

IMO-2125 PLUS RIBAVIRIN GIVES SUBSTANTIAL FIRST-DOSE VIRAL LOAD REDUCTIONS, CUMULATIVE ANTI-VIRAL EFFECT, IS WELL TOLERATED IN NAÏVE GENOTYPE 1 HCV PATIENTS: A PHASE 1 TRIAL

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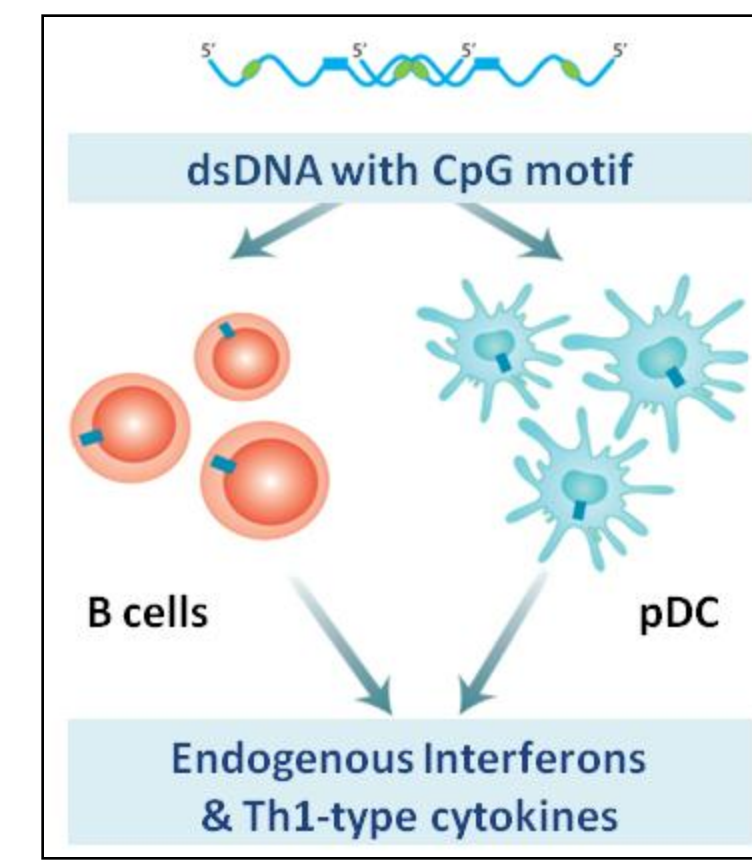
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Introduction

- Primary clinical features of HCV infection
 - 20% of infected patients go on to clear the virus spontaneously
 - 80% of patients progress to chronic infection
- Thus, innate and adaptive host immunity is capable of clearing the infection, but, for unknown reasons, is unsuccessful in most patients.
- Treatment of chronic HCV infection
 - Current standard of care is pegylated-interferon (peg-IFN) plus ribavirin
 - peg-IFN also is used with direct acting antiviral (DAA) agents under development to prevent the emergence of resistance
 - This results in triple or quadruple combination regimens
- peg-IFN has well-described limitations
 - Specifically, adverse effects, poor tolerance and poor compliance
- An immune modulator that provides antiviral activity and could be an alternative to peg-IFN would represent a benefit to patients

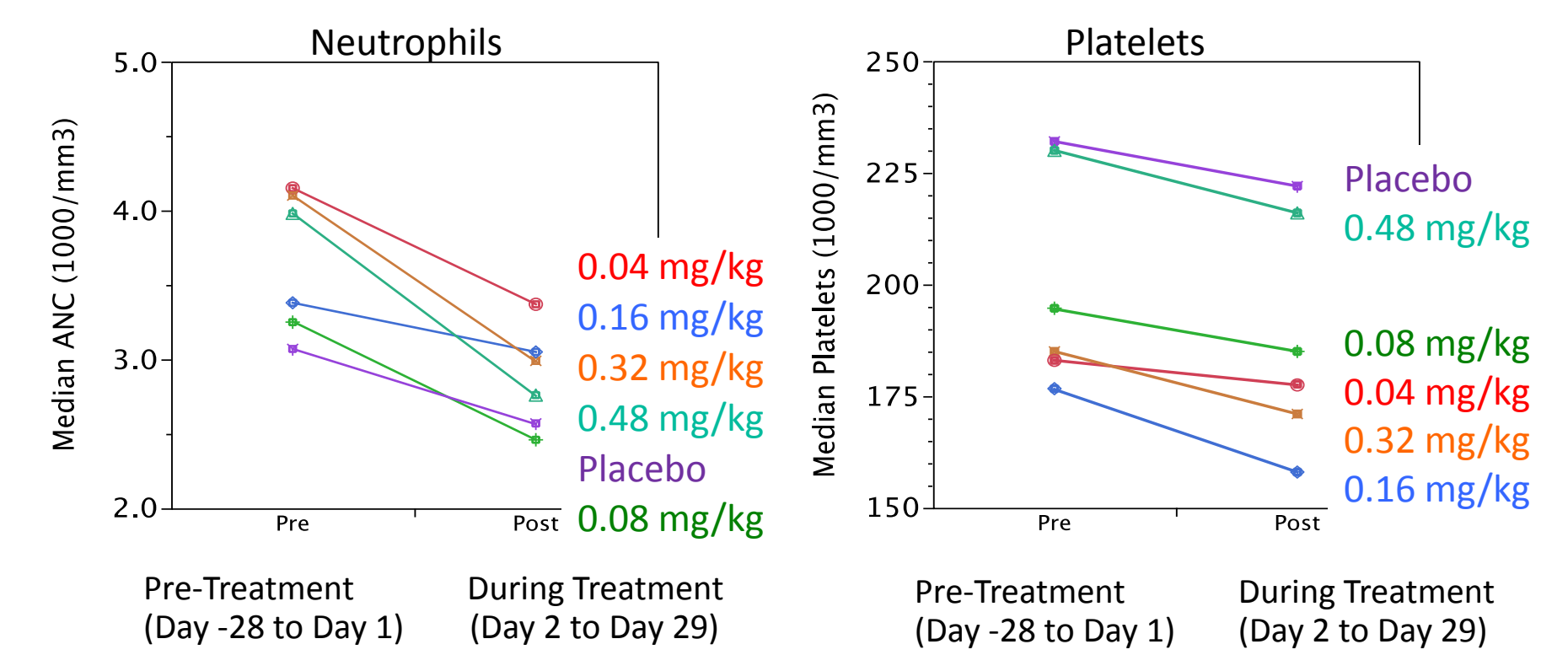
IMO-2125 – A Novel Immune Stimulant

- Synthetic oligonucleotide agonist of Toll-Like Receptor 9 (TLR9), expressed on plasmacytoid dendritic cells (pDC) and B cells
- Directly stimulates innate immune system of the patient
- Induces a broad array of endogenous cytokines and chemokines
 - Includes IFN- α , 2'5'-OAS, IL-1Ra, IL-2R, IL-6, IL-12, IP-10, MCP-1
 - Secondary effects: activates NK cells, monocytes, neutrophils
 - Enhances Th1-type cellular response
 - Provides robust antiviral activity
- Novel mechanism of action as an alternative to peg-IFN
 - Potentially useful in HCV, HBV, other chronic viral infections
- Key differentiating factors:
 - Safety (e.g., less hematologic toxicity)
 - Tolerability (e.g., shorter duration flu-like symptoms)
 - Antiviral activity (e.g., activates multiple antiviral immune responses)



Protocol 2125-001

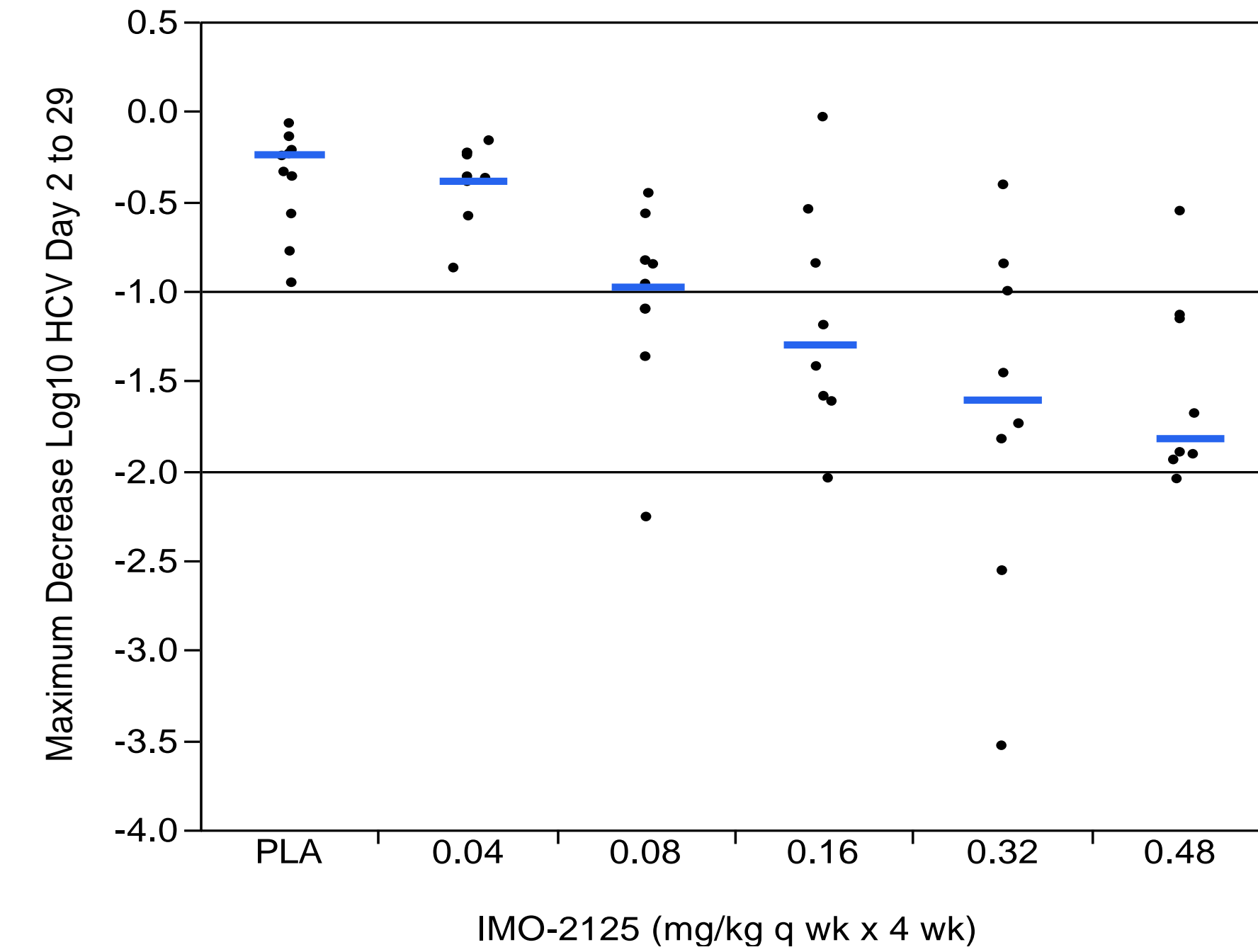
- First-in-man, placebo-controlled, dose-escalation study
- Patient population: "Null-responders"
 - HCV patients who received at least 12 weeks peg-IFN plus ribavirin and never achieved a 2 log₁₀ reduction in HCV viral load
 - Poor prognostic factors:
 - IL28B genotype: CT/TT, 53/58 (91%)
 - IP-10 baseline: >600 ng/mL, 19/48 (40%)
- Treatment
 - IMO-2125 by subcutaneous injection once weekly for 4 weeks
 - Dose levels: 0.04 to 0.48 mg/kg
- Safety profile: well-tolerated
 - No drug-related SAEs or discontinuations; no severe AEs related to treatment
 - Most common AEs were
 - Mild-moderate injection site reactions (erythema and induration)
 - Flu-like symptoms (typically brief duration, \leq 1 day)
- Minimal hematologic toxicity during 4 weeks of treatment
 - Changes in neutrophil and platelet counts were comparable to placebo



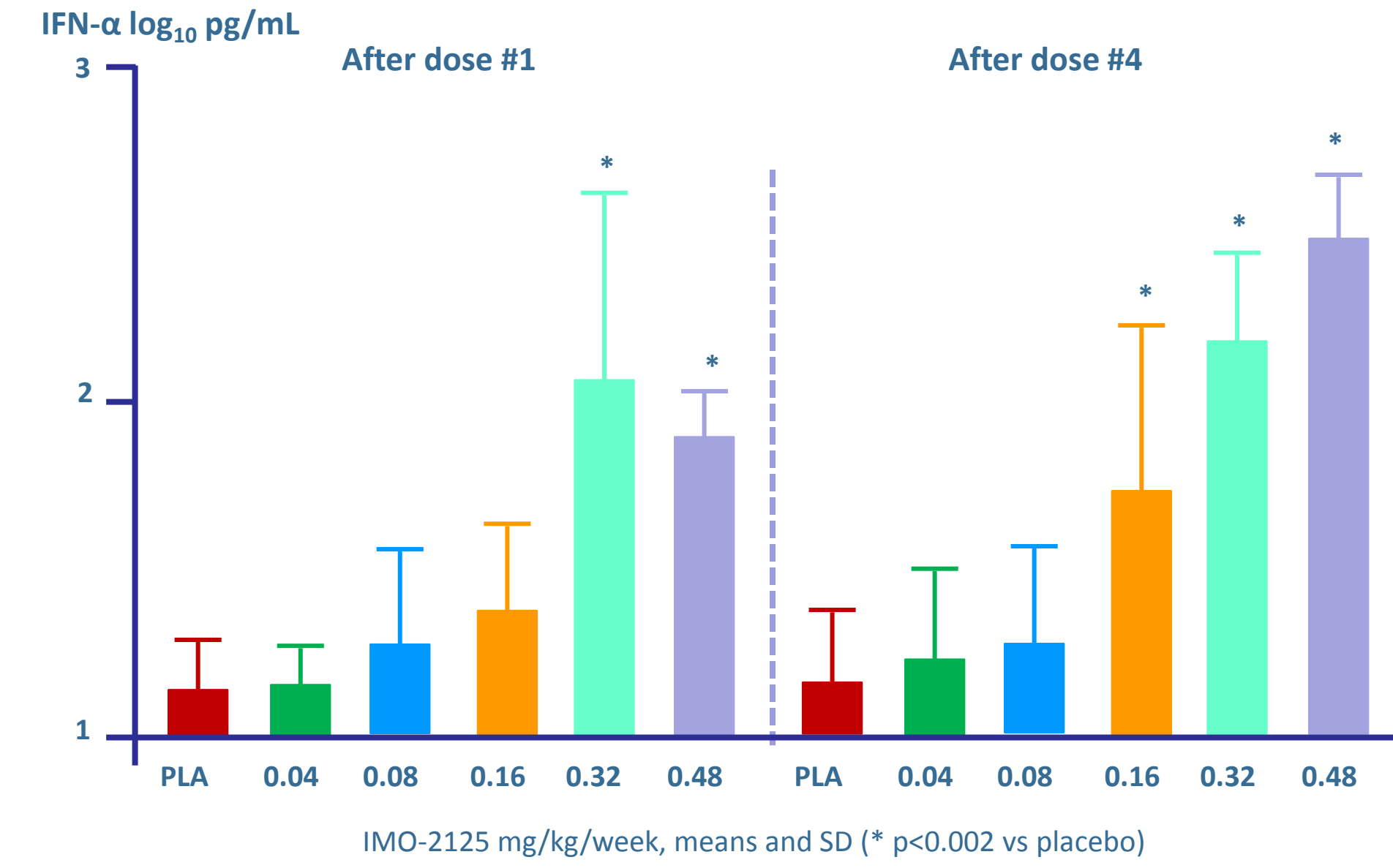
Confirmation of Mechanism of Action

- Dose-dependent increases in cytokines and antiviral proteins
 - IFN- α , 2'5'-OAS, IL-1Ra, IL-2R, IL-6, IL-12, IP-10, MCP-1
- Dose-dependent reduction in viral load, correlated to increased IFN- α

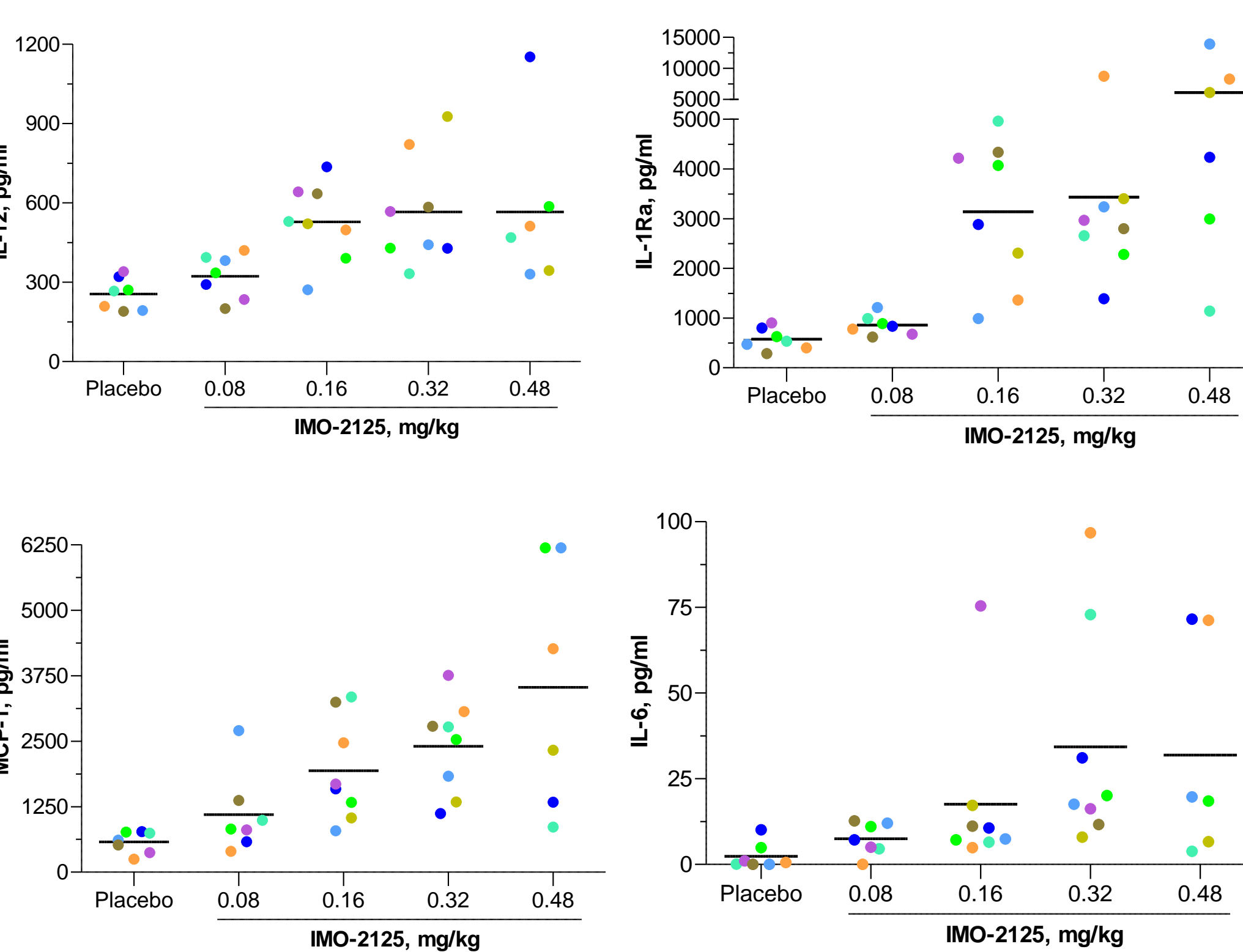
HCV Viral Load in Null Responders



IFN- α in Null Responders



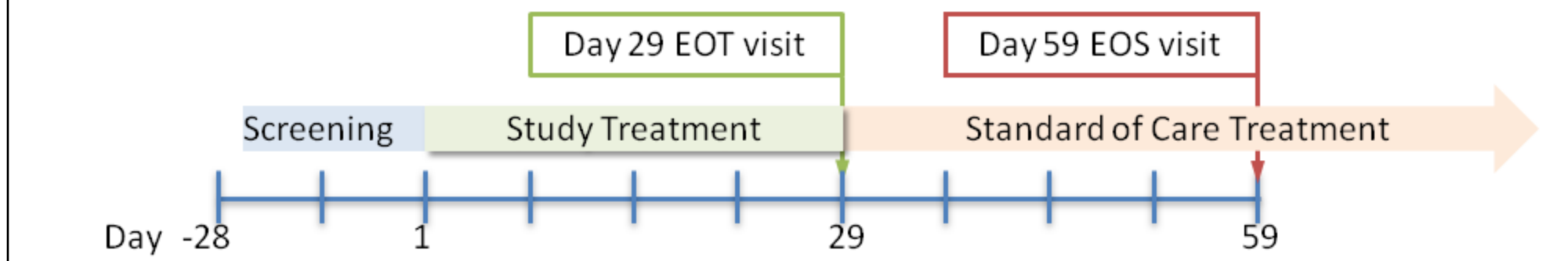
IMO-2125 Induced Cytokines: Comparison at 24 hr post 4th dose



Protocol 2125-201

Comparator-controlled, dose-escalation study in treatment-naïve HCV genotype 1 patients	IMO-2125 once weekly*	IMO-2125 twice weekly*	Comparator*
Cohort 1	0.08 mg/kg	--	Placebo (n=3)
Cohort 2	0.16 mg/kg	--	Pegasys* (n=6)
Cohort 3	0.32 mg/kg	0.16 mg/kg	Pegasys* (n=6)

* All patients receive ribavirin with 4-week study treatment. N=12 except where noted.



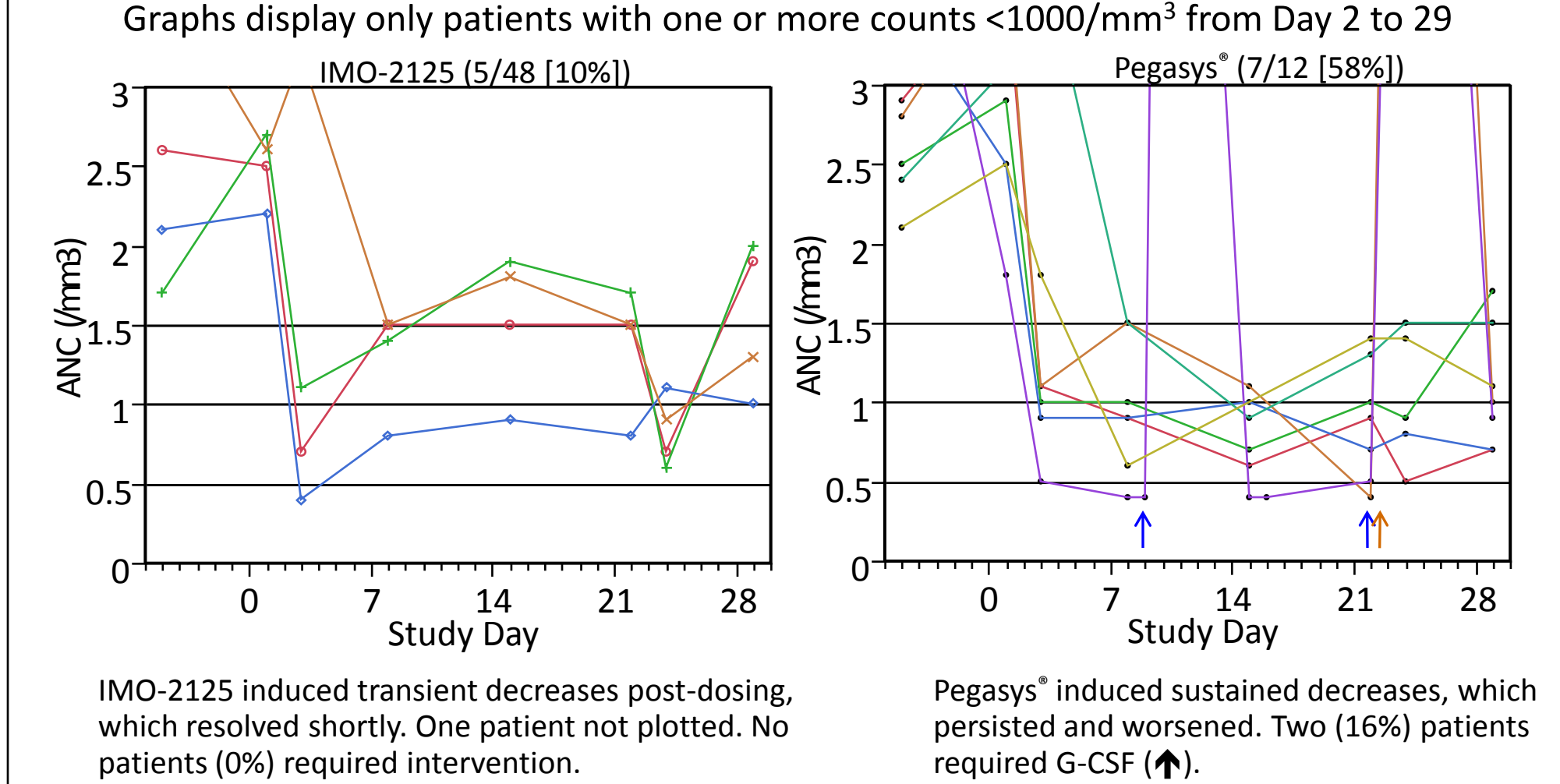
Safety Profile

- IMO-2125 was well-tolerated: no discontinuations, no treatment-related SAEs
- Most common AEs in patients receiving IMO-2125 were
 - Mild-moderate injection site reactions (e.g., erythema, induration, tenderness)
 - Mild-moderate flu-like symptoms (e.g., fever, chills, myalgias)

AE Features Differentiating IMO-2125 and Pegasys*

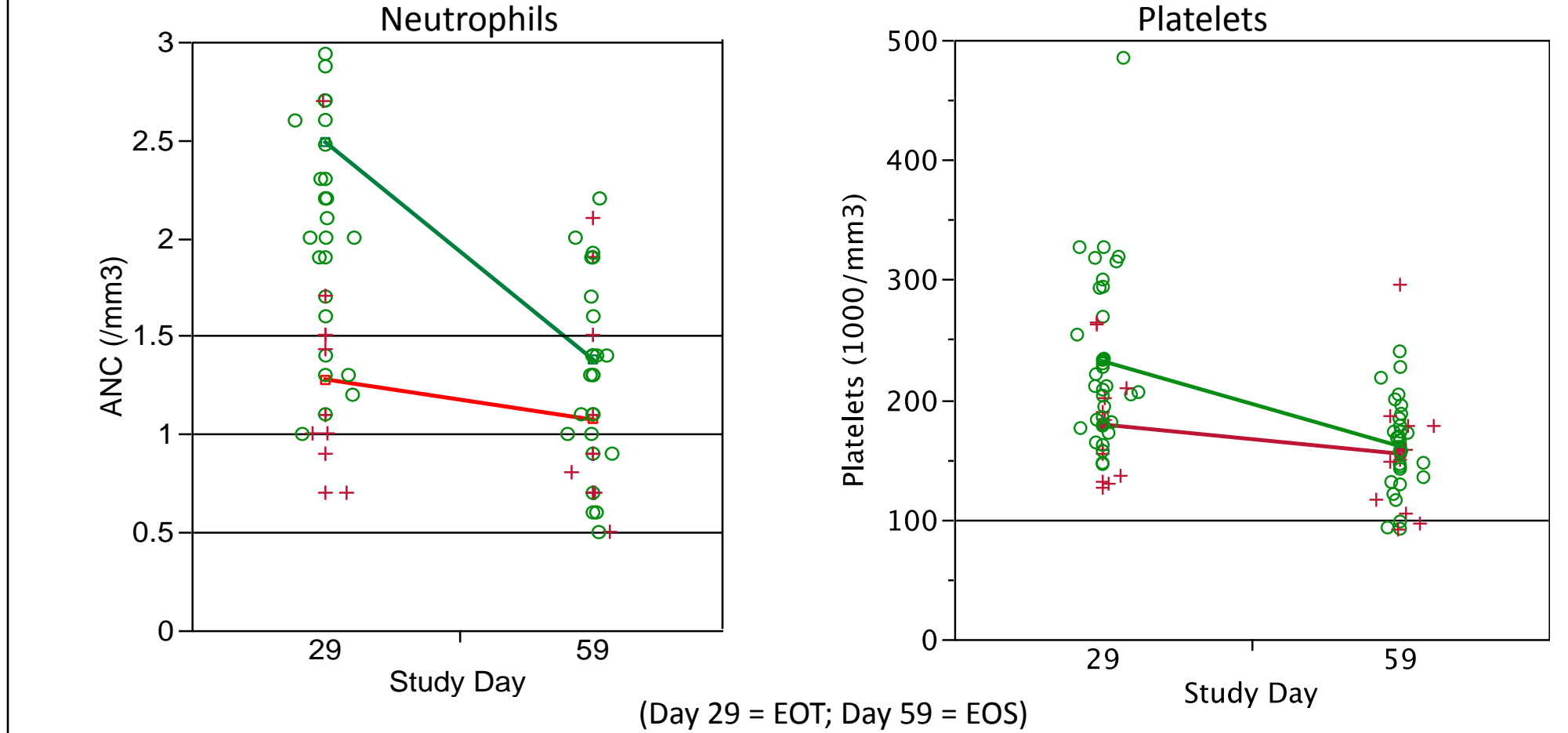
Event	IMO-2125	Pegasys*
Neutropenia	Infrequent, transient, mild	Common, sustained, occ. severe
Thrombocytopenia	At Day 29, all subjects >145k	At Day 29, 25% subjects \leq LLN (130k)
Flu-like symptoms	Onset ~8hr post-injection Typically brief duration (\leq 1 day) Primarily fever, chills	Delayed onset (1-2 days) Longer duration (>2 days) Frequently malaise

Patients with Decreased Neutrophils by Treatment

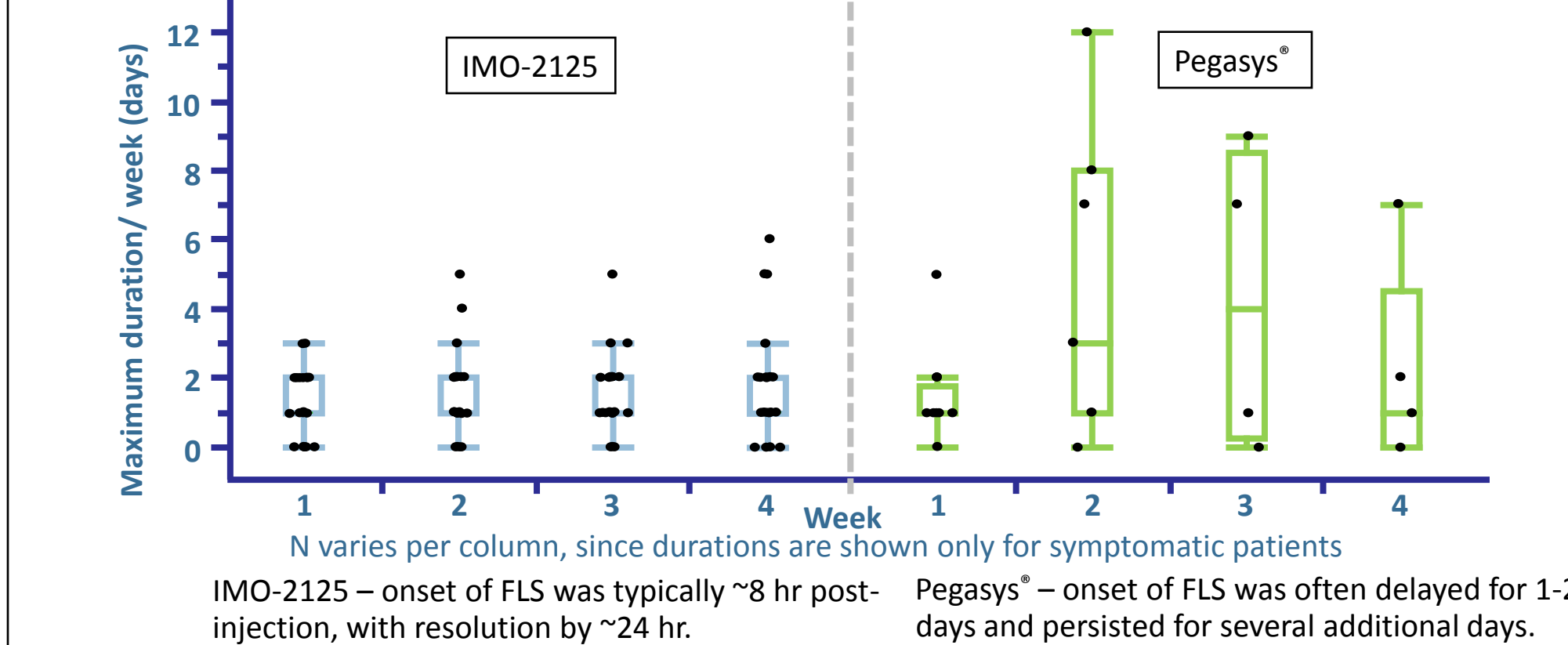


Impact of Pegasys* on Neutrophils and Platelets after IMO-2125

- After Day 29, all subjects received Pegasys* + ribavirin (SoC)
- Subjects previously on IMO-2125 (green line) had significant drop in neutrophils and modest drop in platelets on subsequent SoC



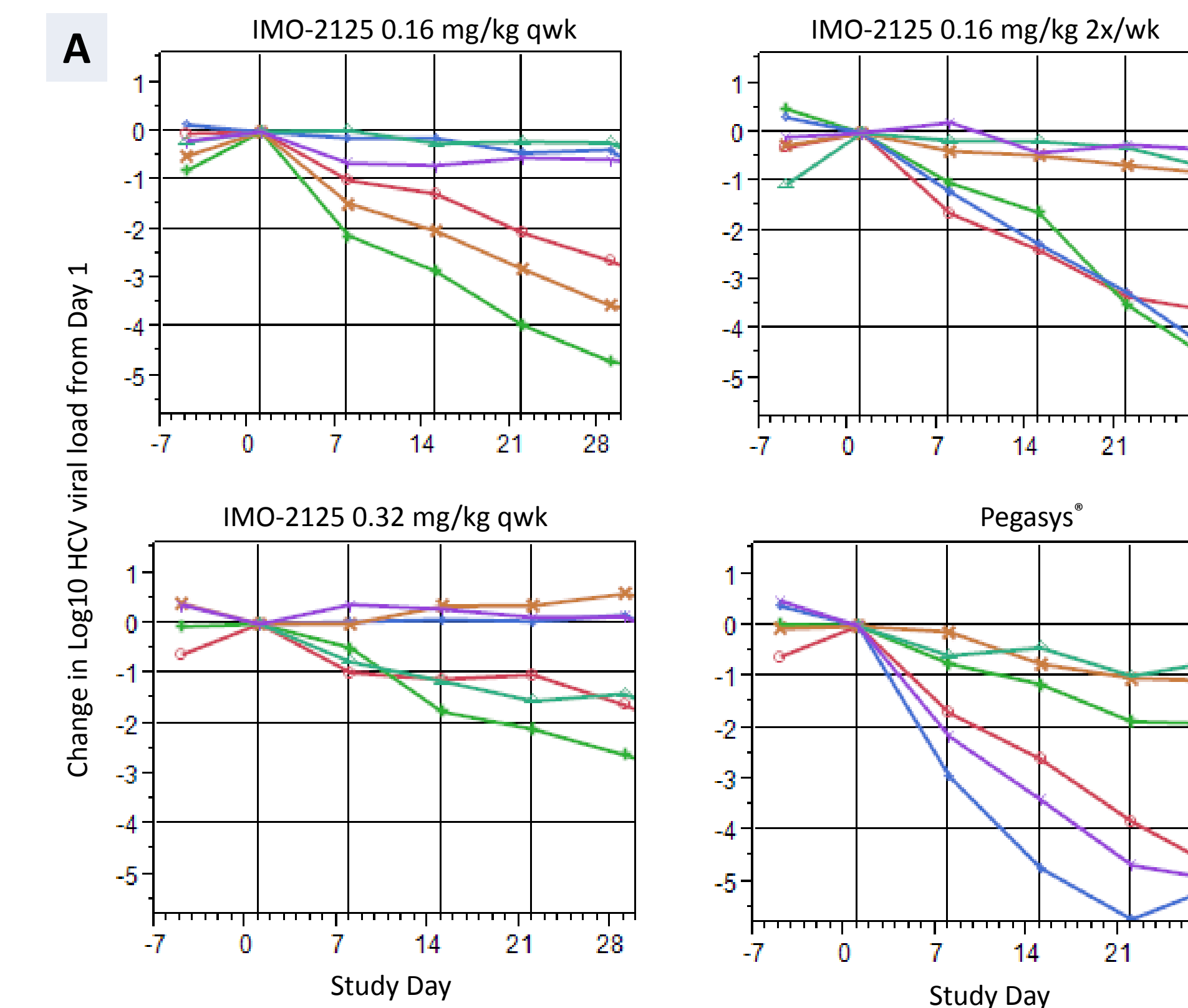
Qualitative Differences in Flu-like Symptoms (FLS)



Effect of IMO-2125 on Viral Load

Cohort	IMO-2125 Regimen†	HCV RNA log ₁₀ – Change From Baseline		
		Mean change at 48h after 1 st dose (range)	Maximum decrease during treatment >1 log ₁₀ >2 log ₁₀	Mean change at Day 29 (range)
1	0.08 mg/kg/wk	-1.1 (0.1 to -2.97)*	75% 42%	-0.9 (0.3 to -1.9)
2	0.16 mg/kg/wk	-2.5 (-0.8 to -3.9)	100% 100%	-1.7 (-0.2 to -4.7)
3	0.32 mg/kg/wk	-1.3 (0.2 to -2.8)	92% 50%	-0.6 (0.6 to -2.7)
3	0.16 mg/kg 2x/wk	-1.6 (-0.5 to -2.9)	92% 75%	-2.4 (-0.3 to -4.5)
2&3	Standard of Care	-1.4 (0.2 to -2.4)	100% 83%	-3.4 (-0.7 to -5.0)

† N=12 per treatment regimen. All subjects received weight-based ribavirin.
* First cohort samples taken 24 hr post-dose.



- Panel A below shows course of viral load changes over 4 weeks of treatment
 - Six of the 12 patients treated with each regimen were selected based on the reduction in viral load at Day 29
 - Three with the greatest reduction in viral load (best response quartile)
 - Three with the least reduction in viral load (least response quartile)
- For all IMO-2125 treatment regimens \geq 0.16 mg/kg/wk
 - One or more patients had progressive reductions in viral load over 4 weeks
 - Typically the reduction was comparable to that of Pegasys*
 - In all treatment groups – including Pegasys* – some patients did not achieve a 1 log₁₀ reduction in viral load at the end of 4 weeks
- Panel B shows the course of viral load changes over an additional 4 weeks of treatment with SoC
 - In all treatment groups – including Pegasys* – additional SoC treatment produced further viral load reductions in one or more patients
 - In all treatment groups – including Pegasys* – additional SoC treatment did not achieve 2 log₁₀ viral load reductions in one or more patients

Distribution of Prognostic Factors

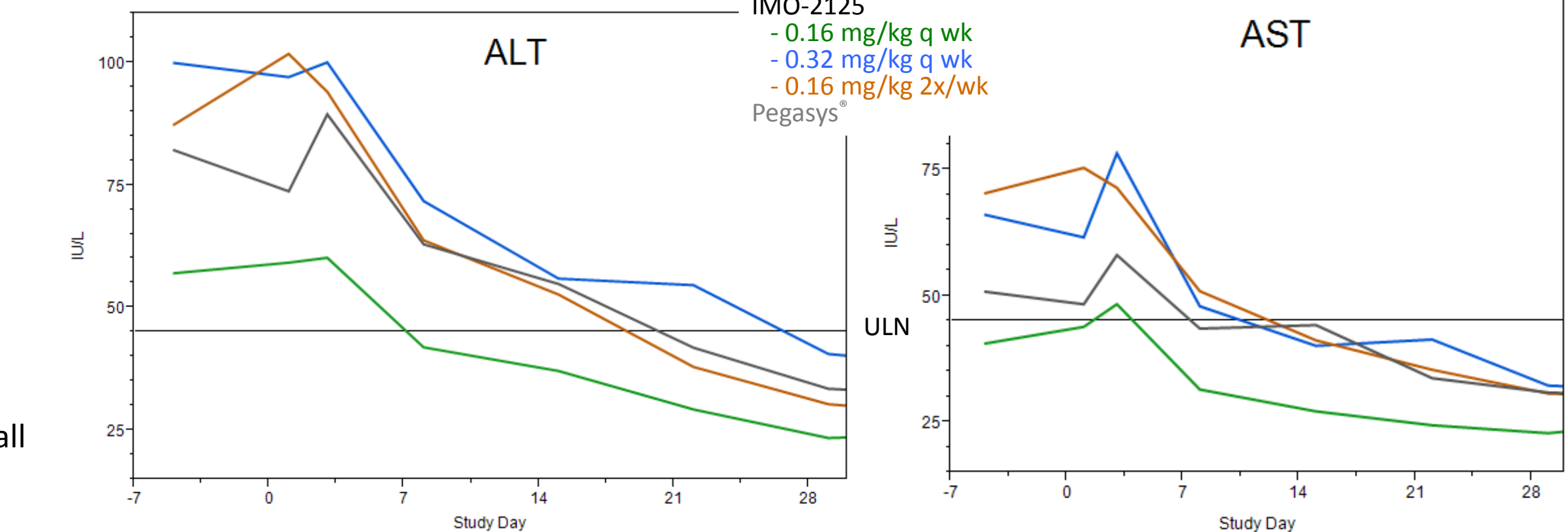
Cohort	Dosing (mg/kg/w)	N	IL28B CT or TT	IP-10 >600 pg/mL	Age >50
1	0.08	12	not available	2 (16%)	3 (25%)
2	0.16	12	pending	1 (8%)	0
	Pegasys*	6	pending	1 (16%)	0
3	0.32	12	9 (75%)	4 (33%)	5 (42%)
	0.16 x 2	12	9 (75%)	5 (42%)	3 (25%)
	Pegasys*	6	3 (50%)	1 (16%)	1 (16%)

Negative prognosis factors contributed to the variability in antiviral response seen in all treatment groups, including Pegasys*.

Summary

- IMO-2125 has a novel mechanism of action to induce production of endogenous IFN- α and other antiviral cytokines.
- IMO-2125 plus ribavirin was well tolerated by treatment-naïve HCV patients in once- or twice-weekly administration for 4 weeks. There was substantial antiviral activity.
- Based on its activity in both treatment-naïve and null responder HCV patients, IMO-2125 could provide an alternative immune modulatory component for HCV therapy.

Improvement in Liver Function Tests During Treatment



Next Steps

- Phase 2 12-week clinical trial of IMO-2125 plus ribavirin in treatment-naïve genotype 1 HCV patients
- Objectives: Provide longer-term safety and antiviral data
- Subsequent development of IMO-2125 as an alternative immune modulator to recombinant interferon in HCV treatment combinations with direct-acting antiviral agents