SILEN-C1: Early Antiviral Activity and Safety of BI 201335 Combined with Peginterferon alfa-2a and Ribavirin in Treatment-naïve Patients with Chronic Genotype 1 HCV infection

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On behalf of the SILEN-C1 study group

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I have financial relationships within the last 12 months relevant to my presentation with: Boehringer Ingelheim Pharmaceuticals. The terms of this arrangement are being managed by the Johns Hopkins University in accordance with its conflict of interest policies

AND

My presentation does include discussion of off-label or investigational use:

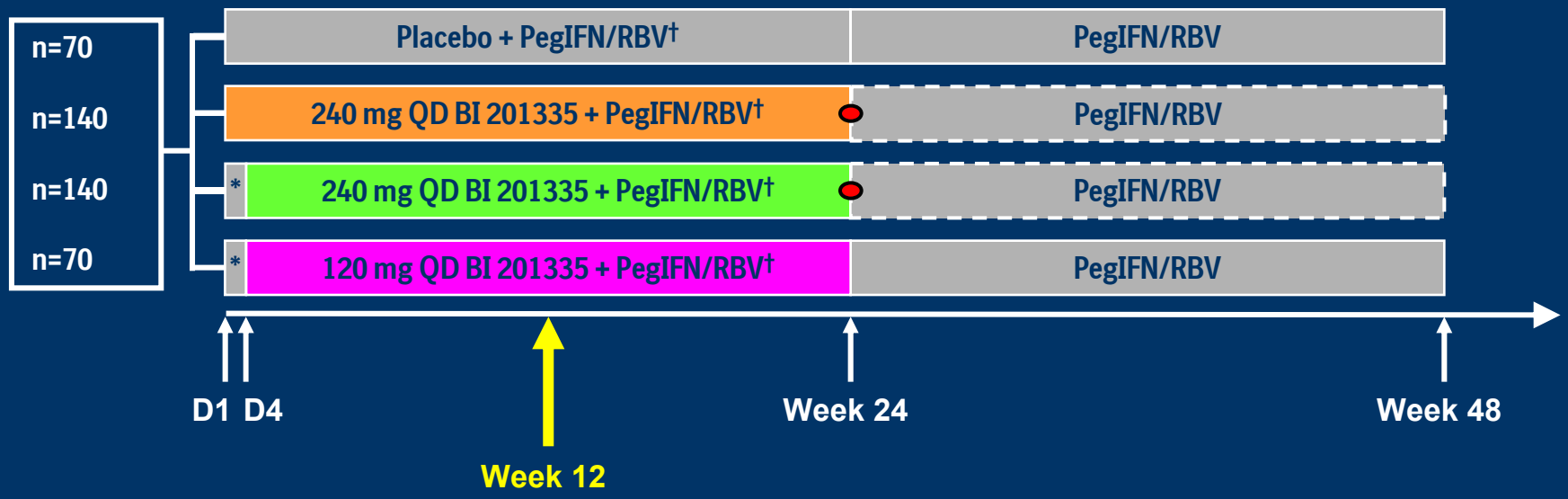
BI 201335

Peginterferon alfa-2a

Ribavirin

SILEN-C1 study

Phase 2, multicenter, randomized, double-blind, placebo-controlled study in treatment-naïve, HCV genotype 1-infected patients (n=420)



Protocol-defined interim analysis

*3-day lead-in period of peginterferon alfa-2a (PegIFN; 180 µg/week) plus ribavirin (RBV; weight-based 1000 mg or 1200 mg daily)

†BI 201335 with 240 mg or 480 mg loading dose at Day 1

● Re-randomization 1:1 of patients with extended RVR to 24 vs 48 weeks of PegIFN plus RBV

Main inclusion criteria

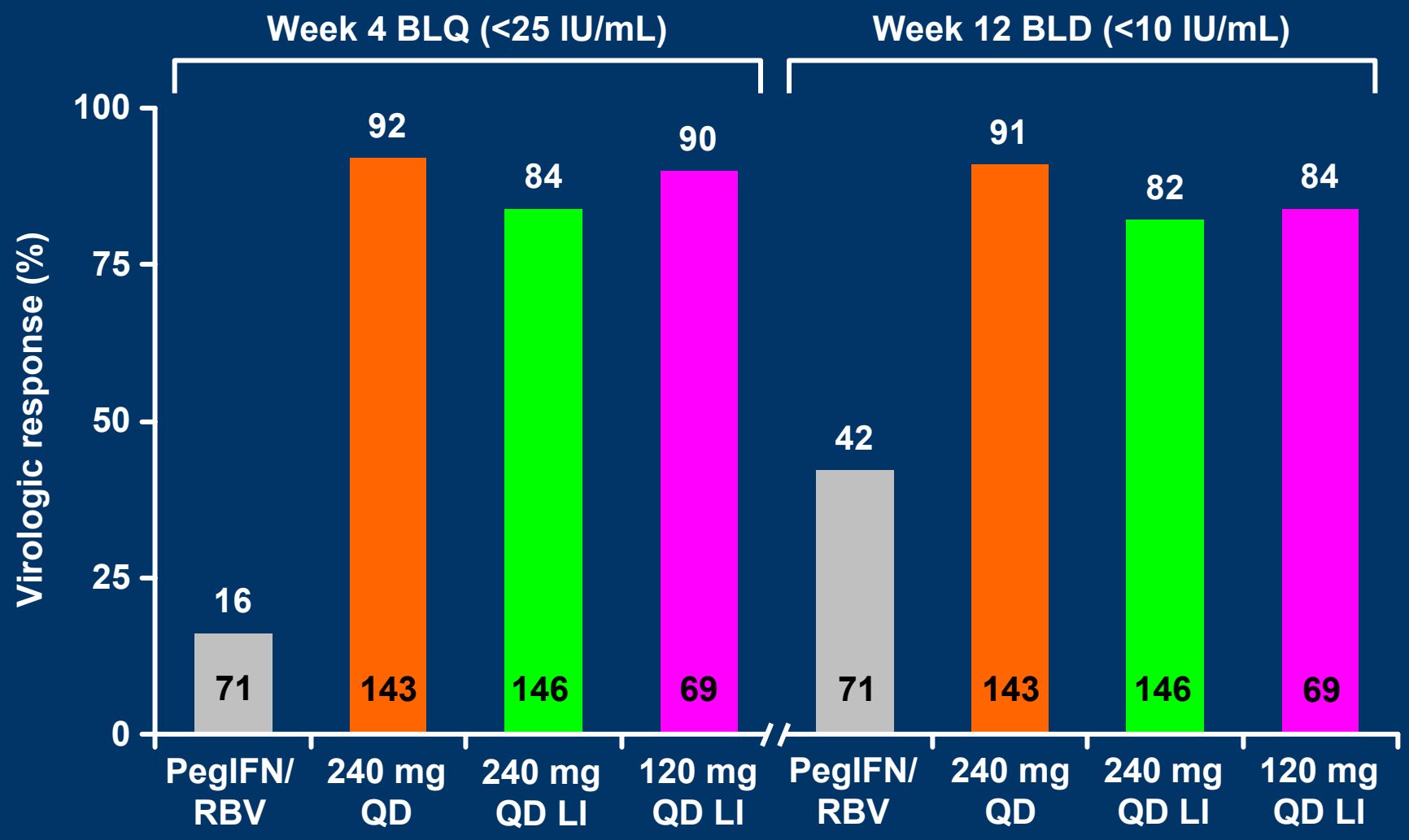
- Age 18 to 65 years
- Chronic hepatitis C infection of genotype 1 confirmed by genotypic testing at screening
- Therapy-naïve to interferon and/or ribavirin for acute or chronic hepatitis C infection
- HCV RNA ≥100,000 IU/mL at screening
- Liver biopsy within 2 years without evidence of cirrhosis

Baseline characteristics and demographics

	PegIFN/RBV	240 mg QD	240 mg QD LI	120 mg QD LI
Total treated (n)	71	146	143	69
Sex, n (%)				
Male	41 (57.7)	79 (54.1)	74 (51.7)	40 (58.0)
Female	30 (42.3)	67 (45.9)	69 (48.3)	29 (42.0)
Race, n (%)				
Asian	8 (11.3)	17 (11.6)	21 (14.7)	9 (13.0)
Black	4 (5.6)	4 (2.7)	1 (0.7)	1 (1.4)
White	57 (80.3)	122 (83.6)	119 (83.2)	58 (84.1)
Other	2 (2.8)	3 (2.1)	2 (1.4)	1 (1.4)
Baseline HCV RNA (log_{10})				
Mean	6.42	6.40	6.45	6.21
SD	0.55	0.60	0.63	0.63
Genotype, n (%)				
1	8 (11.3)	24 (16.4)	21 (14.7)	8 (11.6)
1a	26 (36.6)	40 (27.4)	50 (35.0)	15 (21.7)
1b	37 (52.1)	78 (53.4)	72 (50.3)	45 (65.2)
Age				
Mean	46	46	45	46
SD	10.9	10.5	10.2	10.9
BMI				
Mean	26	26	26	26
SD	5.6	4.6	4.5	4.0

LI = 3-day lead-in; BMI = body mass index

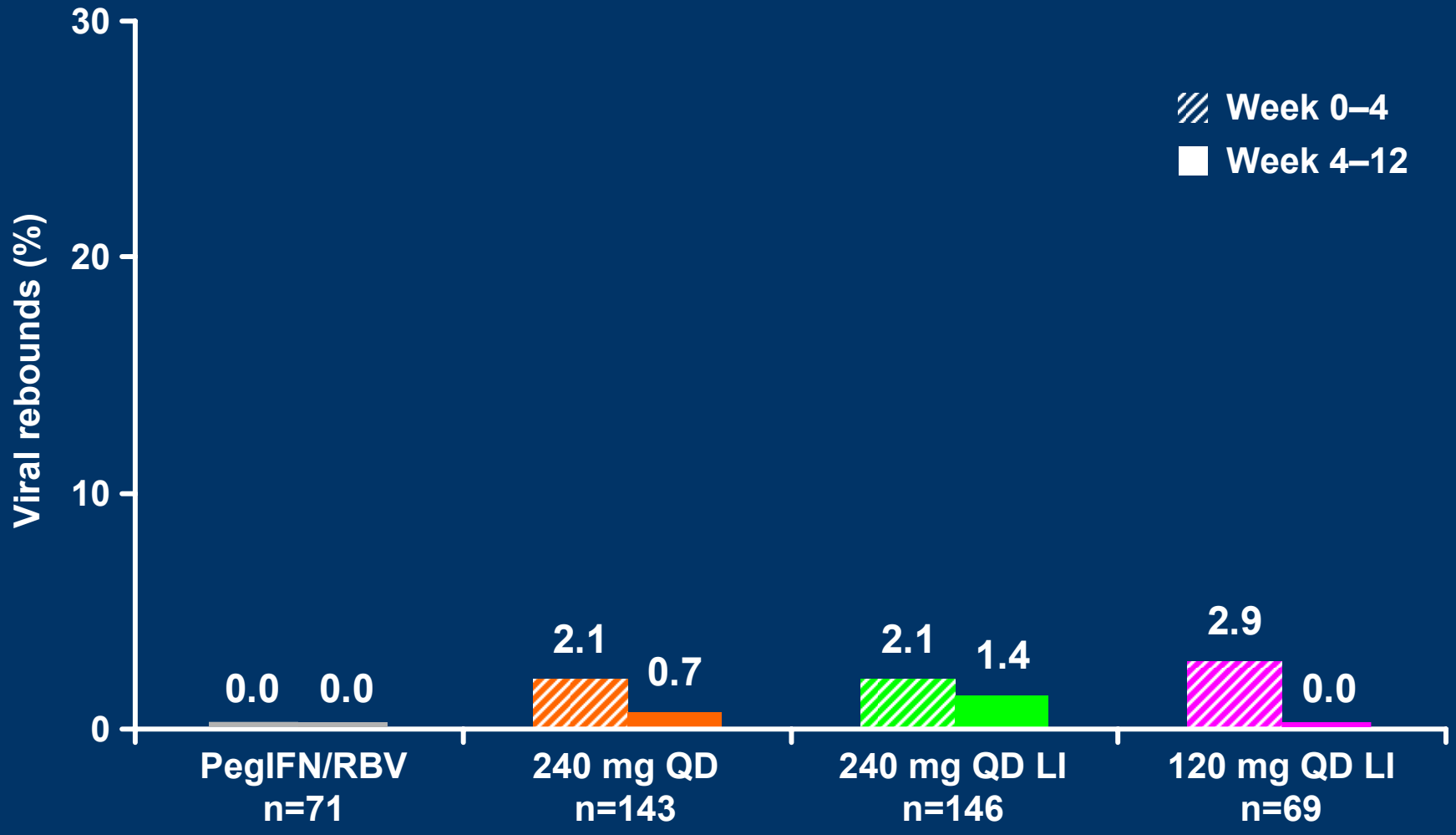
Protocol-defined extended virologic response



BLQ = below limit of quantification; BLD = below limit of detection; LI = 3-day lead-in

Virologic rebound

Virologic rebound defined as ≥1 $\log_{10}$ increase from nadir HCV RNA



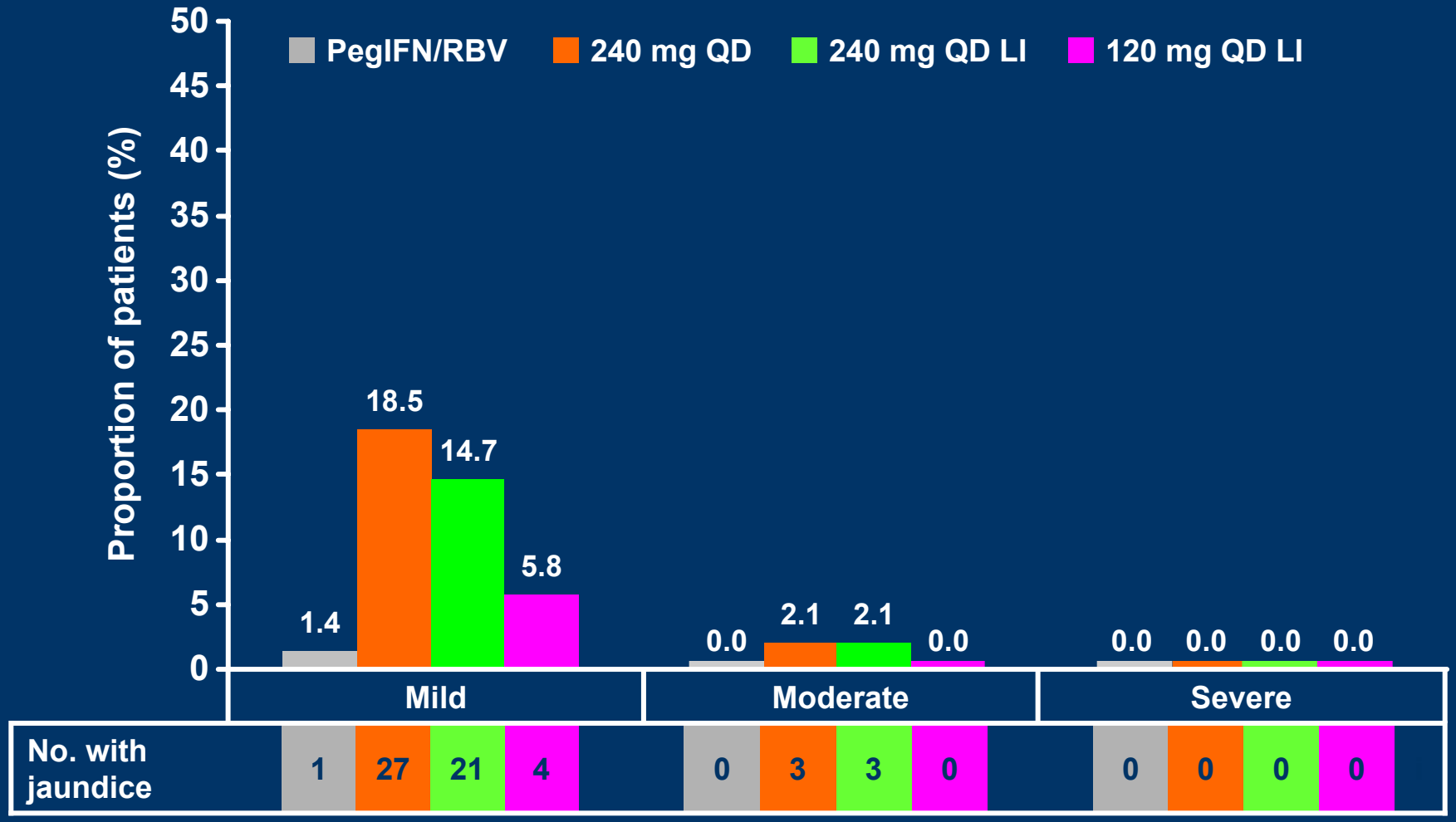
LI = 3-day lead-in

Adverse events: most frequent

AEs	PegIFN/RBV n (%)	240 mg QD n (%)	240 mg QD LI n (%)	120 mg QD LI n (%)
Influenza-like illness	29 (40.8)	50 (34.2)	45 (31.5)	23 (33.3)
Fatigue	22 (31.0)	37 (25.3)	34 (23.8)	15 (21.7)
Insomnia	17 (23.9)	22 (15.1)	18 (12.6)	11 (15.9)
Anemia	11 (15.5)	12 (8.2)	11 (7.7)	8 (11.6)
Neutropenia	6 (8.5)	6 (4.1)	9 (6.3)	6 (8.7)
Headache	23 (32.4)	49 (33.6)	43 (30.1)	21 (30.4)
Nausea	13 (18.3)	60 (41.1)	57 (39.9)	15 (21.7)
Diarrhea	10 (14.1)	38 (26.0)	40 (28.0)	8 (11.6)
Pruritus	7 (9.9)	44 (30.1)	40 (28.0)	18 (26.1)
Jaundice – all grades	1 (1.4)	30 (21.0)	24 (16.4)	4 (5.8)
Rash – all grades	9 (12.7)	38 (26.6)	48 (32.9)	14 (20.3)

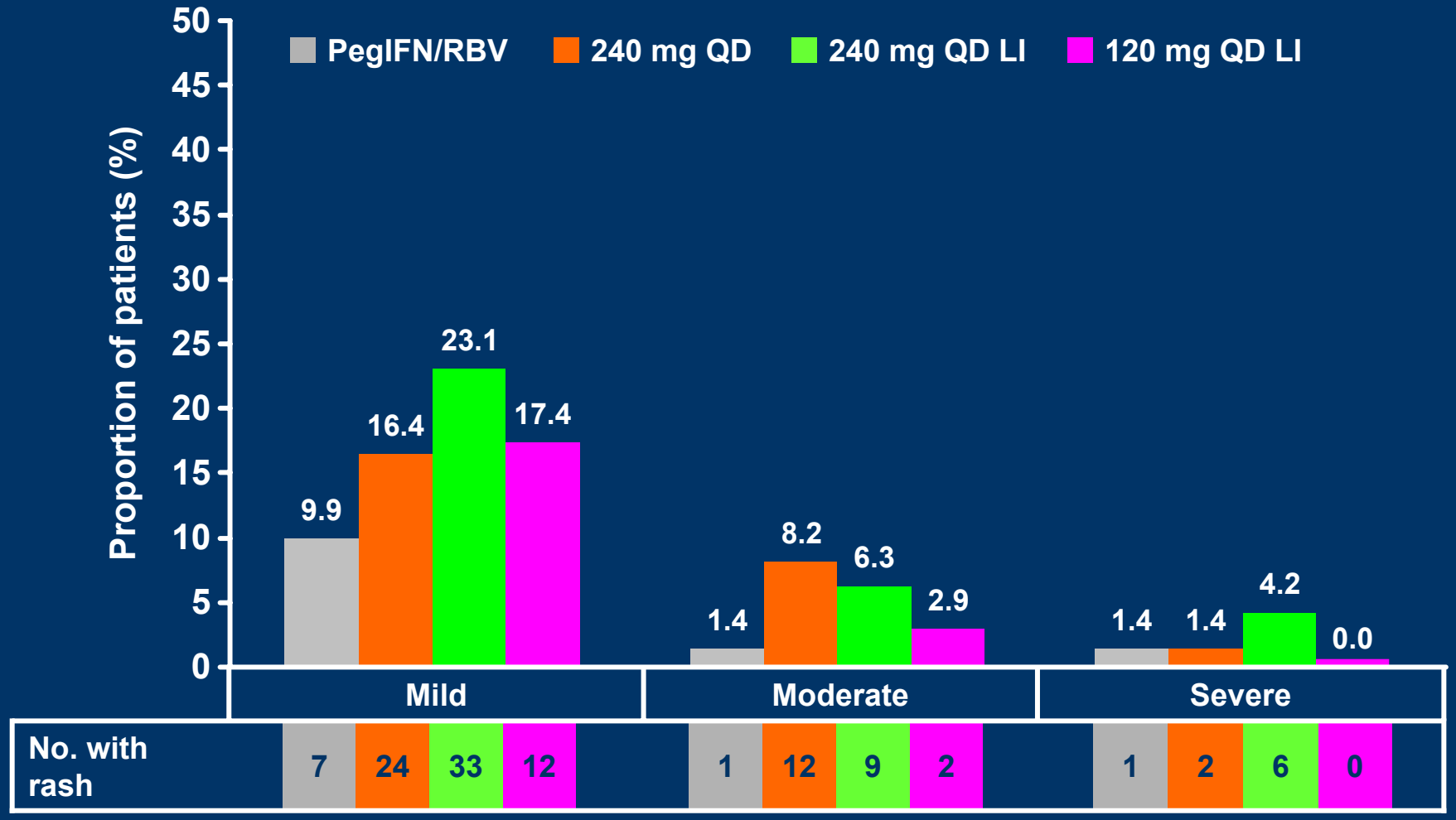
AEs = adverse events; LI = 3-day lead-in

Severity of AEs: jaundice*



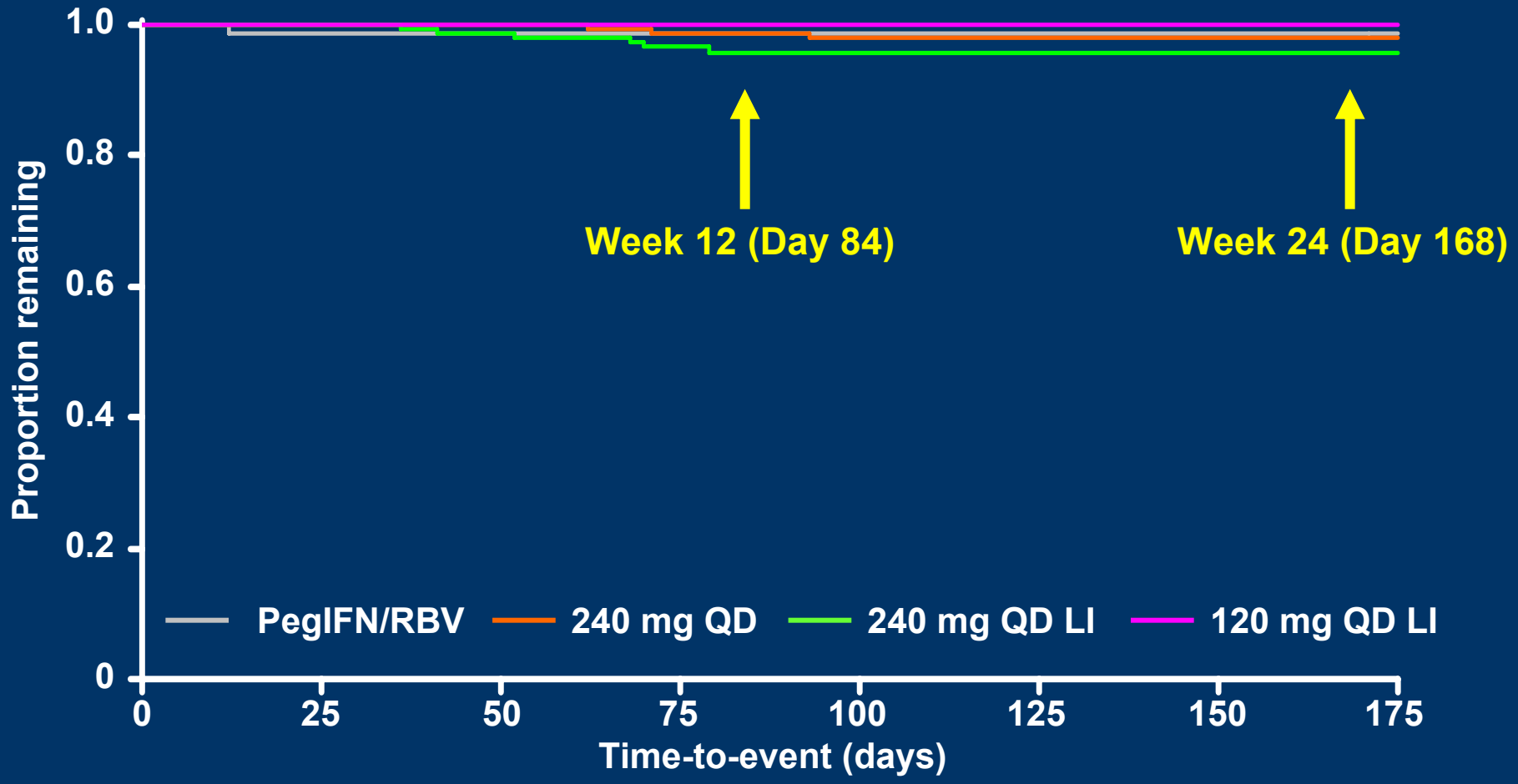
*3 cases of jaundice where the intensity is missing
LI = 3-day lead-in

Severity of AEs: rash*



*Data derived from preferred terms for rash; LI = 3-day lead-in
No Stevens-Johnson syndrome or mucosal detachment observed

Kaplan-Meier estimated probability risk of severe rash



AEs: summary

	PegIFN/RBV n (%)	240 mg QD n (%)	240 mg QD LI n (%)	120 mg QD LI n (%)
All patients (n)	71	146	143	69
With any AE	67 (94.4)	143 (97.9)	138 (96.5)	66 (95.7)
With drug-related AE*	64 (90.1)	140 (95.9)	135 (94.4)	60 (87.0)
With severe AEs	2 (2.8)	10 (6.8)	19 (13.3)	5 (7.2)
With SAE	0 (0.0)	4 (2.7)	8 (5.6)	2 (2.9)
Discontinuations for AEs	0 (0.0)	7 (4.8)	13 (9.1)	2 (2.9)
Discontinuations for				
Rash	0 (0.0)	1 (0.7)	4 (2.8)	0 (0.0)
Jaundice	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)

*Investigator-defined
AE = adverse event; SAE = serious adverse event; LI = 3-day lead-in

Laboratory findings

- ALT observed to be reduced to a greater extent in the BI 201335-treated groups compared with PegIFN/RBV alone
- Total bilirubin increased in a dose-dependent manner with BI 201335
  - Median change from baseline to Week 12: 0.5–1.9 mg/dL
  - All predominantly indirect bilirubin
- Hematological parameters similar between treatment groups

Discussion

- Virologic response
  - 120 mg QD and 240 mg QD BI 201335 in combination with PegIFN/RBV caused a rapid and steep decline in HCV RNA
  - 80–90% of patients achieve HCV RNA <10 IU/mL after 12 weeks of BI 201335 in combination with PegIFN/RBV compared to 42% treated with PegIFN/RBV alone
  - Few virologic rebounds (<3%)
- Adverse events
  - Most AEs were those commonly related to PegIFN/RBV therapy
  - Mild-to-moderate jaundice and rash are the main BI 201335-related adverse events
  - Severe rash: 2.2% vs 1.4% (BI 201335+PegIFN/RBV vs PegIFN/RBV)
  - Rash discontinuation: 1.4% vs 0% (BI 201335+PegIFN/RBV vs PegIFN/RBV)

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