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***APPLICATION NUMBER:***

# 201917Orig1s000

# STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

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| **NDA#:** | 201-917/S-001 |
| **NAME OF DRUG:** | Telaprevir™ (VX-950) |
| **INDICATION:** | Treatment of HCV Infection |
| **APPLICANT:** | Vertex Pharmaceuticals, Inc. |
| **SUBMISSION DATE:** | Nov. 23, 2010 |
| **TYPE OF REVIEW:** | Clinical |
| **BIOMETRICS DIVISION:** | DB4 |
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**STATISTICAL REVIEW AND EVALUATION**

**NDA#:** 201-917

# 1. Executive Summary

The applicant submitted three randomized, controlled, phase 2/3 or 3 clinical trials with telaprevir as part of 3 drug antiviral therapy for HCV. Two of the trials used subjects who were treatment naive patients infected with genotype 1 chronic hepatitis C virus (HCV).

The primary objective of the first naive trial, trial 108, was to compare the efficacy at 72 weeks of two different regimens containing telaprevir (TPV) plus ribavirin (RBV) plus peg-IFN-alpha-2a (PIA-2)to a control regimen of RBV plus peg-IFN-alpha-2a plus placebo (telaprevir dummy). The two test regimens gave TPV for 8 weeks and 12 weeks, respectively.

The primary objective of the second naive trial, trial 111, was to compare the efficacy at 72 weeks of two different durations of PIA-2 plus RBV for subjects initially treated for 12 weeks with a regimen containing TPV plus RBV plus PIA-2. The comparison of interest in this trial was that between an additional 12 weeks of PI+RBV (24 weeks total) and an additional 36 weeks of PI+RBV (48 weeks total) for subjects who achieved viral suppression at weeks 4 and 12 while on the triple regimen.

The primary objective of the trial with prior treatment failures, trial 216, was to compare the efficacy at 72 weeks of three different regimens: first, 12 weeks of TPV plus 48 weeks of PI = peg-IFN (either alpha-2a or alpha-2b) plus RBV versus second, the same drugs but with the start of TPV being delayed by 4 weeks versus third, 48 weeks of PI+RBV.

For treatment naive subjects, there are three basic questions to be answered:

1. Is telaprevir for 8 weeks superior to placebo as an add-on to 24 or 48 weeks of PI+RBV?
2. Is telaprevir for 12 weeks superior to telaprevir for 8 weeks as an add-on to 24 or 48 weeks of PI+RBV?
3. If a patient achieves eRVR after 12 weeks of TPV plus PI+RBV, is continuing PI+RBV out to 48 weeks superior to continuing it only to 24 weeks?

The applicant has demonstrated in these three trials that telaprevir is an effective treatment of genotype 1 chronic Hepatitis C when used for 12 weeks at the indicated dose in combination with 48 weeks of peg-interferon and ribavirin. It is effective in both treatment naive subjects and in subjects who have failed a prior course of peg-interferon and ribavirin.

Furthermore, the applicant has demonstrated that in naive subjects, a response guided therapy in which subjects who achieve viral suppression at 12 weeks need only take a total of 24 weeks of peg-interferon and ribavirin to receive the full benefit of the therapy.

Furthermore, the applicant has demonstrated that in naive subjects, subjects can discontinue telaprevir at 8 weeks, say if toxicity were an issue, and still receive substantial benefit relative to placebo (19-20% increase in chance of SVR24), although such subjects do appear to perform slightly worse efficacy (~6%) than subjects continuing the full 12 weeks of telaprevir.

The questions as to how effective 8 weeks of telaprevir or 12 weeks of telaprevir followed by only 24 weeks of peg-interferon plus ribavirin if suppressed at week 12 is still open for subjects who have failed a prior course of PI+RBV.

There is a noticeable toxicity associated with telaprevir, which is detailed in the clinical review.

# 2. Introduction

## *2.1 Overview*

The applicant submitted three randomized, controlled, phase 2/3 or 3 clinical trials with telaprevir as part of 3 drug antiviral therapy for HCV.

## *2.2 Data Sources*

### *2.2.1 Objectives in Trials*

All subjects in trial 108 were treatment naive patients infected with genotype 1 chronic hepatitis C virus (HCV). The primary objective of trial 108 was to compare the efficacy at 72 weeks of two different regimens containing telaprevir (TPV) plus ribavirin (RBV) plus peg-IFN-alpha-2a (PIA-2)to a control regimen of RBV plus peg-IFN-alpha-2a plus placebo (telaprevir dummy). The two test regimens gave TPV for 8 weeks and 12 weeks, respectively.

At week 12, subjects were sub-divided into three groups, according to their viral response. The worst performing subjects were those who were not EVR (early viral response), defined as a decrease in viral load of less than 2 logs from baseline. Those subjects discontinued all drugs at week 14, regardless of their arm. Subjects who were EVR (more than 2 log decrease in viral load) were subdivided into eRVR (extended rapid viral response), defined as undectable HCV at both weeks 4 and 12, and non eRVR.

Subjects initially randomized to either TPV who were eRVR received 24 weeks of RBV+PIA-2; those in the TPV arms without eRVR received 48 weeks. All the subjects in the control arm received 12 weeks of TPV placebo and were at least EVR at week 12 received 48 weeks of RBV+PIA-2, regardless of whether they were also eRVR.

TPV was administered at 75 mg q8h; PI was administered at 180 mcg/week sci; RBV was administered twice daily at 1000 or 1200 mg/day po (based on weight).

All subjects in trial 111 were treatment naive patients infected with genotype 1 chronic hepatitis C virus (HCV). The primary objective of trial 111 was to compare the efficacy at 72 weeks of two different durations of PIA-2 plus RBV for subjects initially treated for 12 weeks with a regimen containing TPV plus RBV plus PIA-2. The comparison of interest in this trial was that between an additional 12 weeks of PI+RBV (24 weeks total) and an additional 36 weeks of PI+RBV (48 weeks total) for subjects who achieved viral suppression at weeks 4 and 12 while on the triple regimen.

Subjects who achieved eRVR were randomized at week 14 to discontinue their PI+RBV therapy at either week 24 or week 48. Subjects who did not achieve eRVR were treated out to 48 weeks and were followed but were not used in the primary comparison.

The doses in this trial were the same as in trial 108. TPV was administered at 75 mg q8h; PI was administered at 180 mcg/week sci; RBV was administered twice daily at 1000 or 1200 mg/day po (based on weight). In both trials, the variation among arms is one the duration of planned drug treatment; daily doses do not vary across arms.

All subjects in trial 216 were failures of previous treatment with PI+RBV. They were sub-divided into non-responders (who had detectable virus at the end of treatment) and relapsers (who had undetectable virus at end of treatment but detectable virus 24 weeks later). The primary objective of trial 216 was to compare the efficacy at 72 weeks of three different regimens: first, 12 weeks of TPV plus 48 weeks of PI = peg-IFN (either alpha-2a or alpha-2b) plus RBV versus second, the same drugs but with the start of TPV being delayed by 4 weeks versus third, 48 weeks of PI+RBV. Subjects in all arms received 16 weeks of either TPV or TPV placebo to create a blind with respect to the actual assignment. TPV was administered at 75 mg q8h; PI was administered at 180 mcg/week sci; RBV was administered twice daily at 1000 or 1200 mg/day po (based on weight). The doses of PI and RBV are already approved for treatment of hepatitis C.

All results in section 2 will be those of the applicant. Results generated by the FDA reviewer will be contained in section 3.

### *2.2.2 Summary of Study Design*

#### *2.2.2.1 Trial 108*

Trial 108 was a double-blind, placebo controlled, randomized three-arm, multicenter trial. Subjects were genotype 1 HCV chronically infected adults. Subjects were naive to anti-HCV treatments. Subjects were randomized 1:1:1 to TPV 8 weeks, TPV 12 weeks, or placebo Randomization was stratified to optimize balance for baseline HCV load (< or >= 800K IU/ml) and genotype 1 subtype. Both arms also received a background regimen of RBV plus PIA-2, either for 14 weeks (anyone without EVR, where EVR is defined as 2 log decrease in HCV RNA at week 12, 48 weeks (with EVR in the placebo arm and in the EVR, non-eRVR subjects of the two TPV arms) or 24 weeks (in the eRVR subjects of the two TPV arms).

#### *2.2.2.2 Trial 111*

Trial 111 was an open label, randomized two-arm, active controlled, multicenter trial. Subjects were adults chronically infected with genotype 1 HCV who were treatment naive and who achieved an eRVR (undetectable virus at weeks 4 and 12) on a first regimen of 12 weeks of TPV and 20 weeks of RBV plus PI. Subjects were randomized at week 20 1:1 to finish RBV+PI at week 24 or week 48. Subjects who were not eRVR at the week 20 assessment received RBV+PI out to week 48 but were not compared to any control group in the trial. The comparison is thus 24 weeks of RBV+PI vs 48 weeks of RBV+PI for subjects who are eRVR after 12 weeks of TPV+RBV+PI.

One will notice that trial 108 will show that 12 weeks of TPV+RBV+PI can be followed by an additional 12 weeks of RBV+PI if the subject has eRVR and lead to better results than 48 weeks of RBV+PI alone; this study will answer a question left open by trial 108: given a subject is eRVR after 12 weeks of TPV+RBV+PI, does an additional 36 weeks of RBV+PI do any better than only an additional 12 weeks?

#### *2.2.2.3 Trial 216*

Trial 216 was a double blind, randomized three-arm, placebo controlled, multicenter trial. Subjects were adults chronically infected with genotype 1 HCV who had failed to achieve SVR on a previous regimen of PI+RBV. Subjects were randomized 2:2:1 to TPV-12, TPV-12(DS)=delayed start TPV, or Placebo. All arms also received 48 weeks of PI+RBV. Randomization was stratified by prior failure type (partial non-responder, null non-responder, or relapser) and by baseline HCV RNA level (< or >= 800K IU/ml). Here non-responder means detectable virus at EOT; partial means with >=2 log drop in HCV RNA at week 12 of prior therapy; null means with <2 log drop in HCV RNA at week 12; relapser means undetectable virus at EOT, detectable virus at EOT+24 weeks.

### *2.2.3 Patient Accounting and Baseline Characteristics*

#### *2.2.3.1 Trial 108*

In trial 108, 1095 subjects were randomized, 365 to each of the three arms; all but 7 were treated. Patient status is given in table 2.2.3.1 A. Discontinuations are sub-divided once by date and once by reason.

TABLE 2.2.3.1 A
PATIENT STATUS, TRIAL 108 NAIVE

| Arm | TPV_8_wks | TPV_12_wks | Placebo |
|---|---|---|---|
| Randomized | 365 | 365 | 365 |
| Treated | 364 | 363 | 361 |
| Discontinued | 104 | 95 | 159 |
| <12_Weeks | 47 | 36 | 20 |
| 12_Weeks, non-EVR | 7 | 11 | 43 |
| 13-23_Weeks | 11 | 16 | 5 |
| 24-47_Weeks, non-eRVR | 6 | 5 | 16 |
| 24-47_Weeks, viral failure | 33 | 27 | 75 |
| Completed | 260 | 268 | 202 |
| 24_Weeks, eRVR | 191 | 195 | |
| 48_Weeks | 69 | 73 | 202 |

The study population was 59% male and 88% white with a median age of 49 years. 77.1% had baseline HCV RNA levels >=800K

IU/mL. Of the 1088 subjects who received at least 1 dose of study drug, 409 (38%) had no or minimal fibrosis, 448 (41%) had portal fibrosis, 163 (15%) had bridging fibrosis, and 68 (6.3%) had cirrhosis. 58% had HCV genotype 1a.

### *2.2.3.2 Trial 111*

In trial 111, 540 subjects began treatment. 100 of them discontinued before week 20 and were not available for randomization; of these 13 were eRVR at week 12 and would have been eligible for randomization. A further 118 reached week 20 but were not eRVR and thus were not eligible for randomization. 322 subjects were eRVR and were randomized. Patient status is given in table 2.2.3.2 A.

TABLE 2.2.3.2 A
PATIENT STATUS, TRIAL 111 NAIVE

| Status at Week 20 | eRVR+ | eRVR+ | eRVR- |
|---|---|---|---|
| Arm | R+P_24_wks | R+P_48_wks | |
| Randomized | 162 | 159* | |
| Treated | 162 | 159 | 119 |
| Discontinued | 1 | 40 | 39 |
| 13-23_Weeks | 1 | 12 | 7 |
| 24_Weeks, viral failure | . | 4 | 16 |
| 25-47_Weeks, viral failure | . | 2 | 2 |
| 25-47_Weeks, other | . | 22 | 14 |
| Completed | 161 | 119 | 79 |
| At 72 week assessment | 155 | 147 | 103 |

* two eRVR- subjects were erroneously randomized to the 48 week eRVR- group but were discontinued before planned EOT

The study population was 60% male and 79% white with a median age of 51 years. 82% had baseline HCV RNA levels >=800K IU/mL. Of the 540 subjects initially enrolled, 147 (27%) had no or minimal fibrosis, 244 (45%) had portal fibrosis, 88 (16%) had bridging fibrosis, and 61 (11.3%) had cirrhosis. 72% had HCV genotype 1a.

### *2.2.3.3 Trial 216*

In trial 216, 663 subjects were randomized to one of the three arms. All were treated except one placebo subject. Patient status is given in table 2.2.3.3 A. Discontinuations are sub-divided once by reason and once by number of drugs completed.

TABLE 2.2.3.3 A
PATIENT STATUS, TRIAL 216, PRIOR FAILURES

| Arm | TPV-12 | TPV-12-DS | Placebo |
|---|---|---|---|
| Treated | 266 | 264 | 132 |
| Base HCV<800K | 28 | 30 | 18 |
| Base HCV>=800K | 238 | 234 | 114 |
| Relapsers | 145 | 141 | 68 |
| Non-responders | | | |
| Null | 72 | 75 | 37 |
| Partial | 49 | 48 | 27 |
| Completed study | 245 | 248 | 110 |
| Discontinued | 21 | 16 | 22 |
| AE | 1 | 2 | 2 |
| LTFU | 20 | 14 | 20 |
| Completed drugs | | | |
| At least one | 215 | 226 | 88 |
| All three | 166 | 185 | 50 |

The study population was 69% male with a mean age of 50 years. They were 93% white, 5% black. Of the 662 subjects who received at least 1 dose of study drug, 154 (23%) had no or minimal fibrosis, 192 (29%) had portal fibrosis, 147 (22%) had bridging fibrosis, and 169 (26%) had cirrhosis. 53% had HCV genotype 1a.

## *2.2.4 Summary of Methods of Assessment*

### *2.2.4.1 Schedule of Measurements*

In trial 108 patients had HCV RNA measured at weeks 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 36, 40, 48, 60, and 72, as well as at weeks 4, 12, and 24 weeks post EOT, even the subject stopped early. Viral sequencing was done at all these times.

In trial 111 patients had HCV RNA measured at weeks 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, 28, 36, 48, 60, and 72, as well as at weeks 4, 12, and 24 weeks post EOT, even the subject stopped early. Viral sequencing was done at all these times.

In trial 216 patients had HCV RNA measured at weeks 0, 1, 2, 4, 5, 6, 8, 10, 12, 14, 16, 20, 24, 36, 48, and 72, as well as at weeks 4, 12, and 24 weeks post EOT, even the subject stopped early. Viral sequencing was done at all these times.

#### *2.2.4.2 Assessment of Treatment Effects*

In all three trials, the primary efficacy variable was the percent of subjects with sustained viral response (SVR), defined as HCV RNA below limit of quantitation (BLQ) both at planned end of therapy and 24 weeks later. The FDA reviewers also expect the endpoint of undetectable virus to be met at week 72 from start of therapy, regardless of whether treatment ended at week 24 or 48.

### *2.2.5 Summary of Statistical Analysis*

For trials 108, a logistic regression was used to predict SVR as a function of treatment, genotype 1 subtype( 1a or not), and baseline HCV RNA level (a binary variable, < or > 800K IU/ml).

For trials 111, the primary analysis seems to have used a simple normal approximation with supportive analyses using a logistic regression predicting SVR as a function of treatment, genotype 1 subtype, and race (black or non-black) and a Cochran-Mantel-Haenszel interval, using the same covariates as stratifiers.

For trials 216, the logistic regression predicted SVR as a function of treatment, type of prior response, baseline HCV RNA, and the interaction of treatment with type of prior response. Subjects with missing data at week 72 were considered as failures.

Trials 108 and 216 were superiority trials; trial 111 was a non-inferiority trial with the rule for declaring 24 weeks of RBV+PI as non-inferior to 48 weeks of RBV+PI was 10.5%. I.e. as long as a 95% lower confidence bound for the difference was greater than -10.5%

In all trials, the primary analysis used SVR24 post EOT planned, i.e. 24 weeks after the planned time that therapy ended, either week 24 or week 48. A secondary analysis used SVR24 post EOT actual, i.e. 24 weeks after the actual time that therapy ended. Actual either equals planned if the subject does not discontinue or is earlier than planned if the subject discontinues early.

If an HCV RNA measurement from a central laboratory was missing at the 24 week post planned EOT or at week 72, it was imputed with the HCV RNA values from a local laboratory if available. This imputation rule was also applied to any confirmation visits at the 24 post planned EOT and at week 72. A supportive analysis was performed without this imputation; subjects with local but no central laboratory HCV RNA measurements at these time points were considered failures in this analysis. If HCV RNA value was missing, it was replaced with <25 IU/mL HCV RNA undetected if the observations at time points immediately before (including baseline value) and after the missing value both were reported as <25 IU/mL HCV RNA undetected; otherwise, the missing HCV RNA value was imputed via linear interpolation. If no HCV measurements were made posterior to the missing measurement, it was considered above LOQ and thus a failure.

### *2.2.6 Summary of Applicant's Results*

#### *2.2.6.1 Percent SVR24_Post*

Tables 2.2.6.1 A-C give the results of the applicant's analysis on the primary endpoint, percent with sustained viral suppression (SVR) at 24 weeks post planned EOT for trials 108, 111, and 216, respectively.

TABLE 2.2.6.1 A
SVR24_Post, SVR72, SVR24_Actual, TRIAL 108

| Endpoint | Rate_TPV_8_wks | Rate_TPV_12_wks | Rate_Placebo |
|---|---|---|---|
| SVR24_Post | 250/364=69% | 271/363=75% | 158/361=44% |
| 95% Limits-PBO | (18%, 32%) | (24%, 38%) | |
| SVR72 | 243/364=67% | 265/363=73% | 158/361=44% |
| 95% Limits-PBO | (16%, 30%) | (22%, 36%) | |
| SVR24_Actual | 251/364=69% | 274/363=75% | 158/361=44% |
| 95% Limits-PBO | (18%, 32%) | (25%, 39%) | |

In the applicant's analysis of trial 111, one eRVR- subject mistakenly randomized to 48 weeks of RBV+PI was included in the analysis, leading to a denominator of 160 instead of 159. The improperly included subject was a failure. Two sensitivity analyses are given, s1 used the original definition of undetectable, s2 only counted data recorded in the pre-defined visit windows.

TABLE 2.2.6.1 B
SVR24_Post, SVR72, SVR24_Actual, TRIAL 111

| Endpoint | eRVR+ Rate_RP_24_wks | eRVR+ Rate_RP_48_wks | eRVR- Rate_48_wks |
|---|---|---|---|
| SVR24_Post | 149/162=92% | 140/160=88% | 76/118=64% |
| 95% Limits-48wks | (-2.1%, 11.1%) | | |
| SVR24_Post_s1 | 148/162=91% | 137/160=86% | 76/118=64% |
| 95% Limits-48wks | (-1.2%, 12.7%) | | |
| SVR24_Post_s2 | 134/162=83% | 132/160=83% | 73/118=62% |
| 95% Limits-48wks | (-8.1%, 8.5%) | | |
| SVR72 | 141/162=87% | 140/160=87% | 76/118=64% |
| 95% Limits-48wks | (-7.7%, 6.8%) | | |
| SVR24_Actual | 149/162=92% | 144/160=88% | 78/118=66% |
| 95% Limits-48wks | (-4.3%, 8.2%) | | |

TABLE 2.2.6.1 C
SVR24_POST, TRIAL 216

| Population | Rate_T12 | Rate_T12_DS | Rate_Pbo |
|---|---|---|---|
| Overall | 171/266=64% | 175/264=66% | 22/132=17% |
| 95% Limits-PBO | (36.8%, 56.7%) | (39.9%, 59.7%) | |
| 95% Limits-DS | (-13.0%,7.0%) | | |
| Prior Relapser | 121/145=83% | 124/141=88% | 16/68=24% |
| 95% Limits-PBO | (48.8%, 72.2%) | (53.5%, 76.2%) | |
| 95% Limits-DS | (-12.6%, 3.9%) | | |
| Prior Non-Responder | 50/121=41% | 51/123=42% | 6/64=9% |
| 95% Limits-PBO | (22.9%, 47.0%) | (23.4%, 47.3%) | |
| 95% Limits-DS | (-13.6%, 12.9%) | | |
| Null-Responder | 21/72=29% | 25/75=33% | 2/37=5% |
| 95% Limits-PBO | (11.6%, 37.7%) | (15.8%, 42.2%) | |
| 95% Limits-DS | (-19.6%, 11.0%) | | |
| Partial Responder | 29/49=59% | 26/48=54% | 4/27=15% |
| 95% Limits-PBO | (24.7%, 63.6%) | (20.3%, 59.7%) | |
| 95% Limits-DS | (-15.6%, 23.9%) | | |

In this table the SVR percentages in each arm are computed directly; the confidence intervals for the percentage differences telaprevir minus placebo and for TPV - TPV with DS are computed from the logistic regression using treatment, type of prior response, baseline HCV RNA, and the interaction of treatment with type of prior response as predictors. As one can see from the lower bounds in TPV-PBO intervals, those differences are highly significant even with multiple comparison adjustments.

### *2.2.7. Summary of Applicant's Conclusions*

The applicant concluded that in trial 108, higher rates of SVR were attained with telaprevir added on to standard of care (SOC) than with SOC alone for treatment naïve subjects with genotype 1 chronic HCV infection. This was attained across sub-populations including high risk groups such as Blacks, Hispanics, cirrhotics, diabetics, and those with high baseline HCV. Supportive analyses were concordant with the primary analysis. Late relapse rates were very low and eRVR rates as well as SVR rates were higher in the TPV arms.

Trial 111 demonstrated the non-inferiority of the 24 week PI+RBV to the 48 week PI+RBV for subjects who had achieved eRVR on 12 weeks of TPV+PI+RBV. As with trial 108, results were consistent across a wide range of sub-populations, including the high risk subpopulations.

Trial 216 demonstrated the superiority of 12 weeks of telaprevir with 48 weeks of SOC to 48 weeks of SOC alone in subjects who had previously failed an SOC regimen.

# 3. Statistical Evaluation

## *3.1 Evaluation of Efficacy*

### *3.1.1 Basic Findings*

The summary results of re-analysis of the applicant's computer files by the FDA statistical reviewer is given below. Table 3.1.1 A shows the rate of subjects with sustained viral suppression at 24 weeks post EOT

TABLE 3.1.1 A
PERCENT OF SUBJECTS SVR24 BY ARM AND TRIAL

| TRIAL | ARM | SVR24 RATE | Difference vs Comparator | 95% Confidence Limit Lower | Upper |
|---|---|---|---|---|---|
| 108 | TPV_8_wk | 267/364=73% | 27.1% | 19.2% | 34.9% |
| | TPV_12_wk | 287/363=79% | 32.8% | 25.2% | 40.4% |
| | Placebo | 167/361=46% | | | |
| 111 | eRVR+ P+R_24_wk | 150/162=93% | 0.1% | -6.4% | 6.7% |
| | eRVR+ P+R_48_wk | 147/159=92% | | | |
| | eRVR- P+R_48_wk | 83/119=70% | 22.7% | 12.2% | 33.2% |
| 216 | TPV-12 | 174/266=65% | 48.9% | 39.1% | 58.6% |
| | TPV-12-DS | 176/264=67% | 50.1% | 40.4% | 59.8% |
| | PLACEBO | 22/133=17% | | | |

The comparator arms, against which the others in the trial are compared, are placebo in trials 108 and 216 and eRVR+ P+R_48_wk in trial 111. The reader should remember that in trial 111 randomization takes place at week 14 and only eRVR+ subjects are randomized between 24 and 48 weeks of P+R. The comparison to eRVR- is an observational, not a randomized, comparison.

There is a clear pattern here. Telaprevir, even for 8 weeks, is almost 30% better than placebo on the primary endpoint for naive patient when each is added to PI+RBV. TPV for 12 weeks is 50% better than just repeating PI+RBV for prior treatment failures.

Furthermore, for naive subjects, if one achieves eRVR then one can discontinue the somewhat toxic PI+RBV regimen after 24 weeks, instead of 48, with no loss of efficacy. Table 3.1.2 B

below gives the comparison of 24 week PI+RBV regimen for eRVR+ subjects to the 48 week regimen for eRVR- subjects from trial 108. That is a non-randomized comparison with subjects with good prognosis getting 24 weeks and subjects with poor prognosis getting 48 weeks so it is not as useful as the comparison from trial 111 given above.

The SVR24 used in obtaining these totals was computed from the applicant's computer files using the following algorithm. A snapshot of the last HCV in the week 24 window was used and a subject was counted as SVR24 if that HCV was <= 50 IU/ml. If there was no HCV in the week 24 window, then the last post EOT value before week 24 was carried forward (LOCF). If there were no post EOT HCV measurements, then the subject was not SVR24. The justification for this method will be discussed in detail in sections 3.1.4 and 3.1.5 below.

### *3.1.2 Comparisons of Results for Response Guided Therapy*

For treatment naive subjects, there are three basic questions to be answered:

1. Is telaprevir for 8 weeks superior to placebo as an add-on to 24 or 48 weeks of PI+RBV? (Duration of the PI+RBV therapy is to be response-guided.)
2. Is telaprevir for 12 weeks superior to telaprevir for 8 weeks as an add-on to 24 or 48 weeks of PI+RBV?
3. If a patient achieves eRVR after 12 weeks of TPV plus PI+RBV, is continuing PI+RBV out to 48 weeks superior to continuing it only to 24 weeks?

Table 3.1.2 A gives the answers to these questions as best as this NDA can do.

TABLE 3.1.2 A
COMPARISON OF EFFICACY USING SVR24, LOQ=50

| Comparison | Mean Diff | 95%_Limits Lower | Upper | Test Rate | Control Rate |
|---|---|---|---|---|---|
| TRIAL_108(Naive) | | | | | |
| 8_WK_TPV_VS_PBO | 27.1% | 19.2% | 34.9% | 267/364=73.0% | 167/361=46.0% |
| 12_WK_TPV_VS_PBO | 32.8% | 25.2% | 40.4% | 287/363=79.0% | 167/361=46.0% |
| TPV_12_WK_VS_8_WK | 5.7% | -1.4% | 12.8% | 287/363=79.0% | 267/364=73.0% |
| TRIAL_108(Naïve and eRVR- on initial therapy) | | | | | |
| 8_WK_TPV_VS_PBO | 13.5% | 2.8% | 24.3% | 87/157=55.0% | 139/332=42.0% |
| 12_WK_TPV_VS_PBO | 18.8% | 8.0% | 29.6% | 91/150=61.0% | 139/332=42.0% |
| TPV_12_WK_VS_8_WK | 5.3% | -7.4% | 17.9% | 91/150=61.0% | 87/157=55.0% |
| TRIAL_111(Naïve and eRVR+ on TPV) | | | | | |
| 24_WK_P+R_VS_48_WK | 0.1% | -6.4% | 6.7% | 150/162=93.0% | 147/159=92.0% |
| TRIAL_108(Naïve and eRVR+ on initial therapy) | | | | | |
| 8_WK_TPV_VS_PBO | -9.6% | -18.8% | -0.4% | 180/207=87.0% | 28/29=97.0% |
| 12_WK_TPV_VS_PBO | -4.5% | -13.2% | 4.1% | 196/213=92.0% | 28/29=97.0% |
| TPV_12_WK_VS_8_WK | 5.1% | -1.6% | 11.8% | 196/213=92.0% | 180/207=87.0% |
| | . | | | | |
| TRIAL_216(Prior Failure) | | | | | |
| TPV_12_VS_PBO | 48.9% | 39.1% | 58.6% | 174/266=65.0% | 22/133=17.0% |
| TPV_12(DS)_VS_PBO | 50.1% | 40.4% | 59.8% | 176/264=67.0% | 22/133=17.0% |
| TPV_12_VS_TPV_12(DS) | -1.3% | -10.5% | 8.0% | 174/266=65.0% | 176/264=67.0% |

With respect to question 1, one can see that either 8 week or 12 week TPV is superior to placebo, most likely by 27-33% and with 95% confidence by 19-25% when they are added to 48 weeks of PI+RBV in naive subjects. Furthermore, if one looks at the subset

of subjects who failed to achieve eRVR status, the TPV arms still beat the placebo arm by 13-19% and by at least 3-8% with 95% confidence.

With respect to question 2, one can see that 12 weeks of TPV is most likely 5-6% superior to 8 weeks of TPV but with 95% confidence, it is no more than 13% better. This margin of superiority is the same whether or not subjects achieve eRVR+ by week 12.

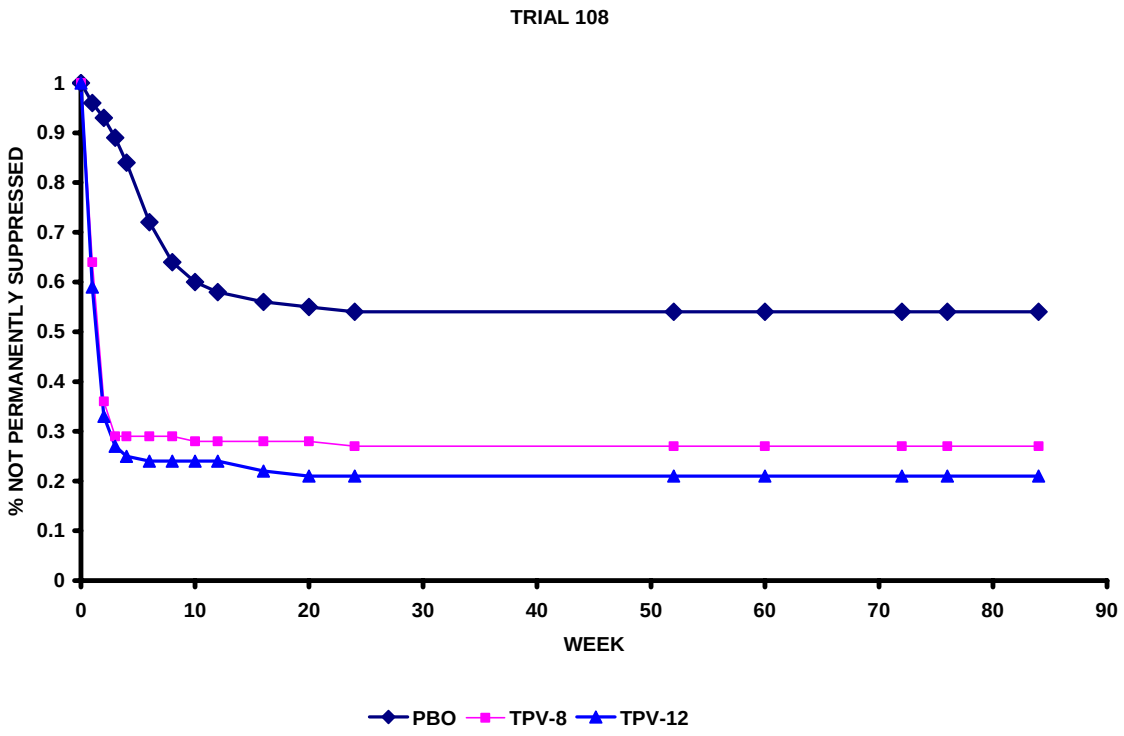
With respect to question 3, one can see that, for subjects in trial 111 with eRVR+ at 12 weeks of triple therapy, there is no benefit in higher SVR24 rates with 48 weeks of PI+RBV compared to only 24 of that regimen. (24 weeks was estimated to be 0.1% better but that has to be statistical noise.) With 95% confidence, 24 weeks can be no more than 6% worse than 48 weeks.

A secondary, non-randomized comparison of 24 vs 48 weeks of PI+RBV can also be drawn from the eRVR+ subjects in trial 108. These subjects were deterministically treated with 24 weeks of PI+RBV if they had been on TPV and with 48 weeks of PI+RBV if they had been on placebo. In this non-randomized comparison, the 48 weeks was slightly better than the 24 weeks: 5% or 10% better depending on whether the TPV had been given for 12 or 8 weeks. One should also notice that the conditional success rate (SVR24), given eRVR+, is consistent across both trials: 92-93%. (The placebo rate was 97% but that was based on a small sample, since only 29 out of 361 placebo subjects were eRVR+. Had there been 27 instead of 28 SVR24’s, the placebo success rate would also have been 93%.)

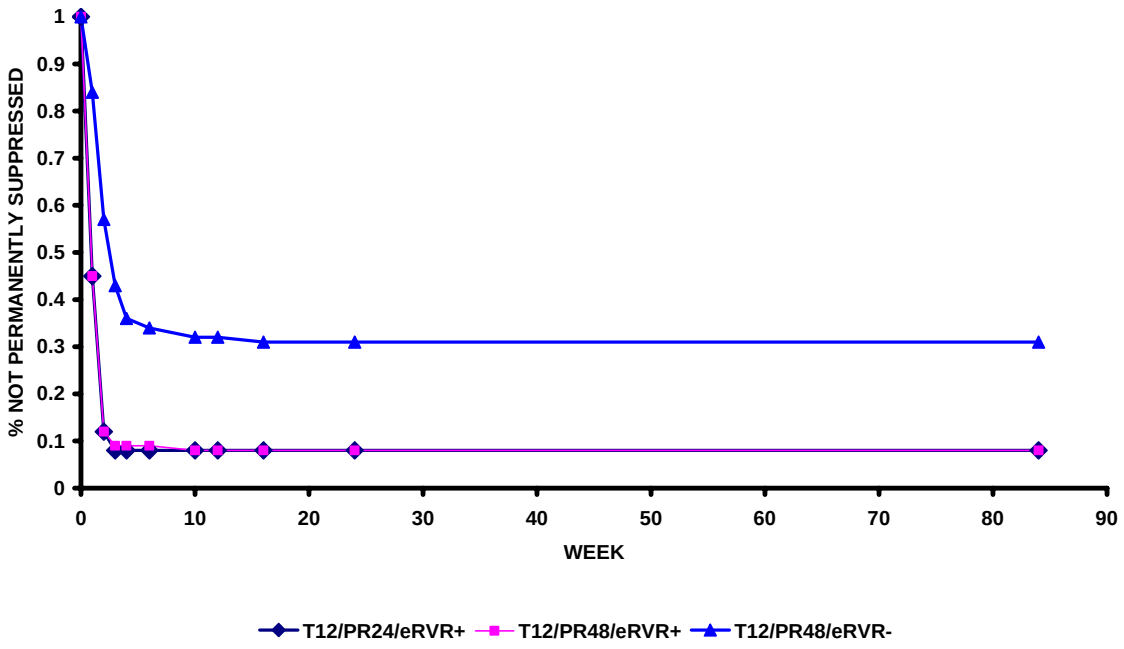
With respect to subjects previously failing a dual PI+RBV therapy, 12 of TPV, with or without a delayed start, gives an improvement in SVR24 rate that is most likely 50% and with 95% confidence is at least 40%. There are no data to address, for subjects with previous PI+RBV treatment failures how 8 weeks of TPV compares to 12 weeks or how 24 weeks of PI+RBV for eRVR+ subjects compares with 48 weeks.

### *3.1.3 Time to Suppression: Kaplan-Meier Curves*

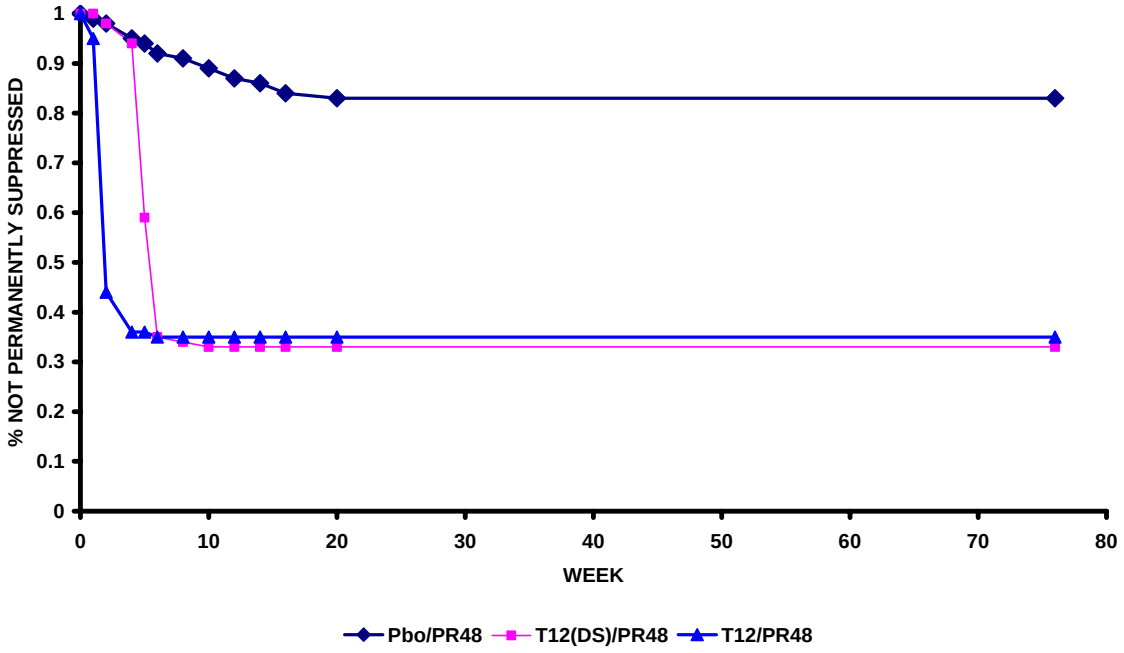
The following curves show the Kaplan-Meier curves for time until first permanent suppression. The curves show the percent of subjects whose virus has not yet become permanently suppressed, i.e. virus will never be above LOQ for the rest of the trial.



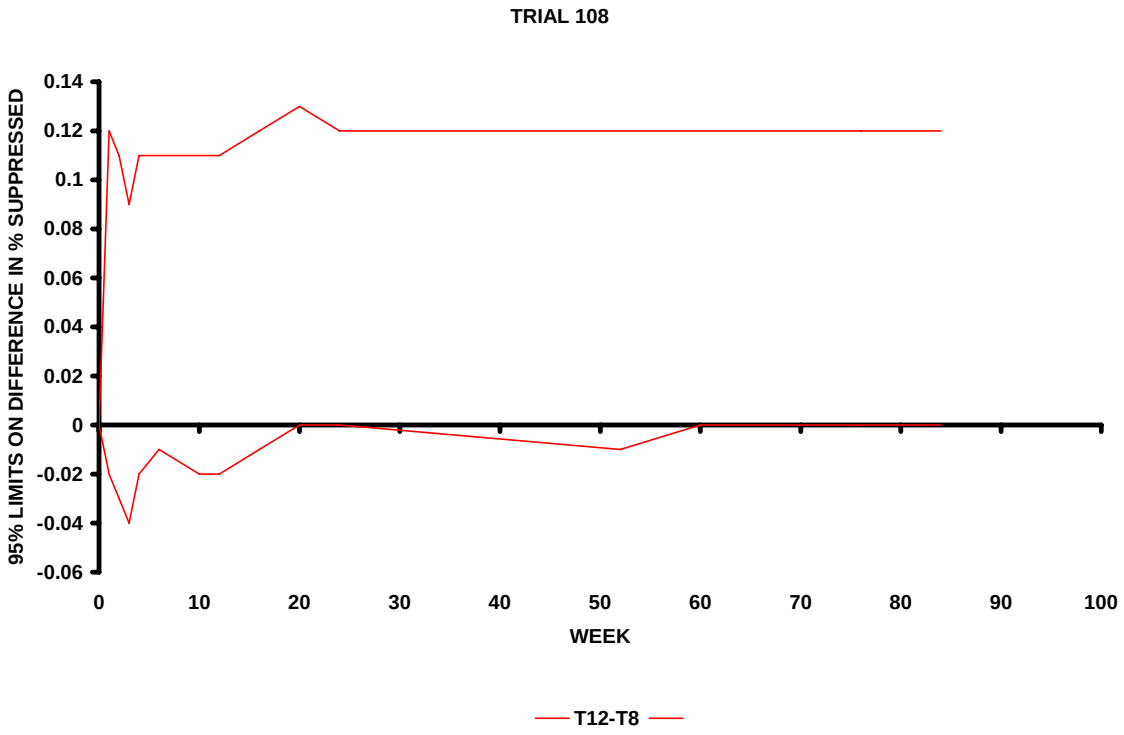
TRIAL 111




TRIAL 216

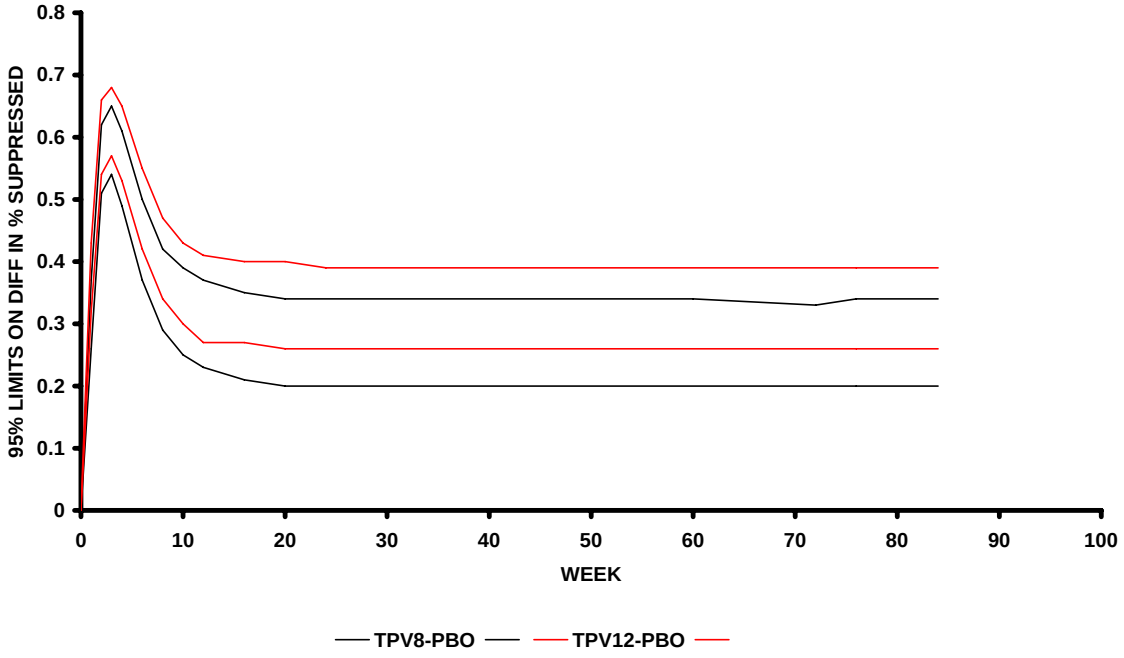


The next curves show the 95% confidence limits for the difference in time to permanently suppressed for several pairs of arms in the three trials: 12 week - 8 week TPV in trial 108

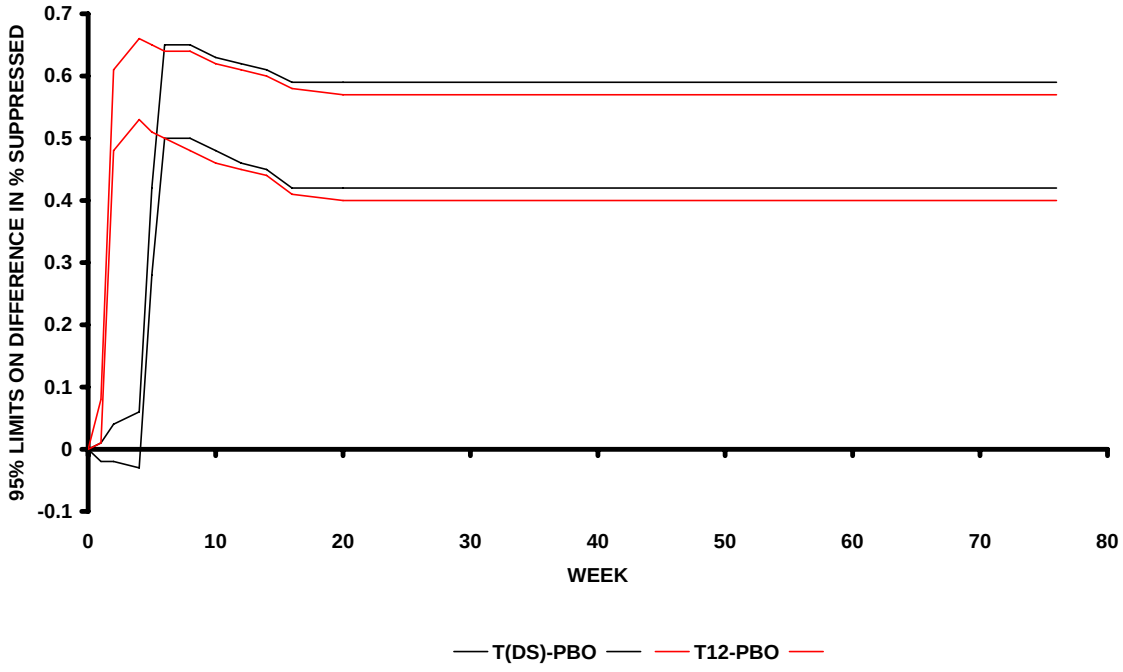



These next two graphs show the differences between TOV and placebo in trials 108 and 216. One will notice that there is clinically meaningful and statistically significant separation by week 12.

TRIAL 108




TRIAL 216



### *3.1.4 Issues with Missing and with Unquantifiable but Detectable Data*

There is a technical difficulty involved in the assessment of BLQ HCV RNA. In the original protocol, the COBAS Taqman assay was considered to have a limit of detection (LOD) = 10 IU/ml but a limit of quantitation (LOQ) = 25 IU/ml. During the course of the study, the applicant concluded from reported measurements that the COBAS Taqman assay can have transient detectable HCV levels. Therefore, the applicant defined suppressed HCV as any of 1) one undetectable HCV RNA, 2) one detectable HCV RNA still below LOQ = 25 IU/ml preceded and succeeded by at least one undetectable HCV RNA, or 2) two detectable but BLQ HCV RNA's preceded and succeeded by at least two undetectable HCV RNA's.

The FDA reviewer finds this problematic because there does not seem to be any explanation as to when it was decided to take multiple measurements within the EOT and 24 week post EOT windows.

Further discussions with the CDRH, the Center which approved the assay itself, revealed that an LOQ of 50 IU/ml is recommended by that Center. This is consistent with AASLD recommendations.

In order to explore the extent to which these issues involving the LOQ and issues involving missing data influence the final efficacy conclusions, the FDA statistical reviewer has recalculated the percent of subjects SVR at week 24 post EOT using several different algorithms:

1. The applicant's own results
2. Using the maximum observed HCV during the EOT to 24 week post window and counting a missing observation at the week 24 post window as failure
3. Using the snapshot at the week 24 post window and replacing a missing value by the last observation carried forward (LOCF) or, if there is a later HCV observation by the next observation carried backward (NOCB).

Algorithms 2 and 3 were computed using both 25 and 50 IU/ml as the LOQ. The visit by visit HCV records for any subject who was not classified the same way by all algorithms were examined individually. The results of these computations may be summarized in table 3.1.4 A.
Across the three trials 70 subjects out of 2191 (3.2%) had SVR24 outcomes that varied with the choice of algorithm.

TABLE 3.1.4 A
DISCREPANCIES IN SVR BY DIFFERENT ALGORITHMS

| APPLICANT | SNAPSHOT WK_24 LOQ=25 | WK_24 LOQ=50 | MAXIMUM EOT-24 | COUNT |
|---|---|---|---|---|
| Concordant | | | | 2121 |
| N | N | N | >50 | 718 |
| Y | Y | Y | <10 | 1403 |
| Discordant | | | | 70 |
| N | Y | Y | <10 | 6 |
| N | Y | Y | >=10, <=25 | 19 |
| Y | Y | Y | >=10, <=25 | 6 |
| Y | Y | Y | >50 or missing | 3 |
| N | N | Y | >25, <=50 | 2 |
| N | Y | Y | >25, <=50 | 1 |
| N | Y | Y | >50 or missing | 33 |

Based on examination the individual HCV histories, the first 6 of these 70 are mistakes by the applicant: the EOT to week 24 post histories were complete and all HCV were <10. (5 of these subjects were in the two TPV arms in trial 108 and the other in the T12/PR48 arm of trial 216. Reclassifying them increases the estimate of the TPV benefit.)

The next 28 discordant subjects had one or more HCV measurements in the EOT to 24 week post window that were >10 but had their final visit at week 24 post with HCV <10. 9 of these 28 had detectable HCV bracketed by undetectables and were counted as SVR24 by the applicant, the other 20 had insufficient undetectables for the applicant’s rule to count them as SVR24. One will notice that 25 out of these 28 had no post EOT HCV>25 and the 3 subjects that had one HCV >50 were all counted as SVR24 by the applicant's rule. Of these 29 subjects, 6 were trial 108 placebos, 17 were trial 108 telaprevirs, 2 were trial 216 placebos, and 3 were trial 216 telaprevirs.

The next 2 discordant subjects were the only two where it mattered whether one used the LOQ of 25 as originally proposed or the LOQ of 50 recommended by the CDRH. These two subjects had week 24 post HCV between 25 and 50. They were both in trial 111 and one was in the non-randomized arm.

The last 34 discordant subjects had either a missing value at the week 24 post visit or had enough post EOT >25 that the applicant's rule counted them as not SVR24 but the snapshot HCV at week 24 post was <25. 27 of these 34 had all their post EOT HCV measurements <10 but were simply missing the last visit; another 5 had maximum post EOT HCV measurement <100. Of these 34, 3 were trial 108 placebos (including the only two with maximum EOT HCV >1000), 15 were trial 108 telaprevirs, one was 24 week P+R in trial 111, 7 were 48 week P+R in trial 111, 5 were non-randomized in trial 111, and 3 were trial 216 telaprevirs.

Table 3.1.4 B gives another summary of the effects of different choices of the algorithm for SVR24. This table shows the minimum and maximum value of percent of SVR24 subjects in each arm of each trial, using the various different algorithm.

TABLE 3.1.4 B
RANGES OF ESTIMATED PERCENT SVR24
WITH DIFFERENT ALGORITHMS

| TRIAL, ARM | PERCENT SVR24 MINIMUM | MAXIMUM |
|---|---|---|
| TRIAL_108 | | |
| PBO | 43.8% | 46.3% |
| TPV-8 | 68.4% | 73.4% |
| TPV-12 | 74.7% | 79.1% |
| | | |
| TRIAL_111 | | |
| T12/PR24/eRVR+ | 92.0% | 92.6% |
| T12/PR48/eRVR+ | 87.5% | 91.9% |
| T12/PR48/eRVR- | 64.4% | 68.6% |
| | | |
| TRIAL_216 | | |
| Pbo/PR48 | 15.0% | 16.5% |
| T12(DS)/PR48 | 65.9% | 66.7% |
| T12/PR48 | 63.9% | 65.4% |

One will notice that the superiority of telaprevir to placebo by some 25% in trial 108 (naive subjects) and by some 50% in trial 216 (previous failures on PI+RBV) is not affected by the choice of algorithm. Likewise the estimated (non-statistically significant) superiority of 12 weeks of telaprevir over 8 weeks by some 5-6% in trial 108 is unaffected as is the smaller estimated superiority of 24 weeks of PI+RBV over 48 weeks of PI+RBV in eRVR+ subjects after 12 weeks of telaprevir in trial 111. Based on these observations, the FDA statistical reviewer will use the snapshot result at week 24 post EOT in the remainder of the analyses in this review. The CDRH recommended limit of 50 will also be used instead of 25, given that that changes results for exactly one randomized subject, in trial 111.

### *3.1.5 Rebounds and Use of LOCF for Missing*

Table 3.1.5 A is intended to justify using LOCF to replace missing values in post EOT HCV measurements. It gives the percentage of observed HCV that are undetectable given that the previous visit's HCV was >LOQ(=50) or <LOQ. The results are given for each post EOT visit. In the table PLAN is the number of weeks before planned EOT; WEEK is the time of the visit used to predict whether the subsequent HCV measurement will be < or > LOQ. One can see that never less than 91% of visits with HCV<50 are followed by visits with HCV<50. HCV>50 after EOT is usually followed by another HCV>50. This table thus confirms the decision to use snapshot at week 24 post EOT with LOCF.

TABLE 3.1.5 A
PERCENT WITH NEXT HCV UNDETECTABLE

| | | CURRENT HCV IS | |
|---|---|---|---|
| PLAN | WEEK | >LOQ | <LOQ |
| TRIAL_108 | | | |
| 24_Weeks | 24 | 0% | 97% |
| | 28 | 0% | 96% |
| | 36 | 3% | 99% |
| | 40 | 0% | 100% |
| | 48 | 0% | 100% |
| | 52 | 0% | 100% |
| | 60 | 6% | 100% |
| | 72 | | 97% |
| 48_Weeks | 48 | 1% | 95% |
| | 52 | 2% | 91% |
| | 60 | 1% | 98% |
| | 72 | 0% | 100% |
| TRIAL 111 | | | |
| Non-rand | 24 | 0% | 97% |
| | 28 | 0% | 96% |
| | 36 | 0% | 98% |
| | 40 | 0% | 100% |
| | 48 | 0% | 95% |
| | 52 | 0% | 99% |
| | 60 | 0% | 98% |
| | 72 | 0% | 100% |

TABLE 3.1.5 A (continued)
PERCENT WITH NEXT HCV UNDETECTABLE

| PLAN | WEEK | CURRENT HCV IS >LOQ | <LOQ |
|---|---|---|---|
| TRIAL_111 | | | |
| 24_Weeks | 24 | 0% | 98% |
| | 28 | 0% | 98% |
| | 36 | 0% | 99% |
| | 40 | 0% | 100% |
| | 48 | 0% | 100% |
| | 52 | 0% | 100% |
| | 60 | 0% | 99% |
| 48_Weeks | 48 | 0% | 100% |
| | 52 | 0% | 99% |
| | 60 | 0% | 100% |
| | 72 | | 100% |
| TRIAL_216 | | | |
| 48_Weeks | 48 | 0% | 92% |
| | 52 | 0% | 93% |
| | 60 | 0% | 98% |
| | 72 | 0% | 100% |

Table 3.1.5 B shows in detail the effect of using LOCF to calculate SVR24 when the last observation is at EOT, EOT+4, EOT+12. The table gives, for all subjects observed successful (i.e. suppressed) at weeks 0, 4, and 12 post EOT, the percentages of such tentatively successful subjects who a) were observed to rebound subsequently, b) were last observed suppressed at week 0, c) were last observed suppressed at week 4, d) were last observed suppressed at week 12, or e) were observed suppressed at week 24. Obviously category b) is not present for subjects observed suppressed at week 4 and similarly.

The salient features of this table are the following:

1. Almost all subjects on telaprevir fall into category e)observed suppressed at week 24 when starting from any of weeks 0, 4, or 12.
2. Placebo subjects are much more likely to rebound than telaprevir subjects after being observed suppressed at week 0 or week 4.
3. Placebo subjects in trial 216 observed suppressed at week 0 are the only group where it is more likely that they will be observed to rebound than that they will be observed suppressed at week 24.

Two points need to be made about the higher proportion of subsequently observed failures for placebo subjects observed to be suppressed at weeks 0 or 4 post EOT. First, there are no placebo subjects who were observed to be suppressed at week 0 and were then lost to follow-up. Thus, the LOCF algorithm makes no imputations for SVR24 based on week 0 post EOT for placebo subjects. Second, with respect to possible use of LOCF in future submissions. these data imply that inferring SVR24 by LOCF from week 0 post EOT will bias conclusions in favor of the placebo. Therefore, any applicant with a new DAA (direct acting anti-viral) will prefer to collect full data rather than depend on the results of LOCF imputations.

TABLE 3.1.5 B

PERCENTAGES OF SUBSEQUENT REBOUNDS OR CONFIRMED SUCCESS FOR SUBJECTS OBSERVED SUPPRESSED BETWEEN EOT AND 24 WEEKS POST

| TRIAL_108 | PBO | TPV-12 | TPV-8 |
|---|---|---|---|
| Observed success at 0 | | | |
| Observed rebound later | 25.6% | 4.0% | 7.0% |
| Last success at 0 | 0.0% | 0.3% | 0.7% |
| Last success at 4 | 0.0% | 0.0% | 1.1% |
| Last success at 12 | 0.9% | 1.0% | 1.4% |
| Last success at 24 | 73.5% | 94.6% | 89.8% |
| | | | |
| Observed success at 4 | | | |
| Observed rebound later | 19.4% | 2.5% | 4.1% |
| Last success at 4 | 0.0% | 0.0% | 1.1% |
| Last success at 12 | 1.0% | 1.1% | 1.1% |
| Last success at 24 | 79.6% | 96.4% | 93.6% |
| | | | |
| Observed success at 12 | | | |
| Observed rebound later | 4.1% | 0.0% | 1.5% |
| Last success at 12 | 1.2% | 1.0% | 1.5% |
| Last success at 24 | 94.8% | 99.0% | 97.0% |

TABLE 3.1.5 B (continued)

PERCENTAGES OF SUBSEQUENT REBOUNDS OR CONFIRMED SUCCESS FOR SUBJECTS OBSERVED SUPPRESSED BETWEEN EOT AND 24 WEEKS POST

| TRIAL_111 | T12/PR24/eRVR+ | T12/PR48/eRVR+ |
|---|---|---|
| Observed success at 0 | | |
| Observed rebound later | 5.7% | 1.4% |
| Last success at 0 | 0.0% | 2.1% |
| Last success at 4 | 0.0% | 0.0% |
| Last success at 12 | 0.6% | 2.8% |
| Last success at 24 | 93.7% | 93.6% |
| | | |
| Observed success at 4 | | |
| Observed rebound later | 3.2% | 1.5% |
| Last success at 4 | 0.0% | 0.0% |
| Last success at 12 | 0.6% | 2.3% |
| Last success at 24 | 96.1% | 96.2% |
| | | |
| Observed success at 12 | | |
| Observed rebound later | 1.3% | 0.0% |
| Last success at 12 | 0.7% | 2.8% |
| Last success at 24 | 98.0% | 97.2% |

TABLE 3.1.5 B (continued)

PERCENTAGES OF SUBSEQUENT REBOUNDS OR CONFIRMED SUCCESS FOR SUBJECTS OBSERVED SUPPRESSED BETWEEN EOT AND 24 WEEKS POST

| TRIAL_216 | Pbo/PR48 | T12(DS)/PR48 | T12/PR48 |
|---|---|---|---|
| Observed success at 0 | | | |
| Observed rebound later | 58.0% | 11.3% | 8.7% |
| Last success at 0 | 0.0% | 0.0% | 0.0% |
| Last success at 4 | 2.0% | 0.0% | 0.0% |
| Last success at 12 | 0.0% | 0.5% | 1.1% |
| Last success at 24 | 40.0% | 88.2% | 90.2% |
| | | | |
| Observed success at 4 | | | |
| Observed rebound later | 32.3% | 6.1% | 6.0% |
| Last success at 4 | 3.2% | 0.0% | 0.0% |
| Last success at 12 | 0.0% | 0.0% | 1.2% |
| Last success at 24 | 64.5% | 93.9% | 92.9% |
| | | | |
| Observed success at 12 | | | |
| Observed rebound later | 8.7% | 1.7% | 1.1% |
| Last success at 12 | 0.0% | 0.6% | 1.7% |
| Last success at 24 | 91.3% | 97.7% | 97.1% |

### *3.1.6 Comparison of SVR Results with Various Times Post EOT*

An additional question concerns the date appropriate for final measurement. In other words, how well does the result at 12 weeks post EOT predict the results at 24 weeks post EOT with respect to SVR? A total of 21 out 1927 subjects (1.1%) in the randomized arms of the three trials had SVR12 not equal to SVR24. There were also 146 subjects in trial 216 who were missing their week 12 measurement but did have their week 24 measurement. Presumably, had SVR12 been the target endpoint, this missingness would have been substantially reduced.

TABLE 3.1.6 A
COMPARISON OF SUPPRESSION AT 12 AND 24 WEEKS POST EOT,
TRIALS 108 AND 111 (NAIVE)

| TRIAL_108 | PBO | TPV-12 | TPV-8 |
|---|---|---|---|
| NOT_SVR | | | |
| BOTH_MISSING | 7 | 3 | 6 |
| 12_MISSING,_24_ALQ | 1 | 0 | 0 |
| 12_ALQ,_24_MISSING | 0 | 1 | 2 |
| BOTH_ALQ | 151 | 48 | 54 |
| DISCORDANT | | | |
| 12_BLQ,_24_ALQ | 7 | 0 | 4 |
| 12_ALQ,_24_BLQ | 1 | 0 | 0 |
| SVR | | | |
| 12_MISSING,_24_BLQ | 1 | 0 | 0 |
| 12_BLQ,_24_MISSING | 2 | 3 | 4 |
| BOTH_BLQ | 163 | 283 | 258 |

| TRIAL_111 | T12/PR24/eRVR+ | T12/PR48/eRVR+ |
|---|---|---|
| NOT_SVR | | |
| BOTH_MISSING | 1 | 5 |
| BOTH_ALQ | 9 | 5 |
| DISCORDANT | | |
| 12_BLQ,_24_ALQ | 2 | 0 |
| SVR | | |
| 12_BLQ,_24_MISSING | 1 | 4 |
| BOTH_BLQ | 149 | 141 |

TABLE 3.1.6 B
COMPARISON OF SUPPRESSION AT 12 AND 24 WEEKS POST EOT,
TRIAL 216 (EXPERIENCED)

| TRIAL_216 | Pbo/PR48 | T12(DS)/PR48 | T12/PR48 |
|---|---|---|---|
| NOT_SVR | | | |
| BOTH_MISSING | 10 | 1 | 2 |
| 12_MISSING,_24_ALQ | 48 | 41 | 50 |
| 12_ALQ,_24_MISSING | 1 | 1 | 0 |
| BOTH_ALQ | 34 | 28 | 17 |
| DISCORDANT | | | |
| 12_BLQ,_24_ALQ | 2 | 3 | 2 |
| SVR | | | |
| 12_MISSING,_24_BLQ | 0 | 3 | 2 |
| 12_BLQ,_24_MISSING | 1 | 3 | 0 |
| BOTH_BLQ | 21 | 172 | 169 |

Table 3.1.6 C compares the suppression rates at week 24 post EOT and at week 72 after start of therapy in trials 108 and 111. These trials had subjects discontinuing therapy at both 24 and 48 weeks after start so 24 weeks post EOT was not the same time from start of trial for all subjects. The table shows that 2 out of 420 subjects (0.5%) in trial 108 and 1 out of 162 subjects (0.6%) in trial 111 who stopped therapy at 24 weeks had rebounds between week 48 and week 72. There seems to be no cause for concern about viral rebound beyond week 24 post EOT or even beyond week 12 EOT.

TABLE 3.1.6 C
COMPARISON OF SUPPRESSION AT WEEK 24 POST EOT AND WEEK 72
TRIALS 108 AND 111

TRIAL_108

| ARMC | SVR24 | SVR72 | COUNT |
|---|---|---|---|
| TPV-12 | N | N | 17 |
| | Y | N | 1 |
| | Y | Y | 195 |
| TPV-8 | N | N | 27 |
| | Y | N | 1 |
| | Y | Y | 179 |

TRIAL_111

| ARMC | SVR24 | SVR72 | COUNT |
|---|---|---|---|
| T12/PR24/eRVR+ | N | N | 12 |
| | Y | N | 1 |
| | Y | Y | 149 |

A related issue is the extent of rebounds for subjects who finish treatment with suppressed virus. Table 3.1.6 D gives a summary answer to this question. The table gives, for subjects with observed suppressed virus at weeks 0, 4, 12, and 24 post EOT the percentages who a) never rebound, b) are observed to rebound at week 4, c) are observed to rebound at week 12, d) are observed to rebound at week 24, and e) are observed to rebound after the week 24 window.

TABLE 3.1.6 D
PERCENTAGES OF POST EOT REBOUNDERS,
BY WEEK OBSERVED SUPPRESSED AND WEEK OF REBOUND

TRIAL_108

| | PBO | TPV-12 | TPV-8 |
|---|---|---|---|
| Suppressed at 0 | | | |
| Never Rebound | 74.4% | 95.6% | 93.0% |
| Rebound at 4 | 8.7% | 2.0% | 2.8% |
| Rebound at 12 | 14.2% | 2.4% | 2.8% |
| Rebound at 24 | 2.7% | 0.0% | 1.4% |
| Rebound > 24 | 0.0% | 0.0% | 0.0% |
| Suppressed at 4 | | | |
| Never Rebound | 80.6% | 97.5% | 95.9% |
| Rebound at 12 | 16.2% | 2.5% | 3.0% |
| Rebound at 24 | 3.1% | 0.0% | 1.1% |
| Rebound > 24 | 0.0% | 0.0% | 0.0% |
| . | | | |
| Suppressed at 12 | | | |
| Never Rebound | 95.9% | 100.0% | 98.5% |
| Rebound at 24 | 4.1% | 0.0% | 1.5% |
| Rebound > 24 | 0.0% | 0.0% | 0.0% |
| Suppressed at 24 | | | |
| Never Rebound | 100.0% | 99.6% | 99.6% |
| Rebound > 24 | 0.0% | 0.4% | 0.4% |

TABLE 3.1.6 D (continued)
PERCENTAGES OF POST EOT REBOUNDERS,
BY WEEK OBSERVED SUPPRESSED AND WEEK OF REBOUND

TRIAL_111

| | T12/PR24/eRVR+ | T12/PR48/eRVR+ |
|---|---|---|
| Suppressed at 0 | | |
| Never Rebound | 94.3% | 98.6% |
| Rebound at 4 | 2.5% | 0.0% |
| Rebound at 12 | 1.9% | 1.4% |
| Rebound at 24 | 1.3% | 0.0% |
| Rebound > 24 | 0.0% | 0.0% |
| Suppressed at 4 | | |
| Never Rebound | 96.8% | 98.5% |
| Rebound at 12 | 1.9% | 1.5% |
| Rebound at 24 | 1.3% | 0.0% |
| Rebound > 24 | 0.0% | 0.0% |
| . | | |
| Suppressed at 12 | | |
| Never Rebound | 98.7% | 100.0% |
| Rebound at 24 | 1.3% | 0.0% |
| Rebound > 24 | 0.0% | 0.0% |
| Suppressed at 24 | | |
| Never Rebound | 99.3% | 100.0% |
| Rebound > 24 | 0.7% | 0.0% |

TABLE 3.1.6 D (continued)
PERCENTAGES OF POST EOT REBOUNDERS,
BY WEEK OBSERVED SUPPRESSED AND WEEK OF REBOUND

TRIAL_216

| | Pbo/PR48 | T12(DS)/PR48 | T12/PR48 |
|---|---|---|---|
| Suppressed at 0 | | | |
| Never Rebound | 42.0% | 88.7% | 91.3% |
| Rebound at 4 | 28.0% | 3.1% | 2.7% |
| Rebound at 12 | 26.0% | 6.7% | 4.9% |
| Rebound at 24 | 4.0% | 1.5% | 1.1% |
| Rebound > 24 | 0.0% | 0.0% | 0.0% |
| Suppressed at 4 | | | |
| Never Rebound | 67.7% | 93.9% | 94.0% |
| Rebound at 12 | 32.3% | 5.0% | 4.8% |
| Rebound at 24 | 0.0% | 1.1% | 1.2% |
| Rebound > 24 | 0.0% | 0.0% | 0.0% |
| . | | | |
| Suppressed at 12 | | | |
| Never Rebound | 91.3% | 98.3% | 98.9% |
| Rebound at 24 | 8.7% | 1.7% | 1.1% |
| Rebound > 24 | 0.0% | 0.0% | 0.0% |
| Suppressed at 24 | | | |
| Never Rebound | 100.0% | 100.0% | 100.0% |
| Rebound > 24 | 0.0% | 0.0% | 0.0% |

The astute reader may notice slight anomalies between the results here and those in table 3.1.5 B. For example, in this table, 4.4% of subjects on TPV-12 who were suppressed at week 0 were observed to rebound whereas in table 3.1.5 B only 4.0% of those same subjects were observed to rebound. This discrepancy is due to one subject who was suppressed at week 0, above LOQ at week 4 and resuppressed at weeks 12 and 24. This table counts the earliest time a subject rebounds after being observed suppressed at a given week; table 3.1.5 B counts the last time a subject was suppressed after being observed suppressed at a given week.

The most salient features of this table are the following:

1. For the six telaprevir arms, the percentage of subjects who never rebound, given once observed suppressed at any time post EOT is always >=88.7%; the percentage who never rebound ever being suppressed at week 24 is always >= 99.3%.
2. The percentage of placebo subjects who never rebound after being suppressed at any week post EOT increases steadily as the week of observed suppression gets later, from 74.4% and 42% at week 0 to 100% at week 24.

## *3.2 Evaluation of Safety*

### *3.2.1 Reasons for Discontinuations*

Tables 3.2.1 A-C contain classifications of the reasons for failure for trials 108, 111, and 216.

TABLE 3.2.1 A
REASONS FOR DISCONTINUATION, TRIAL 108

TRIAL_108

| ARM | REASON | COUNT | PERCENT |
|---|---|---|---|
| PBO | Completed | 320 | 88.6% |
| | Death | 1 | 0.3% |
| | AE | 26 | 7.2% |
| | Other | 14 | 3.9% |
| TPV-12 | Completed | 306 | 84.3% |
| | AE | 36 | 9.9% |
| | Other | 21 | 5.8% |
| TPV-8 | Completed | 300 | 82.4% |
| | AE | 37 | 10.2% |
| | Other | 27 | 7.4% |

TABLE 3.2.1 B
REASONS FOR DISCONTINUATION, TRIAL 111

TRIAL_111

| ARM | REASON | COUNT | PERCENT |
|---|---|---|---|
| T12/PR24/eRVR+ | Completed | 161 | 99.4% |
| | AE | 1 | 0.6% |
| T12/PR48/eRVR+ | Completed | 119 | 74.4% |
| | AE | 20 | 12.5% |
| | VIR_FAIL | 6 | 3.8% |
| | Other | 15 | 9.4% |
| T12/PR48/eRVR- | Completed | 79 | 66.9% |
| | AE | 12 | 10.2% |
| | VIR_FAIL | 18 | 15.3% |
| | Other | 9 | 7.6% |

TABLE 3.2.1 C
REASONS FOR DISCONTINUATION, TRIAL 216

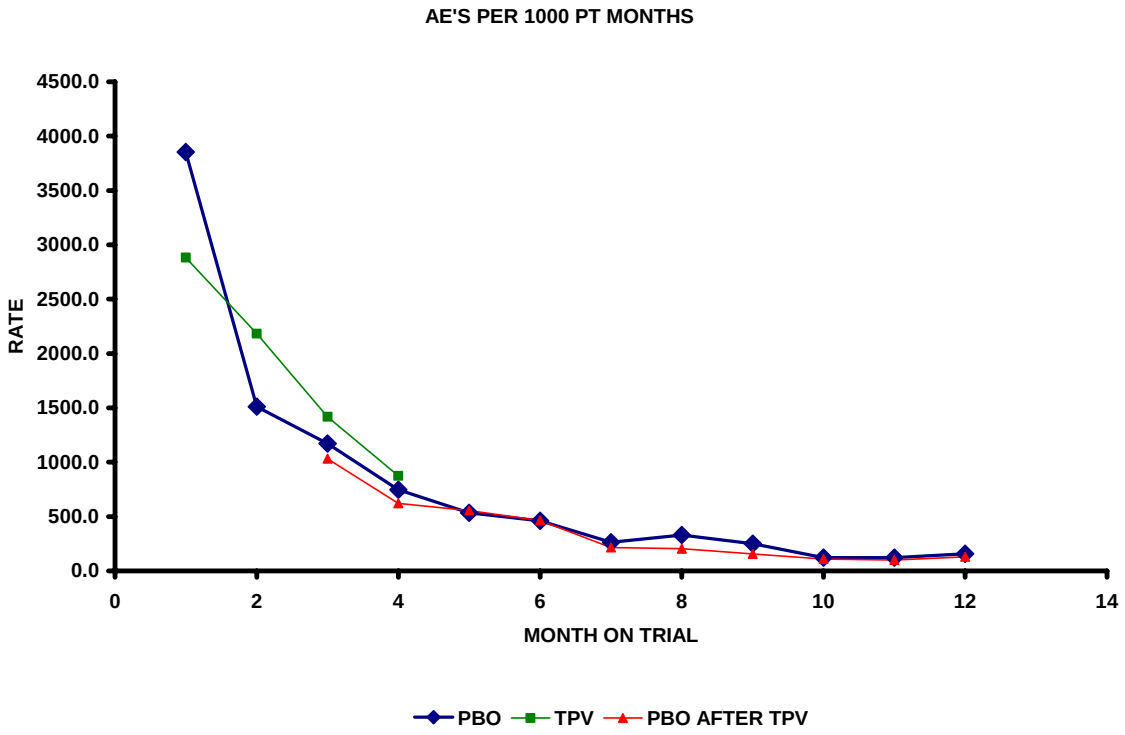
TRIAL_216

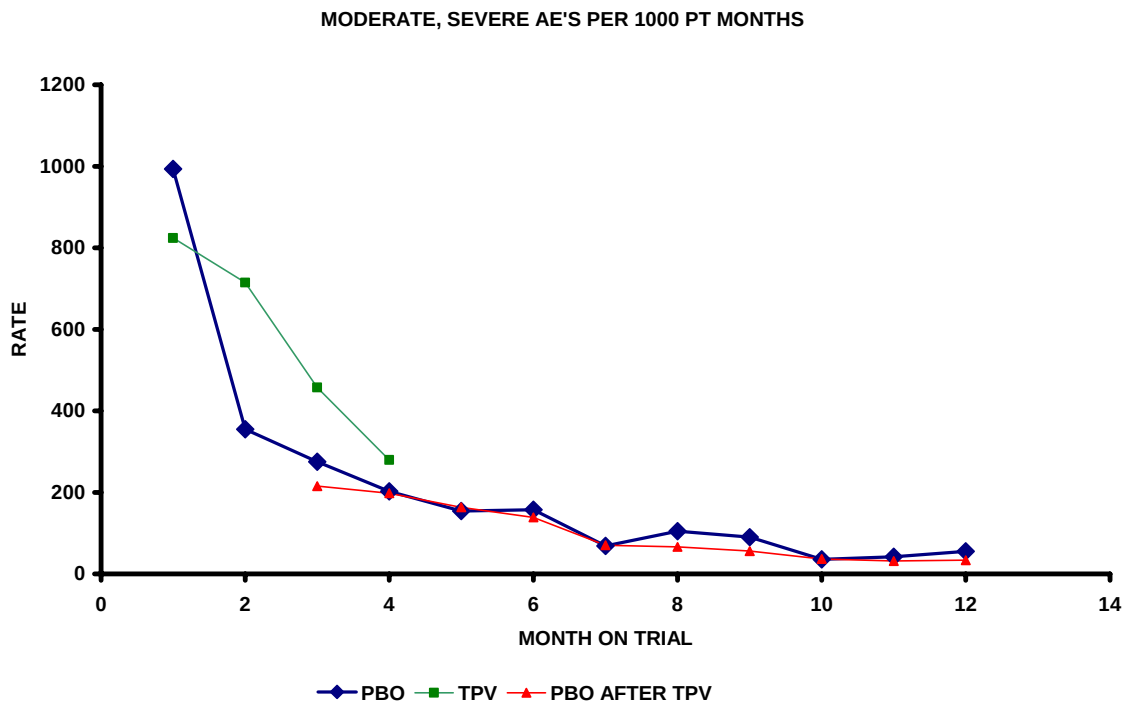
| ARM | REASON | COUNT | PERCENT |
|---|---|---|---|
| Pbo/PR48 | Completed | 110 | 82.7% |
| | AE | 2 | 1.5% |
| | Other | 21 | 15.8% |
| T12(DS)/PR48 | Completed | 248 | 93.9% |
| | AE | 2 | 0.8% |
| | Other | 14 | 5.3% |
| T12/PR48 | Completed | 245 | 92.1% |
| | AE | 1 | 0.4% |
| | Other | 20 | 7.5% |

### *3.2.2 Reasons for Discontinuations*

The following graphs compare incidence rates for all AE's, and for moderate to severe AE's. (There are two few deaths in all three trials to graph deaths separately.) The rates are computed as the number of events per 1000 subjects exposed for each month on the trial. All the results from all three trials are pooled into three groups. Group one consists of subjects who have not been on telaprevir. This comprises all placebo arm subjects in trials 108 and 216 plus the subjects on the delayed start arm in trial 216 for month 1. Group two consists of all subjects who are on telaprevir. It comprises all the first 8 weeks of data for subjects in the TPV-8 arm of trial 108, the first 12 weeks of data for subjects in the TPV-12 arm of trial 108, the first 12 weeks of data for all subjects in trial 111, the first 12 weeks for subjects in the TPV-12 arm of trial 216, and weeks 5-16 for subjects in the delayed start arm of trial 216. Group three consists of all subjects who have finished telaprevir. It comprises week 9 on for subjects in the TPV-8 arm of trial 108, week 17 on for subjects in the delayed start arm of trial 216 and week 13 on for all other telaprevir subjects in all 3 trials.

The objective of the graphs is to look at safety for telaprevir subjects so it is acceptable to pool naive and experienced subjects. Prior failure on PI+RBV should affect efficacy, not telaprevir safety. One can see that telaprevir subjects have slightly higher than placebo subjects. As is usually the case, most adverse events occur earlier and the incidence decreases over time.






With respect to other details of safety, particularly anorectal discomfort, anemia, pruritis, and rash, see the clinical review.

# 4. Results in Special Populations

There was little evidence of interactions between treatment and any interesting covariates.

## *4.1 Gender, Race, and Age*

The following tables show the percentages of subjects with SVR24, computed week 24 snapshots of viral load using the CDRH cutoff of <=50 for LOQ. The tables show the point estimate and 95% confidence limits for the difference between pairwise comparisons between and arms and the rate of SVR24 within each of the two compared arms. Results are presented for the subsets determined by age, gender, race, geographic region and baseline covariates used in stratifying the randomization. Subgroups with too few subjects have been deleted. The p-value of the chi-square test for homogeneity for each method of splitting the data is also included.

TRIAL_108_8_WK_TPV_VS_PBO

| | Mean | 95%_Limits | | TPV_8_wk | Placebo | P-Homog |
|---|---|---|---|---|---|---|
| Covariate | Diff | Lower | Upper | | | |
| All | 27.1% | 19.2% | 34.9% | 267/364=73.0% | 167/361=46.0% | |
| AGEG | | | | | | |
| <=45 | 26.1% | 14.2% | 37.9% | 114/139=82.0% | 80/143=56.0% | 0.8 |
| >45 | 28.1% | 17.9% | 38.3% | 153/225=68.0% | 87/218=40.0% | |
| SEX | | | | | | |
| F | 23.9% | 11.6% | 36.3% | 107/153=70.0% | 69/150=46.0% | 0.41 |
| M | 29.4% | 19.2% | 39.5% | 160/211=76.0% | 98/211=46.0% | |
| RACE | | | | | | |
| Black | 33.9% | 8.2% | 59.6% | 25/40=63.0% | 8/28=29.0% | 0.37 |
| Caucasian | 25.9% | 17.5% | 34.2% | 234/315=74.0% | 154/318=48.0% | |
| Other | 55.6% | 19.6% | 91.5% | 8/9=89.0% | 5/15=33.0% | |
| ETHNICITY | | | | | | |
| HISPANIC | 28.3% | 4.7% | 52.0% | 31/44=70.0% | 16/38=42.0% | 0.95 |
| NOT_HISP | 27.0% | 18.7% | 35.3% | 236/320=74.0% | 151/323=47.0% | |
| REGION | | | | | | |
| EU | 32.0% | 18.1% | 45.9% | 82/100=82.0% | 53/106=50.0% | 0.49 |
| N_America | 26.6% | 16.4% | 36.8% | 158/227=70.0% | 92/214=43.0% | |
| Other | 19.3% | -4.6% | 43.2% | 27/37=73.0% | 22/41=54.0% | |

TRIAL_108_12_WK_TPV_VS_PBO

| Covariate | Mean Diff | 95%_Limits Lower | Upper | TPV_12_wk | Placebo | P-Homog |
|---|---|---|---|---|---|---|
| All | 32.8% | 25.2% | 40.4% | 287/363=79.0% | 167/361=46.0% | |
| AGE | | | | | | |
| <=45 | 32.1% | 21.0% | 43.2% | 125/142=88.0% | 80/143=56.0% | 0.48 |
| >45 | 33.4% | 23.4% | 43.4% | 162/221=73.0% | 87/218=40.0% | |
| SEX | | | | | | |
| F | 34.5% | 22.9% | 46.2% | 120/149=81.0% | 69/150=46.0% | 0.66 |
| M | 31.6% | 21.6% | 41.6% | 167/214=78.0% | 98/211=46.0% | |
| RACE | | | | | | |
| Black | 33.0% | 4.3% | 61.7% | 16/26=62.0% | 8/28=29.0% | 0.43 |
| Caucasian | 31.6% | 23.6% | 39.6% | 260/325=80.0% | 154/318=48.0% | |
| Other | 58.3% | 25.7% | 91.0% | 11/12=92.0% | 5/15=33.0% | |
| ETHNICITY | | | | | | |
| HISPANIC | 35.0% | 11.1% | 59.0% | 27/35=77.0% | 16/38=42.0% | 0.92 |
| NOT_HISP | 32.5% | 24.5% | 40.5% | 260/328=79.0% | 151/323=47.0% | |
| REGION | | | | | | |
| EU | 33.7% | 20.1% | 47.2% | 87/104=84.0% | 53/106=50.0% | 0.65 |
| N_America | 31.8% | 21.7% | 41.9% | 160/214=75.0% | 92/214=43.0% | |
| Other | 35.2% | 14.9% | 55.6% | 40/45=89.0% | 22/41=54.0% | |

TRIAL_111

| Covariate | Mean Diff | 95%_Limits Lower | Upper | P-RBV_24_wk | P-RBV_48_wk | P-Homog |
|---|---|---|---|---|---|---|
| All | 0.1% | -6.4% | 6.7% | 150/162=93.0% | 147/159=92.0% | |
| AGE_Q | | | | | | |
| <45 | 4.5% | -5.3% | 14.4% | 43/44=98.0% | 41/44=93.0% | 0.26 |
| 45-51 | -0.9% | -12.8% | 11.0% | 32/34=94.0% | 38/40=95.0% | |
| 51-55 | -9.1% | -21.9% | 3.6% | 37/42=88.0% | 35/36=97.0% | |
| >=55 | 5.9% | -10.6% | 22.3% | 38/42=90.0% | 33/39=85.0% | |
| AGEGPFL | | | | | | |
| <=45 | 4.3% | -5.2% | 13.8% | 44/45=98.0% | 43/46=93.0% | 0.39 |
| 45-65 | -0.7% | -9.0% | 7.7% | 103/113=91.0% | 101/110=92.0% | |
| >65 | -25.0% | -73.5% | 23.5% | 3/4=75.0% | 3/3=100.0% | |
| SEX | | | | | | |
| F | 1.2% | -8.3% | 10.7% | 55/58=95.0% | 59/63=94.0% | 0.78 |
| M | -0.3% | -9.2% | 8.5% | 95/104=91.0% | 88/96=92.0% | |
| RACE | | | | | | |
| BLACK | -5.9% | -27.6% | 15.8% | 15/17=88.0% | 16/17=94.0% | |
| WHITE | 2.5% | -4.6% | 9.7% | 127/135=94.0% | 119/130=92.0% | |
| ETHNICITY | | | | | | |
| HISPANIC | 3.5% | -19.4% | 26.4% | 17/18=94.0% | 10/11=91.0% | 0.6 |
| NOT_HISP | 0.4% | -6.5% | 7.4% | 130/140=93.0% | 134/145=92.0% | |
| REGION | | | | | | |
| Europe | -1.4% | -36.6% | 33.8% | 7/8=88.0% | 8/9=89.0% | 0.92 |
| N_America | 0.2% | -6.5% | 6.9% | 143/154=93.0% | 139/150=93.0% | |

TRIAL_216_TPV_12_VS_PBO

| Covariate | Mean Diff | 95%_Limits Lower | Upper | TPV-12 | PLACEBO | P-Homog |
|---|---|---|---|---|---|---|
| All | 48.9% | 39.1% | 58.6% | 174/266=65.0% | 22/133=17.0% | |
| PRIOR RESPONSE (AS STRATIFIED) | | | | | | |
| NULL_RESPONDER | 31.0% | 16.6% | 45.3% | 23/68=34.0% | 1/35=3.0% | 0.11 |
| PARTIAL_RESPONDER | 39.3% | 17.3% | 61.4% | 29/53=55.0% | 4/26=15.0% | |
| VIRAL_RELAPSE | 60.5% | 47.4% | 73.6% | 122/145=84.0% | 17/72=24.0% | |
| PRIORR | | | | | | |
| NULL_RESPONDER | 25.2% | 10.4% | 39.9% | 22/72=31.0% | 2/37=5.0% | 0.083 |
| PARTIAL_RESPONDER | 46.4% | 24.5% | 68.3% | 30/49=61.0% | 4/27=15.0% | |
| VIRAL_RELAPSER | 60.9% | 47.7% | 74.2% | 122/145=84.0% | 16/69=23.0% | |
| SCREENING HCV RNA (AS STRATIFIED) | | | | | | |
| <800_K | 49.0% | 20.1% | 77.9% | 28/34=82.0% | 6/18=33.0% | 0.76 |
| >=800_K | 49.0% | 38.9% | 59.2% | 146/232=63.0% | 16/115=14.0% | |
| AGE_Q | | | | | | |
| <45 | 56.2% | 36.9% | 75.5% | 39/55=71.0% | 5/34=15.0% | 0.21 |
| 45-51 | 31.4% | 10.2% | 52.6% | 40/70=57.0% | 9/35=26.0% | |
| 51-55 | 46.8% | 23.7% | 69.8% | 34/53=64.0% | 4/23=17.0% | |
| >=55 | 59.6% | 44.4% | 74.7% | 61/88=69.0% | 4/41=10.0% | |
| SEX | | | | | | |
| F | 44.6% | 26.6% | 62.6% | 54/83=65.0% | 9/44=20.0% | 0.57 |
| M | 51.0% | 39.5% | 62.5% | 120/183=66.0% | 13/89=15.0% | |
| RACE | | | | | | |
| BLACK | 36.4% | -7.9% | 80.7% | 8/11=73.0% | 4/11=36.0% | 0.3 |
| WHITE | 49.0% | 38.9% | 59.1% | 158/246=64.0% | 18/118=15.0% | |
| ETHNICITY | | | | | | |
| HISPANIC | 62.0% | 36.9% | 87.1% | 18/25=72.0% | 2/20=10.0% | 0.33 |
| NOT_HISP | 47.0% | 36.4% | 57.6% | 156/241=65.0% | 20/113=18.0% | |
| REGION | | | | | | |
| EUROPE | 46.9% | 32.7% | 61.0% | 87/127=69.0% | 16/74=22.0% | 0.44 |
| N_AMERICA | 45.6% | 28.8% | 62.4% | 52/89=58.0% | 5/39=13.0% | |
| OTHER | 65.0% | 46.8% | 83.2% | 35/50=70.0% | 1/20=5.0% | |

TRIAL_216_TPV_DS_VS_PBO

| Covariate | Mean Diff | 95%_Limits Lower | Upper | TPV-12-DS | PLACEBO | P-Homog |
|---|---|---|---|---|---|---|
| All | 50.1% | 40.4% | 59.8% | 176/264=67.0% | 22/133=17.0% | |
| PRIOR RESPONSE (AS STRATIFIED) | | | | | | |
| NULL_RESPONDER | 28.5% | 14.3% | 42.7% | 21/67=31.0% | 1/35=3.0% | 0.047 |
| PARTIAL_RESPONDER | 40.4% | 18.3% | 62.5% | 29/52=56.0% | 4/26=15.0% | |
| VIRAL_RELAPSE | 63.3% | 50.4% | 76.1% | 126/145=87.0% | 17/72=24.0% | |
| PRIORR | | | | | | |
| NULL_RESPONDER | 27.9% | 13.2% | 42.7% | 25/75=33.0% | 2/37=5.0% | 0.018 |
| PARTIAL_RESPONDER | 41.4% | 19.2% | 63.6% | 27/48=56.0% | 4/27=15.0% | |
| VIRAL_RELAPSER | 64.8% | 51.8% | 77.7% | 124/141=88.0% | 16/69=23.0% | |
| SCREENING HCV RNA (AS STRATIFIED) | | | | | | |
| <800_K | 46.1% | 16.7% | 75.4% | 27/34=79.0% | 6/18=33.0% | 0.94 |
| >=800_K | 50.9% | 40.8% | 61.0% | 149/230=65.0% | 16/115=14.0% | |
| AGE_Q | | | | | | |
| <45 | 55.5% | 35.3% | 75.7% | 33/47=70.0% | 5/34=15.0% | 0.96 |
| 45-51 | 47.4% | 27.3% | 67.4% | 57/78=73.0% | 9/35=26.0% | |
| 51-55 | 52.6% | 29.7% | 75.5% | 35/50=70.0% | 4/23=17.0% | |
| >=55 | 47.5% | 31.9% | 63.2% | 51/89=57.0% | 4/41=10.0% | |
| SEX | | | | | | |
| F | 44.9% | 26.5% | 63.2% | 49/75=65.0% | 9/44=20.0% | 0.5 |
| M | 52.6% | 41.2% | 63.9% | 127/189=67.0% | 13/89=15.0% | |
| RACE | | | | | | |
| BLACK | 13.6% | -37.6% | 64.9% | 4/8=50.0% | 4/11=36.0% | 0.26 |
| WHITE | 52.2% | 42.3% | 62.1% | 170/252=67.0% | 18/118=15.0% | |
| ETHNICITY | | | | | | |
| HISPANIC | 60.4% | 35.6% | 85.2% | 19/27=70.0% | 2/20=10.0% | 0.43 |
| NOT_HISP | 48.5% | 38.0% | 59.1% | 157/237=66.0% | 20/113=18.0% | |
| REGION | | | | | | |
| EUROPE | 43.8% | 29.8% | 57.9% | 91/139=65.0% | 16/74=22.0% | 0.18 |
| N_AMERICA | 49.7% | 32.1% | 67.2% | 45/72=63.0% | 5/39=13.0% | |
| OTHER | 70.5% | 53.3% | 87.6% | 40/53=75.0% | 1/20=5.0% | |

There is one of these covariates where an interaction appears to occur. In prior treatment failures, the benefit of TPV over SOC is least in null responders and best in viral relapsers. However, in all three groups, TPV was statistically significantly better than SOC, despite the fact that the study was not powered to find statistical significance in individual subgroups containing as few as 20% of the total trial enrollment. The heterogeneity in benefit was statistically significant in the comparison of the delayed start arm to placebo

There is also a small race effect in this same trial: TPV confers an estimated benefit of 36% higher SVR rate on Blacks and a 49% higher SVR rates on Whites. This was not statistically significant using a standard test for heterogeneity.

## *4.2 Other Baseline Covariates*

Results for other baseline covariates are presented here.

TRIAL_108_8_WK_TPV_VS_PBO

| Covariate | Mean Diff | 95%_Limits Lower | Upper | TPV_8_wk | Placebo | P-Homog |
|---|---|---|---|---|---|---|
| BASEVL | | | | | | |
| <.87_M | 12.0% | -2.1% | 26.0% | 75/92=82.0% | 64/92=70.0% | 0.26 |
| .87-2.8_M | 26.6% | 10.5% | 42.6% | 61/91=67.0% | 36/89=40.0% | |
| 2.8-6.7_M | 36.7% | 20.9% | 52.5% | 63/90=70.0% | 28/84=33.0% | |
| >=6.7_M | 34.1% | 18.9% | 49.3% | 68/91=75.0% | 39/96=41.0% | |
| BIOPOSY_RESULTS | | | | | | |
| Bridging_Fibrosis+Cirrhosis | | | | | | |
| | 19.7% | 2.2% | 37.1% | 47/85=55.0% | 26/73=36.0% | 0.17 |
| No/minimal_Fibrosis+Portal_Fibrosis | | | | | | |
| | 29.9% | 21.3% | 38.5% | 220/279=79.0% | 141/288=49.0% | |
| Cirrhosis | 4.2% | -28.0% | 36.4% | 11/26=42.0% | 8/21=38.0% | |
| Bridging_Fibrosis | | | | | | |
| | 26.4% | 5.9% | 46.9% | 36/59=61.0% | 18/52=35.0% | |
| Portal_Fibrosis | | | | | | |
| | 25.2% | 12.9% | 37.5% | 113/151=75.0% | 70/141=50.0% | |
| No/minimal_Fibrosis | | | | | | |
| | 35.3% | 23.5% | 47.1% | 107/128=84.0% | 71/147=48.0% | |
| Genotype subtype (LiPA Method) | | | | | | |
| 1a | 28.6% | 18.3% | 39.0% | 150/210=71.0% | 89/208=43.0% | 0.89 |
| 1b | 25.2% | 13.2% | 37.1% | 116/151=77.0% | 78/151=52.0% | |
| Genotype subtype group (Sequencing) | | | | | | |
| 1a | 27.7% | 17.3% | 38.0% | 152/214=71.0% | 91/210=43.0% | 0.8 |
| 1b | 26.0% | 14.0% | 38.0% | 114/148=77.0% | 76/149=51.0% | |
| DIABETES | | | | | | |
| N | 27.4% | 19.4% | 35.5% | 254/341=74.0% | 160/340=47.0% | 0.73 |
| Y | 23.2% | -9.5% | 55.9% | 13/23=57.0% | 7/21=33.0% | |

TRIAL_108_8_WK_TPV_VS_PBO

| Covariate | Mean Diff | 95%_Limits Lower | Upper | TPV_8_wk | Placebo | P-Homog |
|---|---|---|---|---|---|---|
| BMIGPN | | | | | | |
| <25 | 29.0% | 16.3% | 41.7% | 109/145=75.0% | 60/130=46.0% | |
| 25-30 | 26.1% | 13.4% | 38.8% | 97/131=74.0% | 69/144=48.0% | |
| >=30 | 26.1% | 9.8% | 42.4% | 60/86=70.0% | 38/87=44.0% | |
| HEIGHT | | | | | | |
| <165 | 36.5% | 20.9% | 52.1% | 68/87=78.0% | 35/84=42.0% | |
| 165-172 | 23.3% | 7.5% | 39.2% | 67/95=71.0% | 42/89=47.0% | |
| 172-179 | 16.2% | 0.8% | 31.6% | 66/94=70.0% | 54/100=54.0% | |
| >=179 | 35.0% | 19.3% | 50.6% | 66/87=76.0% | 36/88=41.0% | |
| WEIGHT | | | | | | |
| <65 | 36.0% | 20.7% | 51.4% | 69/86=80.0% | 38/86=44.0% | 0.32 |
| 65-78 | 18.6% | 2.3% | 34.9% | 66/98=67.0% | 40/82=49.0% | |
| 78-90 | 30.8% | 15.5% | 46.2% | 64/85=75.0% | 44/99=44.0% | |
| >=90 | 23.7% | 8.2% | 39.2% | 68/95=72.0% | 45/94=48.0% | |

TRIAL_108_12_WK_TPV_VS_PBO

| Covariate | Mean Diff | 95%_Limits Lower | Upper | TPV_12_wk | Placebo | P-Homog |
|---|---|---|---|---|---|---|
| BASEVL | | | | | | |
| <.87_M | 17.9% | 4.6% | 31.3% | 77/88=88.0% | 64/92=70.0% | 0.037 |
| .87-2.8_M | 28.8% | 12.9% | 44.7% | 63/91=69.0% | 36/89=40.0% | |
| 2.8-6.7_M | 52.4% | 38.4% | 66.4% | 84/98=86.0% | 28/84=33.0% | |
| >=6.7_M | 32.6% | 17.1% | 48.1% | 63/86=73.0% | 39/96=41.0% | |
| BIOPOSY_RESULTS | | | | | | |
| Bridging_Fibrosis+Cirrhosis | | | | | | |
| | 31.5% | 13.9% | 49.1% | 49/73=67.0% | 26/73=36.0% | 0.58 |
| No/minimal_Fibrosis+Portal_Fibrosis | | | | | | |
| | 33.1% | 24.8% | 41.4% | 238/290=82.0% | 141/288=49.0% | |
| Cirrhosis | 38.1% | 6.5% | 69.7% | 16/21=76.0% | 8/21=38.0% | |
| Bridging_Fibrosis | | | | | | |
| | 28.8% | 7.8% | 49.9% | 33/52=63.0% | 18/52=35.0% | |
| Portal_Fibrosis | | | | | | |
| | 29.2% | 17.3% | 41.2% | 123/156=79.0% | 70/141=50.0% | |
| No/minimal_Fibrosis | | | | | | |
| | 37.5% | 26.1% | 49.0% | 115/134=86.0% | 71/147=48.0% | |
| Genotype subtype (LiPA Method) | | | | | | |
| 1a | 31.4% | 21.2% | 41.6% | 158/213=74.0% | 89/208=43.0% | 0.32 |
| 1b | 34.3% | 23.1% | 45.4% | 128/149=86.0% | 78/151=52.0% | |
| Genotype subtype group (Sequencing) | | | | | | |
| 1a | 31.8% | 21.7% | 41.9% | 163/217=75.0% | 91/210=43.0% | 0.2 |
| 1b | 33.5% | 22.1% | 44.9% | 120/142=85.0% | 76/149=51.0% | |
| DIABETES | | | | | | |
| N | 32.2% | 24.4% | 40.0% | 271/342=79.0% | 160/340=47.0% | 0.59 |
| Y | 42.9% | 11.8% | 73.9% | 16/21=76.0% | 7/21=33.0% | |

TRIAL_108_12_WK_TPV_VS_PBO

| Covariate | Mean Diff | 95%_Limits Lower | Upper | TPV_12_wk | Placebo | P-Homog |
|---|---|---|---|---|---|---|
| BMI | | | | | | |
| <25 | 40.3% | 28.7% | 51.9% | 134/155=86.0% | 60/130=46.0% | |
| 25-30 | 26.5% | 13.8% | 39.2% | 96/129=74.0% | 69/144=48.0% | |
| >=30 | 29.0% | 12.6% | 45.5% | 56/77=73.0% | 38/87=44.0% | |
| HEIGHT | | | | | | |
| <165 | 37.3% | 21.6% | 53.1% | 64/81=79.0% | 35/84=42.0% | |
| 165-172 | 31.5% | 16.4% | 46.7% | 74/94=79.0% | 42/89=47.0% | |
| 172-179 | 22.2% | 6.9% | 37.5% | 64/84=76.0% | 54/100=54.0% | |
| >=179 | 41.4% | 27.0% | 55.9% | 84/102=82.0% | 36/88=41.0% | |
| WEIGHT | | | | | | |
| <65 | 42.6% | 28.2% | 57.0% | 79/91=87.0% | 38/86=44.0% | 0.17 |
| 65-78 | 30.0% | 14.6% | 45.4% | 78/99=79.0% | 40/82=49.0% | |
| 78-90 | 23.4% | 7.4% | 39.4% | 57/84=68.0% | 44/99=44.0% | |
| >=90 | 34.2% | 19.4% | 48.9% | 73/89=82.0% | 45/94=48.0% | |

TRIAL_111

| Covariate | Mean Diff | 95%_Limits Lower | Upper | P-RBV_24_wk | P-RBV_48_wk | P-Homog |
|---|---|---|---|---|---|---|
| BASEVL | | | | | | |
| <1.24_M | 4.3% | -4.9% | 13.5% | 47/48=98.0% | 44/47=94.0% | 0.3 |
| 1.24-3.5_M | -4.7% | -15.5% | 6.1% | 38/41=93.0% | 37/38=97.0% | |
| 3.5-9.04_M | -6.6% | -23.5% | 10.4% | 33/39=85.0% | 31/34=91.0% | |
| >=9.04_M | 6.6% | -8.2% | 21.4% | 32/34=94.0% | 35/40=88.0% | |
| BHCVGRFL | | | | | | |
| N | 9.1% | -2.1% | 20.3% | 38/38=100.0% | 30/33=91.0% | 0.042 |
| Y | -2.5% | -10.4% | 5.3% | 112/124=90.0% | 117/126=93.0% | |
| BIOPSY_RESULTS | | | | | | |
| Bridging_fibrosis+cirrhosis | -6.3% | -25.3% | 12.7% | 31/38=82.0% | 29/33=88.0% | 0.27 |
| No/minimal_fibrosis+portal_fibrosis | 2.3% | -4.0% | 8.6% | 119/124=96.0% | 118/126=94.0% | |
| Cirrhosis | -25.0% | -55.7% | 5.7% | 12/18=67.0% | 11/12=92.0% | |
| Bridging_Fibrosis | 9.3% | -11.0% | 29.6% | 19/20=95.0% | 18/21=86.0% | |
| Portal_Fibrosis | -0.1% | -7.9% | 7.8% | 74/78=95.0% | 75/79=95.0% | |
| No/minimal_Fibrosis | 6.3% | -4.0% | 16.7% | 45/46=98.0% | 43/47=91.0% | |
| CIRRHOSIS | | | | | | |
| N | 3.3% | -2.8% | 9.4% | 138/144=96.0% | 136/147=93.0% | 0.048 |
| Y | -25.0% | -55.7% | 5.7% | 12/18=67.0% | 11/12=92.0% | |
| Genotype subtype (LiPA Method) | | | | | | |
| 1a | -1.8% | -10.1% | 6.5% | 104/115=90.0% | 107/116=92.0% | 0.49 |
| 1b | 4.8% | -5.1% | 14.8% | 45/46=98.0% | 40/43=93.0% | |
| Genotype subtype group (Sequencing) | | | | | | |
| 1a | -2.7% | -10.9% | 5.5% | 103/114=90.0% | 107/115=93.0% | 0.16 |
| 1b | 4.9% | -5.3% | 15.1% | 44/45=98.0% | 39/42=93.0% | |
| Other | 50.0% | -29.2% | 129.2% | 3/3=100.0% | 1/2=50.0% | |
| TIME_SINCE_DIAGNOSIS | | | | | | |
| <14.6 | -5.9% | -19.2% | 7.4% | 34/38=89.0% | 41/43=95.0% | |
| 14.6-48 | 0.6% | -7.7% | 8.9% | 42/43=98.0% | 33/34=97.0% | |
| 48-108 | -4.1% | -18.8% | 10.5% | 28/31=90.0% | 34/36=94.0% | |
| >=108 | 5.5% | -9.1% | 20.1% | 40/43=93.0% | 35/40=88.0% | |
| TIME_SINCE_INFECTION | | | | | | |
| <159 | -2.8% | -10.9% | 5.4% | 103/114=90.0% | 108/116=93.0% | 0.086 |
| 159-304 | -5.9% | -18.7% | 6.9% | 16/17=94.0% | 16/16=100.0% | |
| 304-405 | 0.0% | 0.0% | 0.0% | 17/17=100.0% | 14/14=100.0% | |
| >=405 | 30.8% | 2.1% | 59.5% | 14/14=100.0% | 9/13=69.0% | |
| DIABETES | | | | | | |
| N | 0.0% | -6.6% | 6.6% | 143/154=93.0% | 143/154=93.0% | 0.73 |
| Y | 7.5% | -40.4% | 55.4% | 7/8=88.0% | 4/5=80.0% | |

TRIAL_111

| Covariate | Mean Diff | 95%_Limits Lower | Upper | P-RBV_24_wk | P-RBV_48_wk | P-Homog |
|---|---|---|---|---|---|---|
| BMI | | | | | | |
| <25 | 0.5% | -9.0% | 9.9% | 42/44=95.0% | 57/60=95.0% | |
| 25-30 | -1.1% | -11.9% | 9.6% | 52/56=93.0% | 47/50=94.0% | |
| >=30 | 2.4% | -11.1% | 15.9% | 55/61=90.0% | 43/49=88.0% | |
| HEIGHT | | | | | | |
| <165 | 7.8% | -6.1% | 21.6% | 29/30=97.0% | 32/36=89.0% | 0.05 |
| 165-172 | 2.6% | -10.3% | 15.6% | 42/45=93.0% | 39/43=91.0% | |
| 172-179 | 5.6% | -5.4% | 16.6% | 43/44=98.0% | 35/38=92.0% | |
| >=179 | -13.9% | -27.6% | -0.2% | 36/43=84.0% | 41/42=98.0% | |
| WEIGHT | | | | | | |
| <65 | 2.9% | -3.6% | 9.4% | 33/33=100.0% | 33/34=97.0% | 0.6 |
| 65-78 | 1.5% | -12.1% | 15.1% | 21/22=95.0% | 31/33=94.0% | |
| 78-90 | 3.9% | -10.7% | 18.4% | 44/48=92.0% | 36/41=88.0% | |
| >=90 | -4.0% | -16.7% | 8.6% | 52/59=88.0% | 47/51=92.0% | |

TRIAL_216_TPV_12_VS_PBO

| Covariate | Mean Diff | 95%_Limits Lower | Upper | TPV-12 | PLACEBO | P-Homog |
|---|---|---|---|---|---|---|
| BASVLC | | | | | | |
| <800_K | 57.9% | 30.0% | 85.9% | 24/28=86.0% | 5/18=28.0% | |
| >=800_K | 48.1% | 37.9% | 58.4% | 150/238=63.0% | 17/114=15.0% | |
| <1.7_M | 50.9% | 30.2% | 71.6% | 53/66=80.0% | 10/34=29.0% | |
| 1.7-4.4_M | 44.3% | 23.9% | 64.8% | 41/65=63.0% | 6/32=19.0% | |
| 4.4-9.7_M | 39.9% | 22.1% | 57.8% | 34/67=51.0% | 4/37=11.0% | |
| >=9.7_M | 61.0% | 44.7% | 77.3% | 46/68=68.0% | 2/30=7.0% | |
| PRIOR Peg-IFN TYPE | | | | | | |
| PEGASYS | 50.8% | 38.2% | 63.4% | 109/165=66.0% | 11/72=15.0% | |
| PEGINTRON | 45.7% | 30.1% | 61.2% | 64/100=64.0% | 11/60=18.0% | |
| BASELINE HOMA-IR | | | | | | |
| <2 | 43.5% | 23.4% | 63.5% | 67/93=72.0% | 10/35=29.0% | |
| >=2 | 50.3% | 38.8% | 61.7% | 99/161=61.0% | 10/89=11.0% | |
| HCV GENOTYPE (LAB TEST) | | | | | | |
| 1 | 59.0% | 32.7% | 85.2% | 18/27=67.0% | 1/13=8.0% | |
| 1a | 33.1% | 17.0% | 49.1% | 67/118=57.0% | 14/59=24.0% | |
| 1b | 61.7% | 48.7% | 74.7% | 89/121=74.0% | 7/59=12.0% | |
| HCV GENOTYPE (NS3) | | | | | | |
| 1a | 36.5% | 21.8% | 51.1% | 78/136=57.0% | 14/67=21.0% | |
| 1b | 60.7% | 47.6% | 73.8% | 93/126=74.0% | 8/61=13.0% | |
| AFP SEROLOGY AT BASELINE | | | | | | |
| <50 | 49.4% | 39.4% | 59.3% | 172/259=66.0% | 22/129=17.0% | |
| >=50 | 20.0% | -20.1% | 60.1% | 1/5=20.0% | 0/3=0.0% | |
| STATUS OF FIBROSIS | | | | | | |
| Cirrhosis | 33.9% | 14.7% | 53.1% | 34/72=47.0% | 4/30=13.0% | 0.3 |
| No_Cirrhosis | 54.7% | 43.6% | 65.8% | 140/194=72.0% | 18/103=17.0% | |
| Bridging_Fibrosis | 66.4% | 49.9% | 83.0% | 44/60=73.0% | 2/29=7.0% | |
| Portal_Fibrosis | 48.0% | 29.2% | 66.8% | 59/83=71.0% | 9/39=23.0% | |
| No/minimal_Fibrosis | 52.5% | 31.9% | 73.2% | 37/51=73.0% | 7/35=20.0% | |
| TIME_SINCE_DIAGNOSIS | | | | | | |
| <4.4 | 52.5% | 34.2% | 70.8% | 39/61=64.0% | 4/35=11.0% | 0.93 |
| 4.4-8.1 | 47.7% | 28.4% | 67.1% | 39/61=64.0% | 6/37=16.0% | |
| 8.1-13.1 | 42.6% | 20.5% | 64.6% | 50/74=68.0% | 7/28=25.0% | |
| >=13.1 | 50.6% | 31.7% | 69.5% | 46/70=66.0% | 5/33=15.0% | |

TRIAL_216_TPV_12_VS_PBO

| Covariate | Mean Diff | 95%_Limits Lower | Upper | TPV-12 | PLACEBO | P-Homog |
|---|---|---|---|---|---|---|
| BMI | | | | | | |
| <25 | 46.9% | 29.5% | 64.3% | 54/85=64.0% | 7/42=17.0% | |
| 25-30 | 59.9% | 45.8% | 74.1% | 79/108=73.0% | 7/53=13.0% | |
| >=30 | 34.5% | 14.6% | 54.5% | 41/73=56.0% | 8/37=22.0% | |
| HEIGHT | | | | | | |
| <165 | 51.1% | 30.6% | 71.6% | 37/55=67.0% | 5/31=16.0% | |
| 165-172 | 49.5% | 27.9% | 71.2% | 44/64=69.0% | 5/26=19.0% | |
| 172-179 | 33.0% | 13.1% | 52.9% | 51/86=59.0% | 10/38=26.0% | |
| >=179 | 63.4% | 47.8% | 79.1% | 42/61=69.0% | 2/37=5.0% | |
| WEIGHT | | | | | | |
| <71 | 50.0% | 29.5% | 70.5% | 49/70=70.0% | 6/30=20.0% | 0.37 |
| 71-81 | 49.6% | 31.2% | 68.0% | 41/65=63.0% | 5/37=14.0% | |
| 81-92 | 61.1% | 43.2% | 79.0% | 49/65=75.0% | 5/35=14.0% | |
| >=92 | 33.7% | 12.6% | 54.7% | 35/66=53.0% | 6/31=19.0% | |

TRIAL_216_TPV_DS_VS_PBO

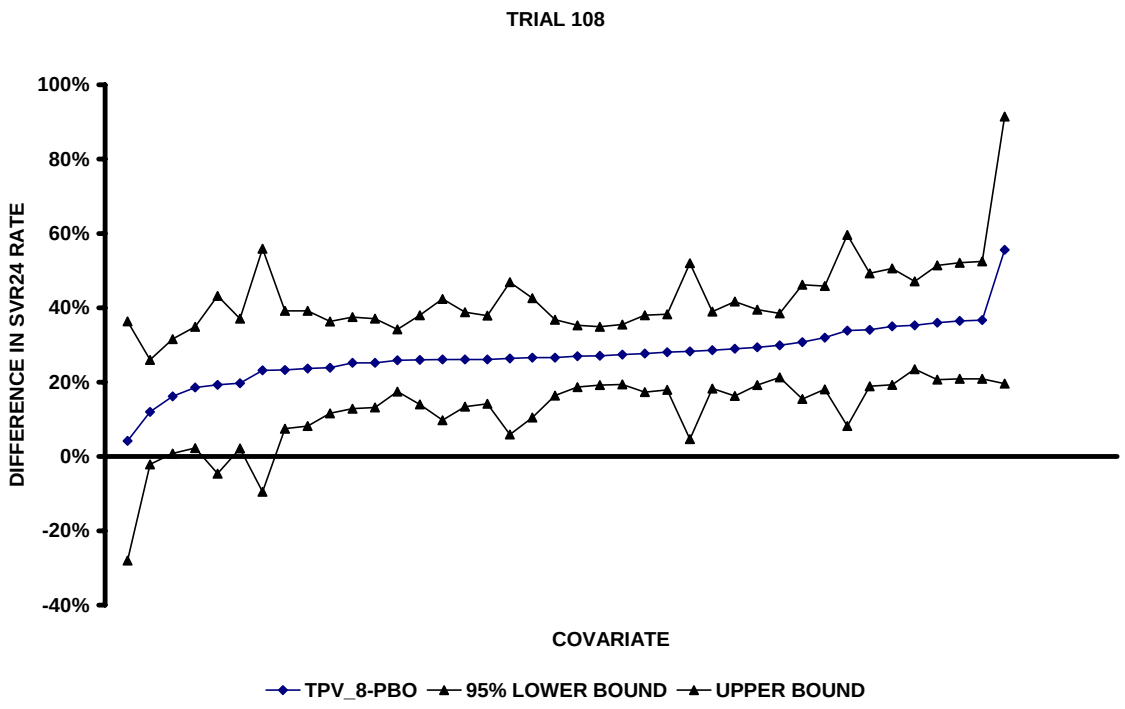
| Covariate | Mean Diff | 95%_Limits Lower | Upper | TPV-12-DS | PLACEBO | |
|---|---|---|---|---|---|---|
| BASVL | | | | | | |
| <800_K | 55.6% | 27.4% | 83.7% | 25/30=83.0% | 5/18=28.0% | |
| >=800_K | 49.6% | 39.4% | 59.9% | 151/234=65.0% | 17/114=15.0% | |
| | | | | | | |
| <1.7_M | 38.8% | 17.0% | 60.5% | 45/66=68.0% | 10/34=29.0% | 0.63 |
| 1.7-4.4_M | 50.8% | 31.0% | 70.6% | 48/69=70.0% | 6/32=19.0% | |
| 4.4-9.7_M | 53.1% | 35.2% | 71.0% | 39/61=64.0% | 4/37=11.0% | |
| >=9.7_M | 58.0% | 41.5% | 74.6% | 44/68=65.0% | 2/30=7.0% | |
| PRIOR Peg-IFN TYPE | | | | | | |
| PEGASYS | 48.6% | 36.1% | 61.0% | 113/177=64.0% | 11/72=15.0% | |
| PEGINTRON | 54.1% | 38.6% | 69.6% | 63/87=72.0% | 11/60=18.0% | |
| BASELINE HOMA-IR | | | | | | |
| <2 | 45.6% | 25.6% | 65.6% | 66/89=74.0% | 10/35=29.0% | |
| >=2 | 51.0% | 39.6% | 62.3% | 102/164=62.0% | 10/89=11.0% | |
| HCV GENOTYPE (LAB TEST) | | | | | | |
| 1 | 56.6% | 30.4% | 82.8% | 18/28=64.0% | 1/13=8.0% | |
| 1a | 37.9% | 22.0% | 53.8% | 74/120=62.0% | 14/59=24.0% | |
| 1b | 60.3% | 47.0% | 73.6% | 83/115=72.0% | 7/59=12.0% | |
| HCV GENOTYPE (NS3) | | | | | | |
| 1a | 42.2% | 28.0% | 56.4% | 94/149=63.0% | 14/67=21.0% | |
| 1b | 57.7% | 44.1% | 71.3% | 80/113=71.0% | 8/61=13.0% | |
| AFP SEROLOGY AT BASELINE | | | | | | |
| <50 | 50.9% | 41.0% | 60.8% | 174/256=68.0% | 22/129=17.0% | |
| >=50 | 25.0% | -9.3% | 59.3% | 2/8=25.0% | 0/3=0.0% | |
| STATUS OF FIBROSIS | | | | | | |
| Cirrhosis | 34.4% | 14.9% | 53.9% | 32/67=48.0% | 4/30=13.0% | 0.39 |
| No_Cirrhosis | 55.6% | 44.6% | 66.6% | 144/197=73.0% | 18/103=17.0% | |
| Bridging_Fibrosis | 53.4% | 35.6% | 71.3% | 35/58=60.0% | 2/29=7.0% | |
| Portal_Fibrosis | 53.0% | 34.1% | 71.9% | 54/71=76.0% | 9/39=23.0% | |
| No/minimal_Fibrosis | 60.9% | 42.3% | 79.4% | 55/68=81.0% | 7/35=20.0% | |
| TIME_SINCE_DIAGNOSIS | | | | | | |
| <4.4 | 56.6% | 39.4% | 73.9% | 49/72=68.0% | 4/35=11.0% | 0.51 |
| 4.4-8.1 | 57.6% | 39.0% | 76.1% | 45/61=74.0% | 6/37=16.0% | |
| 8.1-13.1 | 36.9% | 14.0% | 59.8% | 39/63=62.0% | 7/28=25.0% | |
| >=13.1 | 48.1% | 28.9% | 67.3% | 43/68=63.0% | 5/33=15.0% | |

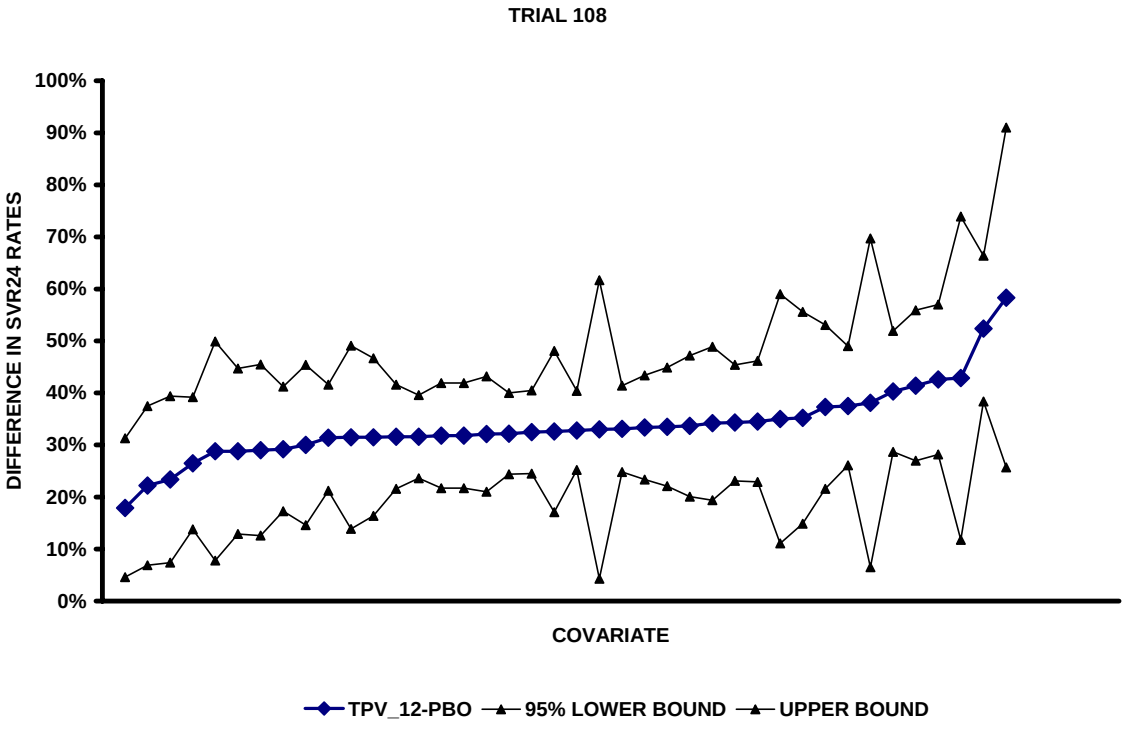
TRIAL_216_TPV_DS_VS_PBO

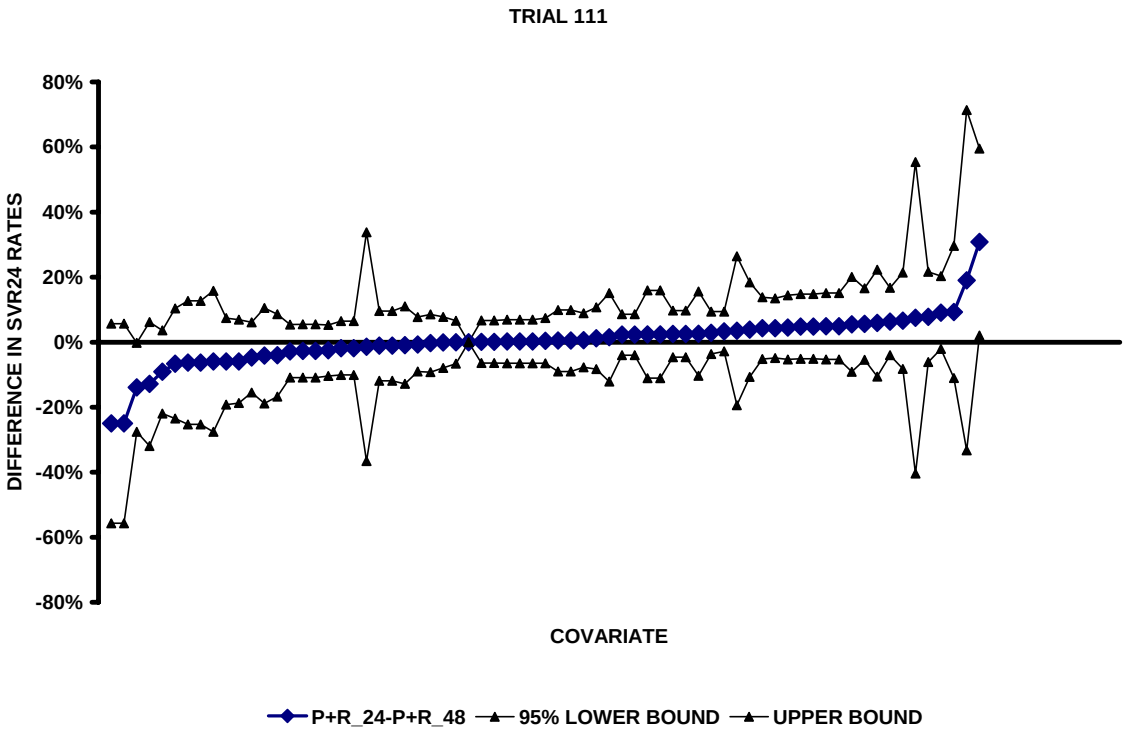
| Covariate | Mean Diff | 95%_Limits Lower | Upper | TPV-12-DS | PLACEBO | |
|---|---|---|---|---|---|---|
| BMI | | | | | | |
| <25 | 50.7% | 33.7% | 67.8% | 60/89=67.0% | 7/42=17.0% | |
| 25-30 | 55.5% | 41.2% | 69.9% | 77/112=69.0% | 7/53=13.0% | |
| >=30 | 39.7% | 19.1% | 60.2% | 38/62=61.0% | 8/37=22.0% | |
| HEIGHT | | | | | | |
| <165 | 47.1% | 25.7% | 68.5% | 31/49=63.0% | 5/31=16.0% | |
| 165-172 | 48.6% | 26.4% | 70.9% | 38/56=68.0% | 5/26=19.0% | |
| 172-179 | 34.7% | 14.4% | 55.0% | 47/77=61.0% | 10/38=26.0% | |
| >=179 | 67.4% | 53.6% | 81.3% | 59/81=73.0% | 2/37=5.0% | |
| WEIGHT | | | | | | |
| <71 | 45.6% | 24.5% | 66.7% | 42/64=66.0% | 6/30=20.0% | 0.81 |
| 71-81 | 47.4% | 28.8% | 66.0% | 39/64=61.0% | 5/37=14.0% | |
| 81-92 | 58.3% | 40.6% | 76.0% | 53/73=73.0% | 5/35=14.0% | |
| >=92 | 47.3% | 26.6% | 68.1% | 42/63=67.0% | 6/31=19.0% | |

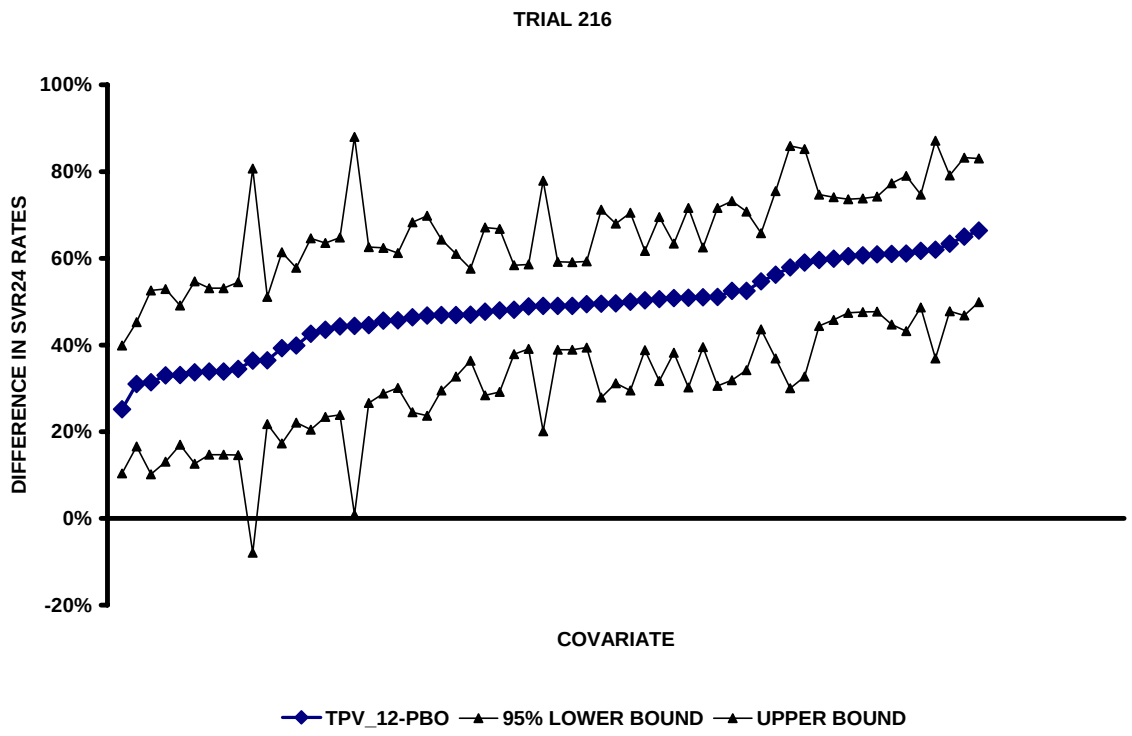
There is a slight hint of an interaction of treatment with cirrhosis in the above tables. For trial 108 (naives), cirrhotics had very low benefit over placebo on the 8 week TPV arm but their benefit over placebo on the 12 week TPV arm was as large as that of non-cirrhotics. Also in trial 216 (prior failures), the benefit over placebo was estimated to be 35% for cirrhotics and 55% for non-cirrhotics. In both subgroups individually, TPV was statistically significantly superior to placebo, despite the fact that significance was calculated on subsets of the whole trial.

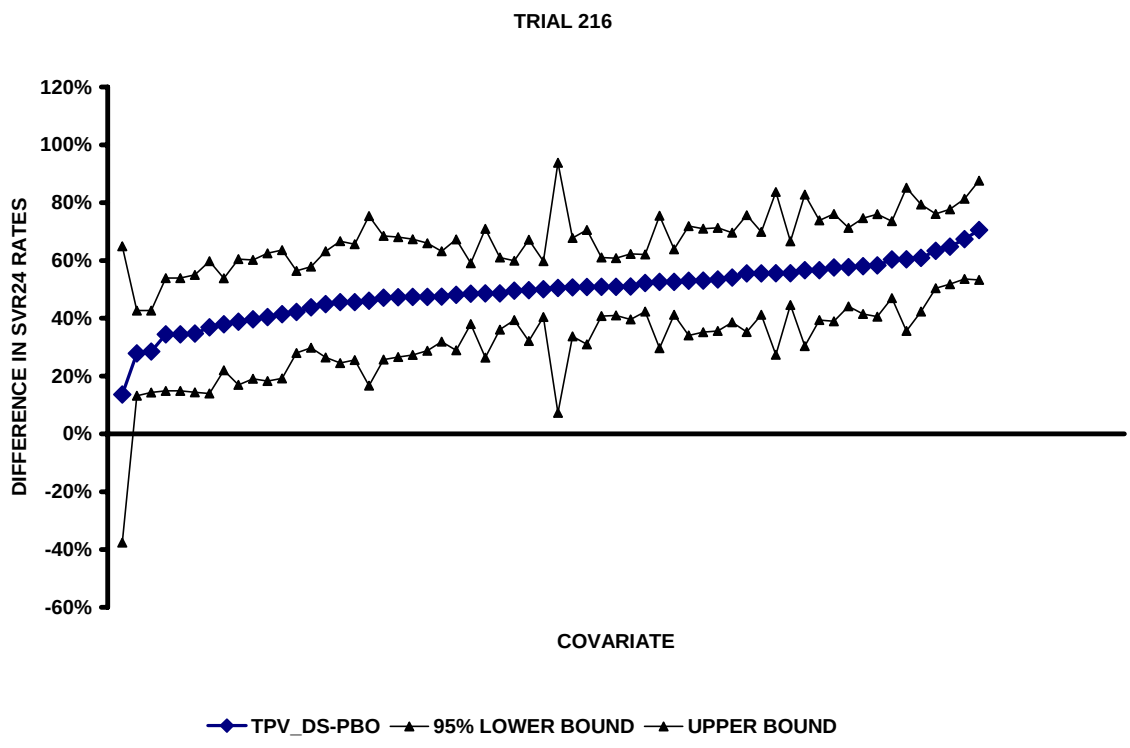
The essential lack of any clinically meaningful interaction between SVR24 rate and most of the covariates studied is confirmed in the graphs below. The point estimates and confidence intervals around the arm differences included in the above tables are displayed in these graphs, sorted in increasing order of the point estimates. The names of the subsets are not given because of lack of room on the x-axis but they are all included in the above tables. One can see that in none of the graphs is there anything that looks different from what one would get with a sequence of normal estimates of the same parameter.






TRIAL 216
100%
80%
60%
40%
20%
0%
-20%
DIFFERENCE IN SVR24 RATES
COVARIATE
TPV_12-PBO
95% LOWER BOUND
UPPER BOUND


TRIAL 216
120%
100%
80%
60%
40%
20%
0%
-20%
-40%
-60%
DIFFERENCE IN SVR24 RATES
COVARIATE
TPV_DS-PBO
95% LOWER BOUND
UPPER BOUND

# 5. Statistical Reviewer's Conclusions

The applicant has demonstrated in three trials that telaprevir is an effective treatment of genotype 1 chronic Hepatitis C when used for 12 weeks at the indicated dose in combination with 48 weeks of peg-interferon and ribavirin. It is effective in both treatment naive subjects and in subjects who have failed a prior course of peg-interferon and ribavirin. The benefit manifests itself as a 25-30% increase in percentage SVR24 in naive subjects and as a ~50% increase in percentage SVR24 in prior failures. In addition, viral suppression is comparatively swift in those subjects who will ultimately be suppressed long-term, occurring within the first 12 weeks.

Furthermore, the applicant has demonstrated that in naive subjects, a response guided therapy in which subjects who achieve viral suppression at 12 weeks need only take a total of 24 weeks of peg-interferon and ribavirin to receive the full benefit of the therapy.

Furthermore, the applicant has demonstrated that in naive subjects, subjects can discontinue telaprevir at 8 weeks, say if toxicity were an issue, and still receive substantial benefit relative to placebo (19-20% increase in chance of SVR24), although such subjects do appear to perform slightly worse efficacy (~6%) than subjects continuing the full 12 weeks of telaprevir.

The questions as to how effective 8 weeks of telaprevir or 12 weeks of telaprevir followed by only 24 weeks of peg-interferon plus ribavirin if suppressed at week 12 is still open for subjects who have failed a prior course of PI+RBV.

There is a noticeable toxicity associated with telaprevir, which is detailed in the clinical review.

Finally, there were few relapses among those subjects who achieved suppression by the first EOT visit in the telaprevir arms. The relapse rate for subjects achieving suppression at EOT is only 5-7% for naïve subjects and 9-11% for previous failures on PI+RBV. The relapse rate was higher in the placebo arms (26% for naives and 58% for prior failures), suggesting that in future submissions with direct acting anti-virals using LOCF to impute missing data will be conservative.

Thomas Hammerstrom, Ph.D.
Mathematical Statistician

Concur: Dr. Soon
cc:
Archival NDA #201-917 (SN 001)
HFD-530
HFD-530/Dr. Birnkrant
HFD-530/Dr. Murray
HFD-530/Dr. Marcus
HFD-530/Mr. Fleischer
HFD-530/Ms. Hong
HFD-725/Dr. Hammerstrom
HFD-700/Dr. Nevius
HFD-725/Dr. Huque
HFD-725/Dr. Lin

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/s/

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THOMAS S HAMMERSTROM
04/08/2011

GUOXING SOON
04/14/2011

# STATISTICAL REVIEW AND EVALUATION

**Biometrics Division: VI (HFD-705)**

| | |
|---|---|
| **NDA NO.:** | 201-917 |
| **SERIAL NO.:** | S-000 |
| **DATE RECEIVED BY THE CENTER:** | July 14, 2010 |
| **DRUG NAME:** | Telaprevir |
| **DOSAGE FORM:** | Tablets |
| **INDICATION:** | Anti-viral |
| **SPONSOR:** | Vertex Pharmaceuticals, Inc. |
| **DOCUMENTS REVIEWED:** | Submission dated July 14, 2010 and subsequent responses |
| **NAME OF STATISTICAL REVIEWER:** | Meiyu Shen, Ph.D. (HFD-705) |
| **PROJECT MANAGER:** | Don Henry |

_____

Meiyu Shen, Mathematical Statistician

Concur: _____
Yi Tsong, Ph.D.
Deputy Director, DBVI

**Distribution**: NDA 201-917
HFD-705/Y. Tsong, Ph.D.
ONDQA/Don Henry

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# EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

## 1.1 Conclusions and Recommendations

1) The sponsor's pooling of (b) (4) factorial experimental designs and production data for developing acceptance criteria is problematical.
2) Design space for particle size is not acceptable because it is observed that the sponsor's (b) (4) .
3) The sponsor's (b) (4) does not possess any physical explanation because the model should be evaluated by (b) (4) .
4) The sponsor's (b) (4) does not consistent with any physical explanation. The model should be evaluated by (b) (4)
5) In model verification for particle size, it is clear that the model (b) (4) did not predict the observed particle size well.
6) In model verification for bulk density, it is also clear that the model (b) (4) did not predict the observed bulk density well.
7) The sponsor didn't provide information regarding the performance of (b) (4). Reviewer can not verify the model for (b) (4) bulk density.
8) The linear regression through origin is misused (b) (4).
9) There is significant amount of unexplained variability after the modeling of the relationship between the dissolution and predictor variables such as bulk density, particle size, and hardness. Hence the design space established by the (b) (4) is not acceptable.

## 1.2 Purpose of this statistical consultation

Vertex is submitting manufacturing process development for NDA 201-917. In the submission, the sponsor pooled 148 observations from a series of (b) (4) factorial experimental designs as listed in Table 1 along with 14 observations from the production line to develop statistical models for particle size and bulk density, separately. Sponsor proposes a design space model in which (b) (4) for the (b) (4) will be utilized for model maintenance and for setting up acceptance criteria. This is described in sections 3.2.P.2.3 and 3.2.P.5.6.

On January 14, 2011, Mr. Don Henry, Drs. Sharmista Chatterjee and Bogdan Kurtyka in Office of New Drug Quality Assessment sent the official request to the statistical team for the following consult: "(b) (4), the applicant proposes a design space model in which (b) (4) will be utilized for model maintenance and for

setting up acceptance criteria. This is described in sections 3.2.P.2.3 and 3.2.P.5.6. A statistical evaluation of this approach is requested."

Later on, Drs. Qi Lin and Christopher Hough requested the statistical reviewer to evaluate the dissolution model and comparability protocol.

## 1.3 Reviewer's principal findings

This statistical reviewer will document the comments in following issues:
1. Pooling of a series of (b) (4) factorial experimental designs listed in Table 1 along with 14 observations from the production line.

The sponsor pooled 148 observations from a series of (b) (4) factorial experimental designs listed in Table 1 along with 14 observations from the production to develop statistical models for particle size and bulk density, separately. The factors which the sponsor tempted to model are (b) (4)

(b) (4)

**Reviewer's comments:**
The sponsor's pooling of (b) (4) factorial experimental designs and production data for developing acceptance criteria is problematical.



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/s/

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MEIYU SHEN
04/12/2011

YI TSONG
04/12/2011

# STATISTICS FILING CHECKLIST FOR A NEW NDA

**NDA Number: 201917** **Applicant: Vertex** **Stamp Date: 11**/22/2010

**Drug Name: Telaprevir** **NDA/BLA Type: Priority** Review

**Reviewers:** Thomas Hammerstrom

On **initial** overview of the NDA/BLA application for RTF:

| | Content Parameter | Yes | No | NA | Comments |
|---|---|---|---|---|---|
| 1 | Index is sufficient to locate necessary reports, tables, data, etc. | X | | | |
| 2 | ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.) | X | | | |
| 3 | Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable). | X | | | |
| 4 | Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets). | X | | | |

**IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ___Yes____**

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

# STATISTICS FILING CHECKLIST FOR A NEW NDA

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

| **Content Parameter (possible review concerns for 74-day letter)** | **Yes** | **No** | **NA** | **Comment** |
|---|---|---|---|---|
| Designs utilized are appropriate for the indications requested. | X | | | |
| Endpoints and methods of analysis are specified in the protocols/statistical analysis plans. | X | | | |
| Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available. | | | X | |
| Appropriate references for novel statistical methodology (if present) are included. | | | X | |
| Safety data organized to permit analyses across clinical trials in the NDA/BLA. | | | X | |
| Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate. | | | X | |

Thomas Hammerstrom 12-10-2010

Reviewing Statisticians Date

Greg Soon

Supervisor/Team Leader Date

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/s/

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THOMAS S HAMMERSTROM
12/22/2010

GUOXING SOON
01/20/2011