

An Interim Analysis of the Canadian POWeR Program (Pegatron Prospective Optimal Weight-Based Dosing Response): Consistent SVR Rates Across All Weight Categories

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Background

- Pegylated interferon (PEG-IFN) alpha-based therapy in combination with ribavirin (RBV) is the current gold standard of treatment for patients with chronic hepatitis C.
- Numerous studies have shown an inverse relationship between body weight and virologic response when PEG-IFN alpha alone or in combination with RBV are administered as flat doses.^{1,3}
- A recent study showed that a weight-based approach to PEG-IFN alpha and RBV dosing may improve treatment outcomes in patients with higher body weight without compromising the responses of patients with lower body weight.⁴
- The WIN-R study, a large community-based trial conducted in the United States, showed a significantly improved response in patients receiving weight-based PEG-IFN alpha-2b (PegIntron[®]) in combination with weight-based RBV compared with those who received flat RBV dosing.⁵ Response rates were consistent across all weight categories.

Aim

The Pegatron Prospective Optimal Weight-Based Dosing Response program (POWeR) is a large, open-label, mixed community- and academic-based clinical outcomes program that evaluates the impact of baseline viral and patient factors on sustained virologic response (SVR) in patients with chronic hepatitis C who received treatment with weight-based PEG-IFN alpha-2b and weight-based RBV.

Methods

Study Design

- Open-label, prospective, community- and academic-based therapeutic outcomes study conducted in treatment-naïve patients with chronic hepatitis C.
- Patients were enrolled at 138 academic and community clinics across Canada between December 2002 and August 2005.
- Patients were treated, followed up, and managed according to current treatment guidelines and standard of care at each site, with no study-related intervention beyond collection of data.

Patients

- At baseline the following patient characteristics were recorded:
 - Body weight: <50 kg, 50 to <64 kg, 64 to <75 kg, 75 to <85 kg, ≥85 kg.
 - Hepatitis C virus (HCV) genotype (G): G1, G2, G3, or other.
 - Extent of fibrosis (METAVIR score F0-F4 determined by liver biopsy).
- PEG-IFN alpha-2b (1.5 µg/kg/wk) plus weight-based RBV (800-1200 mg/d) was given according to standard of care (for 24 weeks in G2/3 patients and for up to 48 weeks in G1 patients).^{6,7} Early in the program, a week 12 virologic assessment was introduced as a standard of care in G1 patients. G1 patients who did not have undetectable HCV RNA or at least a 2 log₁₀ drop from baseline viral load by week 12 were generally discontinued from treatment.

Efficacy Assessments

- Two separate analyses were conducted to determine response:
 - Outcomes analysis:** Patients with completed and queried case report forms, including those who discontinued for any reason, including nonresponse. In this analysis, patients who had detectable HCV RNA at end of treatment (EOT) and for whom no SVR data were available were considered *nonresponders*.
 - Completer analysis:** Study population for whom both final EOT and SVR data were available.
- EOT response was defined as undetectable HCV RNA (<50 IU/mL) after completion of therapy.
- SVR was defined as undetectable serum HCV RNA (<50 IU/mL) 24 weeks after EOT.

Statistical Analyses

- Descriptive statistics were used for the reporting of demographics and SVR rates overall, by genotype, body weight, and fibrosis level.
- Chi-square analysis was conducted to determine significance of the body weight/response relationship.

Results

Baseline Demographics

- A total of 2194 patients were enrolled in POWeR.
- Patient demographics were similar in both analyses (Table 1). Most patients had HCV G1 (~60%); 58% of these patients had high viral load at baseline (defined as >600,000 IU/mL or >2 million copies/mL according to the local laboratory).
- A sizable proportion of patients had severe fibrosis or cirrhosis (F3-F4, ~37%) and approximately 60% of patients enrolled in the program were >75 kg (165 lb), suggesting that this patient cohort would be difficult to treat.

Table 1. Patient Demographics

	Patients for Whom Data Were Available	
	Completer Analysis* (n = 1554)	Outcomes Analysis† (n = 1820)
HCV genotype, n (%)	n = 1519	n = 1779
G1	890 (58.6)	1087 (61.1)
G2	258 (17.0)	280 (15.7)
G3	349 (23.0)	384 (21.6)
Other	22 (1.4)	28 (1.6)
Weight, n (%)	n = 1545	n = 1809
<50 kg	44 (2.8)	54 (3.0)
50 to <64 kg	253 (16.4)	291 (16.1)
64 to <75 kg	336 (21.7)	394 (21.8)
75 to <85 kg	385 (24.9)	449 (24.8)
>85 kg	527 (34.1)	621 (34.3)
Fibrosis stage, n (%)	n = 853	n = 1038
F0-F2	551 (64.6)	640 (61.7)
F3-F4	302 (35.4)	398 (38.3)

Differences in the number of patients in each descriptive demographic variable represent missing data points (ie, a liver biopsy specimen was not available for all patients).

*Only includes patients for whom both EOT and SVR data were available.

†Includes all patients with completed and queried case report forms.

HCV = hepatitis C virus; EOT = end of treatment; SVR = sustained virologic response.

Overall Virologic Response and Discontinuation

- SVR was attained in 64% of patients in the completer analysis and in 55% of patients in the outcomes analysis.
- 459 (25%) of 1820 patients included in the outcomes analysis discontinued treatment prematurely (ie, did not receive a full 24 or 48 weeks of treatment) and were nonresponders in the analysis.

SVR by Body Weight and Degree of Fibrosis

- Chi-square analysis was performed comparing the lowest SVR weight class (75-85 kg) to the mean of the other weight categories. Consistent with data previously reported,^{2,5} there was no statistically significant difference in SVR rates across patient weight categories ($P = .17$) in either analysis (Figure 1, outcomes analysis shown).
- SVR rates decreased with increasing levels of hepatic fibrosis. In the patients with available biopsy data, there was an inverse relationship between SVR rates and baseline fibrosis stage. SVR rates (completers and outcomes analysis) were highest in patients with F0-F1 fibrosis (73% and 64%, respectively) and lowest in patients with F4 cirrhosis (41% and 28%, respectively).

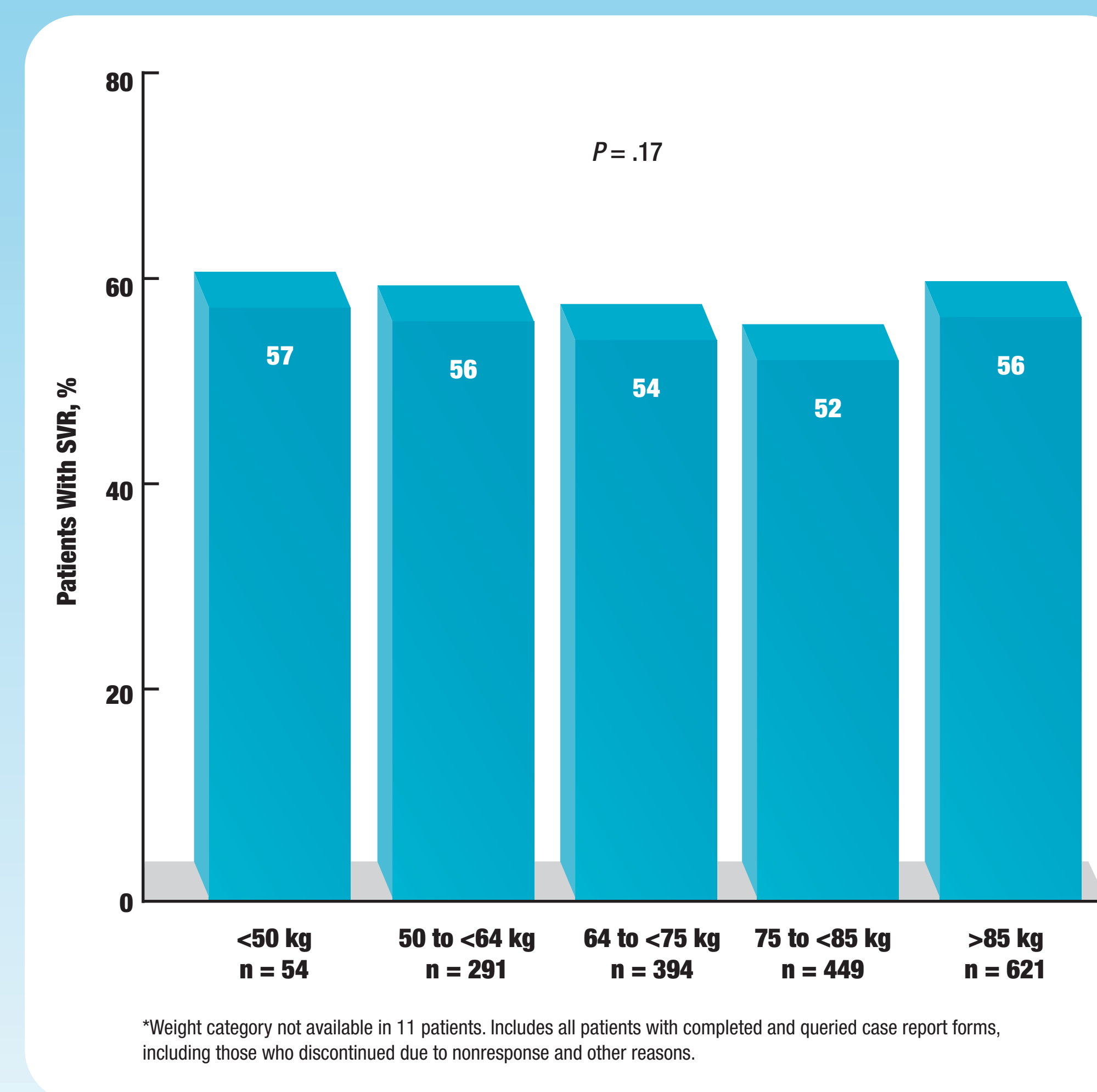


Figure 1. SVR rates stratified by body weight in the outcomes analysis* ($P = .17$)

SVR by Genotype

- Response rates for G1 patients were 52% and 42% in completer and outcomes analyses, respectively (Figure 2).
- G2 patients exhibited the highest SVR rates (87% and 80%, respectively).
- Response rates in G3 patients were 80% and 72%, respectively.

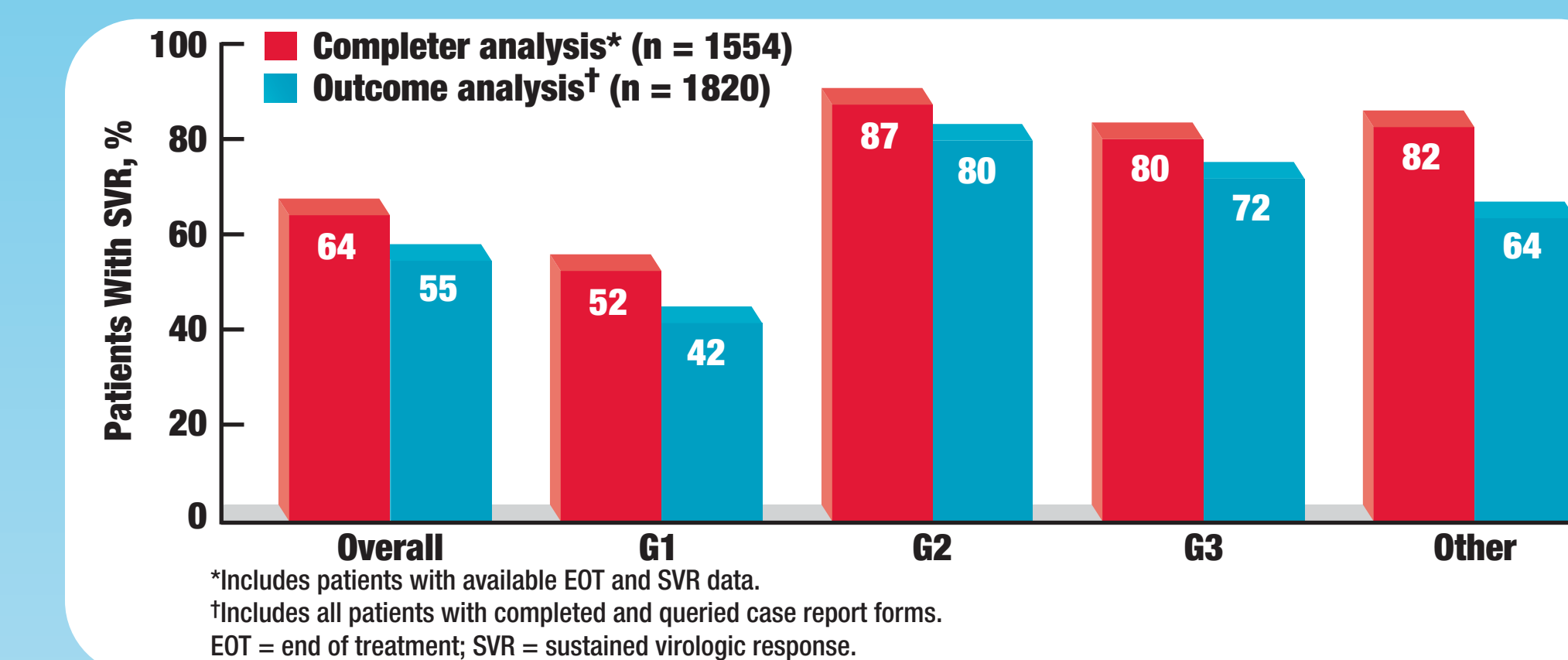


Figure 2. SVR rates stratified by HCV genotype

Relapse rates

- Recognizing the limitations of an interim analysis, relapse rates were calculated using the same patients for whom both EOT and SVR data are available as of September 2006 (best-case scenario).
 - When PEG-IFN alpha-2b and RBV both were dosed by weight, the overall relapse rate was low (11%).
 - When stratified by genotype, relapse rates were higher in G1 patients (16%) than in G2 and G3 patients (7% each).

Conclusions

- In this large, population-based study, treatment-naïve patients with chronic hepatitis C were enrolled to receive weight-based PEG-IFN alpha-2b (1.5 µg/kg/wk) plus weight-based RBV (800-1200 mg/d).
 - Patients did not conform to any inclusion/exclusion criteria and were managed by individual physicians by standard of care only.
 - At baseline, more than one third of patients had advanced fibrosis (35%, >F3) and 58% of G1 patients had high viral load.
- Even with these poor prognostic characteristics, interim results of the POWeR study revealed excellent SVR rates. Importantly, the SVR rates were consistent across all weight categories.
- Patients with G2 chronic hepatitis C had the highest SVR rates, followed by patients with G3 and G1.
- Further analysis is required to complete the program and report SVR in all patients enrolled. More accurate relapse rates will then be defined.

References

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