Population Pharmacokinetic and Viral Dynamic Modeling of VIS410, a Monoclonal Antibody Against Influenza A Virus in a Human Challenge Model

Kashyap Patel^, Patrick Smith^*, Susan Sloan, Georgina Dall^, Mark Lovern^, Jose Trevejo, Ellie Hershberger

Visterra, Inc., Cambridge MA

^Certara, Parsippany, NJ

*Presenting author
Patrick.Smith@certara.com

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ABSTRACT

Background: VIS410 is a novel human IgG1 monoclonal antibody with broad antiviral activity against influenza A, and is currently in Phase 2 clinical development. A population pharmacokinetic (popPK) and influenza viral dynamic (VD) model were developed to support the VIS410 clinical program, integrating data from a Phase 1 healthy volunteer study and a Phase 2a human influenza challenge study.

Methods: Nasal and serum PK data from a Phase 1 study (N=30, single IV doses 2 – 50 mg/kg) and a Phase 2a study (N= 33, single IV doses of 2300 and 4600 mg) were used to develop the popPK model. In the Phase 2a study, subjects were inoculated intranasally with an attenuated influenza A (H1N1) strain, and received placebo or VIS410 24h post-inoculation. Frequent nasal viral load (qPCR and TCID50), serum and nasal PK were measured. The pharmacodynamic analysis included viral load data from intent-to-treat infected subjects (ITT): placebo (n=7), 2300 mg (n=22), 4600 mg (n=4). All analyses were performed in NONMEM 7.3 and qPCR and TCID5050 were modeled separately; BLQ data were handled using the M3 method, with predictive performance evaluated using NPDE (in R).

Results: A 3-compartment model adequately described PK with first-order distribution of VIS410 between nasal and central compartments (mean (%RSE) CLD serum-to-nasal 0.04 (19.5%) mL/h; and nasal-to-serum 1.95 (17.1%) mL/h). Body weight was the only covariate that was retained in the popPK model. Other covariates tested included gender, age and infection status, but were non-influential. A 91% reduction in viral load AUC by qPCR was observed at the 2300 mg dose compared to placebo (p<0.05). Viral dynamics in placebo and ITT subjects were well characterized by a modified VD model comprising virus, target epithelial cells, non-productive and productive infected cells; mAb drug effect was modeled as inhibiting membrane fusion in the nasal compartment, via an Emax function (mean (%RSE) EC50 qPCR = 1.96 (13) µg/mL and EC50 TCID50 = 18.4 (2.6) µg/mL).

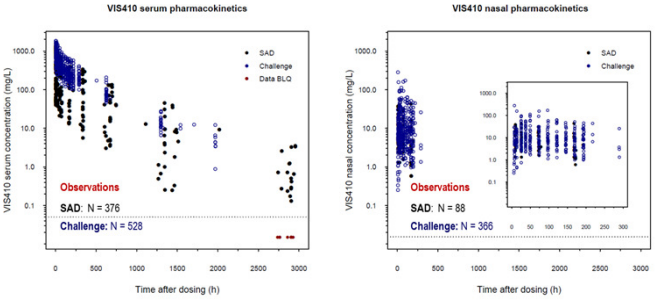
Conclusion: VIS410 demonstrated PK generally typical of IgG1 mAbs, and potent antiviral activity compared to placebo in the H1N1 human challenge model (HCM). A novel semi-mechanistic popPK model, which links mAb nasal concentrations to influenza VD based on the VIS410 mechanism of action was successfully developed. The model describes serum and nasal PK, with impact on viral load, and was used to support dose selection for future clinical development across a spectrum of populations. This approach may be extended to other mAbs targeted against influenza viral infections.

OBJECTIVES and DATA

- **Population PK Model:** Develop a population PK model which characterizes VIS410 exposures in both serum and nasal compartments, and to test for covariates (weight, age, race, etc) associated with differences in PK
- **Viral dynamic (PK/PD) model:** Develop a mechanistic mathematical model which characterizes influenza viral kinetics, and the impact of VIS410 on viral replication
- Data to inform the model were available from 2 studies:
  - A Single Ascending Dose study in healthy volunteers (n=6/2 active/placebo per cohort) at dose levels of 2, 5, 15, 30, and 50 mg/kg
  - A Human challenge study in volunteers (ITT population) inoculated with H1N1 who received placebo (n= 7), 2300 mg (n=22), or 4600 mg (n=4) VIS410.

POPULATION PK MODEL

- Serum and nasal VIS410 concentrations were modeled simultaneously in NONMEM Version 7.3
- The serum PK of VIS410 was similar to other IgG1 monoclonal antibodies, with dose-proportional pharmacokinetics and a long half-life
- The nasal:serum ratio was approximately 4%, with the retention time in the nasal compartment being prolonged, with concentrations exceeding the in vitro EC50 at higher VIS410 dose levels
- Weight (LBW, TBW), sex, infection status, and age were tested as covariates in the model; only weight (TBW) was retained as being a significant factor associated with PK (CL, Vc, Vp)



Serum sampling up to **3000 h** | Nasal sampling up to **300 h**

Serum and Nasal VIS410 concentrations across a range of doses were available to develop the Population PK model

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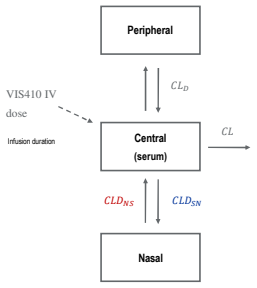
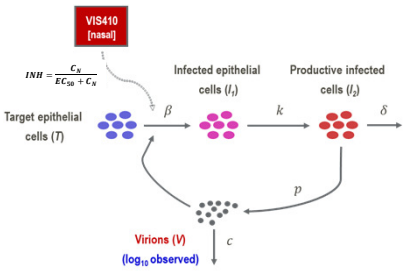
POPULATION PK MODEL



PK Model Parameters	Mean value (%RSE)	%BSV (%RSE)
CL (mL/h)	13.0 * (WT/70)$^{3/4}$ (2.3)	16.9 (8.1)
V_C (L)	2.63 * (WT/70) (2.7)	21.5 (12.5)
CL_D (mL/h)	23.3 (7.8)	42.3 (21.1)
V_P (L)	2.02 * (WT/70) (4.4)	31.8 (11.3)
CLD_{SN} (mL/h)	0.0403 (21.1)	68.1 (10.5)
CLD_{NS} (mL/h)	1.96 (19.3)	-
V_N (L)	0.034 (fixed)	-
RUV_{prop_ser} (CV)	0.143 (4.5)	-
RUV_{add_ser} (mg/L)	0.116 (27.2)	-
RUV_{prop_nas} (CV)	0.703 (4.0)	-

VIRAL DYNAMIC MODEL



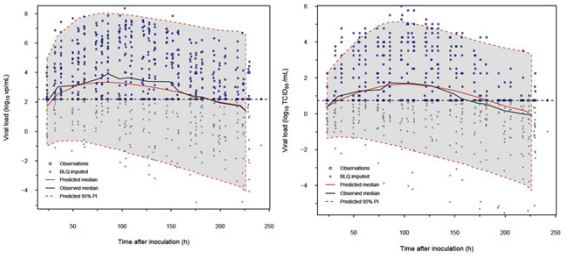
$$\frac{dT}{dt} = -\beta TV$$

$$\frac{dI_1}{dt} = \beta TV - kI_1$$

$$\frac{dI_2}{dt} = kI_1 - \delta I_2$$

$$\frac{dV}{dt} = pI_2 - cV$$

VIS410 inhibits hemagglutinin-mediated cell membrane fusion, thereby preventing viral replication; The effect of VIS410 was modeled as the nasal concentrations inhibiting infection of uninfected target epithelial cells

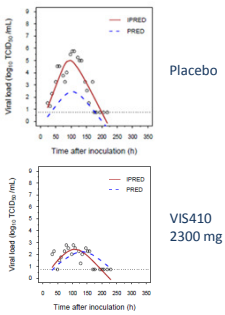


Visual Predictive Checks of the Modeled vs. Observed data demonstrate good predictive performance of the model and lack of bias for both PCR (left) and TCID50 (right) data

VK Model Parameters	qPCR Mean (%RSE)	$TCID_{50}$ Mean (%RSE)
T_0 (cells)*	4×10^8	4×10^8
F_{VL} *	1×10^{-6}	1×10^{-6}
β (1/TCID$_{50}$/mL/h)	6.14×10^{-6} (7.3) (%BSV 341 (9.1 %RSE))	1.99×10^{-4} (9.2) (%BSV 228 (13.1 %RSE)
$1/k$ (h)*	6	6
$1/\delta$ (h)*	6	6
p (TCID$_{50}$/mL/h)	8.44×10^{-5} (10.9) (%BSV 400 (8.2 %RSE)	8.32×10^{-7} (7.0) (%BSV 284 (13.5 %RSE)
c (1/h)	0.08 (1.9)	0.118 (4.6)
$T_{inf} = \sqrt{2/p\beta T_0}$ (h)	3.10	5.49
EC_{50} (mg/L)	1.96 (13.0)	18.4 (2.6)
RUV_{prop_vl} (CV)	1.04 (1.8)	0.776 (2.2)

*fixed parameter

Example Model Fits to Individual Subjects (TCID50)



- VIS410 reduced viral load AUC by 92% at the 2300 mg dose compared to placebo
- The PK/VK model was able to characterize the viral kinetics of influenza and the effect of VIS410
- At 2300 mg, serum and nasal concentrations of VIS410 exceeded the model estimated EC50 for both TCID50 and qPCR for an extended period of time

SUMMARY

- **A Population PK and PK/PD model was developed for VIS410 which characterizes the serum and nasal PK, and impact on influenza viral kinetics from a HCM**
- **Total body-weight was the only statistically significant covariate associated with VIS410 PK**
- **VIS410 demonstrated potent antiviral activity in the HCM, and based on these analyses, VIS410 is expected to be effective at doses of approximately 2300 mg based on exceeding the modeled EC50 target in the nasal compartment.**

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