# Understanding the Dynamics of HBsAg Decline Through Model-informed Drug Development (MIDD) of siRNA and CAM-N for the Treatment of Chronic Hepatitis B Virus Infection

Huybrecht T'jollyn,* Nele Goeyvaerts,* Thomas N. Kakuda, Louis Sandra, Tetsuro Ogawa, Joris Vandenbossche, Xavier Woot de Trixhe, Oliver Lenz, Ronald Kalmeijer, Michael Biermer, Juan Jose Perez Ruixo, Oliver Ackaert

Janssen Research & Development, Beerse, Belgium. *Denotes shared first authorship.

## Introduction

- Despite the availability of an efficacious prophylactic vaccine for hepatitis B virus (HBV) infection, >296 million people worldwide are affected by chronic hepatitis B (CHB) infection[1]
  - Approximately 820,000 people worldwide die annually from cirrhosis and liver cancer due to CHB
- JNJ-3989 is an N-acetylgalactosamine (GalNAc)–conjugated short-interfering RNA (siRNA) consisting of 2 triggers (S-trigger and X-trigger) designed to target all HBV RNAs, thereby reducing all viral proteins[2]
- JNJ-6379 is a capsid assembly modulator–N (CAM-N) that induces the formation of "empty" HBV capsids[3-8]
- The phase 2b REEF-1 study (ClinicalTrials.gov Identifier: NCT03982186) assessed the combination of siRNA 40, 100, and 200 mg as subcutaneous (SC) injections every 4 weeks and/or oral CAM-N 250 mg once daily on a background therapy of nucleos(t)ide analogue (NA)[9]

## Objectives

- To evaluate the relationship between dose, exposure, and response of a combination of siRNA and NA treatment using a pharmacokinetics-pharmacodynamics (PK-PD) modeling approach linking siRNA plasma concentrations to hepatitis B surface antigen (HBsAg) decline
- To define the relative contribution of CAM-N to the response of siRNA in lowering HBsAg

## Methods

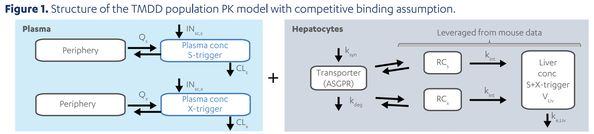
### Data

- Pooled pharmacokinetic (PK) data of phase 1/2b studies included AROHBV1001 (healthy volunteers [HV] and CHB patients), 73763989HPB1001 (Japanese HV), 73763989HPB1002 (hepatic impairment [HI] patients), and 73763989HPB2001 (REEF-1; CHB patients), with 2,540 S-trigger plasma samples and 2,487 X-trigger plasma samples from 439 participants
  - 133 rich PK participants contributed 1,435 samples for the S-trigger and 1,381 samples for the X-trigger
- Pharmacodynamic (PD) data of the phase 2b HPB2001 study at Week 48 (end-of-treatment clinical cutoff) included 9,597 observations from 377 participants across 6 treatment arms (0.5% below the quantification limit)

### siRNA PK Model

- A transporter-mediated drug disposition (TMDD) population PK model with competitive binding behavior[10] was developed; it describes the binding of both triggers to the asialoglycoprotein (ASGPR) receptor (ie, the "transporter"; **Figure 1**)
- ASGPR-mediated liver uptake was accounted for by leveraging information from siRNA concentrations collected from the plasma and liver of HBV-infected mice[11]
- Model assumptions:
  - siRNA liver concentration is driven by ASGPR transporter binding, which is saturated with increasing doses
  - ASGPR expression is constant over time (transporter degradation rate [$k_{deg}$] = transporter internalization rate [$k_{int}$])
  - Binding was assumed to be fast relative to other rate constants, so the drug-receptor complex is at a (quasi) steady state
  - siRNA $k_{int}$ is comparable between mouse and human species

**Figure 1.** Structure of the TMDD population PK model with competitive binding assumption.

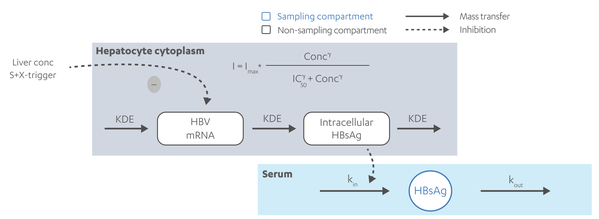



$CL_S/CL_X$, S/X-trigger plasma clearance; $IN_{SC,S}/IN_{SC,X}$, absorption for S/X-trigger after SC administration; $k_{d,LIV}$, elimination rate of S/X-trigger from liver; $k_{syn}$, ASGPR synthesis rate; Liver conc S+X-trigger, summed liver concentration of S+X-triggers; Plasma conc S/X-trigger, S/X-trigger plasma concentration; $Q_S/Q_X$, S/X-trigger distributional clearance; $RC_S/RC_X$, concentration of ASGPR-bound complex with S/X-trigger; $V_{LIV}$, liver volume.

### siRNA PK-PD Model

- The model described the relationship between estimated human liver concentrations and the inhibition of HBsAg production leading to observed HBsAg decline in patients, considering treatment status (not currently treated [NCT] or virologically suppressed [VS]) and hepatitis B e antigen (HBeAg) status (positive or negative) at baseline (**Figure 2**)
- An indirect response model (IRM) with signal transduction delay was used to capture a mixture of immediate and delayed responders to siRNA treatment
- The model accounted for the association of $V_{LIV}$ with body weight, stratified by Japanese race. As a consequence, patients with low body weight (with smaller livers) have higher predicted siRNA liver concentrations[12]
- Model assumptions:
  - Total siRNA liver concentration (sum of 2 triggers) drives the effect on HBsAg
  - RNA-induced silencing complex is not saturated by binding of siRNA
  - siRNA drug effect is defined as inhibition of HBsAg production and is reversible upon stopping treatment (recovery to baseline)
  - The modeling approach is "conservative" as no immune effects are accounted for currently

**Figure 2.** Structure of the PK-PD model: IRM with signal transduction delay (represented as virtual "HBV mRNA" and "Intracellular HBsAg" compartments).



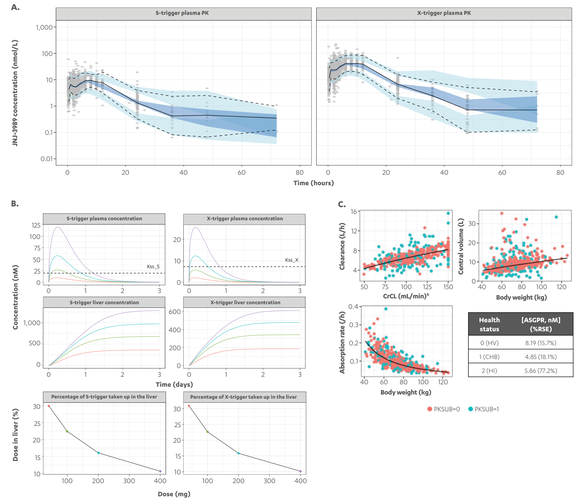

$\gamma$, hill coefficient; $IC_{50}$, concentration at which the effect is half maximal; $I_{max}$, maximal effect; KDE, delay rate constant; $k_{syn}$, HBsAg production rate; $k_{out}$, HBsAg degradation rate; mRNA, messenger RNA.

## Results

### siRNA PK Model Results

- The PK model adequately described the data collected in patients and HV, as judged from the prediction-corrected visual predictive checks (pcVPC; **Figure 3A**)
- The plasma PK for siRNA was determined by absorption and liver transporter kinetics (**Figure 3B**)
  - Absorption after SC injection was rate limiting (ie, "flip-flop" kinetics)
  - Distribution of both triggers was rapid and mainly driven by the liver-targeting GalNAc moiety
  - Liver uptake was saturable through ASGPR, resulting in a decreased fraction of the dose that reaches the liver as the dose increases. Estimated ASGPR affinity was 2.7-fold higher for the X-trigger (7.3 nM) compared to the S-trigger (19.8 nM)
  - Elimination was characterized by a linear clearance that accounted for all potential elimination mechanisms except liver disposition
  - The following covariate relationships were identified (**Figure 3C**):
    - Liver disease (CHB and HI) on estimated ASGPR expression
    - Creatinine clearance (CrCL) on total body clearance and body weight on absorption rate and central volume of distribution

**Figure 3.** PK model results focusing on (A) the adequacy of the PK model as shown in the pcVPC, (B) the plasma and liver kinetics of the S- and X-triggers,[a] and (C) the association for each identified parameter-covariate relationship.



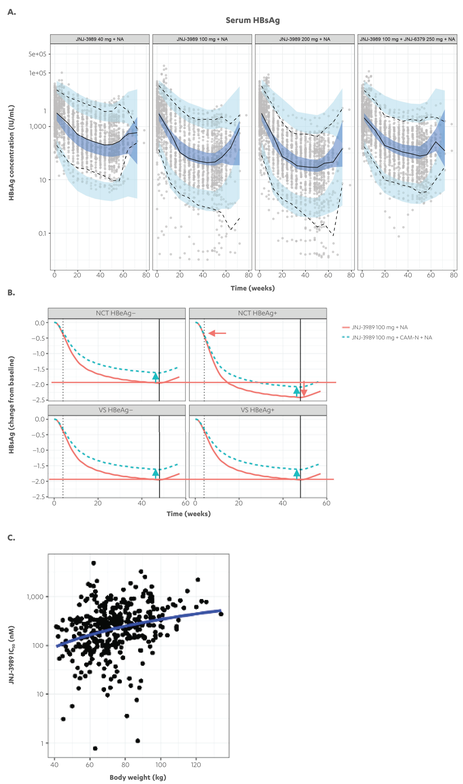

| Health status | [ASGPR, nM] (%RSE) |
|---|---|
| 0 (HV) | 8.19 (15.7%) |
| 1 (CHB) | 4.85 (18.1%) |
| 2 (HI) | 5.86 (77.2%) |

Kss_S/X, steady-state affinity constant for S/X-trigger; PKSUB, (rich) PK subject; RSE, relative standard error.
For panel A: Gray dots indicate individual observed HBsAg levels, the solid back line indicates the median of the observations, and the dashed black lines represent the 5th and 95th percentiles of the observations. The shaded dark blue areas represent the 95% confidence interval around the median, and the shaded light blue areas represent the 95% confidence interval around the 5th and 95th percentiles of simulations.
[a]For clarity, single-dose simulations were plotted.
[b]CrCL was truncated at 150 mL/min.

### siRNA PK-PD Model Results

- The PK-PD model adequately described the collected HBsAg data, as judged from the pcVPC (**Figure 4A**)
- With 48 weeks of treatment with siRNA in REEF-1, HBsAg levels decreased in a dose-dependent manner
- The fastest HBsAg declines in plasma were limited by the "intrinsic" HBsAg degradation, where the HBsAg plasma degradation rate was 0.158/day, corresponding to a half-life of 4.4 days, which was similar to that reported by Loomba et al[13]
- Between-subject variability was high: 112% and 104% on the estimated parameters of $IC_{50}$ (potency) and KDE (delay), respectively
- Drug-specific covariate analyses indicated that (**Figure 4B-4C**):
  - NCT HBeAg+ patients generally had less pronounced delay (KDE, +62% [RSE, 11%]) and more pronounced decline ($IC_{50}$, −52% [RSE, 18%]) in HBsAg compared to other subgroups
  - Combination treatment with CAM-N led to a less pronounced decline in HBsAg ($IC_{50}$, +66% [RSE, 32%])
  - siRNA activity on HBsAg production was inversely associated with body weight (WT) according to $IC_{50}$·(WT/70)$^{-43}$ [RSE, 22%], although between-subject variability remained high and further exploration is needed

**Figure 4.** PK-PD model results focusing on (A) the adequacy of the PK-PD model as shown in the pcVPC as well as the impact of covariate effects on HBsAg change from baseline dynamics for (B) the impact of baseline treatment, HBeAg status, and CAM-N combination treatment on HBsAg change from baseline dynamics and (C) the body weight effect on siRNA $IC_{50}$.




For panel A: Gray dots indicate individual observed HBsAg levels, the solid back line indicates the median of the observations, and the dashed black lines represent the 5th and 95th percentiles of the observations. The shaded dark blue areas represent the 95% confidence interval around the median, and the shaded light blue areas indicate the 5th and 95th percentiles of simulations.
For panel B: Red lines indicate HBsAg change from baseline kinetics under dual treatment (siRNA 100 mg + NA), with red arrows indicating the estimated differences in delay and $IC_{50}$ for the NCT HBeAg+ subgroup. Cyan lines indicate HBsAg change from baseline kinetics under triple treatment (CAM-N 250 mg + siRNA 100 mg + NA), with cyan arrows indicating the estimated (negative) effect of adding CAM-N on to siRNA on a background therapy of NA.

## Key Findings

- With 48 weeks of treatment with siRNA in REEF-1, HBsAg levels decreased in a dose-dependent manner, as described by the PK-PD model
- The dynamics of plasma HBsAg decline were governed by ASGPR-mediated liver accumulation of siRNA, the liver concentration–dependent inhibition of HBsAg production, and the estimated HBsAg plasma degradation rate
- Baseline treatment and HBeAg status, body weight, and combination treatment with CAM-N were important factors impacting HBsAg kinetics under siRNA treatment
- The plasma PK for siRNA were determined by SC absorption and ASGPR transporter occupancy, in line with other GalNAc-conjugated siRNAs[14]

## Conclusions

- The PK-PD model adequately characterized the time course of siRNA plasma concentrations, linking it to predicted siRNA liver concentrations and HBsAg decline within the monthly dose range of 40 to 200 mg in CHB patients (REEF-1)
- Covariate analyses provided a partial explanation of the variability observed in the PK and PD data
- For simplicity and in the absence of clear immune-related effects, the current model did not consider potential immune-related components. However, immune-related effects may have contributed to the large variability observed in HBsAg kinetics between CHB patients

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## Disclosures

HT, NG, TNK, LS, TO, JV, XW, OL, RK, MB, JJPR, and OA are employees of Janssen Pharmaceuticals and hold stock in Johnson & Johnson.

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