

SVR for Controlled-release Interferon Alpha-2B (CR2b) + Ribavirin Compared to Pegylated Interferon Alpha-2B (PEG2b) + Ribavirin in Treatment-naïve Genotype-1 (G1) Hepatitis C: Final Results from SELECT-2

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Introduction and Background

Chronic hepatitis C (CHC) is an important worldwide epidemic that affects more than 200 million people. Left untreated or uncured, CHC results in cirrhosis and or hepatocellular carcinoma. In the USA, CHC is already the most common cause of liver transplantation.

Current standard of care (SOC) in treatment of CHC requires 24-48 weeks of daily oral weight-based ribavirin and weekly subcutaneous pegylated interferon alpha (IFNa) 2a or 2b, with duration depending on viral genotype. This treatment regime carries significant side effects and provides sub-optimal SVR rates, particularly in genotype-1 HCV.

As a result of developments of direct acting antiviral agents as add-ons to SOC, both shorter (response-guided) treatment durations and higher SVR rates seem likely in the near future for genotype-1 HCV, the most difficult genotype to cure. Improvements in SOC for other genotypes are likely to follow.

Currently interferon alpha is the backbone of antiviral treatment in HCV, and there is no evidence this will change in years to come. As a result, improvements in both the dosing schedule and side-effect profile of IFNa remain worthwhile goals.

CR2b (Locteron[®], Biolex Therapeutics, Pittsboro, N. Carolina, USA) is a microsphere-based controlled-release investigational formulation of interferon alpha2b designed to improve upon the pharmacokinetics of pegylated IFNa by slowing the rise to C_{max} , increasing C_{min} , and expanding V_D while extending the dosing interval to every two weeks. This pharmacokinetic profile was anticipated to provide at least equal efficacy, lower side effects, and improved convenience and compliance.

Objectives

The primary objective of this study (SELECT-2) was to assess the virologic response to three dose levels of CR2b, dosed every two weeks, in comparison with pegylated IFNa2b (PEG2b) (PEG-Intron[®], Merck, White House Station, New Jersey, USA) dosed weekly, in treatment-naïve, genotype-1 subjects with chronic hepatitis C receiving weight-based doses of ribavirin.

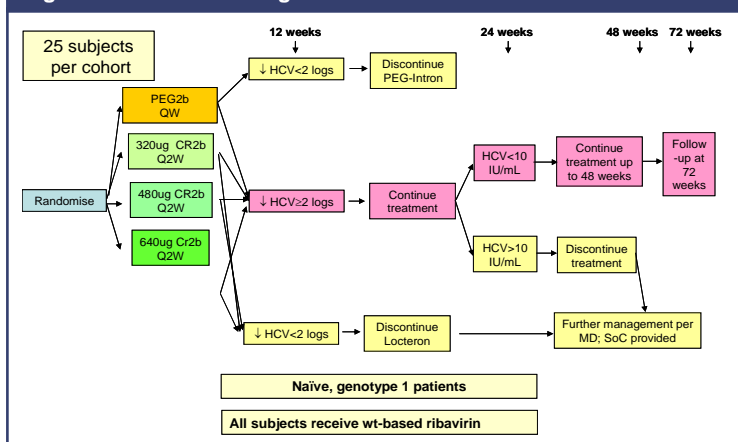
Secondary objectives of SELECT-2 included, for the three dose levels of CR2b compared to PEG2b, assessments of:

- the safety, tolerability and immunogenicity, including the intensity and duration of flu-like symptoms (i.e. fever, chills, myalgia, arthralgia and headache) as measured by ePRO and by clinic visit assessments
- the rates of dose reductions and of study drug discontinuations for tolerability reasons
- the pharmacokinetics (IFNa2b and pegylated IFNa2b levels)
- the impact on general health-related quality of life (HRQL), as measured by SF-36 and HQLQ
- the impact on the onset of depression and depressive symptoms, as measured by the Beck Depression Inventory (BDI)
- the impact on days missed from work during treatment with each of three dose levels of CR2b and of PEG2b
- the incidence of binding and neutralizing antibodies

Design

SELECT-2 was a randomized 72-week Phase 2b study designed to compare three doses of CR2b to the standard dose of PEG2b. The design of SELECT-2 is found in Figure 1 below. The dose of CR2b was double-blind for the first 12 weeks, but investigators and patients knew whether they were randomized to CR2b or PEG2b throughout the trial. IL-28b genotyping was not done because the trial was initiated before the discovery of the association between IL-28b and treatment outcome in HCV.

Figure 1. SELECT-2 Design



Inclusion/Exclusion Criteria

Subjects were required to meet 13 inclusion and 23 exclusion criteria to be eligible for participation in this study. Key inclusion and exclusion criteria were standard for trials in patients with treatment-naïve genotype-1 CHC, and were shown last year at EASL in Vienna.

Results

A total of 116 patients were randomized and dosed in SELECT-2, 57 at 14 sites in the US, and 59 at 10 sites in Bulgaria and Romania. The first patient received his first dose in April 2009, the last patient received his first dose in July 2009, and the last patient received his last dose in June, 2010. The last patient underwent his last follow up visit six months after completion of treatment in November, 2010.

Final efficacy and safety data from this trial are presented in these analyses.

Pharmacokinetic data and data on immunogenicity are not yet available.

Demographics

The four treatment groups were fairly well-balanced at baseline (Table 1). The mild imbalances present that may impact efficacy, such as those in race, sub-genotype, or viral load at baseline, appear to balance each other out.

Table 1. Demographics And Baseline Characteristics In SELECT-2.

	CR2b 640	CR2b 480	CR2b 320	PEG2b	Total
GENDER					
Male	N=17/29[58.6%]	N=16/29[55.2%]	N=18/28[64.3%]	N=20/30[66.7%]	N=71/116[61.2%]
Female	N=12/29[41.4%]	N=13/29[44.8%]	N=10/28[35.7%]	N=10/30[33.3%]	N=45/116[38.8%]
RACE					
White (Caucasian)	N=25/29[86.2%]	N=22/29[75.9%]	N=23/28[82.1%]	N=26/30[86.7%]	N=96/116[82.8%]
Black or African American	N=4/29[13.8%]	N=5/29[17.2%]	N=5/28[17.9%]	N=2/30[6.7%]	N=16/116[13.8%]
Asian	N=0/29[0%]	N=0/29[0%]	N=0/28[0%]	N=1/30[3.3%]	N=1/116[0.9%]
American Indian or Alaskan Native	N=0/29[0%]	N=0/29[0%]	N=0/28[0%]	N=0/30[0%]	N=0/116[0%]
Native Hawaiian or Other Pacific Islander	N=0/29[0%]	N=0/29[0%]	N=0/28[0%]	N=0/30[0%]	N=0/116[0%]
Multi-racial (no primary race)	N=0/29[0%]	N=1/29[3.4%]	N=0/28[0%]	N=0/30[0%]	N=1/116[0.9%]
Not allowed to be captured	N=0/29[0%]	N=0/29[0%]	N=0/28[0%]	N=1/30[3.3%]	N=1/116[0.9%]
Other	N=0/29[0%]	N=1/29[3.4%]	N=0/28[0%]	N=0/30[0%]	N=1/116[0.9%]
Ethnicity					
Hispanic or Latino	N=2/29[6.9%]	N=2/29[6.9%]	N=4/28[14.3%]	N=2/30[6.7%]	N=10/116[8.6%]
Non Hispanic or Latino	N=27/29[93.1%]	N=27/29[93.1%]	N=24/28[85.7%]	N=28/30[93.3%]	N=106/116[91.4%]
Genotype-1 Subtype					
A	N=19/29[65.5%]	N=15/29[51.7%]	N=16/28[57.1%]	N=13/30[43.3%]	N=63/116[54.3%]
B	N=10/29[34.5%]	N=14/29[48.3%]	N=12/28[42.9%]	N=18/30[60%]	N=54/116[46.6%]
HCV RNA Log ₁₀ At BL	6.1	6.1	6	6.2	
Mean Fibro Score At BL	0.37	0.39	0.45	0.42	
AGE (yrs) Mean (SD)	45.7{13.8}	47.4{15.4}	46.4{15.2}	45.1{15.3}	46.2{14.9}
WEIGHT (kg) Mean (SD)	77.1{22}	77.2{23}	77.6{21.1}	82.4{20.8}	78.6{21.7}
BMI (kg/(m ² m)) Mean (SD)	26.1{6.3}	25.9{6.1}	26.1{6.2}	26.4{6.2}	26.1{6.2}

Efficacy

Serial rates of undetectable HCV RNA for the four groups are shown in Table 2 below for all randomized patients who received at least one dose. Despite a higher dropout rate for lack of efficacy on the 320 ug dose of CR2b (Table 3), all three doses of CR2b provided SVR rates that appeared to be at least equivalent to the rate for PEG2b.

Table 2. Serial Rates Of Viral Negativity From Week 12 To SVR24 In SELECT-2*.

Dose	WK12	WK24	WK36	WK48	SVR12	SVR
320 (N=28)	11 (39%)	13 (46%)	12 (43%)	13 (46%)	10 (36%)	10 (36%)
480 (N=29)	10 (34%)	13 (45%)	12 (41%)	12 (41%)	10 (34%)	10 (34%)
640 (N=29)	12 (41%)	15 (52%)	14 (48%)	15 (52%)	13 (45%)	12 (41%)
PEG (N=30)	12 (40%)	17 (57%)	13 (43%)	15 (50%)	9 (30%)	10 (33%)

*Data on viral negativity at Week 4 (RVR) are not available because of a mistake in the naming conventions used in the protocol; baseline was mistakenly called "Week 1", and as a result "Week 4" was actually Week 3.

Overall Safety

The overall safety of the four dose groups is summarized in Table 3. Two deaths occurred, one a suicide in the 640 ug CR2b group, and the other a drug overdose in the PEG2b group. Both occurred two months after the 48 week treatment was completed. Dropouts for any reason and dropouts for AEs were highest on PEG2b; the two lower doses of CR2b appeared to have substantially lower rates of dropouts for AEs than PEG2b. Discontinuations due to lack of efficacy were highest on 320 CR2b. IFNa dose reductions, although higher on 640 CR2b, were largely comparable. Subjects with AEs and moderate AEs were also largely comparable. More subjects had severe AEs in the 480 and 640 CR2b groups than the 320 CR2b and PEG2b groups; bone marrow effects (particularly neutropenia) accounted for these differences.

Table 3. SELECT-2 Overall Safety Profile

Number of Subjects Randomized & Dosed	CR2b 640 (N=29)	CR2b 480 (N=29)	CR2b 320 (N=28)	PEG2b (N=30)
Death	1 {3.45%}	{0%}	{0%}	1 {3.33%}
Subjects who Discontinued Study Medication due to Any Reason	14 {48.28%}	17 {58.62%}	16 {57.14%}	18 {60%}
Subjects who Discontinued Medication due to AEs	6 {20.69%}	4 {13.79}	4 {14.29%}	7 {23.33%}
Subject Discontinued due to Lack of Efficacy	4 {13.79%}	6 {20.68%}	12 {42.85%}	6 {20%}
Subjects who Reduced IFNA2b Dose	11 {37.93%}	8 {27.58%}	8 {28.57%}	9 {30%}
Subjects with Serious Adverse Events	4 {13.79%}	2 {6.9%}	4 {14.29%}	2 {6.67%}
Total Serious Adverse Events	4	2	4	2
Subjects with Adverse Events	29 {100%}	28 {96.55%}	27 {96.43%}	30 {100%}
Subjects who had a Moderate AE	28 {96.55%}	26 {89.66%}	19 {68.86%}	25 {83.33%}
Subjects who had a Severe AE	12 {41.38%}	15 {51.72%}	6 {21.43%}	5 {16.67}
Total Adverse Events	464	429	349	597
Mild	304 {65.52%}	296 {69%}	257 {73.64%}	472 {79.06%}
Moderate	128 {27.59%}	102 {23.78%}	75 {21.49%}	114 {19.1%}
Severe	29 {6.25%}	30 {6.99%}	17 {4.87%}	10 {1.68}

Adverse Event Counts

As shown at the bottom of Table 3, severe AEs were more frequent on all three doses of CR2b than PEG2b, but severe AEs were uncommon in all groups. As above, an excess of bone marrow effects (comprised mostly of neutropenia) accounted for the differences in counts of severe AEs seen in Table 3. Grade 4 neutropenia was not observed on CR2b but did occur on PEG2b. Patients with neutropenia on CR2b also had better viral outcomes (higher rates of EVR) than any of the four individual dose groups, despite more frequent dose reductions (data not shown).

Serious Adverse Events

During this 72 week trial (48 weeks treatment + 24 weeks follow-up), 12 SAEs occurred, 10 on CR2b and 2 on PEG2b (randomization 3:1). The SAEs observed were all different from each other (Table 4), all expected (labeled for IFNa2b), and did not occur in a drug- or dose-dependent pattern: the totals were 4 on 640 CR2b, 2 on 480 CR2b, 4 on 320 CR2b, and 2 on PEG2b.

Table 4. Serious Adverse Events That Occurred During Treatment Or Follow Up In SELECT-2.

Patient ID	Age/Gender	SAE	Dose^	Study Day	Relationship	Outcome
103-0006	48/F	Dehydration	PEG2b	Day 348	Not related	Resolved
103-0029	49/F	Anemia	CR2b 640	Day 77	Related	Resolved
103-0036	52/F	Pancreatitis	CR2b 320	Day 18	Related	Resolved
104-0026	54/M	Suicide	CR2b 640	Day 398	Not related	Fatal
106-0021	28/M	Bipolar exacerbation	CR2b 480	Day 88	Related	Resolved with sequellae
106-0028	36/M	Knee abscess	CR2b 320	Day 63	Related	Resolved
113-0095	60/M	Generalized muscle weakness	CR2b 320	Day 5	Related	Resolved
115-0084	57/F	Injection site necrosis	CR2b 640	Day 361	Related	Resolved
116-0046	27/M	Drug overdose	PEG2b	Day 394	Not related	Fatal
125-0093	67/M	Atrial fibrillation	CR2b 480	Day 13	Not related	Resolved
128-0072	49/M	Chest muscle pain	CR2b 320	Day 19	Not related	Resolved
132-0042	50/M	Acute psychosis	CR2b 640	Day 73	Unknown	Resolved

^2 SAEs on PEG2b, 4 SAEs on 640 CR2b, 2 SAEs on 480 CR2b, and 4 SAEs on 320 CR2b.

Most Common Adverse Events

The ten most common adverse events occurring in the trial are shown in descending order of overall frequency in Table 5.

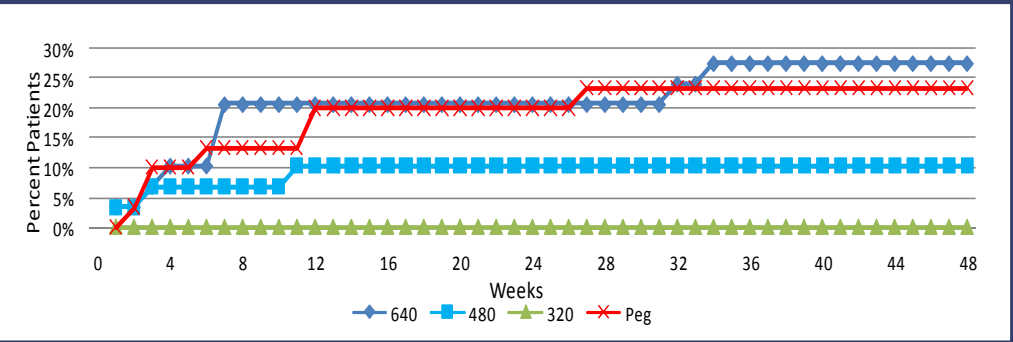
Table 5. Ten Most Frequent AEs In SELECT-2 Over 48 Weeks In Descending Order Of Overall Frequency

Event	LOCTERON 640 (N=29/29)	LOCTERON 480 (N=28/29)	LOCTERON 320 (N=27/28)	PEG (N=30/30)
Pyrexia	24	14	22	101
Myalgia	22	33	24	64
Headache	26	26	30	60
Fatigue	27	23	25	35
Neutropenia	32	29	16	18
Arthralgia	13	20	12	47
Nausea	21	13	13	12
Anaemia	16	13	9	10
Leukopenia	15	14	4	10
Insomnia	10	12	12	8
TOTAL	206	197	167	365

Depression

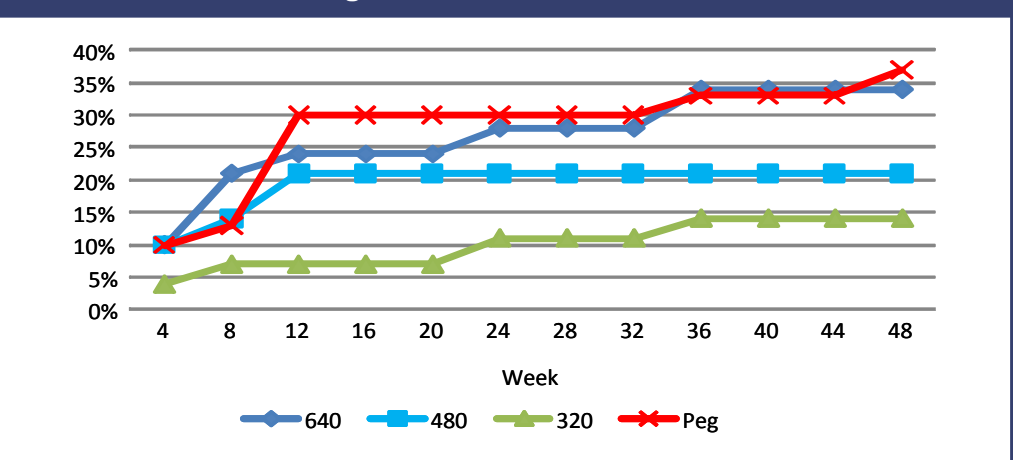
As shown in Figure 2, depression recorded at clinic visits as an adverse event occurred early in all dose groups (>25% of cases by Week 4, >50% by Week 8, and >75% by Week 12). Depression was less frequent on the two lower doses of CR2b than on PEG2b, and related to CR2b dose. Note that the AE of depression was not recorded on the 320 ug dose of CR2b.

Figure 2. Percent Unique Patients With The Adverse Event Of Depression Through 48 Weeks In SELECT-2.



In Figure 3, counts of unique patients (expressed as %) who had mild depression or worse (BDI >baseline and >16) by BDI scores during treatment in SELECT-2 are shown. Note that BDI scores >baseline and >16 on CR2b also occurred early in all treatments groups (>25% of cases by Week 4, >50% by Week 8, and >75% by Week 12). Note also that BDI scores > baseline and >16 occurred in a dose-related pattern on CR2b, that both the 320 and 480 ug doses of CR2b had lower rates of BDI scores >baseline and >16 than PEG2b, and that 640 ug CR2b had the same rate of BDI scores >baseline and >16 as PEG2b.

Figure 3. Percent Unique Patients with BDI Scores >Baseline and >16 in SELECT-2 Through 48 Weeks.

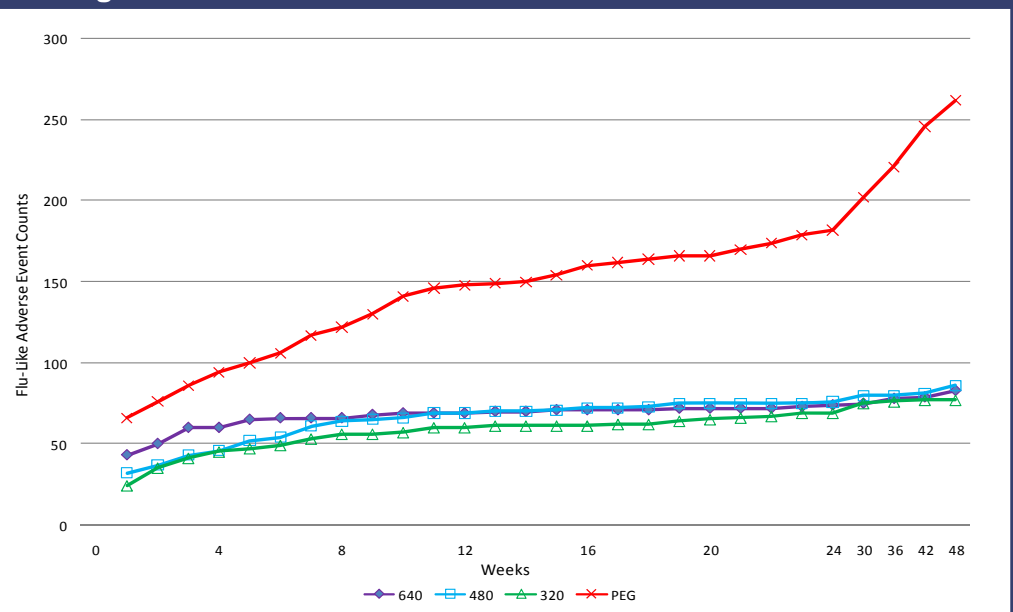


A comprehensive analysis of the effects of CR2b versus PEG2b on depression in SELECT-2 (including depression diagnosed by BDI scores and by antidepressant use) is presented in poster #446 (abstract #1307) in this session (1).

Flu-Like Adverse Events Recorded At Clinic Visits

As shown in Figure 4, flu-like adverse events recorded at clinic visits were less frequent on CR2b than on PEG2b, and were related to CR2b dose. Differences in flu-like adverse event counts were evident at Day 7, immediately prior to the second dose of IFN α in the PEG2b group, and well-prior to the second dose of IFN α in the CR2b groups (the second dose of CR2b occurred on Day 14). The differences in flu-like adverse event counts on all doses of CR2b versus PEG2b evident early during treatment continued to increase over the entire 48 weeks of treatment because of continued events on PEG2b.

Figure 4. Total Flu-Like Adverse Event Counts At Clinic Visits Through 48 Weeks In SELECT-2.



By Week 48, 272 flu-like adverse events at clinic visits had occurred in the PEG2b group, and 77, 86 and 83 flu-like adverse events had occurred at clinic visits in the 320, 480, and 640 ug CR2b groups respectively. The vast majority of flu-like adverse events at clinic visits were rated as mild in all four groups.

The differences in flu-like adverse event counts at clinic visits in the first 12 weeks between the three CR2b arms and PEG2b were all highly statistically significant (Table 6).

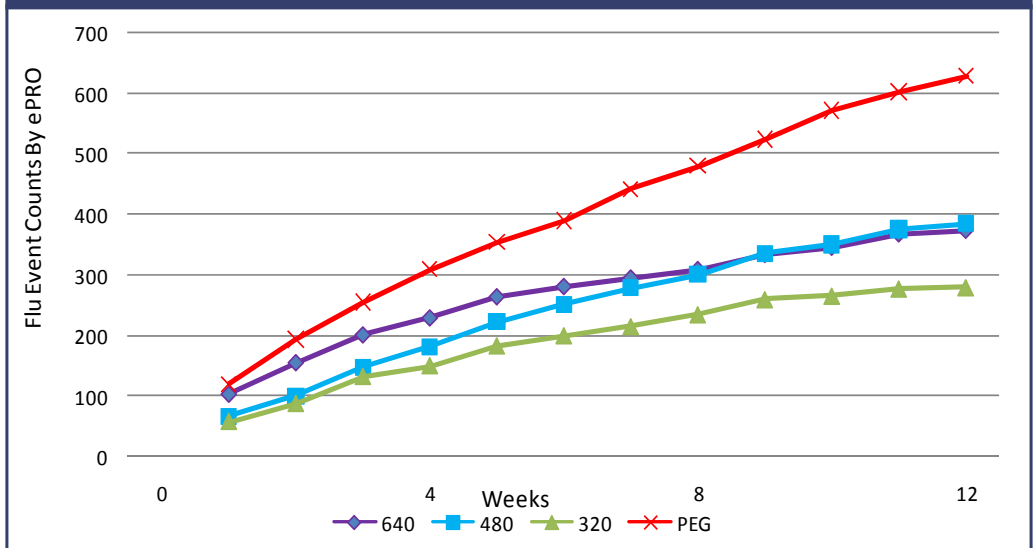
Table 6. Total Flu-like Adverse Event Counts At Clinic Visits Expressed Per Patient During The First 12 Weeks Of SELECT-2

	CR2b 320 ug (N=28)	CR2b 480 ug (N=29)	CR2b 640 ug (N=29)	PEG2b 1.5 ug/kg (N=30)
Mean (SD)	2.2 (2.1)	2.3 (2.1)	2.4 (1.8)	4.9 (5.2)
Median	2.0	2.0	2.0	3.5
Min, Max	0, 8	0, 7	0, 6	0, 25
DIFF LSMEAN (95% CI)	2.1 (-4.57, -1.38)	-2.86 (-4.45, -1.28)	-2.82 (-4.41, -1.24)	
P-Value	p<0.001	p<0.001	p<0.001	

Flu-Like Events By ePRO

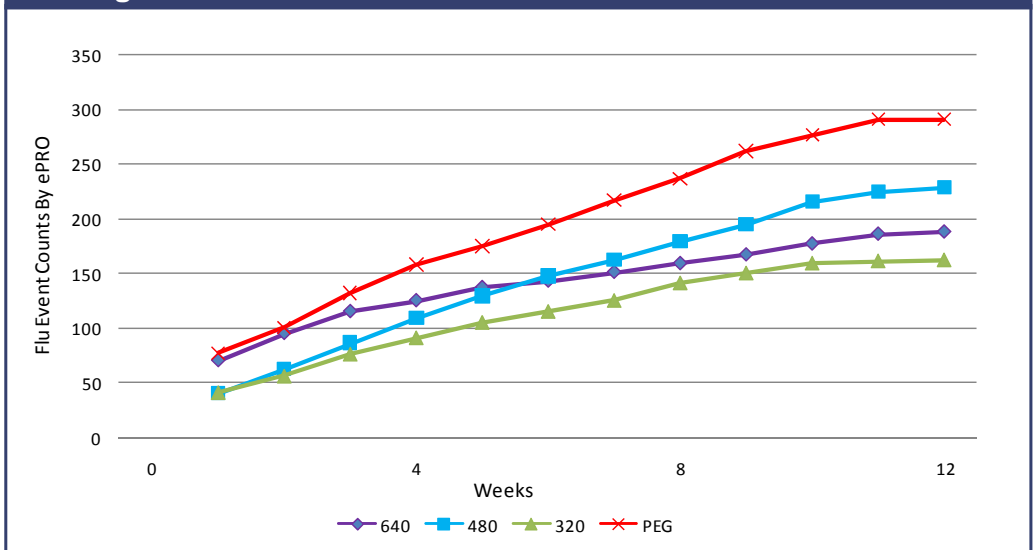
Flu-like events were also recorded daily by patients using electronic devices (ePRO) for the first 12 weeks of treatment. By daily ePRO, total flu-like event counts in the first 12 weeks were approximately 5-fold higher than by weekly clinic visits for all four groups. Nevertheless, as for flu-like events recorded at clinic visits, total flu-like event counts recorded by ePRO were substantially less frequent on all doses of CR2b than PEG2b, and were related to CR2b dose (Figure 5a).

Figure 5a. Total Counts Of Flu-Like Events By ePRO Through 12 Weeks In SELECT-2.



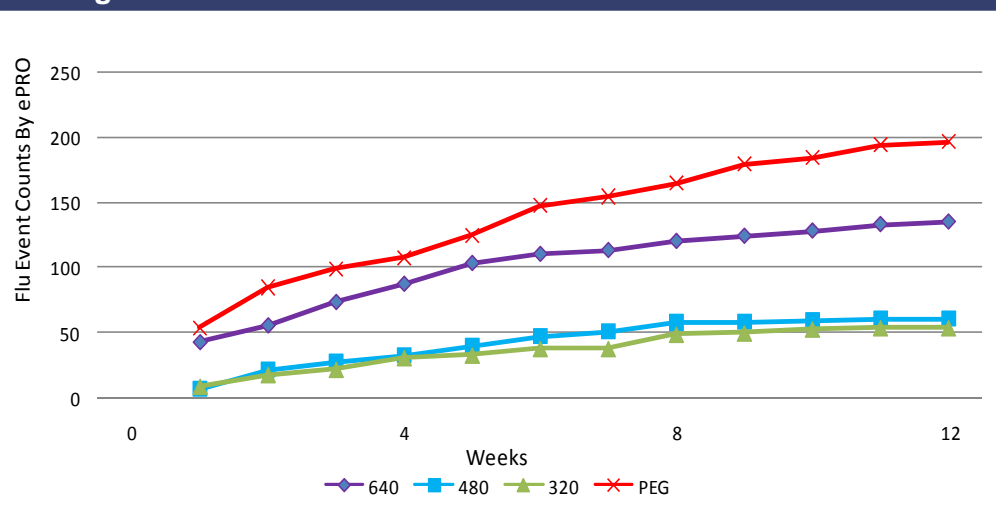
In contrast to flu-like adverse event reports at weekly clinic visits, the great majority of the flu-like events recorded by ePRO were either of moderate intensity (Figure 5b), or of severe intensity (Figure 5c) for all four dose groups. As for flu-like adverse events recorded at clinic visits, and as for total flu-like events recorded by ePRO, both moderate and severe flu-like events recorded by ePRO were less substantially frequent on CR2b. The reductions in moderate and severe flu-like events recorded by ePRO on CR2b in comparison to PEG2b were again inversely related to dose (Figures 5b and 5c).

Figure 5b. Total Counts Of Moderate Flu-Like Events By ePRO Through 12 Weeks In SELECT-2.



By Week 12 by ePRO, 291 moderate flu-like events had occurred in the PEG2b group, and 162, 228 and 188 moderate flu-like events had occurred in the 320, 480, and 640 ug CR2b groups respectively. A similar pattern was present for severe flu-like events: by Week 12 by ePRO, 196 severe flu-like events had occurred in the PEG2b group, and 53, 60 and 135 severe flu-like events had occurred in the 320, 480, and 640 ug CR2b groups respectively.

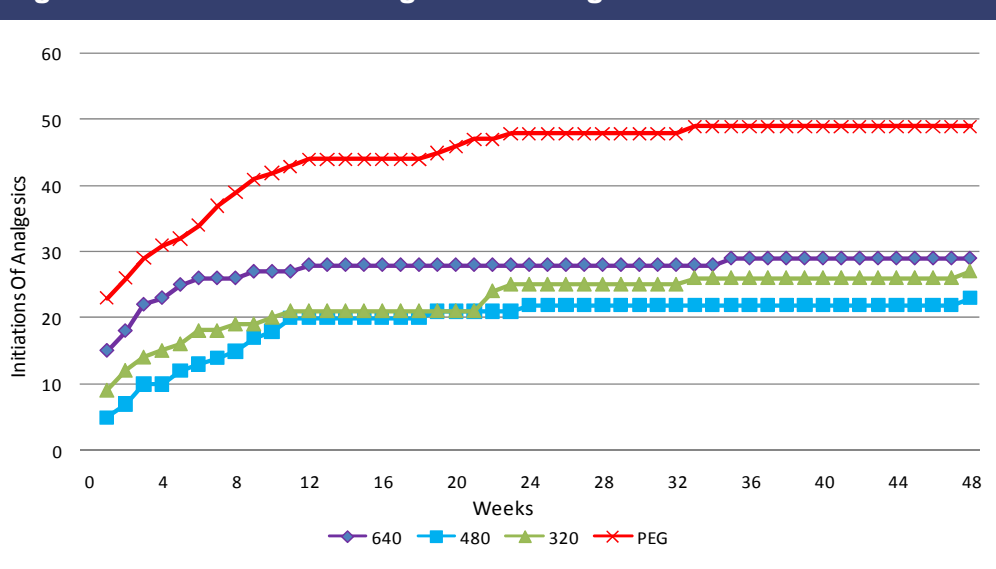
Figure 5c. Total Counts Of Severe Flu-Like Events By ePRO Through 12 Weeks In SELECT-2.



Analgesic Use

Initiations of analgesics on CR2b were less frequent and occurred later in comparison to PEG2b (Figure 6). Reductions in concomitant medication use provide evidence that the reductions in flu-like adverse event counts on CR2b versus PEG2b by adverse event reporting at clinic visits and by ePRO were clinically significant.

Figure 6. Initiations Of Analgesics Through 48 Weeks In SELECT-2.



Injection-Site Reactions

Injection site reactions (ISRs) were also recorded at clinic visits as observed by the investigative staffs (Table 7), and as reported by the patients (Table 8). ISRs as observed by investigative staffs occurred in approximately 2/3 of the patients on CR2b and nearly all patients on PEG2b. Erythema was less frequent on CR2b than on PEG2b (Table 7). Induration (rare in all groups) appeared to occur at slightly higher rates on the 480 ug and 640 ug CR2b doses (Table 7).

ISRs as reported by patients at clinic visits occurred in approximately 1/3 of the patients in all groups and were fairly variable among the dose groups; no relation to CR2b dose was evident (Table 8).

Table 7. Injection Site Reactions Observed By Investigators At Clinic Visits Over 48 Weeks In SELECT-2.

Symp	CR2b 640 N=20/29	CR2b 480 N=20/29	CR2b 320 N=20/28	PEG2b N=28/30
Bruising	1	9	3	5
Erythema	147	176	178	198
Tenderness (pain when area touched)	1	7	5	0
Warmth	1	3	0	0
Induration (hardened area)	4	5	1	1

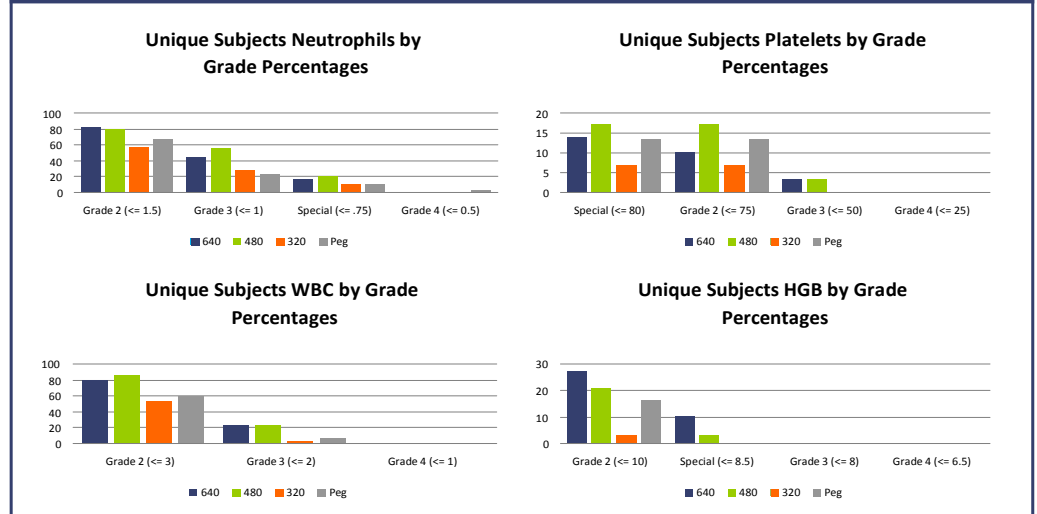
Table 8. Injection Site Reactions Reported By Patients At Clinic Visits Over 48 Weeks In SELECT-2.

Symp	CR2b 640 N=9/29	CR2b 480 N=9/29	CR2b 320 N=9/28	PEG2b N=10/30
Pain (without touching)	3	4	4	0
Itching (associated with injection)	8	16	2	13
Tenderness (pain when area touched)	5	21	13	5
Warmth	1	5	1	5

Laboratory Findings

The only noteworthy findings in the safety laboratory measurements occurred in the hematological assessments. As shown in Figure 7, higher rates of CTCAEv3 Grade 2 and Grade 3 reductions in WBC, platelets, hemoglobin, and particularly neutrophils were observed on the two higher doses of CR2b in comparison to PEG2b, but not on the 320 ug dose of CR2b. CTCAEv3 Grade 4 reductions were not observed on CR2b; one patient on PEG2b did experience a CTCAEv3 Grade 4 neutrophil count (<500).

Figure 7. Cumulative Counts Of Various Toxicity Grades For Hematological Measurements Through 48 Weeks In SELECT-2.



Neutropenia

In this study, the patients who experienced neutropenia on CR2b had higher EVR rates than than any of the four individual treatment groups despite higher rates of dose reductions (data not shown). Neutropenia during IFNa and ribavirin treatment of chronic HCV has consistently been shown not only to predict a good viral response to treatment, but also to carry no increased risk of infection (2-7).

Conclusions

Final data from this 72-week trial in patients with chronic genotype-1 HCV show that doses of CR2b every other week in combination with oral weight-based ribavirin are associated with:

- SVR rates for all three doses of CR2b at least equivalent to the SVR rate of weekly PEG2b (in combination with oral weight-based ribavirin)
- Lower rates of dropouts due to AEs for the 320 ug and 480 ug doses of CR2b than PEG2b
- Lower rates of depression for the 320 ug and 480 ug doses of CR2b than PEG2b
- A 50% or greater reduction in flu-like adverse event counts at clinic visits through 48 weeks for all three doses of CR2b versus PEG2b
 - ⦿ Flu-like adverse event reductions at clinic visits on CR2b precede the possible influence of the change in dosing interval
 - ⦿ Differences in flu-like adverse event at clinic visits on CR2b versus PEG2b increase throughout the 48 week treatment because of continued flu-like adverse events on PEG2b
- A 35% or greater reduction in flu-like event counts by ePRO during the first 12 weeks for all three doses of CR2b versus PEG2b
 - ⦿ Flu-like event reductions on CR2b by ePRO also precede the possible influence of the change in dosing interval
 - ⦿ Differences in flu-like event counts by ePRO on CR2b versus PEG2b increase throughout the first 12 weeks because of higher rates of flu-like adverse events on PEG2b
 - ⦿ Reductions in moderate and severe flu-like events on CR2b by ePRO are substantial
- ISRs on all three doses of CR2b equivalent to those of PEG2b
- Higher rates of Grade 2 and Grade 3 neutropenia for the 480 ug and 640 ug doses of CR2b than PEG2b
 - ⦿ Neutropenia during HCV treatment is a predictor of viral response
 - ⦿ Neutropenia during treatment of HCV is not associated with increased risk of infection

Summary

The final results from the SELECT-2 trial provide encouraging evidence that in comparison to weekly dosing of PEG2b, every other week dosing with CR2b at doses of 320 ug to 480 ug will likely provide:

- Efficacy at least equivalent to that of PEG2b
- Reductions in depression
- Reductions in flu-like adverse events

Further studies of the 320 ug and 480 ug doses of CR2b are planned.

References

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