# Individual virtual controls as surrogate for a control arm:

## Application for siRNA and NA therapy in chronic hepatitis B infection

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### Introduction of the concept

- Clinical studies often include a control arm, either placebo or standard-of-care (SOC), to determine the (additional) effect of an investigational treatment on endpoints (e.g. predictive biomarker).
- Substitution and/or reduction of a control arm is possible by borrowing from data sources external to the trial ("historical borrowing"), platform trials, and/or Real-World Data[1,2]
- Subject-specific biomarker data during a first treatment '*training*' period can be used to predict the most likely biomarker trajectory for a second '*prediction*' period, where the cohort receives add-on treatment (addTx)
- For each subject, the predicted biomarker trajectory can be used as its own 'virtual control' to calculate the net drug effect of an add-on treatment. The general workflow (Fig.1) and the concept of the VC as a control arm (Fig.2) are provided below.
- In order to investigate the performance of the VC methodology, a simulation study is presented to evaluate the approach.

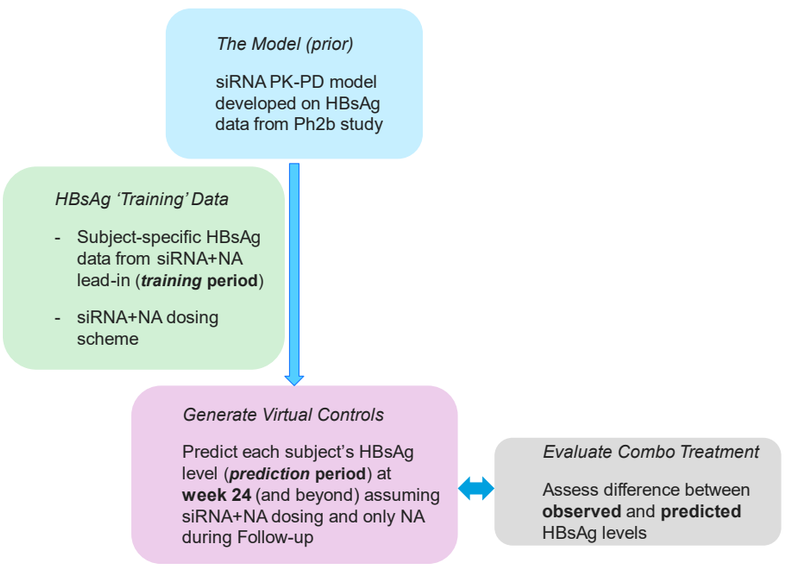


**Figure 1. Workflow to Generate Virtual Controls and evaluate the combo treatment vs the Virtual Control arm**

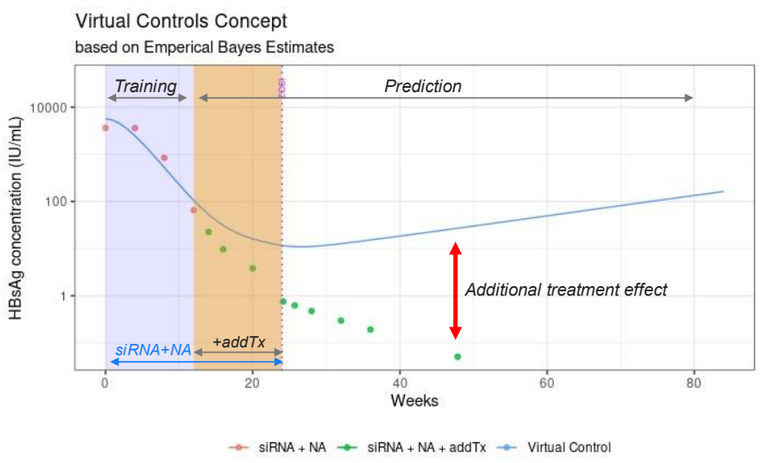


**Figure 2. Virtual Control (VC) Concept for a hypothetical subject with the current Simulated Study Design (see Methods).**
Blue area: dosing of siRNA+NA; Orange area: dosing of siRNA+NA continues + dosing of addTx
Red dots: first 12 weeks of HBsAg data (training period)
Green dots: HBsAg data collected under combo treatment (prediction period)
Red arrow: the difference between the observed HBsAg under combo treatment and the VC.

### Objective

- Investigate the performance of Virtual Controls (VC) through a simulation framework with a PK-PD model for HBsAg (viral marker), developed under siRNA+NA treatment for Hepatitis B
- Key questions
  - How reliable are predictions at an individual level?
  - What about on- and off-treatment periods?

### Methods: Model & Simulation Study Design

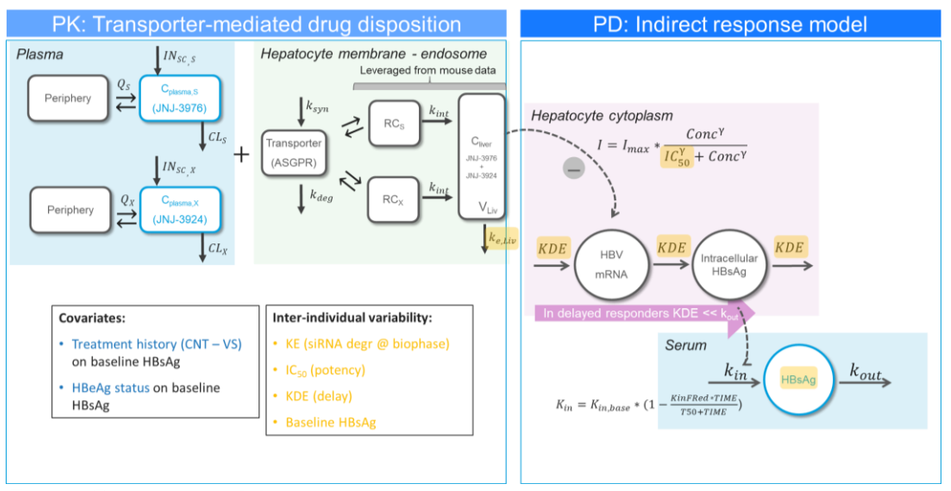


**Figure 3. PK-PD model structure**

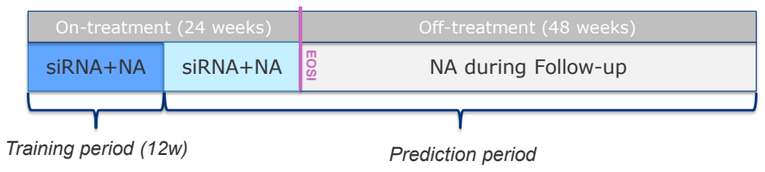


**Figure 4. Design of the Simulation Study focused on Assessing Virtual Controls' Performance .**
Blue areas: dosing of siRNA+NA; EOSI: End Of Study Intervention

**PK-PD Model**

- PK-PD indirect response model with signal transduction delay to describe HBsAg dynamics during siRNA + NA treatment, developed based on interim Ph2 data[3,4] (Fig.3)

**Simulation study**

- 1000 virtual subjects received siRNA + NA for 24 weeks (on-treatment), after which siRNA treatment was stopped and NA continued for 48 weeks (off-treatment) (Fig.4).
- Empirical Bayes Estimates (EBE) and individual-level variance-covariance estimates (phi matrix) obtained by fitting the *training* period data to predict the individual biomarker trajectory for the *prediction* period (Fig.4)

**Evaluation performance**

- Prediction performance was assessed, by calculating (i) the absolute prediction error (PE = $\log_{10}$(pred/true)), and (ii) the PI coverage, i.e. number of 'true' HBsAg data points inside the individual-level 95% prediction intervals

## Results & Discussion

### *Endpoint Analysis (End of Study Intervention at week 24) (Fig.5)*

**Table I. HBsAg prediction error (PE) distribution at week 24**

| PE ($\log_{10}$ IU/mL) | HBsAg prediction | % of VC subjects |
|---|---|---|
| < -0.5 | Underpredicted | 7.7% |
| [-0.5;0.5] | Acceptable | 87% |
| > 0.5 | Overpredicted | 5.7% |

- HBsAg underprediction (purple dots) is linked to an underestimation of both the delay in response for the majority of subjects (KDE) and the (shrunk) potency ($IC_{50}$). High shrinkage indicates lack of information in the '*training*' period to inform parameter estimation
  - Linked to a low estimated KDE, i.e. 'apparent delayer'
- HBsAg overprediction (yellow dots) is linked to an overestimation of both the KDE and $IC_{50}$
  - Linked to a low true KDE, i.e. 'true delayer' misclassified as an estimated non-delayer
- Limited/no association for $k_{eLiv}$, indicative of lack of information in the '*training*' period to inform parameter estimation

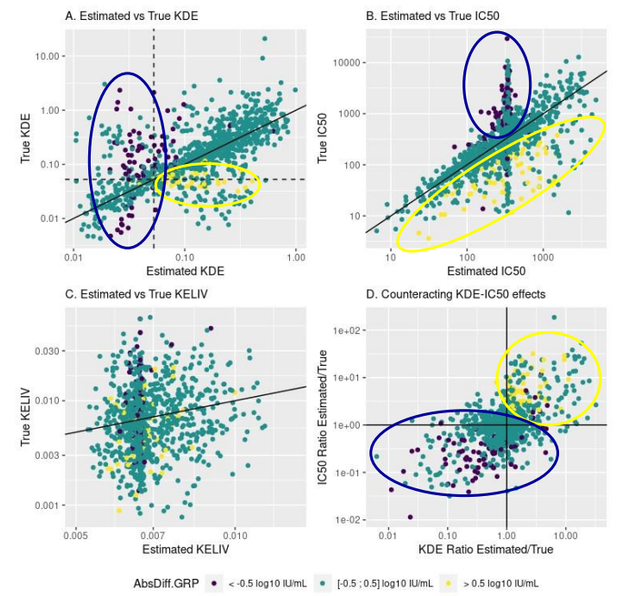


**Figure 5. Estimated vs True parameter associations**

### *Longitudinal Analysis (including prediction uncertainty) (Fig.6)*

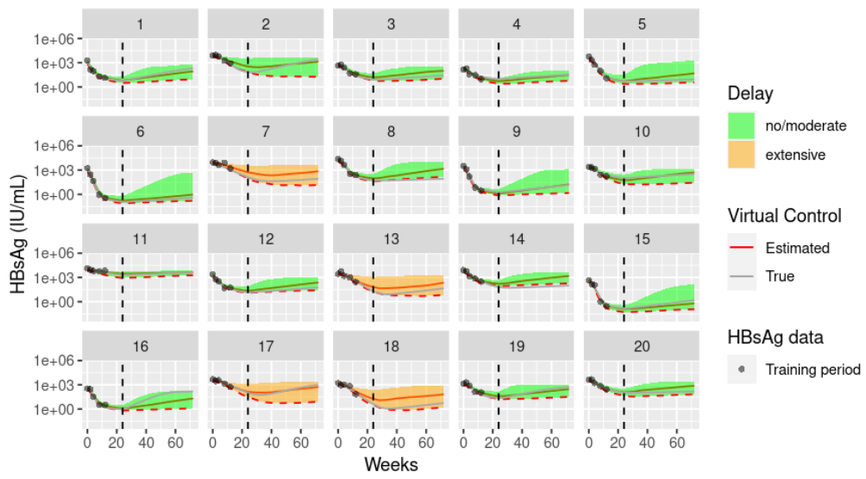


**Figure 6. Example Subset of (n=20) VC subjects with uncertainty prediction**
Dashed red line indicates the 2.5th percentile.

- On-treatment model performance is robust
  - First 12 weeks: narrow prediction intervals (*training* period)
  - Week 12 – 24: wider prediction intervals, mostly for delayers (*prediction* period)
- Off-treatment model performance (*prediction* period) strongly depends on the delay status
  - 90% PI coverage for moderate – no delayers[$]
  - 75-80% PI coverage for extensive delayers[$]: due to bias in the off-treatment prediction

[$] extensive delayer KDE<kout/3 ; moderate - no delayer KDE> kout/3

### Conclusion

- The application of VC may obviate the need for an actual control arm, as shown in this simulation framework
  For example, VC of siRNA+NA could be used to compare against siRNA+NA and a third compound instead of enrolling an siRNA+NA+placebo arm
- The approach allows to make the best possible prediction, based on each individual's initial response (i.e. '*training*' period) to treatment, for the expected future biomarker course (i.e. '*prediction*' period).
- Correlation between parameter estimates due to the "short" lead-in time in the '*training*' period, in particular for delayed responders, may present a limitation to this approach and may need to be further optimized

### References

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2. Su L, Chen X, Zhang J, Yan F. Comparative Study of Bayesian Information Borrowing Methods in Oncology Clinical Trials. JCO Precis Oncol. 2022 Mar;6:e2100394. doi: 10.1200/PO.21.00394.
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