

Identification of a dual mechanism of action (MoA) for Danoprevir (DNV), a protease inhibitor currently in phase 2, using a mechanistic viral kinetic (VK) model

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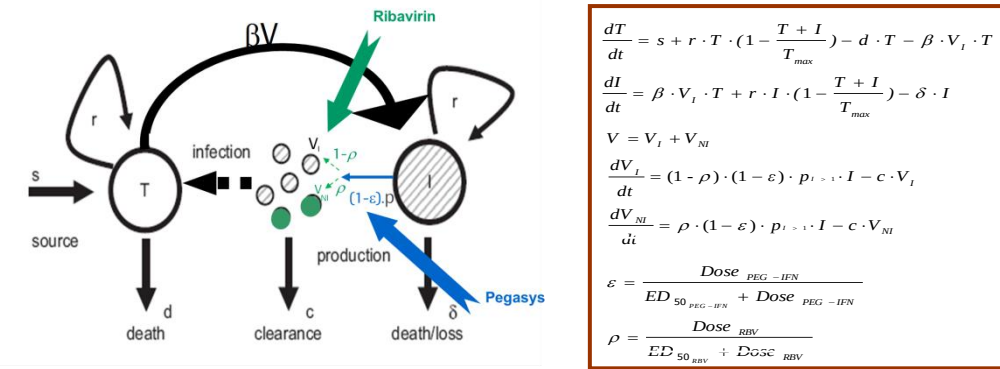
1 – Background

- Danoprevir (DNV) is an inhibitor of the HCV NS3/4A protease, an enzyme required for viral replication, that demonstrated a potent in-vitro and in-vivo activity against HCV
- Danoprevir is currently in Phase 2 development for the treatment of Chronic Hepatitis C (CHC) in combination with standard of care (SOC): Pegasys® (PEG-IFN alpha-2a) and Copegus® (Ribavirin - RBV), using Ritonavir (RTV) at low, sub-therapeutic doses, to enhance the exposures of HIV protease inhibitors.
- A well established VK model that was developed using a large viral load database composed of 2,100 CHC patients treated with PEG-IFN, alone or in combination with Ribavirin [1] provides a framework for mechanistic exploration of treatment outcome

2 – Method:

Data from four phase 1 and 2 clinical trials were pooled.
A total of 4446 Viral Load measurements from 287 G1 naïve patients were available.
A detailed description of the data is provided in the table below

Study	Duration	DNV Treatment	Status
DNV Monotherapy (phase 1) (NSHC-002) part A in G1 naïve (n=32)	DNV: 14 days	100 and 200 mg BID 100 and 200 mg TID	Completed
DNV + Peg-IFN/RBV (phase 1) (NSHC-003) in G1 naïve (n=44)	DNV+P/R: 15 days	100, 200 and 300 mg TID 400, 600 and 900 mg BID	Completed (external validation)
DNV/r + Peg-IFN/RBV (phase 1) (NP22660) first 3 cohorts in G1 naïve (n=25)	DNV+P/R: 15 days	100 mg BID 200 mg BID or QD	Completed
DNV + Peg IFN/RBV (phase 2a) (NV21075) in G1 naïve (n=212, 180 treated with DNV, 97 with observed troughs, 87 with imputed trough)	DNV 12 +P/R: 24/48 weeks	300 mg TID 600 and 900 mg BID	Ongoing Week 60 IA SVR24 from all patients

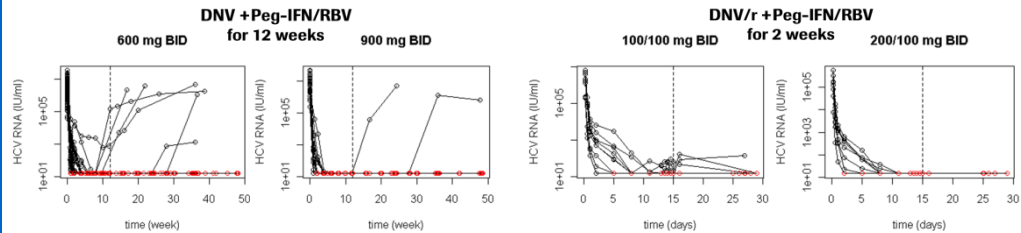


where target cells T, produced at a rate s, replicate and die at rate r and d, respectively. Infected cells I are produced from T at a rate constant bV and lost with a rate d. Free virions are produced from I at a rate p and are cleared with a clearance rate c. The effect of PEG-IFN was described by inhibition of the virus production by dose dependent fraction ε. RBV effect was described by causing a fraction of the newly produced virion to become noninfectious by dose dependent fraction ρ.

- Some system and PEG-IFN effect parameters were re-estimated to take advantage of the rich early viral kinetic information from the phase 1 studies
- DNV treatment effect was investigated including an exposure-dependent inhibition and/or induction on various model parameters. Parameters were estimated using MONOLIX [2].
- **Integration of the DNV effect:**
 - Protease inhibitors seem to both inhibit the virion production and restore the host immune response [3].
 - Dual efficacy “but only at concentrations far in excess of the antiviral EC50[4]”
- **Model evaluation:**
 - Internal evaluation simulating 300 times the Phase 2 and comparing the simulated response rates with the observed ones
 - External evaluation simulating 300 times the NSHC-003 study and overlapping the individual profiles with the range of simulated time courses

3 – Results: The Model Development

Individual Viral load time course: Clear dose-response observed



Better estimation of the SOC parameters: Due to the correlation between the SOC disease/drug parameters, it was necessary to re-estimate jointly c, p and ED50peg in order to improve the description of the early drop and get a better estimation of c.

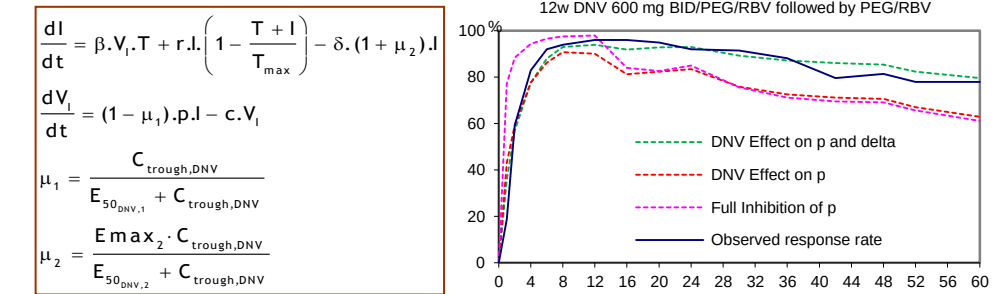
Model	Description	Nparam	Likelihood	c (SE)
1	Effect on p, fixing SOC parameters	3	6059.1	4.53 fixed
2	Effect on p, reestimating c	5	6063.0	2.52 (6)
3	Effect on p, reestimating c and p	5	5826.6	6.77 (10)
4	Effect on p, reestimating c and ED50peg	7	6013.1	2.51 (6)
5	Effect on p, reestimating c, p and ED50peg	7	5722.7	7.51 (10)

Identification of the dual MoA: DNV effect was best described using dual MoA; inhibition of the virus production (p) with a multiplicative effect with Pegasys, and an increase in the clearance of the infected cells (δ)

Model	Description	Nparam	Likelihood	c (SE)
5	Effect on p only	7	5722.7	7.51 (10)
6	Effect on p and delta	12	5337.3	9.15 (11)
7	Effect on p and c	12	5688.8	2.33 (16)
8	Effect on p and beta	12	5567.9	6.36 (9)

4 – Results: The Updated Viral Kinetic Model

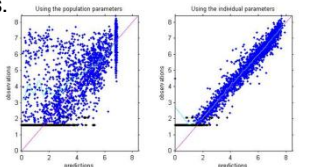
The simulations with the different models shows that estimating an effect only on the virus production would not allow to reproduce the observed response rate. Even simulating a full inhibition of p would allow to reach high response rate during triple combination, but this would drop when stopping DNV



Effect	Parameter	units	Estimate (%RSE)
virion clearance rate	c	/day	9.15 (11)
virion production rate	p	virion.cells /day	132 (11)
Inhibition of p by PEG	ED50peg	µg/week	35.5 (21)

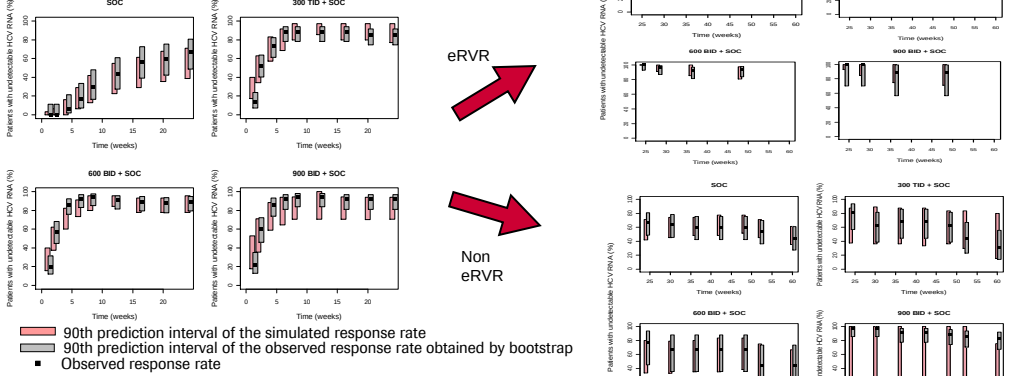
The newly estimated infected cells clearance rate (c) is closer to the expected value [5,6] as compared to the value estimated in the SOC model [1]
Model parameters were estimated with good precision, DNV being able to enhance the infected hepatocytes loss rate by more than 3 fold.

Diagnostic plots indicates that the model provides reasonable population and individual fits, with especially good individual predictions. No major patterns were observed in the residual plots.



5 – Results: The Evaluation of the Model

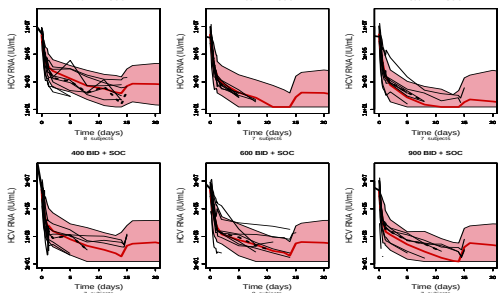
a. Viral Response VPC: Week 60 IA NV21075



Tendency to slightly over predict DNV onset at week 2, predictions of DNV offset at week 12 are in agreement with the observed data

b. External Evaluation of DNV + P/R phase 1

The model predicts reasonably well the median viral load kinetic. Both first and second phase of the early drop seems well described



6 – Discussion/Conclusion

- A mechanistic VK model was developed to describe the effect of DNV on HCV viral load alone and in combinations with P/R and with or w/o RTV.
- Several system parameters were re-estimated (c, p, ED50peg) to take advantage on the rich viral kinetic data from the phase 1 studies with regards to the early viral load drop.
- The effect of DNV + P/R on HCV viral load was described using a combination of inhibition of virion production rate and enhancement of the infected hepatocytes loss rate.
- The secondary effect of DNV on the clearance of the infected hepatocytes is in agreement with previous reports on the enhancement of the host response to HCV by protease inhibitors [3,4,7]
- This model represents a key element of a modeling and simulation framework used in the development of DNV to support Phase 3 study designs and other DAA Combinations

7 – References

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