

Combination Therapy With A Nucleoside Polymerase (RG7128) And Protease (RG7227/ITMN-191) Inhibitor In HCV: Safety, Pharmacokinetics, And Virologic Results From INFORM-1

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**Edward Gane MD
Auckland Clinical Studies Unit
and New Zealand Liver Transplant Unit**

I have no financial relationships to disclose within the past 12 months relevant to my presentation

AND

My presentation does include discussion of investigational use of protease inhibitor RG7227 and nucleoside polymerase inhibitor RG7128

Rationale for Combining RG7128 and RG7227

- Different mechanisms of action: nucleoside analogue versus protease inhibitor
- High RG7128 barrier to resistance
 - RG7128 has no observed clinical resistance
 - No cross resistance between molecules
 - Combination with RG7128 in vitro suppresses emergence of RG7227 resistance in replicon system¹
- Low likelihood of drug interactions
 - No pharmacokinetic interaction for RG7128 / RG7227 combination
 - Different routes of elimination (renal and hepatic)
- No overlapping toxicities
- Potential for all oral, twice daily regimen

INFORM-1 Study Overview

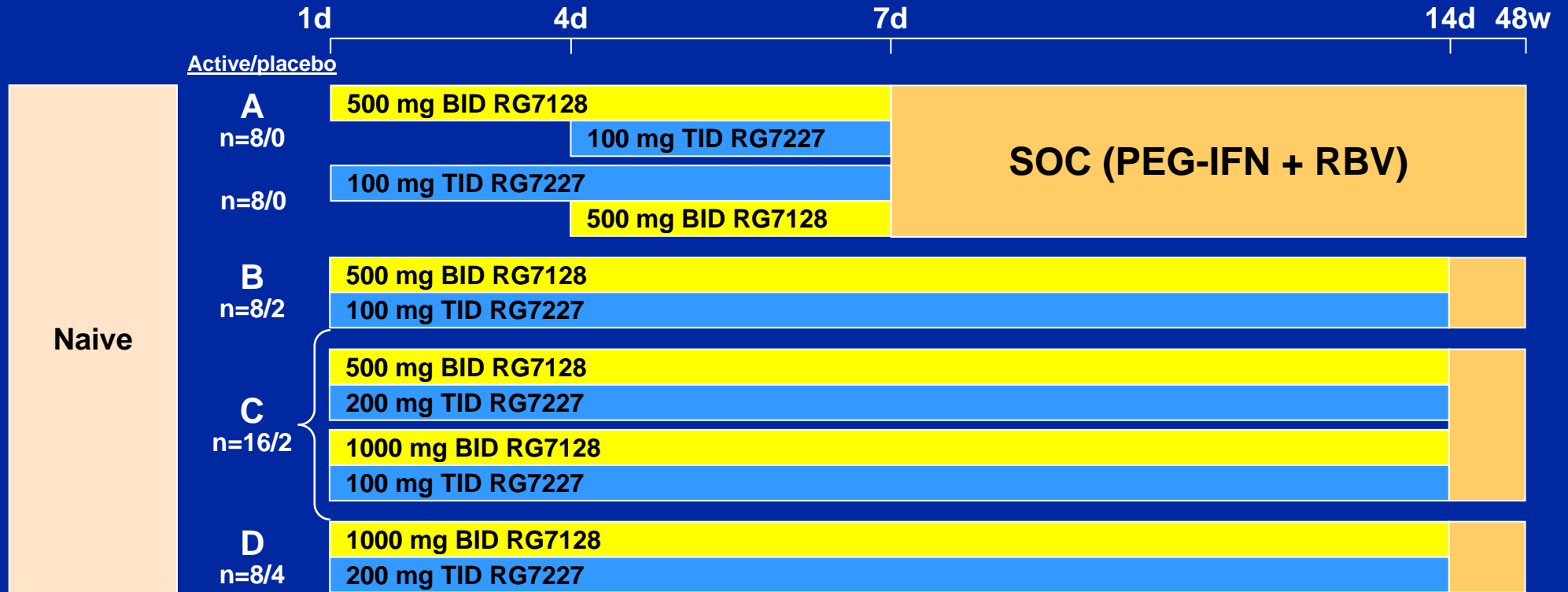
Primary objective

- Safety, tolerability and antiviral activity of an IFN-free regimen of RG7128 and RG7227 administered in combination at increasing doses for up to 13 days

Population

- HCV-positive GT-1 males/females, non-cirrhotic, screening HCV RNA $>10^5$ IU/mL
- Treatment naive
- Treatment experienced
 - Relapsers and partial responders
 - Documented IFN null responders
 - HCV RNA reduction of $<1 \log_{10}$ IU/mL in 4 weeks or $<2 \log_{10}$ IU/mL in 12 weeks

INFORM-1 Study Design: Randomized, Double-blind, Dose Escalation Trial



INFORM-1 Treatment-related Safety Data

Cohorts B-G

Cohort (N)	Placebo (14)	B (8)	C1 (8)	C2 (8**)	D (8)	E (8)	F (8)	G (8)
SAEs	-	-	-	-	-	-	-	-
Tx-related Discontinuations	-	-	-	-	-	-	-	-
Grade 3 /4 Lab Abnormalities	-	-	-	-	-	-	-	-
Total AEs*/ Pts with AE	14/7	14/6	3/2	13/5	7/3	13/7	11/6	4/3
Headache	4	1	1	4	3	4	3	1
Dysgeusia	-	-	1	1	-	1	-	-
Nausea	1	1	-	-	-	-	3	1
Diarrhoea	-	1	1	-	-	-	2	-
Dry mouth	-	2	-	-	-	-	-	-
Dyspepsia	-	-	-	1	1	-	-	-
Chest pain	-	1 [^]	-	-	-	-	-	1 [^]
Rash	-	1	-	-	1	1	-	1
Dry eyes	-	1	-	2	-	-	-	-

* AEs that occurred in ≥ 2 patients across active therapy arms that were possibly or probably treatment-related

[^] Non-cardiac related

** 1 patient voluntarily withdrew from the study on Day 10 for personal reasons

INFORM-1 Antiviral Activity

Cohorts B-G

	Regimen (RG7128 mg / RG7227 mg)	Baseline HCV RNA (Log ₁₀ IU/mL) Median	N	Patient Population	HCV RNA Median Change from Baseline (Log ₁₀ IU/mL) (range)	HCV RNA <LLOQ (<43 IU/mL) N (%)	HCV RNA <LLOD (<15 IU/mL) N (%)
B	500 BID/100 TID	6.5	8	Naive	-3.9 (-5.0 to -2.9)	1/8 (13)	1/8 (13)
C₁	500 BID/200 TID	6.9	8	Naive	-5.2 (-5.5 to -3.1)	5/8 (63)	2/8 (25)
C₂	1000 BID/100 TID	6.4	7	Naive	-4.8 (-5.7 to -4.5)	5/7 (71)	2/7 (29)
D	1000 BID/200 TID	6.3	8	Naive	-4.8 (-5.5 to -2.7)	5/8 (63)	2/8 (25)

LLOQ = lower limit of quantification by Roche TaqMan Assay (<43 IU/mL) LLOD = lower limit of detection by Roche TaqMan Assay (<15 IU/mL)

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G	1000 BID/900 BID	6.5	8	Naive	-5.1 (-5.9 to -3.0)	7/8 (88)	5/8 (63)

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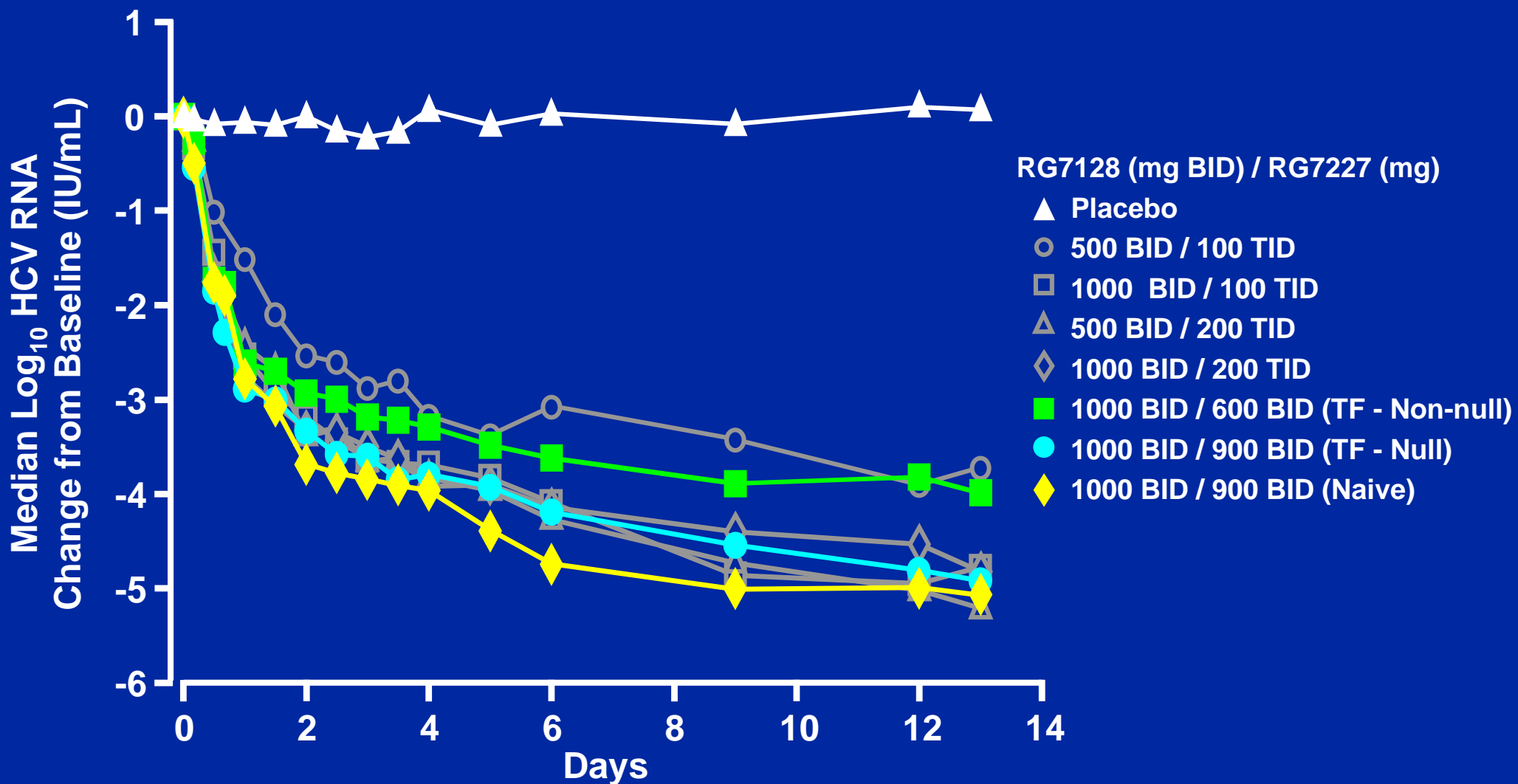
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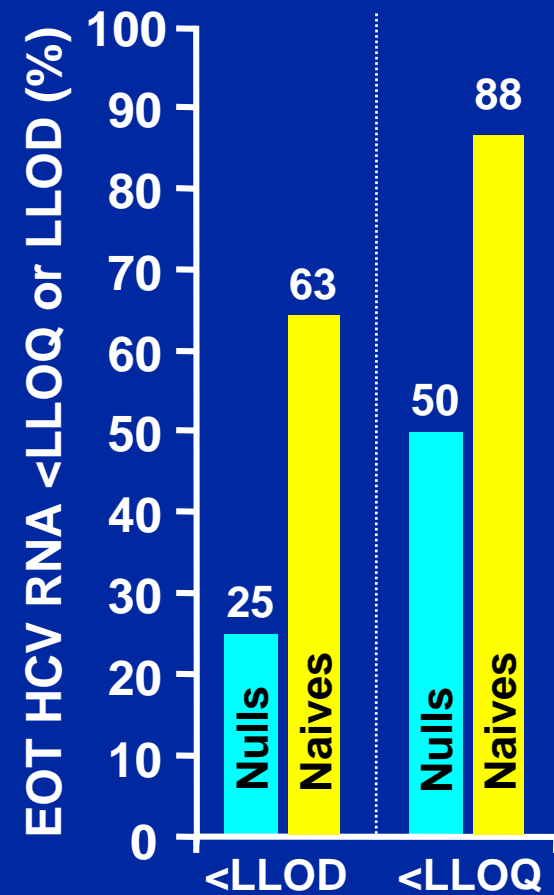
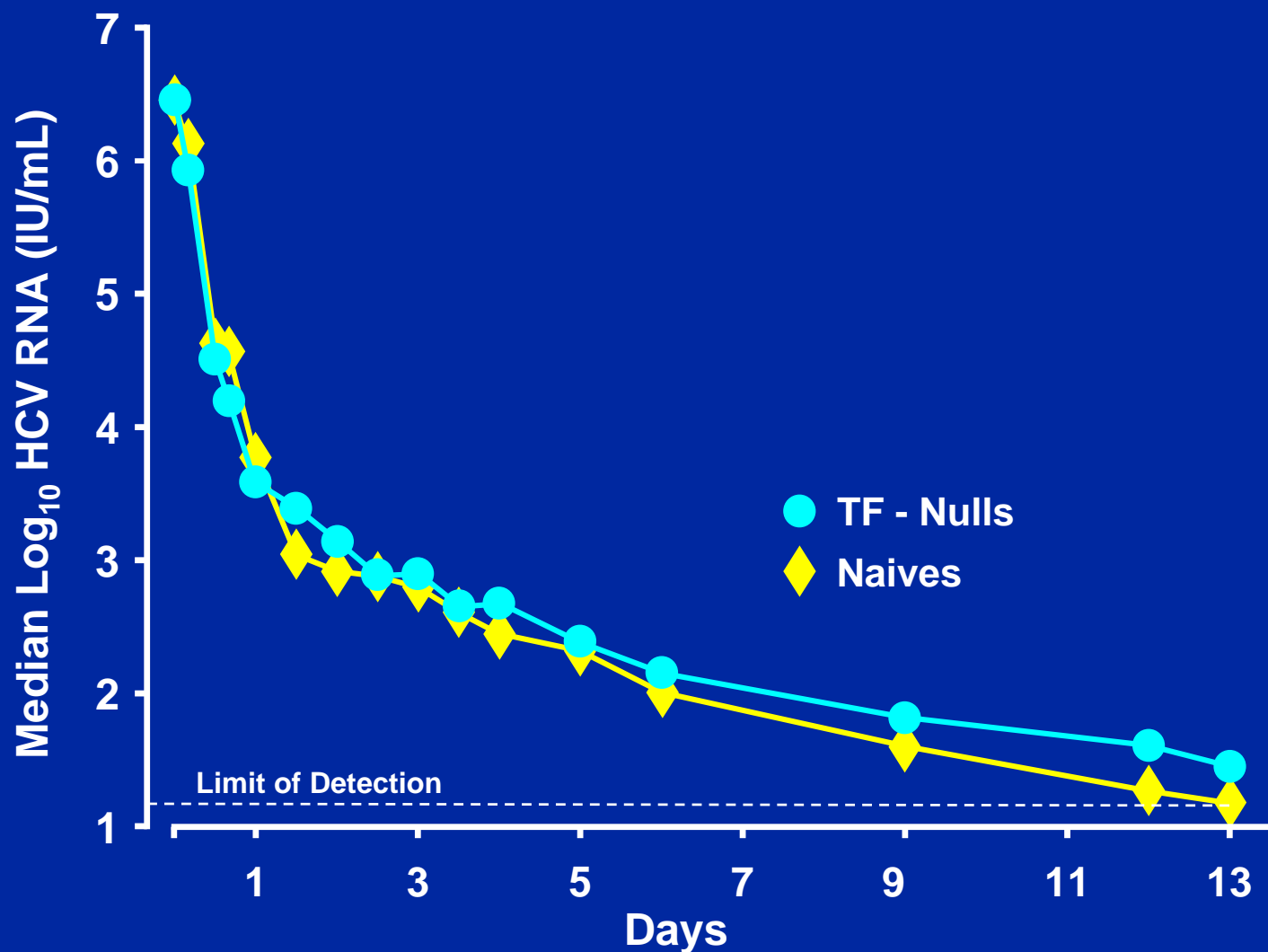
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Median Change from Baseline by Treatment Group

Cohorts B–G



Potent Antiviral Activity in HCV G1 Interferon Naive and Null Responders with a BID Oral Regimen of RG7128 and RG7227



RG7128 1000 mg BID + RG7227 900 mg BID

Similar Antiviral Activity of RG7128 + RG7227 Against HCV Genotypes 1a and 1b

(i) All Patients (Cohorts A-G)

Median Reduction in HCV RNA (log ₁₀ IU/mL) at End-of-treatment*	
All Patients (n=54)	- 4.8
1a (n=42)	- 4.8
1b (n=12)	- 4.9

*All patients, all doses combined

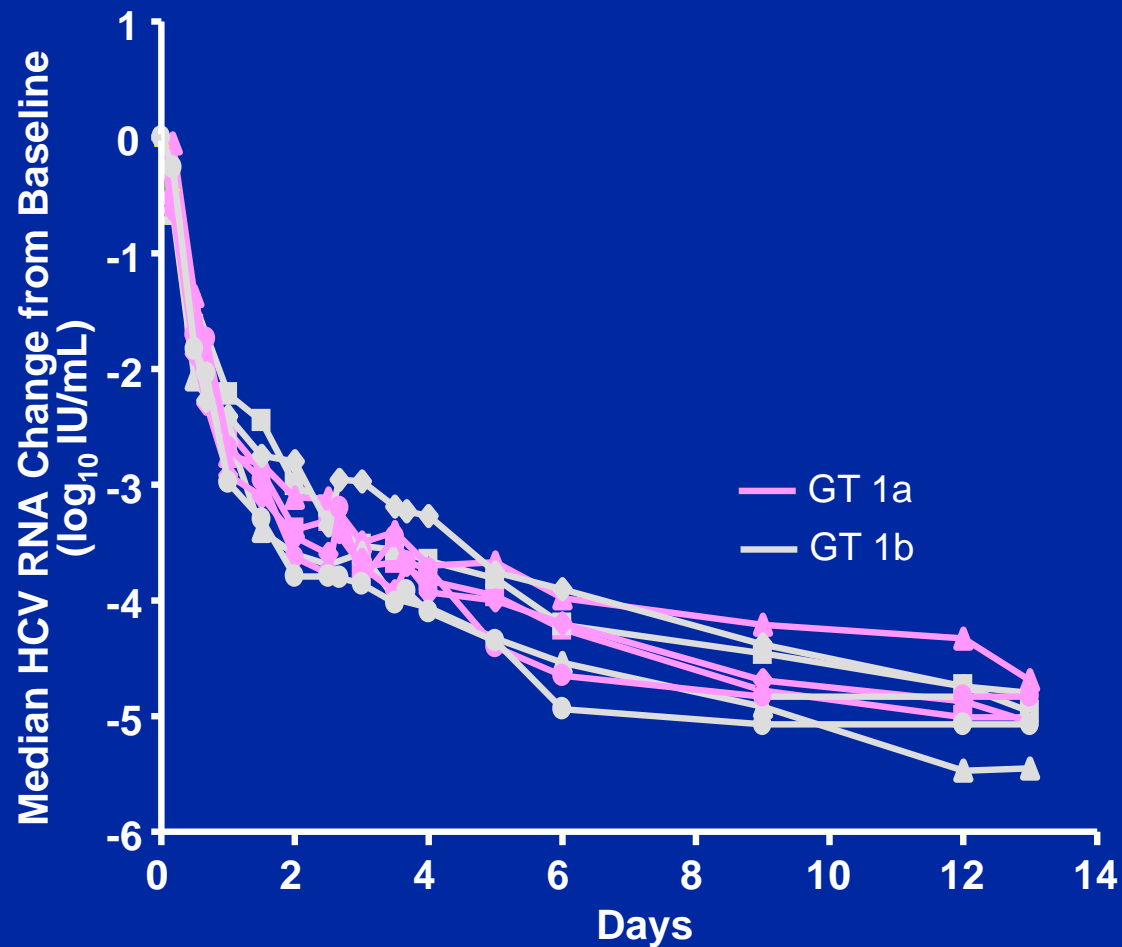
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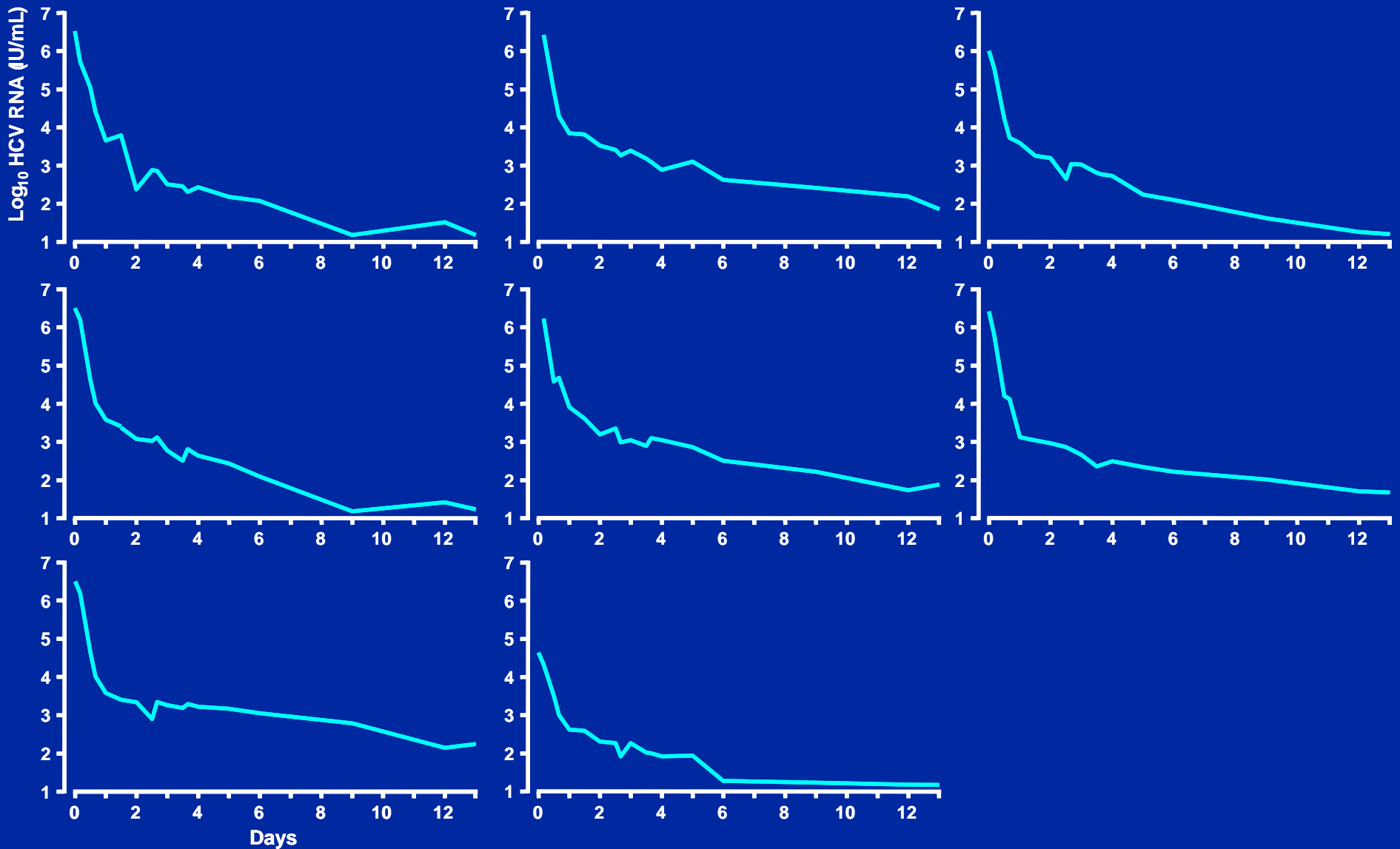
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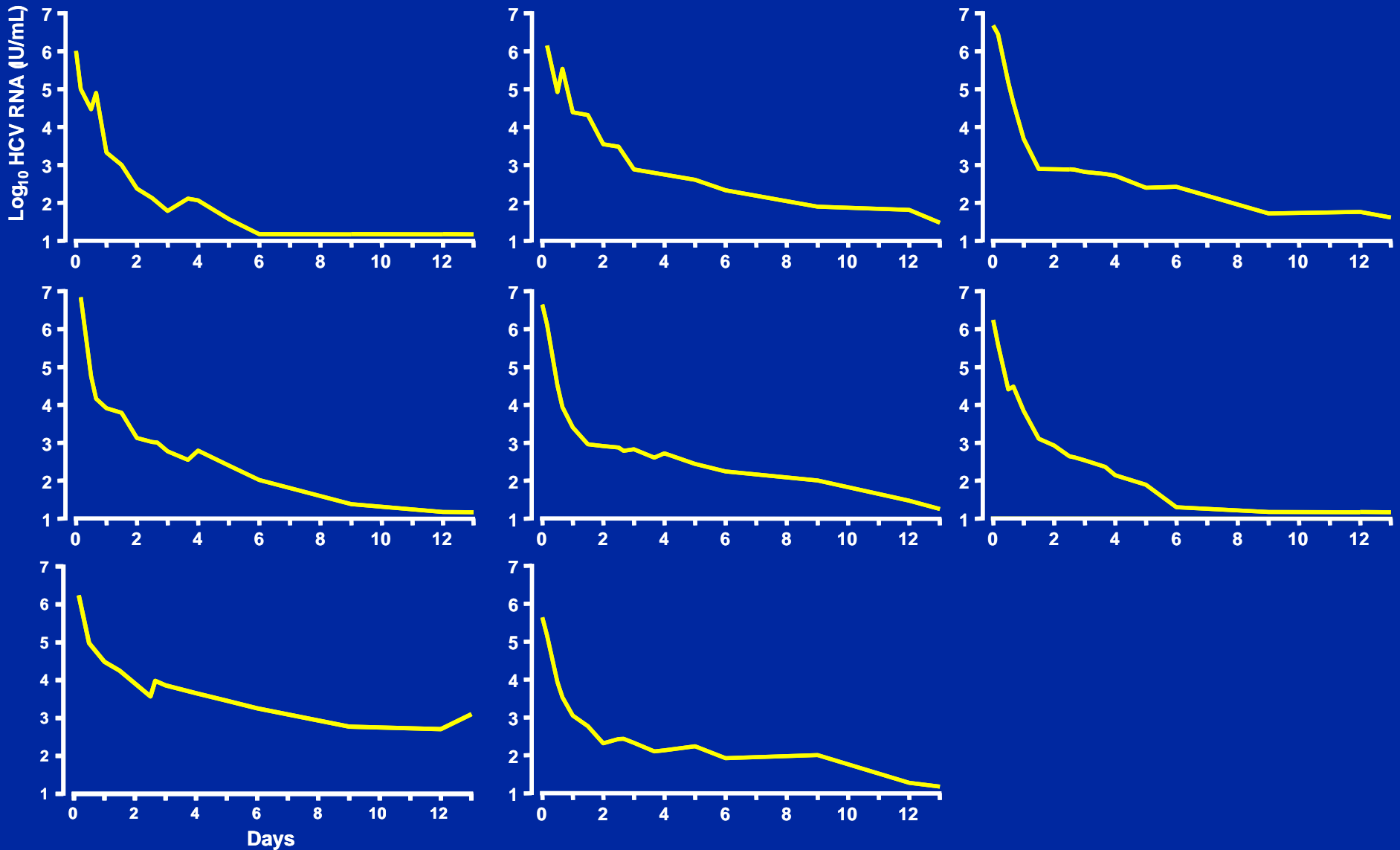
(ii) Higher Dose Cohorts (D-G)



Null Responder Cohort F – Individual Viral Kinetic Profiles (RG7128 1000 mg BID / RG7227 900 mg BID)

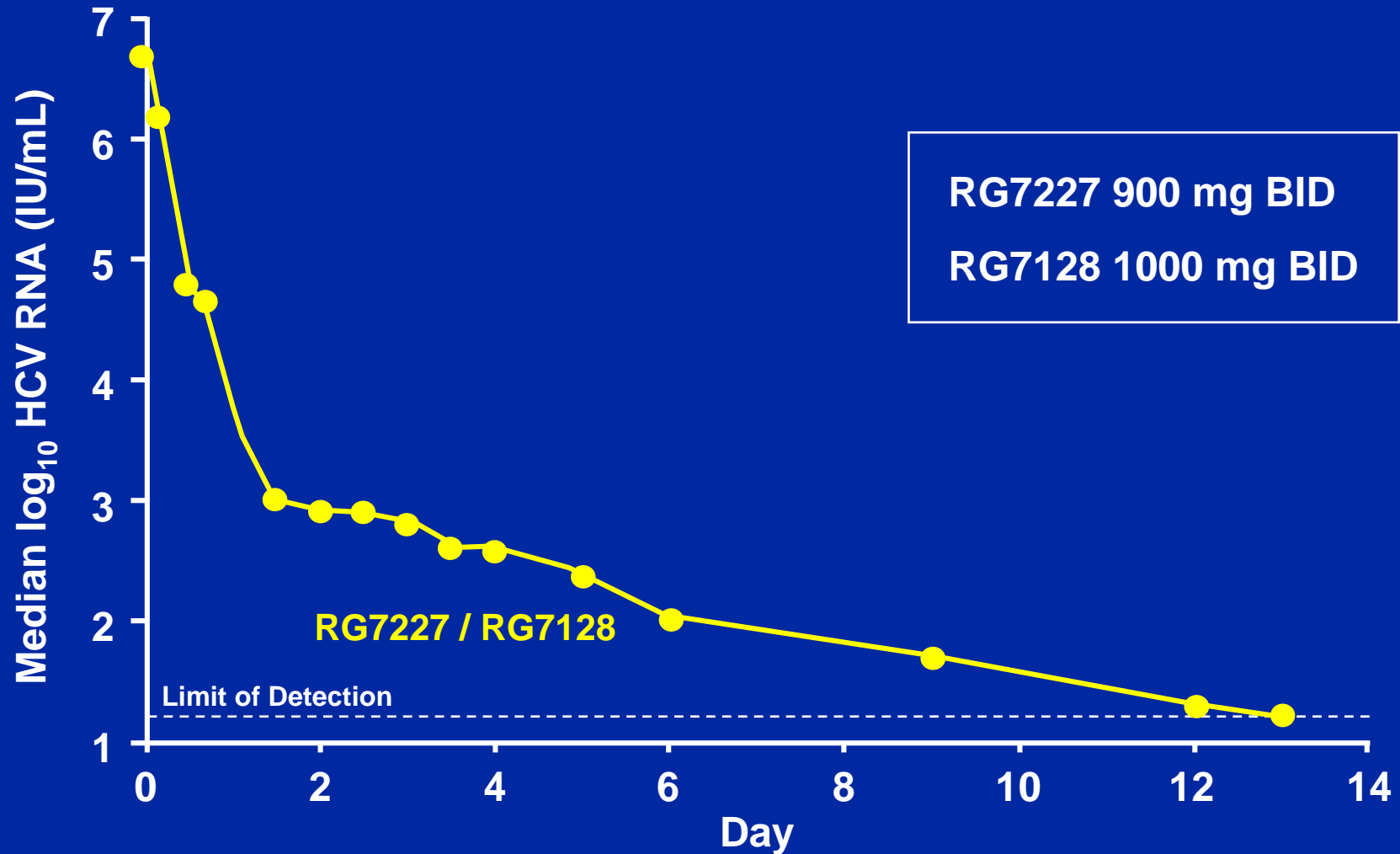


Naive Cohort G – Individual Viral Kinetic Profiles (RG7128 1000 mg BID / RG7227 900 mg BID)



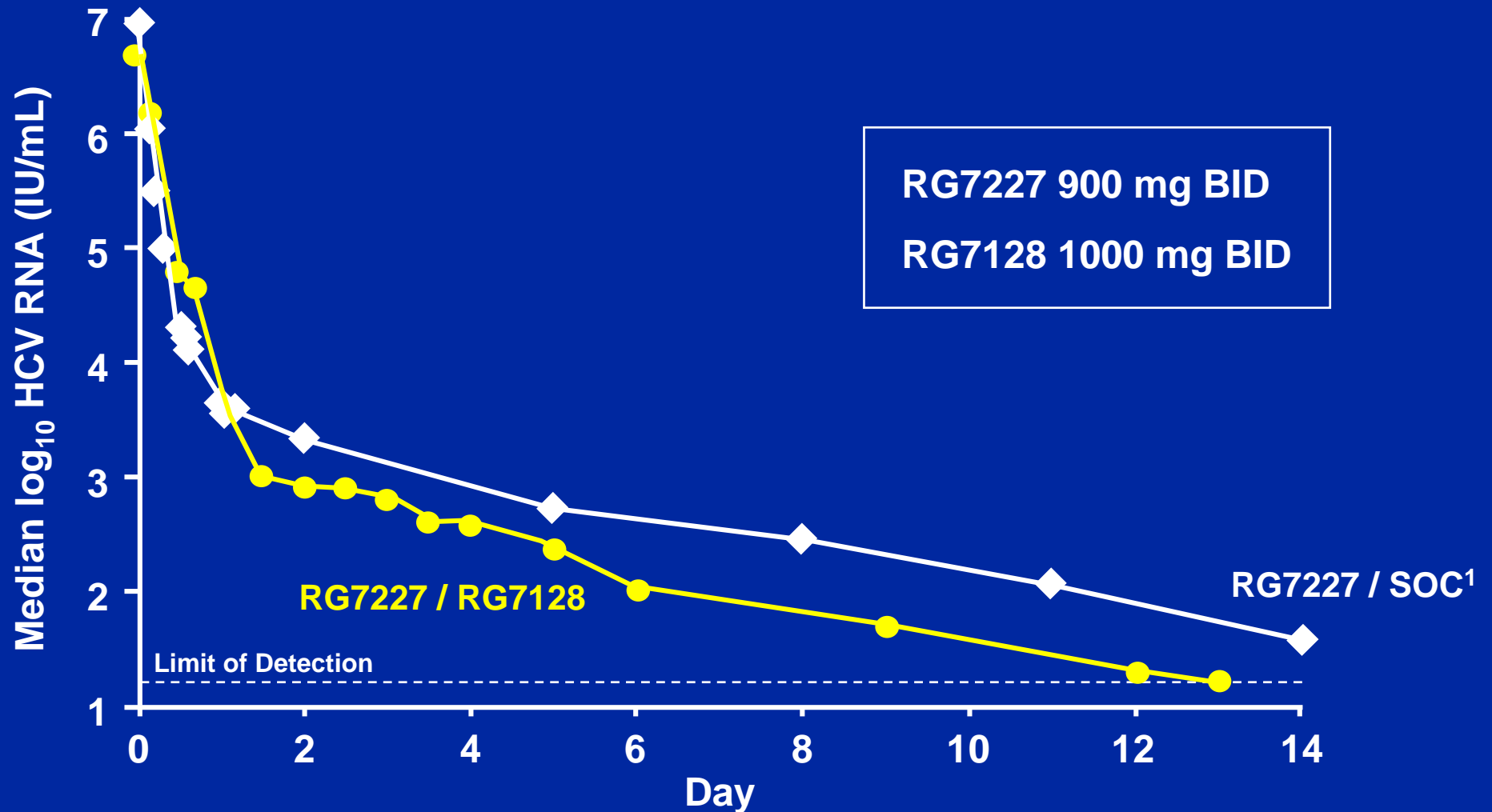
Comparison of Viral Kinetic Profiles of RG7227 plus RG7128 versus RG7227 plus SOC in G1 Naive Patients

see Morcos et al., AASLD 2009 poster #1594



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1. Forestier et al. EASL 2009; Abstract #1847

No Evidence of Emergence of Resistance During Treatment

see Le Pogam et al, AASLD 2009 poster # 1585

- No treatment-emergent resistance identified
- RG7128 / RG7227 achieved continuous viral load decline (73 of 74 patients)
- Viral load rebound ($1.4 \log_{10}$ IU/mL) observed in a one patient in low dose cohort (500 mg RG7128 BID/200 mg RG7227 TID)
 - No resistance mutations identified by population or clonal sequence analysis
 - Phenotypic data showed patient was susceptible to RG7227
 - Patient's viral load rapidly suppressed by SOC

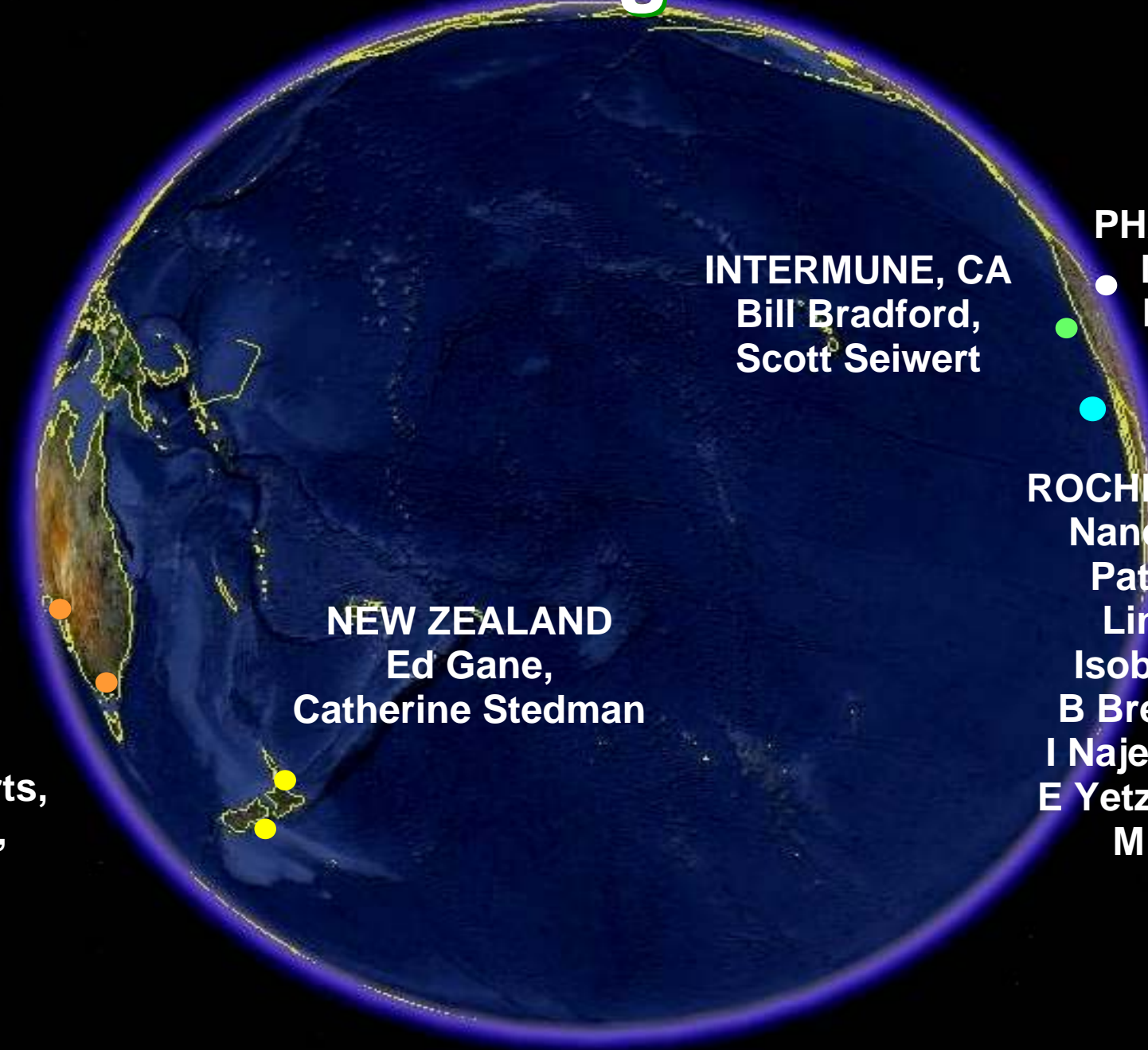
INFORM-1 Study Conclusions

- This is the first study to demonstrate that an IFN-free, all oral and twice daily two-drug combination produces similar antiviral activity compared to triple therapy (SOC plus protease) over 2 weeks of treatment
- Over a 13-day treatment duration, the twice daily orally-administered combination of RG7128 and RG7227 demonstrated:
 - Significant antiviral potency in:
 - Treatment naive patients
 - Treatment failures (null, partial responders and relapsers)
 - GT-1a and GT-1b
 - Promising safety and tolerability
- RG7128 plus RG7227 is an attractive combination regimen for HCV therapy, and the results of INFORM-1 support longer duration clinical trials

Next Steps

- INFORM-2
 - Twice-daily dosing of DAA
 - 4-week duration of therapy
 - GT-1 treatment failures excluding null responders
 - Cohorts
 - RG7128 / RG7227
 - RG7128 / RG7227 plus PEGASYS®
 - RG7128 / RG7227 plus RBV
 - RG7128 / RG7227 plus PEGASYS® plus RBV
 - PEGASYS® plus RBV
- Longer term studies evaluating sustained virologic response (SVR) are anticipated for the first half of 2010

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