

Controversies and Updates in Liver Disease

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Outline: DDW and EASL data

- Hepatitis C Clinical Practice Pearls
 - Who is getting treated, who is not?
 - Treatment extension: Success
 - High dose induction: Chariot
 - Maintenance: Epic
 - Fibrosis Regression: HALT C
 - Anemia is a good thing: IDEAL

- Hepatitis C New Molecules
 - Albinterferon
 - Telaprevir
 - Boceprevir
 - Cyclophilin inhibitors
 - Taribavirin

- Hepatitis B Clinical Practice
 - Updates on Tenofovir, Entecavir, Telbivudine: efficacy, resistance, novel side effects

- Hepatic Encephalopathy
 - Something other than lactulose

Majority of Chronic Hepatitis C Patients in US Do Not Receive Anti-Viral Therapy

■ Background

- Studies from the VA found only 12% of veterans with CHC received anti-viral therapy, and a small insurance company database found 30% of patients receive anti-viral therapy
- No information exists on a broader patient mix which would be more reflective of current practice

■ Objective

- To determine the national trend of ambulatory visits with a diagnosis of hepatitis C and the prescription of anti-viral therapy

■ Methods

- Retrospective analysis of national cross-sectional ambulatory visits database, the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS)
- All ambulatory visits from 2000-2006
- All ICD-9 codes of hepatitis C were included in the search
- Anti-viral therapy was determined by any alfa- or consensus interferon preparations in the prescription fields

Majority of Chronic Hepatitis C Patients in US Do Not Receive Anti-Viral Therapy

■ Results

- During the study period (2000-2006), there were a total of 7.7 billion ambulatory visits in the US
- Of these, 16.5 million visits (0.21%) carried a diagnosis of hepatitis C
- Characteristics of the hepatitis C patients are as follows:
65% male; 71% white and 22% black; 2%, 29%, 58%, 11% were under 25, 25-44, 45-64 and over 64 year old, respectively
- 47% had private insurance, 24% had Medicaid and 12% had Medicare
- Only **9.1% of these patients were on prescription** anti-viral medications.
- No significant difference between those who received anti-viral therapy and those who were not prescribed anti-viral therapy in term of age, gender, race and insurance status

■ Authors' Conclusions

- Fewer than 10% of the ambulatory visits for hepatitis C have an associated prescription for anti-viral therapy
- Insurance status and age do not appear to play a role
- Reason for the low treatment rate is not clear but deserves further investigation

Extended Treatment Duration in Chronic Hepatitis C Genotype 1 Infected Slow Responders

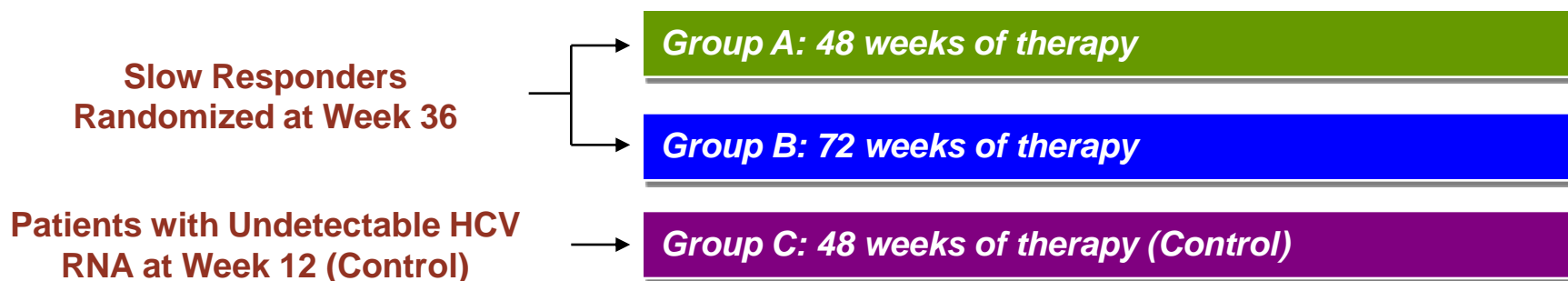
Final Results of the SUCCESS Study

■ Background & Objective

- Previous studies show that extending duration of treatment with Peg-IFN/RBV to 72 weeks in Gt 1 patients with slow response to therapy is associated with increase in SVR
Slow responder: Detectable HCV RNA with ≥ 2 log viral reduction at Week 12 but undetectable at Week 24
- Objective: To evaluate the effect of extending treatment duration among Gt 1 slow responders

■ Methods

- Prospective, randomized, multinational, multicenter clinical trial



Extended Treatment Duration in Chronic Hepatitis C Genotype 1 Infected Slow Responders

Final Results of the SUCCESS Study

■ Results

- 1427 patients were treated. At week 24, 11% patients were identified as slow responders
- Frequency of AEs, including anemia and depression, were similar in both treatment groups. Therapy discontinuation was higher in Group B (72 weeks)

	<i>Group A: 48 Weeks</i>	<i>Group B: 72 Weeks</i>	<i>Group C: Control</i>
<i>SVR Rates, ITT</i>	43%	48%	79%
<i>SVR Rates in 80/80/80 Compliant</i>	44%	57%	Not done

■ Authors' Conclusions

- There was no statistically significant difference between 48 and 72 weeks
- However, in slow responders, extending therapy is associated with better SVR with similar incidence of AEs

High-Dose PegIFN Induction Therapy and Standard RBV Enhances Early but Not Sustained Virological Responses in HCV Genotype 1 Patients

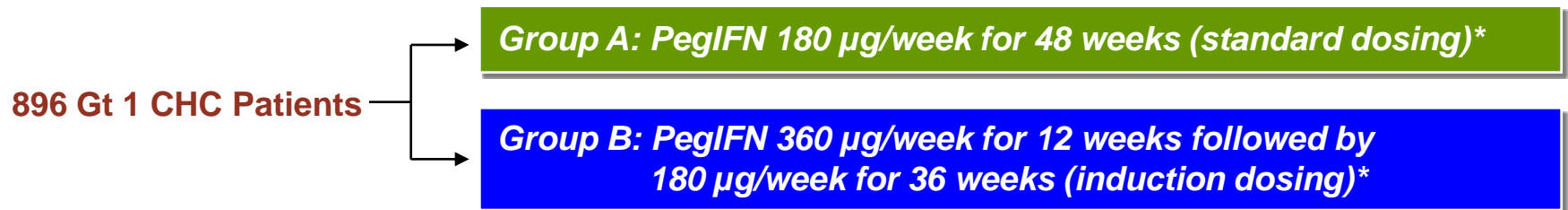
Final CHARIOT Study Results

■ Background & Objective

- Gt 1 infected CHC patients are difficult to treat
- Hypothesis: Double dose PegIFN for the first 12 weeks would increase EVR and improve SVR in treatment naïve patients with Gt 1 CHC

■ Methods

- International, multicenter, open-label study



■ Results

- Baseline patient characteristics similar between two groups
- Virological responses at weeks 4 and 12 were significantly higher among patients receiving high-dose induction therapy
- SVR rate was not significantly higher in high-dose induction therapy group

High-Dose PegIFN Induction Therapy and Standard RBV Enhances Early but Not Sustained Virological Responses in HCV Genotype 1 Patients

Final CHARIOT Study Results

	<i>Induction Dosing n=433, %</i>	<i>Standard Dosing n=438, %</i>
<i>Efficacy (as HCV RNA <15 IU/mL)</i>		
Week 4 RVR	36.0 *	26.3
Week 12 complete EVR	74.4 **	61.6
Week 24	75.1 #	67.8
Week 48 EOT	70.0	66.0
Week 72 SVR	53.0	50.0
<i>Safety</i>		
Overall Treatment discontinuations	27	31
Treatment discontinuations due to AEs or lab abnormalities	9	7
SAEs	11	10
Dose modifications (Peg-IFN α-2a (40KD))	27	18
Neutropenia (<0.5 x 10⁹/L)	8	4
Thrombocytopenia (<50 x 10⁹/L)	4	3
Anemia (<10 g/dL)	17	15

Cochran-Mantel-Haenszel test: * $P < 0.001$; ** $P < 0.0001$; # $P < 0.05$

Statistics not provided for safety

Roberts S, et al. Presented at EASL 2009. Abstract #124.

PegIntron Maintenance Therapy in Cirrhotic (Metavir F4) HCV Patients, Who Failed to Respond to Interferon/RBV Therapy. Jordi Bruix, Thierry Poynard, Massimo Colombo, Eugene R. Schiff, Jurg Reichen, Kelly W. Burak, Jenny Heathcote, Thomas Berg, Jorge L. Poo, Carlos E. Brandao-Mello, Rainer Günther, Claus Niederau, Ruben Terg, Navdeep Boparai, Joann Harvey, Louis H. Griffel, Margaret Burroughs, Clifford A. Brass, Janice Albrecht

Final Results of the EPIC-3 Cirrhosis Maintenance Trial

■ Background & Objective

- To assess efficacy and safety of long-term low-dose maintenance PegIntron in subjects who previously failed treatment with any alfa-interferon/RBV

■ Methods

- 631 subjects randomized to PegIntron 0.5 µg/kg/wk or observational control
- Primary efficacy measure: Time to development of first clinical event:
 - Liver decompensation (Variceal bleeding, Child-Pugh Class C, ≥Grade 2 hepatic encephalopathy, ascites requiring therapeutic paracentesis and/or additional therapy)
 - Development of hepatocellular carcinoma (HCC)
 - Death
 - Liver transplantation
- Secondary efficacy analyses: Time to disease progression including additional events of Child-Pugh Class B, emergence of varices, and enlargement of pre-existing varices requiring additional therapy

PegIntron Maintenance Therapy in Cirrhotic (Metavir F4) HCV Patients, Who Failed to Respond to Interferon/RBV Therapy

Final Results of the EPIC-3 Cirrhosis Maintenance Trial

	<i>Treatment Arm</i>	<i>Control Arm</i>	<i>P-Value</i>
<i>Primary analysis: Clinical Events</i>	27 subjects	36 subjects	0.14
<i>Secondary analysis: Clinical Events</i>	63 subjects	87 subjects	0.01

■ Results

- Mean treatment duration of IFN: 32 months
- Primary endpoint failed: time to clinical event
- No effect on occurrence of HCC
- The main events causing the difference on secondary analysis were emergence or enlargement of varices (43 control, 16 treatment)
- In subjects with **baseline esophageal varices (n=82), there were 14 events in the control arm and only 4 in the treatment arm (P=0.01)**
- Safety profile for PegIntron was similar to that in previous studies; however, there were more infectious SAEs in the treatment group (25 vs 3)

PegIntron Maintenance Therapy in Cirrhotic (Metavir F4) HCV Patients, Who Failed to Respond to Interferon/RBV Therapy

Final Results of the EPIC-3 Cirrhosis Maintenance Trial

■ Conclusions

- In the primary analysis, PegIntron **maintenance was not superior** to observational control in preventing the occurrence of clinical events
- However, there was a statistically significant reduction in clinical events of hepatic decompensation on protocol-defined secondary analysis as well as in subjects with pre-existing esophageal varices
- These data suggest that PegIntron **therapy may delay the progression of portal hypertension and associated bleeding events**

Five Year Prospective Evaluation of Liver Histology in Patients with Chronic Hepatitis C Virus (HCV) Following Treatment with IFN/PegIFN and RBV

■ Background & Objective

- Long-term impact of IFN treatment on fibrosis progression in HCV patients without SVR and fibrosis regression with SVR remains undefined
- This prospective study was initiated in 1998 to evaluate the long-term impact of IFN treatment on liver histology

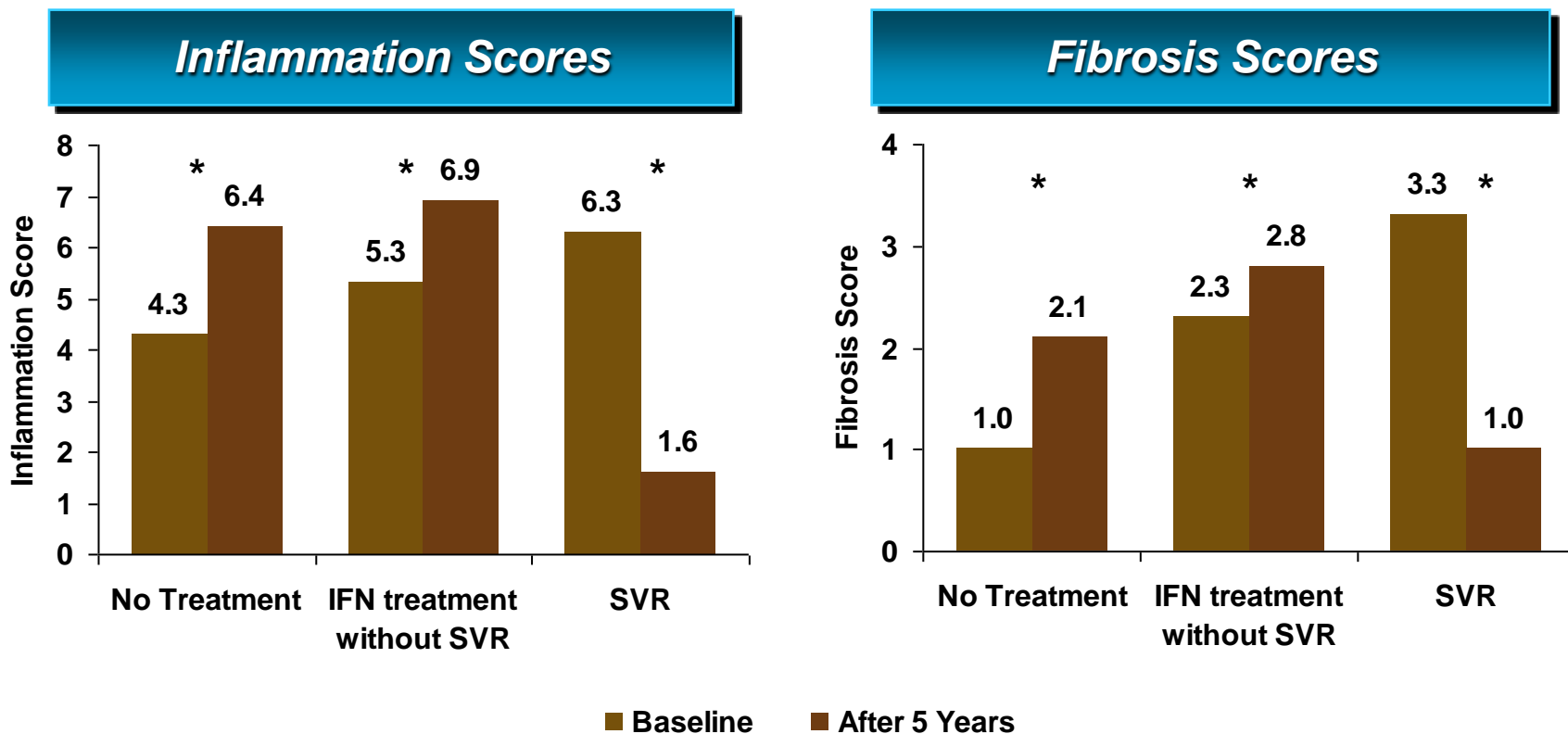
■ Methods

- 755 patients underwent baseline liver biopsy and received a single course of IFN treatment or no treatment
- 332 patients were followed without additional treatment for 5 years and then underwent repeat liver biopsy
- Histology was assessed by Knodell (inflammation) and Ishak (fibrosis)

Five Year Prospective Evaluation of Liver Histology in Patients with Chronic Hepatitis C Virus (HCV) Following Treatment with IFN/PegIFN and RBV

■ Results

- After 5 years inflammation/fibrosis scores increased significantly in patients receiving no treatment and IFN treatment without SVR



* Scores $P < 0.001$ vs baseline.

Shiffman M, et al. Presented at EASL 2009. Abstract #128.

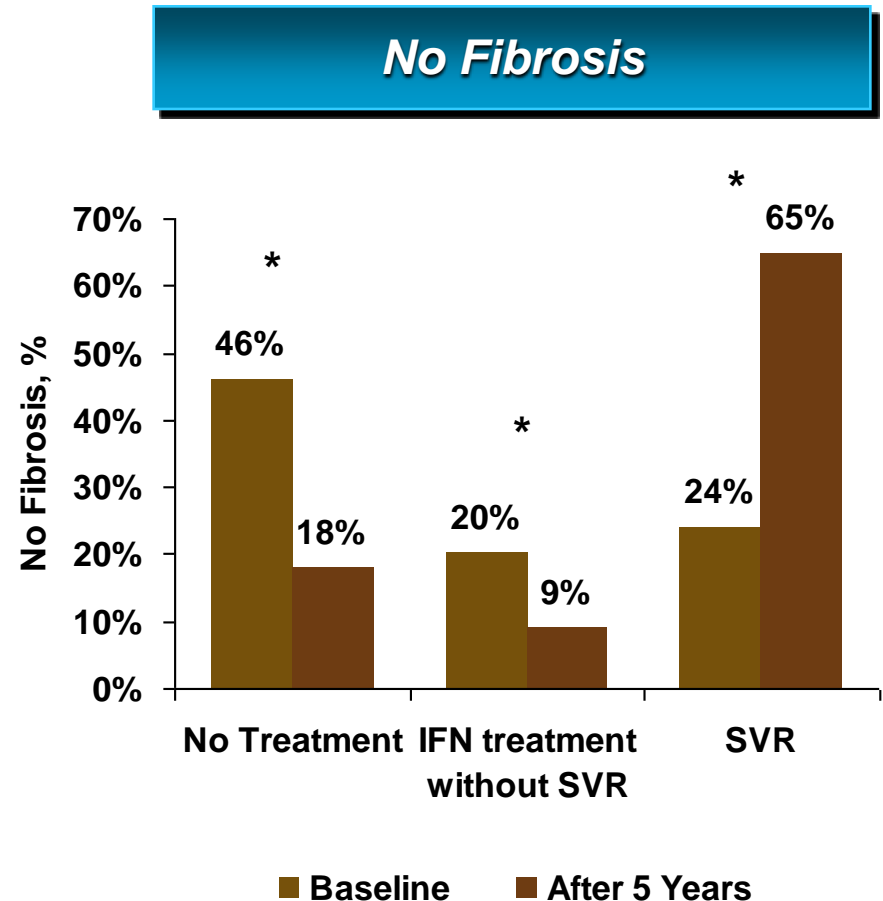
Five Year Prospective Evaluation of Liver Histology in Patients with Chronic Hepatitis C Virus (HCV) Following Treatment with IFN/PegIFN and RBV (IFNTx)

■ Results

- After 5 years, more patients with no fibrosis and no treatment progressed (28% vs 11%)
- In contrast, histology improved significantly with SVR

■ Authors' Conclusions

- IFN treatment reduces the rate of histologic progression over 5 years compared to no treatment even in HCV patients with no Fibrosis
- Patients with HCV who achieve SVR resolve fibrosis and after 5 years liver histology returns to normal in most patients



* Scores $P < 0.01$ vs baseline.

Shiffman M, et al. Presented at EASL 2009. Abstract #128.

Hemoglobin Decline Is Associated with SVR Among HCV Gt 1 Infected Persons Treated with PegIFN/RBV

Analysis from the IDEAL Study

■ Background & Objective

- PegIFN/RBV causes significant hemoglobin (Hgb) decline leading to side effects and RBV reduction in 30% of patients
- The effect of Hgb loss on SVR is unknown

■ Methods

- Anemia was defined as Hgb <10 g/dL
- Erythropoietin (EPO) permitted in anemic patients after protocol-defined RBV reduction
- Viral response rates were assessed according to maximum Hgb decline

3070 Patients
with Gt 1 CHC
Randomized
1:1:1

Arm 1: PEG IFN alfa-2b 1.5 μ g/kg/wk + RBV 800-1400mg/day (n=1019)

Arm 2: PEG IFN alfa-2b 1.0 μ g/kg/wk + RBV 800-1400mg/day (n=1016)

Arm 3: PEG IFN alfa-2a 180 μ g/wk + RBV 1000-1200mg/day (n=1035)

48 weeks

Hemoglobin Decline Is Associated with SVR Among HCV Gt 1 Infected Persons Treated with PegIFN/RBV

Analysis from the IDEAL Study

■ Results

- Anemia occurred in 28% patients. 52% of these patients used EPO
- Among all patients, mean maximum Hgb decline was 4 ± 1.4 g/dL
- SVR was associated with magnitude of Hbg decline
 - >3 g/dL: 43.7%; ≤ 3 g/dL, 29.9%, $P < 0.0001$
- EPO was associated with higher SVR rate in patients with early anemia (≤ 8 weeks)
 - Anemia, no EPO: 25.9%; Anemia, EPO: 45.0%, $P = 0.0002$
- EPO was not associated with higher SVR rate in patients with late anemia (> 8 weeks)
 - Anemia, no EPO: 59.3%; Anemia, EPO: 55.0%, $P = 0.33$

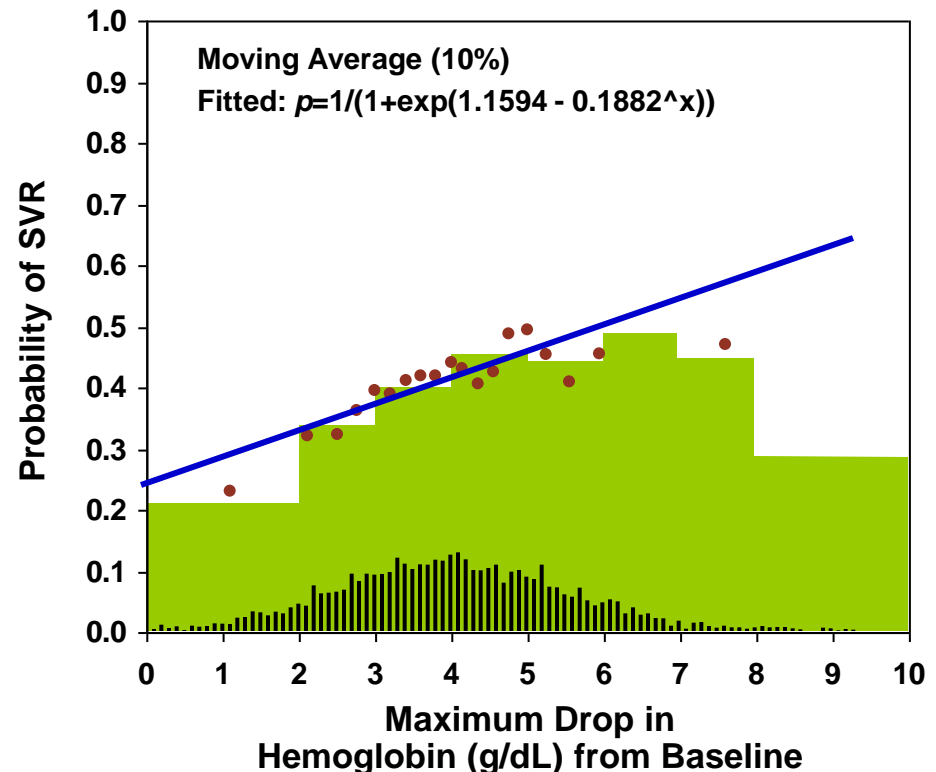
Hemoglobin Decline is Associated with SVR Among HCV Gt 1 Infected Persons Treated with PegIFN/RBV

Analysis from the IDEAL Study

■ Authors' Conclusions

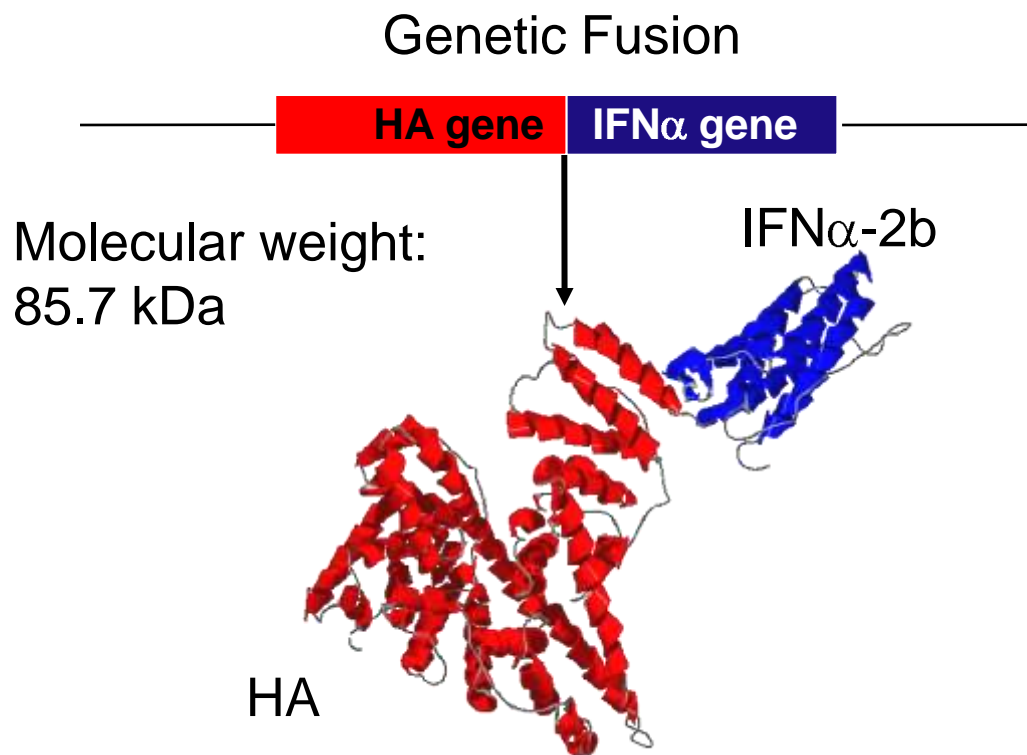
- Among HCV Gt 1 infected patients treated with PegIFN/RBV, magnitude of Hgb decline is associated with likelihood of SVR
- Effect of EPO varied by time to anemia; no benefit was observed for patients who became anemic after treatment week 8
- These data suggest that Hgb decline may be a pharmacodynamic marker of treatment effectiveness and the primary effect of EPO was to prevent treatment discontinuation in patients with early anemia

*Sustained Virologic Response:
All Treated Patients (N=3,023)*



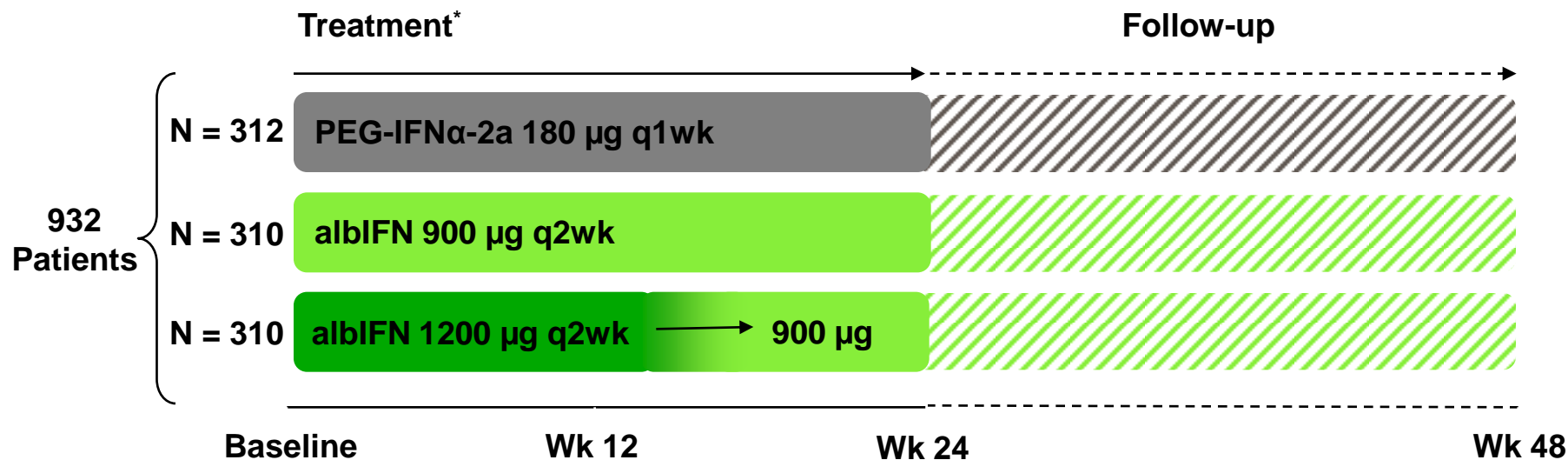
Albinterferon alfa-2b (albIFN)

- **Novel recombinant polypeptide with a long serum (160 h) half-life**
- **Sustained antiviral pressure over dosing interval of 2 weeks**
- **Rational for Phase 3**
 - 900 µg dose: Efficacy and safety comparable to Peg-IFN
 - 1200 µg dose: Improve antiviral activity



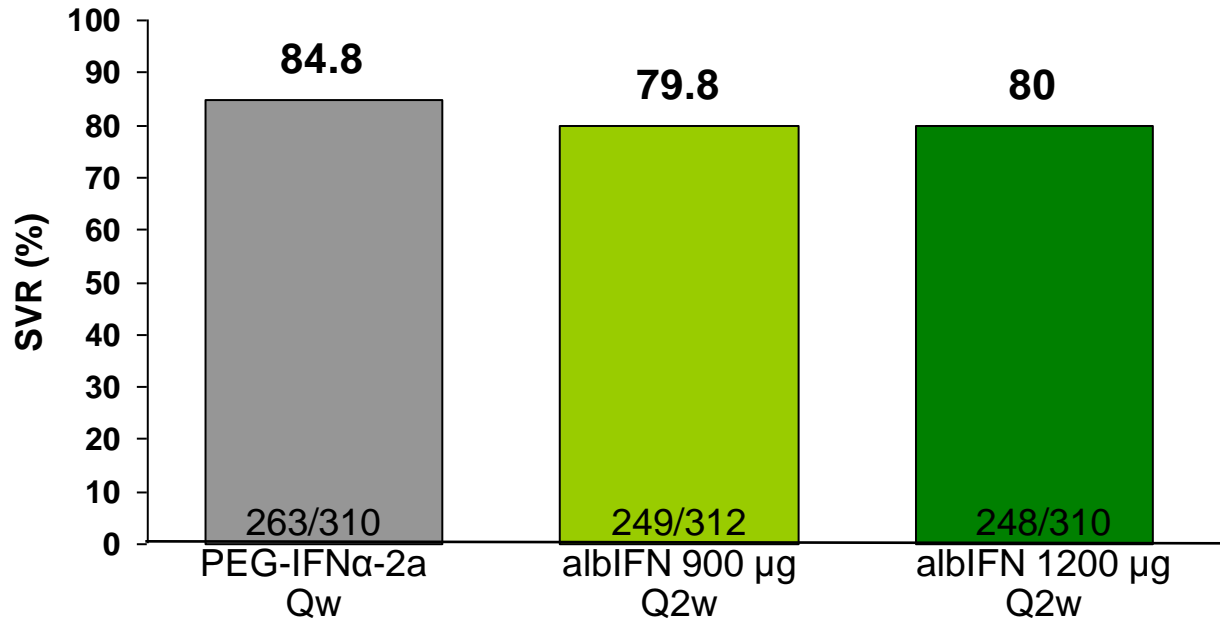
ACHIEVE 2/3 Study Design

- Randomized, open-label, active control, Phase 3
- IFN α treatment-naïve, HCV genotype 2/3
- 3 cohorts stratified by
 - HCV RNA (<800,000 IU/mL vs. \geq 800,000 IU/mL)
 - Genotype (2 vs. 3)
- RBV 800 mg/day



*Dose modification on 23 Jan 2008 per DMC recommendation
38.1% of patients in the albIFN 1200 μ g arm dose reduced to 900 μ g q2wk

SVR in ITT Population

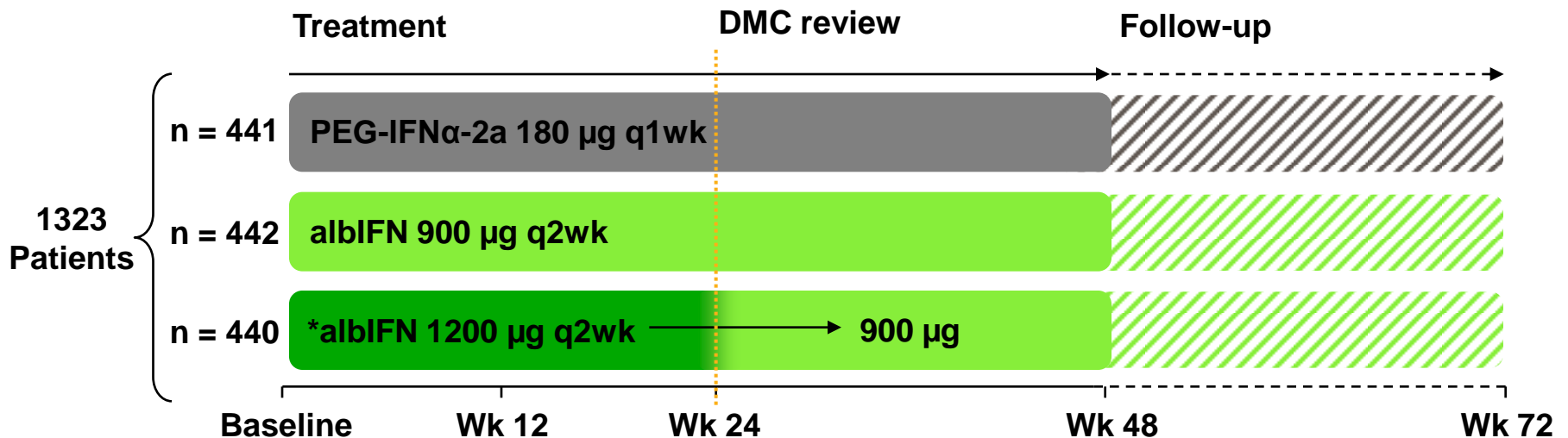


	albIFN 900 μg Q2wk	albIFN 1200 μg Q2wk
SVR difference (95% CI)* vs PEG-IFNα-2a	-4.8% (-10.7%, 1.1%)	-4.5% (-10.3%, 1.4%)
P value for non-inferiority*	0.009	0.006

*Adjusted for baseline stratification factors HCV RNA and Genotype per FDA's request

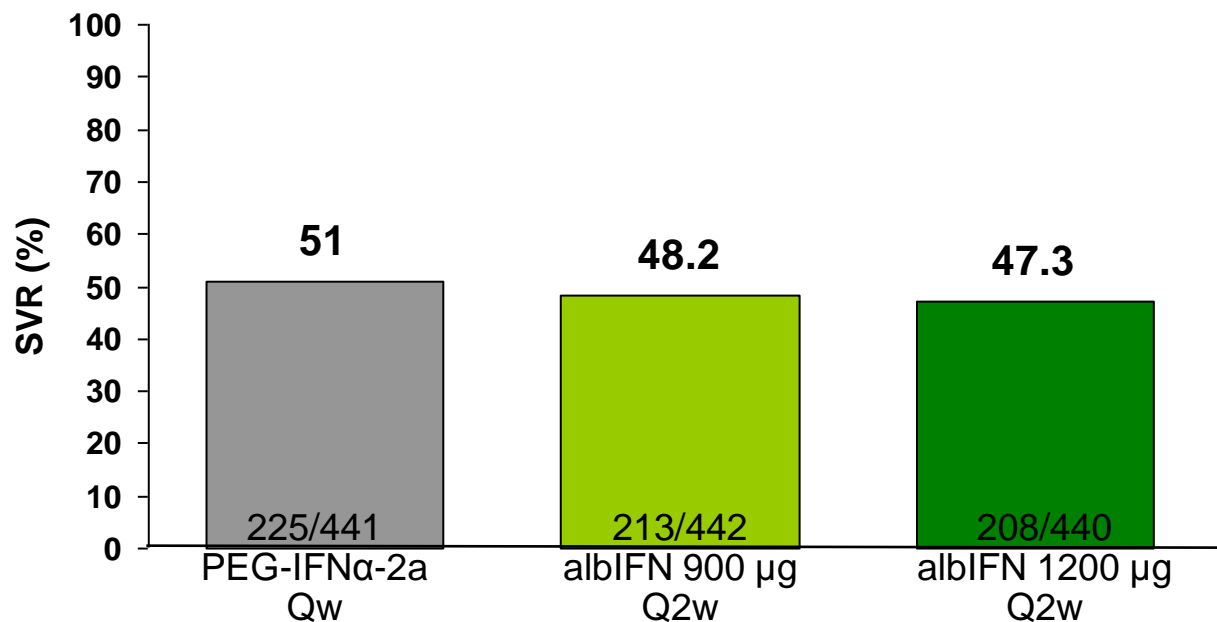
ACHIEVE 1 Study Design

- Randomized, open-label, active control, Phase 3
- IFN α treatment-naïve, HCV genotype 1
- 3 cohorts stratified by
 - HCV RNA (<800,000 IU/mL vs. \geq 800,000 IU/mL)
 - BMI (<25 kg/m² vs. \geq 25 kg/m²)
 - Race (Black/African Heritage vs. Other)
- Weight based RBV 1000-1200 mg/day



*Dose modification on 23 Jan 2008 per DMC recommendation
51% of patients in the albIFN 1200 μ g arm dose reduced to 900 μ g q2wk

Sustained Virologic Response (SVR)



	albIFN 900 µg Q2wk	albIFN 1200 µg Q2wk
SVR difference (95% CI)* vs PEG-IFNα-2a	-1.8% (-8.1%, 4.5%)	-3.1% (-9.4%, 3.2%)
P value for non-inferiority	0.0008	0.0029

^aAdjusted for baseline stratification factors HCV RNA, BMI, and race per FDA's request.

Safety

	PEG-IFN 180 µg Q1wk (N = 441)	albIFN 900 µg Q2wk (N = 442)	albIFN 1200 µg Q2wk (N = 440)
Serious Adverse Events^a	48 (10.9%)	49 (11.1%)	60 (13.6%)
Severe Adverse Events^b	86 (19.5%)	91 (20.6%)	106 (24.1%)
Severe and/or Serious Adverse Events	102 (23.1%)	106 (24.0%)	124 (28.2%)
Discontinuations due to non-efficacy reasons	50 (11.3%)	93 (21.0%)	102 (23.2%)
DC due to Adverse Events	18 (4.1%)	46 (10.4%)	44 (10.0%)
Death^c	1 (0.2%)	—	2 (0.5%)

^aAEs that were fatal, life-threatening, resulted in hospitalization, or were otherwise medically important

^bGrade 3 and 4 severity

^c1 suicide in PEG-IFN; 1 ILD in albIFN 1200 µg arm; 1 bacterial pneumonia in albIFN 1200 µg arm

Common Adverse Events

MedDRA Preferred Term	PEG-IFN 180 µg Q1wk (N = 441)	albIFN 900 µg Q2wk (N = 442)	albIFN 1200 µg Q2wk (N = 440)
Fatigue	245 (55.6%)	230 (52.0%)	248 (56.4%)
Headache	200 (45.4%)	205 (46.4%)	217 (49.3%)
Pyrexia	149 (33.8%)	163 (36.9%)	185 (42.0%)
Insomnia	157 (35.6%)	162 (36.7%)	164 (37.3%)
Alopecia	108 (24.5%)	182 (41.2%)	177 (40.2%)
Nausea	148 (33.6%)	156 (35.3%)	157 (35.7%)
Cough	113 (25.6%)	166 (37.6%)	175 (39.8%)
Myalgia	143 (32.4%)	142 (32.1%)	145 (33.0%)
Arthralgia	114 (25.9%)	108 (24.4%)	119 (27.0%)
Pruritus	100 (22.7%)	92 (20.8%)	113 (25.7%)
Chills	77 (17.5%)	101 (22.9%)	126 (28.6%)
Mood altered	108 (24.5%)	106 (24.0%)	89 (20.2%)
Diarrhoea	78 (17.7%)	92 (20.8%)	106 (24.1%)
Weight decreased	65 (14.7%)	105 (23.8%)	104 (23.6%)
Depression	84 (19.0%)	86 (19.5%)	93 (21.1%)
Dry skin	81 (18.4%)	77 (17.4%)	96 (21.8%)
Rash	87 (19.7%)	61 (13.8%)	102 (23.2%)
Anorexia	61 (13.8%)	70 (15.8%)	91 (20.7%)

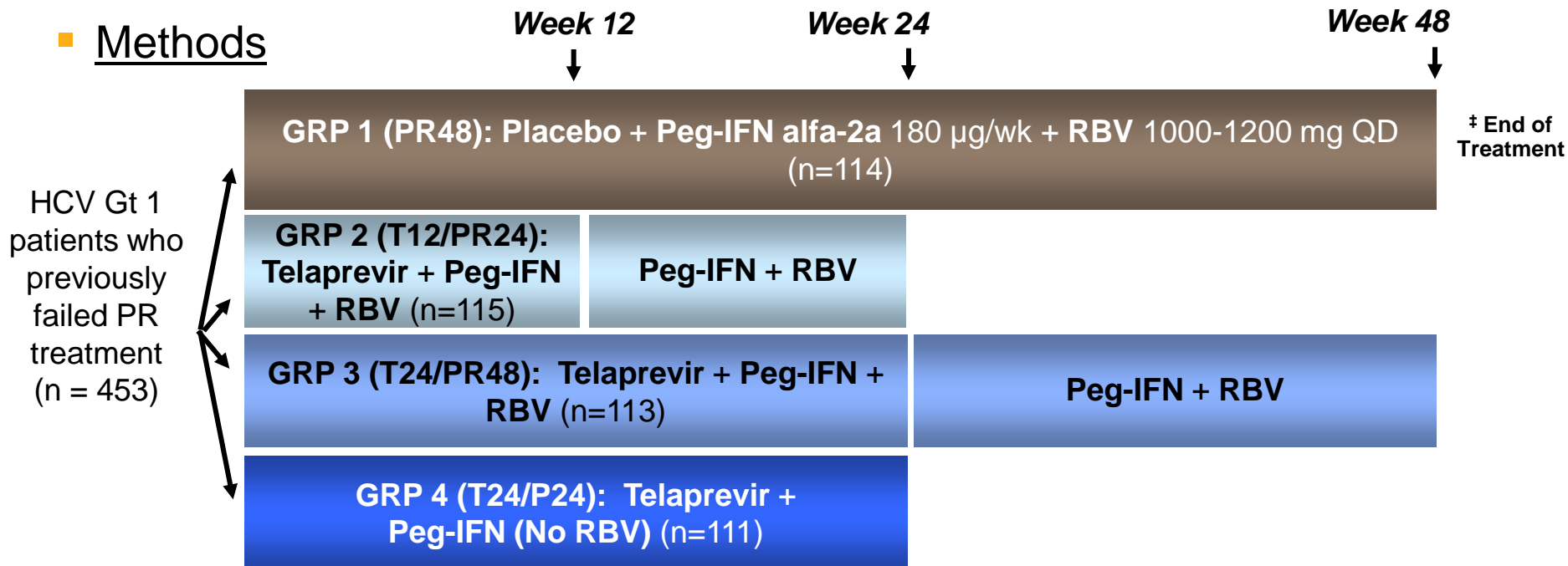
Telaprevir in Hepatitis C Gt 1 Infected Patients with Prior Non-Response, Viral Breakthrough or Relapse to PegIFN alfa-2a/b and RBV Therapy

SVR Results of the PROVE 3 Study

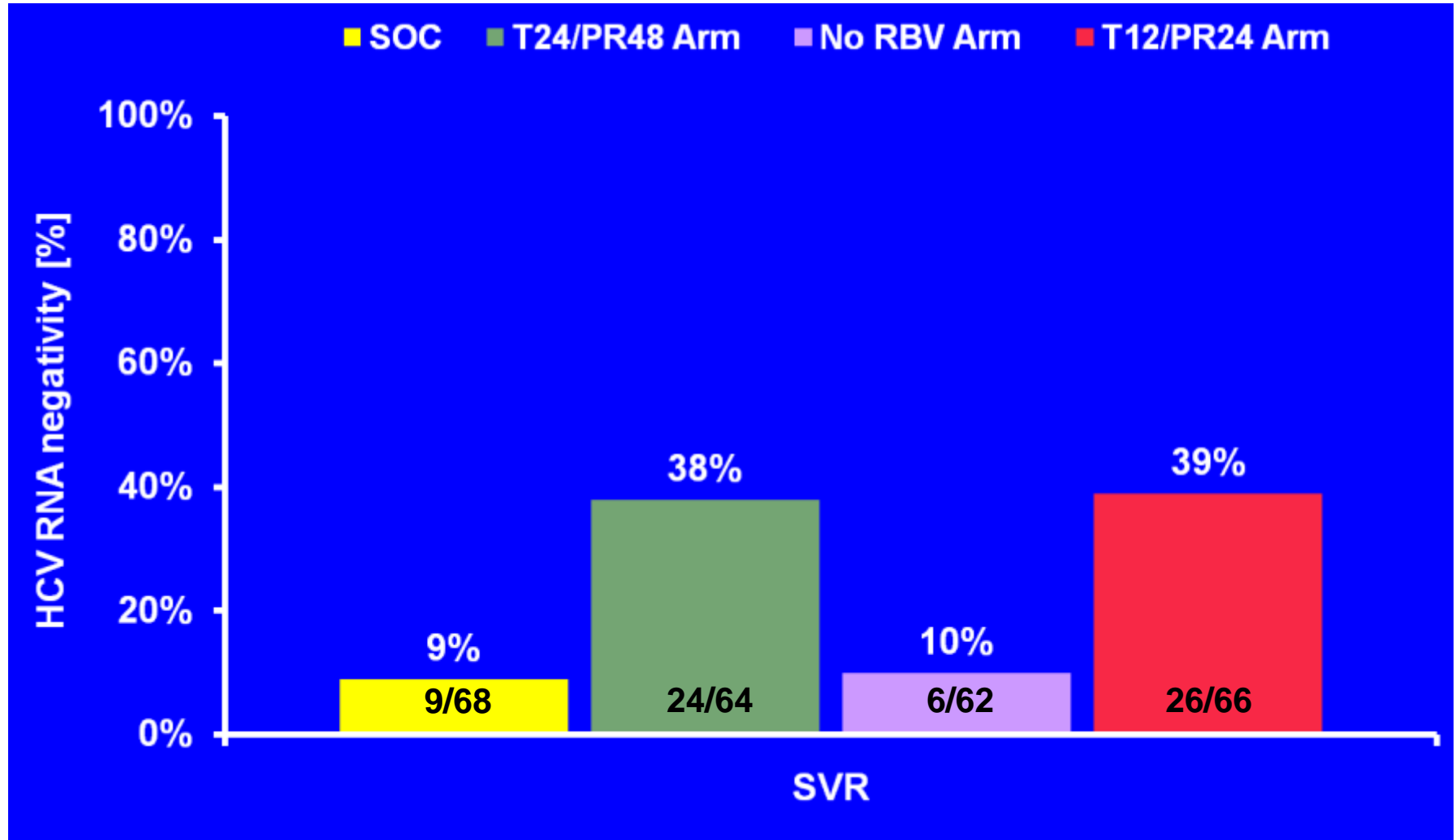
■ Background & Objective

- PROVE 3 is a randomized, placebo-controlled Phase 2 study assessing safety and efficacy of telaprevir plus PegIFN alfa-2a (P) ± ribavirin (R) in HCV Gt 1 patients who previously failed PR treatment

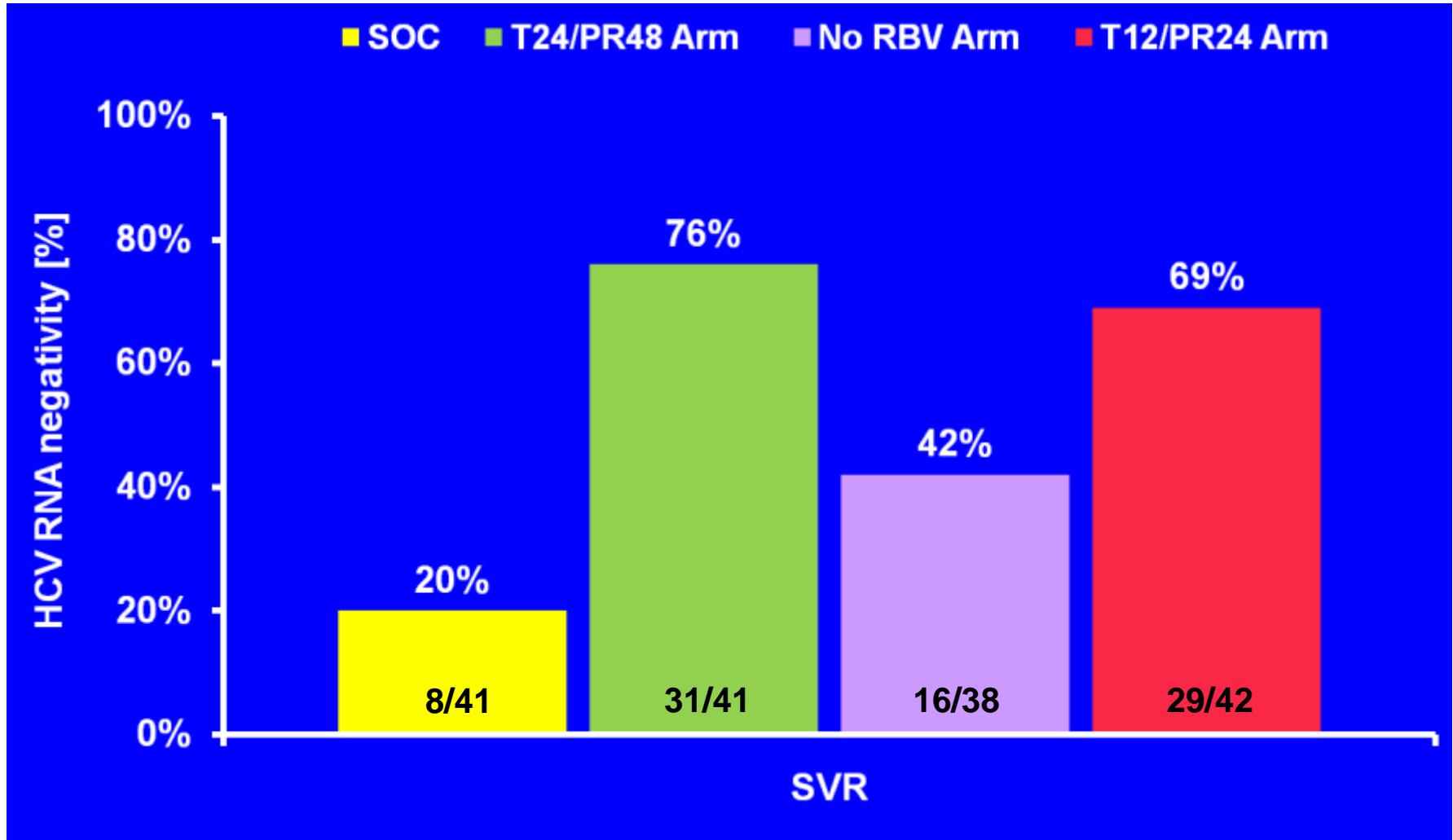
■ Methods



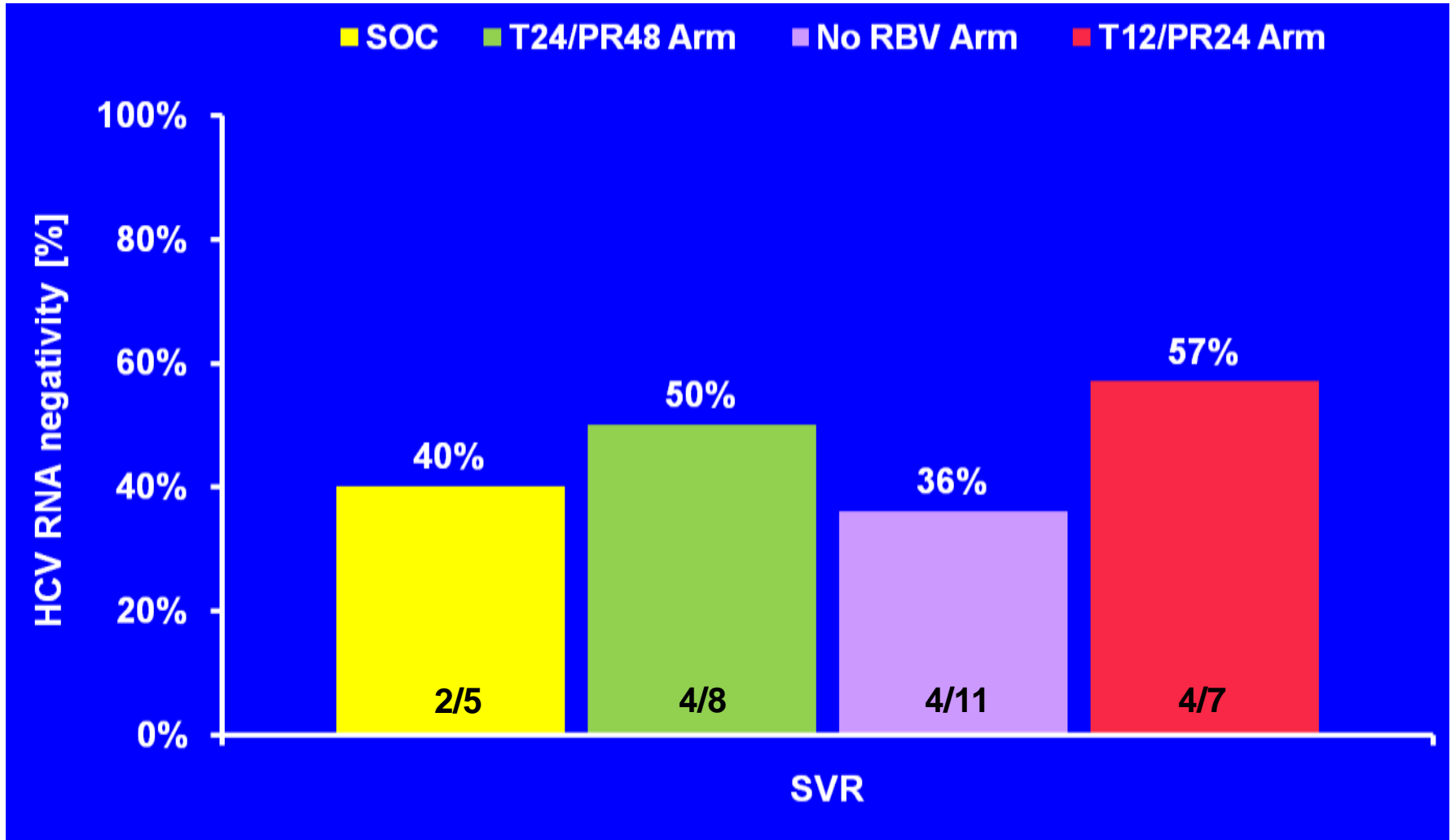
PROVE 3 – SVR in Prior G1 Non-Responders



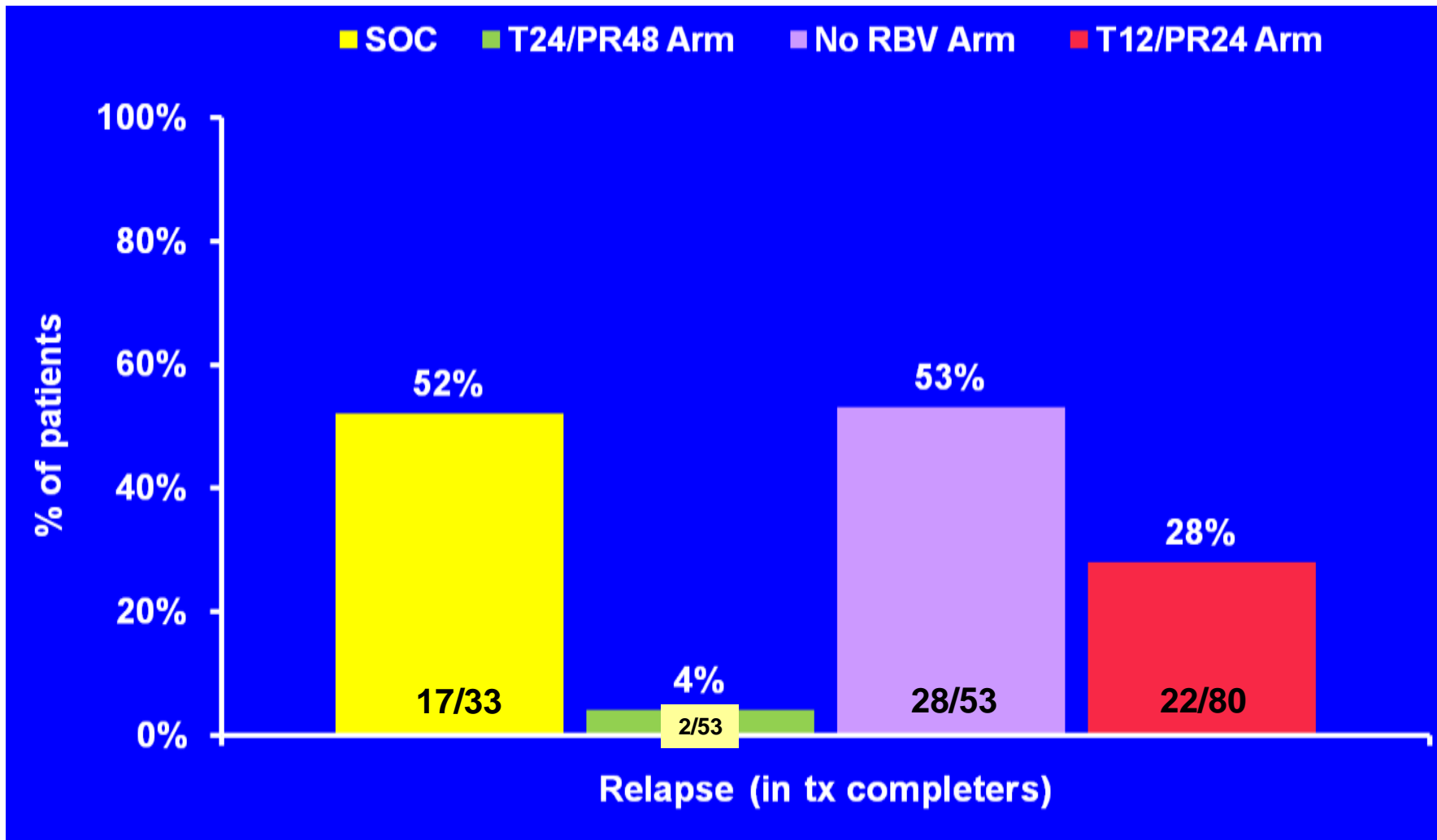
PROVE 3 – SVR in Prior G1 Relapsers



PROVE 3 – SVR in Prior G1 Breakthroughs



PROVE 3 – Relapse Rates

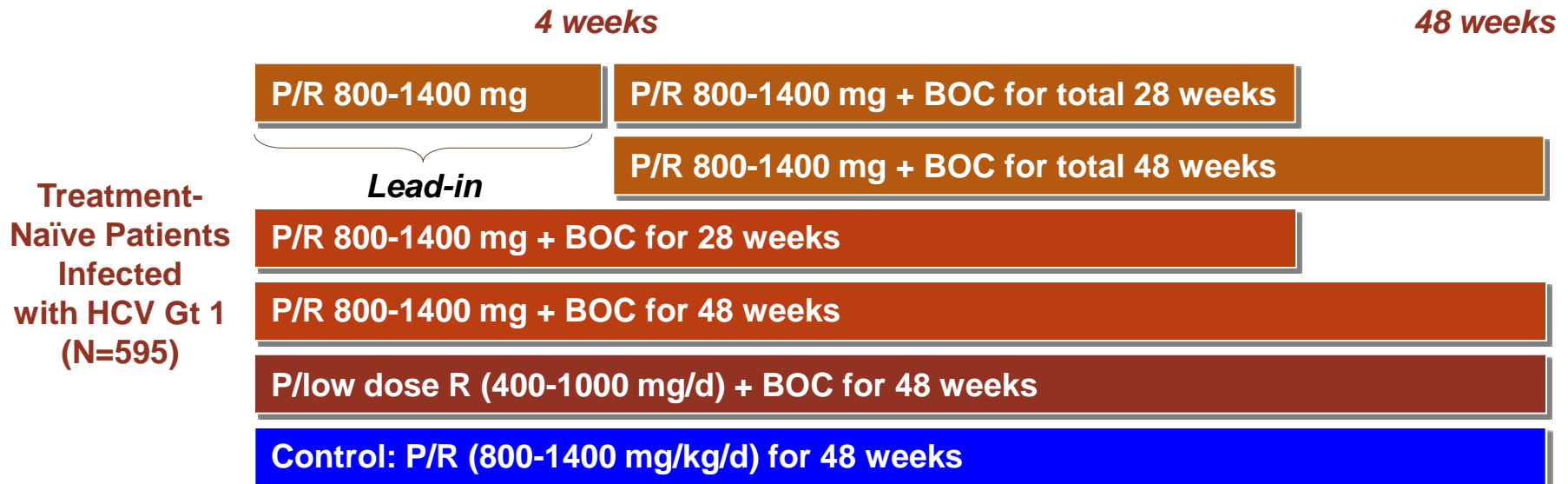


HCV SPRINT-1 Final Results: SVR 24 from a Phase 2 Study of Boceprevir Plus PegIntron/RBV in Treatment-Naïve Subjects with Gt 1 Chronic Hepatitis C

■ Background & Objective

- HCV SPRINT-1 assessed the safety and efficacy of boceprevir (BOC), an oral inhibitor of HCV-NS3 protease, plus PegIntron/RBV

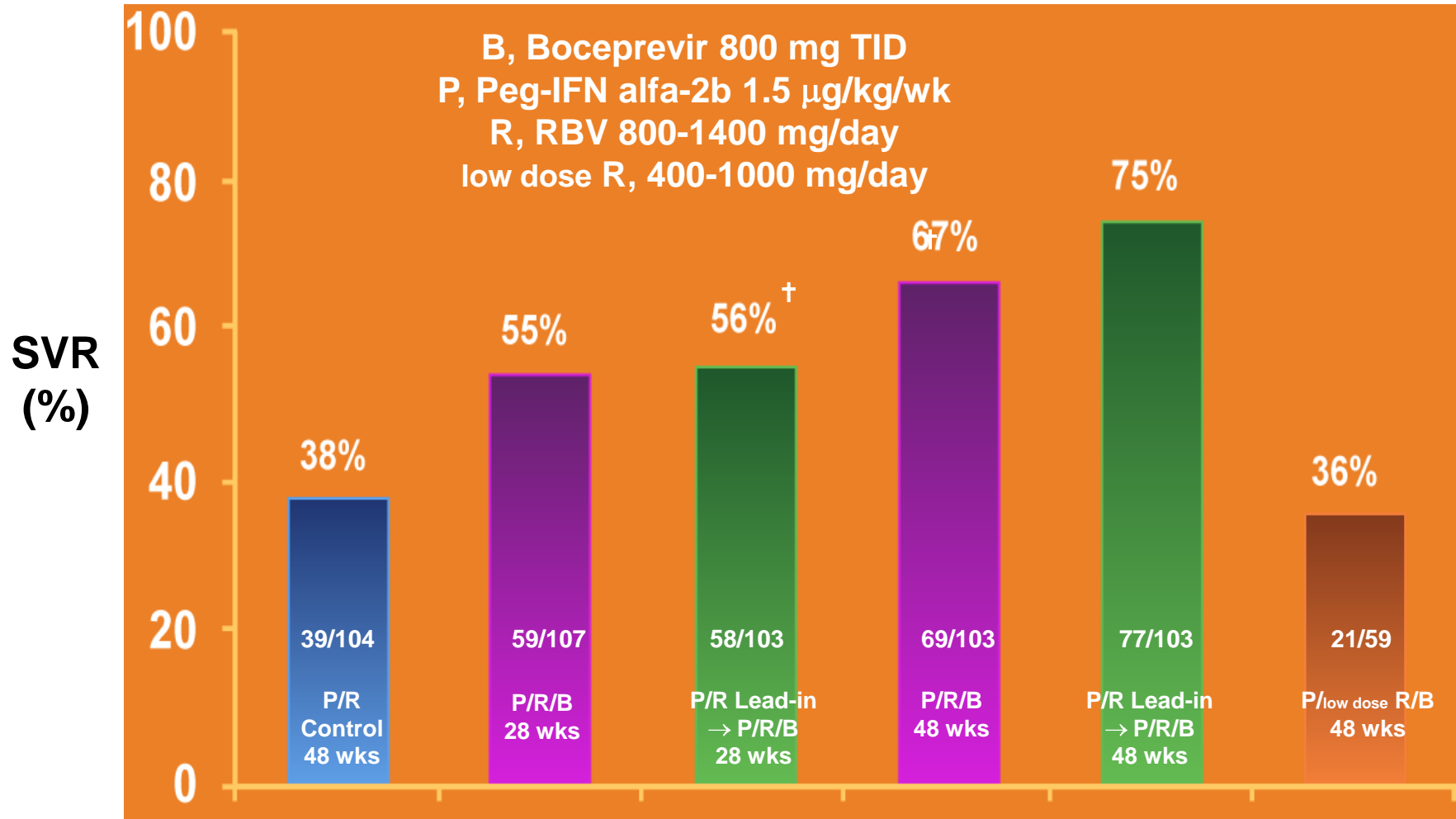
■ Methods



Primary Endpoint: SVR at 24 Weeks of Follow Up
Using Roche COBAS Taqman:
Lower limit of detection (LLD) 15 IU/mL

SPRINT-1: SVR

Treatment-Naive GT1 Patients



* $p=0.0082$, $^{\dagger}p=0.0048$, $^{\S}p<0.0001$ compared to P/R control.

Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of Nitazoxanide Plus PegIFN/RBV in HCV Gt 1 Patients

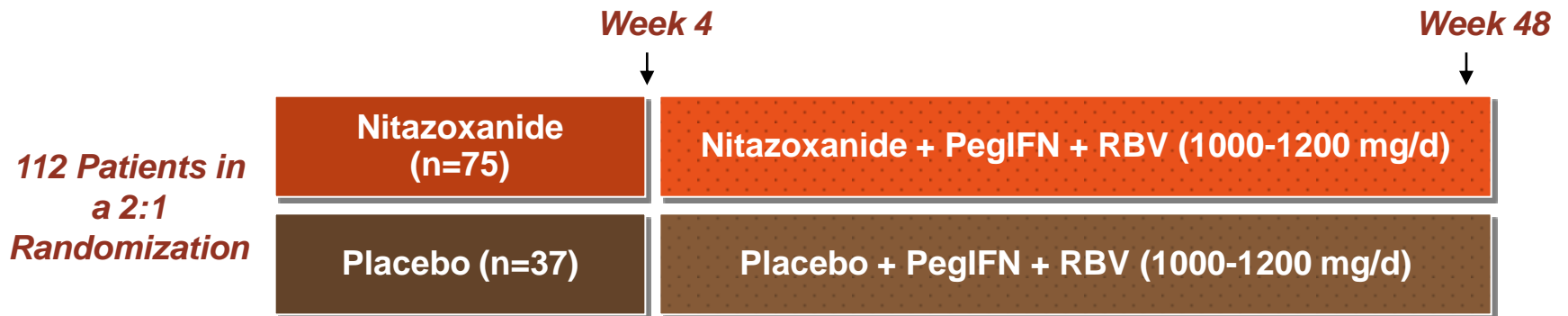
Interim Analysis Shows Increase in EVR

■ Background & Objective

- The antiviral mechanism of action of nitazoxanide (NTZ) appears to be induction of PKR, a mediator of cellular antiviral responses
- The aim of this study is to determine the efficacy of NTZ in combination with PegIFN/RBV in naïve patients with CHC Gt 1

■ Methods

- Double-blind, placebo controlled study in 112 treatment-naïve patients with CHC Gt 1



Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of Nitazoxanide Plus PegIFN/RBV in HCV Gt 1 Patients

Interim Analysis Shows Increase in EVR

■ Results

- In patients with HCV RNA levels >600,000 IU/mL, cEVR and EVR rates were higher in the NTZ group vs placebo (57% vs 39% and 79% vs 61%, respectively)
- SAEs were reported in 10 patients: 6 in the NTZ + PegIFN/RBV, and 4 in the placebo + PegIFN/RBV
- No significant differences in proportions of AEs, except for higher discolored yellow urine in NTZ group ($p < 0.0001$). There were 2 deaths due to pneumonia (NTZ + PegIFN/RBV) and acute respiratory failure and cardiac arrest (placebo + PegIFN/RBV)

<i>Treatment Group</i>	<i>RVR</i>	<i>cEVR</i>	<i>EVR</i>
<i>NTZ + PegIFN + RBV (n=75)</i>	12%	60%	80%
<i>Placebo + PegIFN + RBV (n=37)</i>	19%	49%	68%

NS

First-in-Man Demonstration of Potent Antiviral Activity with a Nucleoside Polymerase (R7128) and Protease Inhibitor (R7227/ITMN-191) Combination in HCV

Safety, PK and Virologic Results from INFORM-1

■ Background & Objective

- The combination of two potent direct-acting antivirals (DAA), targeting two distinct viral enzymes, may offer advantages over single DAA strategies by enhancing potency, reducing emergence of drug resistance, and possibly eliminating the need for PegIFN ± RBV
- The combination of R7128/R7227 offers the potential for a highly potent regimen with a high genetic barrier to resistance

■ Methods

- INFORM-1 is a randomized, double-blind, ascending dose Phase I trial in treatment naïve Gt 1 HCV infected adults

First-in-Man Demonstration of Potent Antiviral Activity with a Nucleoside Polymerase (R7128) and Protease Inhibitor (R7227/ITMN-191) Combination in HCV

Safety, PK and Virologic Results from INFORM-1

■ Results

- Groups A & B, HCV RNA change from baseline at Day 7 was similar [combined mean (SD) -3.0 (0.8) log₁₀ IU/mL]
- Combination of R7128 and R7227 provided greater than additive antiviral activity, with no viral rebound (sustained viral load increase >0.5 log₁₀)

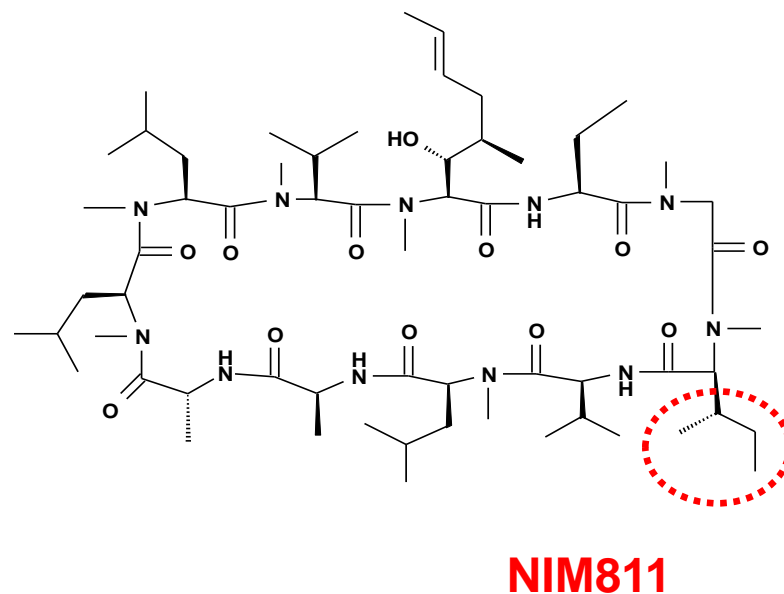
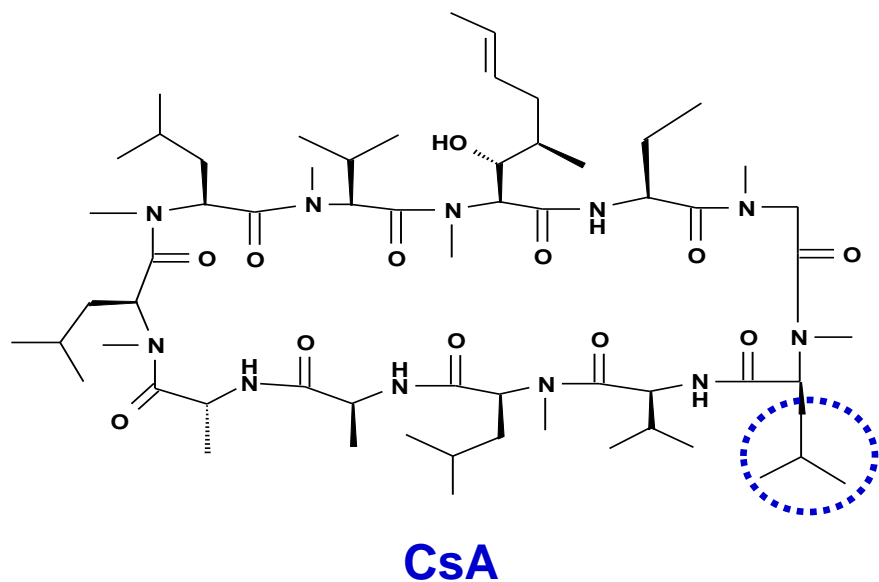
<i>Treatment Group: R7128 / R7227 Dose</i>	<i>Change in RNA from Baseline</i>	<i>% < LLOQ</i>
<i>Group C: 500 / 100</i>	-3.9	13
<i>Group D: 1000 / 100</i>	-5.2	63
<i>Group E: 500 / 200</i>	-4.8	71
<i>Group F: 1000 / 200</i>	-4.8	63

- Resistance data not available yet; in low dose arm, **one patient had rebound** and responded to standard of care

Pharmacokinetics, Safety and Tolerability of NIM811, a Novel Cyclophilin Inhibitor for Treatment of Hepatitis C, Following Single and Multiple Ascending Doses in Healthy Volunteers and HCV-infected Patients

■ Background & Objective

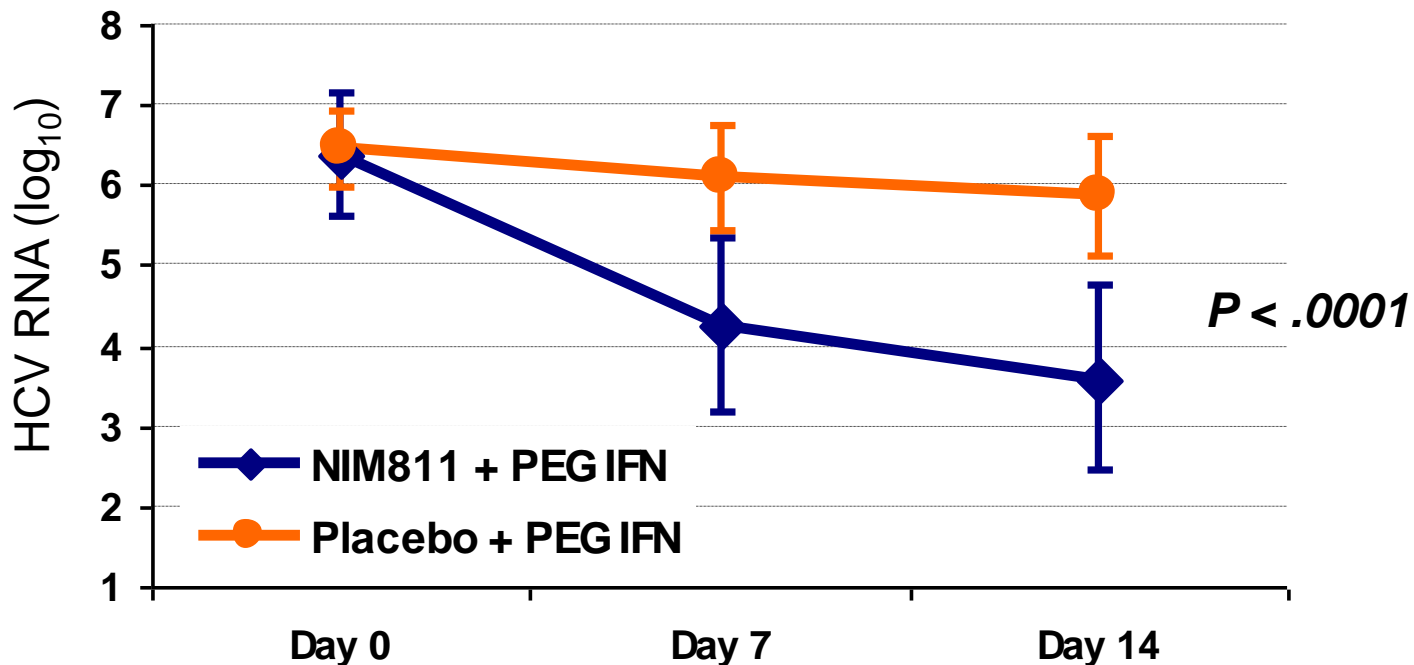
- NIM811, is a cyclophilin inhibitor with substantially lower immunosuppressive activity compared with cyclosporine A
- NIM811 shows potent *in vitro* anti-HCV activity and was evaluated in a two-week proof of concept study for antiviral activity in HCV Gt 1 patients



Safety and Antiviral Efficacy of 14 days of the Cyclophilin Inhibitor NIM811 in Combination with PegIFN in Relapsed Gt 1 HCV Infected Patients

■ Results

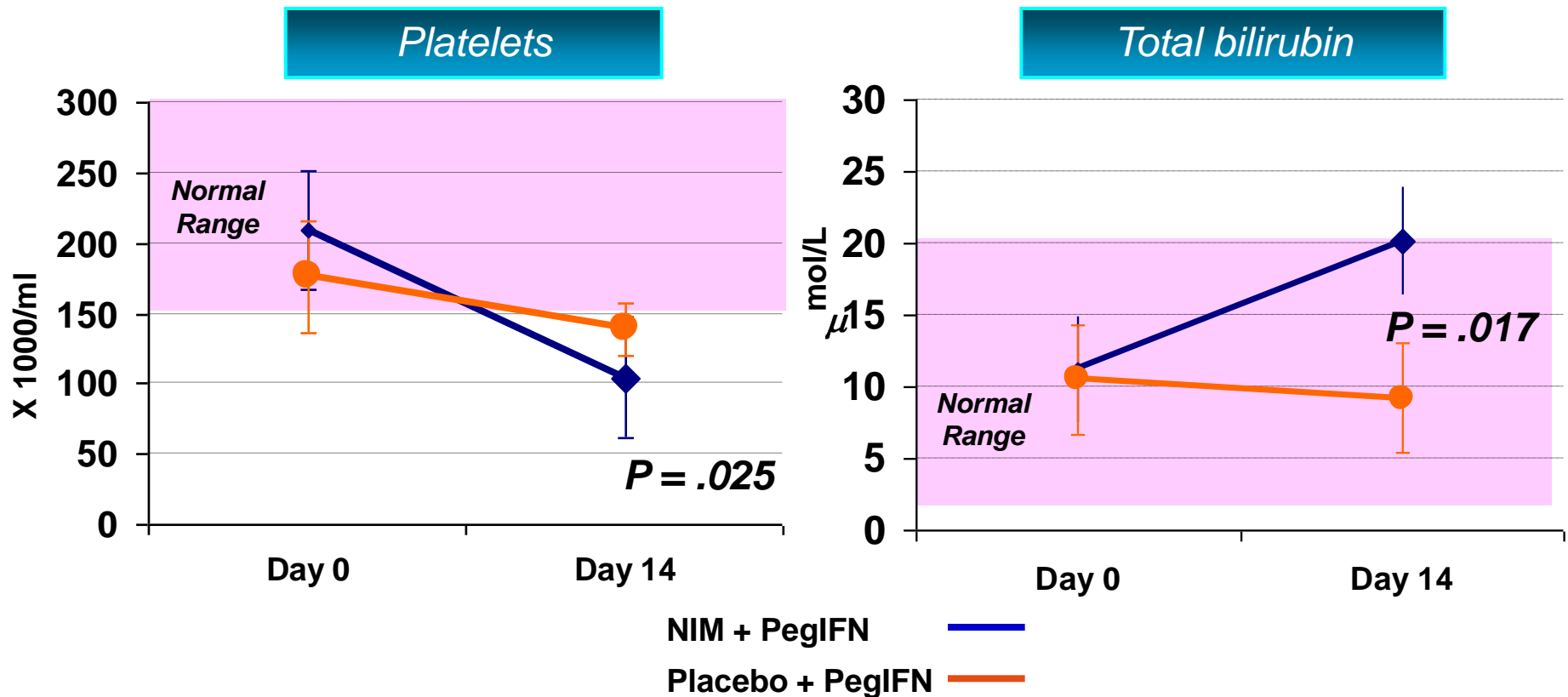
- Mean log decrease 2.7 log in NIM811 group vs. 0.58 in placebo
- NIM811 as monotherapy did not decrease HCV RNA
- NIM811 has comparable PK whether used along or in combination with PegIFN



Safety and Antiviral Efficacy of 14 days of the Cyclophilin Inhibitor NIM811 in Combination with PegIFN in Relapsed Gt 1 HCV Infected Patients

Results

- Increases in bilirubin were statistically but not clinically significant
- No significant AEs compared to Peg-IFN and well tolerated
- Similar incidence of myalgias and other expected side effects



SVR12 Results of Weight-based Taribavirin Versus Weight-based Ribavirin, Both with Peginterferon alfa-2b, in Naïve Chronic Hepatitis C, Genotype 1 Patients

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⁴Virginia Commonwealth University Medical Center, Richmond, VA, USA

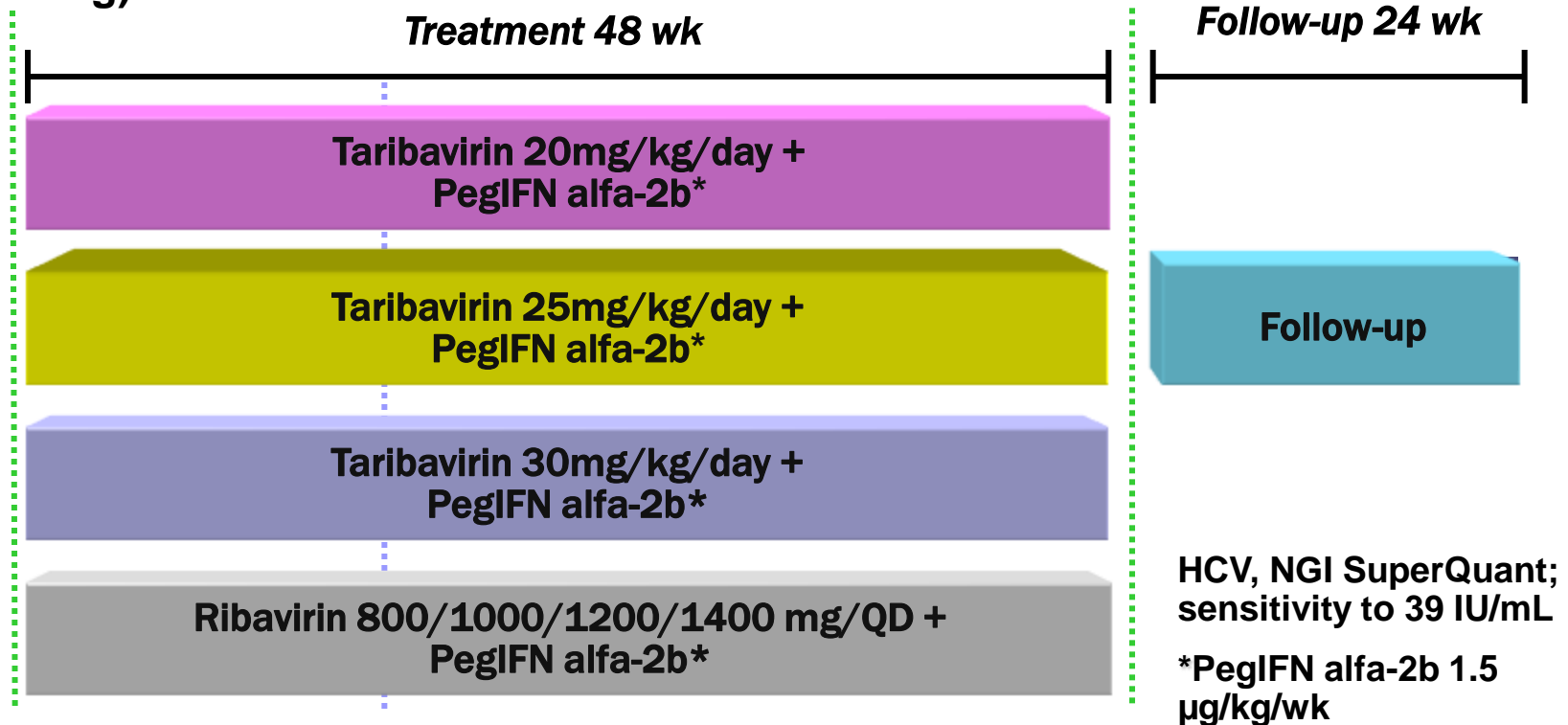
⁵St. Louis University School of Medicine, St. Louis, MO, USA

⁶University Hepatitis Center at Bach and Godofsky, Sarasota, FL, USA

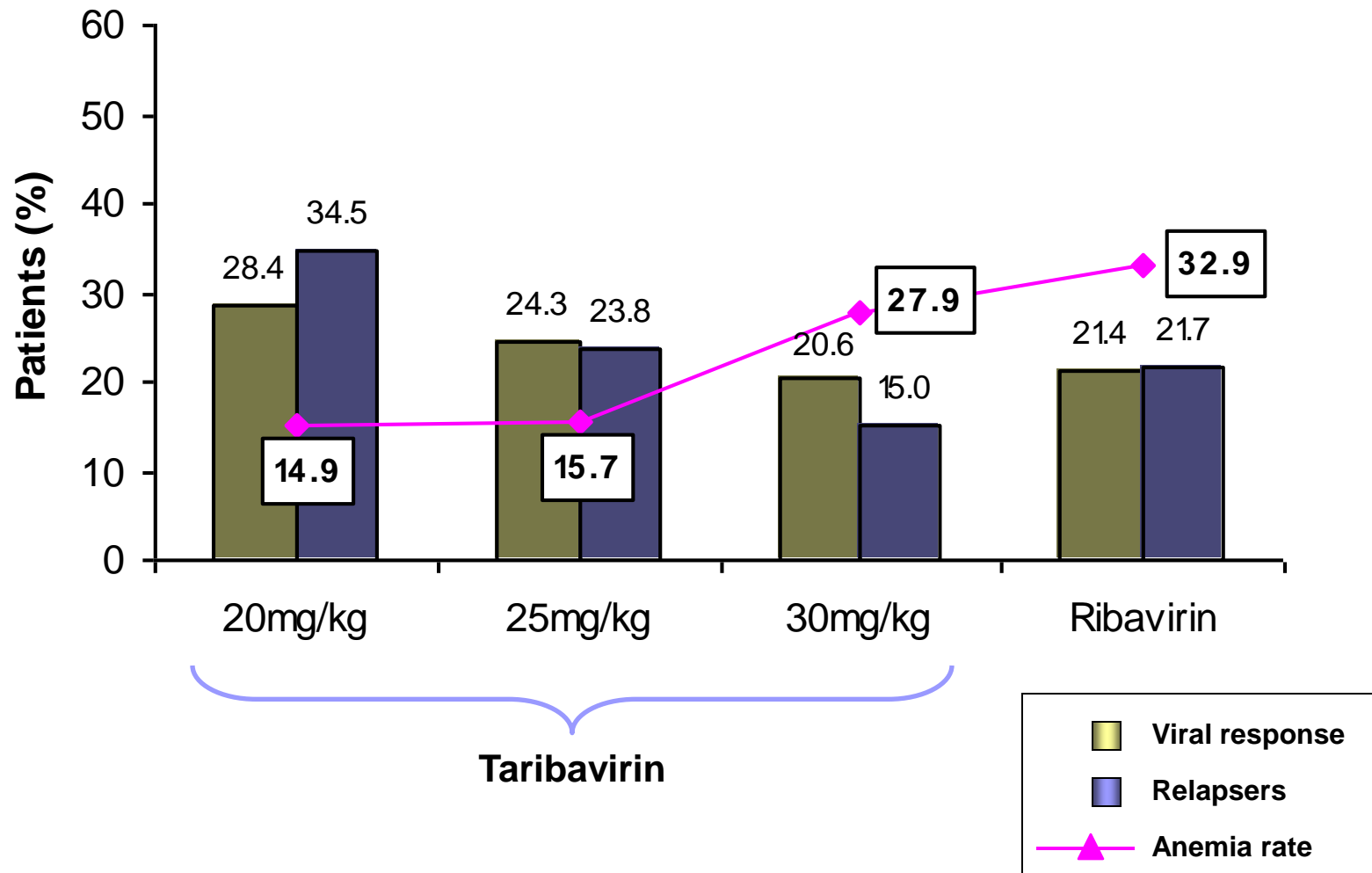
⁷Valeant Pharmaceuticals North America, Aliso Viejo, CA, USA

Taribavirin Phase 2b Study Design

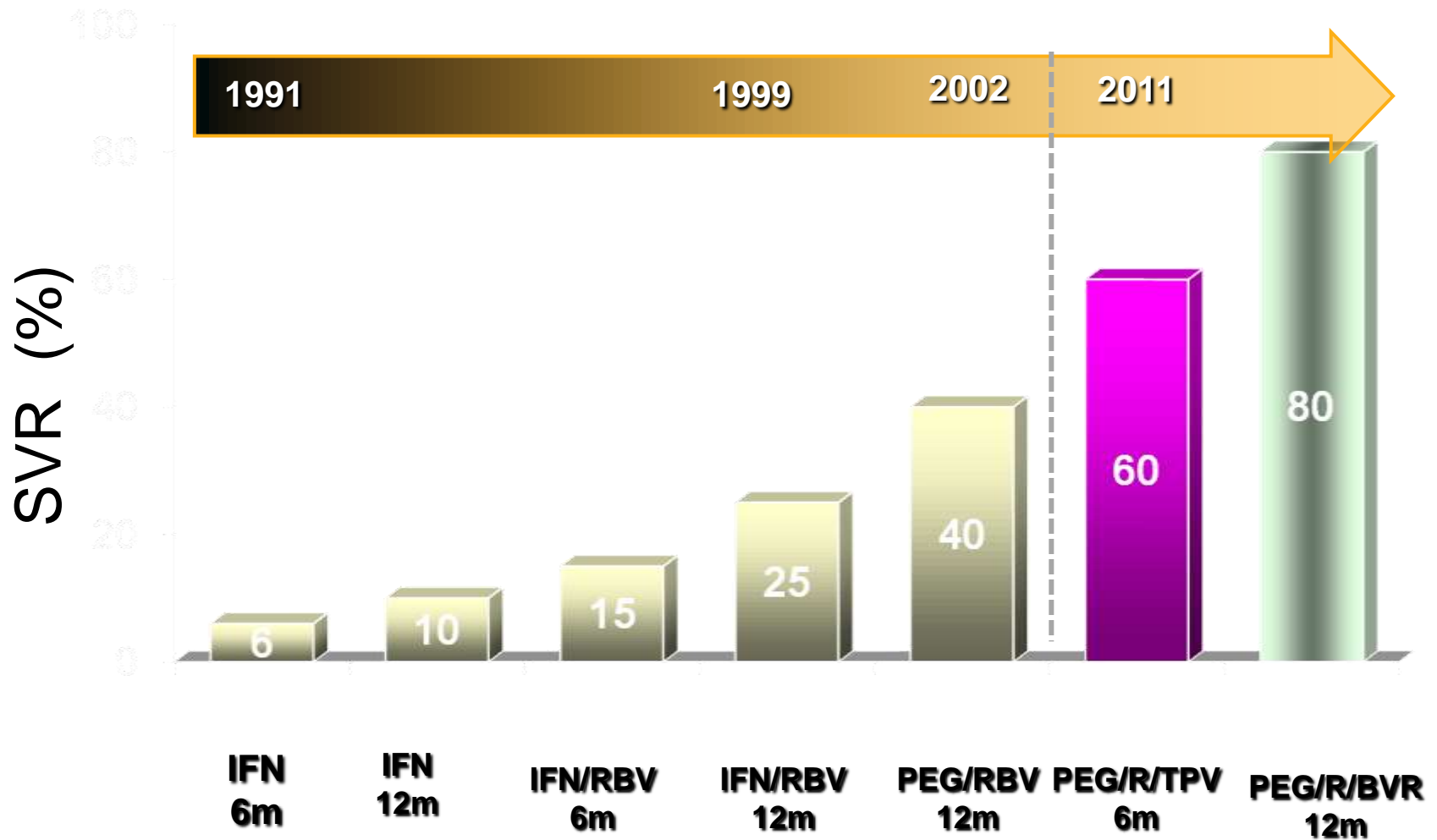
- Multicenter, randomized, parallel-group, open-label study in treatment-naïve, genotype 1 patients (N = 275)
- Patients stratified by baseline HCV RNA titers and body weight (≤ 75 kg or >75 kg)



Virologic Response, Relapse and Anemia at SVR12



R and D in Therapy of HCV Genotype 1



Hepatitis B Virus Abstracts

Prolonged Efficacy and Safety of 3 Years of Continuous Telbivudine Treatment in Pooled Data from GLOBE and 015 Studies in Chronic Hepatitis B Patients

■ Background

- Telbivudine demonstrated superior efficacy vs lamivudine in adults with HBeAg-positive and HBeAg-negative CHB in GLOBE and 015 studies
- Most patients from these studies continued on telbivudine treatment in a 2-year extension trial

■ Objective

- To evaluate the efficacy and safety of 3 years of continuous telbivudine treatment in patients from study 015 and GLOBE

■ Methods

- 3 year efficacy analysis included patients treated per protocol who did not develop genotypic resistance during treatment of up to 2 years (n=503)
- Safety analysis included all patients who enrolled into the extension study for continuing telbivudine treatment

Prolonged Efficacy and Safety of 3 Years of Continuous Telbivudine Treatment in Pooled Data from GLOBE and 015 Studies in Chronic Hepatitis B Patients

<i>Efficacy Parameter in Per-Protocol Patients w/o Genotypic Resistance at 2 Years</i>	<i>HBeAg-Positive (n=293)</i>	<i>HBeAg-Negative (n=210)</i>
<i>PCR negativity*</i>	75%	85%
<i>Maintained PCR negativity**</i>	85%	87%
<i>ALT normalization</i>	83%	84%
<i>HBeAg loss</i>	55%	N/A
<i>HBeAg seroconversion</i>	39 %	N/A
<i>HBsAg loss</i>	1.5%	0%
<i>HBsAg seroconversion</i>	0.4%	0%
<i>Resistance in Overall Population (Per-Protocol Patients)</i>	<i>HBeAg-Positive (n=409)</i>	<i>HBeAg-Negative (n=227)</i>
<i>Genotypic Resistance</i>	n=36 (8.8%)	n=13 (5.7%)

*Quantification limit = 300 copies/mL by COBAS® amplicor

**Patients PCR negative at end of year 2 who maintained response during year 3

Hsu C-W, et al. Presented at EASL 2009. Abstract #911.

Prolonged Efficacy and Safety of 3 Years of Continuous Telbivudine Treatment in Pooled Data from GLOBE and 015 Studies in Chronic Hepatitis B Patients

■ Results

- Long term telbivudine treatment demonstrated a favorable safety profile, comparable with 2 year GLOBE and 015 safety results
- New onset of grade 3-4 CK elevation was reported in 13% of patients
- Rate of ALT flares from baseline to Week 156 was 5.8%
- Myalgia was reported in 4.1%, muscular weakness in 0.6%, and myositis in 0.3% of patients
- Rate of peripheral neuropathy (including paresthesia, neuralgia, polyneuropathy and sensory loss) was low, 0.9%
- No new safety signals observed with continued telbivudine treatment to 3 years

Increased Risk with Combination of Telbivudine and PegIFN in Study CLDL600A2406, Compared to Uncommon Rate with Telbivudine Monotherapy from Novartis Global Database

■ Background & Objective

- Recently, data from the terminated study CLDL600A2406 reported an increased risk of developing peripheral neuropathy when PegIFN and telbivudine were given as combination treatment, compared to either drug given as monotherapy
- This report presents an updated assessment of peripheral neuropathy associated with telbivudine in the telbivudine Global Clinical Trial Program

■ Methods

- Serious and Non-serious adverse events of “peripheral neuropathy” were evaluated from all Phase II-IV telbivudine clinical trials
- Electromyogram and or Nerve Conduction Velocity confirmations are not consistently conducted or reported by investigators. Therefore, at least one of the following symptoms must be present to support the diagnosis of peripheral neuropathy
 - Muscular weakness with diminished tone, or
 - Flaccid paralysis (diminished tendon reflexes and wasting),
 - Sensory disturbances, including pain and impairment of autonomic function

Increased Risk with Combination of Telbivudine and PegIFN in Study CLDL600A2406, Compared to Uncommon Rate with Telbivudine Monotherapy from Novartis Global Database

■ Results

- In the Global Clinical Trial Program, approximately 3,500 patients have been treated with telbivudine as of 28 February, 2009
- **Nineteen peripheral neuropathy SAEs** have been reported in the safety database, 9 cases with the use of the combination of telbivudine + Peg-IFN and 10 with telbivudine monotherapy
- The peripheral neuropathy SAEs that occurred with the combination of telbivudine and Peg-IFN had a time to onset of 2-6 months, while time to onset was longer in the telbivudine monotherapy arm, with an average of 14 months

	<i>Telbivudine + Peg-IFN Combination Therapy CLDT600A2406</i>	<i>Telbivudine Monotherapy All Telbivudine Trials</i>
<i>Incidence of peripheral neuropathy</i>	18.75% (9/48)	0.28% (10/3,500)
<i>Time to onset (Range)</i>	4.5 Months (2-6 months)	14 months (4-25 months)
<i>Improvement of peripheral neuropathy</i>	67% (6/9)	90% (9/10)

Increased Risk with Combination of Telbivudine and PegIFN in Study CLDL600A2406, Compared to Uncommon Rate with Telbivudine Monotherapy from Novartis Global Database

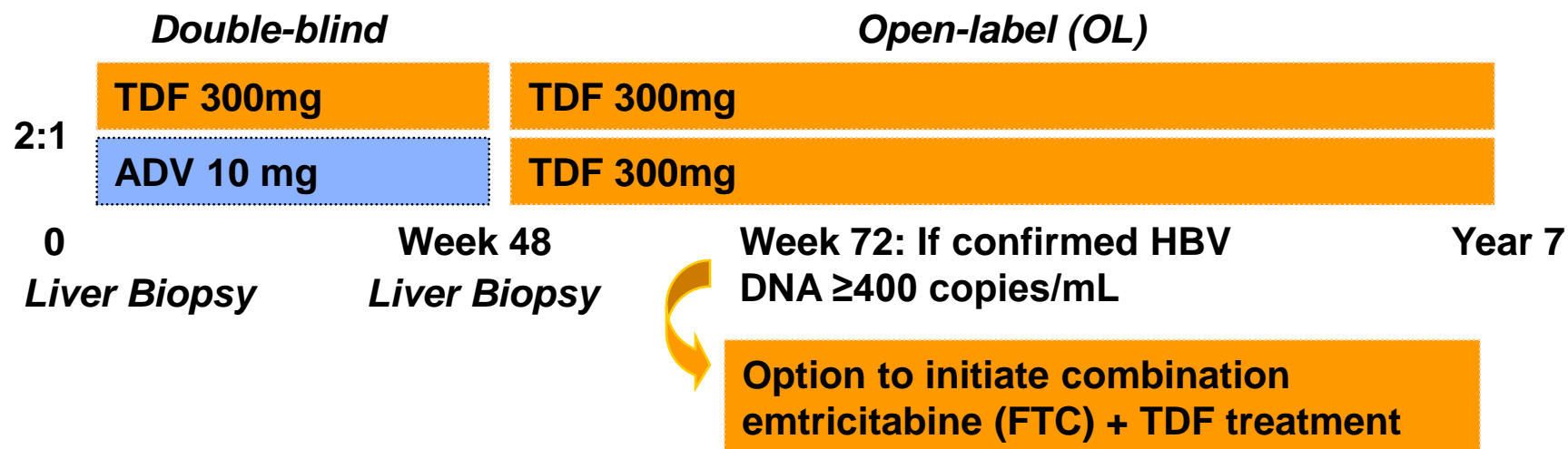
■ Authors' Conclusions

- This analysis identifies that the risk of peripheral neuropathy is increased with the telbivudine + Peg-IFN combination compared to telbivudine alone
- Patients reporting symptoms of peripheral neuropathy should be clinically assessed and appropriate investigations conducted to confirm the diagnosis
- Telbivudine use should be interrupted if it is suspected and discontinued if confirmed
- Concomitant use of telbivudine with Peg-IFN should be avoided. The increased risk of peripheral neuropathy cannot be excluded for other interferons

Safety and Tolerability of 96 Weeks of Tenofovir Disoproxil Fumarate (TDF) Treatment in HBeAg Negative and Positive Patients Infected with Chronic Hepatitis B (CHB)

■ Methods

- Randomized, double-blind, active-controlled phase III study
 - Study 103 is a study in treatment-naïve patients with **HBeAg positive (+)** chronic hepatitis B (CHB)
 - Study 102 is a study in patients with **HBeAg negative (-)** CHB

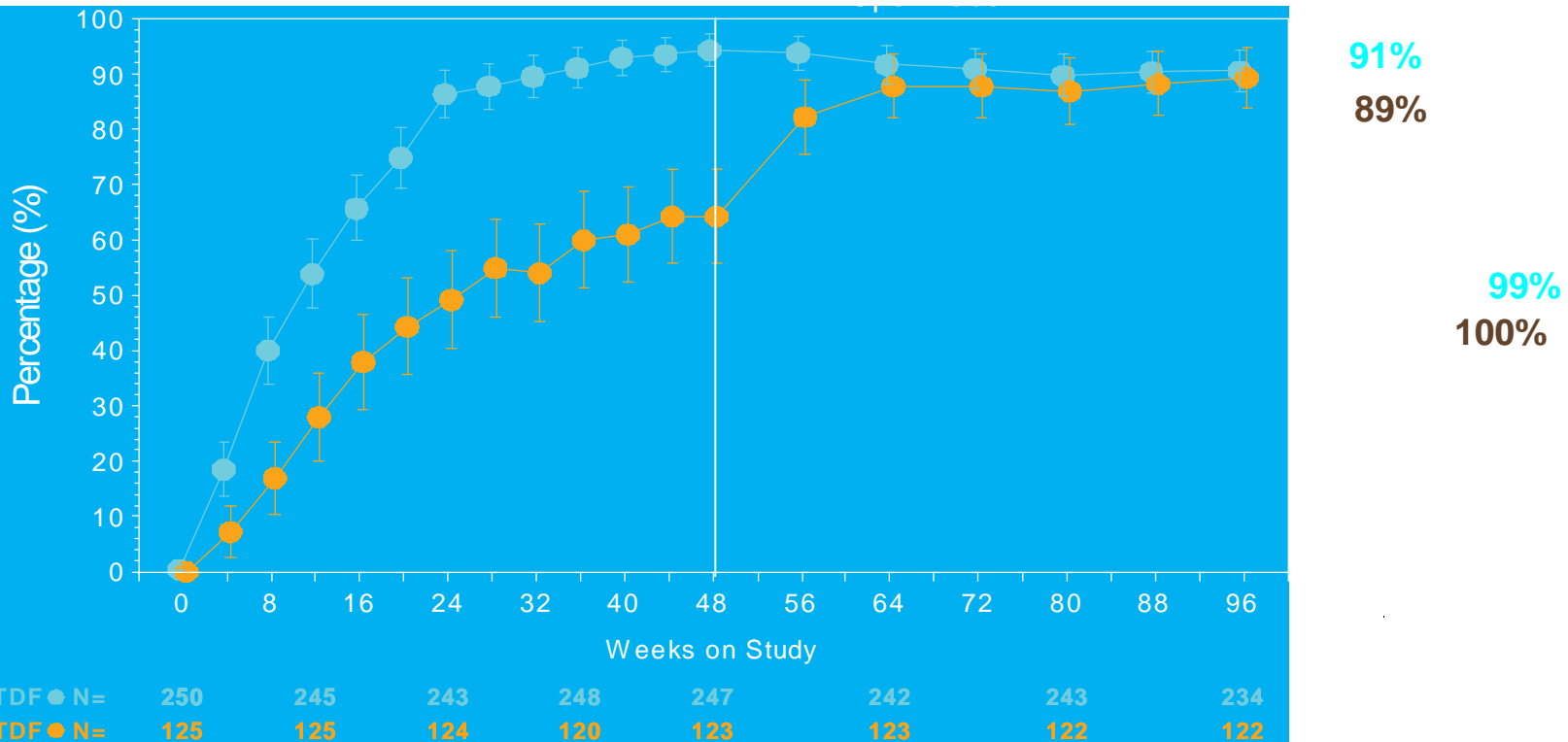


■ Results

- 389 patients included in this week 96 analysis

HBeAg (-) Study 102

% Patients with HBV DNA <400 c/mL by Visit (95% CI) (Long Term Evaluation, ITT)

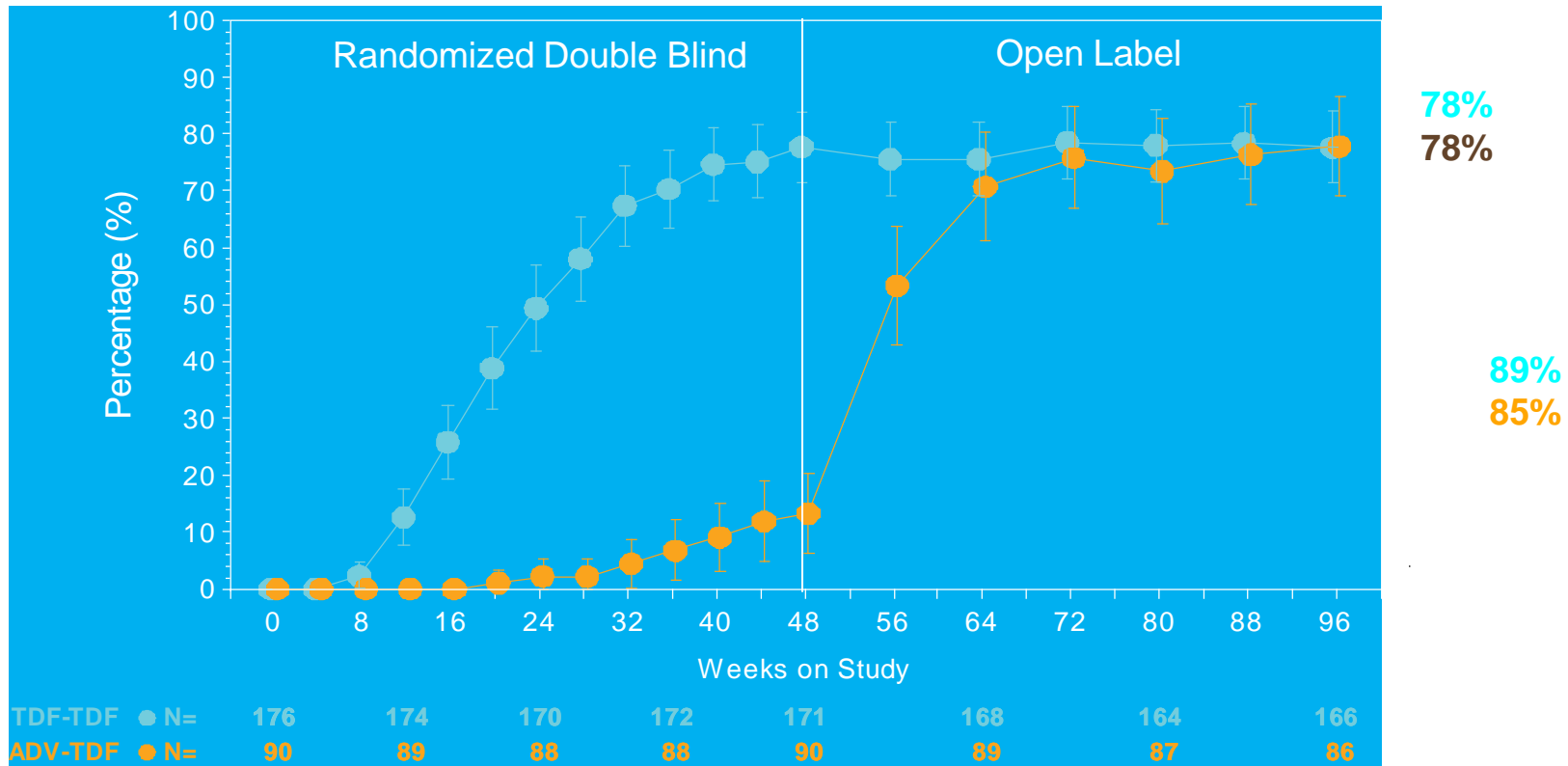


1 Patient was <400 copies/mL on FTC + TDF at Week 96.

Long Term Evaluation ITT Analysis: Patients who discontinued for administrative reasons with HBV DNA <400 copies/mL were excluded for visits after discontinuation (N= 7). At Week 96, 12 patients were missing data at random.

HBeAg (+) Study 103

% Patients with HBV DNA <400 c/mL by Visit (95% CI) (Long Term Evaluation ITT)



Five patients were <400 copies/mL at Week 96 on FTC + TDF

Long Term Evaluation: Patients who discontinued for administrative reasons with HBV DNA <400 copies/mL were excluded for visits after discontinuation (N = 8). At Week 96, 7 patients were missing data at random and were excluded.

Safety and Tolerability of 96 Weeks of Tenofovir Disoproxil Fumarate (TDF) Treatment in HBeAg Negative and Positive Patients Infected with Chronic Hepatitis B (CHB)

■ Results

- During OL TDF, no TDF patient treated for 96 weeks had a confirmed: decrease in creatinine clearance <50 mL/min, increase in creatinine of 0.5 mg/dL or graded serum creatinine abnormality.
- No patient experienced bone fractures that were considered related to TDF, considered pathological, or associated with abnormalities in calcium, phosphorus, alkaline phosphatase or renal laboratory parameters.

■ Authors' Conclusions

- The safety and tolerability profile of tenofovir DF was good and did not show any new or unexpected adverse events in the HBV-infected population
- The renal safety of tenofovir DF was good and confirms the profile established in patients with HIV-infection
- No new HBV pol/RT amino acid substitutions associated with tenofovir DF resistance were detected through 96 weeks.

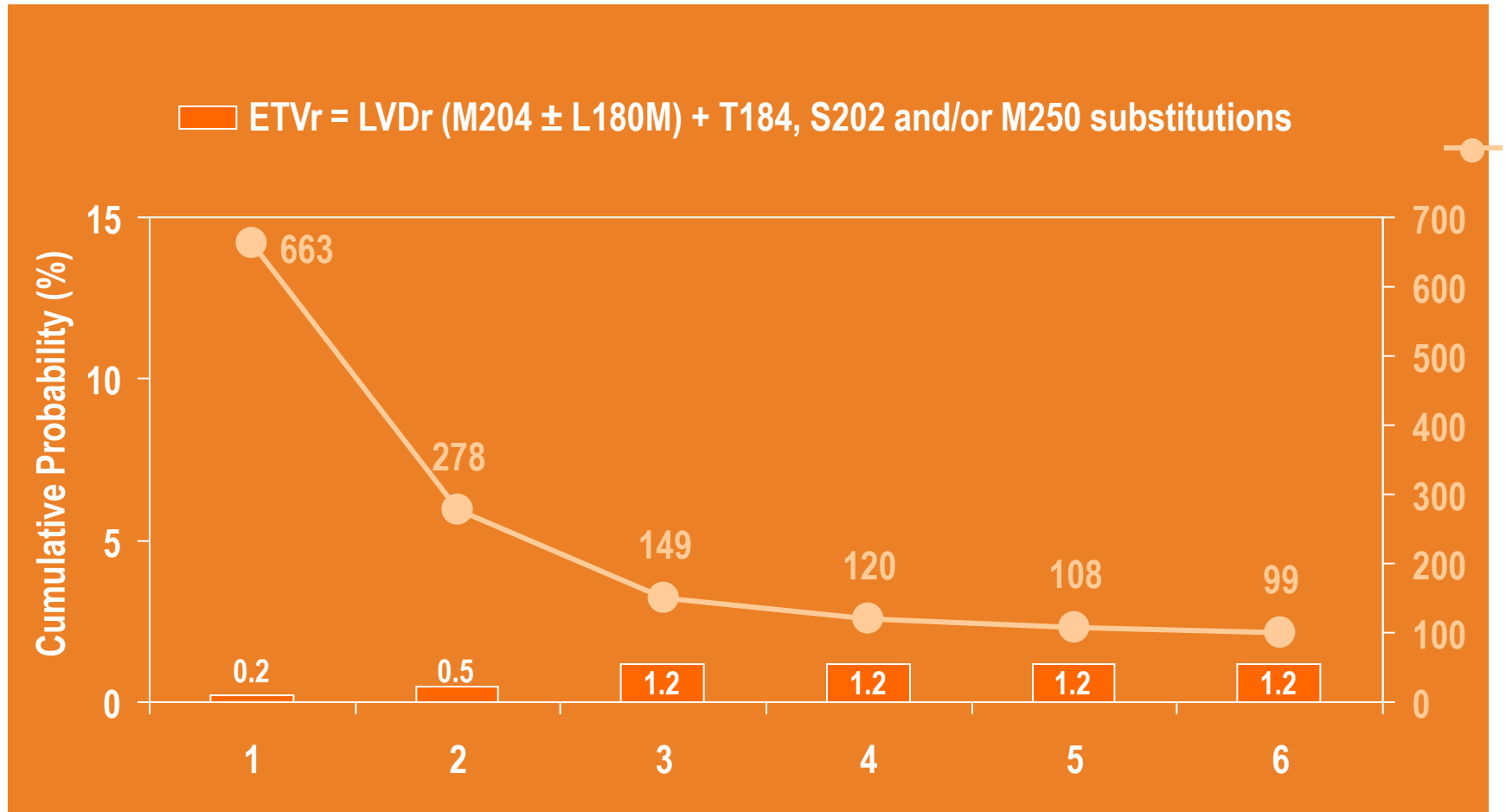
Entecavir Maintains a High Genetic Barrier to HBV Resistance Through 6 Years in Naïve Patients

■ Methods

- All patients receiving continuous therapy in registration trials were monitored for resistance through Year 6
- 2 Cohorts: Naïve and LVD-refractory
- Sequencing was performed on serum samples with detectable HBV DNA (≥ 300 copies/mL) at each cross-sectional end-of-year analysis, or with viral breakthrough at anytime, or at discontinuation from study with detectable HBV DNA.
- Cumulative probabilities of resistance were determined through Year 6

6-year Assessment of ETV Resistance: Naïve Patients

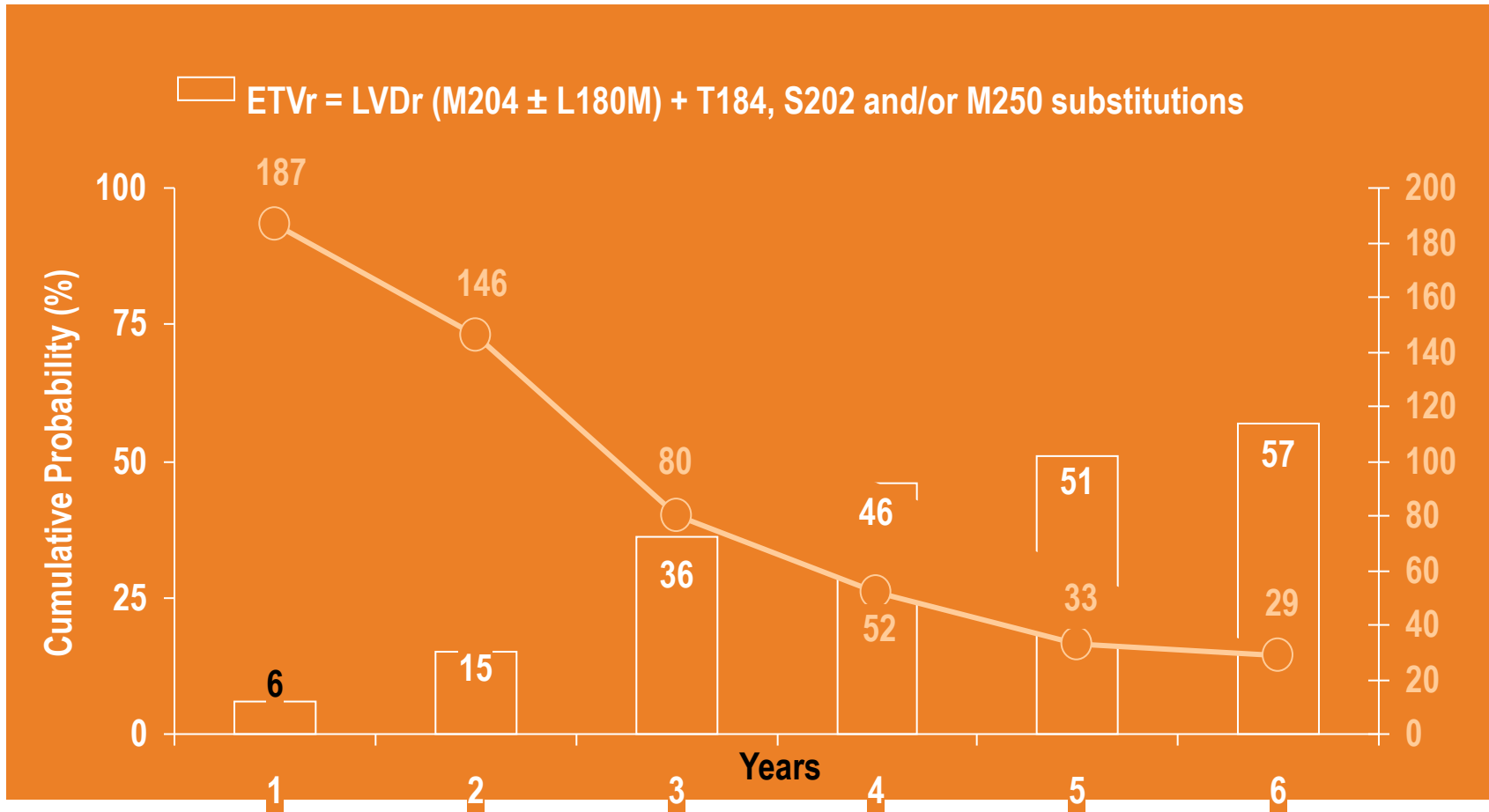
Nucleoside-Naïve Cohort, HBeAg(+) & HBeAg(-): Cumulative Probability of ETV Resistance Through 6 Years



- HBV DNA <300 copies/mL in 94% of patients in Year-6 (N=99)
- HBV DNA <300 copies/mL at last on-treatment visit in 89% of those discontinuing

Lamivudine-Refractory Cohort, HBeAg (+) : Cumulative Probability of ETV Resistance Through 6 Years

6-year Assessment of ETV Resistance: Lamivudine-Refractory Patients



- 74/187 (40%) achieved HBV DNA <300 copies/mL
- 5/74 (7%) with HBV DNA <300 copies/mL had subsequent genotypic ETV resistance

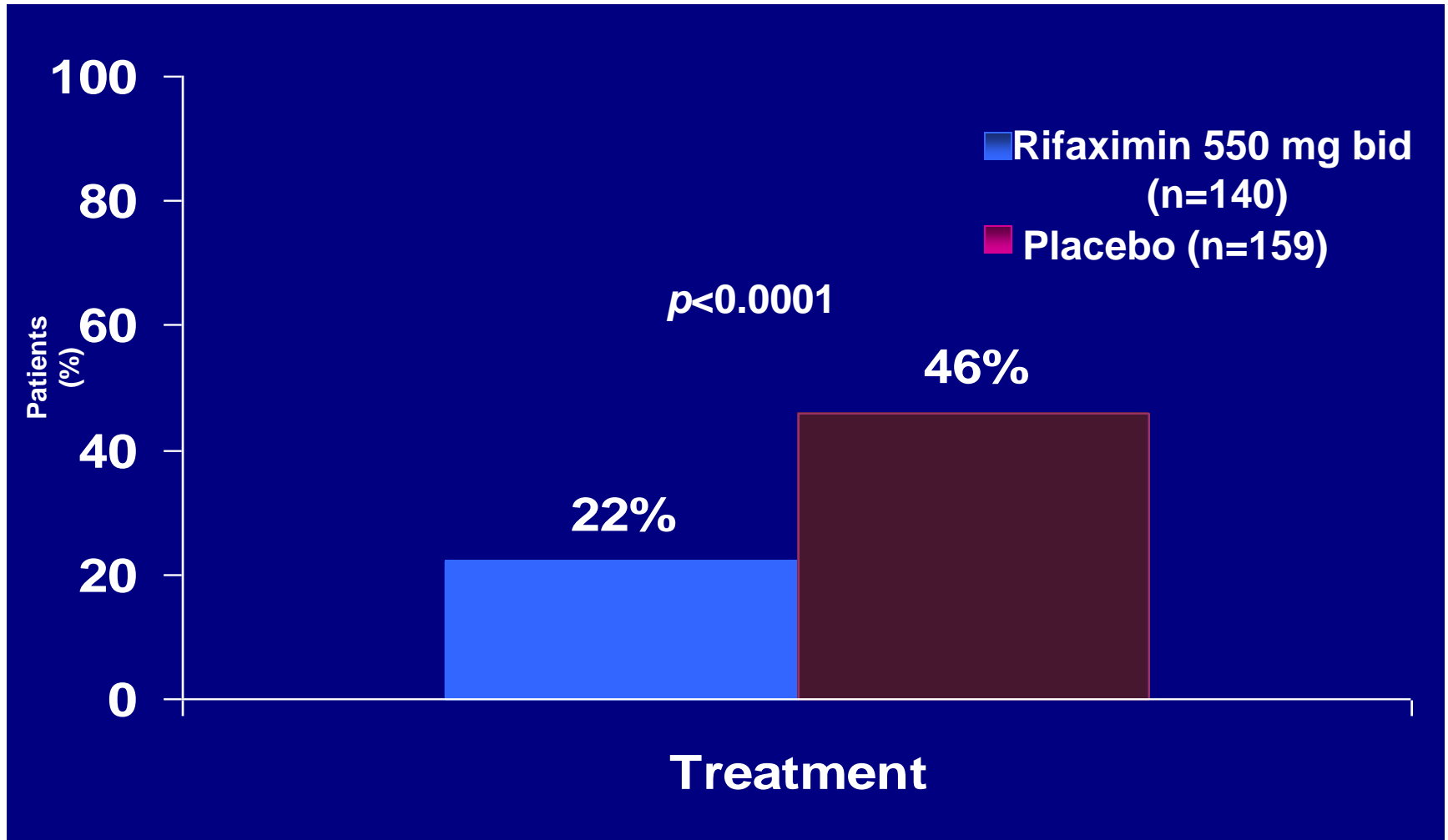
Rifaximin is Effective in Maintaining Remission in Hepatic Encephalopathy: Results of a Large, Randomized, Placebo-Controlled Study. Bass N, Mullen K, Sigal S, Sanyal A, Poordad F, Merchant K, Huang S, Shaw A, Borley E, Forbes W

SAFETY OF RIFAXIMIN IN PATIENTS WITH HEPATIC ENCEPHALOPATHY: RESULTS OF A RANDOMIZED, PHASE 3, PLACEBO-CONTROLLED CLINICAL TRIAL

K. Mullen¹, S. Sigal², M. Sheikh³, N. Bass⁴, F. Poordad⁵, K. Merchant⁶, S. Huang⁶, A. Shaw⁶, E. Bortey⁶, W. Forbes⁶

- **Methods:** Rifaximin (550 mg twice daily) was compared with placebo in a randomized, double-blind, placebo-controlled trial for 6 months in patients with a history of HE. Continued therapy with lactulose was permitted.

Breakthrough HE Episodes* Over 6 Months: Rifaximin vs. Placebo



*Patients who had ≥ 2 episodes of HE (Conn score ≥ 2) within 6 mo prior to screening and who were in remission at trial start
Bass N et al. Oral presentation at 44th Annual Meeting of the European Association for the Study of the Liver, April 25, 2009, Copenhagen, Denmark. Abstract 93.

Treatment-emergent Adverse Events in Patients with HE: Rifaximin vs. Placebo*

	Rifaximin (n=140) (%)	Placebo (n=159) (%)
Ascites	11	9
Dizziness	13	8
Fatigue	12	11
Peripheral edema	15	8
Infection	33	31
Urinary Tract Infections	6	9
Drug-related AEs	19	21
Severe AEs	26	31
Serious AEs	36	40
Death	7	7

*Rifaximin 550 mg bid vs placebo for 6 mo in patients who had ≥ 2 episodes of HE (Conn score ≥ 2) within 6 mo prior to screening and who were in remission at trial start.

Mullen K et al. Poster presentation at 44th Annual Meeting of the European Association for the Study of the Liver, April 23, 2009, Copenhagen, Denmark. Abstract 207.

The Effect of Prognostic Factors On the Maintenance of Remission in Hepatic Encephalopathy Patients Treated with Rifaximin

Samuel Sigal, F. Fred Poordad, Kimberly L. Beavers, Kunal Merchant, Shirley Huang, Audrey L. Shaw, Enoch Bortey, William P. Forbes

- Background and aims: In this multinational, placebo-controlled trial, rifaximin significantly reduced the risk of breakthrough HE in the overall intent-to-treat (ITT) population by 58% (hazard ratio, 0.421; $p < 0.0001$). This analysis investigates the potential effect of prognostic factors contributing to breakthrough HE
- Methods: This randomized, double-blind, placebo-controlled trial evaluated rifaximin 550 mg twice daily for 6 months in patients with a history of HE. Patients with cirrhosis and who had ≥ 2 episodes of HE (Conn score ≥ 2) within 6 months prior to screening and were currently in remission (Conn score = 0 or 1) were enrolled. Continued therapy with lactulose was permitted.
- The most influential prognostic factors for maintenance of remission in this covariate analysis were **age ($p=0.022$), baseline MELD score ($p=0.0005$)**.
- Conclusions: Rifaximin at a dose of 1100 mg/d demonstrates a highly significant protective effect (59% risk reduction) in preventing HE breakthrough during the 6-month treatment period after controlling for influential prognostic factors.

Rifaximin Reduces the Risk of Hospitalizations in Patients with Previous Episodes of Hepatic Encephalopathy:

Results from a Phase 3 Placebo-Controlled Trial

Guy Neff, Carroll B. Leevy, Todd Frederick, Kunal Merchant, Shirley Huang, Audrey L. Shaw, William P. Forbes

- Methods: randomized, double-blind, placebo-controlled trial evaluated rifaximin 550 mg twice daily for 6 months
- Results: A total of 299 patients were randomized to either rifaximin (n=140) or placebo (n=159). Demographics and baseline characteristics were similar between the groups.
- Rifaximin significantly reduced the risk of an HE-related hospitalization by 48% compared to placebo (hazard ratio=0.521; 95% confidence interval, 0.313-0.868; p=0.01).
- At 6 months the percentage of patients on rifaximin who had been hospitalized for reasons related to HE was significantly less than placebo (16% vs. 26%, respectively; p=0.04)

Summary

- Hepatitis C therapy is evolving rapidly
 - New molecules
 - New side effects
 - Resistance

- Hepatitis B is stagnant
 - No novel therapies
 - Debate about who to treat, who not to
 - Interferon is attempting a comeback

- Hepatic Encephalopathy
 - Rifaximin may offer a less messy alternative to lactulose