

Timing and Frequency of Depression During HCV-Treatment with Controlled Release IFNa2b (CR2b) vs. Pegylated IFNa2b (PEG2b): Results from SELECT-2, a Randomized Open-label 72-Week Comparison in 116 Treatment-Naïve Patients with Genotype 1 HCV

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Introduction and Background

Depression is an important side effect of current HCV treatment that affects treatment compliance (1). In a recent prospective discrete choice experiment survey study of 150 patients with HCV, depression was the adverse event with largest impact on likely treatment adherence (1). Some (2,3), but not all (4), studies have shown that patients who do develop depression during HCV treatment have a reduced chance of achieving SVR. Complications of depression can result in further morbidity or mortality and close monitoring for depression is an important part of patient management during HCV treatment.

Risk of depression during HCV treatment is higher among patients with dysphoria at baseline (i.e., patients with higher scores at baseline on depression severity rating scales such as BDI, MADRAS, HAM-D, or Zung SDS) (5). Patients who develop mild or moderate depression during HCV treatment usually respond well to reductions in the dose of interferon and/or initiation of antidepressant drugs during continued HCV treatment (6). Prophylactic antidepressants have been shown to lessen elevations in MADRAS scores during HCV treatment (7).

Ribavirin alone and IFNa alone have both been shown to cause depression in patients during treatment of HCV. In a double-blind, placebo-controlled, 36-week trial in 57 patients with chronic HCV, 3% of patients receiving placebo and 21% of patients receiving ribavirin 600 mg bid developed depression (8). Depression associated with fatigue, an important side effect of ribavirin, has been termed “neurovegetative” depression (6). In an open-label randomized comparison of 24 weeks vs. 48 weeks of IFNa2b alone vs. IFNa2b+ribavirin (1000 mg/1200 mg) in 912 patients with HCV (9), depression occurred in 25% of patients treated with IFNa2b alone for 24 weeks vs. 32% of patients treated with IFNa2b+ribavirin for 24 weeks. In patients treated for 48 weeks (9), the rates of depression for IFNa2b vs. IFNa2b+ribavirin were the same (37% vs 36%).

Innovative therapy that reduces the rates of depression during treatment of HCV would be welcome, as chronic hepatitis C (HCV) is an important global disease that affects more than 200 million people and carries high morbidity and mortality at the end of its natural history if left untreated or after treatment failure.

The ongoing developments of direct acting antiviral agents (DAAs) as add-ons to weekly subcutaneous pegylated interferon and daily oral ribavirin show much promise in achieving both shorter (response-guided) treatment durations and higher SVR rates in the near future in chronic genotype 1 hepatitis C.

However, shortened HCV treatment durations from DAAs may be unlikely to eliminate the problem of depression. Studies of IFNa alone three times per week in HCV (10) have shown that 24% of all episodes of depression occur by week 4 of treatment, and that 74% of all episodes of depression occur by week 8 of treatment. In another study of IFNa alone in treatment of HCV (11), mean MADRS increased from 4.7 to 10.4 in one month of treatment. The time of onset of depression has not been as well characterized in studies of pegylated interferon alone weekly in HCV (9).

The time of onset of depression for the combination of weekly pegylated IFNa and daily oral ribavirin during HCV treatment is not well-characterized either. A recent comprehensive review described onset of depression over “several months” in dual therapy(6). However, in a study of 164 patients with HCV treated with the combination of weekly pegylated IFNa and daily oral ribavirin, significant ($p<0.001$) elevations in Zung SDS scores occurred by week 4 (5).

The purpose of this analysis was to compare the time course and frequency of depression using two different IFNa-related products in combination with oral weight-based ribavirin for treatment of patients with treatment-naïve genotype-1 HCV.

Materials and Methods

The data on depression for this analysis came from SELECT-2, a Phase 2b trial designed and executed to compare three doses of a microsphere-based controlled-release formulation of interferon alpha2b (CR2b) (Locteron®, Biolex Therapeutics, Pittsboro, N. Carolina, USA) injected every two weeks to pegylated IFNa2b (PEG2b) (PEG-Intron®, Merck, White House Station, New Jersey, USA) dosed weekly, in treatment-naïve subjects with genotype-1 chronic hepatitis C receiving weight-based doses of ribavirin.

CR2b was 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 designed to provide at least equal efficacy, lower side effects, and improved convenience and compliance.

The primary objective of SELECT-2 was to assess the virologic response to three dose levels of CR2b, dosed every two weeks, in comparison to pegylated IFNa2b (PEG2b) dosed weekly in treatment-naïve, genotype-1 subjects with chronic hepatitis C receiving weight-based doses of ribavirin. The final results from SELECT-2 including antiviral effects and overall safety are presented at another poster (poster #444, abstract #2616) in this session (12).

A key secondary objective of SELECT-2 was to assess the impact of three dose levels of CR2b versus PEG2b on the onset of depression and depressive symptoms measured by self-report using the Beck Depression Inventory (BDI), and measured by adverse events assessed at clinic visits.

Another key secondary objective of SELECT-2 was to assess the impact of three dose levels of CR2b versus PEG2b on the onset of changes in quality of life, as measured by Short Form 36 (SF-36). In this analysis, special attention was paid to changes in subscales of SF-36 that have been shown to be predictive of, or associated with depression (13,14), the mental health scale and the mental health component summary scale.

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 presented in poster #444 (abstract #2616) in this session (12). The assigned dose of CR2b was double-blind for the first 12 weeks, but assignment to CR2b or PEG2b was not blinded.

Inclusion/Exclusion Criteria

As was shown in a poster last year at EASL, key inclusion/exclusion criteria were standard for trials in patients with treatment-naïve genotype-1 HCV. Patients with a history of moderate, severe, or uncontrolled psychiatric disease including depression were excluded. Use of antidepressants during the trial was not prohibited.

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 was dosed 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.

Demographics

The overall demographics are shown in poster #444 (abstract #2616) in this session (12). Baseline factors that might affect depression are shown in Table 1. Risks for depression at baseline appeared to be fairly well-balanced across groups, except for the 640 ug CR2b group. The 640 ug CR2b group had more prior depression, more antidepressant use at randomization, and higher BDI scores at baseline; all three are established risk factors for development of depression during HCV treatment (6). The SF-36 mental health score (MHS), and SF-36 mental health component summary scale score (MHCSSC) at baseline appeared comparable across groups.

Table 1. Demographics And Baseline Characteristics Pertinent To Depression In SELECT-2.

	CR2b 640 N=29	CR2b 480 N=29	CR2b 320 N=28	PEG2b N=16
Male	N=17/29[58.6%]	N=16/29[55.2%]	N=18/28[64.3%]	N=20/30[66.7%]
Female	N=12/29[41.4%]	N=13/29[44.8%]	N=10/28[35.7%]	N=10/30[33.3%]
AGE (yrs) Mean (SD)	45.7{13.8}	47.4{15.4}	46.4{15.2}	45.1{15.3}
WEIGHT (kg) Mean (SD)	77.1{22}	77.2{23}	77.6{21.1}	82.4{20.8}
BMI (kg/(m*m)) Mean (SD)	26.1{6.3}	25.9{6.1}	26.1{6.2}	26.4{6.2}
History of Depression (%)	20.6	13.8	3.6	10.0
Antidepressant Use at Randomization (%)	17.2	10.3	3.6	10.0
BDI (Mean)	8.43	6.48	4.18	4.67
SF-36 Mental Health Scale Norm Based Score (Mean)	46.74	52.09	51.63	49.69
SF-36 Mental Health Component Summary Scale Score (Mean)	47.07	53.09	51.63	49.63

Efficacy

Serial rates of undetectable HCV RNA for the four groups are shown in Table 2 below for randomized patients who received at least one dose. Despite a higher dropout rate for lack of efficacy on the 320 ug dose of CR2b (12), all three doses of CR2b provided what appeared to provide rates of SVR at least equivalent to that of PEG2b.

Table 2. Percent Patients Who Were Viral Negative Over Time 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.

Safety

The complete safety analysis is presented in poster #444 (abstract #2616) in this session (12). That analysis documents another key finding: all three doses of CR2b are associated with >50% reductions in flu-like adverse event counts at clinic visits, and with >35% reductions by daily electronic patient reported outcomes (ePRO). A detailed analysis of these findings was reported at AASLD last year (15).

Depression

We used eight available lines of evidence to compare the onset time, incidence, and severity of depression on the three doses of CR2b to those of PEG2b: 1) changes in mean BDI scores over time, 2) counts of unique patients with mild (BDI score >16) depression by patient self-report on BDI over time, 3) counts of unique patients with moderate (BDI score >20) depression by patient self-report on BDI over time, 4) counts of unique patients with the adverse event of depression as assessed by clinic staff over time, 5) counts of patients initiating antidepressant drugs during treatment over time, 6) changes in SF-36 scores on scales pertinent to depression/mental health over time, 7) counts of unique patients over time with >5 point drops (the threshold for a clinically important difference) on the mental health scale of SF-36, an individual SF-36 scale pertinent to depression/mental health, 8) counts of unique patients over time with >3 point drops (the threshold for a clinically important difference) on the mental health component summary scale of SF-36, the aggregated SF-36 scale pertinent to depression/mental health.

Changes In BDI Scores Over Time

BDI is a validated 21-question instrument for the assessment of depression that is completed by patients. On the BDI scale, increases in BDI scores represent increases in dysthymia. As is evident in Figure 2, BDI scores were higher at baseline in SELECT-2 on the two higher doses of CR2b than on PEG2b or on 320 ug CR2b. Mean BDI scores increased in all four dose groups by Week 4 of treatment, peaked by Week 12 of treatment, and remained elevated compared to baseline through Week 48 of treatment. Interestingly, after cessation of treatment at Week 48, mean BDI scores fell to values below baseline, indicating improved mood post treatment compared to pretreatment (baseline) in all treatment groups.

Figure 2. Mean BDI Scores During Treatment And Follow Up in SELECT-2.

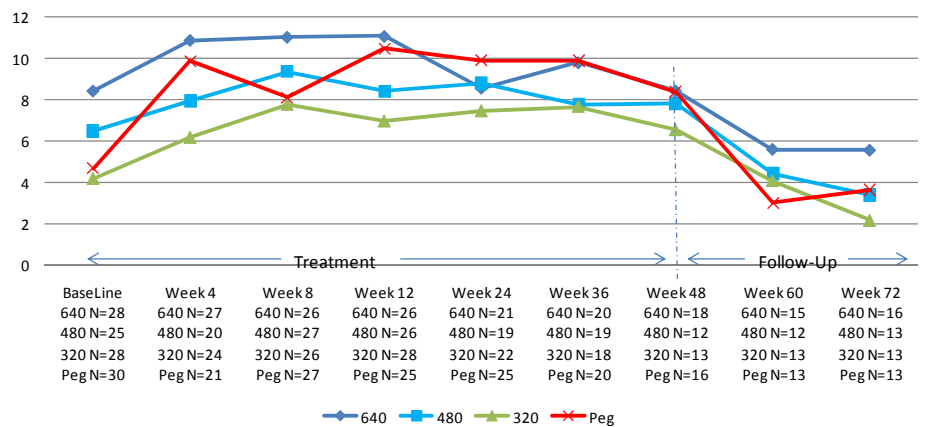
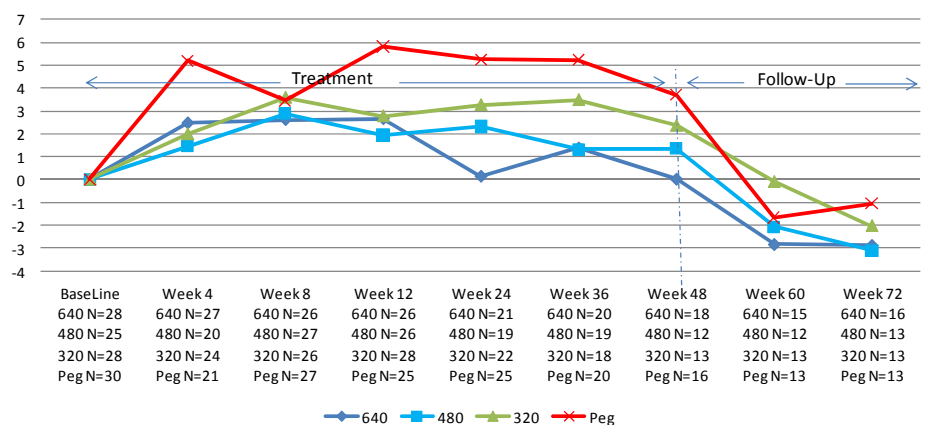


Figure 3 shows mean changes in BDI during treatment and follow-up. Mean increases in BDI from baseline were of lower magnitude on all three doses of CR2b than on PEG2b. Mean increases in BDI appeared to be related to CR2b dose only at Week 4. The improved mood post treatment compared to pretreatment (baseline) evident in Figure 2 is also evident in Figure 3.

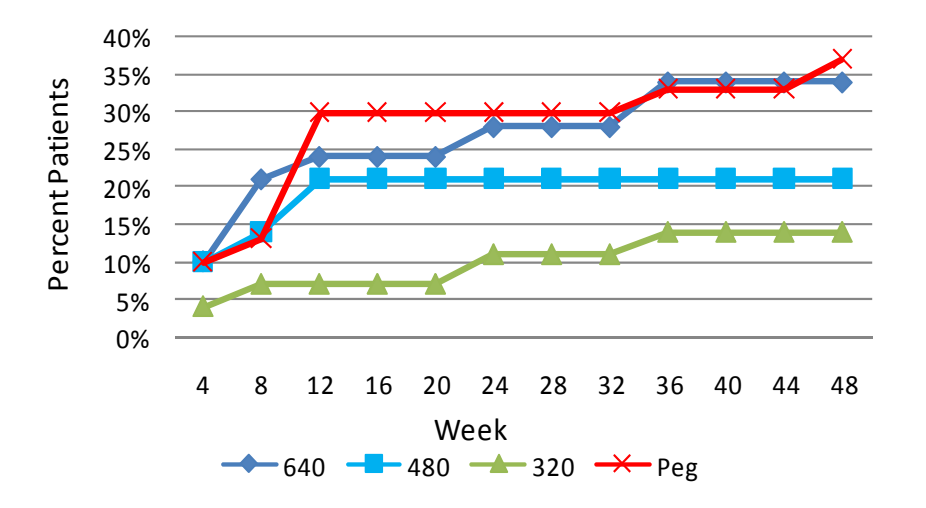
Figure 3. Mean Changes In BDI During Treatment And Follow Up in SELECT-2.



BDI Scores >Baseline and >16

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

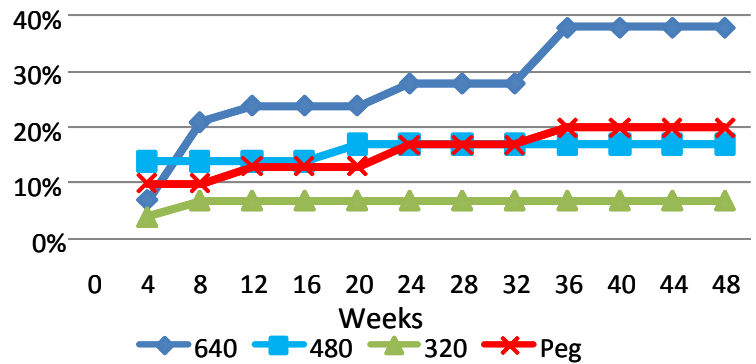
Figure 4. Percent Unique Patients With Mild Depression Or Worse By BDI Scores Through 48 Weeks in SELECT-2.



BDI Scores >Baseline and >20

In Figure 5, counts of unique patients (expressed as %) who had moderate depression (or worse) by BDI scores (BDI >baseline and >20) during treatment in SELECT-2 are shown. Note that moderate depression also occurred early in all treatments groups (again, >25% of cases by Week 4, >50% by Week 8, and >75% by Week 12). Note also that the 320 ug dose of CR2b had a substantially lower rate of moderate depression than PEG2b, that the 480 ug dose of CR2b had a slightly lower rate of moderate depression as PEG2b, that the 640 ug CR2b had a higher rate of moderate depression than PEG2b, and that moderate depression occurred in a dose-related pattern on CR2b.

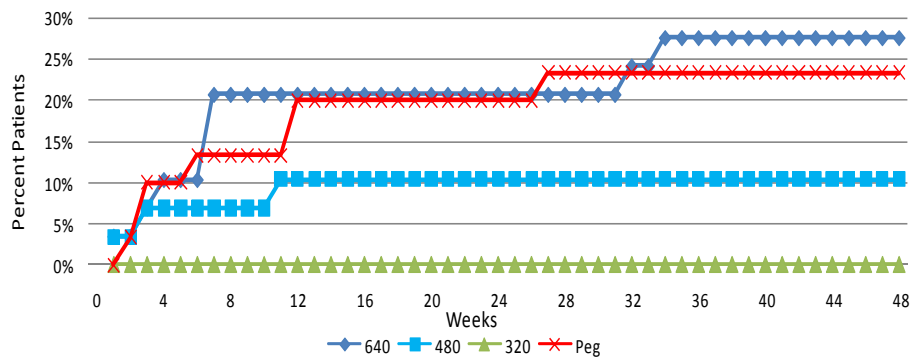
Figure 5. Percent Unique Patients With Moderate Depression or Worse By BDI Scores Through 48 Weeks In SELECT-2.



Depression As An Adverse Event Identified By Clinic Staff

Counts of unique patients (expressed as %) who had depression as an adverse event during treatment in SELECT-2 are shown in Figure 6. Note that depression as an AE also occurred early in all treatments groups (>25% by Week 4, >50% by Week 8, and >75% by Week 12). Also note that the adverse event of depression occurred in a dose-related pattern on CR2b, that the 320 ug and 480 ug doses of CR2b had lower rates of depression than PEG2b, and that 640 ug CR2b had a higher rate of depression than PEG2b. No patient on the 320 ug dose of CR2b had depression identified as adverse event.

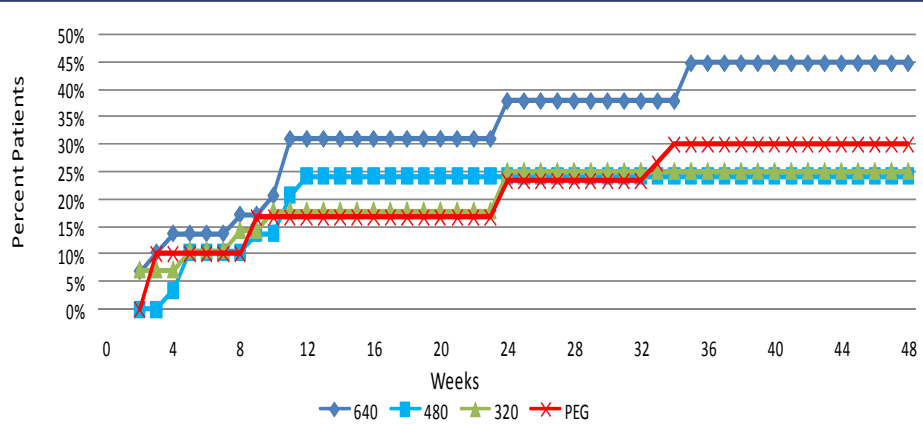
Figure 6. Percent Unique Patients With The Adverse Event of Depression Through 48 Weeks in SELECT-2.



Use Of Antidepressants

We also compared the onset time and frequency of use of antidepressants in the four dose groups during treatment in SELECT-2 through through Week 48 (Figure 7). As can be seen in Figure 7 below, antidepressants were initiated in all four dose groups by Week 4. By Week 12, usage of antidepressants ranged from 15-30% in the four groups and >50% of total use through Week 48 was initiated. These observations show that depression occurs early during HCV treatment. Both the 320 ug and 480 ug doses of CR2b had lower rates of antidepressant use than PEG2b. The highest rate of antidepressant use was on the 640 ug dose of CR2b.

Figure 7. Percent Unique Patients Initiating Antidepressants Through 48 Weeks in SELECT-2.



Changes In SF-36 Scores On Scales Pertinent To Depression/Mental Health Over Time

SF-36 is a validated quality of life instrument completed by patients that contains 36 items (questions). The scores on these 36 questions are aggregated to eight individual scales, one of which is the mental health scale. The scores are also aggregated to two summary scales, one of which is the mental health component summary scale (the other summary measure is the physical health component summary scale). The mental health component summary scale measure is composed of four scales: vitality, social functioning, role-emotional, and mental health scale. The two mental health scales from SF-36 have been shown to be effective screening tools for depression (13,14).

On the SF-36 scale, decreases in scores represent decreases in quality of life. As is evident in Figure 8, mental health scale scores declined quickly after initiation of treatment. Declines were evident in all four dose groups by Week 4 of treatment, and peaked by Week 12 of treatment. Scores on the mental health scale remained depressed compared to baseline through Week 48 of treatment on all four doses. For the first eight weeks, the drops in mental health scale scores on CR2b less than those on PEG2b, and appeared to be related to CR2b dose. Drops in mental health scale scores on the 320 ug dose of CR2b were smaller than those on PEG2b throughout the entire 48 weeks of treatment.

After cessation of treatment at Week 48, mental health scale scores rose to values above baseline, indicating improved mental health post treatment compared to pretreatment (baseline) in all four dose groups.

A similar pattern was evident for changes from baseline in mental health component summary scale scores (Figure 9). Mental health component summary scale scores also declined rapidly after initiation of treatment. Declines were evident in all four dose groups by Week 4 of treatment; the declines peaked by Week 8 of treatment, except for the 480 ug CR2b dose which peaked at 24 weeks. Scores on the mental health component summary scale remained depressed compared to baseline through Week 48 of treatment on all four doses. Drops in mental health component summary scale scores on 320 ug and 480 ug CR2b were less than those on PEG2b, and the changes appeared to be dose-related. Drops in mental health component summary scale scores on the 320 ug dose of CR2b were less than those on PEG2b through Week 48 of treatment.

After cessation of treatment at Week 48, mental health component summary scale scores rose to values above baseline, again indicating improved mental health post treatment compared to pretreatment (baseline) for all doses except 480 ug CR2b.

Figure 8. Changes From Baseline In SF-36 Mental Health Scale Scores Over Time In SELECT-2.

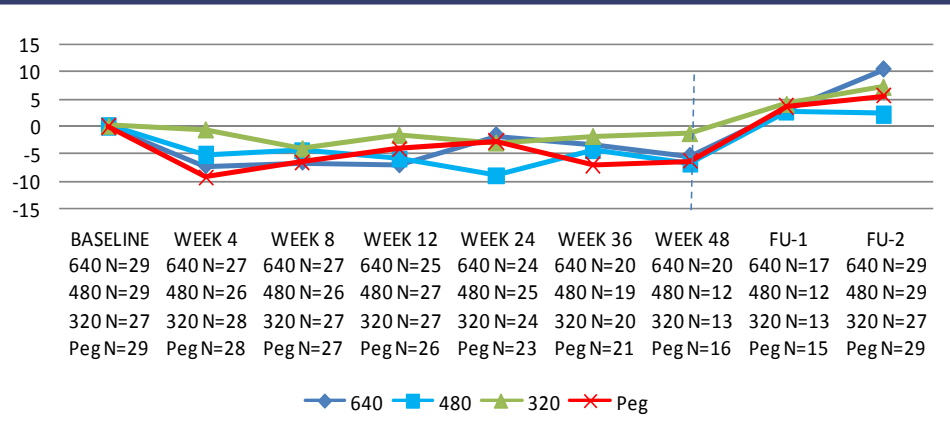
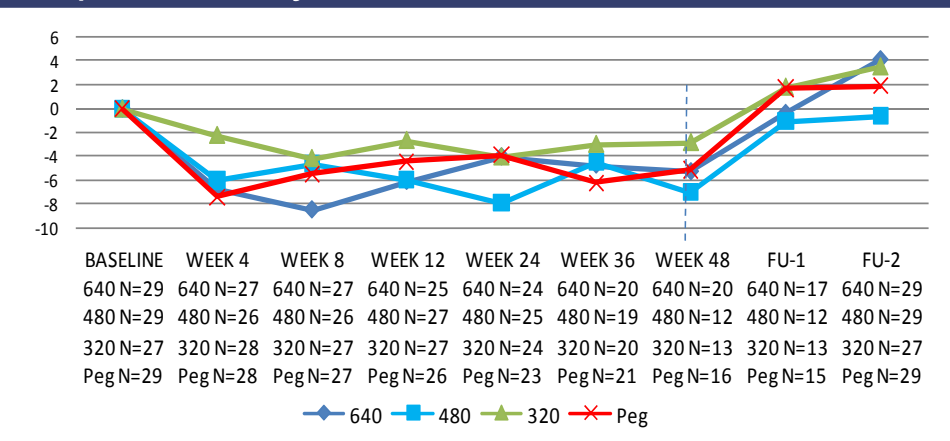


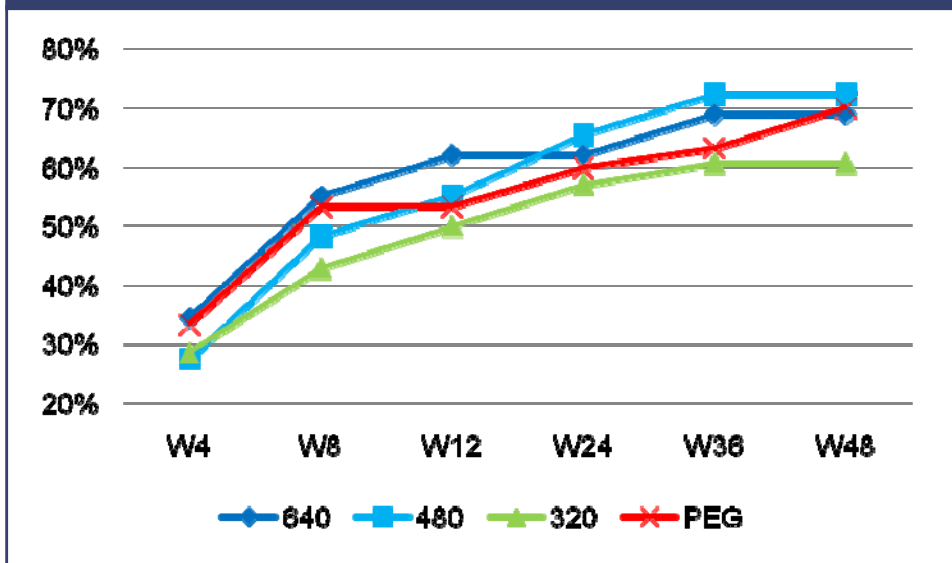
Figure 9. Changes From Baseline In SF-36 Mental Health Component Summary Scale Scores Over Time in SELECT-2.



Using established thresholds for clinically important differences on SF-36 mental scales (≥ 5 change on mental health scale, and ≥ 3 change on mental health component summary scale), we also compared the proportions of patients over time who exhibited clinically important declines in scores on the mental health scale (Figure 10), and on the mental health component summary scale (Figure 11) in SELECT-2.

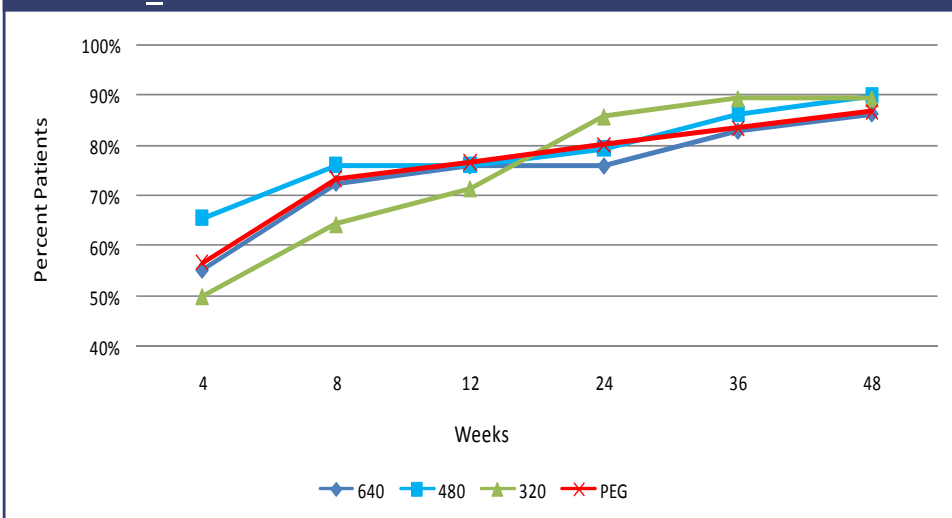
As can be seen in Figure 10, ≥ 5 point drops in mental health scale scores also occurred early (with $>50\%$ of cases presenting by Week 8 and $>75\%$ by Week 12) and were more frequent than >16 increases in BDI. Drops in mental health scale scores ≥ 5 points were related to CR2b dose through Week 12. Drops in mental health scale scores ≥ 5 points on 320 ug and 480 ug CR2b were less frequent than on PEG2b through Week 8. Drops ≥ 5 points in mental health scale scores on the 320 ug dose of CR2b were less frequent than those on PEG2b through Week 48 of treatment.

Figure 10. SF-36 Mental Health Scale Score Declines ≥ 5 Over Time in SELECT-2.



As can be seen in Figure 11, ≥ 3 point drops in mental health component summary scale scores occurred even earlier than ≥ 5 drops in mental health scale scores; $>50\%$ of cases presented by Week 4 and $>75\%$ presented by Week 8. ≥ 3 point drops in mental health component summary scale scores were more frequent than not only >16 increases in BDI but also more frequent than ≥ 5 drops on the mental health scale. Drops ≥ 3 points in mental health component summary scale scores on CR2b were not dose-related, were less frequent on 320 ug CR2b than on PEG2b through Week 12, and higher thereafter.

Figure 11. SF-36 Mental Health Component Summary Scale Score Declines ≥ 3 Over Time in SELECT-2.



Conclusions

- In comparison to PEG2b, all three doses of CR2b provide equivalent rates of SVR
- Depression by BDI scores, depression as an AE, and antidepressant use are frequent and occur early during treatment of HCV
 - >25% of cases by Week 4
 - >50% of cases by Week 8
 - >75% of cases by Week 12
- SF-36 mental health scales show even earlier and more frequent disturbances of mental well-being
- In comparison to PEG2b, the 320 ug and 480 ug doses of CR2b show promise of lower rates of:
 - Depression by AE reporting,
 - Mild and moderate depression by BDI scores
 - Pharmacologic treatment of depression
- 640 ug CR2b showed higher rates of depression than PEG2b
 - Higher risk factors for depression at baseline may account for this observation (more prior depression, more antidepressants at baseline, and higher BDI scores at baseline)
- In comparison to PEG2b, the 320 ug dose of CR2b show smaller declines in SF-36 mental health scores

Summary

- Depression is common problem during treatment of HCV, and it occurs much earlier than many think.
- The 320 ug and 480 ug doses of CR2b may offer the important advantage of equivalent efficacy with lower rates of depression in the treatment of HCV.
- Further studies of the 320 ug and 480 ug doses of CR2b are planned, including studies with direct-acting antiviral agents.

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