

Early Clinical Experience with BI 201335, a Novel Hepatitis C Virus NS3-NS4A Serine Protease Inhibitor

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I have a financial relationship within the last 12 months relevant to my presentation with:

*Abbott, Astra Zeneca, Boehringer-Ingelheim, Human Genome Sciences, Globeimmune,
Pharmasset, Roche, Vertex*

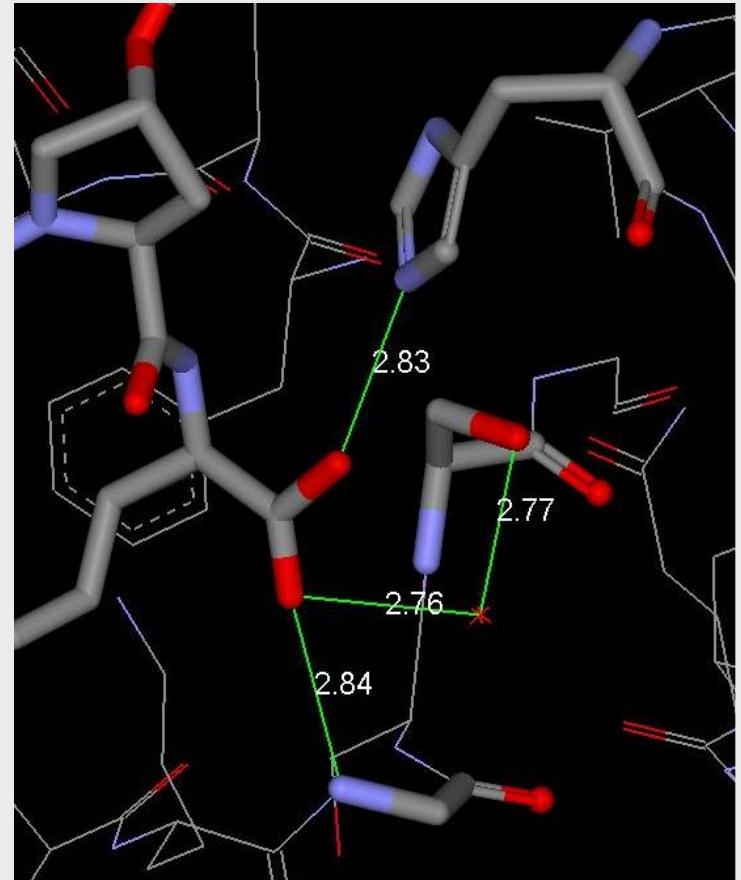
AND

My presentation includes discussion of an investigational agent
BI 201335

Background

■ BI 201335

- Orally bioavailable, once-daily administration
- Structurally optimized for HCV genotype-1 infection
- Potent and specific NS3/NS4A serine protease inhibitor
- Similar activity in enzymatic and cellular assays (EC_{50} 3–6 nM)



BI 201335 bound to active site.
C-terminal noncovalent binding group
imparts specificity and contributes to
potency

Phase 1b: dose range finding

- 1220.2: multinational dose range finding trial in HCV genotype-1 patients
 - Part 1: treatment-naïve patients (n=34)
 - Part 2: treatment-experienced patients (n=19)
 - Part 3: treatment-experienced with compensated liver cirrhosis (n=13)

■ Results

BI 201335 QD	Maximum HCV RNA reduction from baseline (BL), median (min, max), log ₁₀ IU/mL						
	Placebo	20 mg	48 mg	120 mg	240 mg	240 mg QD	240 mg BID
Part 1: monotherapy TN (BL–D14)	0.04 (–0.2, 0.3)	–2.9 (–3.7, –1.1)	–3.5 (–3.8, –2.8)	–3.7 (–4.0, –3.3)	–4.0 (–4.8, –3.6)	–	–
Part 2: triple therapy TE (BL–D28)	–	–	–5.0 (–5.9, –3.4)	–5.2 (–6.0, –3.9)	–5.3 (–6.1, –4.7)	–	–
Part 3: triple therapy TE cirrhotic (BL–D28)	–	–	–	–	–	–4.8 (–5.6, –4.6)	–5.4 (–5.5, –3.9)

BL = baseline; TN = treatment-naïve; TE = treatment-experienced

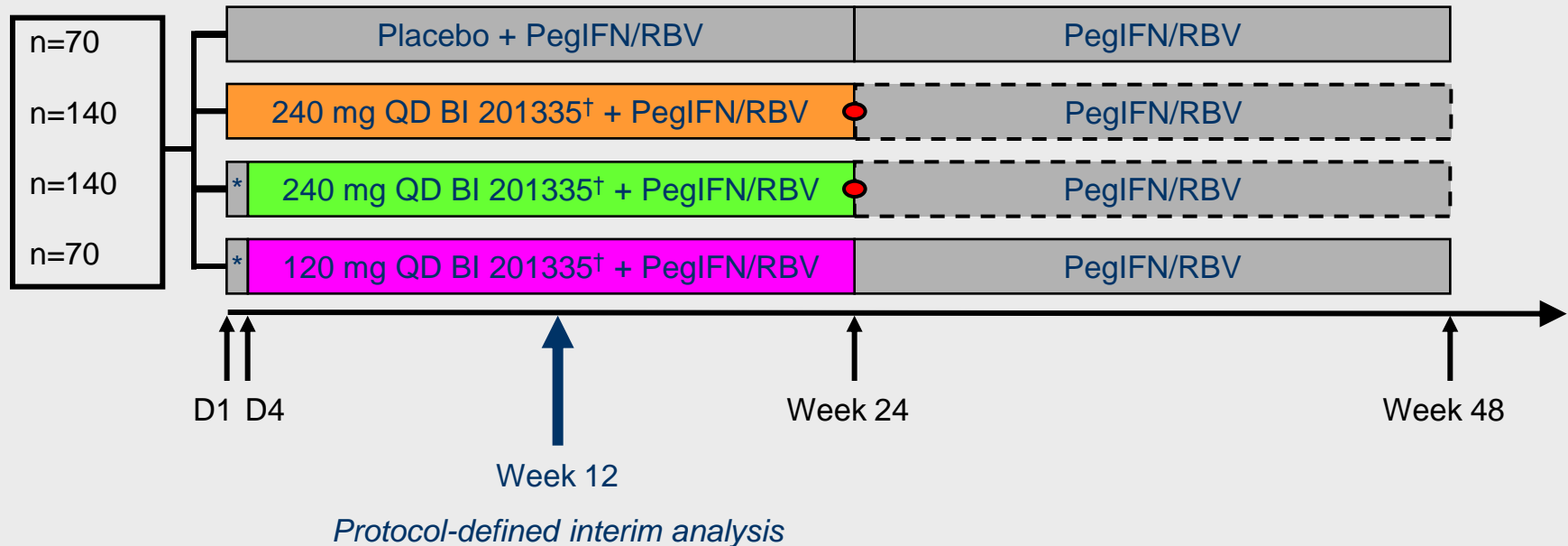
■ Conclusions

- BI 201335 produced a steep and rapid decline in HCV RNA in treatment-naïve and treatment-experienced patients, as well as those with compensated liver cirrhosis
- Adverse events were mostly mild-to-moderate and typical of PegIFN/RBV
- Changes in bilirubin were observed with increasing doses of BI 201335
 - At higher doses, an increased incidence of unconjugated hyperbilirubinemia was observed

1. Manns MP, et al. AASLD, San Francisco, CA, USA; 2008. Abstract 1849
2. Manns MP, et al. AASLD, San Francisco, CA, USA; 2008. Abstract 1882
3. Pol S, et al. AASLD, Boston, MA, USA; 2009. Abstract LB16

Phase 2: SILEN-C1 study

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



*3-day lead-in period of peginterferon alfa-2a (PegIFN; 180 µg/week) plus ribavirin (RBV; weight-based 1,000 mg or 1,200 mg daily)

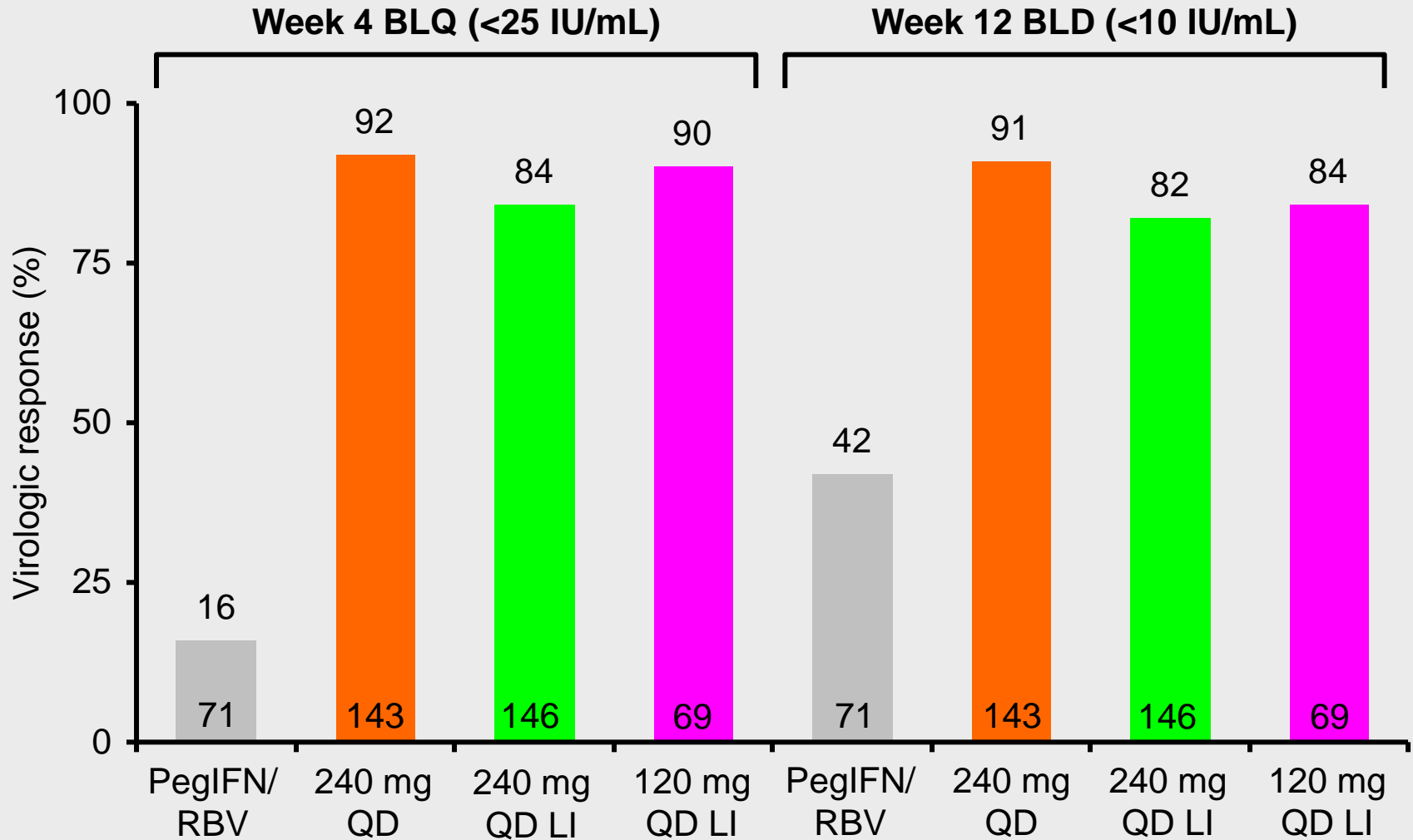
[†]BI 201335 with 240 mg or 480 mg loading dose at Day 1

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

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

Protocol-defined extended virologic response

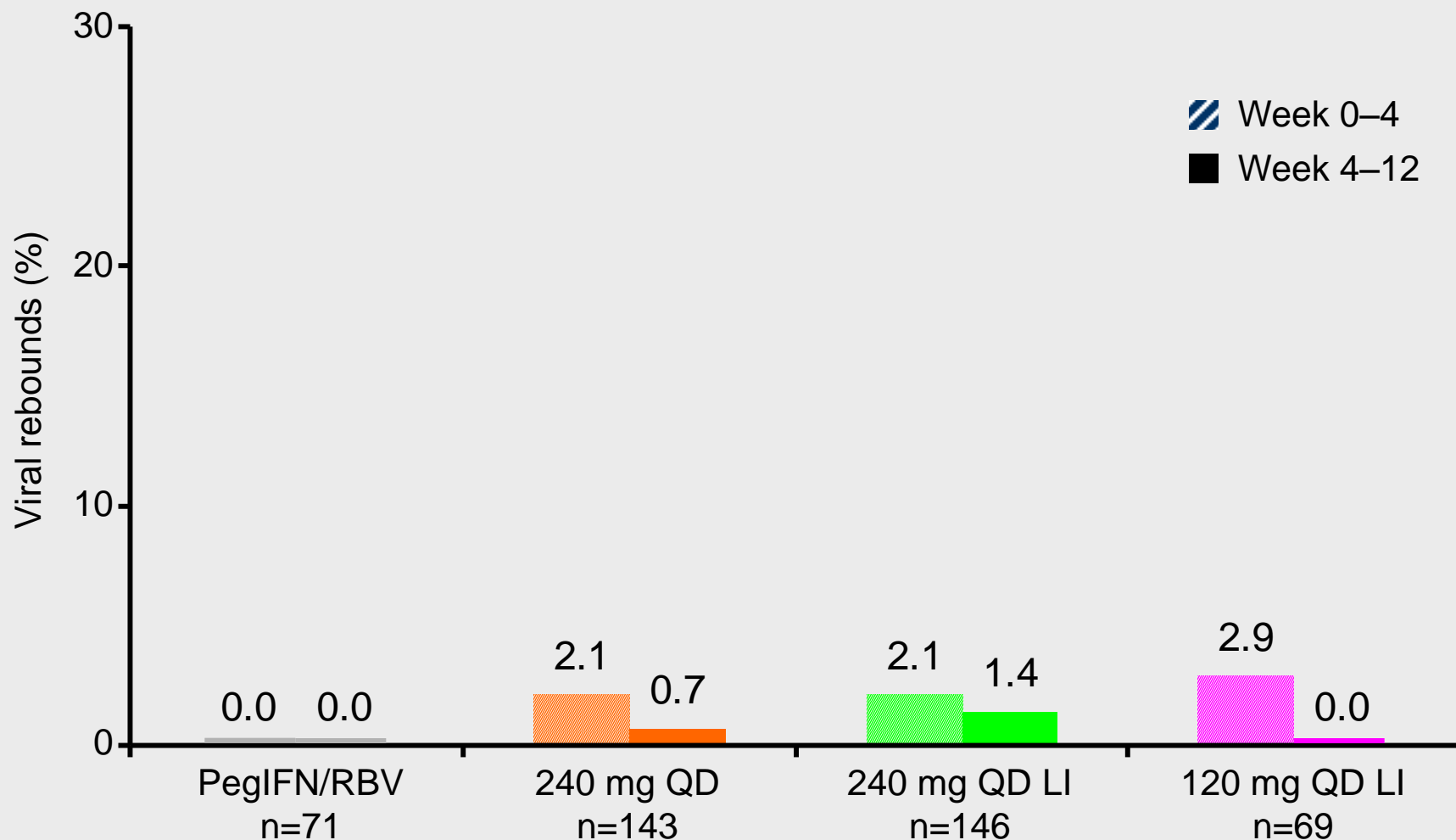


Plasma HCV RNA levels were measured using the Roche COBAS TaqMan®
BLQ = below limit of quantification; BLD = below limit of detection

Sulkowski MS, et al. AASLD, Boston, MA, USA; 2009. Abstract LB3

Virologic rebound

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



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)

■ 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)

Laboratory findings

- ALT 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 (unconjugated) bilirubin not associated with hemolysis, elevation of liver enzymes or other signs of liver toxicity
 - inhibition of UGT 1A1 by BI 201335 likely to play a role in observed unconjugated hyperbilirubinemia
- Hematological parameters similar between treatment groups

Summary

■ Adverse events

- Most AEs were those commonly related to PegIFN/RBV therapy
- Dose-related jaundice and rash are the main BI 201335-related AEs

■ 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 with 42% treated with PegIFN/RBV alone
- Few virologic rebounds (<3%)

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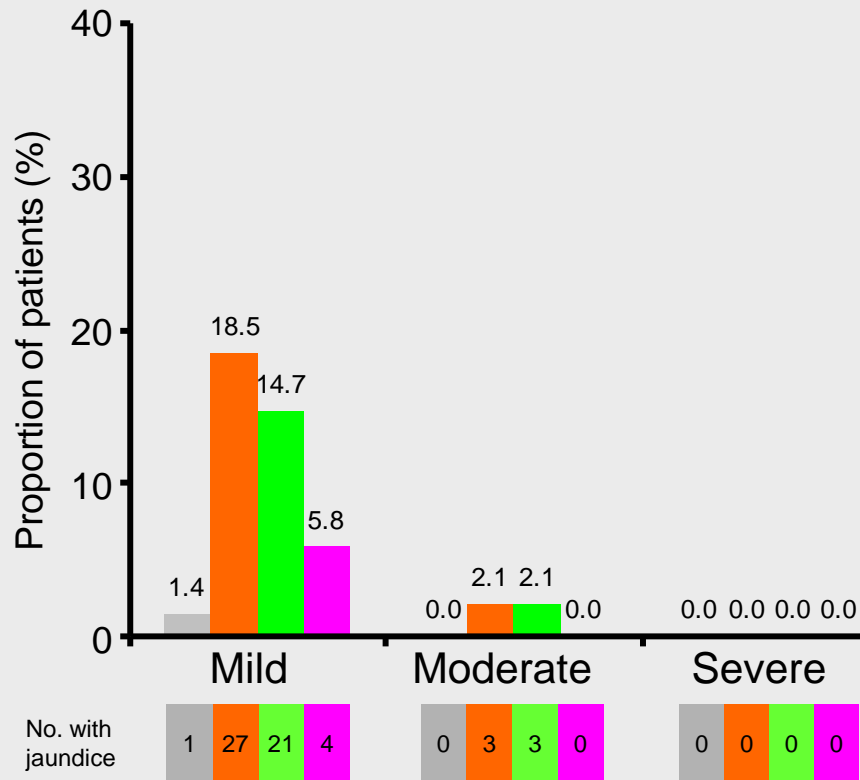
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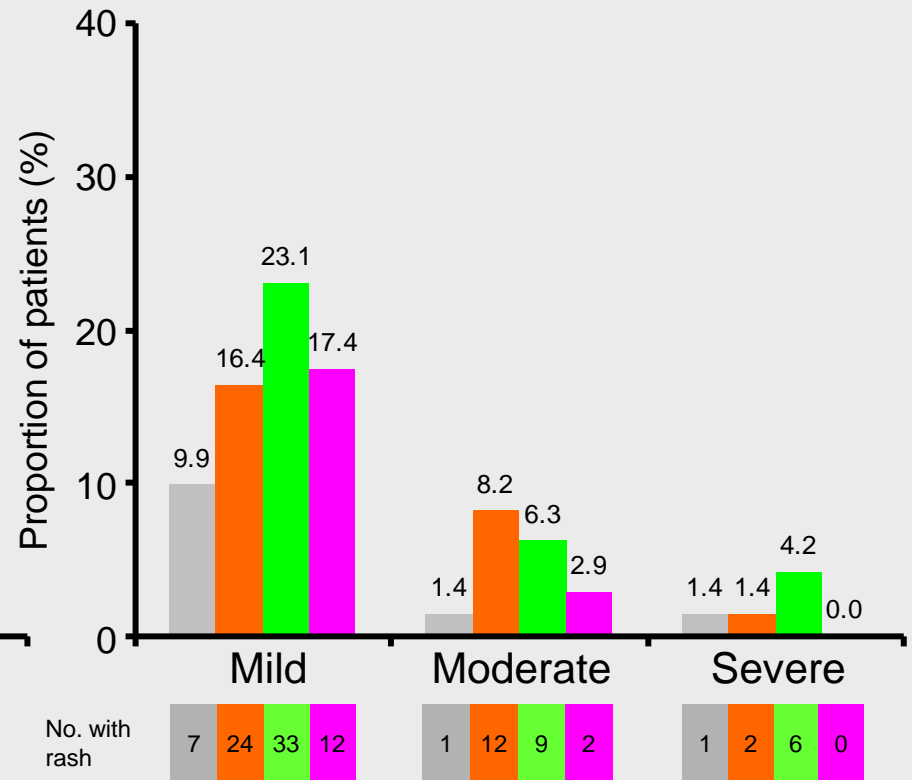
Thank you

Severity of adverse events

Jaundice*



Rash†



PegIFN/RBV
 240 mg QD
 240 mg QD LI
 120 mg QD LI

*3 cases of jaundice where the intensity is missing

†Data derived from preferred terms for rash

No Stevens-Johnson syndrome or mucosal detachment observed