Mechanistic modeling to optimize the design of a phase 2b clinical trial of a new combination therapy for chronic hepatitis B infection

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Introduction

Context

- **Standards of care (SOC)** for chronic hepatitis B virus (HBV) infection (CHB), including nucleos(t)ide analogues (NUCs, such as entecavir (ETV)) and PEG-interferon α (IFN), **are often not curative** (persistence of HBsAg at the end of treatment).
- ENYO Pharma is **evaluating in Phase 2 Vonafexor (VFX),** a Farnesoid X receptor (FXR) agonist, a promising target to **inhibit HBV replication**. VFX may exhibit combinatorial effect with SOCs [1].
- **Phase 2b and 3 clinical trials face challenges** such as trial length considerations and many possible treatment combinations.
- **Mechanistic modeling** integrates qualitative and quantitative knowledge of disease physiology, pharmacokinetics and pharmacodynamics of drug candidates. The generated *in silico* data predict therapeutic efficiency for various trial conditions and help **derisking clinical programs**[2].

Objective

- Test a **large set of treatment modalities** (doses, durations, combinations) with **HBsAg decrease at end of treatment (EOT) as the primary outcome** for efficacy of VFX in combination with SOC **using mechanistic modeling to simulate *in silico* trials**, to optimize the design of Phase 2b clinical trials.

Method

In silico study protocol

After implementation and calibration of a mechanistic model, a population of virtual patients was studied *in silico* following a **multi-arm clinical trial (about 130 different designs) with VFX combined with SOC designs and their respective comparators** using a placebo (pbo) instead of VFX. Treatment features differed between designs (see *Fig. 1*). Main outputs of the simulations were **HBsAg** (primary endpoint) and **HBV DNA serologies** (secondary endpoint) which decreases were evaluated between treatment start date (T_0) and EOT for each design.

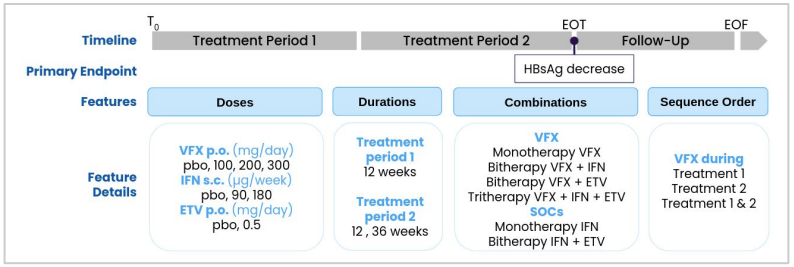

Figure 1: Each simulated design includes two successive treatment periods (period 1 & 2) and a follow-up from the end of treatment date (EOT) until the end of follow up date (EOF) with administration of ETV 0.5mg/day p.o. Simulated designs differ by their levels of **drug doses**, treatment period 2 **duration**, administration of drugs **alone or in combinations** (mono-, bi- or tritherapies) and the **period during which Vonafexor** is administered.

Simulation of a HBeAg negative population

Each design was simulated with a cohort of **500 HBeAg negative** (HBeAg-) **virtual patients** with CHB infection and baseline characteristics as summarized in *Table 1.*

Table 1: Demographics of the simulated patients

Characteristic	Virtual Population (N=500)
Sex : male — n (%)	362 (72.4)
Age (years) — Mean ±SD	40.5 ±11.6
Weight (kg) — Mean ±SD	72.9 ±12.4
ALT (IU/L) — Median (range)	63.9 (10.6 - 453.0)
HBV DNA (log10 copies/mL)	
Median (range)	4.46 (2.26 -7.99)
Mean ±SD	5.34 ±2.15
HBsAg (log10 IU/mL)	
Median (range)	3.69 (2.87-5.46)
Mean ±SD	3.73 ±0.49
HBeAg undetectable — n (%)	500 (100)

Results

Model calibration accuracy

The model and Virtual Population were calibrated based on summary statistics from published clinical data (e.g. mean, SD, percentage of responders) for SOC treatments (*Fig. 2*) and ENYO's individual patient data for VFX.

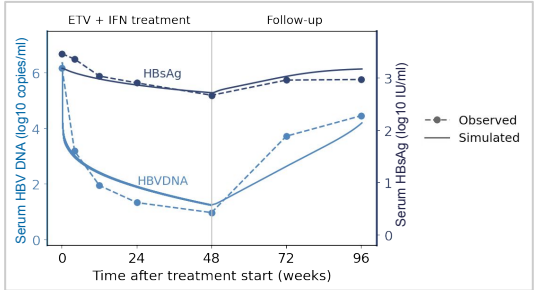

Figure 2: Goodness of fit of observed (Tangkijvanish *et al.*, 2015 [3], combination therapy arm N=63) vs. simulated viral serology values for a representative patient under ETVxIFN treatment administered during 48 weeks to HBeAg- patients, with a follow-up period of 48 weeks for (i) HBV DNA (light blue solid and dashed line) and (ii) HBsAg (dark blue solid and dashed line).

Primary outcome can be analyzed *in silico* at the patient and population level

Synthetic Comparator Arms were generated for each VFX design as control. This allowed to test and predict dynamics and final serum HBsAg decrease at EOT (*Fig. 3*).

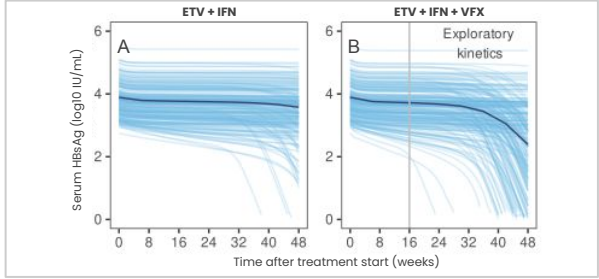

Figure 3: Mean (dark blue) and individual (light blue) simulated serum HBsAg dynamics under two 48 weeks treatment combinations; **(A)** ETV+IFN bitherapy (comparator arm). **(B)** ETV+IFN+VFX tritherapy. Dynamics under VFX tritherapy are calibrated on ENYO's data for the first 16 weeks of treatment. After that (grey vertical line), simulated dynamics are exploratory. Simulated administered drug doses are respectively: ETV 0.5 mg/day p.o., IFN 180 µg/week s.c and VFX 200 mg/day p.o.

Effect of variation in treatment modalities on the main outcome

The level of HBSAg decrease at EOT to several treatment modalities, varying separately or in combination, was simulated prior to the next phase 2b clinical trials. Here we present a selection of results regarding the impact of the variations of VFX dose, treatment duration and combined effect of IFN and ETV with VFX.

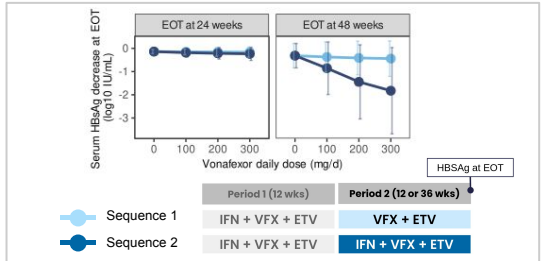

Figure 4: Simulated exploratory effect of Vonafexor (VFX) daily dose on serum HBsAg decrease at EOT (data are mean ±SD) for two different period 2 durations (12 and 36 weeks), under two treatment sequences. IFN is administered as 180 µg/week s.c. and ETV as 0.5 mg/day p.o.

Discussion

In silico approach allowed to investigate the effect of many different trial designs on most common clinical endpoints

- **Over 130 different treatment designs** were tested in a shorter time than would be needed to run one real clinical trial.
- Simulations suggest that the **best treatment designs** to reduce HBsAg at EOT are those combining Vonafexor and SoCs for a treatment duration of 48 weeks.
- Data produced by the model suggest a **combinatorial effect** between the Vonafexor and IFN that could be investigated *in vivo*.
- **Secondary endpoints** (serum HBsAg decrease at EOF, but also serum HBV DNA serology, percentage of responders and optimal sample sizes) were simulated and compared between designs (results not shown in this poster).

This mechanistic modeling approach relies on assumptions made according to published studies and to Vonafexor first clinical trial results

- HBV replication cycle is naturally repressed by **natural killer** (NKC) and **cytotoxic T cells**.
- **Viral particles** and **virions** secreted in the serum regulate the activity of immune cells.
- HBV cycle is sensitive to the metabolism of bile acids through competition between bile acids and virions fixation on **NTCP** and through **FXR nuclear receptor** that stimulates cccDNA synthesis and its transcription.
- ETV acts on the virus replication cycle by **inhibiting pgRNA** retrotranscription into rcDNA [4].
- IFN acts both on the virus cycle by **inhibiting cccDNA transcription**, and on the activity of the immune system by stimulating the mitosis of NKC [5].
- VFX **inhibits both cccDNA formation** from entering rcDNA, and **transcription of cccDNA** via conformational changes of FXR.
- **No direct interaction between treatments** is implemented.

A model under continuous development

- The model can be **complexified** if novel biological mechanisms are uncovered. For instance, novel data suggest that Vonafexor may enhance cross-talks between FXR and innate immunity pathways, producing a combinatorial effect with IFN.
- Calibration of the population is being **refined** to better reflect literature and ENYO's data.
- Model results are still exploratory and the model behavior under various treatment conditions might be **validated** with upcoming clinical trial results.

Conclusion

- Mechanistic modeling enabled testing *in silico* a **large set of possible treatment combinations** (*Fig. 1*), which would have required 6450 real patients assuming 50 patients per arm.
- We have **explored best treatment modalities** showing that combining VFX with SOC for a 48-weeks treatment period was the best combination to reduce mean serum HBsAg at EOT (*Fig. 4*).
- Data generated with the model will be used to **finalize the design of the actual Phase 2b clinical trial**.

References

[1] EASL-ICL 201 Abstract No. 2844: "A phase 2 study testing FXR agonist Vonafexor in treatment naive patients with chronic hepatitis B (CHB): preliminary week 16 results." Scalfaro P. et al. International Liver Congress 2021, 23–26 June **[2]** Kuepfer L, Lippert J, Eissing T. Multiscale mechanistic modeling in pharmaceutical research and development. Adv Exp Med Biol. 2012;736:543–61. doi: 10.1007/978-1-4419-7210-1_32. PMID: 22161351. **[3]** Tangkijvanich et al., 2015, 'A randomized clinical trial of peginterferon[...]', Journal of Viral Hepatitis, vol. 23, no. 6, pp. 427–438 (doi:10.1111/jvh.12467). **[4]** Langley DR, Walsh AW, Baldick CJ, Eggers BJ, Rose RE, Levine SM, Kapur AJ, Colonno RJ, Tenney DJ. Inhibition of hepatitis B virus polymerase by entecavir. J Virol. 2007 Apr;81(8):3992–4001. doi: 10.1128/JVI.02395–06. Epub 2007 Jan 31. PMID: 17267485; PMCID: PMC1866160. **[5]** Shuldiner SR, Gong L, Muir AJ, Altman RB, Klein TE. PharmGKB summary: peginterferon-a pathway. Pharmacogenet Genomics. 2015;25(9):465–474. doi:10.1097/FPC.0000000000000158

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