



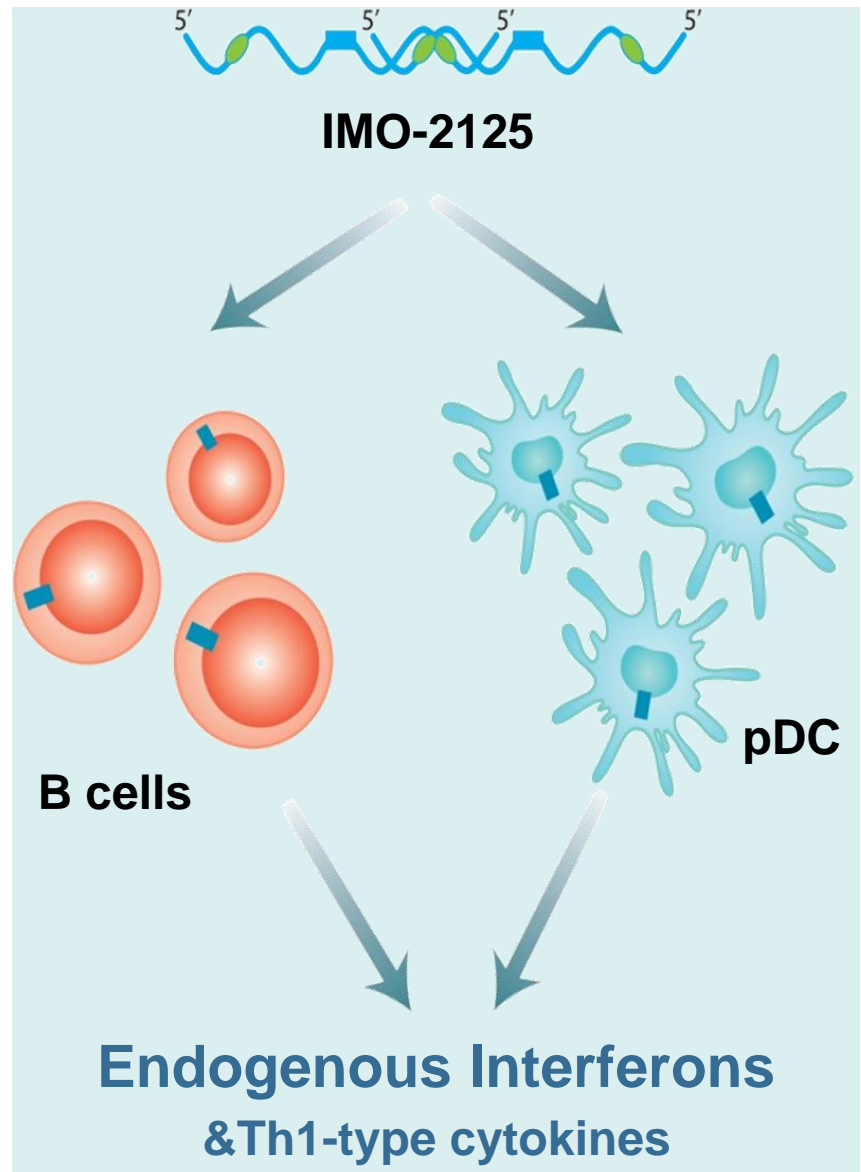
**IMO-2125, a TLR9 Agonist,  
Induces Immune Responses  
Which Correlate With Reductions In Viral Load  
In Null Responder HCV Patients**

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# IMO-2125: An Agonist of Toll-like Receptor 9 (TLR9)

## IMO-2125

- Is an agonist of TLR9
- Stimulates innate immune responses
- Activates dendritic cells and B cells
- Induces anti-viral cytokines, e.g., IFN- $\alpha$ , IFN- $\beta$ , IFN- $\lambda$ , IP-10
- Secondary effects:
  - activates NK cells, monocytes, and neutrophils
  - enhances Th1-type cellular response



# 2125-001 First-in-Human Study in HCV Null Responders



- Phase 1: dose-escalation, proof of concept, safety study
- Population: null responder HCV patients
- Design: placebo-controlled, randomized (8:2), double-blind
- Treatment: IMO-2125 or saline placebo, S.C., weekly x 4
- Dose escalation: 0.00, 0.04, 0.08, 0.16, 0.32, 0.48 mg/kg/week
- Pharmacodynamic endpoints:
  - Immunophenotypes of circulating lymphocytes
    - NK, CD4<sup>+</sup> T cells, CD8<sup>+</sup> T cells, others
  - Serum cytokines: IFN- $\alpha$ , IP-10, 2',5'-OAS
  - Relationship of immune response to viral load

# 2125-001 Null Responder Patients



Characteristic	Value or Incidence	Comment
HCV genotype 1	50/51 (98%)	Least responsive genotype
Maximum VL reduction during prior standard treatment	$<2 \log_{10}$	Definition of null-responder
HCV RNA ( $\log_{10}$ copies/mL) <sup>a</sup>	$6.8 \pm 0.5$	High VL consistent with refractory disease
Serum IP-10 (pg/mL) <sup>a</sup>	$561 \pm 271$	$<150$ pg/mL predicts responsive disease <sup>c</sup>
Serum IFN- $\alpha$ $<25$ pg/mL <sup>b</sup>	51/51 (100%)	Indicates inadequate immune response

<sup>a</sup> mean  $\pm$  SD

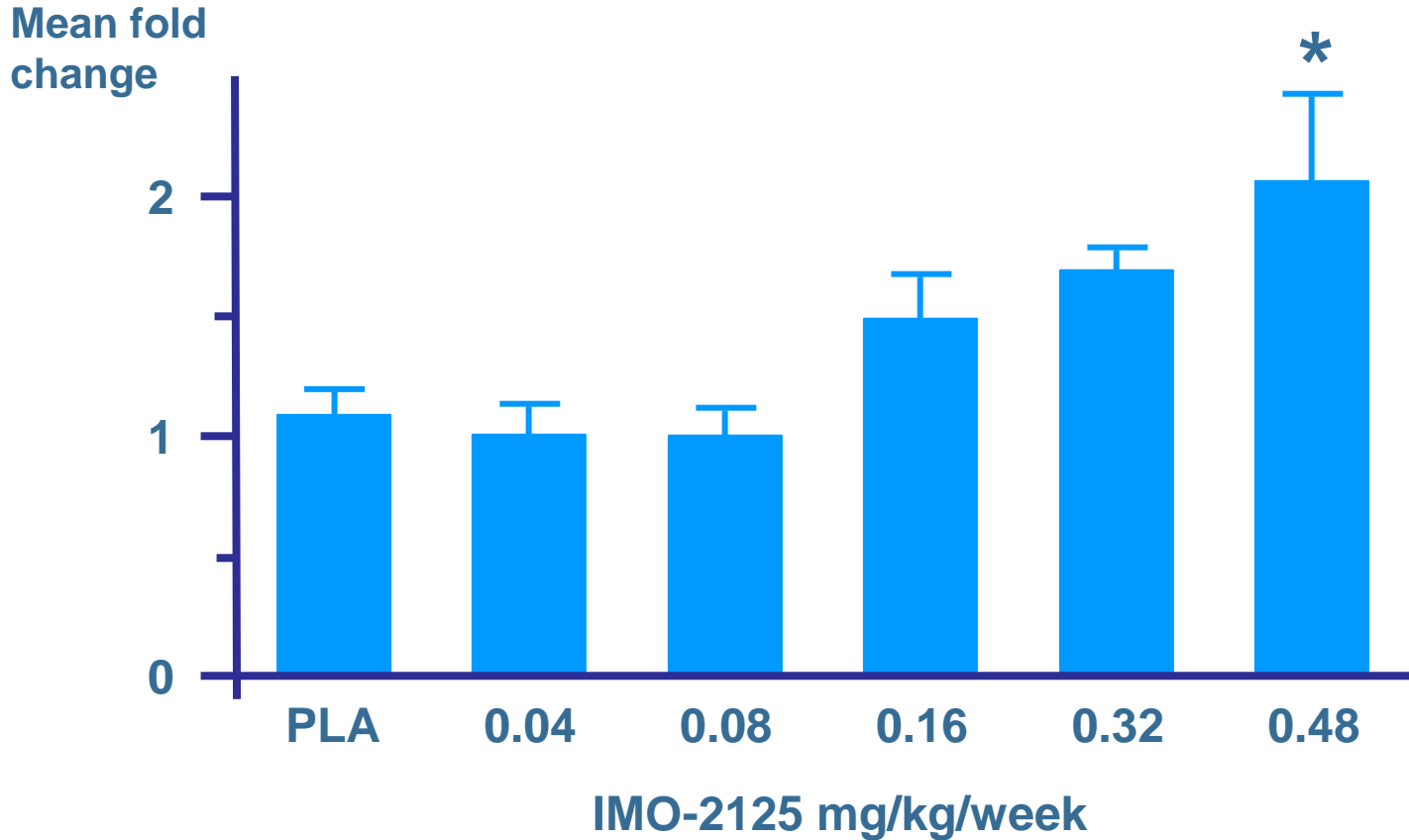
<sup>b</sup>  $<$ Lower Limit of Quantification

<sup>c</sup> Romero AI et al. J Infect Dis. 2006;194(7):895-903

# IMO-2125 Dose-dependent Induction of NK Cells



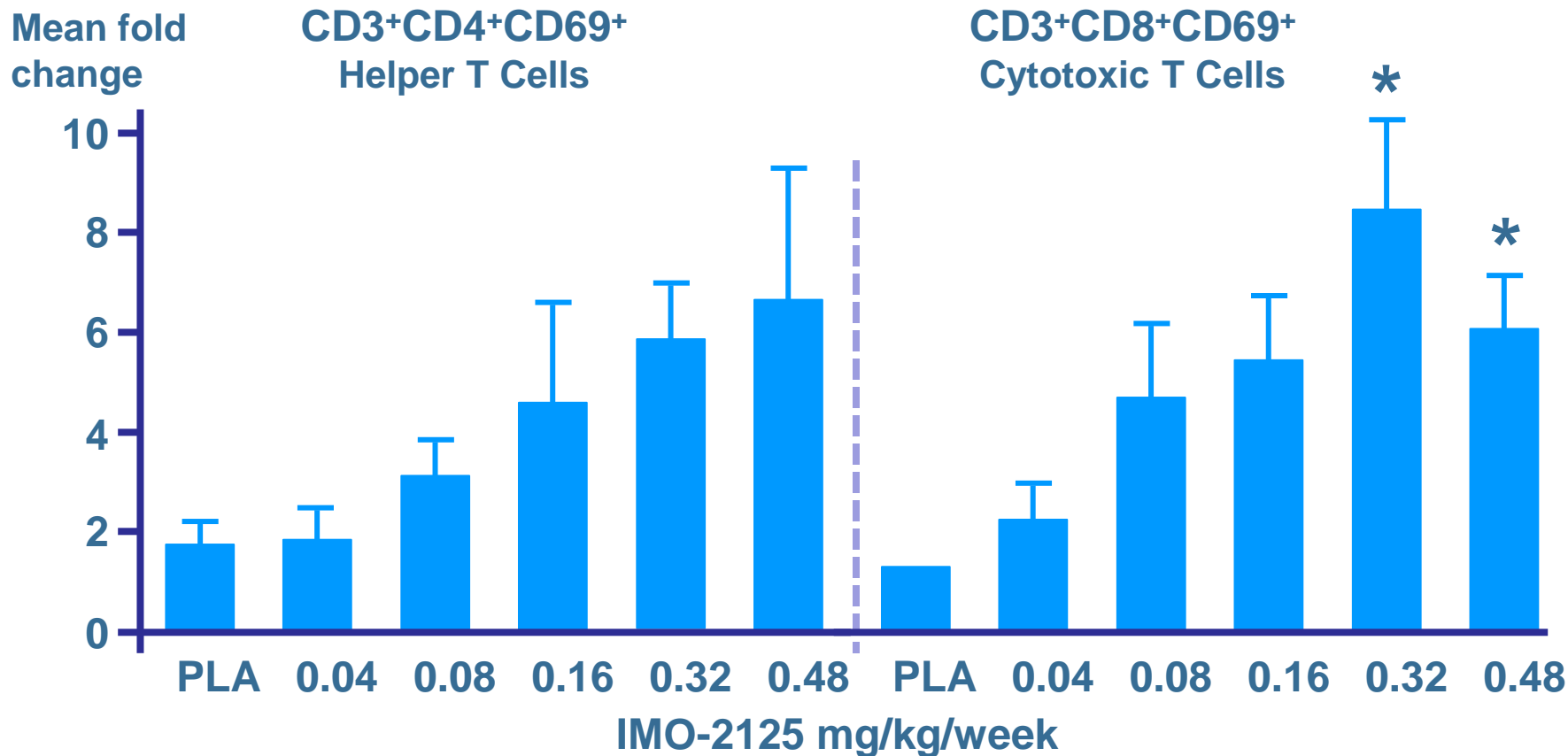
Mean fold change in frequency of lymphocytes with NK phenotype at 24 h after dose #1 compared to pre-dose



\*  $p < 0.05$  vs placebo  
Data are means and SEM

# IMO-2125 Dose-dependent T Cell Activation

Mean fold change in % circulating lymphocytes with CD69<sup>+</sup> phenotype at 24 h after dose #1 compared to pre-dose



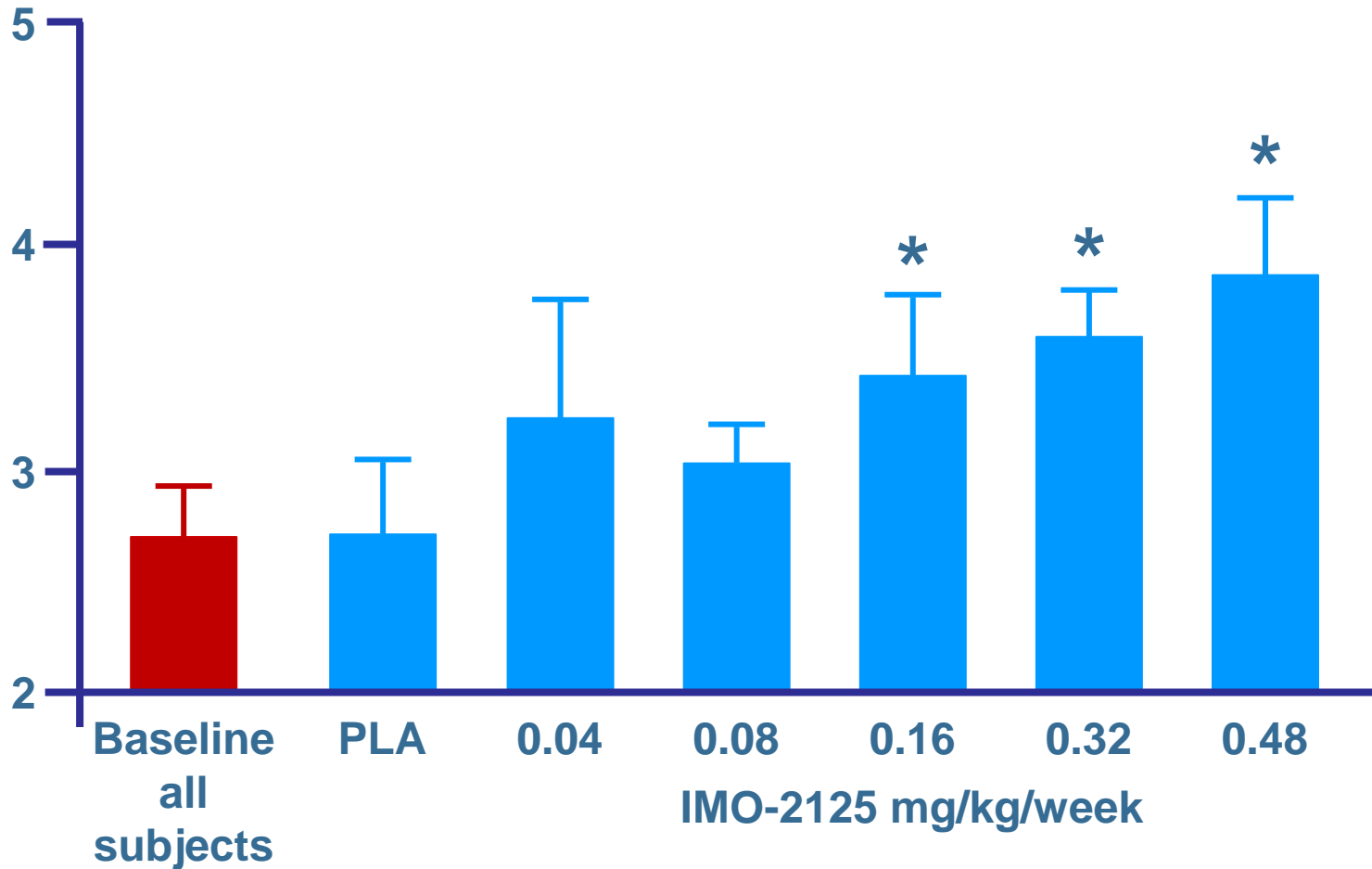
\* p<0.05 vs placebo  
Data are means and SD

# IMO-2125 Dose-dependent Induction of Serum IP-10



IP-10 (log<sub>10</sub> pg/mL)

After dose #4

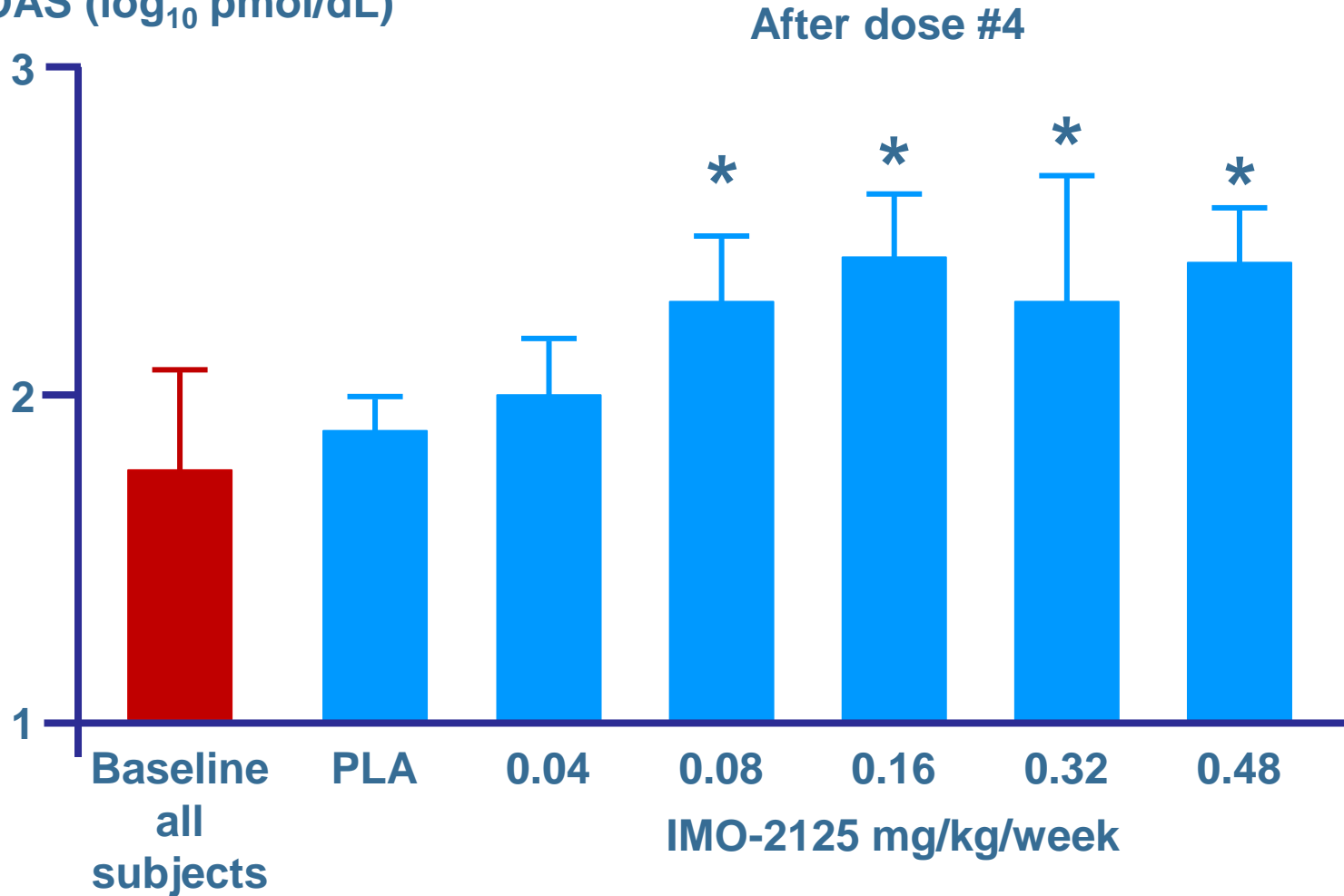


\* p<0.0001 vs baseline  
Data are means and SD

# IMO-2125 Dose-dependent Induction of Serum 2'5'-OAS



2'5'-OAS ( $\log_{10}$  pmol/dL)

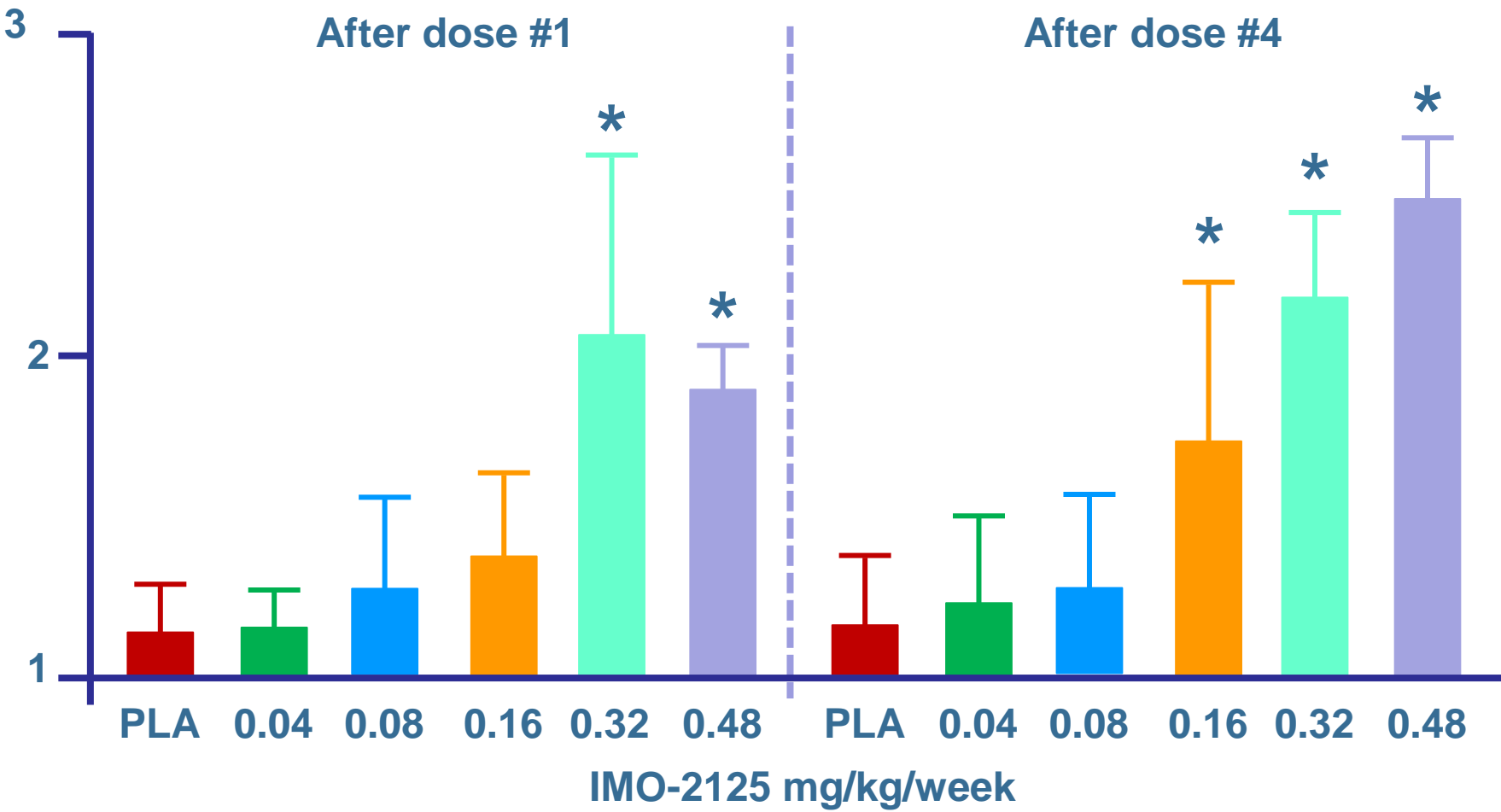


\*  $p < 0.0001$  vs baseline  
Data are means and SD

# IMO-2125 Dose-dependent Induction of IFN- $\alpha$

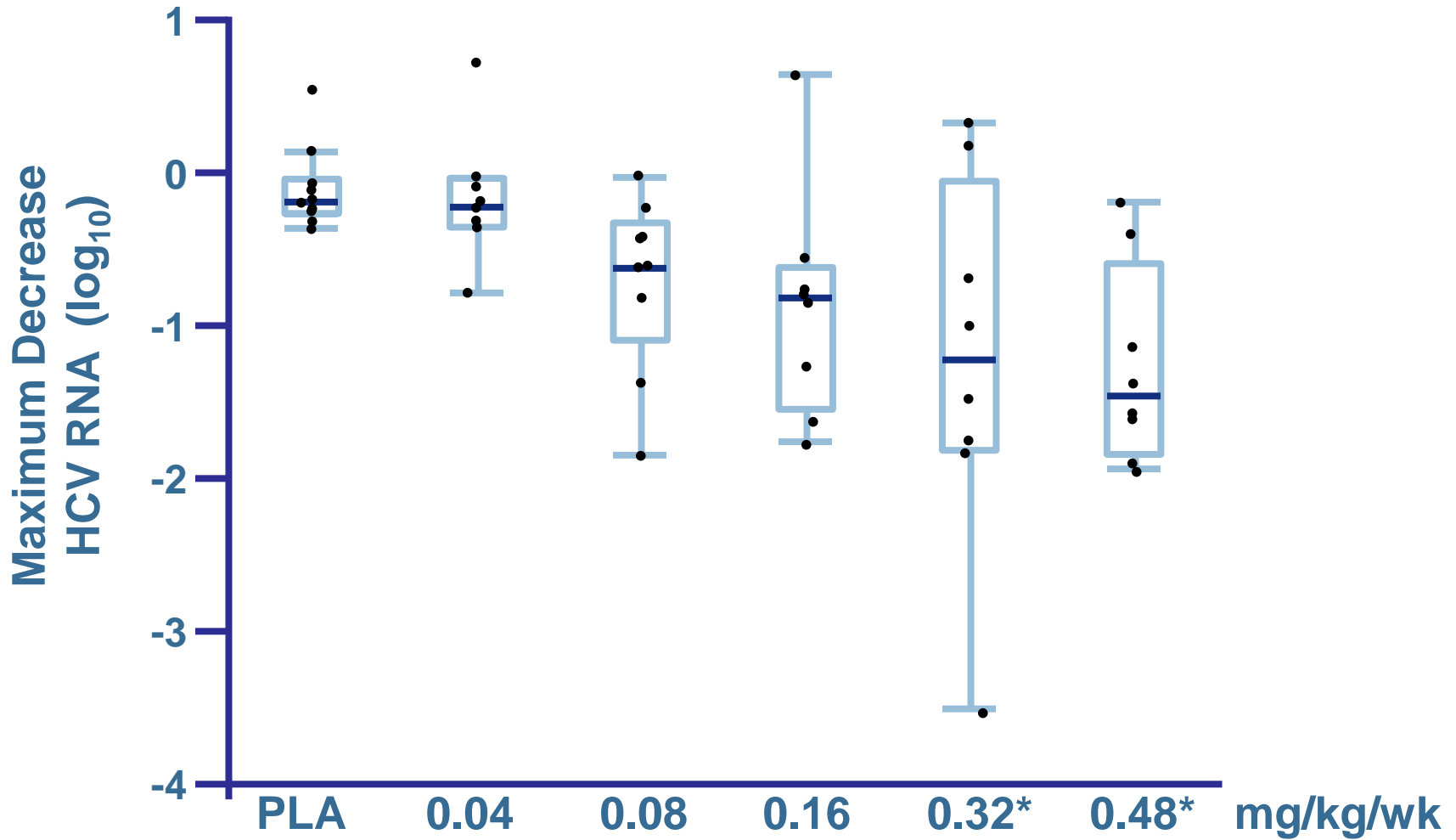


IFN- $\alpha$  log<sub>10</sub> pg/mL



\* p < 0.002 vs placebo  
Data are means and SD

# IMO-2125 Dose-dependent Reduction in Plasma HCV RNA

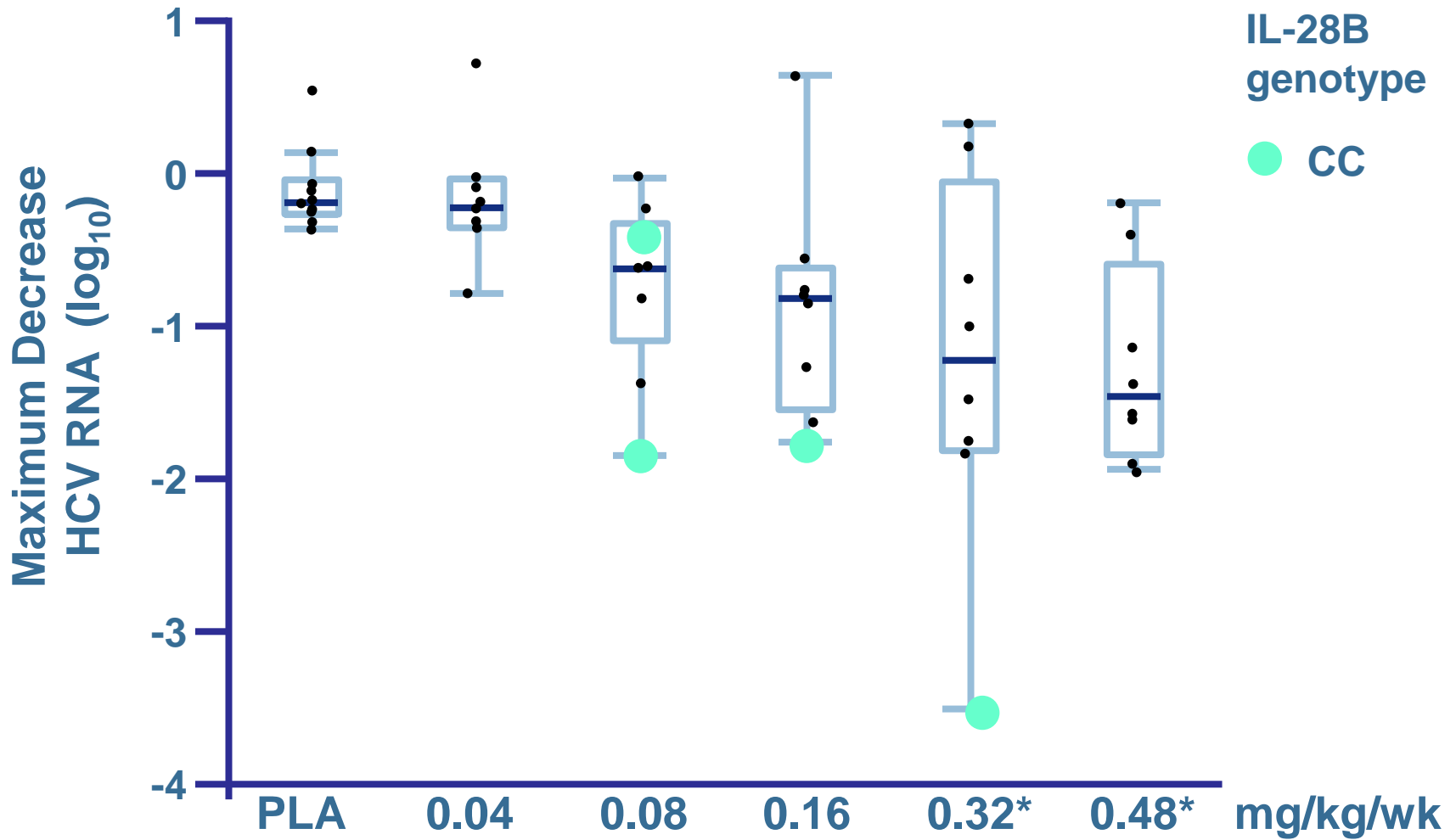


$\geq 1 \log_{10}$  decrease

Dose (mg/kg/wk)	Number of Patients
PLA	0/10
0.04	0/8
0.08	4/9
0.16	5/8
0.32*	6/8
0.48*	7/8

\*  $p < 0.001$  vs placebo

# IMO-2125 HCV RNA Reduction by IL-28B Genotype

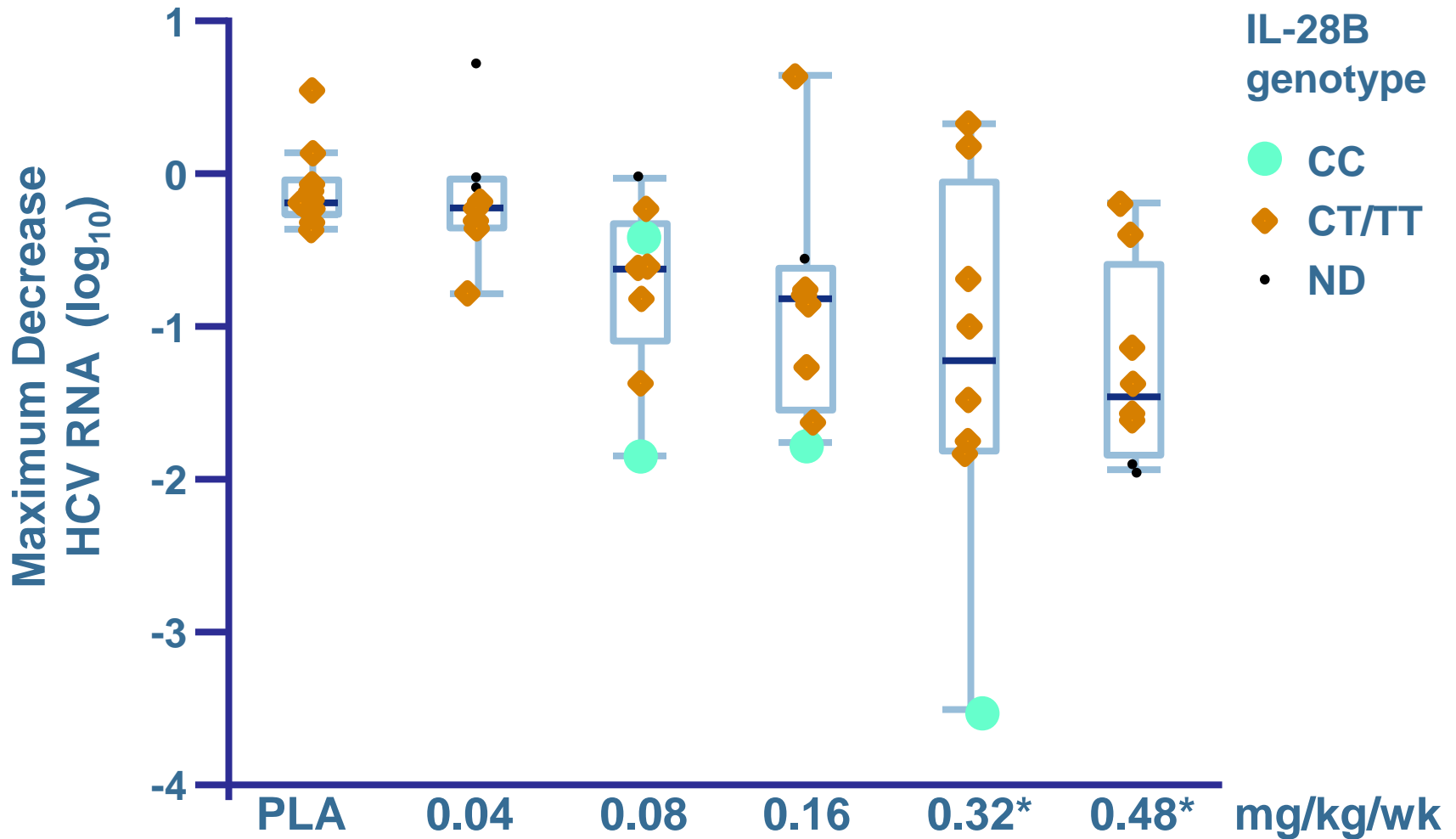


$\geq 1 \log_{10}$  decrease

mg/kg/wk	$\geq 1 \log_{10}$ decrease
PLA	0/10
0.04	0/8
0.08	4/9
0.16	5/8
0.32*	6/8
0.48*	7/8

\*  $p < 0.001$  vs placebo

# IMO-2125 HCV RNA Reduction by IL-28B Genotype



IL-28B genotype

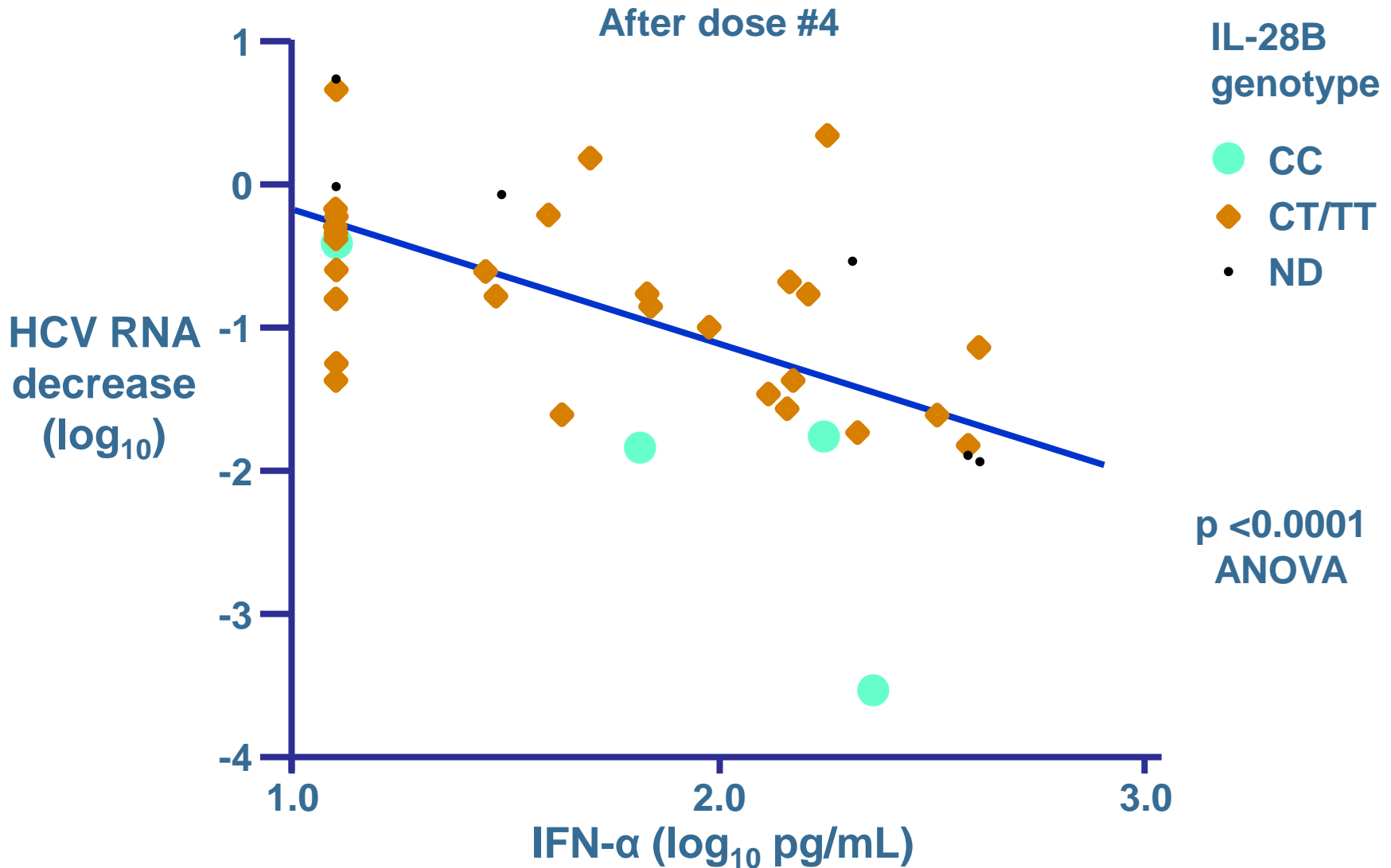
- CC
- ◆ CT/TT
- ND

≥1 log<sub>10</sub> decrease

0/10    0/8    4/9    5/8    6/8    7/8

\* p < 0.001 vs placebo

# Decrease in HCV RNA Correlates with Induction of IFN- $\alpha$



Data not available for 2 (5%) of 41 IMO-2125 patients

# IMO-2125 in HCV Null Responders: Conclusions



1. 75% of subjects receiving 0.16 to 0.48 mg/kg/wk x 4wk had  $\geq 1$  log<sub>10</sub> decrease in viral load
2. There was IMO-2125 dose-dependent immune activation
  - Increase in NK cells and helper and cytotoxic T cells
  - Increase in antiviral cytokines and chemokines
  - Dose-dependent induction of endogenous interferon- $\alpha$
3. Reduction in viral load correlates with IFN- $\alpha$  induction
  - CT/TT genotypes show induction of endogenous interferon- $\alpha$  and viral load reduction
4. Proof of concept achieved in null responders
  - Supports further development and studies in other populations
5. Ongoing studies
  - Twice-weekly dosing
  - Combination with ribavirin in treatment-naïve patients

# Acknowledgements



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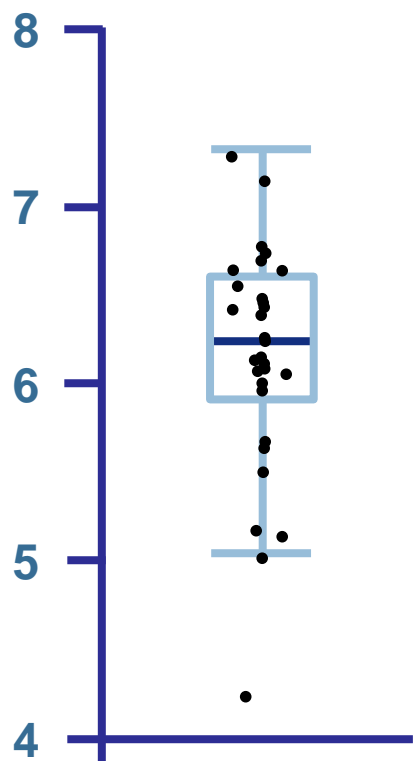
2125-001 AASLD 2010

# BACK-UP SLIDES

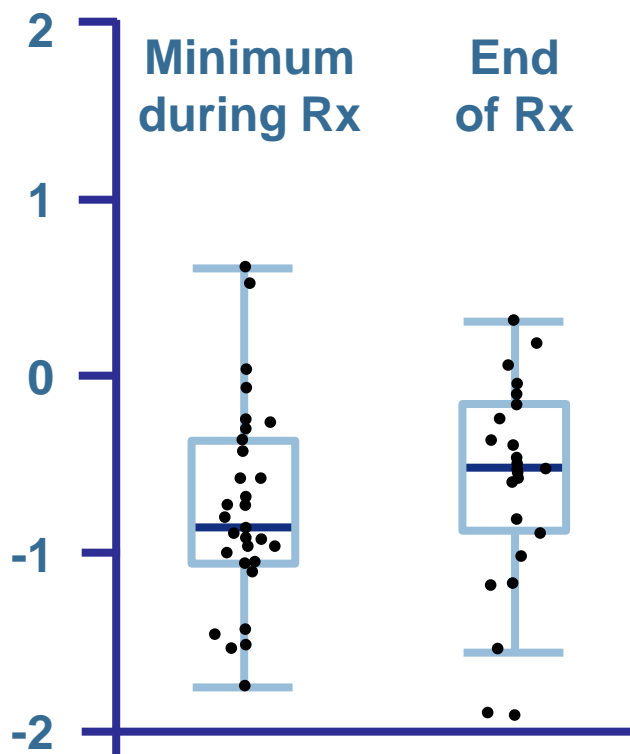
# Patients Were Null Responders to Standard of Care



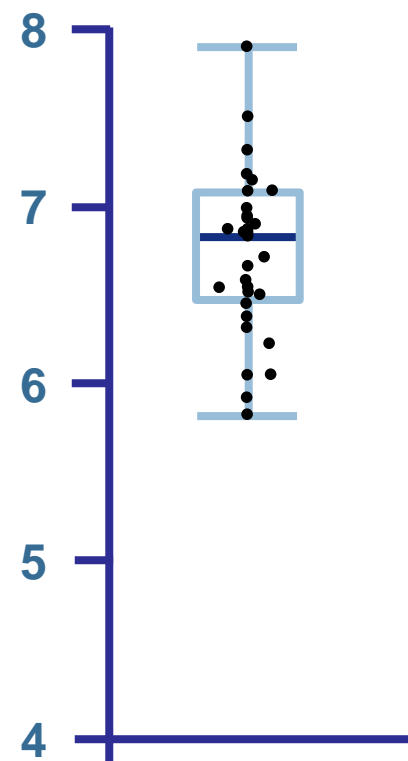
Log HCV RNA  
prior to SOC



Change in log HCV RNA  
compared with pre-SOC



Log HCV RNA  
at enrollment



## Interval

Start to End of SOC Treatment

SOC Treatment to Study Enrollment

## Duration (weeks)\*

33 (12-146)

119 (6-443)

\* median (range)

# IMO-2125 Adverse Events at 0.04 to 0.48 mg/kg x4 weeks



Preferred Term*	IMO-2125 (N=41)	Injection Site Reactions	IMO-2125 (N=41)
One or more AE	40 (98%)	Erythema	38 (93%)
Flu-like symptoms	25 (61%)	Induration	27 (70%)
Headache	13 (32%)	Pruritus	12 (29%)
Chills	9 (22%)	Tenderness	15 (37%)
Myalgias	7 (17%)	Blistering	0
Arthralgias	7 (17%)	Ulceration	0
Fever	7 (17%)	Necrosis	0
Nausea	5 (12%)		

\*Reported for >10% of IMO-2125 subjects in cohorts 1-5

**Of 10 placebo subjects, 6 (60%) had 1 or more AEs  
1 (10%) had injection site induration, tenderness**



- Blood sample collection times:
  - Screening
  - 24 h and 48 h after first dose
  - Prior to and 24 h after fourth dose
  
- Example data available
  - CD69 activation of T-helper and T-cytotoxic cells
  - NK cell frequency
  - B cell activation
  - Memory T-cells



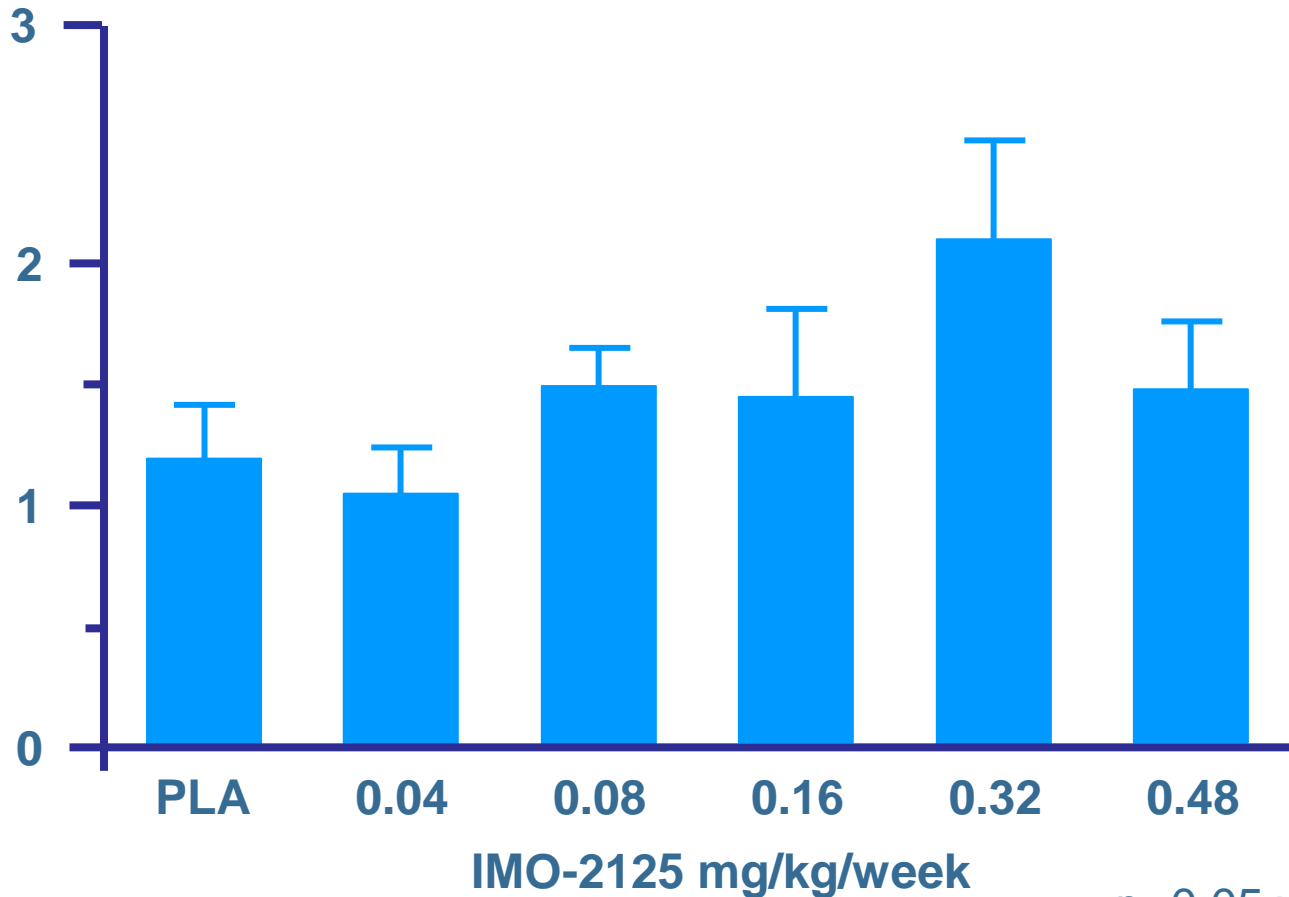
- CD69 activation of T-helper and T-cytotoxic cells
  - Cells were stained with CD8-FITC, CD3-PerCP, CD4-APC, and CD69-PE
  - Gating strategy: Small lymphocyte gate → CD3+CD4+ or CD3+CD8+ gate → CD3+CD69+ gate (gate frequencies noted on dot plots)
- NK cell frequency
  - Cells were stained with CD16-FITC, CD56-FITC, CD3-PerCP, CD19-APC, and CD86-PE
  - Gating strategy: Small lymphocyte gate → CD3-CD16/56+ gate (gate frequencies noted on dot plots)
- B cell activation
  - Cells were stained with CD16-FITC, CD56-FITC, CD3-PerCP, CD19-APC, and CD86-PE
  - Gating strategy: Small lymphocyte gate → CD3-CD19+ gate → CD19+CD86+ gate (gate frequencies noted on dot plots)

# 2125-001: B Cell Activation 24 Hours after Dosing



Mean fold change in % circulating CD19<sup>+</sup> lymphocytes with CD86<sup>+</sup> phenotype at 24 h post-dose #1 compared to pre-dose

Mean fold change



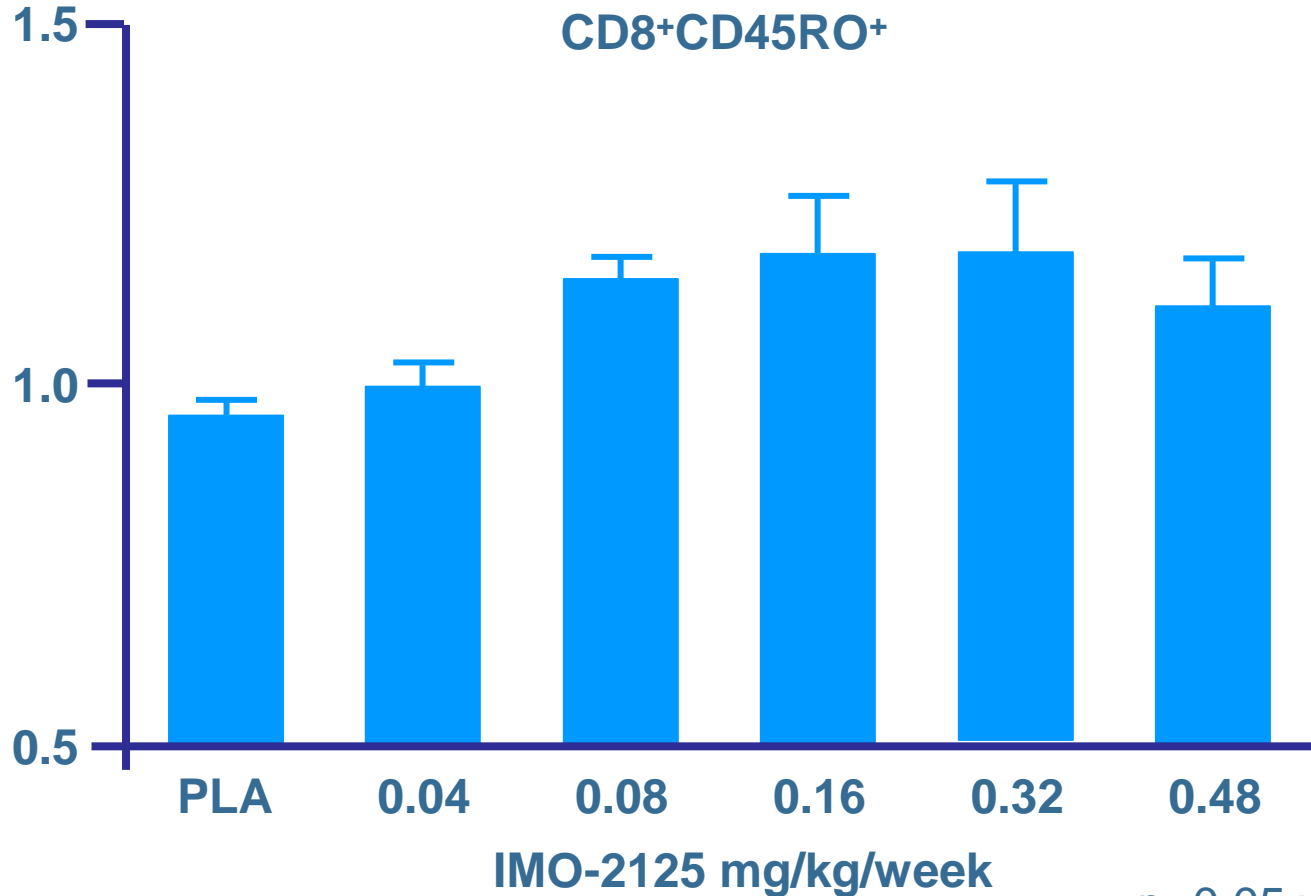
$p > 0.05$  vs placebo  
Data are means and SEM

# 2125-001: Memory CD8<sup>+</sup> T Cells 24 Hours after Dosing



Mean fold change in % circulating cytotoxic T cells with CD45RO<sup>+</sup> phenotype at 24 h post-dose #1 compared to pre-dose

Mean fold change



p>0.05 vs placebo  
Data are means and SEM

# 2125-001: Summary of AASLD 2010 Data



IMO-2125 dosage, mg/kg/w (N=8 or 9; N=10 for placebo)	Median serum concentrations			Mean fold change <sup>c</sup> % CD69+ T cells		Decrease in HCV RNA <sup>d</sup> (log <sub>10</sub> )		
	IFN-α pg/mL <sup>a</sup>	IP-10 pg/mL <sup>b</sup>	2,5-OAS pmol/d <sup>b</sup>	CD4+	CD8+	Mean fold change <sup>c</sup> % NK cells	Pts with > 1 log <sub>10</sub> decrease (range)	Median decrease (25-75% quartiles), all pts
Placebo	38 (N=1)	451	75	1.85 ± 0.38	1.35 ± 0.32	1.09 ± 0.10	0/6	-0.3 (-0.2 to -0.6)
0.04	32 (N=2)	1320	105	1.88 ± 0.62	2.29 ± 0.60	1.01 ± 0.13	0/8	-0.5 (-0.3 to -0.6)
0.08	47 (N=3)	1052	214	3.18 ± 0.68	4.69 ± 1.44	1.00 ± 0.12	4/9 (-1.1 to -2.3)	-1.0 (-0.7 to -1.2)
0.16	38 (N=5)	3915	249	4.68 ± 1.93	5.41 ± 1.32	1.49 ± 0.18	5/8 (-1.2 to -2.0)	-1.3 (-0.6 to -1.6)
0.32	110 (N=7)	4401	246	5.90 ± 1.05	8.46 ± 1.75	1.69 ± 0.10	6/8 (-1.0 to -3.5)	-1.6 (-0.9 to -2.4)
0.48	87 (N=8)	7605	285	6.66 ± 2.61	6.03 ± 1.07	2.06 ± 0.37	7/8 (-1.1 to -1.9)	-1.6 (-1.1 to -1.9)

<sup>a</sup> Dose 1 medians above limit of detection (25 pg/mL); number detectable in parentheses

<sup>b</sup> Dose 4 maximums from 4-24 h post-dose

<sup>c</sup> 24 h post-dose 1 compared to pre-dose, ± SEM

<sup>d</sup> Maximum decrease during treatment period