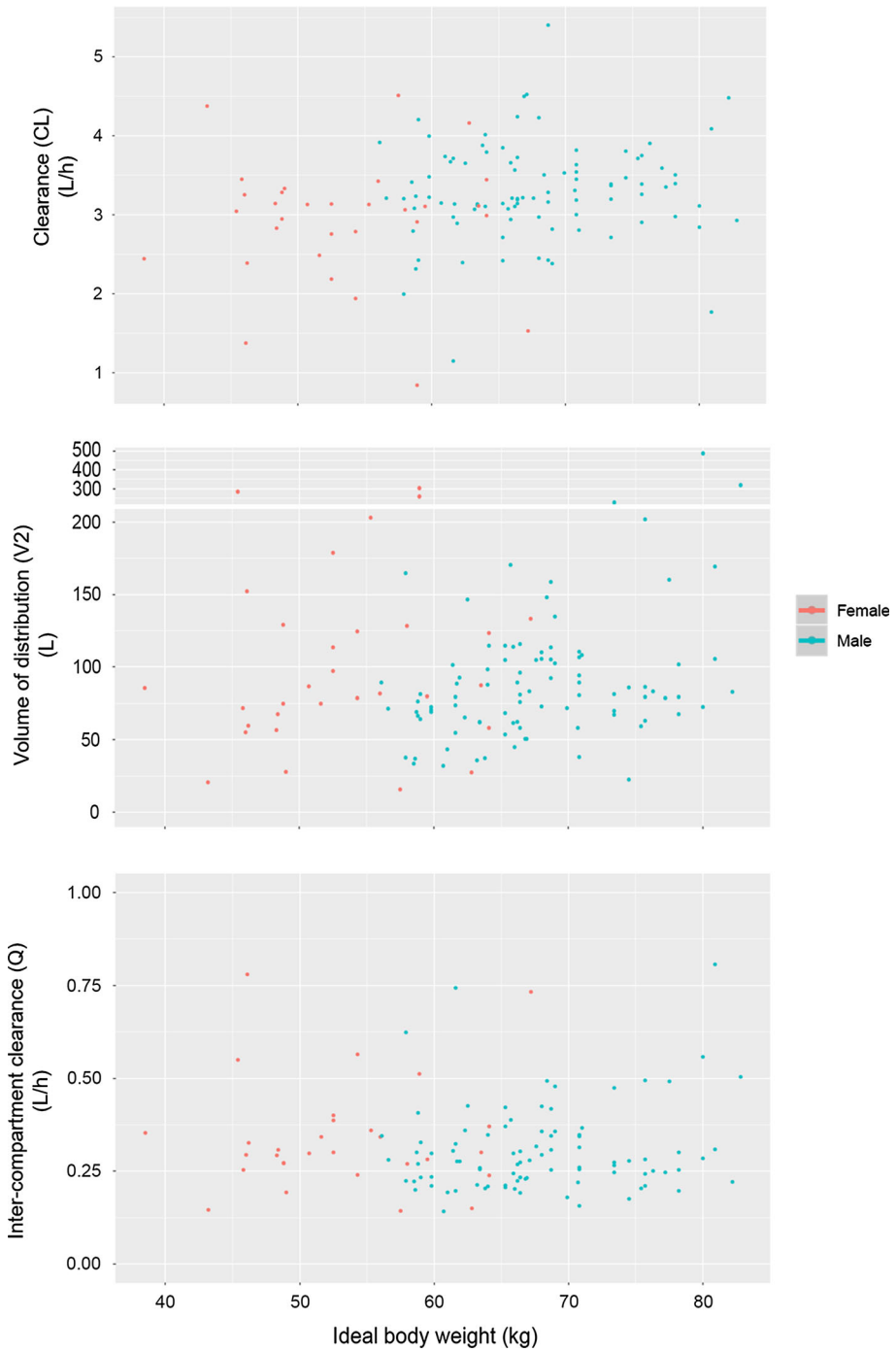

Fig. 1 Relationship between CL, V2, and Q versus IBW

Q and V_2 were performed through the SCM procedure. None of the covariates were found to significantly impact danvatirsen PK. Consequently, the base model was deemed the final PK model.

The parameter estimates of the final model and non-parametric bootstrap (n = 1000) results are shown in Table 3. The parameters were estimated with good precision (relative standard error < 20%). Shrinkage of the parameters were reasonable as well, all were < 20% except IIV and IOV of V_2. This is expected due to long terminal half-life and lack of sufficient data point at later time, which indicates a large V_2 with moderate variability. The typical diagnostic plots for the final model of danvatirsen indicate a reasonable goodness-of-fit to the data (Fig. 2). The model individual fit from 4 typical patients are shown in Fig. 3. The slight trend for CWRES versus TIME at far end might be due to limited number of data points. The VPC of the final model suggests that central tendency and

Table 3 Parameter estimates for the final PK model

Parameter	Description	Final model		Bootstrap estimates		
		Estimate	RSE (%)	Median	2.5%	97.5%
θ1	CL, clearance (L/h)	3.11	3.86	3.09	2.88	3.33
θ2	V_1, central volume of distribution (L)	5.56	3.02	5.57	5.25	5.93
θ3	Q, inter-compartment clearance (L/h)	0.30	5.17	0.30	0.27	0.35
θ4	V_2, peripheral volume of distribution (L)	87.3	7.82	88.3	72.5	105.8
Inter-individual variability (CV%)						
$\omega_{1,1}$	Inter-individual variability of CL	27.0	19.1	27.9	18.6	37.2
$\omega_{2,2}$	Inter-individual variability of Q	47.6	17.5	48.3	35.0	60.0
$\omega_{3,3}$	Inter-individual variability of V_2	63.9	16.4	63.6	46.1	78.0
Inter-occasional variability (CV%)						
$\omega_{4,4}$	Inter-occasional variability of V_2	37.9	31.6	37.6	27.5	49.4
Residual variability						
θ5	Proportional error	0.35	9.31	0.34	0.29	0.41

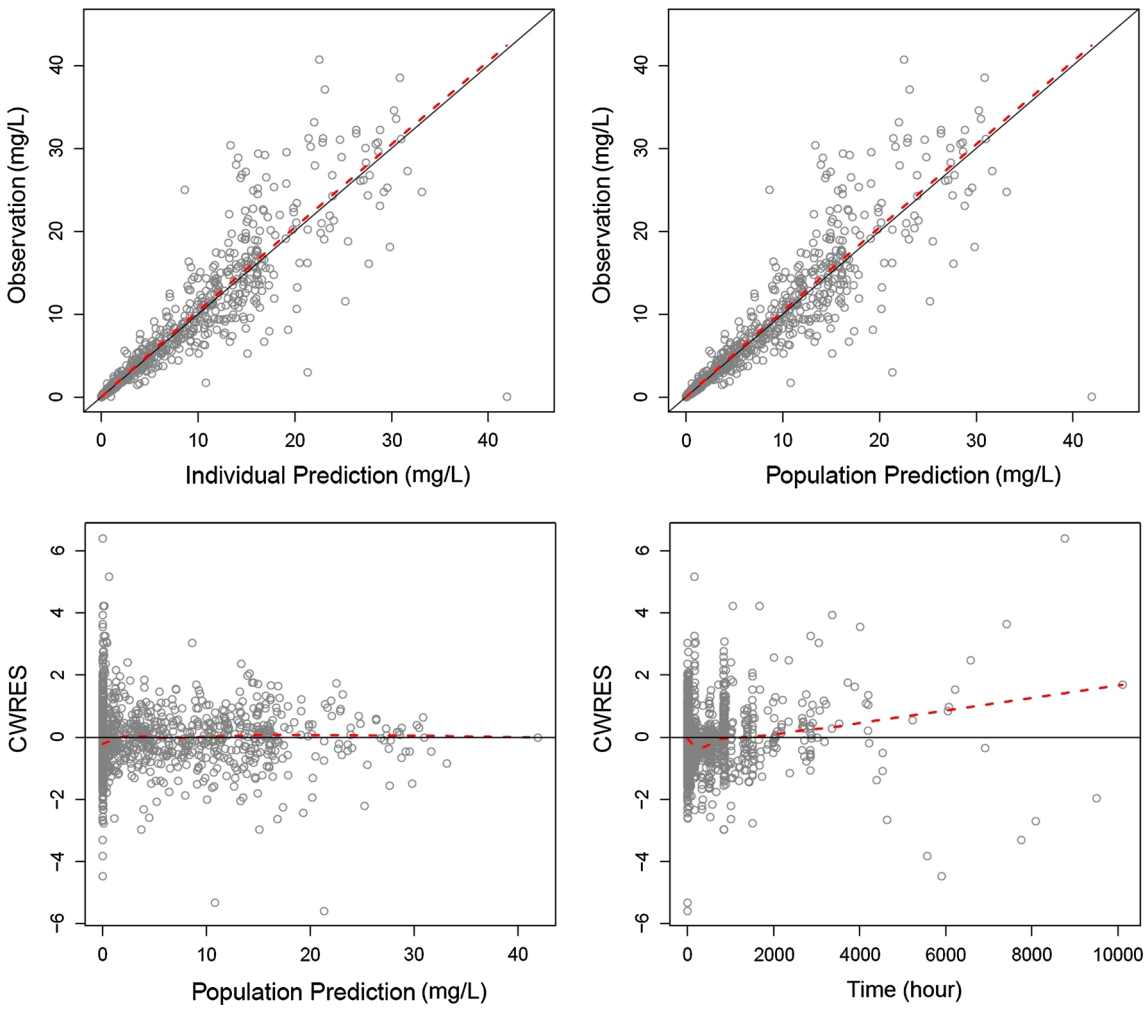

Fig. 2 Goodness-of-fit plot for the final danvatirsen PK model. *Note* Upper panels show observed concentrations versus individual predictions (left) population predictions (right). Lower panels show CWRES versus population prediction (left) and time after first dose (right). *CWRES* conditional weighted variables; *PK* pharmacokinetic

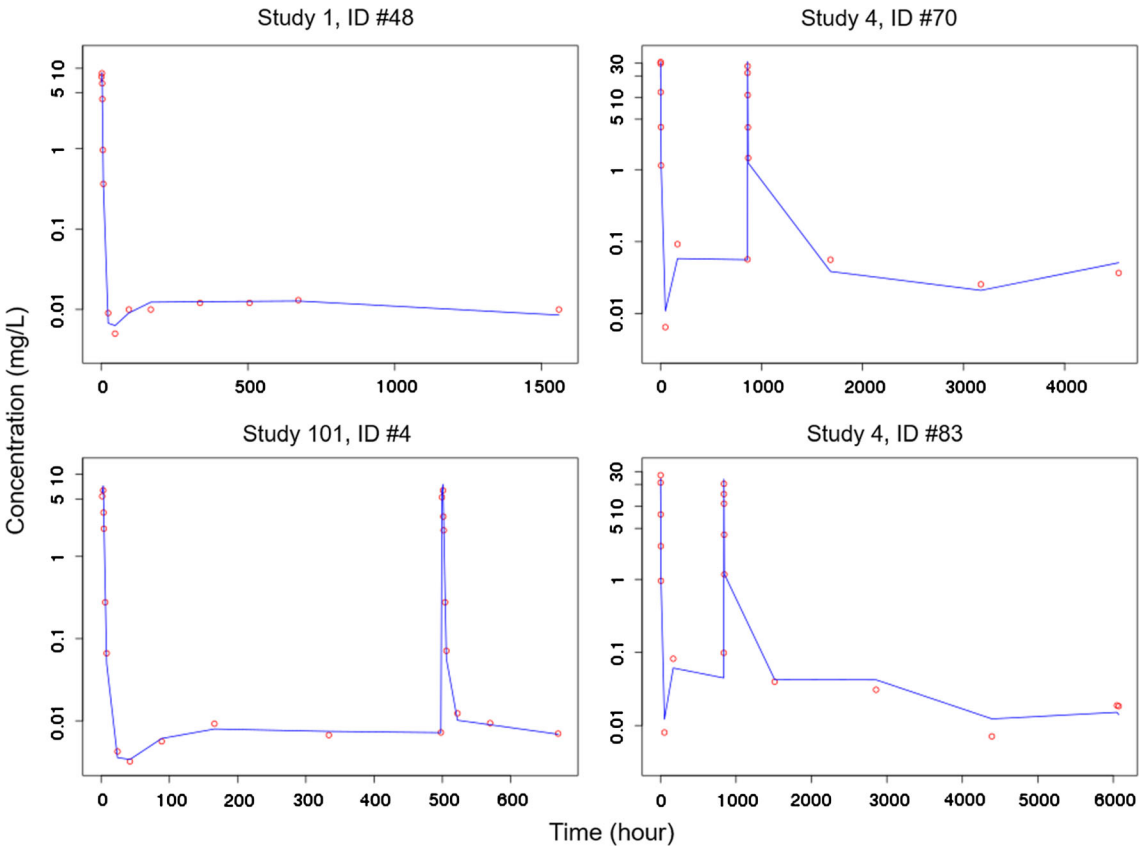

Fig. 3 Individual fit from typical patients

variability are reasonably predicted for each study (Fig. 4). The nonparametric bootstrap results suggest very limited bias in estimates and reasonable 95% prediction intervals (CIs) around the estimates.

Flat dosing simulation

The final PopPK model was used to simulate danvatirsen steady state exposure of *AUC* and *Cmax* after IBW-based RP2D dose of 3 mg/kg versus a flat dose of 200 mg. The simulated *AUC* and *Cmax* for 1000 patients are shown in Fig. 5. Median *AUC* and *Cmax* are very similar between two dosing strategies with slightly less overall inter-individual variability with the flat dosing regimen. The simulated geometric mean steady state weekly *AUC* were 62.5 and 63.4 mg h/L for 3 mg/kg and 200 mg flat dosing (ration = 0.99); the steady state *Cmax* were 26.2 mg/L, and 26.5 mg/L for 3 mg/kg and 200 mg flat dosing (ration = 0.99).

With the support of comparable simulation results, the flat dose (200 mg) was tested in the ongoing Phase Ib/II study (D5660C00016, Study 16). An interim analysis from Study 16 was then performed to cross validate the model prediction. Observed week 5 day 1 danvatirsen concentrations after the 200 mg every week (n = 3) in Study 16 were overplayed with the population PK model predictions (Fig. 6). The predicted danvatirsen concentrations were in agreement with the observed data.

Discussion

Population PK modeling has been widely utilized in drug development, such as paediatric dose selections [8–11] bridging formulations [12], predicting potential drug-drug interactions [13], which often plays an important role in regulatory submissions and labelling. A Population PK model for danvatirsen was developed in patients with DLBCL, HCC and SCCHN and the simulation results suggested ideal body weight-based dosing could be switched to flat dosing with minimal change on the overall exposure (steady state *AUC* and *Cmax*).

A linear 2-compartment disposition model adequately described danvatirsen concentration time course following multiple danvatirsen iv. dose administration. The estimated typical population CL was 3.11 L/h, V_1 was 5.56 L, Q was 0.30 L/h, V_2 87.3 L for danvatirsen. CL of 3.11 L/h is equivalent to 0.049 L/h/Kg (mean IBW of 63 kg in HCC study), which is very close to 0.050 L/h/Kg from non-compartmental analysis for 3 mg/kg group reported in IB.

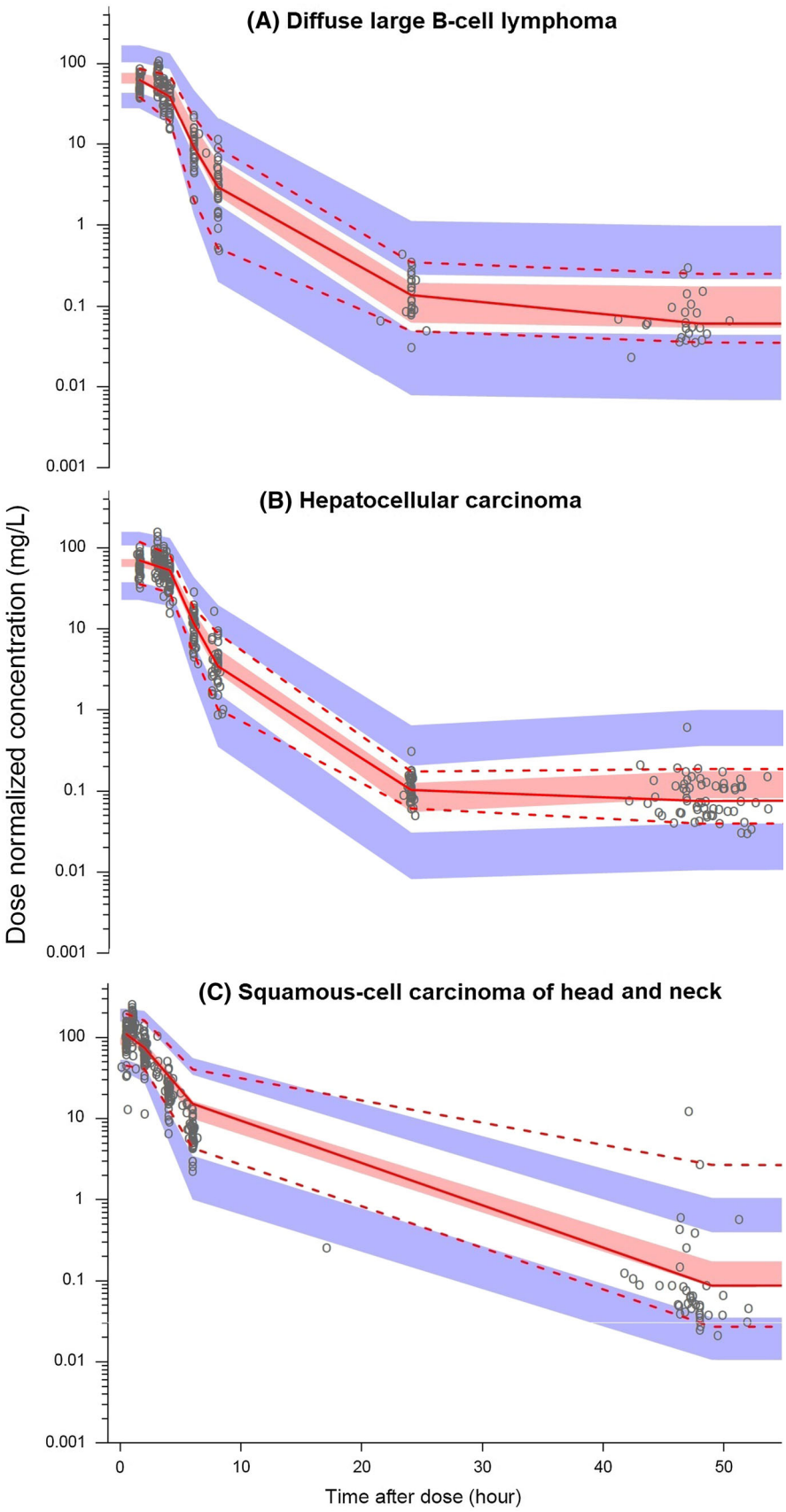

Fig. 4 Visual predictive check for the final danvatirsen PopPK model. *Note* The red and blue shaded areas represent the 90% CI around the predicted median, 5th and 95th percentiles. The red solid line was observed median and dotted lines are observed 5th and 95th percentiles of the data. The circles are individual observations (Color figure online)

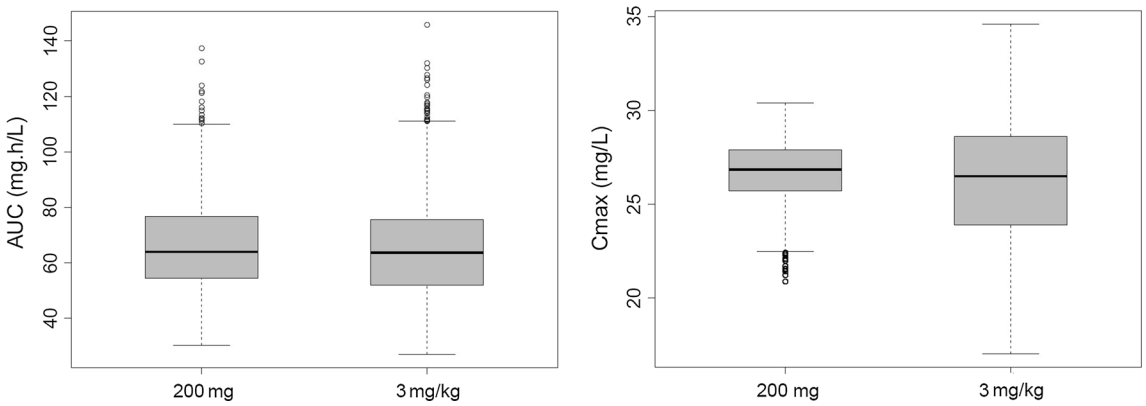

Fig. 5 Simulated steady state *AUC* and *Cmax* after flat dose and body weight based dose (200 mg vs. 3 mg/kg). Typical box-and-whisker plot. The band inside the box is the second quartile (the median), the boxes indicate the first and third quartiles, and the ends of the whiskers represent the lowest datum still within 1.5 interquartile range (IQR) of the lower quartile, and the highest datum still within 1.5 IQR of the upper quartile

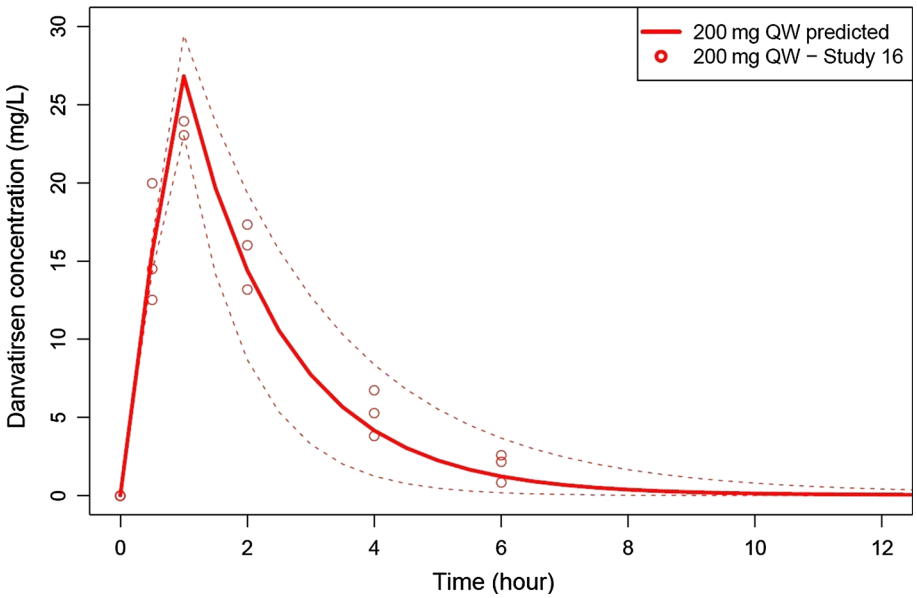

Fig. 6 Model predicted versus observed danvatirsen concentrations after 200 mg weekly flat doses. Solid line: model predicted median concentration at week 5 day 1 after 200 mg weekly dosing with 3 × 200 mg loading doses in week 1 (day 1, 3, 5). Dashed lines: 90% model prediction interval. Open circles: observed concentrations on week 5 day 1 from study 16

The estimated BSVs (CV%) were for CL 27%, for Q 48%, for V_2 64%, indicating moderate PK variability. A 3-compartment model slightly improved the conditional weighted residual error (CWRES) at later time points however the goodness fit of observed versus predicted concentration were worse in 3-compartment model (data not shown). The 2-compartment model was selected over 3-compartment model as 3-compartment model didn't not significantly improve the OFV comparing to 2-compartment model (− 728.738 vs. − 730.879) by adding 4 additional parameters to the model.

A population PK model was developed for a generation 2.5 ASO custirsen [14]. The reported CL was 2.4 L/h, which is in the similar range of danvatirsen. In their PK model, age, body weight and serum creatinine were found to be predictors of CL. However, the predicted ratios relative to the reference were between 0.9 and 1.15 for *AUC* and *Cmax*, suggesting although they are statistically significant covariates, their extent of impact on PK exposure is limited. In the current danvatirsen model, none of the covariates (age, ideal body weight, race and sex) were found to significantly impact danvatirsen PK. Similarly, race does not impact first-in-class ASO mipomersen (Kynamro®), as no PK differences were found between Japanese and Western population in the mipomersen phase I study [15].

The lack of association between ideal body weight and danvatirsen PK concluded from the PopPK model suggested that the danvatirsen exposure was not impacted by ideal body weight and flat dosing is a viable alternative dosing strategy for danvatirsen administration. The PK simulation confirmed the mean exposure (*AUC* and *Cmax*

at steady state) with a flat dose of 200 mg being very similar to the 3 mg/kg IBW based dosing. The overall variability is also smaller with the flat dosing. In other ASOs, Mipomersen (Kynamro®) was approved as an adjunct to lipid-lowering medications as a flat dose of 200 mg given subcutaneously [16].

The modelling report was submitted to regulatory agencies as part of IND submission and the approach has been approved by multiple regulatory agencies, including FDA, EMA, PMDA and ANSM. The flat dosing is currently being evaluated in ongoing clinical trials. The interim analysis from an ongoing phase Ib/II study (D5660C00016, NCT03421353) in patients with advanced, solid tumours and in patients with non-small-cell lung cancer showed the danvatirsen PK profile after 200 mg once week was in good agreement with the simulation results from the final population PK model. The final dosing strategy will be based on an overall benefit-risk assessment of efficacy and safety.

In conclusion, the developed danvatirsen population PK model and simulation provided good rationale to switch from ideal body weight based dosing to flat dosing. The PopPK model could be further utilized in subsequent exposure-response efficacy and safety modelling to support full assessment of different dosing strategies.

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