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APPLICATION NUMBER:

202258Orig1s000

SUMMARY REVIEW

Addendum to Decisional Memorandum to the File

Date:	May 12, 2011
From:	Jeffrey S. Murray, M.D., M.P.H. Deputy, Division of Antiviral Products
Subject:	Summary and Recommendations
NDA/BLA #:	202258
Proprietary / Generic (USAN) names	Victrelis/Boceprevir
Dosage forms / strength	200 mg capsules
Proposed Indication(s)	For the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alpha and ribavirin, in adult patients (≥18 years of age) with compensated liver disease who are previously untreated or who have failed previous therapy.

This memorandum is an addendum to the Decisional Memorandum archived on May 5, 2011. This addendum provides an update on final labeling discussions. In the May 5, 2011, memorandum I stated that the Division had decided to go with Option 2 for Dosage and Administration recommendations. Option 2 is shown below followed by Final Dosage and Administration Recommendations that will appear in product labeling. Differences between these recommendations and rationale for the changes are provided below.

Option 2, Doasage and Administration Recommendations, as stated in my May 5 memorandum

For patients without Cirrhosis

ASSESSMENT (HCV RNA Results[1])			
At Treatment Week 8	At Treatment Week 12	At Treatment Week 24	Action
Undetectable	Undetectable	Undetectable	**Previously untreated patients:** Complete three-drug regimen at Treatment Week 28 **Patients who Failed Previous Therapy:** Complete three-drug regimen at Treatment Week 36 and continue with 12 more weeks of PR .
Detectable	<100 IU/mL	Undetectable	**Previously untreated patients and patients who failed previous therapy*:** Complete three-drug regimen at Treatment Week 36 and continue with 12 more weeks of PR
Any Result	≥100 IU/mL at TW12, OR Confirmed Detectable HCV RNA at TW24		Treatment Futility. Discontinue three-drug regimen

[1] In clinical trials, HCV-RNA in plasma was measured using a Roche COBAS® TaqMan® assay with a lower limit of quantification of 25 IU/mL and a limit of detection of 9.3 IU/mL. See Laboratory Tests (5.5) for a description of HCV RNA assay recommendations. Patients with < 2 log decline at week 12 with prior PR treatment should complete three-drug regimen at week 44.

In addition to the table the following statements could be included:

All patients with cirrhosis should receive 44 weeks of triple therapy after the 4 week PR lead-in period.

Final Dosage and Administration Recommendations

2.1 VICTRELIS Combination Therapy: Patients Without Cirrhosis Who Are Previously Untreated or Who Are Previous Partial Responders or Relapsers to Interferon and Ribavirin therapy

- Initiate therapy with peginterferon alfa and ribavirin for 4 weeks (Treatment Weeks 1-4).
- Add VICTRELIS 800 mg (four 200-mg capsules) orally three times daily (every 7-9 hours) to peginterferon alfa and ribavirin regimen after 4 weeks of

treatment. Based on the patient's HCV-RNA levels at Treatment Week (TW)8, TW12 and TW24, use the following Response-Guided Therapy (RGT) guidelines to determine duration of treatment (see Table 1).

Table 1
Duration of Therapy Using Response-Guided Therapy (RGT) Guidelines in Patients Without Cirrhosis Who Are Previously Untreated or Who Are Previous Partial Responders or Relapsers to Interferon and Ribavirin Therapy

	ASSESSMENT* (HCV-RNA Results†)		ACTION
	At Treatment Week 8	At Treatment Week 24	
Previously Untreated Patients	Undetectable	Undetectable	Complete three-medicine regimen at TW28.
	Detectable	Undetectable	1. Continue all three medicines and finish through TW36; and then 2. Administer peginterferon alfa and ribavirin and finish through TW48.
Previous Partial Responders or Relapsers	Undetectable	Undetectable	Complete three-medicine regimen at TW36.
	Detectable	Undetectable	1. Continue all three medicines and finish through TW36; and then 2. Administer peginterferon alfa and ribavirin and finish through TW48.

***TREATMENT FUTILITY**
If the patient has HCV-RNA results greater than or equal to 100 IU/mL at TW12, then discontinue three-medicine regimen.
If the patient has confirmed, detectable HCV-RNA at TW24, then discontinue three-medicine regimen.

†In clinical trials, HCV-RNA in plasma was measured using a Roche COBAS® TaqMan® assay with a lower limit of quantification of 25 IU/mL and a limit of detection of 9.3 IU/mL. See Warnings and Precautions (5.5) for a description of HCV-RNA assay recommendations.

Response-Guided Therapy was not studied in subjects who had less than a 2-$\log_{10}$ HCV-RNA decline by treatment week 12 during prior therapy with peginterferon alfa and ribavirin. If considered for treatment, these subjects should receive 4 weeks of peginterferon alfa and ribavirin followed by 44 weeks of VICTRELIS 800 mg orally three times daily (every 7-9 hours) in combination with peginterferon alfa and ribavirin. In addition, consideration should be given to treating previously untreated patients who are poorly interferon responsive (as determined at TW4) with 4 weeks peginterferon alfa and ribavirin followed by 44 weeks of VICTRELIS 800 mg orally three times daily (every 7-9 hours) in combination with peginterferon alfa and ribavirin in order to maximize rates of SVR *[see Clinical Studies (14)]*.

2.2 VICTRELIS Combination Therapy: Patients with Cirrhosis

Patients with compensated cirrhosis should receive 4 weeks peginterferon alfa and ribavirin followed by 44 weeks VICTRELIS 800 mg orally three times daily (every 7-9 hours) in combination with peginterferon alfa and ribavirin.

Notable changes include the following:

1) Formatting changes to make it clear that the recommendations in the table apply to patients without cirrhosis and patients who were previously untreated or relapsers or partial responders to previous treatment.
2) To avoid confusion and ensure that all possible viral load outcomes were covered, the 12 week futility time point was moved to the bottom of the table.
3) Additional treatment recommendations/considerations for poorly-interferon responsive patients are included after the table.
4) A separate section for dosing in patients with cirrhosis follows the table.
5) The only change to specific dosing recommendations in the table is for previous relapsers and partial responders who have an undetectable HCV RNA at treatment week 8. For this group, Option 2 recommended stopping boceprevir at week 36 and continuing PR for 12 more weeks. Final recommendations are to stop all treatments at week 36 (no 12 week PR tail).

Rationale for Change #5 (above)

Regarding Treatment Experienced, Early Responders, the May 5 memorandum included the following information:

> *For Trial P05101, the sponsor and FDA conducted analyses comparing SVR among boceprevir-containing treatment arms for early and late responders similar to that done for Trial P05216. In contrast, to the treatment naïve study analyses, RGT appeared to perform slightly worse for early responders. For early responders there was a numerical difference of approximately 7% favoring Arm 3 and for late responders there was a similar numerical difference (6%) favoring Arm 2. The results are shown in Table 5.*

Table 5. Trial P05101 ; SVR by TW8-12 Response Category and Treatment Arm

Response Category	***RGT SVR n/N (%)***	***BOC44 SVR n/N (%)***

	PR4/BOC+PR32	***PR4/BOC+PR44***
Early Responders	*61/68 (90)*	*68/70 (97)*
	PR4/BOC+PR32/PR12	***PR4/BOC+PR44***
Late Responders	*27/34 (79)*	*29/40 (73)*

It should be noted that these are subgroup analyses with relatively small numbers. In addition the numerical differences between arms are similar in magnitude but in opposing directions for early and late responders. Nonetheless, the relapse rate in Arm 2 (as reported in Dr. Mishra's review) was 5/66 in Arm 2 compared to 0/68 in Arm 3. The sponsor noted even more relapsers (7) in Arm 2. Most of these patients were previous relapsers. Some have raised the concern that stopping PR at 32 weeks is insufficient and could result in relapse in previously treated patients. Although these differences are not concerning from a statistical sense, the occurrence of virologic breakthroughs upon treatment cessation raises concerns from a virologic/mechanistic point of view.

Upon further consideration of these analyses, we were concerned that the numerical treatment differences in the early responders and the difference in relapse rates (5 vs. 0)[1] may be a chance event for a couple of reasons: 1)These analyses are not ITT, because they exclude people who failed or discontinued treatment prior to reaching treatment week 36, 2) The relapse rate of zero in the 44 week arm appears lower than expected based on other subgroups 3) In late responders, shorter duration of boceprevir treatment was numerically (by 6%) better than 44 weeks of treatment and there is no plausible explanation for this finding. When one looks at SVR in all patients who had a treatment week 8 value of undetectable (not excluding failures prior to the end of treatment period), SVRs are the same. See the Table below.

Sustained Virologic Response (SVR) by HCV-RNA Detectability at TW8 in Subjects Who Have Failed Previous Therapy

	VICTRELIS-RGT	**VICTRELIS-PR48**	**PR48**
SVR by TW8 Detectability, % (n/N)*	N=146	N=154	N=72
Undetectable	88 (65/74)	88 (74/84)	100 (7/7)
Detectable	40 (29/72)	43 (30/70)	14 (9/65)
*Denominator included only patients with HCV-RNA results at TW8.			

[1] Two patients that Merck had originally reported as relapsers were not true relapsers. Both patients discontinued while still on treatment (weeks 10 and 24) with undetectable HCV RNA.

In addition, in trial P05216 (treatment naïve study) relapse rates between the RGT arm and the 44 week treatment arm were the same overall and were similar for the early responders. One could predict that approximately 20-30% of the treatment naïve early responders on boceprevir containing arms would have been relapsers or partial responders to PR alone. In P05216 early responders stopped all treatment at 28 weeks, eight weeks shorter than in trial P05101. Therefore, if the 5 vs. 0 relapse difference between treatment arms in the subset of early responders in P05101 was a true signal, one would have expected a similar signal in the P05216 early responders in which therapy was even shorter. This was not the case.

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/s/

JEFFREY S MURRAY
05/13/2011

Decisional Memorandum to the File

Date:	May 5, 2011
From:	Jeffrey S. Murray, M.D., M.P.H. Deputy, Division of Antiviral Products
Subject:	Summary and Recommendations
NDA/BLA #:	202258
Proprietary / Generic (USAN) names	Victrelis/Boceprevir
Dosage forms / strength	200 mg capsules
Proposed Indication(s)	For the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alpha and ribavirin, in adult patients (≥18 years of age) with compensated liver disease who are previously untreated or who have failed previous therapy.

1. Introduction

Boceprevir is an NS3/4A serine protease inhibitor in the ketoamide class of direct-acting antiviral agents active against hepatitis C virus (HCV) genotype 1. Boceprevir is the first direct-acting antiviral agent submitted for marketing approval for treatment of chronic hepatitis C. The drug has not been marketed internationally to date.

The pivotal trials in the development program were based superiority trials (add-on of new drug to standard of care) in subjects with chronic hepatitis C who were treatment-naïve or treatment-experienced (received prior pegylated interferon/ribavirin therapy) with the goal of improving SVR, and potentially shortening treatment duration. Direct-acting antiviral agents such as boceprevir may address an unmet medical need, particularly in patients who previously failed pegylated interferon/ribavirin therapy.

2. CMC

2.1. General Product Quality considerations

Please refer to Dr. Mark Seggel's review of the Chemistry and Manufacturing section of the NDA. Dr. Seggel concludes the following:

- the applicant has provided sufficient information on raw material controls, manufacturing processes and process controls, and adequate specifications for assuring consistent product quality of the drug substance and drug product.
- the NDA also has provided sufficient stability information on the drug product to assure strength, purity, and quality of the drug product during the expiration dating period.

Important facts about the drug substance/product are the following:

- The drug substance is a white to off-white amorphous powder that is an approximately equal mixture of two diastereomers. The two diastereomers rapidly interconvert in plasma; the predominant diastereomer is pharmacologically active and the other diastereomer is inactive.

- The drug product is a hard gelatin capsule containing 200 mg of boceprevir and the following inactive ingredients: sodium lauryl sulfate, microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, pre-gelatinized starch, and magnesium stearate.

- Four capsules of boceprevir (800 mg) are administered three times a day for up to (b) (4) The drug product is supplied cartons of twenty-eight 12-count HPDE bottles, each bottle containing one day's dose.

2.2. Facilities Review/Inspection

The Office of Compliance has issued an overall recommendation of 'Acceptable' based on the satisfactory cGMP status of the manufacturing facilities.

3. Microbiology/Virology

Please refer to the Virology review prepared by Dr. Patrick Harrington for details relating to clinical virology and clinical resistance. Important points pertinent to labeling include:

- Boceprevir is an inhibitor of the hepatitis C virus (HCV) non-structural protein 3 (NS3) serine protease.

- Resistance to boceprevir was characterized in biochemical and replicon assays and in the clinic. Boceprevir potency was reduced by the following major resistance resistant-associated amino acid variants (RAVs): V36M, T54A, R155K, A156T and A156, and V170A. Cross resistance to boceprevir and other HCV protease inhibitors in development is expected.

- In boceprevir-treated subjects who did not attain sustained virologic response (SVR) for whom samples were analyzed, 53% had post-baseline RAVs detected. The pattern of resistance mutations differs for genotype 1a and 1b.

- Trial subjects who had poor interferon responsiveness during the lead-in period with PR were more likely to develop RAVs.

- Although RAVs appear to diminish over time (by population analysis) when patients have stopped therapy, approximately 25% of patients had one or more RAVS after 2.5 years of follow-up. It is not know how the presence of RAVs or the previous presence of RAVs will affect subsequent treatment with HCV protease inhibitors in the context of other regimens.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Review was performed by Dr. Chris Ellis who concludes that the sponsor provided sufficient nonclinical safety information on boceprevir in support of marketing approval in the U.S. Important points in the Nonclinical Pharmacology review that were pertinent to labeling discussions include the following:

- Carcinogenicity
  Boceprevir was not mutagenic or genotoxic in a battery of in vitro or in vivo assays, including bacterial mutagenicity, human peripheral blood lymphocyte and mouse micronucleus assays. Two-year carcinogenicity studies in mice and rats were conducted with boceprevir. No increases in the incidence of drug related neoplasms were observed in the highest doses tested. In mice the exposures at highest doses were several-fold higher than the exposures expected in humans and in rats the exposures at the highest doses studied were similar to human exposures.
- Impairment of Fertility/Testicular Toxicity
  Decreased fertility was observed in male rats, most likely as a consequence of testicular degeneration, at exposure levels less than those attained in patients at the recommended clinical dose. Testicular toxicity appeared to be reversible in a 3-month rat study with a 2-month treatment-free period. In addition testicular toxicity was not observed in rats or cynomolgus monkeys at exposures several-fold higher than that achieved at clinical doses. In addition, analysis of inhibin B and semen in humans did not show effects. Thus testicular toxicity may be limited to rats.

5. Clinical Pharmacology/Biopharmaceutics

For details on Clinical Pharmacology, refer to the review prepared by Dr. Ruben Ayala. Dr. Ayala concurs with approval of boceprevir but specifies a number of postmarketing requirements. Important points in the Clinical Pharmacology review are summarized below.

- Food enhanced the exposure of boceprevir by up to 60% at the 800 mg three times daily dose when administered with a meal, relative to the fasted state. The label will recommend that boceprevir be taken with food. Gender, race and age had no effect on pharmacokinetic exposure.

- Boceprevir is eliminated with a mean plasma half-life ($t_{½}$) of approximately 3.4 hours. Boceprevir is eliminated primarily by the liver. In a study of patients with varying degrees of stable chronic liver impairment (mild, moderate and severe), no clinically significant differences in pharmacokinetic parameters were found. However, AUC was increased in subjects with severe

liver impairment. No dosage adjustment will be recommended for liver impairment.

- Boceprevir was evaluated for the effect on QT/QTc intervals at supratherapeutic (1200 mg three times daily) and therapeutic (800 mg three times daily) doses in 36 healthy subjects. There was no significant difference in the QTc interval between boceprevir and placebo.

Drug Interactions

Because boceprevir is an inhibitor of Cyp3A it is recommended not to co-administer boceprevir with sensitive substrates of 3A4. Drugs that are highly dependent on CYP3A4/5 for clearance, and for which elevated plasma concentrations are associated with serious and/or life-threatening events such as orally administered midazolam, pimozide, amiodarone, flecainide, propafenone, quinidine, and ergot derivatives (dihydroergotamine, ergonovine, ergotamine, methylergonovine) should be contraindicated.

Boceprevir is a substrate for P-gp and may be an inhibitor of P-gp, based on in vitro study results. A drug interaction trial was not conducted to assess the effect of boceprevir on a sensitive P-gp substrate (e.g. digoxin), but will be requested as a postmarketing requirement.

Although a drug interaction study with boceprevir and a commonly used oral contraceptive, drospirenone/ethinyl estradiol (Yaz) was conducted, the label will recommend against coadministration of boceprevir and oral contraceptives for the following reasons:

1) There were flaws in the conduct of the drug interaction study with drospirenone/ethinyl estradiol. Notably, the oral contraceptive was only administered for 7 days which left insufficient time for both of the components to reach study state as expected according to product labeling.
2) Boceprevir increased the mean AUC of drospirenone by 99% and decreased the mean AUC of ethinyl estradiol by 24%. This could result in possible more adverse reactions due to increases in exposure of drospirenone and perhaps breakthrough bleeding or loss of effectiveness due to decreases in exposure of the ethinyl estradiol component.

Given the above findings, we will request that Merck conduct another DDI study with boceprevir and oral contraceptives. In the interim, the labeling will recommend that patients use a second form of reliable birth control.

Unfortunately, a drug-drug interaction study with boceprevir and methadone has not been completed. Given that many individuals contracted HCV through intravenous drug use, the potential for interactions with methadone needs to be evaluated. This will be a postmarketing requirement.

6. Clinical/Statistical

6.1. Phase 3/Essential Clinical Studies

Efficacy was assessed in approximately 1500 adult subjects in two Phase 3 trials in patients who were previously untreated (SPRINT-2 also called P05216) or who had failed previous therapy (RESPOND-2 also called P05101). In both studies, boceprevir was added to what is considered current standard of care, peginterferon alpha and ribavirin (PR).

Treatment Naïve Patients

P05216 was a randomized (1:1:1), double-blinded, placebo-controlled study comparing two therapeutic regimens (standard vs. response guided therapy) of boceprevir 800 mg orally three times daily in combination with PR [PegIntron 1.5 µg/kg/week subcutaneously and weight-based dosing with Ribavirin (600-1400 mg/day orally divided twice daily)] to PR alone. Trial subjects were adults who had chronic hepatitis C (HCV genotype 1) infection with detectable levels of HCV-RNA and were not previously treated with interferon. There were two cohorts (Cohort 1/non-Black and Cohort 2/Black). Subjects were randomized to one of the following three treatment arms:

P05216 Treatment Arms

Arm 1	**PR** 48wks		
Arm 2	LI-4wks	**PR + B** 24 wks	**PR** 20 weeks
Arm 3	LI-4wks	**PR + B** 44 weeks	

*LI = Lead-in with PR only
TW = Treatment Week

In Arm 2, the response guided therapy (RGT) arm, the following applied:

- Subjects with undetectable HCV-RNA at TW8 (early responders) and who were also negative through TW24 discontinued therapy and entered follow-up at the TW28 visit.
- Subjects with detectable HCV-RNA at TW8 (late responders) or any subsequent treatment week but subsequently negative at TW24 were changed in a blinded fashion to placebo at the TW28 visit and continued therapy with PR for an additional 20 weeks, for a total treatment duration of 48 weeks.

All subjects with detectable HCV-RNA in plasma at TW24 were discontinued from treatment. Sustained Virologic Response (SVR) to treatment was defined as undetectable plasma HCV-RNA at follow-up week 24. It is important to note that for the purpose of labeling, we will define SVR as HCV RNA levels below the limit of quantification rather than the limit of detection. It appears that most off-treatment HCV RNA values that are between the assay limit of detection and quantification are false positive results. Moving forward, it will be more efficient to use the quantification limit to avoid reconciling potential false positive results.

P05216 Treatment Naïve Study Results

Results are shown in the Table 1 below. The primary efficacy comparisons were that of the combined cohorts (black and nonblack). Both Arms 2 and 3, boceprevir arms, were statistically superior to Arm 1. The difference in SVR from adding boceprevir was substantial, approaching a two-fold increase.

Table 1. P05216: SVR by Cohort and Treatment Arm

Study Cohorts	Arm 1 PR48 (Control)	Arm 2 – RGT BOC/PR	Arm 3 BOC/PR48
Cohort 1 Plus Cohort 2			
SVR % (n/N)	38 (138/363)	63 (233/368)	66 (242/366)
Relapse % (n/N)	22 (39/176)	9 (24/257)	9 (24/265)
Cohort 1 (non-Black)			
SVR % (n/N)	41 (126/311)	67 (211/316)	69 (213/311)
Cohort 2 (Black)			
SVR %	23 (12/52)	42 (22/52)	53 (29/55)

For cohort 2, black patients, there was an 11% numerical difference between Arm 2 and Arm 3 favoring Arm 3. This difference was not statistically significant but of clinical concern. The study was not designed to address noninferiority between Arms 2 and 3. The sponsor contends that approximately half of this numerical difference can be explained by two factors 1) an imbalance in the number of patients discontinuing therapy during the PR lead-in (no patients in Arm 3 discontinued) and 2) an imbalance between poor responding patients with cirrhosis. FDA analysis confirms that the difference in SVR narrows when taking these factors into account. However, these analyses are post hoc and some uncertainty remains.

Another efficacy issue outlined in Dr. Singer's review and the Clinical Pharmacology review is the SVR difference (not statistically significant) between Arm 2 and Arm 3 for treatment naïve late responders. These analyses compared late responders receiving at least 28 weeks of therapy in Arm 2 with a similar subset in Arm 3. The analyses allowed for a cleaner comparison of the effect of continuing boceprevir in addition to PR from study weeks 28 to 48. Patients in both arms were receiving PR during this time period but only Arm 3 continued boceprevir. FDA's analysis differed from the sponsor's analysis for this comparison. In the sponsor's analysis the difference in SVR was only 3% but in FDA's analysis the difference was 9% favoring Arm 3 (See Table 2). FDA excluded 14 people from the analysis that the sponsor had included. These 14 people were assigned to longer treatment (as would be a late responder) because of HCV-RNA

lab tests that were detectable between weeks 8 and 24. However, on retesting, these samples were deemed to be undetectable. Although it remains a judgment call, FDA believes these people should be excluded from the analysis for a more fair comparison because these patients were likely to be true early responders.

Table 2. Trial P05216 ; SVR by TW8-24 Response Category and Treatment Arm

Response Category	**RGT SVR n/N (%)**	**BOC44 SVR n/N (%)**
	PR4/BOC+PR24	**PR4/BOC+PR44**
Early Responders	156/161 (97)	155/161 (96)
	PR4/BOC+PR24/PR20	**PR4/BOC+PR44**
Late Responders	45/68 (66)	55/73 (75)

Additionally, FDA noted that the difference between Arm 2 and Arm 3 occurred primarily because of viral breakthroughs shortly after boceprevir was stopped (even though PR was still on board). We believe that this suggests a longer duration of boceprevir may be needed to prevent virologic breakthroughs. As discussed below, treatment experienced patients received a longer duration of boceprevir (32 weeks). Dr. Florian's analyses suggest that treatment naïve late responders are more similar to treatment experienced patients when comparing interferon responsiveness during the first 4 weeks. As will be discussed below, treatment experienced, late responders in Arm 2 did not have more viral breakthroughs after boceprevir cessation compared to patients receiving continued triple therapy in Arm 3. This suggests that <u>at least</u> 32 weeks of boceprevir therapy may be needed for treatment naïve late responders.

<u>Treatment Experienced Patients</u>

P05101 was a randomized, double-blinded trial comparing two regimens of boceprevir 800 mg orally three times daily in combination with PR compared to PR alone. Trial participants were adult subjects with chronic hepatitis C (HCV genotype 1) infection who had not achieved SVR with prior PR therapy. Partial responders and relapsers were included but prior null responders were excluded. Subjects were randomized in a 1:2:2 ratio and stratified based on response to their previous qualifying regimen (relapsers vs. non-responders) and by HCV subtype (1a vs. 1b) to one of the following treatment arms:

P05101 Treatment Arms

Arm 1	**PR** 48wks		
Arm 2	LI-4wks	**PR + B** 32 wks	**PR** 12 weeks
Arm 3	LI-4wks	**PR + B** 44 weeks	

For Arm 2, the RGT arm, the following applied:

- Subjects with undetectable HCV-RNA at TW8 (early responders) and TW12 completed therapy at TW36 visit.
- Subjects with a detectable HCV-RNA at TW8 but subsequently undetectable at TW12 (late responders) were changed in a blinded fashion to placebo at the TW36 visit and continued treatment with PR for an additional 12 weeks, for a total treatment duration of 48 weeks.

All subjects with detectable HCV-RNA in plasma at TW12 were discontinued from treatment. Sustained Virologic Response (SVR) to treatment was defined as undetectable plasma HCV-RNA at follow-up week 24.

> *Of note, null responders were excluded from Trial P05101 because the phase 2 trial in treatment experienced subjects was not interpretable, as stated in Dr. Singer's memorandum. At the time of the design of phase 3 trials, FDA and the sponsor agreed that it would be prudent to first confirm efficacy in the naïve population, prior relapsers and partial responders before studying null responders, the most difficult to treat subset. Since that time the Division has recognized that the treatment naïve population also consists of patients who are poorly interferon responsive and are destined to be null responders.*

Efficacy results for P05101 are presented in Table 3. Both boceprevir arms were statistically superior to PR and the differences in SVR were substantial (approaching 3 fold).

Table 3. P05101: SVR by Treatment Arm

Efficacy Parameter	**Arm 1 PR48 (Control)**	**Arm 2 RGT BOC/PR**	**Arm 3 BOC/PR48**
SVR % (n/N)	23 (18/80)	59 (96/162)	66 (107/161)
Relapse % (n/N)	28 (7/25)	14 (16/111)	12 (14/121)

There was a numerical difference of 7% favoring Arm 3 (triple therapy with 44 weeks of PR plus boceprevir) over Arm 2. The sponsor contends that this numerical difference in undetectable viral load levels was observed early on when patients were still receiving the same duration of treatment. They also state that there is no numerical difference between treatment arms when patients with cirrhosis are excluded. The longer treatment duration appears to have its greatest numerical advantage in patients with cirrhosis. FDA analyses confirm the effect that cirrhosis has on treatment outcomes between the two arms (See Table 4). Both FDA and the company agree that patients with cirrhosis should receive 44 weeks of triple therapy and that the presence of cirrhosis may explain some, if not most, of the treatment differences observed between Arms 2 and 3.

Table 4. Trials P05216 and P05101: The Effect of Cirrhosis on Treatment Outcome

	Arm 1 PR 48 n/N (%)	Arm 2 RGT n/N (%)	Arm 3 BOC/PR 48 n/N (%)
P05216 (Naive)			
All Subjects	*138/363 (38)*	*233/368 (63)*	*242/366 (66)*
Cirrhosis NO YES	 127/339 (38) 6/13 (46)	 222/337 (66) 5/16 (31)	 223/331 (67) 10/24 (42)
P05101 (Experienced)			
All Subjects	*18/80 (23)*	*96/162(59)*	*107/161(67)*
Cirrhosis: NO YES	 17/66 (26) 0/10 (0)	 86/132 (65) 6/17 (35)	 85/128 (66) 17/22 (77)

For Trial P05101, the sponsor and FDA conducted analyses comparing SVR among boceprevir-containing treatment arms for early and late responders similar to that done for Trial P05216. In contrast, to the treatment naïve study analyses, RGT appeared to perform slightly worse for early responders. For early responders there was a numerical difference of approximately 7% favoring Arm 3 and for late responders there was a similar numerical difference (6%) favoring Arm 2. The results are shown in Table 5.

Table 5. Trial P05101 ; SVR by TW8-12 Response Category and Treatment Arm

Response Category	**RGT** **SVR n/N (%)**	**BOC44** **SVR n/N (%)**
	PR4/BOC+PR32	**PR4/BOC+PR44**
Early Responders	61/68 (90)	68/70 (97)
	PR4/BOC+PR32/PR12	**PR4/BOC+PR44**
Late Responders	27/34 (79)	29/40 (73)

It should be noted that these are subgroup analyses with relatively small numbers. In addition the numerical differences between arms are similar in magnitude but in opposing directions for early and late responders. Nonetheless, the relapse rate in Arm 2 (as reported in Dr. Mishra's review) was 5/66 in Arm 2 compared to 0/68 in Arm 3. The

sponsor noted even more relapsers (7) in Arm 2. Most of these patients were previous relapsers. Some have raised the concern that stopping PR at 32 weeks is insufficient and could result in relapse in previously treated patients. Although these differences are not concerning from a statistical sense, the occurrence of virologic breakthroughs upon treatment cessation raises concerns from a virologic/mechanistic point of view.

6.2. Other efficacy studies

SPRINT-1 (P03523) evaluated the use of boceprevir in combination with PR with or without a four-week lead-in period with PR compared to PR alone in subjects who were previously untreated patients. In this trial, different durations of boceprevir treatment in combination with PR were studied, 28 weeks vs. 48 weeks. In addition the effect of a 4 week lead-in period was evaluated. The longer duration of treatment and the lead-in conferred a numerical advantage over shorter treatment periods and arms without PR lead in periods. Longer duration appeared to be more advantageous for later virologic responders.

6.4. Issues needing resolution

Most of the efficacy issues needing resolution were taken to the advisory committee and are discussed in detail under sections 6.1 and 9. These issues were:

– Whether to include null responders in the treatment indication. Historical null responders were not included in the treatment experienced trial. However, the sponsor contends that people who have interferon responsiveness comparable to that of prior null responders were studied in the naïve trial. It is important to understand that naïve populations contain patients who will prove to be relapsers, partial responders and null responders. The 4 week lead-in period in Merck's trials allows one to determine or predict interferon responsiveness. The sponsor claims that less than a 1 log decline in HCV RNA at 4 weeks is a good surrogate for null response, which is otherwise defined as less than a 2 log decline at week 12 Differences in SVR between boceprevir arms and PR for those who had less than a 1 log decline during lead-in was 28-38%, indicating that these poorly interferon responsive patients are still expected to have a treatment effect from adding boceprevir to PR. The FDA conducted analyses on this issue to further assess whether the 4 week interferon response could serve as a surrogate for null response. Similar to the sponsor's analyses, we compared 4 week and 12 week responses in patients in the PR group. Approximately 69% of individuals with a 1 log decline at week 4 would eventually be classified as a null responder in patients receiving PR only. Using a 0.5 log cut-off, approximately 90% with decreases less than this value at week 4 would be classified as null responders. In terms of early viral load declines, these would be the poorest interferon responders of the null response group; most null responders have greater than a 0.5 log decline at week 4. Among treatment naïve patients who had less than a 0.5 log drop at week 4 in the boceprevir arm, approximately 30% had an SVR, indicating that poorly interferon-responsive patients (approximately 90% would be predicted to be null responders) had a substantial treatment effect. No patients achieving less than a 0.5 log decline in the PR arm achieved an SVR. In my opinion, these analyses offer evidence that boceprevir offers the likelihood of a substantial

treatment effect in null responders. However, optimal treatment duration in this subgroup was not studied. Thus the sponsor proposed a full 44 weeks of triple therapy for this subgroup.

– The optimal treatment durations for treatment naïve late responders, black patients and patients with cirrhosis or advanced fibrosis were other unresolved issues prior to the advisory committee meeting. This is discussed in detail in section 6.1 and section 9 of this memo.

6.3. Safety

The sponsor evaluated the safety of the combination of boceprevir with PR in 2095 subjects with chronic hepatitis C in one Phase 2, open-label trial and the two Phase 3 clinical trials discussed above. In the sponsor's safety data base the mean age was 49 years (3% of patients were >65 years of age), 39% were female, 82% were white and 15% black. Subjects received boceprevir 800 mg three times daily in each study. In the pooled studies, the median exposure was 201 days in subjects receiving boceprevir in combination with PR and 198 days in subjects receiving PR alone. During the entire course of treatment, the proportion of subjects who discontinued treatment due to adverse reactions was 13% for subjects receiving the combination of boceprevir with PR and 12% for subjects receiving PR alone. Events resulting in discontinuation were similar to those seen in previous studies with PR.

FDA analysis of safety was conducted on phase 3 studies. Anemia was the most common adverse event occurring at a greater frequency in boceprevir containing arms and was reported both as a clinical and laboratory adverse event. Boceprevir also increased the frequency of neutropenia and thrombocytopenia but to a lesser extent than anemia. Because anemia, neutropenia and thrombocytopenia are primarily laboratory diagnoses, I believe it is more precise to look at these events by laboratory cut-offs as shown in Table 6 below.

Table 6. Hematologic Adverse Events (Laboratory Cut-offs) by Treatment Arm

Laboratory Event	**BOC/PR N = 1057 n (%)**	**PR N=443 n (%)**
Anemia (Laboratory Event)		
Hgb ≤ 10 g/dL	547 (52)	141 (32)
Hgb ≤ 8.5 g/dL	92 (9)	16 (4)
Neutropenia		
0.5 to <0.75 x 10^9/L	239 (23)	57 (13)
<0.5 x 10^9/L	71 (7)	19 (4)
Thrombocytopenia		
25 to < 50 x 10^9/L	38 (4)	5 (1)
< 25 x 10^9/L	2(<1)	0

The additional anemia associated with boceprevir resulted in a higher frequency of dose reductions of ribavirin and a higher frequency of use of erythropoietin stimulating agents (a common clinical practice in hepatitis C treatment but nonetheless an off-label use for hepatitis C). In addition, dyspnea, dizziness and syncope occurred at a slightly higher frequency on the boceprevir containing arms.

In the phase 3 trials and the phase 2 trial (Sprint-1), there were four serious infections that occurred in close proximity to severe neutropenia. These cases are a signal that serious neutropenia-related infections may occur with use in broader populations. Diligent monitoring of hematologic parameters will be required.

7. Risk Management

A medication guide will be required for boceprevir. The medication guided will inform patients of the many potential adverse reactions that could occur when boceprevir is used with pegylated interferon and ribavirin. Pegylated interferon products and ribavirin products also have medication guides and address adverse reactions and also address pregnancy risks given that these drugs are used in combination and given that ribavirin is a category X drug with known teratogencity in animals.

8. Summary of Regulatory Issues

The boceprevir NDA was given a priority review and presented before an advisory committee meeting as discussed below. Although the primary endpoint used in the phase 3 trials is a virologic measurement (undetectable virus 6 months after the end of therapy referred to as SVR), FDA considers this endpoint clinically validated. Therefore approvals using this endpoint will not fall under accelerated approval regulations. The expected regulatory action will be regular (traditional) approval.

FDA has stated in recent draft guidance that SVR is a clinically validated endpoint based on evidence from multiple observational cohorts. A recent review by Pearlman and Traub, entitled, "Sustained Virologic Response to Antiviral Therapy for Chronic Hepatitis C Virus Infection: A Cure and So Much More," published in Clinical Infectious Diseases 2011 summarizes the association between SVR and clinical outcomes. Nineteen cohorts evaluated clinical outcomes comparing those who achieved SVR vs. those who were nonresponders. Among patients who achieved SVR there were substantial reductions in important outcomes such as progression to decompensated liver disease, hepatocellular carcinoma, liver mortality and all cause mortality.

9. Advisory Committee Meeting

The Antiviral Drugs Advisory Committee was convened on April 27, 2011. FDA posed the following questions to the committee:

1) Please comment on the safety of boceprevir in patients with chronic hepatitis C genotype 1, focusing mainly on the hematological effects of boceprevir in combination with pegylated interferon and ribavirin (PR).
2) Considering the overall potential risk and benefits of boceprevir, do the available data support approval of boceprevir for treatment of patients with chronic hepatitis C genotype 1 in combination with pegylated interferon and ribavirin? If no, what additional studies are recommended?
3) Please comment on the strength of the evidence for use of boceprevir in combination with pegylated interferon/ribavirin in prior null responders (defined as < 2 log10 decrease in HCV RNA at 12 weeks during previous PR therapy), who were not included in the Phase 3 treatment-experienced trial (P05101).
4) Please comment on the strength of the evidence to support response-guided therapy (RGT) with boceprevir in combination with pegylated interferon and ribavirin. Should certain groups of patients receive longer durations of boceprevir plus PR therapy than that evaluated in RGT arms?
   a. Treatment-naïve patients with detectable HCV RNA at Week 8 and undetectable at Week 24 (late responders)
   b. Patients such as blacks or those with advanced fibrosis or cirrhosis
   c. Null responders (if recommended for inclusion in the indication)
5) In addition to pediatric studies, are there any other postmarketing studies you would recommend to further define risks or optimal use of boceprevir in clinical practice?

In response to Question 1, the committee agreed that the major safety concerns of adding boceprevir were an amplification of the hematologic toxicities characteristically seen with interferon and ribavirin. Dr Geraldine Schecter, a hematology consultant for the committee, and several of the hepatologists stated that these toxicities could be successfully monitored and managed and, in fact, are a part of routine management in the treatment of hepatitis C with the current standard of care. Some raised concerns that boceprevir may result in a more brisk decline in hematologic parameters and recommended that the label make clear that physicians be vigilant in checking complete blood counts more frequently in patients deemed at risk or exhibiting a sharp decline in RBCs, WBCs or platelets.

Question 2 asked the committee to balance the risk and benefits and vote on marketing approval of boceprevir for the treatment of chronic hepatitis C. The question did not specify approval by subgroups because specific subgroups and recommendations for treatment duration were to be addressed in questions 3 and 4. The committee voted unanimously (18- yes, 0- no) for the approval of boceprevir. All stated that the benefits outweighed the risks and that the treatment effect of boceprevir represented an improvement over current standard of care.

Question 3 asked the committee to comment on the strength of the evidence for including null responders in the treatment indication. In short, there was no

consensus on this issue. Some of the advisory committee members stated that the evidence was not convincing since patients who were prior null responders were not specifically studied in phase 3 clinical trials. Some advisory committee members were persuaded by the argument that poor interferon response, identified in the 4 week lead in the naïve population, was a reasonable surrogate for prior null responders. Some were not completely persuaded by the argument but suggested that any mention in the label for use in a null responder might caution that this recommendation was based on inferences from data in the naïve population. In summary, there was not consensus for including null responders but some of our experts agreed that a substantial treatment effect in this group is likely. The optimal duration of treatment in null responders is not known, but the sponsor requests 44 weeks treatment duration.

Question 4 was a multiple part question that asked the committee to give advice on the optimal duration for certain subgroups of patients that are known to be difficult to treat, such as blacks and cirrhotics, and patient subgroups who showed numerically lower SVR in RGT compared to 44 weeks of therapy with three drugs. For this question there was no consensus on all points. In general, however, the committee expressed a desire for some permissiveness in labeling such that physicians and patients could make decisions regarding optimal treatment duration on an individual basis as appropriate for the clinical situation, particularly for patients who may have adverse reactions. Some committee members stated that the label could disclose risks and benefits for a range of dosing without specifically recommending shorter boceprevir dosing per se. Some of the members voiced the concern that too much complexity in labeling recommendations could result in physician errors and perhaps translate into lack of adherence. Simplifying treatment recommendations as much a possible was considered a worthwhile objective.

I got the impression that the committee weighed the achievement of SVR a bit more heavily than reducing additional toxicity related to treatment duration. Perhaps this is because SVR is viewed as a cure and therapy is time limited. One hepatologist commented, that adding an extra 12 weeks of therapy after several months of an interferon based regimen, would be acceptable to patients if longer treatment duration insured higher SVR.

Subgroups that were specifically addressed with regard to treatment duration included treatment naïve late responders (those who were detectable at week 8 but undetectable at week 24). When presented with the option of using 44 weeks of boceprevir vs. 32 weeks of boceprevir, many of the advisory committee members showed a preference for 44 weeks. FDA had presented the argument that naïve late responders were similar to the patients enrolled in the treatment experienced trials which had received 32 weeks of boceprevir and thus consideration to giving this subgroup 32 weeks of therapy might be reasonable. In the treatment naïve trial subjects in the RGT arm late responders received 24 weeks of boceprevir therapy in combination with PR followed by 20 more weeks of PR. It was noted that a small percentage of patients had breakthrough shortly after boceprevir was stopped in the

RGT arm despite continuation of PR. Although most of the committee seemed to favor the longer duration of boceprevir as studied in arm 3, some also conceded that many physicians may want to use 32 weeks of treatment as part of individualizing therapy. In addition, Susan Ellenberg, the committee statistician pointed out that the differences observed between RGT and 44 weeks of triple therapy were not statistically significant and were in small numbers of patients in post hoc subgroup analyses. From a statistical point of view, she did not believe that there was evidence to show that RGT was inferior to 44 weeks of triple therapy.

The committee discussed the most appropriate treatment duration for black patients. Overall the numerical difference in SVR between RGT and 44 week triple therapy was 11%, but not statistically significant. However, this trial was not designed with sufficient power to assess noninferiority/equivalence of the two boceprevir arms overall, much less for subgroups. The sponsor had presented data which suggested that half of the 11% difference may be explained by early discontinuations during the lead-in period on the RGT arm (none on the 44 week triple therapy arm) and due to low response rates in patients with cirrhosis. The numerical difference was smaller when cirrhotics were excluded. The committee did not give definitive advice on this, but several committee members stated that 44 weeks duration of treatment would be most prudent; however, at the same time many committee members suggested that a label might be permissive to RGT particularly for those without cirrhosis.

During their presentation, the sponsor conceded that patients with cirrhosis may need 44 weeks of triple therapy. The committee agreed with the longer treatment duration for this subgroup.

The last subgroup addressed with respect to treatment duration was null responders. The committee could not reach consensus on whether null responders should be specifically excluded from the indication. However, the sponsor is recommending 44 weeks of triple therapy for historical null responders, should this group be included in the label.

Question 5 asked the committee to list studies/trials that the sponsor should conduct postmarketing. At the top of the list of suggested trials were drug-drug interaction trials including, methadone, antidepressant therapies, commonly used HIV antiretrovirals such as protease inhibitors, transplant immunosuppressants and another drug-drug interaction study with an oral contraceptive. Other suggested trials included:

- a trial evaluating shorter treatment durations of pegylated interferon and ribavirin with and without boceprevir in patients with the IL28B rs12979860 C/C genotype.
- a trial in previous null responders (< 2 $\log_{10}$ HCV RNA reduction at TW12) to pegylated interferon and ribavirin therapy to establish the optimal duration of therapy of boceprevir in combination with pegylated interferon and ribavirin in this population.

- a trial in which treatment-naïve late-responders are randomized to different durations of boceprevir plus peginterferon/ribavirin to determine the optimal duration of boceprevir treatment in this group.
- a trial in patients with compensated cirrhosis to determine optimal duration of boceprevir/PR treatment in this group.
- more data in Black and Hispanic patients to determine optimal duration of boceprevir/PR treatment in these groups
- a trial in patients 65 years and older to assess efficacy of boceprevir in combination with PR.
- a trial to compare lead-in phase with PR to no lead-in phase.

10. DSI Audits

Clinical Inspections found the data acceptable for review.

11. Conclusions and Recommendations

11.1. Regulatory Action

I concur with FDA reviewers and the Advisory Committee that boceprevir should be approved for the treatment of genotype 1, chronic hepatitis C, in combination with pegylated interferon and ribavirin in adult patients. The committee voted unanimously that benefits greatly outweigh risks and that boceprevir should receive marketing approval. I concur that the treatment effect is robust, substantial, and highly statistically significant. Substantial treatment effects from adding boceprevir to PR were observed across multiple subgroups including race, gender, baseline viral load, and other baseline characteristics. Adverse reactions associated with adding boceprevir to PR are those known to providers and can be reasonably well monitored and managed.

The indication should include previously untreated patients and patients who have previously failed treatment with an interferon with or without ribavirin. In my opinion there is sufficient evidence to expect a substantial treatment effect from adding ribavirin to PR in null responders. The difference in treatment effect of adding boceprevir to PR compared to those receiving PR alone is estimated to be approximately 28-30%. This treatment difference is of the same magnitude observed with other subpopulations (Naïve, partial responders, etc.). Therefore, I propose that the indication not specifically exclude null responders. However, the review team will add a bulleted Usage stating that previous null responders were not studied. In addition, the basis for the estimate of the treatment effect in null responders based on naive patients with poor interferon response during the lead in period will be briefly described in the Clinical Studies Section of the label. Additional labeling comments regarding optimal treatment duration for various subgroups are addressed below in section 11.3.

11.2. Postmarketing Trials

As of the required completion date of this memorandum, we are still reaching agreement with the sponsor regarding the complete list of postmarketing requirements and commitments. However, the Division envisions that most of the

drug-drug interaction trials mentioned in section 9 under question 5 will become post-marketing requirements.

11.3. Labeling

As of the required completion date of this memorandum, we are still working on product labeling. The key labeling issues are: 1) the exact wording of the Indication and Usage as discussed in section 11.1 and 2) the optimal duration of dosing to be described in the Dosage and Administration section. The latter is particularly challenging because there are multiple subgroups to consider and treatment effects may be correlated across specific subgroups. Randomized and statistically powered comparisons are not available for every subgroup (and were not expected). In fact, trials were not powered to demonstrate equivalence of the two boceprevir containing arms for all patients randomized. The trials were statistically powered to show differences between the boceprevir-containing arms and the control regimen (PR). To discern more subtle differences between response-guided boceprevir regimens and 44 week triple regimens, much larger clinical studies would have been needed. In addition, predicting which subgroups should have been targeted for specific comparisons was challenging prior to trial completion. Some on-treatment milestones were of uncertain importance until the trial had been completed and randomized. Therefore we have relied on the totality of data and our understanding of viral kinetics and disease pathogenesis in attempts to make sense of numerical differences between response-guided therapy and standard therapy (44 weeks triple therapy).

Our overall understanding of the committee's priorities regarding the optimal duration of treatment were the following: 1) simplified instructions 2) preference for regimens and durations that had been directly studied 3) importance of achieving SVR 4) some permissiveness for shorter durations of therapy as clinically appropriate.

With these priorities in mind we considered the following two options.

<u>Option 1</u>

Treatment Naïve Patients without cirrhosis and with an undetectable viral load at week 8 and 24 should receive shortened duration of therapy, 24 weeks of boceprevir plus PR after a the 4 week PR lead-in. All others, including cirrhotics will receive 44 weeks of triple therapy after the 4 week PR lead-in. This is described in detail in the following Table. The fact that patients with cirrhosis will receive 44 weeks of triple therapy and all groups except treatment naïve early responders will receive 44 weeks of therapy should ensure the black patients receive optimal duration, since most of the poor responding black patients were late responders or had cirrhosis.

ASSESSMENT (HCV RNA Results[1])			
At Treatment Week 8	At Treatment Week 12	At Treatment Week 24	Action
Undetectable	Undetectable	Undetectable	**Previously untreated patients:** Complete three-drug regimen at Treatment Week 28 **Patients who Failed Previous Therapy:** Complete three-drug regimen at Treatment Week48.
Detectable	<100 IU/mL	Undetectable	**Previously untreated patients and patients who failed previous therapy:** Continue all three medications through TW48*
Any Result	≥100 IU/mL at TW12, OR Confirmed Detectable HCV RNA at TW24		Treatment Futility. Discontinue three-drug regimen

[1] In clinical trials, HCV-RNA in plasma was measured using a Roche COBAS® TaqMan® assay with a lower limit of quantification of 25 IU/mL and a limit of detection of 9.3 IU/mL. See Laboratory Tests (5.5) for a description of HCV RNA assay recommendations.

In addition to the table, we propose the following statements to allow for alternative dosing.

Guidelines for duration of therapy using RGT were chosen to maximize rates of sustained virologic response (SVR), defined as HCV RNA <25 IU/mL 24 weeks after the end of treatment. Consideration may be given to treating with 4 weeks peginterferon and ribavirin followed by 32 weeks Victrelis in combination with peginterferon and ribavirin followed by 12 weeks of peginterferon and ribavirin alone in patients who are unable to continue Victrelis combination treatment due to adverse reactions or other reasons [see Clinical Studies (14)].

The advantages of Option 1 are: 1) it is relatively simple and can be explained in one table, 2) it gives the longest duration studied in subgroups where there was concern of suboptimal response with response guided therapy, and 3) it appears to fulfill the committee's key priorities.

The disadvantages of this option are: 1) it likely gives longer duration of boceprevir (12 weeks) to many patients who would respond well without the longer duration. The longer duration of boceprevir will translate into prolonged hematologic toxicity and prolonged ESA use. 2) Both RGT and 44 weeks of therapy were efficacious and it is uncertain whether numerical differences in SVR represent true differences.

Option 2

Option 2 is similar to Option 1 for treatment naïve patients with undetectable HCV RNA at weeks 8 and 24. It should provide sufficient coverage for black patients as in option 1.

For patients without Cirrhosis

ASSESSMENT (HCV RNA Results[1])			
At Treatment Week 8	At Treatment Week 12	At Treatment Week 24	Action
Undetectable	Undetectable	Undetectable	**Previously untreated patients:** Complete three-drug regimen at Treatment Week 28 **Patients who Failed Previous Therapy:** Complete three-drug regimen at Treatment Week 36 and continue with 12 more weeks of PR .
Detectable	<100 IU/mL	Undetectable	**Previously untreated patients and patients who failed previous therapy*:** Complete three-drug regimen at Treatment Week 36 and continue with 12 more weeks of PR
Any Result	≥100 IU/mL at TW12, OR Confirmed Detectable HCV RNA at TW24		Treatment Futility. Discontinue three-drug regimen

[1] In clinical trials, HCV-RNA in plasma was measured using a Roche COBAS® TaqMan® assay with a lower limit of quantification of 25 IU/mL and a limit of detection of 9.3 IU/mL. See Laboratory Tests (5.5) for a description of HCV RNA assay recommendations. Patients with < 2 log decline at week 12 with prior PR treatment should complete three-drug regimen at week 44.

In addition to the table the following statements could be included:

All patients with cirrhosis should receive 44 weeks of triple therapy after the 4 week PR lead-in period.

Advantages of Option 2 include shorter durations of boceprevir (administered three times daily) for many more patients. This can reduce the duration of additional anemia and neutropenia and perhaps reduce off-label ESA use and its toxicities. Toxicity reduction and patient tolerability and convenience are improved over a 12 week period.

Disadvantages of Option 2 include: 1) it is slightly more complicated than Option 1 with a third treatment regimen for cirrhotics and a three drug regimen plus a PR tail for some subgroups 2) the 36 week regimen (32 triple after 4 week PR lead-in) for treatment naïve late responders is based on an extrapolation of data from the treatment experienced study, 3) the 12 week PR tail in treatment experienced early responders is based on extrapolation from the late responder subgroup.

After careful, prolonged, and thorough consideration of the two options, the review team reached consensus that Option 2 offers the best balance of risk and benefit. All treatment regimens recommended have been studied in a comparable of more-difficult-to treat subgroup. In addition the recommended regimens in option 2 fall between the shorter and longer durations studied in the two trials. Both boceprevir-containing regimens in both trials had robust activity. The numerical differences between Arms 2 and 3 in these trials for most subgroups were small and unstable to a few patients. An important priority for the review team was to minimize unnecessary toxicity when the likelihood of gain is minimal. Recommending 44 weeks of triple therapy for patients with cirrhosis should correct for the largest portion of any numerical differences observed between subgroups. In addition, except for treatment naïve early responders, all other patients without cirrhosis will get 32 weeks of triple therapy followed by 12 weeks of PR. This was the regimen studied in P05101 in treatment experienced late responders. SVR in this group was equal (actually numerically better but probably by a chance occurrence) to that of the 44 week triple therapy regimen in treatment experienced late responders. Therefore this regimen is expected to offer a favorable outcome in comparable or easier-to-treat subgroups such as, treatment experienced early responders and treatment naïve late responders.

Our analyses and consideration of an optimal dosing regimen by assessing the totality of data in multiple studies and subgroups is not precedent setting. For example, when choosing pediatric dosing for HIV drugs, the Division has often used a comparable process to determine a dose or exposure that falls close to the adult range for several pharmacokinetic parameters but also allows for minimization of toxicity.

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/s/

JEFFREY S MURRAY
05/05/2011