ANSWERING REVIEWERS

February 12, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7417-R1.doc).

Revised Title: Adjuvant Heparanase Inhibitor PI-88 for Hepatocellular Carcinoma

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 7417

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewers

Reviewer 1:

(1) Please, check again the spelling of some words.

Answer (A): This manuscript had been edited through a professional English language editing company (Wallace Academic Editing); certificate is attached. We have checked our manuscript again.

(2) It is important to make clear whether the patients were receiving other therapy during the follow period.

A: Overall, 36% of the originally recruited patients ever received other therapy for recurrent HCC. Details of the treatment status for patients with recurrent HCC are shown in page 11 and revised Table 2 (page 24).

(3) Please, it would be correct to mention again the PI-88 drug form and the pharmaceutical manufacturer.

A: We described the PI-88 drug form and the pharmaceutical manufacturer in the revised manuscript (page 8, first paragraph).

Reviewer 2:

(4) It is not clear how other treatments or medications were handled during the extended follow-up period. If that data is available, it would be helpful for evaluation of the treatment effects.

A: For patients experiencing recurrence of HCC in this phase II and follow-up studies, the responsible physician would provide suitable treatment strategy for the tumor, based on Taiwanese HCC treatment guidelines. Overall, 36% of the originally recruited patients ever received therapy or trial medication for recurrent HCC. Details of the treatment status in different group of patients are shown in page 11 and revised Table 2 (page 24).

(5) How was compliance with the study regimen evaluated? The authors note that PI-88 at 250 mg/day was associated with adverse effects that resulted in dropout, but were subjects who remained on that dose also less compliant?

A: Compliance was defined as those patients receiving >=80% of the scheduled medication during the

phase II study period (12 doses/cycle * 9 cycles * 80%). We provided the rate of compliance in different subgroups of patients in revised Table 4 (page 26).

(6) Findings of the study included persistent benefit in time to recurrence and disease free survival over the 3 year study. Overall survival was not affected. Subgroup analyses demonstrated improved disease free survival in the higher risk cohort. Overall, the limitation for analysis of a reduced sample size in this follow-up study are understood. However, in spite of this decreased power, more comprehensive reporting of statistics needs to be presented in the Results, especially p-values and confidence intervals.

A: We added p-value and CI in relevant statistics in the revised tables (pages 22-28).

(7) For most part, the Discussion is well-written. However length and exuberance may be tempered. For instance, the brief paragraph on PI-88's role as a cytostatic agent seems redundant when the next paragraph contains an excellent summary of potential mechanisms and interactions that would bolster PI-88's effect.

A: We modified and shortened the content of the discussion part (pages 14-16).

(8) The Tables provide important data but need to be more clearly labeled and include relevant p-values. I presume that the values in Table 1 are presented as mean (%) for every row except Age (year), but that needs to be made clear.

A: We added p-values and described the statistics part in revised Table 1 clearly (pages 22-23).

(9) Also, I presume that ITT stands for intention-to-treat, but please specify. Table 2 notes more frequent adverse events in the 250 mg/day group. P-value and confidence intervals are needed for the differences observed in Tables 2 and 4.

A: We added p-value, CI and differences in revised Tables 2 and 4 (pages 24 and 26).

Reviewer 3:

(10) Treatment compliance as well as access to other therapies. The impact is not minor since authors did not observe a difference in overall survival, and I feel that discussion of these limitations should be reinforced. Potential impact of side effects in compliance deserves discussion since they are higher among patients receiving higher doses.

A: We provided the rate of compliance in different subgroups of patients in revised Table 4 (page 26). In general, compliance was lower in Group C than that in Group B. For those subjects remaining in the phase II study, the rate of compliance was also lower in Group C compared with Group B although not statistically significant. We also added relevant discussion on compliance and access to other therapies for HCC.

(11) 95%CI should be reported in the results section.

A: We added 95% CI in relevant tables (pages 22-28).

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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