

Model informed dose projection for SAB-176 using a joint time-to-event modeling approach in high-risk (HR) patients infected with Influenza

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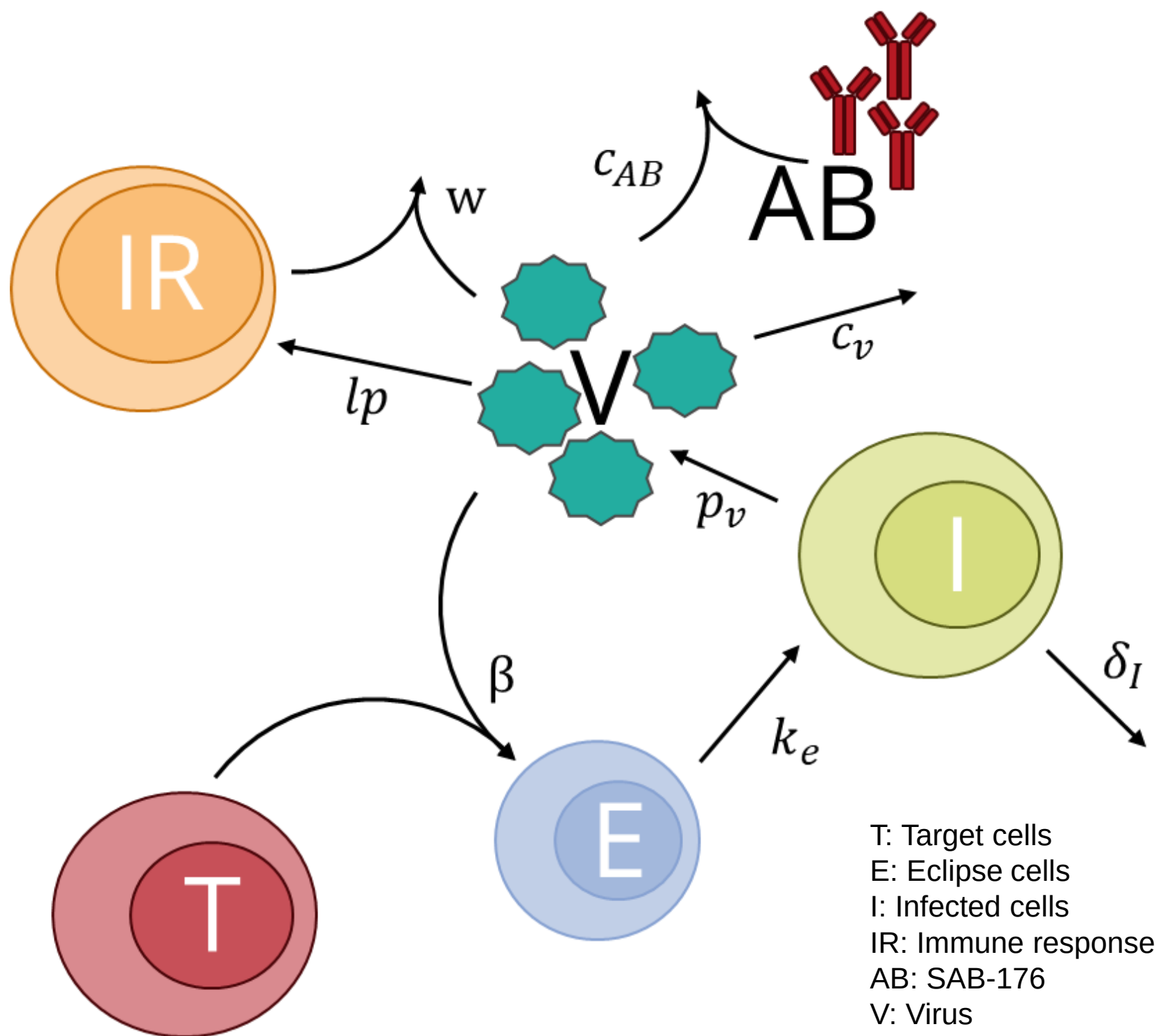
Background

SAB Biotherapeutics has developed SAB-176, a fully human polyclonal Immunoglobulin G antibody produced in transchromosomal bovines (TcB), which has shown high-titer neutralizing activity against multiple strains of Influenza A and B, offering potential for treating high-risk (HR) patients. Data from a phase 2a study and published data were combined to develop a model that simulates time to symptom alleviation based on the viral load dynamics in both otherwise-healthy (OwH) and high-risk patients infected with Influenza A or Influenza B. The model was used to project doses of a Phase 2b study.

Methods

The analysis was conducted in three steps:

1. A mechanistic viral load was parameterized to reflect the influenza infection dynamics in healthy patients based on public literature data and a Phase 2a study [1,2]. The model is based on a target-cell limited model [1]. A simplified immune response model was included to reflect differences between OwH and HR patients.



2. The time to alleviation of symptoms (TTAS), was described by a time-to-event model for OwH and HR patients. A log-logistic distributed hazard function was assumed for OwH patients [3]. The hazard of HR patients was described using a link function based on the difference in viral load between HR and OwH patients.

$$TTAS(t) = e^{-H(t)}$$
$$H(t) = \int_0^t h_{HR}(\tau) d\tau$$

$$h_{HR}(t) = h_0(t) \cdot \exp^{\beta_{Link} \cdot (\log(1+V_{HR}) - \log(1+V_{OwH}))}$$
$$h_0(t) = \frac{\frac{k}{\lambda} \left(\frac{t}{\lambda}\right)^{k-1}}{1 + \left(\frac{t}{\lambda}\right)^k}$$

3. Different treatment scenarios were simulated varying the dose of SAB-176, time of treatment after infection and virus variants. Additionally, effects such as antibody-dependent cellular cytotoxicity and phagocytosis were not reflected in the viral load model. Thus, additional simulations with 5x and 10x higher efficacy were conducted.

References:

[1]: Smith et al., Influenza A virus infection kinetics: quantitative data and models. Wiley Interdiscip Rev Syst Biol Med. 2011
[2]: Hayden et al., Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents. N Engl J Med. 2018
[3]: Retout et al., A Pharmacokinetics-Time to Alleviation of Symptoms Model to Support Extrapolation of Baloxavir Marboxil Clinical Efficacy in Different Ethnic Groups with Influenza A or B. Clin Pharmacol Ther. 2022

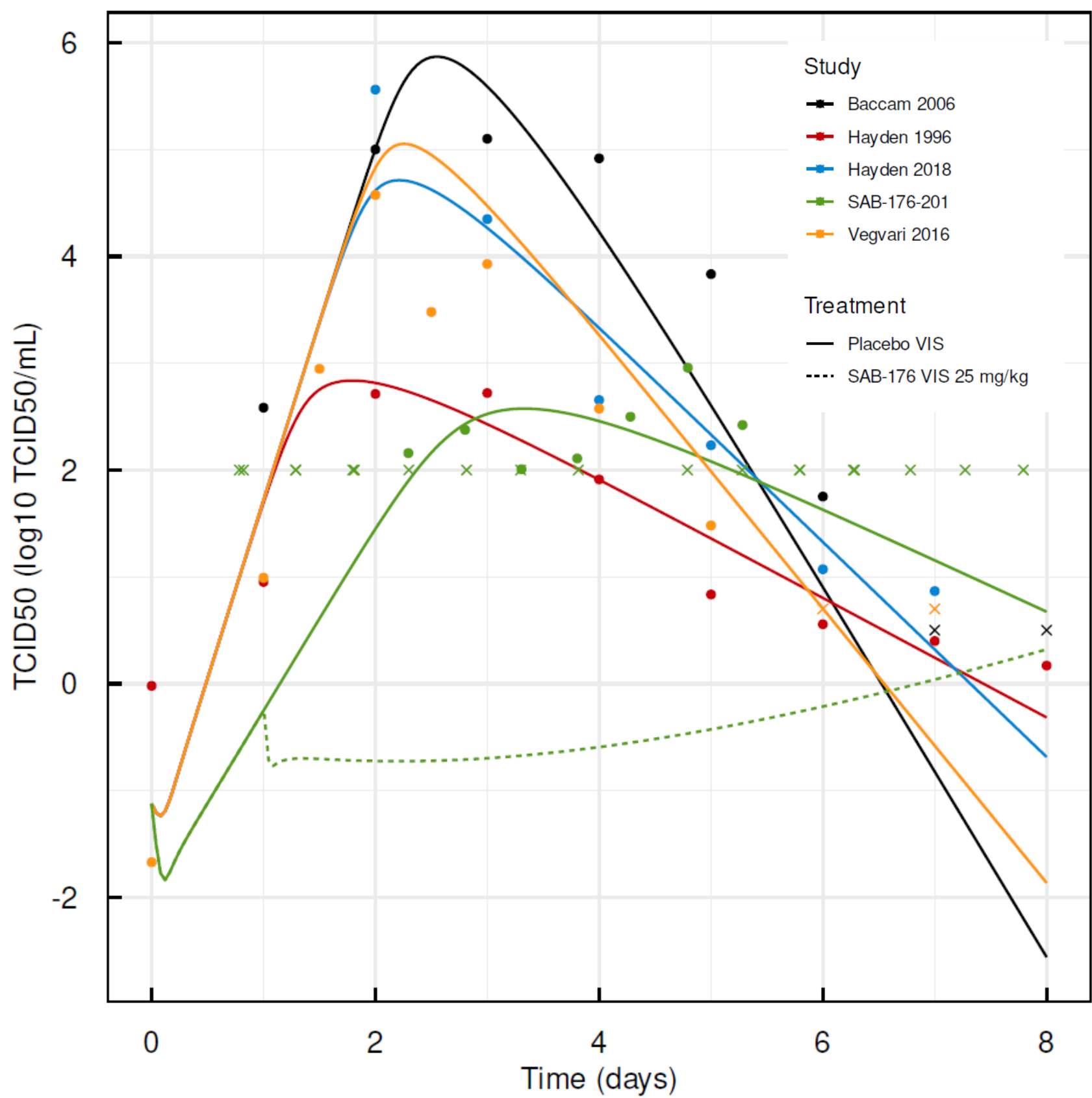
Funding: SAB Biotherapeutics funded the analysis.

Conclusion

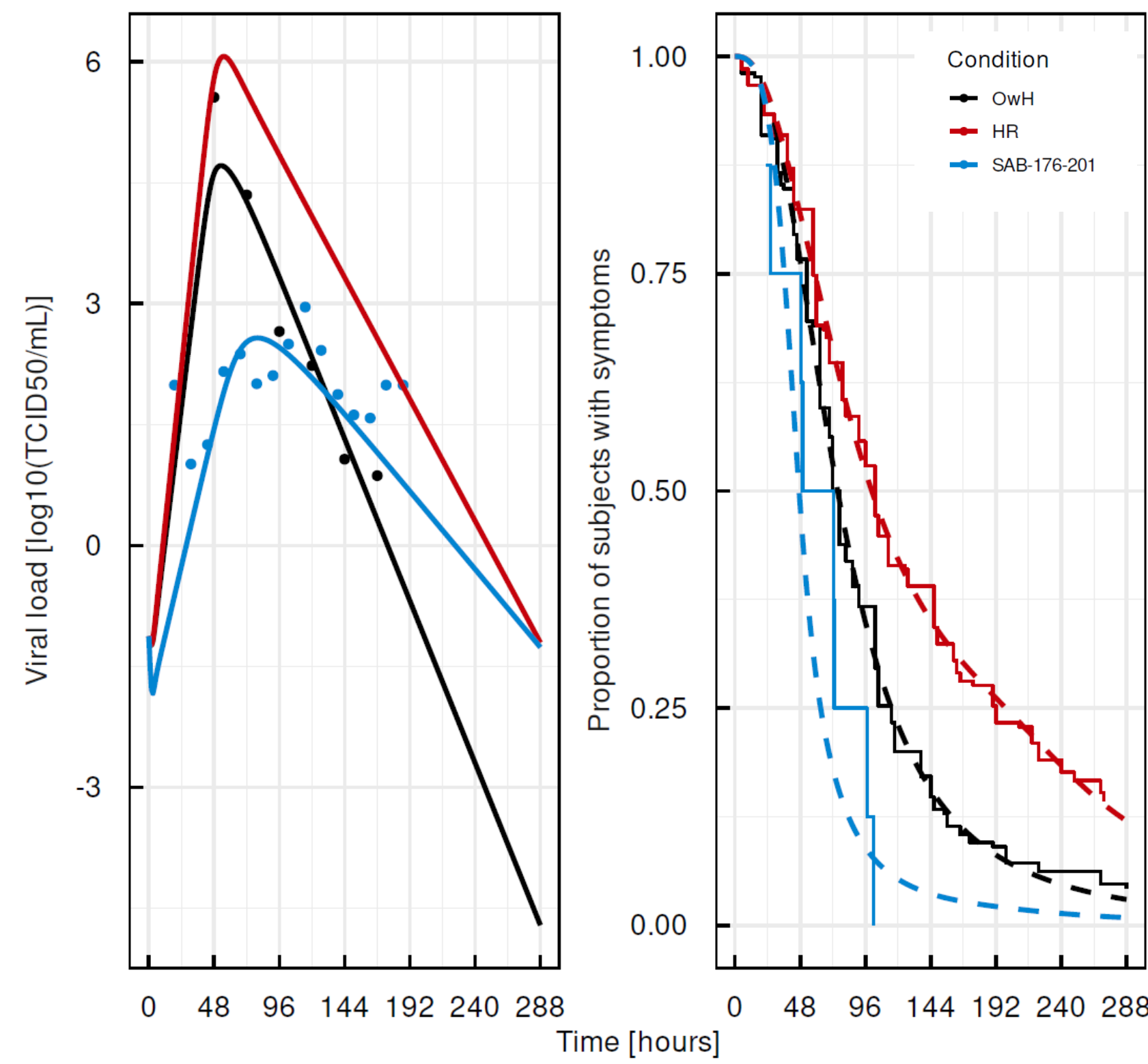
A mechanistic viral load model, based on public literature and data from a phase 2a study, was developed, revealing that SAB-176 significantly reduced viral load. A joint Time-to-event model was developed, linking viral load and symptom alleviation time. High-risk patient data exhibited higher viral loads, prolonged viral shedding, and longer symptom alleviation times. The model accurately predicted these outcomes. A favorable dosing scenario was simulated to reduce symptom duration from approximately 200 hours to around 140 hours, an effect size similar or better to the one observed with approved anti-influenza treatments [2].

Results

- The mechanistic viral load model fitted data from public literature and the Phase 2a study well.
- Parameters k_e, δ_I, c_v, p_v were fixed to previously published values.
- The differences between the viral load in different studies was described by a covariate on the immune activation parameter lp .
- Only the lower limit of the antibody-mediated neutralization of virus was identifiable due to the low viral loads in the Phase 2a study.



- The joint time-to-event model established a link between viral load and TTAS data of OwH and HR patients [2,3].
- The data suggests that the immune response was lower (decreased lp) and infected cells had a lower death rate (δ_I) in HR patients.
- Thus, the model predicts a higher and more sustained viral load in HR patients
- The model was validated using data from the Phase 2a study.



- The joint model was used to simulate the effect of various dosing scenarios of SAB-176 treatment.
- A favorable scenario (top projected dose, treatment after 48 hours of infection) reduced the time at which only 25 % of HR still had symptoms from approximately 200 hours in the untreated group, to 140 hours in treated HR patients.

