Once Daily Narlaprevir (SCH 900518) in Combination with Peginterferon alfa-2b/ Ribavirin for Treatment-Naive Patients with Genotype-1 Chronic Hepatitis C: Interim Results from the NEXT-1 Study

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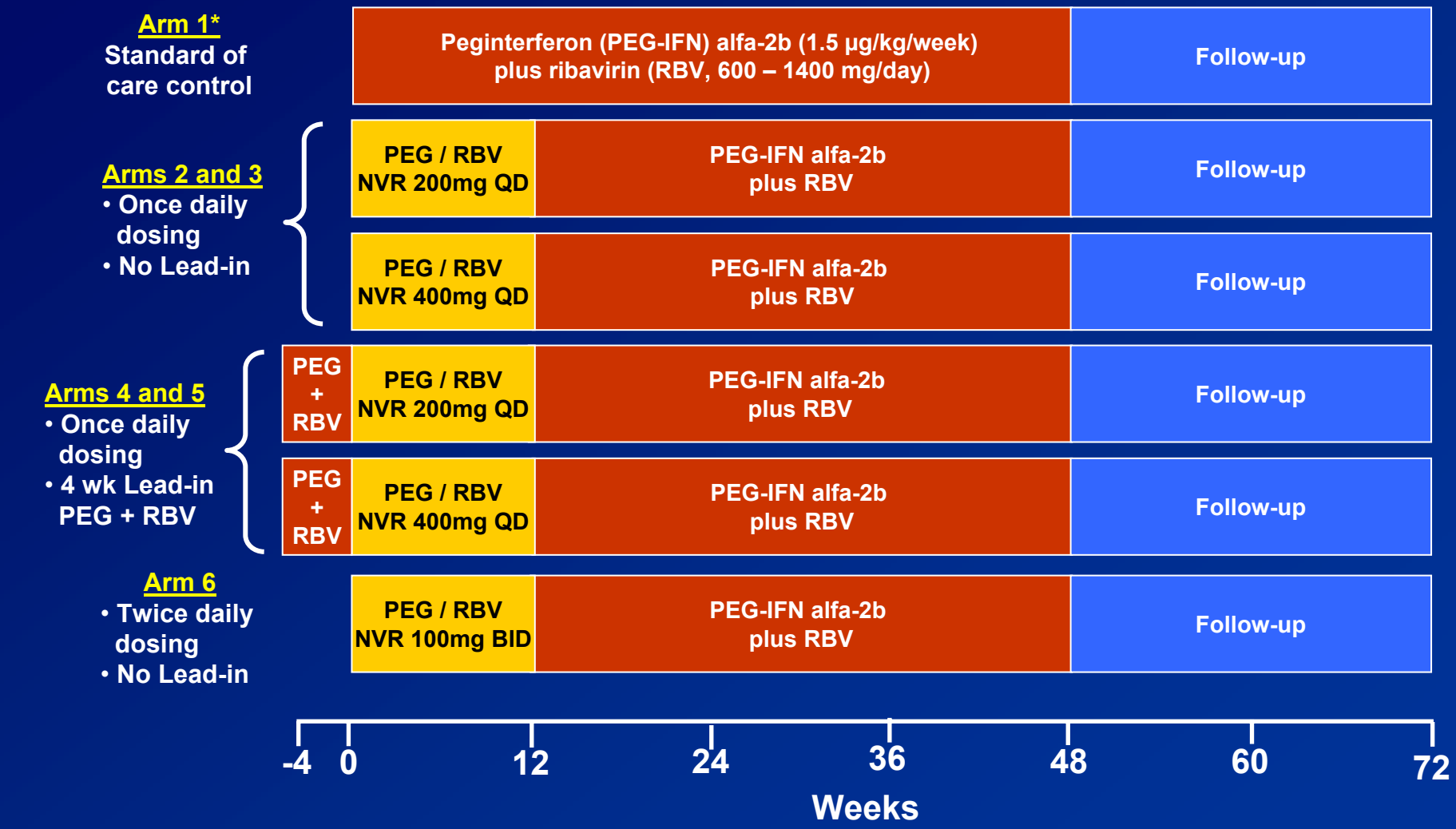
Background: Narlaprevir (SCH 900518)

- Potent, mechanism-based inhibitor of the HCV NS3 serine protease
  - Metabolism primarily mediated by CYP3A4
  - PK enhanced by co-administration of ritonavir, allowing once daily dosing
- Replicon assay using HCV genotype 1b
  - EC_{50} = 20 nM, EC_{90} = 40 nM
  - IFN-alfa enhanced antiviral activity
- Resistance profile of narlaprevir in vitro
  - Similar to other NS3 protease inhibitors
  - Reduced emergence of resistance when combined with IFN-α

Methods

- Treatment Naive HCV-1
- Comparison of
  - Narlaprevir (NVR) + Ritonavir (RTV) + SOC
  - SOC alone
- Endpoint:
  - Undetectable HCV-RNA at Week 4 and Week 12
- Goal of study:
  - To guide the design of the Phase 2b NVR study (NEXT-2)

Study Design



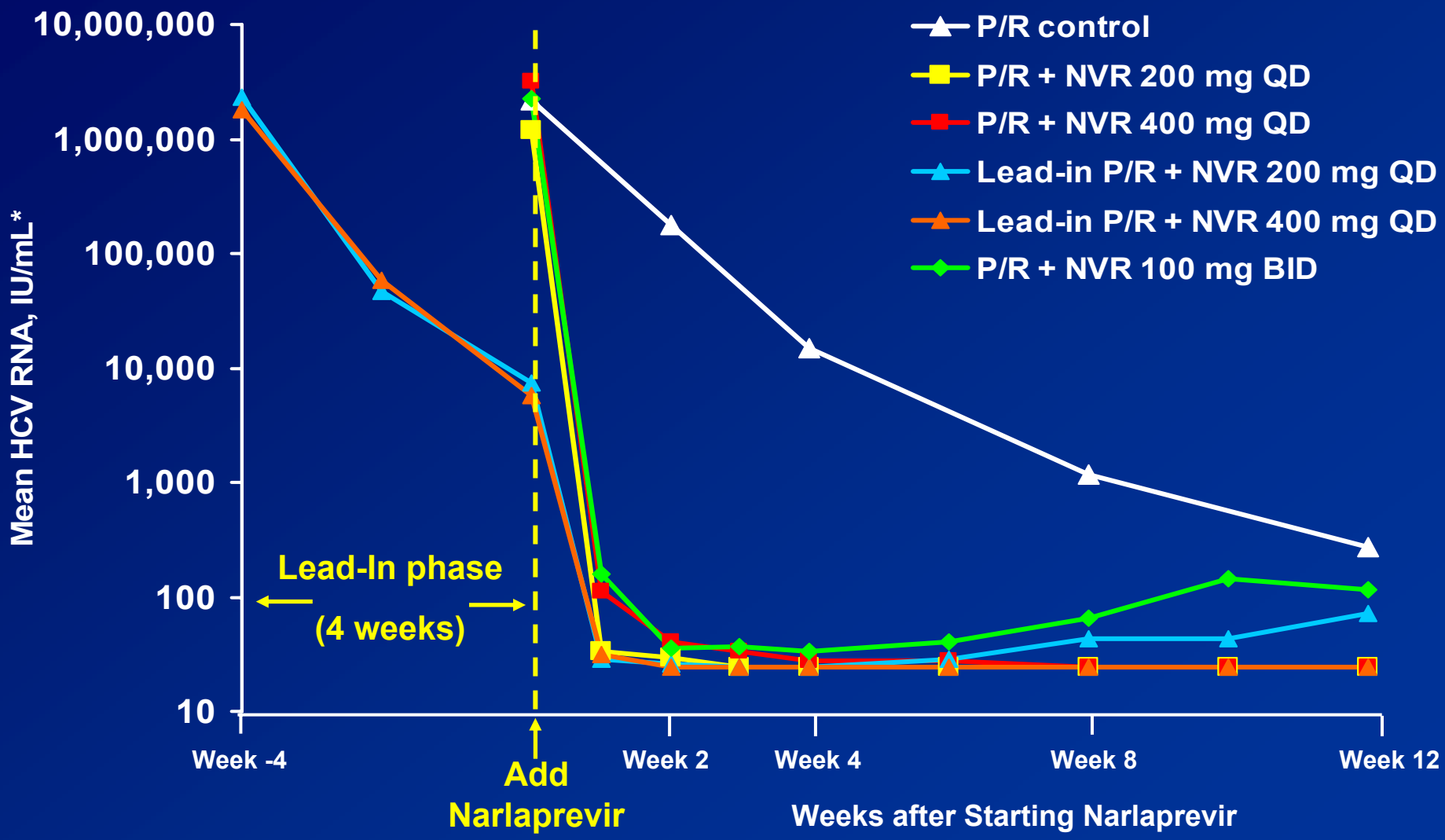
Each dose of narlaprevir (NVR) administered with ritonavir (RTV) 100mg
Erythropoietin and G-CSF use was permitted in the study
*Standard of care arm included futility stopping rule at week 12

Patient Demographics

	PEG-IFN alfa-2b (1.5 µg/kg/week) + ribavirin (600-1400 mg/day)			
	Arm 1 Control n = 18	Arms 2 & 4 NVR 200mg QD n = 37	Arms 3 & 5 NVR 400mg QD n = 39	Arm 6 NVR 100mg BID n = 17
Male, n (%)	10 (56)	21 (57)	24 (62)	9 (53)
Caucasian, n (%)	13 (72)	35 (95)	31 (79)	15 (88)
Age, years (SD)	46 (7)	Arm 2: 43 (9) Arm 4: 45 (10)	Arm 3: 45 (11) Arm 5: 46 (9)	46 (9)
Weight, kg (SD)	81 (20)	Arm 2: 80 (11) Arm 4: 76 (16)	Arm 3: 85 (10) Arm 5: 82 (18)	80 (18)
BMI, kg/m^2 (SD)	28 (6)	Arm 2: 29 (5) Arm 4: 26 (5)	Arm 3: 28 (2) Arm 5: 28 (4)	27 (4)
Genotype 1a, n (%)	11 (61)	22 (59)	23 (59)	12 (71)
Viral Load >600,000 IU/mL, n (%)	15 (83)	27 (73)	31 (79)	14 (82)

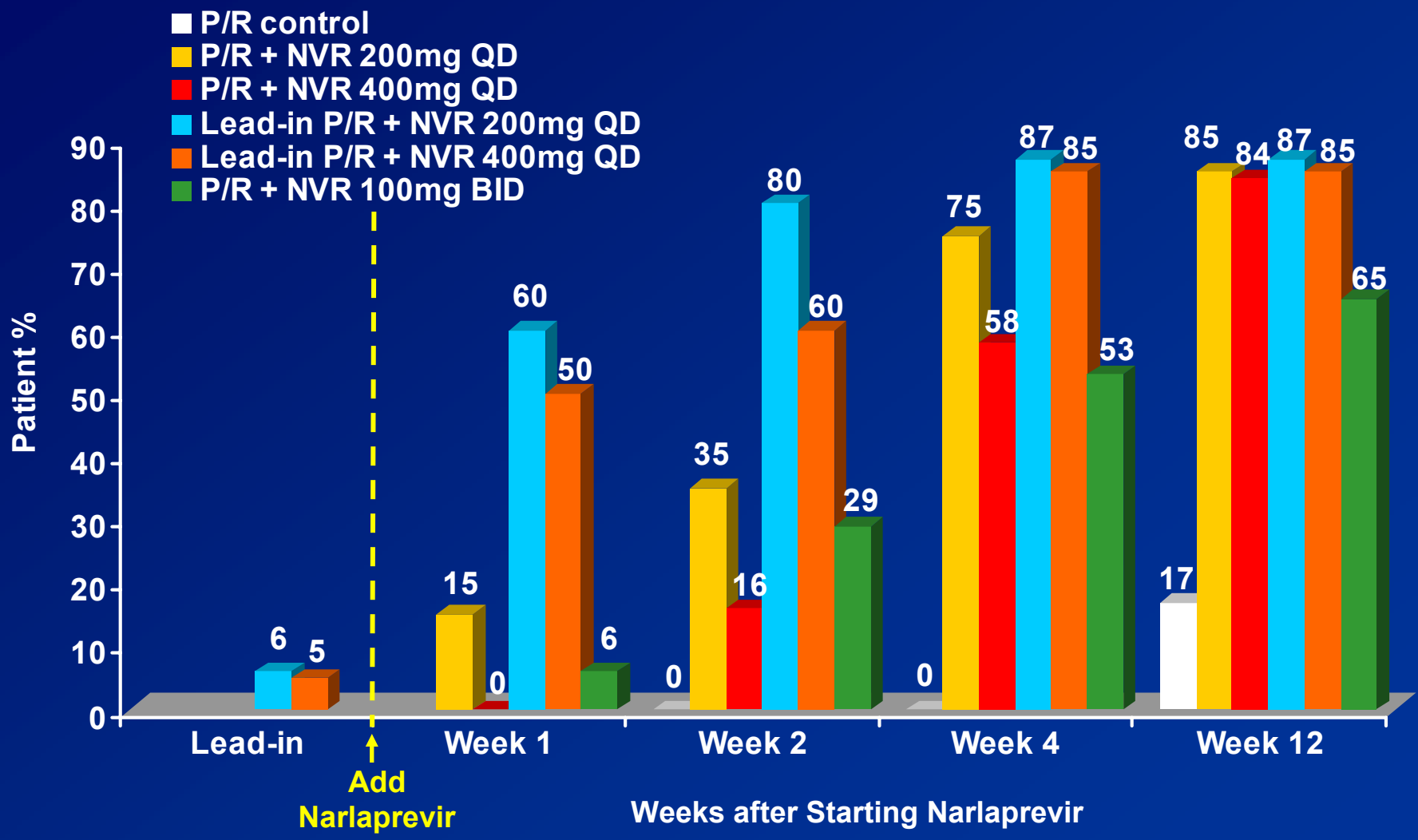
Each dose of narlaprevir (NVR) administered with ritonavir 100mg
Lead-in and no lead-in arms combined for each NVR dose level

Decrease in Mean Plasma HCV-RNA



*Roche Taqman 2.0 LLQ 25 IU/mL / LLD 10 IU/mL
Each dose of narlaprevir (NVR) administered with ritonavir 100mg

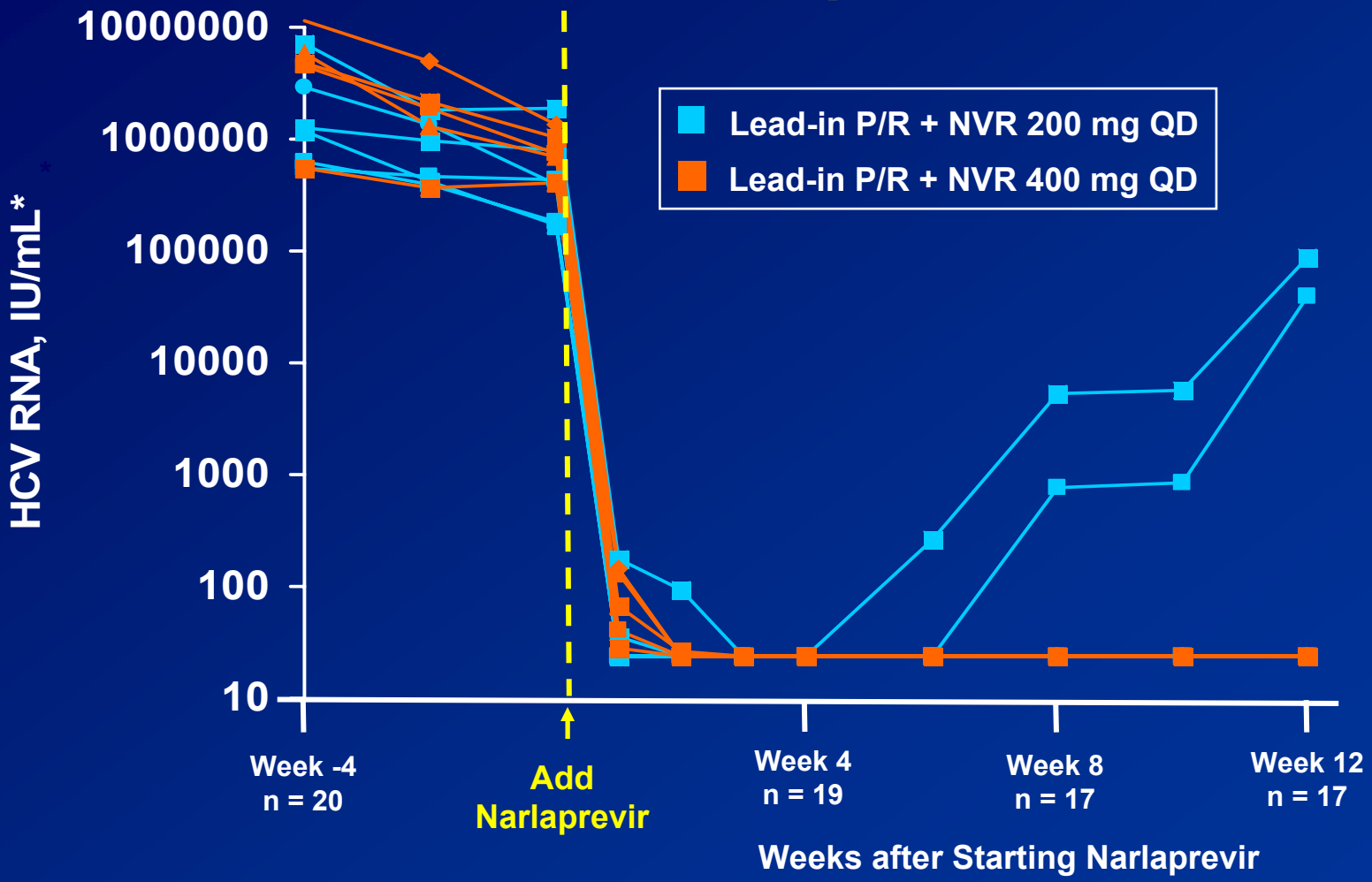
Undetectable* HCV-RNA by Treatment Week



Each dose of narlaprevir (NVR) administered with ritonavir 100mg

*HCV RNA < 10 IU/mL (includes all patients that received at least one dose of NVR, excluding control)

Plasma HCV-RNA Levels for 11 Individual Null Responders[Ŧ]

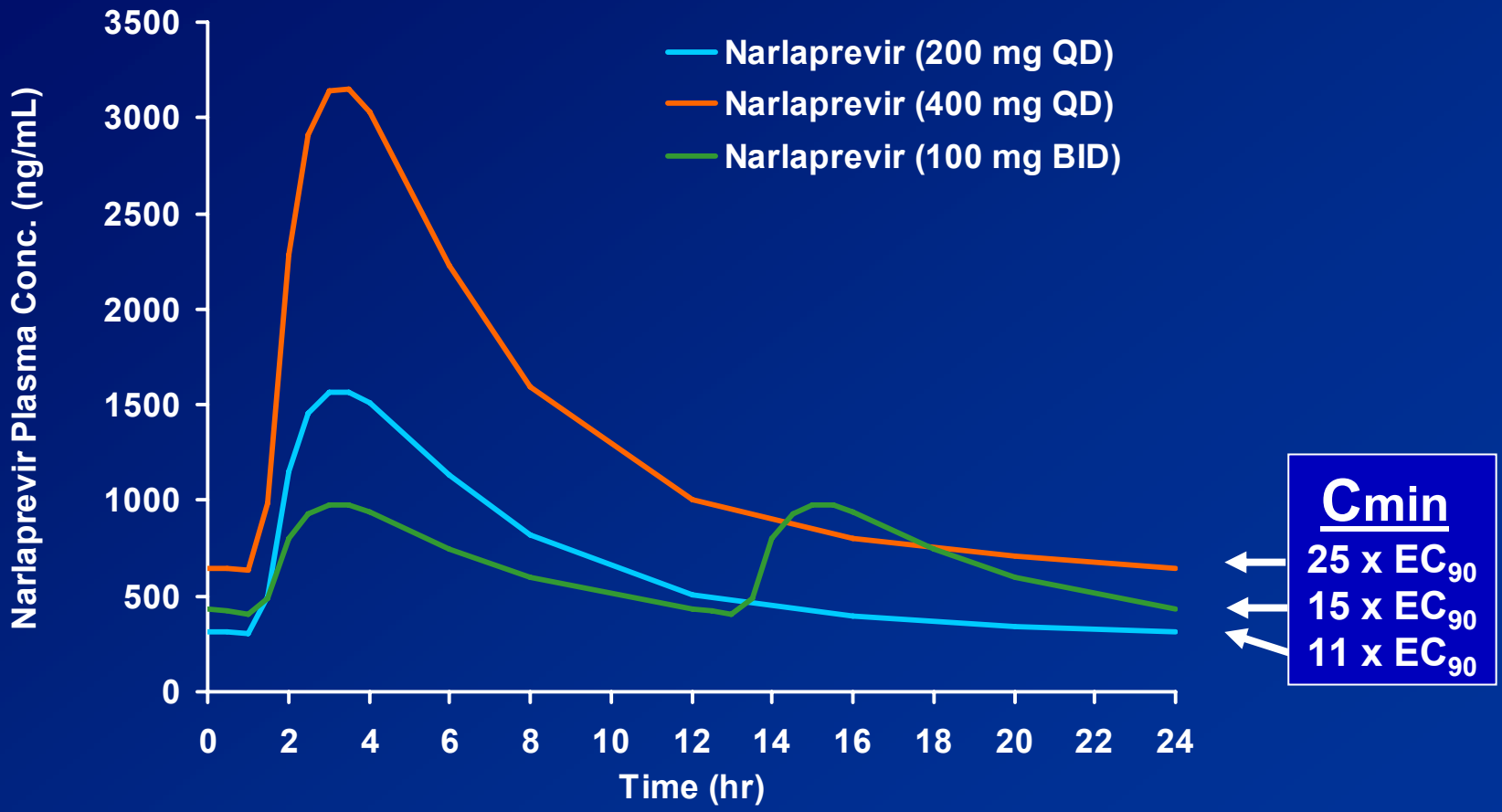


*Roche Taqman 2.0 LLQ 25 IU/mL / LLD 10 IU/mL

[Ŧ]Defined as < 1 log decline in HCV-RNA after 4 weeks of PEG-IFN/RBV

Each dose of narlaprevir (NVR) administered with ritonavir 100 mg

Mean Narlaprevir Concentration/Time Profiles Based on Daily or Twice Daily Dosing from NEXT-1*



Daily and twice daily dosing achieved by metabolic inhibition with ritonavir

*Generated using Sparse Sampling and Population PK Model (No Lead-in Arms)

Patient Discontinuations

	PEG-IFN alfa-2b (1.5 µg/kg/week) + ribavirin (600-1400 mg/day)			
	Arm 1 Control n = 18	Arms 2 & 4 NVR 200mg QD n = 37	Arms 3 & 5 NVR 400mg QD n = 39	Arm 6 NVR 100mg BID n = 17
Total discontinued, n (%)	7 (39)	6 (16)	5 (13)	2 (12)
Adverse events*	1 (6)	3 (8)	5 (13)	0
Treatment failure	0	0	0	1 (6)
Lost to follow-up	4 (22)	0	0	0
Investigator decision to D/C	0	1 (3)	0	0
Patient declined to continue	2 (11)	1 (3)	0	0
Non-compliance	0	1 (3)	0	1 (6)

*nausea, GERD, depression, homicidal ideation, suicidal ideation, lethargy, hypoaesthesia, tinnitus, retinal exudates, ↑AST/ALT/CPK, anorexia

Each dose of narlaprevir (NVR) administered with ritonavir 100mg

Lead-in and no lead-in arms combined for each NVR dose level

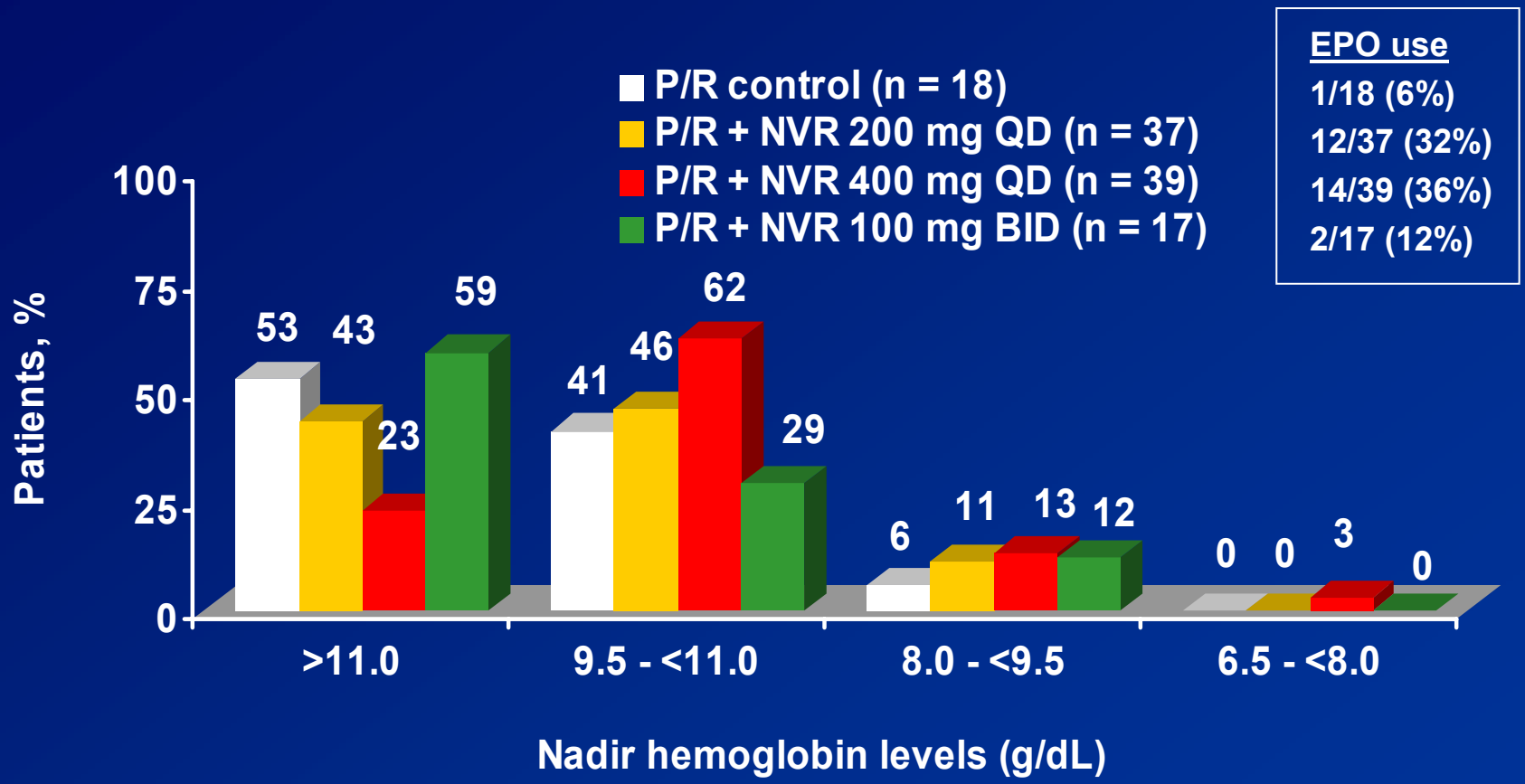
Adverse Events Reported During 12 Weeks of Narlaprevir Treatment (≥15% total combined)

PEG-IFN alfa-2b (1.5 µg/kg/week) + ribavirin (600-1400 mg/day)

	Arm 1 Control N=18	Arms 2 & 4 NVR 200mg QD N=37	Arms 3 & 5 NVR 400mg QD N=39	Arm 6 NVR 100mg BID N=17
Fatigue	56 %	57 %	56 %	47 %
Nausea	50 %	51 %	49 %	53 %
Flu-like illness	44 %	32 %	54 %	53 %
Headache	39 %	35 %	38 %	35 %
Insomnia	28 %	35 %	33 %	29 %
Anemia	6 %	30 %	44 %	18 %
Arthralgia	28 %	19 %	33 %	18 %
Diarrhea	17 %	16 %	28 %	35 %
Pyrexia	17 %	22 %	26 %	29 %
Irritability	28 %	22 %	18 %	18 %
Alopecia	17 %	22 %	10 %	18 %
Dizziness	6 %	24 %	26 %	18 %
Vomiting	28 %	19 %	13 %	35 %
Chills	17 %	11 %	26 %	29 %
Anxiety	17 %	19 %	15 %	12 %
Decreased Appetite	17 %	11 %	23 %	18 %
Depression	22 %	14 %	18 %	6 %

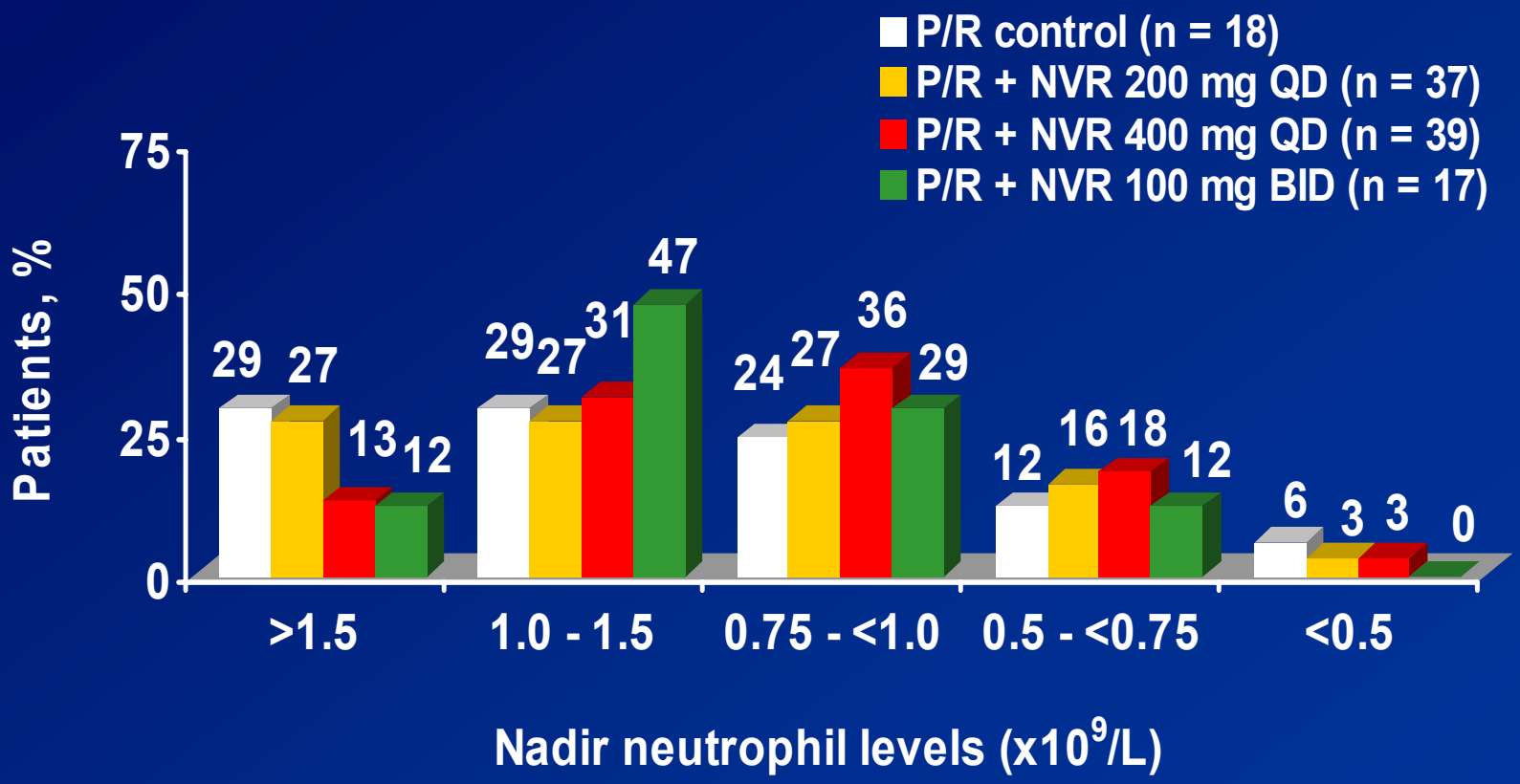
Each dose of narlaprevir (NVR) administered with ritonavir 100mg
Lead-in and no lead-in arms combined for each NVR dose level

Nadir Hemoglobin During 12 Weeks of Narlaprevir Treatment



Each dose of narlaprevir (NVR) administered with ritonavir 100mg
Lead-in and no lead-in treatment arms pooled for the NVR 200 mg QD & 400 mg QD dosages

Nadir Neutrophils During 12 Weeks of Narlaprevir Treatment



Each dose of narlaprevir (NVR) administered with ritonavir 100mg
Lead-in and no lead-in treatment arms pooled for the NVR 200 mg QD & 400 mg QD dosages

Summary

- NVR QD with RTV has potent anti-HCV activity
  - Trough NVR concentrations achieved 11-25 times the EC_{90}
  - 200 mg / 400 mg NVR QD rapidly achieved undetectable HCV-RNA levels
    - Week 4 - 58-87% of patients
    - Week 12 - 84-87% of patients
- No unique or treatment limiting adverse events
  - Use of low-dose RTV as a metabolic inhibitor was well tolerated
  - AE profile consistent with PEG/RBV with the following observations
    - Increased frequency of anemia; no discontinuations due to anemia
    - Similar rates of nadir neutrophil levels below 0.75 x 10^9/L
- Studies evaluating 200 mg and 400 mg NVR QD with RTV (with and without a lead-in) are currently planned

Acknowledgements

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- We also wish to thank the following people for their participation and contribution:
  - Participating Investigators:

    Vierling J, Poordad F, Lawitz E, Ghalib R, Lee W, Ravendhran N, Galati J, Bacon B, Flamm S, Balart L, Freilich B, Schiff E, Jacobson I, Kwo P, Gordon S, Sulkowski M
  - SPRI Team:

    Valanzola R, Linaberry M, Treitel M, Li J, Keung A, Chaudhri E, Boparai N, Brass C, Hughes E, Albrecht J