Title: Boceprevir for Previously Untreated Patients with Chronic Hepatitis C Genotype 1 Infection: A US-Based Cost-Effectiveness Modeling Study

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Author's response to reviews: see over
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Philippa Harris, PhD
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Subject: MS: 1213417687727327 - Boceprevir for Previously Untreated Patients with Chronic Hepatitis C Genotype 1 Infection: A US-Based Cost-Effectiveness Modeling Study

Dr. Harris:

Please find the attached updated manuscript titled “Boceprevir for Previously Untreated Patients with Chronic Hepatitis C Genotype 1 Infection: A US-Based Cost-Effectiveness Modeling Study”. This version of the manuscript addresses the comments provided by our reviewers. We appreciate the careful review and thoughtful comments provided and believe that their suggestions have helped us improve our manuscript. Thank you for giving the opportunity to respond to the reviewers’ comments and incorporate their suggestions. A point-by-point description of our responses is summarized on pages 2-15 of this letter.

If you have any questions, please feel free to contact me at the address given below.

Sincerely,

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Responses to Reviewers’ Comments

Reviewer 1’s Report

Major Compulsory Revisions

Abstract:

Methods: please describe the model in the methods section as recommended by state of the art guidelines (model type, simulation technique, data assessment, target population, index year, currency, discounting).

To address these comments we modified the Methods section as follows:

A Markov model was used to estimate the incidence of liver complications, discounted costs (2010 US$), quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs) of three treatment strategies for treatment-naïve patients with chronic HCV genotype 1. The model simulates the treatment regimens studied in SPRINT-2 in which PR was administered for 4 weeks followed by: 1) placebo plus PR for 44 weeks (PR48); 2) boceprevir plus PR using response guided therapy (BOC/RGT); and 3) boceprevir plus PR for 44 weeks (BOC/PR48) and makes projections within and beyond the trial. HCV-related state-transition probabilities, costs, and utilities were obtained from previously published studies. All costs and QALYs were discounted at 3%.

Results: ICER versus next non-dominated strategy should be inserted: BOC/PR48 vs. BOC/RGT.

We modified the Results section by adding the following sentence:

The ICER for BOC/PR48 compared to BOC/RGT was $807,804.

Conclusions: please be more explicit, e.g. …increase the QALYs in treatment naïve patients with HCV genotype 1… Compared to standard treatment boceprevir-based treatment strategies were projected to be cost-effective at a reasonable threshold. In general the conclusion in the abstract should be the same as in the manuscript: …clinical benefit with shorter duration of therapy …

We incorporated these suggestions and changed the wording of the Conclusions to the following:

The boceprevir-based regimens used in the SPRINT-2 trial were projected to substantially reduce the lifetime incidence of liver complications and increase the QALYs in treatment-naïve patients with hepatitis C genotype 1. We also demonstrated that boceprevir-based regimens offer patients the possibility of experiencing great clinical benefit with a shorter duration of therapy. Both boceprevir-based treatment strategies were projected to be cost-effective at a reasonable threshold in the US when compared to treatment with PR48.
Methods:

p.8: Model structure: Please describe explicitly the model type and simulation technique.

Changed 1st sentence in Model Structure sub-section in Methods to:

We created an Excel-based (Microsoft Corp., Redmond, Washington) Markov cohort model to project health-related outcomes and to estimate the expected costs and quality adjusted life-years (QALYs) associated with the three treatment strategies studied in SPRINT-2.

p.10: Patients who were permanently cured were considered to be neither at risk for developing further HCV-related liver complications nor for reinfection. This is an assumption that should be discussed in the discussion section. There is still a risk of developing HCC in moderate HCV even if patients had an SVR.

Following reviewer’s suggestion, we have added the following sentences to the first paragraph in the Conclusions section:

There are a small number of studies which suggest that patients with moderate HCV may develop HCC even after achieving an SVR with drug therapy. The limited data suggest that the probability of this transition is very close to zero. Because of the limited information available and since the transition is negligible, we did not include it in our model.

Figure 1.: in patients with SVR even in those with cirrhosis, there is no progression to more severe health states considered? That would be a great bias in favor of antiviral treatment! However, you mentioned, that cirrhotic patients with SVR are considered partially cured. That would suggest that there is the possibility to develop decompensated cirrhosis and HCC etc. Please show this in the figure.

We thank the reviewer for pointing this out. In the revised figure, we now explicitly show that cirrhotic patients who achieve SVR can develop DC or HCC.

p.12, patient characteristics: ...In the model, a series of 20 cohorts progressed through each treatment regimen... Please explain the differences of the cohorts and why you used 20 cohorts. If you used a Markov model with a cohort simulation, why didn’t you use the mean values for the patient characteristics from the trial?

We wanted to include patients with each of the baseline METAVIR scores and be able to track their transitions separately. Our model also allows us to define separate inputs for treatment characteristics for patients with and without cirrhosis and if they are black or nonblack. Because of differential mortality between men and women, we also simulated cohorts of men and women separately. Our approach is better than using a single cohort with mean values for the patient characteristics form the trial because allows us to capture the non-linear relationship between the inputs and outcomes. Whereas, the single cohort approach (erroneously) assumes that the relationship between the inputs and outcomes is linear, and thus adds bias in the results.
As mentioned on page 17, we used the mean values for the patient characteristics from the trial to obtain an overall weighted average of the results.

The following sentence was added to the Patient Characteristics subsection:

The cohorts represent all possible combinations of gender, race cohort, and baseline METAVIR fibrosis score (2x2x5=20).

p.15, Cost Data: ... *We included the costs AV therapy, management of anemia, and management of HCV disease in patients who did not achieve SVR...* The assumption that HCV patients with an SVR cause no costs for managing the remaining disease should be stated more explicitly and discussed as a limitation in the discussion section. This might contribute to an underestimation of total costs.

We added sensitivity analyses including a cost associated with the SVR health states and the results are summarized in supplementary table 1. In the scenario where an annual cost of $509 was applied to patients who achieve SVR, the ICERs did not change drastically from the base case. The ICERs for BOC/RGT compared PR48 is approximately $21,000; BOC/PR48 compared with PR48 is approximately $59,000; BOC/PR48 compared with BOC/RGT is approximately $816,000.

**Results:**

p.20: Please state here also the ICER to the next non-dominated strategy (e.g. BOC/PR48 vs. BOC/RGT) as recommended by the actual guidelines for cost-effectiveness studies. As the ICER of BOC/PR48 is much more unfavorable when comparing directly to BOC/RGT, the favored choice would be BOC/RGT. In addition a figure with a cost-effectiveness frontier would be of much value for the reader. In this graph, one can also implement the FDA strategy for comparison reason.

We added the following sentence:

The ICER for treatment with BOC/PR48 compared with BOC/RGT was $807,804/QALY.

p.21, first paragraph: please describe more consent which parameters are sensitive and which are not. Please state rather the absolute ranges of ICER vs. PR48 (e.g. ranging from x to y) than the change value as $6K/QALY etc.

The first paragraph in the Results section has been changed to:

The ICERs compared with PR48 from the one-way sensitivity analyses of chronic disease progression rates, rate of developing advanced liver disease, all health state costs, and most utility values were within $6K/QALY and $11K/QALY of the BOC/RGT (range: $1,747 to $42,983/QALY) and BOC/PR48 (range: $21,016 to $88,789/QALY) base case ICERs, respectively (*See Supplementary Table 1 online*). The ICERs that fell out of these ranges were
obtained when the lower bound of the quality of life of the SVR state for patients who had a baseline METAVIR score of F1 was assumed (BOC/RGT: $25,685 and BOC/PR48: $87,264) and when assumptions concerning treatment efficacies were varied. When the efficacy of PR48 was assumed to be 45.4%, the upper limit of the 95% confidence bound, and the efficacies for BOC/RGT and BOC/PR48 remained the base case values, the ICERs of BOC/RGT and BOC/PR48 increased to $29,369 and $81,237, respectively. Conversely, when the efficacies of the boceprevir-based regimens were assumed to be the upper limits of the confidence bounds, and the efficacy of PR48 was assumed to be the base case value, both BOC/RGT and BOC/PR48 became cost-saving compared to dual therapy.

Included the following in the 4th paragraph of Conclusions:

Only 5 of the 103 scenarios evaluated resulted in an ICER comparing BOC/RGT to PR48 that was more than $5000 different from the base case analysis. Specifically, assumptions regarding the utility of the SVR-F1 health state, efficacy of PR48 and BOC/RGT, and the discount rates were most impactful on the ICER. Similarly, only 18 of the 103 scenarios evaluated resulted in an ICER comparing BOC/PR48 to PR48 that was more than $5000 different from the base case analysis. Specifically, assumptions regarding the transition rates from F4 to DC and F4 to HCC; utility of the F1-F4, SVR-F1, SVR-F2 health states; efficacy of PR48 and BOC/PR48; and the discount rates were most impactful on the ICER.

p.22, first paragraph: please state always explicitly ICER vs. PR48. As comparing all three strategies, as would be state-of-the-art procedure, BOC/PR48 would not be cost-effective in the base-case and the CEAC would be different.

This change has been made. The paper has been updated such that the comparator is always explicitly stated when the ICER is given and/or when a conclusion regarding cost-effectiveness is provided.

p.22: In the subset analyses the ICER of BOC/PR48 vs. BOC/RGT is missing. This would be very important to conclude on cost-effectiveness of treating black HCV patients longer with triple therapy. A cost-effectiveness frontier graph would show this. In addition absolute numbers instead of incremental numbers in the corresponding table would allow for calculations on this.

Following reviewer’s suggestion, we have added the ICER of BOC/PR48 versus BOC/RGT and have included the cost-effectiveness frontier in the appendix. In addition, we added text to the conclusion to explain this phenomena.

p.23, first paragraph: In general, it would be of more value to include the FDA label strategy into the base-case analysis and show the results compared to all other strategies in table 4 and in addition in a cost-effectiveness frontier (xyfigure with x absolute discounted costs, and y absolute discounted QALYs).

The results of the boceprevir label analysis have been summarized. Since the boceprevir label strategy is a post-hoc analysis, we do not think it is appropriate to directly compare the results with the treatment strategies studied in SPRINT-2.
Conclusions:

p.24: First paragraph, in the conclusion of cost-effectiveness: we would not conclude that BOC/PR48 is cost-effective. It is only cost-effective, if BOC/RGT is not considered at all. At least it should be written explicitly and discussed.

Following the reviewer’s suggestion, we have modified the manuscript so that the comparators are explicitly stated when the ICERs are given or to conclude the cost-effectiveness of different treatment strategies. Both BOC/RGT and BOC/PR48 are cost-effective in comparison with PR48; however, BOC/PR48 is not cost-effective in comparison to BOC/RGT. In addition, the following sentence has been added to the first paragraph of the Conclusion section:

In addition, the ICER of BOC/PR48 compared to BOC/RGT was $807,804/QALY, which implies that BOC/PR48 is not cost-effective at commonly used thresholds when compared to treatment with BOC/RGT.

p.25, third paragraph: it should be stated that analyses results suggest that there might be an additional benefit to treat black HCV patients longer than non-black patients, as QALYs gained are higher in the BOC/PR48 compared to BOC/RGT. ICER of BOC/PR48 vs. BOC/RGT should be stated and conclusion should be drawn from this ICER, as it reflects the study question of which regimen strategy would be the best for this cohort. In contrast, non-black patients do not profit from longer treatment at all (no additional QALY gained).

The following text was modified to reflect black patients may benefit from longer treatment with boceprevir.

The ICERs corresponding to BOC/PR48 compared with PR48 for both race cohorts were similar - $50,423 and $56,013 for the non-black and black cohorts, respectively. There was a greater difference in the ICERs between the boceprevir-based treatment strategies compared to dual therapy for the non-black subgroup. This is because the efficacies between the two boceprevir-based regimens are very similar even though the treatment cost of BOC/PR48 is much greater than the treatment cost of BOC/RGT. This implies that a longer duration of treatment may not result in additional clinical benefits. Conversely, treatment with BOC/PR48 resulted in an incremental gain of 0.21 QALYs compared to treatment with BOC/RGT in the black population. This implies that a longer duration of treatment with boceprevir may result in additional clinical benefit for black patients.

p.26, second paragraph: the FDA approved label strategy should be compared to the other strategies as competing strategies and best shown in a graph with the cost-effectiveness frontier.

The results of the boceprevir label analysis have been summarized. Since the boceprevir label strategy is a post-hoc analysis, we do not think it is appropriate to directly compare the results to the treatment strategies studied in SPRINT-2.
The results of the subset analysis of the label strategy are given. A table summarizing the results of the one-way sensitivity analyses and a figure displaying the results of the probabilistic sensitivity analyses have been added to the appendix. The conclusion has been modified to include a discussion concerning the results:

The results of the one-way sensitivity analyses suggest that the cost-effectiveness of the boceprevir label strategy is generally robust to the assumptions made regarding the input parameters. The ICER was only more than $5000 different from the base case scenario in only 8 of the 103 sensitivity analyses (range: $111-$47,171/QALY). The parameters which were most impactful are the progression from F4 to hepatocellular carcinoma, excess mortality associated with decompensated cirrhosis, the utility applied to the SVR, F1 health state, and the discount rates. We further tested the robustness of the results with a PSA. In over 98% of the simulations, the boceprevir label strategy was cost-effective compared to dual therapy when a threshold of $50,000/QALY was applied.

Last sentence of third paragraph: Most modeling studies considered also treatment in cirrhotic patients with partial cure if SVR (e.g. Siebert, Wong, Buti etc.). Therefore, it is not new to your model and we would suggest deleting it.

To address this comment we have deleted the sentence and replaced it with the following:

This differs from the majority of previous models in that we incorporated that patients with cirrhosis who achieve SVR are at risk of developing decompensated cirrhosis and hepatocellular carcinoma.

p.27, second paragraph: It would be nice to state here the major differences (e.g. societal perspective vs. payers, cost for HCV with SVR, different utilities, etc) and to compare the results based on these differences.

We think the perspectives of the two studies are the same even though Liu et al claimed to have adopted a societal perspective (they included out-of-pocket expenses). In addition to the previously listed major differences between our study and Liu et al, we added the following:

Specifically, the transition probabilities, health state utilities, and costs included in our model are based on more recent data than those applied in the Liu model. Unlike Liu et al which included cost for HCV with SVR and out-of-pocket expenses as part of the base case scenario, we only tested the influence of cost for HCV with SVR in the sensitivity analysis and we did not consider out-of-pocket expenses.

We also included the following in the paragraph on Limitations:

Seventh, this analysis was done from the payer perspective. Patients with chronic HCV or the sequelae of cirrhosis have been shown to result in incur increased work and productivity losses, activity impairment, and increased indirect medical costs compared to people without HCV (X). Inclusion of such costs would result in lower ICERs for both boceprevir-regimens compared to
dual therapy since the treatment efficacy of both BOC/RGT and BOC/PR48 are greater than the efficacy of treatment with PR48.

p.28: further limitations to be discussed here may be underestimation of costs, assumptions about utilities etc.

We acknowledge that there is a lot of variability in the clinical and cost inputs reported. The impact of our assumptions – including SVR healthcare costs and assumptions about utilities – have been addressed with the sensitivity analyses.

Minor Essential Revisions

Abstract:

p.2: QALYs instead of QALYS

The change has been made.

Background:

p.5: Please state a more actual number for direct and indirect costs of treating HCV and related liver diseases ($5.46 billion in 1997)

This number has been updated and the sentence has been changed to:

The total 2011 healthcare cost associated with HCV in the U.S. was estimated at $6.5 ($4.3-$8.4) billion (9).

p.5: ...Prior to 2011, the standard of care for chronic HCV genotype 1 infection was 48 wks of antiviral treatment with a combination of a pegylated interferon alfa and ribavirin... This sentence suggests that there is now a more actual different recommendation for standard therapy. If this is true, it should be described in detail and cited. Anyway the actual guideline recommendations should be cited here.

The references have been added to the prior and current guideline recommendations. The following sentences have been modified and added.

Prior to 2011, the standard of care for chronic HCV genotype 1 infection was 48 weeks of antiviral (AV) treatment with a combination of a pegylated interferon alfa and ribavirin (15).

As a result, the AASLD guidelines were updated in 2011 to recommend including the protease inhibitors in the treatment regimens of patients infected with HCV genotype 1 (23).

p.6, last paragraph: ...in pre-specified subsets of the population and in sensitivity analyses... As all of those analyses were sensitivity analyses, you may delete the word “and“
We have kept the word “and” to refer to both the subset analyses and the one-way, multivariate, and probabilistic sensitivity analyses.

Table 1: only the mean values for age, sex and METAVIR baseline score are available. Please insert also the percentage of black/non-black. Please give the standard variation or range.

Information regarding race cohort has been added to the table.

Table 2: please add 95% confidence intervals or ranges to all parameter

Because of the limited amount of space on the table, we are unable to include this information. Please note that the only inputs from this table that are varied in sensitivity analyses are the SVR rates and the 95% confidence interval is provided for them. For the other inputs, there is enough information on the table give for the reader to easily calculate the 95% confidence intervals if desired. We included the counts for calculating the probability of discontinuation before Week 24.

Table 3: please change the title of last column in A. to PSA, distribution.

The column heading has been changed.

Please state also the values used in other sensitivity analyses than PSA (oneway etc.).

The values applied in the one-way sensitivity analyses are summarized in Table 3.

In section B, please use the word utilities instead of QALY.

QALY has been changed to Utilities

Which time horizon (1 year?) is used for the costs (e.g. F0-F4, DC, HCC, liver transplantation)?

Sub Column heading has been added above the health state costs – Annual Costs.

Currency and index year should be stated. Please cite the source for SVR, F0-F4. Insert reference for transition from F4 to DC and HCC for patients with SVR.

This information has been added to the manuscript.

**Methods:**

p. 8, 1st paragraph: ... *(abbreviated as BOC/RGT)*... not necessary because BOC/RGT was previously introduced in the same paragraph. In general, the abbreviation should be enough, the words abbreviated as may be deleted.
The second (BOC/RGT) has been deleted and the words “abbreviated as” have been deleted as well.

p.12: refer in text to table 1 patients characteristics.

The last sentence has been changed to:

The reported distributions of gender, baseline fibrosis level, and race from sprint-2 were assumed for the treatment population (12, TABLE 1).

p.12, treatment characteristics: do not refer in text to table 1 “patients characteristics”.

This has been changed.

p.13, progression of HCV Infection: …Some studies only provided aggregated progression rates from mild HCV to moderate HCV and moderate HCV to cirrhosis… The cited studies are only modeling studies and not original studies. However, all of the cited modeling studies use a different system of scoring histology of the liver in HCV patients (not METAVIR). Therefore, data cannot be used in your model for this reason. So, I suggest deleting the sentence. As well the citations for the first sentence of this paragraph are not appropriate. If you mention the diversity of progression rate values in the literature, actual systematic reviews should be cited and this topic should be rather part of the discussion section and not within the methods section.

We agree with your comment and deleted the sentences you suggested.

Methods, p.14, end of first paragraph: Please state here, that table 3 shows all values used in the model.

This change has been made.

Methods, p.14: abbreviation UNOS, please write the full name.

We have added the name and put the abbreviation in parenthesis.

Methods, p. 18: “The baseline values, range of values examined in sensitivity analyses, distribution of parameters assumed for the PSA, and references for all parameters are included in Table 3“. Sustained virologic response rates were also varied in sensitivity analyses, as shown in supplementary table 1. The distribution appears in table 2.

We thank the reviewer for catching this discrepancy. We modified the text as follows to address this:

The baseline values, range of values examined in sensitivity analyses, distribution of parameters assumed for the PSA, and references for clinical, economic, and utility parameters are included in Table 3. The baseline values, range of values examined in sensitivity analyses, and
distribution of parameters assumed for the PSA for the treatment efficacy rates are included in Table 2. The results of the PSA were based on 10,000 Monte Carlo simulation runs.

Results, p.20, first paragraph: text could be shortened (e.g. the number needed to treat to avoid one case of DC, HCC, liver transplant … is 21, …). In general be more explicit and give the time period if stating incidence or cumulative probability. In the literature, 20-year risks or lifetime risks are often stated.

We kept the information on number needed to treat to avoid a complication as may be useful to many readers. The time period is stated in the 2nd sentence. It begins with “Over the lifetime of this cohort…”

Results, p.20, second paragraph: are these lifetime costs and effects? Are those discounted? If so, please write total discounted lifetime costs and QALYs…

We have changed the text to reflect that these are “total discounted lifetime costs and QALYs”.

Table 4: suggestion for title: base-case analysis results: discounted lifetime costs, QALYs and incremental cost-effectiveness ratios of BOC/RGT and BOC/PR48 compared to PR48. Are costs and QALYs discounted? Lifetime costs and QALYs? Please state currency. Please insert also ICER BOC/PR48 vs. BOC/RGT. Please state the unit for ICER (US$/QALY).

We followed the reviewer’s suggestions and changed the title of the Table to “Base-Case Cost-effectiveness results (per patient): discounted lifetime costs, QALYs and incremental cost-effectiveness ratios of BOC/RGT vs. PR48 and BOC/PR48 vs. PR48”, added the currency, and the unit for the ICER.

Results, p.22: Last sentence: ICER $30,6277/QALY -> $30,628/QALY

We thank the reviewer for identifying this error – the value in the last sentence has been corrected ($30,627/QALY).

Results, p.23, first paragraph: table 5 instead of table 4.

We have modified the text to reflect this.

Table 5: Please write incremental QALY instead of utilities, incremental costs, state currency, and unit of ICER (US$/QALY). As all outcomes are discounted state this in the title and only once for all in the table. Label-Based Analyses should be explained in the legend. Disaggregated (absolute costs and QALYs for all strategies) would be of more value. Remark: Label-Based Analyses is not a population subset analysis. Therefore, state it explicitly in the title or (better) show it together with other base case analysis.
To address this comment, the title of the table has been changed to: Change in total discounted lifetime costs (2010 US$) and quality adjusted life years of boceprevir-based regimens compared with PR48 in multi-way sensitivity and subset analyses. In addition, Utilities has been changed to QALYs. Because of spatial restraints, we prefer to keep the discounted costs and QALYs in the table instead of the disaggregated costs and QALYs for each of the three treatment strategies.

We respectfully disagree with the reviewer that the label-based strategy is not a population subset analysis. The label-based strategy is a population subset analysis because the label-based recommendation for treatment naïve patients without cirrhosis is similar to the BOC/RGT strategy and the label-based strategy for treatment naïve patients with cirrhosis is similar to the BOC/PR48 strategy. The inputs for the label-based strategy (and for the dual therapy comparator) were obtained through subset analyses of the data studied in SPRINT-2 and applying an additional futility rule.

Conclusions, p.23: …we also examined the impact of the FDA-approved label-based strategies on the lifetime burden and HCV-related complications and the cost-effectiveness of these regimens. In this sentence the part “lifetime burden and HCV-related complications” should be deleted and “lifetime costs, QALYs” inserted instead, as the model doesn’t project the burden of the disease.

We modified the sentence as follows: We also examined the impact of the FDA-approved label-based strategies on the incidence of HCV-related complications, lifetime costs, QALYS, and assessed the cost-effectiveness of these regimens.

Conclusions, p. 24, second paragraph: …implying that the ICERs of BOC/RGT and BOC/PR48 are robust to changing the values of the input parameters individually… Suggestion: implying that the ICERs of BOC/RGT and BOC/PR48 versus PR48 are robust, if a single model parameter at a time is changed.

We agree that the suggested wording is more clear. The sentence has been changed to “These results imply that in comparison to treatment with dual therapy, the ICERs of BOC/RGT and BOC/PR48 are robust if a single model parameter is changed.”

Conclusions, p.25, first sentence of second paragraph: suggestion: The PSA allows to evaluate the impact of varying several parameter values simultaneously on the projected outcomes of the model. Compared to PR48 BOC/RGT was cost-effective …

In addressing another comment, we modified the manuscript to include the comparators whenever ICERs or conclusions regarding cost-effectiveness are provided.

Supplementary table 1: Change “SVR to DC” and “SRV to HCC” in “SVR, F4 to DC” and “SVR, F4 to HCC”, as in table 3

We kept the variable as is to reflect that we assume in our model that patients without cirrhosis who achieve SVR are considered permanently cured.
Figure 2: Please write the full name for DC, HCC, LT, LD or state it in a footnote.

We added a footnote with the definitions associated with the abbreviations.

Optional Revisions
Undiscounted life years gained and QALYs for the base-case analysis would be good for comparison with other modeling study results.

We agree that this information is important. The total undiscounted lifetime costs and QALYs are provided in Supplementary Table 1. We added the following sentence to describe the impact of PR48 on life expectancy:

In addition, treatment with BOC/RGT and treatment with BOC/PR48 are associated with an overall increase in life expectancy of 0.97 and 1.07 years, respectively, when compared with PR48 treatment.
Reviewer 3's report

Major points:

- ICERs for BOC/RGT vs. BOC/PR48 appear to differ significantly. This needs to be discussed, and for example the last statement in the abstract simply saying that both regimens are cost-effective appears to oversimplify the results.

The following sentences were modified/adDED in the Conclusions section:

Thus both BOC/RGT and BOC/PR48 are considered cost-effective at commonly used thresholds (59) when compared to treatment with PR48. In addition, the ICER of BOC/PR48 compared to BOC/RGT was $807,804/QALY, which implies that BOC/PR48 is not cost-effective at commonly used thresholds when compared to treatment with BOC/RGT. The high ICER obtained from comparing BOC/PR48 to BOC/RGT is mostly explained by the small difference in SVR rates between the two treatment strategies (BOC/PR48: 66% vs. BOC/RGT: 63%) and the difference in AV therapy costs (BOC/PR48:$69,928 vs. BOC/RGT: $47,582).

- Methods, section “Model inputs”: can you explain the statement “comprehensive literature search” in the last sentence more in detail?
We modified the last sentence:

Baseline values and plausible ranges to be used in deterministic and probabilistic sensitivity analyses for model inputs describing the clinical characteristics of HCV and the utility values applied to each of the health states were obtained from published studies. All inputs used in the model are summarized in Error! Reference source not found..

- Results: Is it possible to additionally provide data for your model on cumulative risks for no treatment vs. PR48, not only for PR48 vs. BOC/RGT, BOC/PR48? This would help to compare the here applied modeling with previously published ones.

Per your suggestion, we have included the following subsection assessing the impact of treatment with PR48 on the incidence of liver complications and the total discounted lifetime costs, QALYs, and ICERS when compared to treatment with PR48.
Over the lifetime of this cohort, our model predicted that treatment with PR48 will result in relative decreases in the cumulative incidence by 37% in DC, 38% in HCC, 38% in liver transplants, and 38% in liver-related deaths compared to no treatment. The total discounted lifetime costs and QALYs associated with no treatment are $37,230 and 13.67, respectively. The total discounted lifetime costs and QALYs associated with PR48 treatment are $58,761 and 14.55, respectively. The corresponding ICER comparing PR48 treatment with no treatment is $24,435/QALY.
- Most importantly, we cannot find a clear and convincing description / assessment of the additional burden of side-effects of boceprevir-based treatment compared to PR48. Please clarify. Furthermore, the unfavourable short-term effect of treatment in general should be discussed (to my knowledge there were several deaths in the boceprevir trials, probably not related to boceprevir, but nevertheless this seems to indicate a higher mortality than in an untreated population).

In SPRINT-2, there were a total of 6 deaths – 4 in the control group (PR48) and 2 in the BOC arms. Two suicides (one in the PR48 group and 1 in the BOC/RGT group) were determined to be possibly related to peginterferon. No other deaths were considered to be drug-related. Because the deaths were not considered to be related to boceprevir, we did not mention them in the manuscript.

We added the following sentences to the Quality of Life Section:

Side effects associated with pegylated interferon and ribavirin are well-documented and include IFN induced bone marrow depression, flu-like symptoms, neuropsychiatric disorders, autoimmune syndromes, and anaemia (57). In addition to these side effects, the boceprevir-based regimens are also associated with a higher probability of anemia and dysguesia (57).

In addition, we made the following changes to the Conclusion:

Our model also demonstrated that boceprevir-based regimens offer patients the possibility of experiencing great clinical benefit with a shorter duration of therapy that may minimize the time patients experience an HCV-treatment decrement to their quality of life. In addition both BOC/RGT and BOC/PR48 were projected to be cost-effective from the payer perspective at a reasonable threshold in comparison with treatment with peginterferon and ribavirin alone.

Minor point:

- The first statement of Conclusions that SVR for mild and moderate HCV (better hepatitis C?) is associated with lacking risk for serious and costly complications associated with HCV is not fully justified, e. g. in view of results by Innes et al., Hepatology 2011:54:1547-58. Furthermore, authors may consider to discuss a very recent, but important study on outcomes of SVR-patients with advanced disease (Van der Meer et al, JAMA Dec. 2012.)

We thank the reviewer for bringing these studies to our attention. We have revised our conclusions as follow.

In our model, we assumed that SVR is a cure for mild and moderate HCV and that patients who achieve an SVR through AV therapy will not be at risk for developing serious and costly complications associated with HCV. However, a small number of studies have suggested that patients with moderate HCV may develop HCC even after achieving an SVR with drug therapy. The limited data suggests that the probability of this transition is very close to zero. Because of the limited information and since the transition is negligible, we did not include it in our model.
Data also suggests that cirrhotic patients may have a regression of fibrosis if they achieve an SVR, which would lower their risk of developing HCV-related liver complications. A recently published study by van der Meer et al. showed that the all-cause mortality in patients who achieved SVR and who did not achieve SVR was 8.9% and 27% at 10 years, respectively. They also reported that 10-year cumulative incidence rate of HCC and decompensated cirrhosis in patients who achieved SVR was 5.1% and 2.1%, respectively. In our analysis, we also included a progression of disease in cirrhotic patients who achieved SVR, and the incidence rates reported by van der Meer et al. were included in our sensitivity analysis range.