Model-based Clinical Efficacy Prediction and Study Design Support for VIS410, a Novel Neutralizing mAb, in Combination with Oseltamivir, in Hospitalized Patients with Influenza A

ARP0028

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ABSTRACT

Background: Seasonal influenza is a major cause of morbidity and mortality in high risk populations. VIS410 is a novel neutralizing mAb, active across a broad range of influenza A viral strains, and may have utility for treating hospitalized patients with influenza. Trials of VIS410 alone and in combination with one of the neuraminidase inhibitors (NAIs) oseltamivir (OS) have yielded promising results in animal studies and in a human challenge study. This work was performed to support design of VIS410 trials in combination with OS, focusing on duration of oxygen (O2) support as a clinical endpoint. The main objectives were to predict efficacy of the combination in hospitalized pts on supplemental O2 therapy, and to optimize clinical trial design with respect to patient population and VIS410+OS combination regimens.

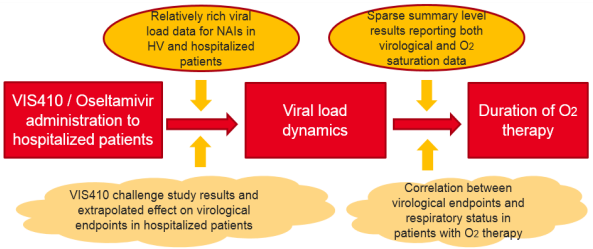
Methods: Two key knowledge gaps were bridged using published data to characterize relationships between treatment, virologic response, and duration of O2 therapy in hospitalized patients with influenza A: 1) correlation of virologic response in Human Influenza Challenge model and hospitalized patients; 2) impact of virologic response on duration of O2 therapy. The first gap was addressed by adapting a viral dynamic model to reflect data from the VIS410 Challenge study using a H1N1 influenza A virus. This model was extended to account for the combined effects of OS+VIS410, the impact of different viral strains, and baseline disease severity and respiratory status on viral dynamics. The second gap was addressed by using literature data to characterize the relationship between virologic response and O2 saturation. Clinical trial simulations were then performed to evaluate various treatment regimens.

Results: Simulations predicted that combination therapy with VIS410 doses > 2000 mg would likely yield substantial therapeutic benefit relative to OS alone, reducing duration of O2 therapy by ≥ 1.5 days. In addition, baseline O2 saturation correlated well with the benefit of the combination therapy. Subjects with baseline O2 < 90% were predicted to have greater benefit from combination therapy compared to those with baseline O2 > 90%.

Conclusion: In this work, integrating data from published and conducted clinical trials allowed us to estimate the impact of VIS410 in combination with OS. This model extends prior analyses to focus on clinically relevant endpoints, going beyond linking drug exposure to viral clearance.

QUANTITATIVE MODELS AS A DATA INTEGRATION TOOL

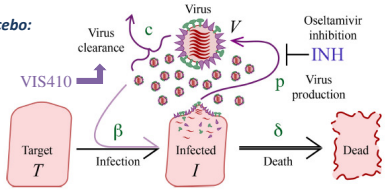
- **Key knowledge gaps**
  - What is the correlation between the virologic response to therapies in Human Influenza Challenge models and that of hospitalized patients?
  - What is the correlation between virologic response and the duration of O2 therapy in patients requiring supplemental O2?



- **Viral dynamic model:** making a semi-mechanistic connection between viral kinetics, mechanisms of actions from treatments, and virologic response in patients with a wide range of severity levels (adapted from *Kamal 2015*)

Natural viral titer dynamics for placebo:

$$dT/dt = -\beta TV$$
$$dI/dt = \beta TV - \delta I$$
$$dV/dt = pI - cV$$



Oseltamivir effect:

$$p = 10^{\theta - [E_{max} \times Dose/(Dose + ED50)]}$$

Added VIS410 effect: $c_{drug} = c_{pcb} \cdot (1 + E_{max} \cdot C168/(C168 + EC50))$

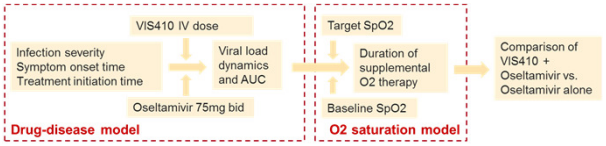
VIS410 inhibits hemagglutinin-mediated cell membrane fusion, thereby preventing viral replication; it therefore indirectly increases the extracellular exposure of the free virus to antibodies, which would bind and remove free virus.

- **O2 saturation model:** characterizing the relationship between virologic response and O2 saturation from literature data

$$SpO2(t) = SpO2_{BL} + (SpO2_{Normal} - SpO2_{BL}) * (1 - e^{-k*t/AUCvl\hat{}2})$$

Source of data	Type of NAI	Dosing regimen	Number of patients	Target O2 saturation	Median duration of O2 therapy	Viral load AUC (log10 TCID50/ml*d)
Ison 2014	Peramivir	300mg BID IV	35	92%	22 hours	14.0
		600mg QD IV	52		46 hours	15.7
Lee 2011	Oseltamivir	75/150mg BID	28	95%	6 days	18.2
Lee 2013	Oseltamivir	75mg BID	70	92%~95%	3 days	12.1
		150mg BID		92%~95%	3 days	

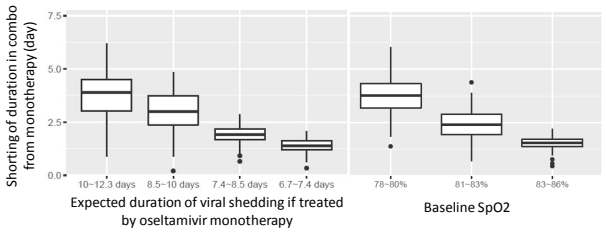
CLINICAL TRIAL SIMULATIONS



- **Infection characteristics**
  - Infection severity: viral shedding duration 1~2 weeks with NAI monotherapy
  - Symptom onset time: 1~3 days after infection
  - Treatment initiation time: 1~4 days after symptom onset
- **Strains considered in simulations**
  - 41 influenza A strains that were tested for VIS410 neutralization potency *in vitro*
    - EC50 of H1N1pdm09: 1.34 μg/ml
    - 80% of tested strains have an EC50 <= 9 μg/ml
- **Target patient population**
  - Approximately 25% most severe patients require ICU, similar to the ICU population in *Hung 2011*
    - Baseline SpO2 ~ 80%, viral shedding 10~12 days with NAI monotherapy
  - The rest 75% hospitalized patients require O2 therapy, similar to the severe pneumonia patients in *Lee 2011*
    - Baseline SpO2 up to 88%, viral shedding 7~10 days with NAI monotherapy

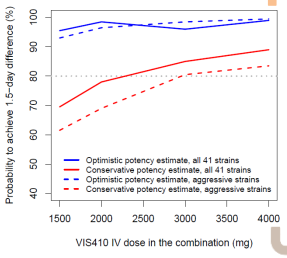
SIMULATION PREDICTION OF EFFICACY FOR COMBO THERAPY

- **The improvement from OS+VIS410 combination is predicted to be more prominent in populations with higher infection severity and lower baseline SpO2.**

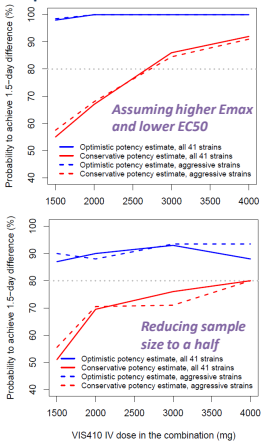


- **While a VIS410 dose ≥2000 mg is most likely to achieve a ≥1.5-day reduction in O2 therapy duration between the combination and oseltamivir monotherapy, the probability of success is also dependent on multiple other factors.**

Uncertainty in parameter estimates for VIS410 effects could lead to changes in the predicted probability.



Lowering the sample size in a simulated trial will decrease the probability of success.



SUMMARY

- **Quantitative models were developed and clinical trial simulations were conducted to predict the efficacy of the OS+VIS410 combination therapy.**
- **The improvement from the OS+VIS410 combination is predicted to be more prominent in patients with higher infection severity and lower baseline SpO2.**
- **VIS410 doses ≥2000mg in combination with OS are likely to achieve a ≥1.5-day reduction in supplement O2 therapy in hospitalized influenza A patients.**

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