Case study

Hepatitis B



Introduction

The purpose of this case study is to showcase the standard workflow of a modeling & simulation project NOVA undertook in Hepatitis B (HBV). For more details on NOVA's *in silico* trial approach and methodology, refer to "Modeling and simulation methodology at NOVA".

Our HBV model was developed to explore drug candidate efficacy of an FXR agonist on HBV chronic infection and to optimize the design of a Phase 2 trial with the potential treatment, on behalf of ENYO Pharma. Exploring drug candidate (EYP001), the NOVA team simulated a Phase 2 trial, exploring a number of treatment regimens on a large variety of patients and treatment combinations.

Problem formulation

Addressing research questions with an *in silico* clinical trial

- Map out the mechanistic link between HBV replication cycle dynamics in the liver and bile acids metabolism chronobiology
- Given the short half-life of the drug candidate, estimate what is the best drug regimen maximizing the differential antiviral effects
- Identify the best study population for a faster proof of concept involving fewer patients
- Explore the synergistic effect of the combination of the drug candidate with additional Standard of Care (SOC) treatments for HBV

Model scope

Developing a computational model composed of 7 submodels to address the research questions

	SUBMODELS	DESCRIPTION
1	HBV replication & excretion	This submodel describes binding and entry of HBV into hepatocytes, transcription of viral RNAs, and production of virus components, as well as virus assembly and its excretion into plasma. This Knowledge Model contains sections on Hepatitis B virus replication & gene expression (general HBV information, virus & host cell interactions, reciprocal regulation of hepatic metabolic processes and HBV replication) and viral material excretion (viral material, viral material secretion, and viral material quantification)
2	Bile acid metabolism	This submodel includes bile acids synthesis and associated regulation, excretion, and transport including re-absorption. This Knowledge Model contains sections on bile acids signalling molecules (FXR, TGR5), synthesis, regulation, bile acid metabolic control, bile transport, hepatocellular transport of bile acids (NTCP, BSEP), intestinal transport of bile acids (ASBT, OST α-OST β), renal bile acids transport and circulation/chronobiology.
3	Cholesterol synthesis	This submodel details how cholesterol is synthesized, regulated, transported, and excreted. This Knowledge Model contains sections on cholesterol metabolism, sources of body cholesterol, cholesterol homeostasis, cholesterol metabolism in HBV infection context.
4	Drug model of FXR agonist	This submodel describes the pharmacokinetics of the drug and its effect. This Knowledge Model contains sections on enterohepatic circulation and pharmacodynamics of two biomarkers (FGF19 and C4)
5	Drug models of two additional treatments	These two submodels describe the pharmacokinetics of two Standard Of Care (SOC1 and SOC2) drug models and their effects.
6	Impact of HBV on hepatocytes	This submodel describes the impact of HBV virus and particles on physiology, described in the complete model (e.g. hepatocyte metabolism, immune system, fibrosis). This Knowledge Model contains sections on experimental methods, impact of HBV on cholesterol metabolism, impact of HBV on bile acids metabolism, impact of HBV on liver fibrosis, inflammation and the immune system and impact on other metabolisms impacted by HBV like nucleic acids, cell cycle, and HCC, transcription factors impacted by HBx.
7	Immune system and inflammation	This submodel describes immune reactions arising from HBV infection. This Knowledge Model contains sections on the innate immune response, adaptive immune response and interactions between HBV and the immune system (HBx, the core and envelope proteins, HBeAg and the viral polymerase involvement in the regulation of the immune system (HBsAg, HBcAg (and pre-core protein), HBeAg, HBV polymerase)

The computational model (Figure 1) of our HBV model is a system of differential equations that integrates 300+ biological variables and 600+ parameters. With 8 mechanistic submodels (including the effect of FXR agonist on HBV replication, HBV excretion, bile acid physiology and EYP001, SOC1, and SOC2 drug models), the model has been used to predict quantitative efficacy of treatments on disease-related endpoints (eg. plasma HBV DNA and HBsAg concentrations) in a virtual population. All the submodels are ultimately combined into a multi-scale Computational Model simulating the dynamics of biological entities at the molecular, cellular and organ levels. Figure 1 below illustrates the structure of the integrated Computational Model.

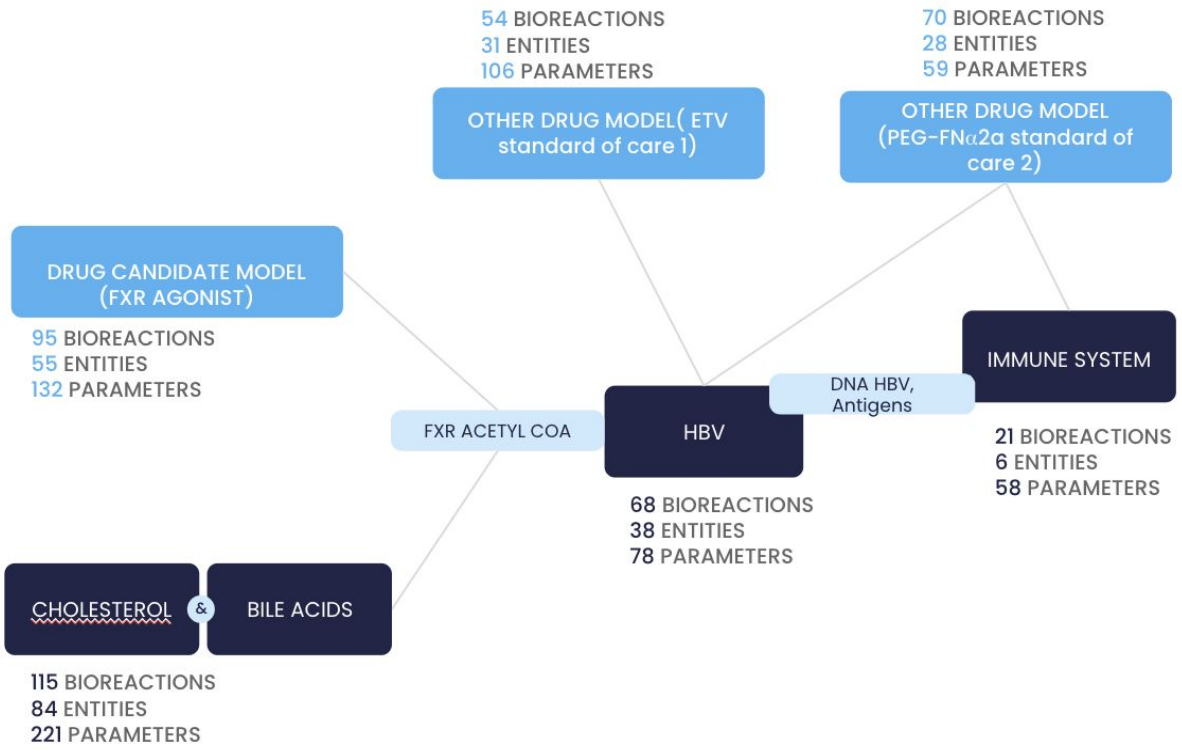


Figure 1. Illustration of the integrated full Computational Model of HBV.
Dark blue rectangles represent the submodels and small light blue rectangles represent a non-exhaustive list of entities used as connectors between submodels to get a complete integrated model.
Sky blue rectangles represent the drug submodels.

In silico drug trial

Performing an *in silico* clinical trial on the targeted HBV virtual population using NOVA's Jinkō® platform

The project's *in silico* simulation of a Phase 2 trial had a total of 78 scenarios to explore. Scenarios are defined as combinations of the following factors: treatment regimen, patient meals, and dietary status. A Virtual Population of 200 patients was generated and each virtual patient was simulated under 78 different conditions. In addition to the 3 treatment administration periods, observation phases were simulated before and after treatment. These simulated post-treatment follow-ups can be as long as needed, in order to explore the proportion of patients relapsing after treatment. In the case of the HBV project, follow-ups of 2 and 6 months were simulated. In the last stage, we explored the synergistic effect of an FXR agonist in combination with two additional Standard of Care treatments.

Results

NOVA's *in silico* clinical trial enabled ENYO Pharma to make better and informed decisions on their next *in vivo* clinical study

Phase 1 results were well reproduced *in silico*, including the effects of the drug candidate (EYP001) on the FXR response markers 7 α-hydroxy-4-cholesten-3-one (C4) and fibroblast growth factor 19 (FGF19), and on HBV DNA plasma concentrations (Figures 2 and 3).

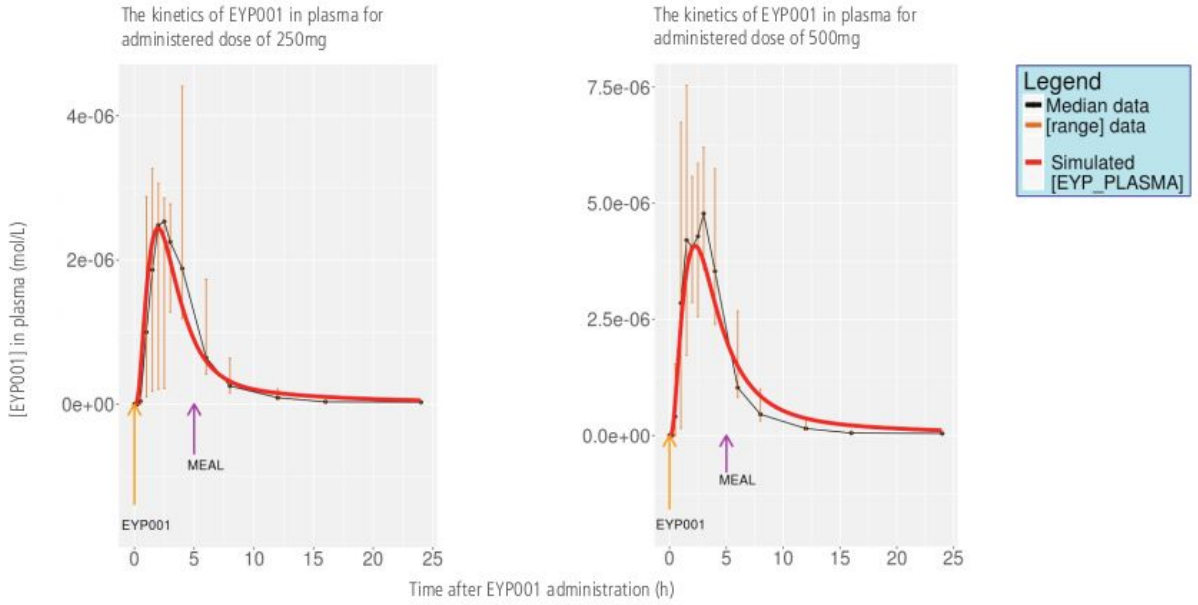


Figure 2. Kinetics of EYP001a in plasma for the administered doses of 250mg (on the left) and 500mg (on the right). The black dots and the brown bars represent respectively the median and the minimum-maximum range of experimental data. Red solid lines correspond to the EYP001a simulated concentrations.

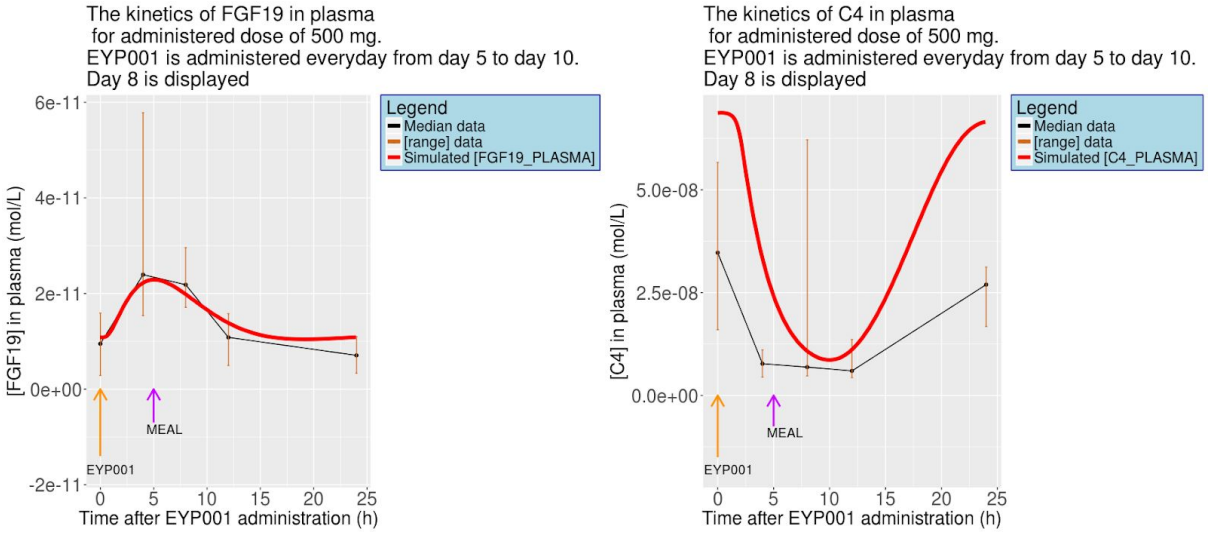


Figure 3. Kinetics of FGF19 (on the left) and C4 (on the right) biomarkers in plasma for the administered dose of EYP001a of 500mg. Black dots separated by black lines and brown bars represent respectively the median data and the minimum-maximum range of experimental data. Red solid lines represent the simulated concentration of biomarkers.

The model accurately predicted the short-term impact of FXR agonism on FGF19 concentrations and its impact on reducing HBV DNA and HBsAg concentrations.

In silico Phase 2 trial simulations allowed us to identify the 24-week bi-therapy of EYP001 and SOC2 as the best combination in reducing plasma HBV DNA and HBsAg levels, and in minimizing relapse after a 24-week follow-up period (Figures 4 and 5). The percentage of relapsing patients 2 months after the end of 24 weeks treatment was 26.5% for the bitherapy with EYP001 QD 400mg and SOC2, whereas it was of 94.2% for patients taking SOC2 only, and 100% for the no treatment group.

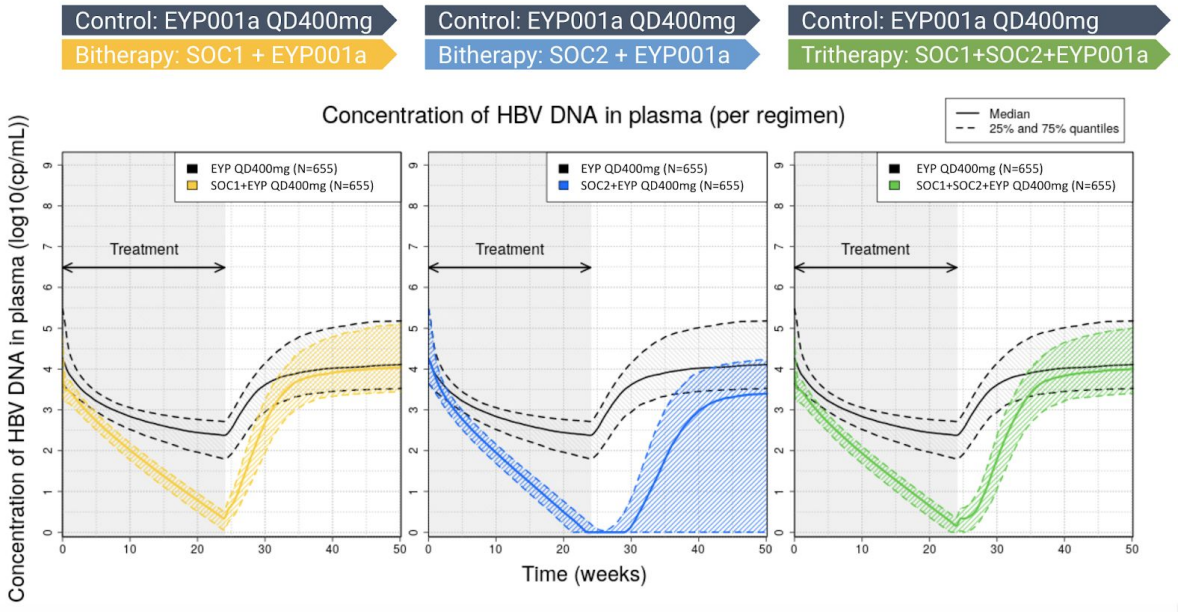


Figure 4. HBV DNA levels in plasma (log10 (copies/mL)) after 24 weeks of treatment and 24 weeks of follow-up. Comparison of control (EYP001a QD 400mg) with SOC1 + EYP and SOC2 + EYP bitherapies and EYP + SOC1 + SOC2 tritherapy. (Tr.: treatment; SOC1: Standard Of Care 1; SOC2: Standard Of Care 2; EYP: EYP001a)

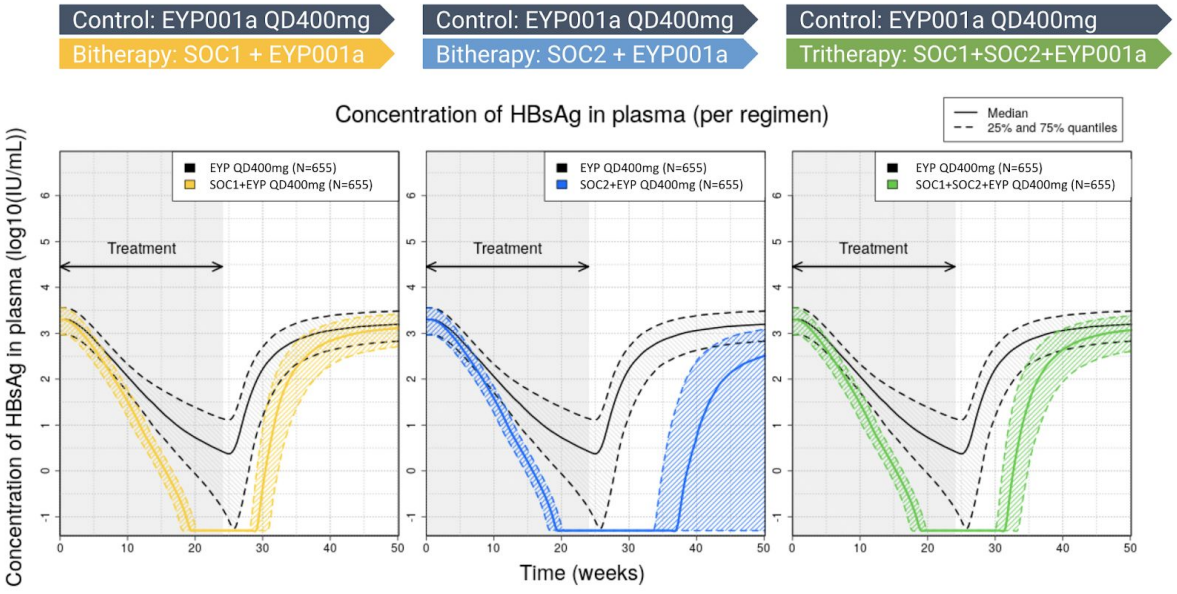


Figure 5. HBsAg levels in plasma (log10 (copies/mL)) after 24 weeks of treatment and 24 weeks of follow-up. Comparison of control (EYP001a QD 400mg) with SOC1 + EYP and SOC2 + EYP bi-therapies and EYP + SOC1 + SOC2 tritherapy. (Tr.: treatment; SOC1: Standard Of Care 1; SOC2: Standard Of Care 2; EYP: EYP001a).

Conclusion

NOVA's *in silico* approach allows for optimization of upcoming studies including: protocol design, treatment dose, duration and patient responders

Despite decades of research, there is still no curative treatment for chronic hepatitis B. The last few years have seen an increased interest for the combination of antiviral therapies with the mutual objective of increasing the rate of HBV eradication.

We used computational modeling to improve the design, dose, duration, and patient selection for combination therapies based on EYP001 treatment.

The *in silico* model accurately reproduced all drug plasma concentration profiles as well as their independent characteristics and effects.

These preliminary results suggest the drug candidate combined with SOC2 is an optimal regimen and supports the selection of EYP001 regimens in Phase 2 trials.