Preclinical Characterization and Prediction of Human Pharmacokinetics and Efficacious Dose for VIP236, a Novel αvβ3 Binding Small Molecule-Drug Conjugate (SMDC)

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INTRODUCTION

- αvβ3 integrins show an abundant expression in tumor microenvironment of aggressive cancers which is correlated with metastatic disease and poor prognosis[1]. Anti-angiogenic therapies antagonizing αvβ3 showed good safety profile with optimal homing to the tumor and metastases, but with limited efficacy[2].
- Due to insufficient internalization of αvβ3 binders, we sought for new mechanisms for activation and payload release using enzymes present in the tumor microenvironment. Neutrophil elastase (NE) belongs to a family of serine proteases that degrades extracellular matrix proteins and contributes to tumor evasion and metastasis. NE expression and neutrophil tumor infiltration have been correlated with metastatic potential and poor prognosis[3].
- VIP236 is a small molecule drug conjugate (SMDC) consisting of an alpha v beta 3 (αvβ3) integrin binder linked to an optimized camptothecin (optCPT) payload (VIP126), which is released by NE in the tumor microenvironment[4,5]. Here we describe the preclinical characterization and prediction of human pharmacokinetics of VIP236. VIP236 is currently in Phase 1 clinical trial.

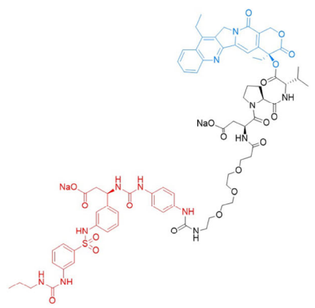


Figure 1. Chemical structure of VIP236.

METHODS

- Male C57BL/6 mice, male Sprague-Dawley rats, and male Beagle dogs were administered a single intravenous dose of VIP236 at 2 mg/kg in mice and rats, and at 1 mg/kg in dogs. Cumulative urine was collected in dogs. Serial plasma samples were collected and concentrations of VIP236 and VIP126 were quantitated by LC/MS/MS. Pharmacokinetic parameters were estimated using non-compartmental analysis.
- Bile-duct cannulated rats were administered a single intravenous dose of VIP236 at 10 mg/kg IV. Cumulative collection of urine and bile was collected for 48-hour post dose. VIP236 and VIP126 concentrations in bile and urine were quantified using LC/MS/MS.
- Plasma protein binding of VIP236 (1 µM) was assessed by equilibrium dialysis using mouse, rat , dog and human plasma.
- VIP236 permeability was determined in MDCKII cell monolayers. VIP236 was assessed as a substrate of OATP1B1, OATP1B3, OATP2B1, NTCP, MATE1, MATE2-K, P-gp and BCRP using either cells or membrane vesicles expressing the specific human transporters being evaluated.
- Prediction of human clearance (CL) or volume of distribution (V_{dss}) was performed using in vivo data from mouse, rat, and dog, and allometric scaling methods.
- VIP236 anti-tumor efficacy was evaluated in MX-1 breast cancer xenograft mice given intravenous doses of vehicle, 26, 36, and 40 mg/kg IV on a 3 on/4 off regimen. VIP236 anti-tumor effect was quantified by serial tumor area measurements over 79 days.
- Projections of human efficacious dose were made using a PK/PD model built using tumor area data from MX-1 xenograft mice given doses of VIP236. Dose projections were based on simulations performed using the MX-1 PK/PD driven by predicted human pharmacokinetics. The target tumor growth inhibition for simulations (TGI 65% or 75% at the end of 5 cycles of dosing a 2 on/ 5 off regimen) was based on irinotecan anti-tumor activity in MX-1 xenograft mice following 5 cycles of dosing with clinically relevant exposures/regimens.

RESULTS

Pharmacokinetics of VIP236 in Mouse, Rat, and Dog Show Low Plasma Clearance and Low Plasma Exposure of optCPT Payload

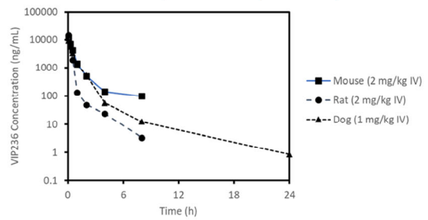


Figure 2. Mean VIP236 Plasma Concentration Versus Time Plot Following Single Dose Intravenous Administration to Mice, Rats, and Dogs (n=3 per timepoint)

Table 1. Pharmacokinetics (Mean ± SD) of VIP236 Following Single Dose Intravenous Administration to Mice, Rats, and Dogs.

Parameters	C57BL/6 Mice	Sprague Dawley Rats	Beagle Dogs
No. of animals	6a	3	3
Sex	Male	Male	Male
Dose (mg/kg)	2	2	1
CL (mL/min/kg)	4.4	6.6 ± 1.5	2.7 ±0.4
t½ (hr)	0.93	1.54 ±0.04	3.07 ± 1.82
Vss (L/kg)	0.25	0.11 ± 0.02	0.14 ± 0.02
VIP236 AUClast (ng·hr/mL)	7720	5210 ± 1300	6160 ± 770
VIP126 AUClast (ng·hr/mL)	3.12	NCb	11.9 ± 8.6
CLR (mL/min/kg)	NA	NA	0.05 ± 0.03

AUC_{last} = Area under the concentration-time profile from time 0 to last measurable concentration; CL = Plasma clearance; CL_R = Renal clearance; $t_{½}$ = terminal half-life; NA = Not available; V_{ss} = Volume of distribution at steady state.
[a]3 samples/timepoint
[b]AUC_{last} was not calculated (NC) as VIP126 concentrations were detected in only 2 plasma samples (5.5 ng/mL and 17.4 ng/mL)

Excretion of VIP236 is Primarily in the Bile in the Form of Unchanged Drug in Rats

Table 2. Mean Recovery of VIP236 and VIP126 from Bile-Duct Cannulated Rat Studies (n=3) Administered 10 mg/kg IV VIP236.

Matrix	% Dose Recovered in 48 hours
	VIP236
Bile	107%
Urine	2.4%
% Dose	109%*
	VIP126 from VIP236
Bile	1.9%
Urine	0.3%
% Dose	2.1%
% Total Dose Recovered	111%*

*considered complete recovery as experimental error exists

VIP236 is Highly Plasma Protein Bound

Table 3. Unbound fraction of VIP236 in Mouse, Rat, Dog and Human Plasma

Species	Unbound Fraction
	VIP236*
Mouse	2.4%
Rat	2.1%
Dog	3.2%
Human	1.7%

*determined by equilibrium dialysis (data presented for 1 µM incubation)

Allometric Methods Predict Low Human VIP236 Clearance and Volume of Distribution

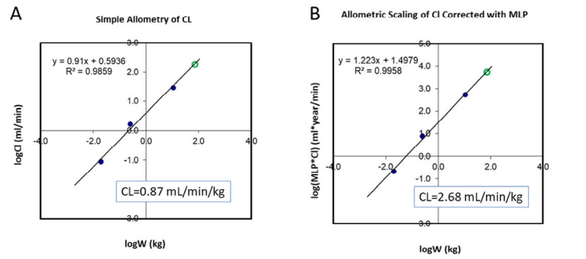


Figure 3. Prediction of Human Clearance Using Simple Allometry (A) and Allometry Corrected With Maximum Life-Span Potential (MLP) (B)

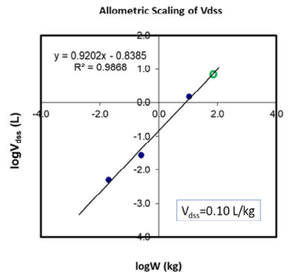
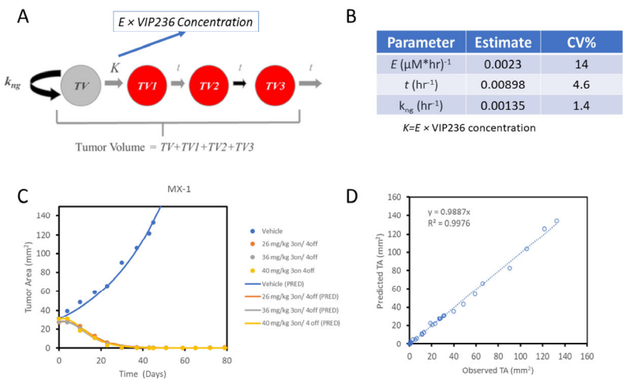


Figure 4. Prediction of Human Volume of Distribution (V_{dss}) Using Simple Allometry

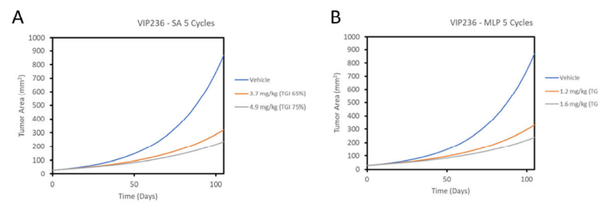


Parameter	Estimate	CV%
E (µM*hr)$^{-1}$	0.0023	14
t (hr^{-1})	0.00898	4.6
k_{ng} (hr^{-1})	0.00135	1.4

K=E × VIP236 concentration

Figure 5. Pharmacokinetic/Pharmacodynamic Modeling of VIP236 in Human Breast Cancer MX-1 Xenograft Mice. Indirect Response Model Characterizing Drug Effect on Tumor (A). Fitted Pharmacodynamic Parameters Characterizing VIP236 Anti-tumor Effect on MX-1 Xenograft Mice (B). Observed Tumor Area (TA) Versus Model Predicted TA (C, D).

Projected Human Doses Range from 1-5 mg/kg Using MX-1 Engrafted Mouse Models



C

CL Prediction Method	Target * (5 Cycles)	Predicted Efficacious Dose (2 on, 5 off)	Cmax (µM)	Daily AUC0-24 (µM × h)	Weekly AUC0-24 (µM × h)
Simple Allometry	TGI 65%	3.7 mg/kg	24.3	15.6	31.2
	TGI 75%	4.9 mg/kg	31.9	20.5	41.1
MLP Allometry	TGI 65%	1.2 mg/kg	7.66	15.2	30.4
	TGI 75%	1.6 mg/kg	10.2	20.3	40.5

*target based on irinotecan anti-tumor activity in MX-1 xenograft mice following 5 cycles of dosing

Figure 6. Projection of Human Efficacious Doses Using Predicted Human CL based on Simple Allometry (A) or Allometry Corrected With Maximum Life-Span Potential (MLP) (B). Predicted Human Pharmacokinetics Associated with Projected Human Efficacious Doses (C).

SUMMARY

- VIP236 had low plasma clearance in mice, rats, and dogs (CL=2.7-4.4 mL/min/kg) and low volume of distribution (V_{dss} = 0.11 to 0.25 L/kg). Terminal half-life ranged from 0.93 hour in mice to 3.07 hours in dogs. VIP236 renal clearance was very low in dogs. Very low concentrations of VIP126 were observed in plasma in all species evaluated.
- In BDC rats, VIP236 was primarily excreted in bile with biliary clearance accounting for essentially all of the total body CL. There was minimal to no metabolites in rat bile and urine.
- In vitro VIP236 exhibited low permeability in MDCKII cell monolayers (0.15 × 10^{-6} cm/sec) and was identified as a substrate of BSEP and MRP2.
- VIP236 was highly protein bound to plasma protein with fraction unbound being <5% in all species tested.
- VIP236 showed robust tumor regression in MX-1 xenograft mice at all doses tested.
- Allometric methods were used to predict a low human VIP236 CL (0.87-2.68 mL/min/kg) and V_{dss} (0.10 L/kg).
- Projected human doses ranged from 1-5 mg/kg IV on a 2 days on/ 5 days off regimen based on translational PK/PD modeling using MX-1 xenografted mice.
- VIP236 is currently being evaluated in a first-in-human study in patients with advanced or metastatic solid tumors (NCT05712889).

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