A CONTINUING MEDICAL EDUCATION ACTIVITY

THE 46TH ANNUAL MEETING OF THE EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

Online Expert Poster Review and Discussion

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC.

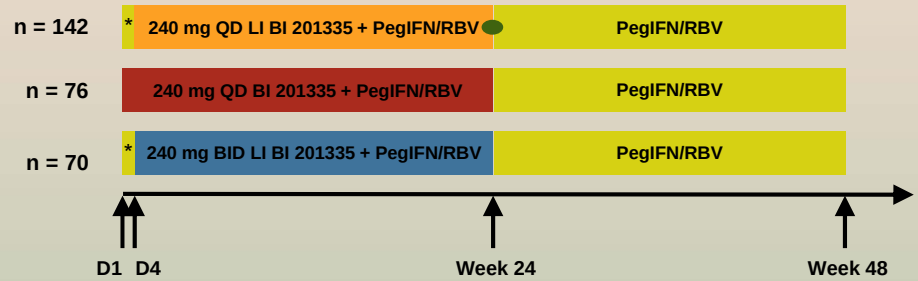
SILEN-C2: Sustained Virologic Response (SVR) and Safety of BI201335 Combined with Peginterferon Alfa-2a and Ribavirin (P/R) in Chronic HCV Genotype-1 Patients with Non-response To P/R

M.S. Sulkowski, M. Bourliere, J.-P. Bronowicki, A. Streinu-Cercel, L. Preotescu, T. Asselah, J.-M. Pawlotsky, S. Shafran, S. Pol, F.A. Caruntu, S. Mauss, D. Larrey, C. Häfner, Y. Datsenko, J.O. Stern, R. Kubiak, W. Böcher, G. Steinmann

46th EASL Congress, Berlin, Germany
March 30-April 3, 2011
Abstract 66

SILEN-C2 trial

- Double-blind, placebo-controlled, phase IIb study in HCV genotype-1 (GT-1) patients with nonresponse to previous PegIFN/RBV



*3-day lead-in period (LI) of PegIFN alfa 2a (180 µg/week) plus ribavirin (1,000 mg or 1,200 mg/day);
Re-randomisation 1:1 of patients with eRVR (extended rapid virological response) to 24 versus 48 weeks of PegIFN/RBV
QD, once daily; BID, twice daily

Main Inclusion Criteria

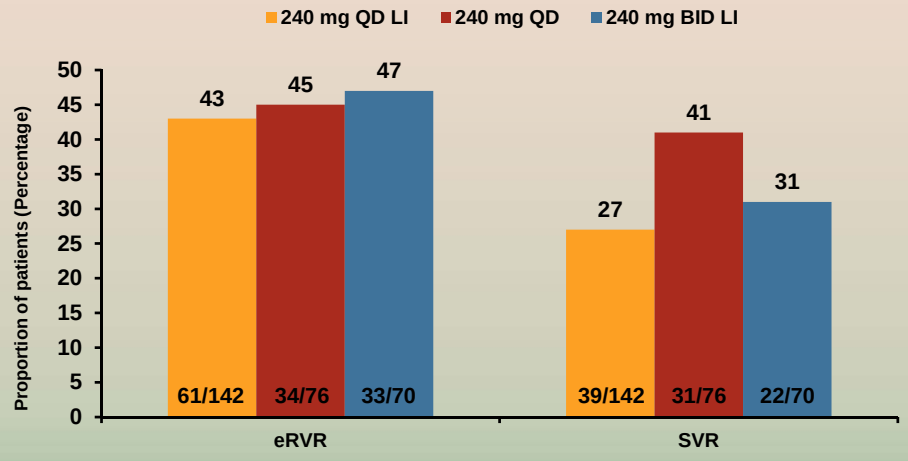
- Age 18 to 65 years
- Chronic hepatitis C GT-1 infection
- Confirmed nonresponse during previous PegIFN/RBV treatment
  - ≥12 weeks of an approved dose of PegIFN/RBV
  - Null response: <1 log10 maximum HCV RNA reduction any time during treatment
  - Partial response: >1 log10 maximum HCV RNA reduction, but never undetectable (with a sensitive assay)
  - Relapsers were excluded
- HCV RNA ≥100,000 IU/mL at screening
- Liver biopsy within 2 years without evidence of cirrhosis

Baseline characteristics

	240 mg QD LI n=142	240 mg QD n=76	240 mg BID LI n=70
Mean age (years)	48.7	49.6	50.1
Male gender (%)	71.1	65.8	58.6
Ethnicity (%)			
White	92.3	84.2	92.9
Black	3.5	9.2	4.3
Asian	4.2	6.6	2.9
Mean HCV RNA (log_{10})	6.60	6.56	6.55
Genotype[a] (%)			
1a	54.9	55.3	38.6
1b	43.0	43.4	60.0
1, other subtypes[b]	2.1	1.3	1.4
Prior response to PegIFN/RBV (%)			
Null response	40.1	52.6	54.3
Partial response	38.0	34.2	34.3
Nonresponse	9.2	3.9	7.1
Others	12.7	9.2	4.3

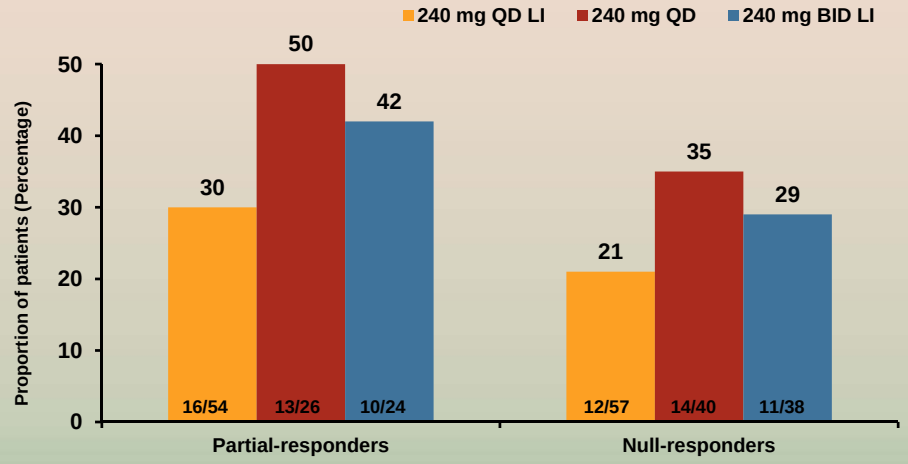
[a]Based on NS3/4A sequencing; [b]Other genotypes were 1C (n=1), 1D (n=1) and 1G (n=1). 1 patient was GT-1 but subgenotype could not be determined

Virological response



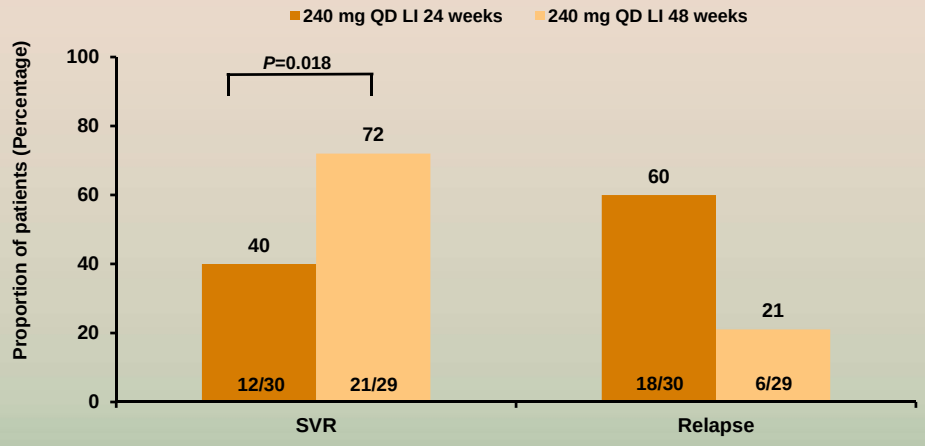
eRVR: HCV RNA < 25 IU/mL at Week 4 and undetected at Weeks 8 to 20

SVR in partial- and null-responders



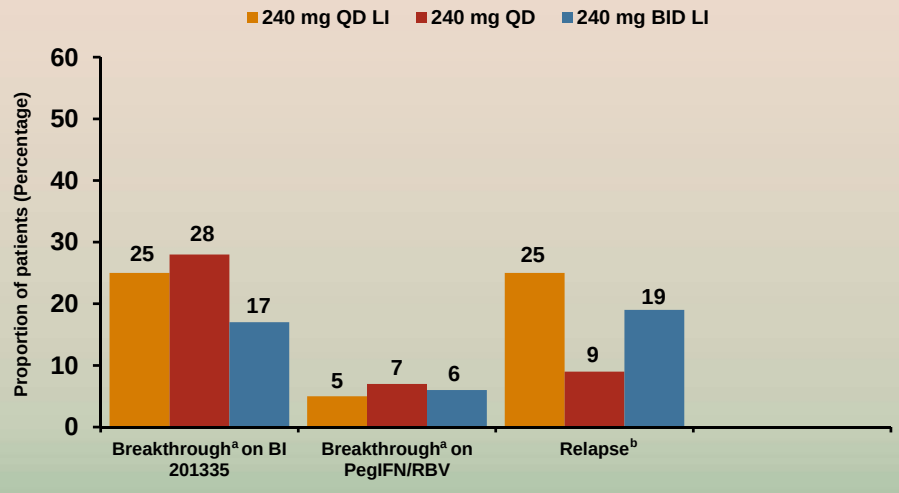
Null response, <1 log10 maximum HCV RNA reduction any time during treatment;
Partial response, > 1 log10 maximum HCV RNA reduction, but never undetectable (with a sensitive assay)

SVR and relapse in eRVR patients by duration of PegIFN/RBV



Relapse: rebound from undetectable at end of all treatment

Virological failures



[A] ≥1 $\log_{10}$ rebound from nadir, or rebound to ≥ 100 IU/mL if nadir < lower limit of detection (LLOD) on treatment, confirmed in a second sample
[B] Rebound after end of all treatment from nadir < LLOD after end of treatment

Adverse events[a]

	240 mg QD LI (%)	240 mg QD (%)	240 mg BID LI (%)
All patients (n[b])	141	76	69
Rash[c]	34.0	27.6	42.0
Mild	27.7	23.7	15.9
Moderate	5.7	2.6	20.3
Severe	0.7	1.3	5.8
Jaundice	19.0	21.1	41.4
Severe	0	0	0
Nausea	48.2	52.6	63.8
Diarrhea	31.9	31.6	39.1
Vomiting	17.0	22.4	31.9

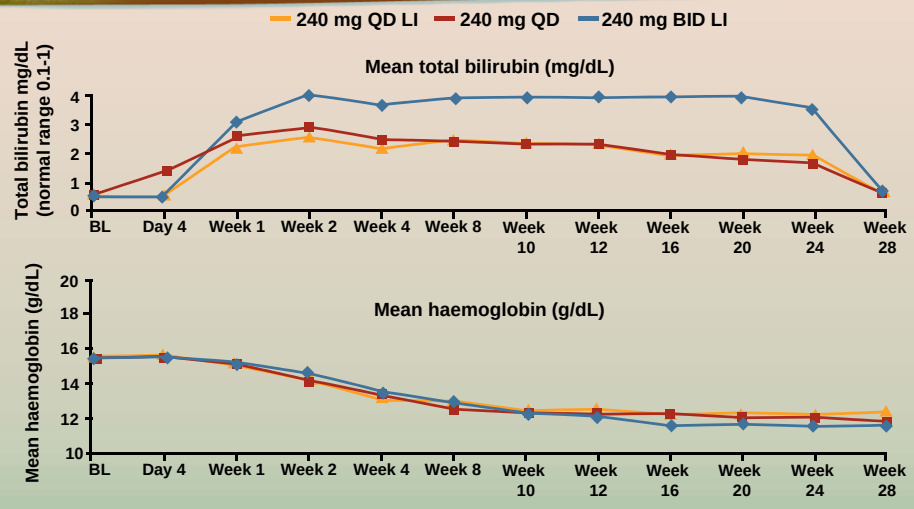
[a]Adverse events > 10% compared with PegIFN/RBV
[b]Number quoted is according to given treatment
[c]No cases of Stevens-Johnson syndrome, erythema multiforme or drug rash with eosinophilia and systemic symptoms

Adverse events: overall summary

	240 mg QD LI (%)	240 mg QD (%)	240 mg BID LI (%)
All patients (n[a])	141	76	69
With severe adverse events	14.2	14.5	27.5
Fatalities	0	0	0
Discontinuations for adverse events	5.7	3.9	23.2
Discontinuations for			
Rash	0	1.3	14.5
Photosensitivity	0	0	1.4
Jaundice	0.7	0	1.4
Others[b]	5.0	2.6	5.8

[a]Number quoted is according to given treatment
[b]Other discontinuations mainly due to general disorders and administration site conditions, gastrointestinal and others

Effect of BI 201335 on bilirubin and haemoglobin



BL, baseline

Discussion and conclusion

- Virological response
  - robust SVR rates up to 41% at 240 mg QD
    - dose selected for phase III
  - response-guided therapy was not effective for nonresponsive patients achieving eRVR
  - 3-day PegIFN/RBV lead-in did not increase SVR
- Safety and tolerability
  - most adverse events were those commonly related to PegIFN/RBV therapy
    - no excess effect on haemoglobin
  - mild-to-moderate jaundice and rash are the main BI 201335-related adverse events and are dose-dependent
    - jaundice is due to isolated indirect hyperbilirubinaemia
- **In treatment-experienced patients, BI 201335 240 mg QD appears to offer the best safety/efficacy balance**
  - **phase III trial in preparation**