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ORIGINAL ARTICLE

A population pharmacokinetic analysis of the oral CYP17 lyase and androgen receptor inhibitor seviteronel in patients with advanced/metastatic castration-resistant prostate cancer or breast cancer

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Abstract

Purpose Seviteronel is an orally-administered selective cytochrome P450c17a 17,20-lyase and androgen receptor inhibitor with anti-tumor activity in vitro and in vivo, and clinical activity in men with advanced castration-resistant prostate cancer (CRPC) and men and women with advanced breast cancer. The purpose of this study was to assess the pharmacokinetics (PK) of seviteronel across the aforementioned populations.

Methods This report describes the PK of seviteronel (50–750 mg, QD or BID) using noncompartmental and population approaches from 243 patients with advanced breast or prostate cancer pooled across 4 clinical studies. First dose and steady-state PK were examined, as well as covariates including prandial status, sex and concomitant dexamethasone.

Results Seviteronel PK can be characterized by transit absorption and a bi-phasic first-order elimination while accounting for covariance between random effects. Prandial status did not significantly affect any parameters to a clinically-relevant extent. Both sex and body weight were significant covariates on clearance, explaining 37% of the interindividual variability on that parameter. There were no significant effects from the race or the presence of a corticosteroid (either dexamethasone or prednisone).

Conclusions Seviteronel demonstrates linear PK over the dose range of 50–750 mg given either BID or QD in men with advanced CRPC or men and women with breast cancer. The disposition of seviteronel following oral administration is well described by this population PK model and can be used for accurate simulations for future studies with body weight and sex affecting clearance, but not to a clinically-meaningful degree requiring a change in the current dosing scheme.

Keywords Seviteronel CYP17 lyase · Population pharmacokinetics · Prostate cancer

Introduction

Prostate (PC) and breast (BC) cancer are highly prevalent diseases that are predicted to account for an estimated 164,690 new cases (29,430 deaths), and 266,120 new cases (40,920 deaths), respectively, in the United States in 2018 [1]. Standard of care (SOC) cytotoxic chemotherapy for advanced PC, often presenting in the metastatic castration-resistant (mCRPC) setting, includes the taxanes docetaxel and cabazitaxel [2, 3]. Similarly, for advanced BC, especially for triple-negative BC (TNBC) that does not express the estrogen (ER), progesterone (PR) or human epidermal growth factor receptor 2 (HER2), chemotherapy (including

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capecitabine, eribulin, and ixabepilone) is the current SOC, despite limited efficacy and extensive toxicity [4]. The recent development of more potent inhibitors of the androgen receptor (AR) (e.g. enzalutamide) and intra-tumoral androgen synthesis (e.g. abiraterone) has enabled the use of AR-targeted therapies in the setting of mCRPC [5]. Given that the AR has been demonstrated to be expressed on 70–90% of BC [6–8], the AR has also become a therapeutic target in BC.

The activity of enzalutamide (oral second generation AR antagonist) in mCRPC was demonstrated by a 2.4 and 4.8 mo improvement in overall survival (OS) and an overall reduction in risk of death of 29 and 37%, pre- and post-chemotherapy compared to placebo, respectively [9, 10]. Similarly, abiraterone acetate (oral cytochrome P450C17A1 (CYP17) inhibitor) in combination with prednisone conferred a similar 4.4 and 3.9 mo improvement in overall survival (OS) and an overall reduction in risk of death of 19 and 35%, pre- and post-chemotherapy compared to prednisone alone, respectively [11, 12]. With the approval and adoption of these agents in mCRPC there has been interest in AR targeting in BC, namely TNBC [13]. In a single-arm, open-label study of enzalutamide in women with AR + (≥ 10% by IHC) TNBC, radiographic progression-free survival (rPFS) was 14.7 weeks [14]. Similarly, abiraterone acetate in combination with prednisone resulted in an rPFS of 11.2 weeks in women with AR + (> 0% by IHC) TNBC [15]. These findings in TNBC are promising given that chemotherapy in these women has diminishing activity beyond first-line treatment (PFS ranging from 6–12 weeks) [16–18].

Seviteronel (INO-464) is an oral selective CYP17 17,20-lyase (lyase) and AR inhibitor currently in Phase 2 clinical development for men with advanced CRPC and men and women with advanced ER + or TNBC. In addition to improved selectivity to CYP17 lyase over abiraterone [19], seviteronel is also a competitive antagonist to mutations that confer resistance to both abiraterone (e.g. T878A) and enzalutamide (e.g. F876L) [20]. The activity of seviteronel has been demonstrated nonclinically in relevant PC and BC models [20, 21].

The safety and tolerability of seviteronel, as well as the initial clinical activity in men with CRPC and women with BC, was previously reported, where women taking 450 mg QD had a very similar C_{MAX} (4506 ± 618 ng/mL) compared to men taking 600 mg QD (4403 ± 1817 ng/mL) [22, 23]. This potential sex effect was one reason a population analysis was performed to better understand what, if any, covariates affects the disposition of seviteronel. The recommended Phase 2 dose for seviteronel was determined to be 450 mg once daily (QD) in women and 600 mg QD in men, and for both it is co-administered with 0.5 mg QD dexamethasone. Seviteronel was shown to be predominantly cleared via hepatic metabolism, with cytochrome P450 isozymes 2C9 and 2C19 having major roles, and 3A4 with a relatively minor role.

The purpose of this report is to describe the PK of seviteronel across multiple clinical studies using a population PK approach using sparse and dense data and assess the impact of several covariates including steroid co-dosing and sex, which will help guide seviteronel dosing in subsequent clinical development. A secondary purpose of the analysis is to evaluate dense PK of seviteronel using extended sampling and a NCA approach to further estimate seviteronel half-life and impact of prandial status.

Materials and methods

Study design

The PK of seviteronel was evaluated using population PK and NCA in patients with advanced breast or prostate cancer enrolled across four clinical studies (Table 1). The clinical studies were conducted according to IRB-approved protocols and all accrued subjects provided written informed consent.

Seviteronel was administered at a 100–900 mg total daily dose as either a single (QD) or split dose (BID) in 28-day continuous dosing cycles, with or without dexamethasone co-administration (0.5 mg QD), depending upon the study protocol (Table 1). Blood samples were collected immediately before or at known time points after oral seviteronel administration either as part of dense or sparse PK assessments. For dense PK assessments, blood samples were collected up to 24 h (pre-dose, 0.5, 1, 2, 4, 8, and 24 h) for Studies 001, 004 and 006 or 48 h (pre-dose, 0.5, 1, 2, 4, 6, 8, 12, 18, 24, 36, and 48 h) for Study 002 post single-dose of seviteronel either prior to/the start of Cycle 1 and/or at steady state (Cycle 2 Day 1). Several patients in Study 001 were titrated up to their Cycle 1 Day 1 dose level of 450 mg BID or QD or 600 mg QD.

There were no food restrictions with seviteronel administration except when patients were instructed to undergo an overnight fast as part of the Phase 1 assessment the impact of prandial status on seviteronel PK (Study 001). Twenty-five of the 28 patients underwent repeat dense PK assessments in a fed or fasted state split by a 1 week washout prior to continuous dosing with seviteronel. For population PK model development, the two sets of "first dose" scenarios included in the model as separate patients.

For sparse PK assessments, blood samples were collected starting at Cycle 1 Day 14 and then at the start of every other cycle thereafter. In addition to seviteronel dose level and time of the last dose, clinical and demographic data were

Table 1 Patient demographics and study design details

	INO-VT-464-CL-001 (NCT02012920)	INO-VT-464-CL-002 (NCT02130700)	INO-VT-464-CL-004 (NCT02361086)	INO-VT-464-CL-006 (NCT02580448)
Study design	Phase 1/2 study of BID or QD SEVI or SEVI-D in men with advanced CRPC*	Phase 2 study of SEVI in men with advanced CRPC after enzalutamide	Phase 1 study of QD SEVI in men with advanced CRPC*	Phase 1 study of SEVI in women with advanced ER + or TNBC; Phase 2 study of SEVI or SEVI-D in men and women with advanced ER + or TNBC
Dosing regimen	SEVI: 50–450 mg BID or 600–750 mg QD SEVI-D–600 mg QD	SEVI: 600–750 mg QD	SEVI: 600–900 mg QD	SEVI: 450–750 mg QD (Phase 1); 450 mg QD (Phase 2 women) and 600 mg QD (Phase 2 men) SEVI-D: 450 mg QD women (Phase 2) and 600 mg QD men (Phase 2)
Total patients (*n*)	80	8	21	134
Body weight (kg)	88.3 (63.1–133)	85.4 (74.3–112)	92.2 (72.3–142)	75.9 (45.4–129)
Sex	80 Males	8 Males	21 Males	10 Males 124 Females
Race	2 Asian 5 African 72 Caucasian 1 Other	7 Caucasian 1 Multiple	2 African 19 Caucasian	2 Asian 9 African 119 Caucasian 2 Other 2 Unknown
Cancer type	80 CRPC	8 mCRPC	21 CRPC	ER + : 9 males, 57 females TNBC: 1 male, 67 females

CRPC castration-resistant prostate cancer, *mCRPC* metastatic castration-resistant prostate cancer, *ER +* estrogen receptor positive breast cancer, *TNBC* triple negative breast cancer, *SEVI* seviteronel, *SEVI-D* seviteronel in combination with 0.5 mg dexamethasone

*Prior treatment with 0–2 lines of novel AR-targeted agent (e.g., enzalutamide, apalutamide, abiraterone acetate, orteronel)

collected for covariate analysis including sex, body weight, prandial status, and dexamethasone co-administration.

Although seviteronel is almost tenfold more selective for inhibition of CYP17 lyase versus hydroxylase, it can harbor some hydroxylase inhibition activity at higher doses, which can result in cortisol suppression, increased adrenocorticotropic hormone (ACTH) and steroid accumulation [19, 22–24]. Therefore, co-dosing of seviteronel with steroids was initiated in ongoing BC and PC trials, which is reflected in 41/243 (17%) of the patients in the current analysis having concomitant steroid use. Most of these 41 patients (88%; 36/41) received dexamethasone (0.5 mg daily), while just 5/41 (12%) received prednisone (ranging from 5 to 10 mg daily). To ensure there was no impact on seviteronel exposure with the known CYP3A4 inducer dexamethasone [25], steady-state trough values were compared between patients who did vs did not receive dexamethasone.

Bioanalytical procedures

Blood samples for PK analysis were processed using a refrigerated centrifuge with plasma stored at or below − 20 °C until the determination of seviteronel concentrations by a validated assay involving liquid chromatography (LC) with tandem mass spectrometric (MS/MS) detection (Tandem Laboratories, Durham NC). Briefly, 25 µL of plasma was diluted with 975 µL of acetonitrile containing seviterionel-d6 as internal standard, the mixture was vortexed and centrifuged before 200 µL of the supernatant was isolated and diluted with 400 µL of water. The assay calibration range was 20–25,000 ng/mL, with acceptable runs meeting criteria for precision and accuracy of ≤ 15% and < 15% relative error, respectively.

Noncompartmental analysis

Noncompartmental was used to calculate plasma PK parameters of seviteronel for each patient on Study 001, while patients on Study 002 having sufficiently dense data only had half-life determinations using Phoenix WinNonlin 7.0 (Certara Pharsight, Cary, NC). As the NCA for patients in Study 004 [23] and Study 006 [22] were recently published, and the resulting data will not be shown. Likewise, the full NCA results of Study 002 other than half-life will also not be presented here in detail due to its planned inclusion in a future clinical analysis. Any plasma concentration measured below the LLOQ (BQL; 20 ng/mL or 0.02 mg/L) was not included in the NCA.

The maximum plasma concentration (C_{MAX}) and time to C_{MAX} (T_{MAX}) were recorded as observed values. The area under the plasma concentration vs time curve (AUC) was calculated using the linear up/log down trapezoidal method to the last time point (AUC_{LAST}), extrapolated to infinity ($AUC_{INF} = AUC_{LAST} + C_{LAST}/k_{EL}$), and AUC_{TAU} at steady-state (Cycle 2 only). Apparent oral clearance was calculated as Dose/AUC_{INF} (CL/F) for single-dose cycles 0 and 1 and Dose/AUC_{TAU} (CLss/F) for steady-state cycle 2. Apparent oral volume of distribution at the terminal phase (V_Z/F) was calculated as CL/F divided by k_{EL}; half-life (HL) was calculated as $\ln 2/k_{EL}$. All statistical analyses were performed, and figures generated, using GraphPad Prism, v7.01 (GraphPad Software, San Diego, CA), where an $\alpha = 0.05$ was used to determine statistical significance.

Population PK analysis

Population PK models were developed using the software package Phoenix NLME (version 8.1; Certara Pharsight, Cary, NC). To increase the robustness of the modeling, an initial "model-building test set" was developed and then was validated with a "data-splitting validation set". Computations were performed on an Intel-based personal computer under the Windows 7 operating system. A first-order conditional estimation method with extended least squares (FOCE-ELS) and the Laplacian algorithms was explored during the model-building procedure. The modeling approach using the model-building test set was implemented in a series of steps which are outlined below. Any plasma concentration measured below the LLOQ (BQL; 20 ng/mL or 0.02 mg/L) was not included in the population analyses.

Development of a structural (base) population PK model

The base PK model was defined as the model that best described the seviteronel concentration–time data without consideration of covariate effects. One-compartment, two-compartment and three-compartment open models with first order or saturable absorption and elimination were evaluated. An exponential inter-individual (aka between-subject) error model was used to describe variability between patients for particular population parameters (Eq. 1), where the individual parameter estimate (θ_i) is the product of the population parameter estimate (θ_{POP}) and the exponentiated IIV estimate for that individual (η_i).

$$(\theta_i = \theta_{pop} \times e^{\eta_i}). \quad (1)$$

Additive, proportional, exponential and combination additive/proportional (mixed) random intra-individual residual error models were explored to account for the intraindividual variability.

Development of a population PK covariate model

Identification of potential covariate effects on parameters was made by visual and statistical relationships between individual post hoc eta (η) estimates for each parameter and covariate values. The possible influences from the following potential covariates were explored to identify their contribution towards the explanation of the random variability in seviteronel PK: Body weight (continuous; scaled to the dataset median of 82.4 kg), Sex (categorical: 0 for female; 1 for male), Dose Level (categorical: 50 mg, 100 mg, 200 mg, 300 mg, 450 mg, 600 mg, and 750 mg), Prandial status (categorical: 0 for fasted; 1 for fed), Cycle (categorical between occasion: 0, 1, 2, 4, 6, or 8), Arm (categorical: 0 for seviteronel; 1 for seviteronel + dexamethasone), and Study (categorical: 1, 2, 4, or 6).

A stepwise covariate screening by Phoenix NLMEv7.0 was performed by adding the potential covariates, one at a time, into the optimized base model toward a full model, and then backward elimination. Several functions were explored when adding the potential covariates to the structural model, namely, linear additive function, normalization by the median value, centering by median value, power function, and (for categorical covariates) fraction change. Ultimately, continuous covariates were incorporated per Eq. 2, where "COVi" is the covariate value for that individual, "COVmed" is the population median value, and θ_{chng} is as an estimable parameter. Categorical covariates were included per Eq. 3, where θ_{COV} refers to the exponential change relative for that covariate on the parameter.

$$\theta_i = \theta_{pop} \times \left(COV_i/COV_{med}\right)^{\theta_{chng}} \times \exp(\eta_i), \quad (2)$$

$$\theta_i = \theta_{pop} \times \exp(\theta_{COV}) \times \exp(\eta_i). \quad (3)$$

Model evaluation

The objective function value (OFV), calculated by Phoenix NLME 7 as minus two times the log-likelihood ($-2 \times LL$), was used for model diagnostics. Using the likelihood ratio test, a significant ($\alpha = 0.05$) improvement between nested models requires a delta OFV > 3.84, based on χ^2 distribution. For non-nested model comparisons, the Akaike information criterion (AIC) was used, as calculated by $-2 \times LL + 2 \times P$ (P = number of estimable model parameters). Visual inspection of the model included goodness-of-fit plots, such as observed concentrations (dependent variable, DV), population predicted (PRED) and individual predicted (IPRED) concentrations versus time, DV versus PRED, DV versus IPRED, and conditional weighted residuals (CWRES)

versus time or IPRED. Quantile–quantile (QQ) plots for each η parameter were assessed to check the assumption of normal distribution. The η-shrinkage for each parameter was also assessed and the IIV estimates for parameters with high η-shrinkage (> 30%) were interpreted with caution due to insufficient individual observations that shrink the individual estimate towards the population estimate [26]. Covariance between parameters was evaluated using an omega block variance–covariance matrix. Correlation between continuous covariates was assessed using a scatter matrix plot (R v3.1.3) where a correlation > 0.5 was considered significant.

Model validation

Prior to validation, the ability of the final model to predict the DV was tested by visual predictive checks (VPC) using Phoenix NLME 7.0 and visualized using the 'vpc' package in R v3.5.1. Parameter estimates and variances were used to simulate data for 200 replicates and the 5th, 50th and 95th predicted percentiles were calculated for the VPC in bins defined by explicit centers at 0, 0.5, 1, 2, 4, 6, 8, 10, 24, and 48 h post first dose, then visually compared with observed data and corresponding distributions. A separate VPC was performed during the cycle 2, day 1 dose (the other data-rich timeframe) with bins defined by explicit centers at 672, 674, 676, 678, 680, 690, 696, 700, and 720 h post first dose (0–48 h since last dose). Once VPC demonstrated reliably predictive simulations, the model was internally validated via bootstrap resampling, with standard errors and 95% confidence intervals based on 200 replicate simulations.

Additionally, the data-splitting validation dataset was used to separately validate the model similar to an external validation, except this "validation" dataset was split from the same clinical studies as the test dataset, so it technically was not an "external" validation but was treated as such. This validation dataset is mostly consistent with trough samples drawn at baseline, predose on cycle 1 day 14 (336 h post baseline), cycle 2 day 1 (672 h post baseline), cycle 3 day 1 (1368 h post dose), cycle 4 day 1 (2040 h post dose) and cycle 6 day 1 (3384 h post dose). Therefore, in this "external" VPC, bins were assigned to explicit centers at these timepoints (in hour post baseline).

Results

Datasets

Patient demographics are presented in Table 1 for the 243 unique patients enrolled across four clinical trials and included in the present PK analysis. A pooled dataset of 1619 PK time-points, containing sparse and dense PK data, was used for population PK model development (Table 2). The model-building test data set contained 1342 samples (roughly equal parts sparse and dense data) from 187 unique patients, and the remaining 277 samples (almost exclusively sparse data through 6 cycles of therapy save for 1 patient with dense data) from 94 patients were used for the data-splitting validation data set. The 94 patients in the data-splitting validation data set included new data from model-building test set patients and new patients not included in the model-building validation test set.

The main data set for the main NCA presented herein contains dense PK data out to 24 h after dosing from 28 unique patients from Study 001. A second data set containing dense PK data out to 48 h after dosing from 8 unique patients from Study 002 was used for half-life determinations.

Noncompartmental analysis

The seviteronel plasma concentration vs time profiles depicting dense sampling are displayed in Fig. 1 by dose. The noncompartmental results for Study 001 are presented in Tables S1, S2. Overall, seviteronel was well absorbed with a minimal lag time, demonstrated linear PK (Figure S1) with no statistically-significant food effect (Table S2; data from Study 001 that had both fasted and fed data), and had a mean estimated terminal half-life of 6.6 h (± 2.1 h). It was determined that dense sampling for only 24 h did not fully capture elimination and underestimated the half-life, which ultimately underestimated the predicted accumulation to steady-state.

The noncompartmental PK of patients in Study 004 [23] and Study 006 [22] were recently published, and the resulting data will not be shown. Likewise, the full noncompartmental results of Study 002 will also not be presented here due to its imminent inclusion in a future clinical analysis. Each of these studies administered either 600 mg or 750 mg QD to men with CRPC (Study 002 and 004) or 450 mg to 750 mg QD to women and men with breast cancer (Study 006) that demonstrated comparable half-lives ranging from 6 to 9 h. However, Study 002 sampled out to 48 h and, therefore, half-life estimates from this dataset could more accurately predict steady-state exposures; the longer sampling period had a mean estimated half-life of 13.9 h, which was ~ 60% longer than calculated with 0–24 h sampling. Finally, because a majority of patients co-administered a corticosteroid received dexamethasone, a comparison was made between trough levels, but no statistically significant differences were observed (Figure S2).

Pharmacokinetic base model development

In Study 001, 25 of 28 patients in the "test" dataset had dense PK sampling (0–8 h) after a single dose in a fed state and then a repeat dense PK sampling after a 1-week washout

Table 2 Patient demographics by datasets

	INO-VT-464-CL-001[a] (NCT02012920)	INO-VT-464-CL-002 (NCT02130700)	INO-VT-464-CL-004[b] (NCT02361086)	INO-VT-464-CL-006 (NCT02580448)	Total
Model-building test set					
Number of patients (*n*)	28	8	17	134	187
Number of samples (*n*)	516	163	133	530	1342
Body weight (kg)	88.9 (63.1–119)	85.4 (74.3–112)	93.9 (72.6–142)	75.9 (45.4–129)	
Sex	28 Males	8 Males	17 Males	10 Males 124 Females	63 Males 124 Females
Race	2 Asian 3 African 22 Caucasian 1 Other	7 Caucasian 1 Multiple	1 African 16 Caucasian	2 Asian 9 African 119 Caucasian 2 Other 2 Unknown	
Cancer type	80 CRPC	8 mCRPC	17 CRPC	ER + : 9 males 57 females TNBC: 1 male 67 females	
PK sampling	Pre, 0.5, 1, 2, 4, 8, 24 h	Pre, 0.5, 1, 2, 4, 6, 8, 12, 18, 24, 36, 48 h	Pre, 0.5, 1, 2, 4, 8, 24 h	Pre, 0.5, 1, 2, 4, 8, 24 h	
Data-splitting validation set					
Number of patients (*n*)	74	0	20	0	94
Number of samples (*n*)	215	n/a	62	n/a	277
Body weight (kg)	87.5 (63.1–134)	n/a	92.2 (73.1–142)	n/a	
Sex	74 Males	n/a	20 Males	n/a	94 Males
Race	2 Asian 5 African 66 Caucasian 1 Other	n/a	2 African 18 Caucasian	n/a	
Cancer type	74 CRPC	n/a	20 CRPC	n/a	

CRPC castration-resistant prostate cancer, *mCRPC* metastatic castration-resistant prostate cancer, *ER+* estrogen receptor positive breast cancer, *TNBC* triple negative breast cancer

[a]Study 001 Model-building test set contained 28 unique male CRPC patients, while the data-splitting validation set used additional sparse data from 21 of these 28 patients along with sparse data from 53 additional patients

[b]Study 004 Model-building test set contained 17 unique male CRPC patients, while the data-splitting validation set used additional sparse data from 16 of these 17 patients along with sparse data from 4 additional patients

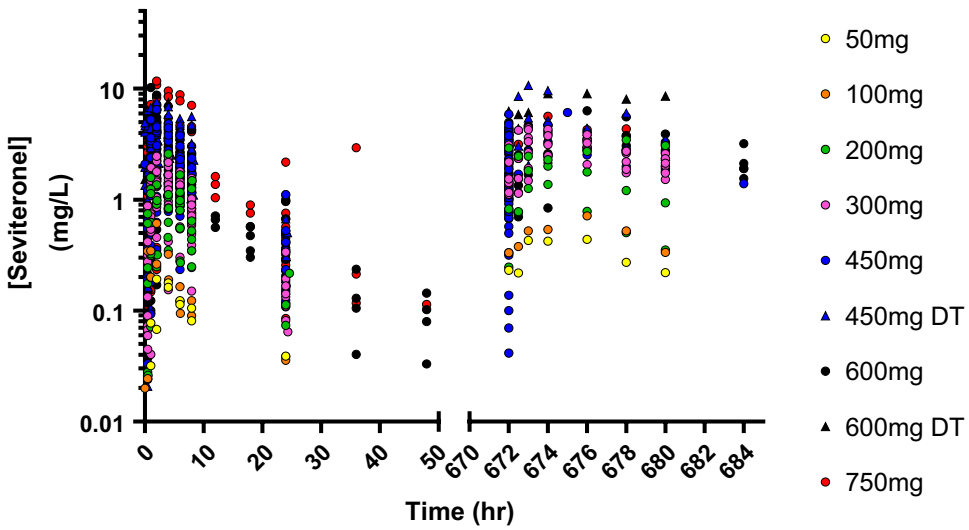

Fig. 1 Seviteronel plasma concentration vs time curve. All measured seviteronel plasma concentrations from all 187 patients on varying cycles and doses. Seviteronel was well absorbed and appeared to increase in a dose-dependent manner. There was also evidence of moderate (~60%) accumulation at steady-state that was accurately captured by the model. Patients who had their doses titrated (DT) were already at steady-state at time zero

in a fasted state. These two sets of "first dose" scenarios within each patient were treated separately. Thus, during model development, there were 212 "subjects," 187 of which were unique subject IDs. A two-compartment open model with first-order absorption via a transit model and first-order elimination that accounted for steady-state dosing was found to best describe seviteronel concentration–time data in a robust fashion. Beginning with a single compartment with additive residual variability (OFV = 4425.0), the addition of a second, peripheral compartment improved the model fit immensely (OFV = 4086.2; $P = 4.5e-27$). With respect to the residual unexplained variability (RUV), a mixed (proportional and additive) model was used to describe the data, which significantly improved the model fit (OFV = 4064.7; $P = 3.6e-06$). The addition of a third compartment did not significantly improve the model (OFV = 4062.4; $P = 0.67$). Incorporating a saturable elimination instead of first-order resulted in a model that could not consistently converge, likely due to misspecification, therefore such a model was abandoned for this reason, as well as a general lack of visual evidence of saturable absorption from the NCA. When a transit absorption model replaced the typical first-order absorption, the model was greatly improved (OFV = 4012.7; $P = 5.17e-12$). Accounting for steady-state sampling drastically lowered the OFV to 3706.7. Additionally, there was moderate covariance between several of the random effects and therefore, an omega block matrix was used to estimate covariance between the random effects. Strong correlations (defined by $\rho > 0.40$) were found between etaCL/F and etaV/F ($\rho_{CL,V} = 0.48$), etaV/F and etaVt/F ($\rho_{V/F,Vt/F} = -0.57$), etaCL/F and etaVt/F ($\rho_{CL/F,Vt/F} = -0.73$), and etaKa and etaQ/F ($\rho_{Ka,Q/F} = 0.82$), and helped account for unexplained variability in the model as indicated by the significant drop in the OFV to 3616.9 ($P = 1.07e-12$).

Covariate model development

Using a univariate stepwise forward inclusion ($P < 0.005$), backward elimination ($P < 0.001$) approach, two covariates significantly improved the model: (1) sex on clearance, and (2) body weight on clearance. The former covariate is consistent with the observed similarity in seviteronel Cmax between women taking 450 mg PO QD and men taking 600 mg PO QD [22, 23]. In this population analysis, which included the same data presented by Bardia et al., males were shown to have faster clearance than females, with an overall BSV on CL/F of 59.6%. After accounting for this sex effect, the BSV on CL/F decreased to 45%, meaning that sex explained 25% of the overall BSV on clearance. There was also an increasing trend in clearance with increasing body weight that when factored onto the clearance parameter, accounted for an additional 17% of unexplained BSV on CL/F. Overall, sex and body weight decreased the BSV on CL/F from 59.6 to 37.4%. No other significant covariates were identified following both a stepwise and a shotgun search. However, due to the strong covariance between etaV/F and etaCL/F when sex and body weight were included on CL/F, the BSV of V/F dropped 18% from 62.9 to 51.4%. Distributions of the random effects are plotted in Figure S3 and demonstrate normal distribution. Final model parameter estimates are presented in Tables 3, 4.

To better understand this sex effect and the clinical decision to reduce females to 450 mg to achieve comparable exposure to males given 600 mg [22, 23], simulations were performed on 100 simulated patients, randomly assigned a sex of male or female as well as a body weight (in kg) based on their assigned sex. The randomization produced 53 females and 47 males, which were then simulated a single dose of 450 mg or 600 mg, respectively. A 24-h window of simulated concentrations was generated and the exposures were remarkable similar, confirming that the clinical dose reduction to 450 mg in females was indeed optimal in terms of achieving a similar exposure to males taking 600 mg (Figure S4).

Model evaluation

A VPC, performed using 200 Monte Carlo simulations of the final model to determine the predicted 5th, 50th, and 95th confidence intervals, suggested the model can adequately describe the data, as the observed 5th and 9th percentiles were within the shaded confidence intervals (Fig. 2). There was a good correlation between the observed vs IPRED and vs PRED based on the final model (Figure S5A, B). The conditional weighted residuals revealed no apparent trends with time or PRED (Figure S5C, D) and were normally distributed (Figure S5E). Internal validation of the final model was also verified by bootstrap analysis ($n = 200$ replicates) that provided parameter estimate precision (Tables 3, 4). Further, a data-splitting validation VPC was performed and demonstrated no apparent bias in the model built on different data (Figure S6).

Discussion

Seviteronel (INO-464) is a selective and potent CYP17 lyase and AR inhibitor in Phase 2 clinical development in combination with 0.5 mg dexamethasone for the treatment of advanced BC and PC. Recently, the clinical PK of seviteronel were described for the first time in men with advanced CRPC (INO-VT-464-CL-004) [23] and women with ER + or TNBC (INO-VT-464-CL-006) [22] using noncompartmental methods. Both studies administered seviteronel once daily and the noncompartmental analysis examined single-dose characteristics with sampling out to 24 h. Estimated

Table 3 Final seviteronel population pharmacokinetic model parameter fixed effects estimates

Parameter	Base model estimate	Final model estimate	Bootstrap mean estimate	Standard error	Relative bias[a] (%)	%CV	Bootstrap 95% CI
V/F (L)	69.9	99.97	99.97	0.123	−0.00023%	0.123%	99.87–100
CL/F (L/h)	7.15	6.69	6.89	0.296	2.93%	4.29%	6.293–7.501
Vp/F (L)	369	343.4	352.6	14.19	2.68%	4.03%	330.6–379.9
Q/F (L/h)	6.99	6.99	6.99	0.00159	−0.0091%	0.023%	6.99–7.00
Ktr (l/h)	1.99	1.99	1.98	0.074	−1.18%	3.75%	1.72–2.00
Ka (1/h)	1.99	2.49	2.47	0.093	−0.84%	3.79%	2.19–2.49
σ_1 (additive portion of RUV) (mg/L)	0.777	0.785	0.662	0.290	−15.6%	43.8%	0.209–1.09
σ_2 (proportional portion of RUV) (%)	9.13	8.52	24.0	0.114	181%	47.3%	0.021–1.09
dCLdSex	n/a	0.58827	0.55898	0.1011	−4.97%	18.1%	0.333–0.728
dCLdWt	n/a	0.25144	0.35948	0.142	42.9%	39.6%	0.118–0.649

V/F apparent oral volume of distribution of the central compartment, *Vp/F* apparent oral volume of distribution of the peripheral compartment, *CL/F* apparent oral total systemic clearance, *Q/F* apparent oral inter-compartmental clearance, *Ka* first-order absorption rate, *Ktr* transit rate between compartments of the transit absorption model, *dCLdSex* covariate effect on CL/F by Sex (for females relative to males), *dCLdWt* covariate effect on CL/F by body weight

[a]The relative bias was calculated based on the following function: relative bias (%) = (Bootstrap mean − final model estimate)/final model estimate

Table 4 Final seviteronel population pharmacokinetic model parameter random effects estimates

Parameter	Omega variance (ω^2)	Between subject variability (%CV; ω)	Bootstrap mean estimate (ω^2)	Bootstrap BSV (%CV) (ω)	Bootstrap %RSE	Relative bias* (%)
$w^2_{V/F}$	0.2639	51.4%	0.3198	56.6%	27.7%	10.1%
$w^2_{CL/F}$	0.1397	37.4%	0.1569	39.6%	15.4%	6.00%
w^2_{Ktr}	0.901	94.9%	0.8990	94.8%	30.1%	−0.11%
w^2_{Ka}	1.760	133%	1.444	120%	65.3%	−9.45%
$w^2_{Vp/F}$	0.1286	35.9%	0.1544	39.3%	21.1%	9.57%
$w^2_{Q/F}$	0.2653	51.5%	0.3532	59.4%	37.7%	15.4%
Covariance	ρ (correlation)	ω (covariance)	Bootstrap mean estimate (ρ)	Bootstrap ω	Bootstrap %RSE	Relative bias* (%) covariance
$\omega_{Cl,V}$	0.4770	0.0917	0.5085	0.1139	72.8%	24.2%
$\omega_{CL,Vp}$	−0.7281	−0.0976	−0.3849	−0.0599	154%	38.6%
$\omega_{Ka,Q}$	0.8182	0.5591	0.6610	0.4720	39.3%	15.6%
$\omega_{V,Vp}$	−0.5653	−0.1041	−0.2648	−0.0588	191%	43.5%

*The relative bias was calculated based on the following function: Relative Bias (%) = (Bootstrap mean − final model estimate)/final model estimate

mean first-dose half-lives from these reports ranged from 6.4 to 9.2 h, which predict accumulation to steady-state of 37–68% with BID dosing. Based on the observed exposures in Study 001 (Table S1), the actual accumulation at steady-state (not reported for Studies 004 and 006 [22, 23]) ranged from 73 to 128% in Cmax and 12 to 153% for AUC during BID dosing, suggesting the initial half-life range was greatly underestimated.

To correct for this, study INO-464-CL-002 sampled out to 48 h at both cycle 1 day 1 first dose, following once daily dosing, and at steady-state cycle 2 day 1. In Study 002 with extended sampling, the mean estimated half-life was 13.9 h, which predicted a steady-state accumulation of 43% with QD dosing. By steady-state, the AUC_{TAU}, ~60% higher than first-dose AUC_{INF}, was a closer estimate than prior attempts. One of the main objectives of this population model was to

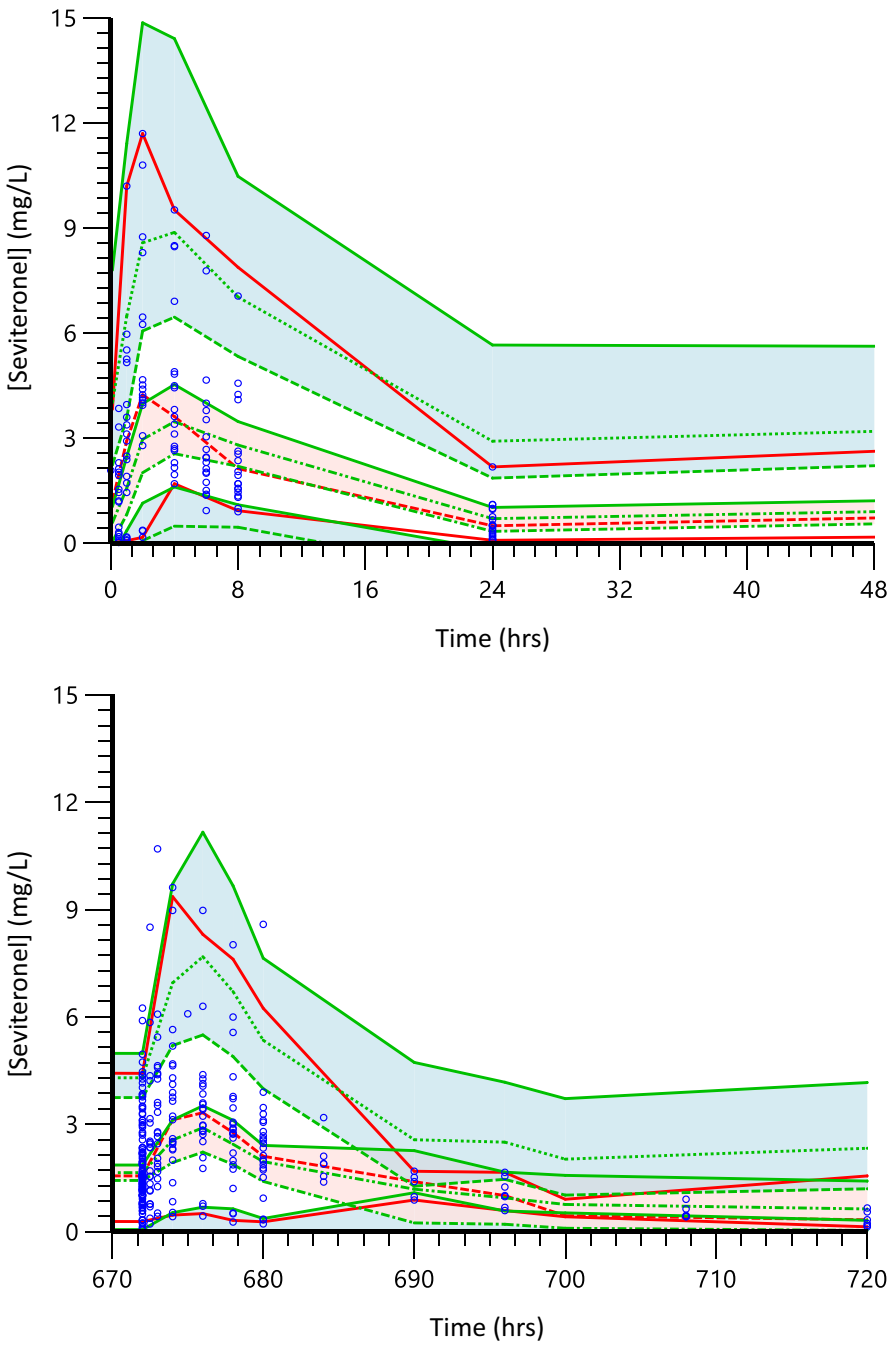

Fig. 2 Visual predictive check. A visual predictive check (VPC) was performed without using any prediction correction and replicated 200 times. Binning occurred at explicit centers at 0.1, 0.5, 1, 2, 4, 8, 10, 12, 24, and 48 h for first-dose (**a**), and 672, 674, 676, 678, 680, 690, 696, 700 and 720 h post start for cycle 2 steady-state (**b**). The VPC was performed separately for these two-time frames as they contained the majority of observations that produced confidence and prediction intervals. Within each time frame, the majority of observations (blue dots) were contained within the 5th and 95th simulated percentile (solid red lines), with the simulated 50th percentile (median) represented by the dashed red line. The blue shaded areas (bordered by green lines) represent the 95% confidence bands around the 5th and 95th simulated percentiles. The red shaded area (bordered by green lines) represents the 95% confidence band around the 50th simulated percentile

better characterize the elimination rate and half-life. Based on the final model, the simulated half-life of 17.5 h (geometric mean of 187 simulations based on this dataset) predicts 164% accumulation with BID dosing and 63% with QD dosing, which more closely aligns with observed accumulation. The longer half-life calculated in the current analysis better accounts for the observation in CRPC men treated with seviteronel that drug-related adverse events were taking up to 2–3 weeks to resolve to baseline [23].

Another main objective was to determine what (if any) variables may be predictive of seviteronel PK within a given population. In this report, any available covariate data was used to develop the first known population analysis of seviteronel to better understand what factors may influence the absorption, distribution, metabolism, or elimination to a clinically-relevant extent. To study this, a two-compartment structural model design best described the bi-phasic nature of seviteronel disposition, which was supported by the varying half-life estimates based on 24 h of sampling vs 48 h sampling. Although a lag time parameter did improve the model fit, this parameter is a simplified way to account for slow absorption and is not very physiologically meaningful.

Transit absorption models have been increasingly used to capture the absorption phase more accurately since Karlsson et al. first described them in 2007 [27]. Implementing a variation of the transit absorption model here lowered the OFV by 51.9 points ($P = 5.2e-12$) and more accurately captured the changes in T_{MAX} between the first dose and steady-state. Furthermore, Phoenix NLME v8.1 allows users to designate which doses were taken during steady-state, to differentiate them from first dose administration and to account for measurable drug during steady-state pre-dose sampling. This improved the model fit tremendously, by 306.1 points.

The clinical efficacy of seviteronel in men with mCRPC is still being fully evaluated, however, this agent has also shown much promise for men and women in the 70–90% of invasive breast cancer cases where the androgen receptor is expressed [6–8]. The recommended Phase 2 dose of seviteronel in men, either with PC or BC, is 600 mg QD and 450 mg QD for women with BC. These doses were determined based upon initial assessment of safety and tolerability in PC and BC populations [22, 23]. A sex difference was suggested as women taking 450 mg had a comparable exposure to men taking 600 mg [22]. This dose selection was largely based on sex differences in toxicity due to differing exposures, with the 600 mg QD dose causing five times more Grade 1 events and almost doubling (7 vs 4) the instances of Grade 2 events in women; the 450 mg QD dose had no reported DLTs [22]. For patients taking 600 mg QD, females had an overall incident rate of 4.5 events per patient, whereas in men taking 600 mg QD, the incident rate was 3.9 [23].

This sex effect was likely caused either by a difference in body size, possibly reflective of distribution volume or by some difference in clearance. Regarding the former, body weight (the lone body size metric available for all 187 patients) was not a significant covariate on volume of distribution ($P = 0.23$). However, clearance and volume were moderately correlated with each other, and body weight was a significant covariate on the CL/F parameter ($p = 3.7e-05$) while decreasing BSV on CL/F by only 8.4%. Although this statistically improved the model fit, it was not enough to warrant a dosing change normalizing to body weight. Additionally, the inclusion of body weight on CL/F also decreased the BSV on the V/F parameter by 18% due to covariance.

The incorporation of sex onto the CL/F parameter significantly improved the model by 42 points ($p = 6.6e-11$) and decreased BSV on CL/F by 16.7%. There are several possible explanations for a sex effect due to clearance difference, including involvement of the hepatic CYP450 isozymes that most predominantly metabolize seviteronel, and likely not just due to differences in body weight. Based on in vitro studies, seviteronel is completely metabolized by CYP2C9 and CYP2C19 (100% loss of 1uM substrate over 60 min), and to a lesser extent CYP3A4 (57% loss of 1μM substrate over 60 min) (unpublished data on file). It is possible there are sex differences in expression of these isozymes, however, no significant sex differences in CYP2C9 [28] and CYP2C19 [29] expression were reported. Interestingly, females have almost twice as much hepatic CYP3A4 expression compared to males [30], which should manifest as faster seviteronel clearance (granted intestinal CYP3A4 expression is not considered here). In this dataset, however, the opposite is true with males having faster clearance, which could be explained by the fact that CYP3A4 only contributes partially to seviteronel hepatic metabolism. It was though a concomitant medication may be involved in this sex difference in clearance, but aside from dexamethasone (which was shown to have no significant effect), there were no such medications given with seviteronel. While the mechanism currently remains unclear, it nonetheless is necessary to further explore this sex difference in future clinical studies for a more clear understanding.

In conclusion, seviteronel demonstrates excellent oral bioavailability, first-order absorption and elimination, the latter of which involves clearance pathways influenced by body weight and sex. Considering that there was no significant sex difference in CYP2C9 or CYP2C19 expression, it is entirely possible that the sex difference in clearance was due to some other drug, taken for female breast cancer treatment, inhibiting CYP2C9 or CYP2C19 to an extent that reduced overall clearance, relative to men. Further studies are necessary to rule out any endogenous or biological difference. The addition of body weight on clearance explained 8.4% of the BSV and sex 16.7%; but when body weight was added on top of the sex effect, this resulted in a total of 37% decrease in BSV on CL/F. This is a clinically-relevant covariate (sex and body weight), which this model confirms the decision to lower the dose based on sex (females 450 mg QD; males 600 mg QD). The ultimate utility of this model is to serve as the PK backbone and eventually add a response (PD) aspect, such as a biomarker for efficacy or toxicity. This will allow the model to have tremendous clinical relevance for making informed and personalized dosing decisions.

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Compliance with ethical standards

Conflict of interest JRE is an employee and shareholder and VVB is an employee of Innocrin Pharmaceuticals. All other authors declared no conflicts of interest and have nothing to disclose.

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