

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

ESPS manuscript NO: 25600

Title: Telbivudine vs tenofovir in hepatitis B e antigen-negative chronic hepatitis B patients: Optima roadmap study

Reviewer's code: 03384301

Reviewer's country: Egypt

Science editor: Shui Qiu

Date sent for review: 2016-03-18 10:58

Date reviewed: 2016-04-01 17:46

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input checked="" type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Duplicate publication	
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input type="checkbox"/> Minor revision
	<input type="checkbox"/> Grade D: Rejected	BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

Comments to the Author 1-The paper is well written with good English language 2- This manuscript announces that this was the first prospective, randomised, non-inferiority study in HBeAg-negative CHB patients that compared telbivudine and tenofovir administered as per roadmap concept. I have some queries : 1- Method of measurement of HBv DNA through the different centers involved in the study was it central lab recruitment or local lab in each center? the method of standardization and the machine use this should be clear in the methods as one of the difficulties in HBV treatment and follow up is the falicies in HBV DNA measurements. 2- In the Patient demographics and clinical characteristics (A total of 241 patients (121 in the telbivudine arm and 120 in the tenofovir arm) were randomised in this study.A total of 20 (16.5%) patients in the telbivudine arm and 11 (9.2%) patients in the tenofovir arm discontinued prematurely from the study. The most common reasons for discontinuation in the telbivudine arm were consent withdrawal (n=6), lost to follow-up (n=5) and administrative reasons (n=4). In the tenofovir arm, the most common reasons for discontinuation were AEs (n=4) and lost to follow-up (n=4). What was the AE in the



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remaining 5 patients in telbivudine arm and 3 patients in Tenofovir arm? 2- the authors mentioned (A total of 113 (93.4%) patients in the telbivudine arm and 117 (97.5%) patients in the tenofovir arm comprised the rITT population and were included in the primary efficacy analysis. The per-protocol population consisted of 103 (85.1%) patients in the telbivudine arm and 113 (94.2%) patients in the tenofovir arm. The safety population comprised 120 patients in each of the 2 arms. One patient in the telbivudine arm was excluded from the safety population as this patient did not receive any study treatment.) The numbers need to be more clarified is it on 113 patients or 103 in telbivudine arm and the Tenofovir arm also. In addition i suggest a study design chart to simplify this issue including the discontinuations number, the patients with Ae, and the rITT

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

ESPS manuscript NO: 25600

Title: Telbivudine vs tenofovir in hepatitis B e antigen-negative chronic hepatitis B patients: Optima roadmap study

Reviewer's code: 02445121

Reviewer's country: China

Science editor: Shui Qiu

Date sent for review: 2016-03-18 10:58

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

COMMENTS TO AUTHORS

This paper is a randomized clinical trial, which investigated the efficacy and safety comparison of telbivudine-roadmap and tenofovir-roadmap in hepatitis B e antigen (HBeAg)-negative chronic hepatitis B (CHB) patients. This was the first prospective, randomised, non-inferiority study in HBeAg-negative CHB patients that compared telbivudine and tenofovir administered as per roadmap concept. Both treatments based on the roadmap approach were effective over a 104-week treatment period. Non-inferiority of telbivudine arm to tenofovir arm was demonstrated at Week 52, with over 92% of patients in each treatment arm achieving HBV DNA level <300 copies/mL. Both treatments showed a good safety profile. Moreover, telbivudine showed an improvement in eGFR from baseline. This is a well conducted study. The experiments are described in detail, the results are impressive. This study is suggested for publishing in the journal.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

ESPS manuscript NO: 25600

Title: Telbivudine vs tenofovir in hepatitis B e antigen-negative chronic hepatitis B patients: Optima roadmap study

Reviewer's code: 00761439

Reviewer's country: Greece

Science editor: Shui Qiu

Date sent for review: 2016-03-18 10:58

Date reviewed: 2016-03-29 02:56

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input type="checkbox"/> No	

COMMENTS TO AUTHORS

This is a very interesting and well written randomized trial regarding the administration of telbivudine vs tenofovir in 241 HBeAg negative chronic hepatitis B patients. The authors concluded that both treatments based on the roadmap concept were effective over the 104-week treatment period. Moreover, telbivudine showed an improvement in eGFR from baseline. There are few issues which should be addressed by the authors 1) In Table 1: variables without normal distribution should be presented as median (range) 2) Can the authors provide more data regarding which adverse events were significantly different between the two arms? 3) Improvement of GFR was observed in those with telbivudine plus tenofovir or only in those under telbivudine monotherapy? 4) In conclusions, the authors should add that tenofovir was added more frequently in telbivudine arm.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

ESPS manuscript NO: 25600

Title: Telbivudine vs tenofovir in hepatitis B e antigen-negative chronic hepatitis B patients: Optima roadmap study

Reviewer's code: 00051373

Reviewer's country: Taiwan

Science editor: Shui Qiu

Date sent for review: 2016-03-18 10:58

Date reviewed: 2016-03-31 16:17

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

This is an extensive randomized study to compare the road-map treatment strategy between telbivudine and tenofovir on HBeAg(-) chronic B hepatitis patients. As we know, antiviral treatment may be a life-long treatment until the present of HBsAb. Therefore, the renal protection is one of the majority strategies for the chronic B hepatitis patients not only, but also the hepatitis B related recipients underwent liver transplantation. The current manuscript should be benefit feedback to the hepatologists and liver transplantation center worldwide.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

ESPS manuscript NO: 25600

Title: Telbivudine vs tenofovir in hepatitis B e antigen-negative chronic hepatitis B patients: Optima roadmap study

Reviewer's code: 02444774

Reviewer's country: China

Science editor: Shui Qiu

Date sent for review: 2016-03-18 10:58

Date reviewed: 2016-03-31 17:54

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good		<input type="checkbox"/> Duplicate publication	
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Minor revision
	<input type="checkbox"/> Grade D: Rejected	BPG Search:	<input type="checkbox"/> Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

This was a pharma-sponsored RCT of non-inferiority design to compare telbivudine and tenofovir administered as per roadmap concept. The sample size was respectable. Major comments: 1. The sample size estimation was based on the assumptions of 96% and 97% HBV DNA <300 copies/mL at Week 52 in the telbivudine arm and the tenofovir arm, respectively. The 10% non-inferiority margin might be too generous. 2. I cannot understand why TDF arm needed add-on telbivudine, as the resistance rate was so low and patients would have increased chance of undetectable HBV DNA with time. 3. What were the explanations on exceptionally low week 104 HBV DNA undetectable rate? The rate in TDF arm was as low as 74.4%, which was even lower than keeping TDF monotherapy without adding LdT. 4. Using virological endpoint at two years may not be sufficient. With time probably more patients in the LdT arm need add-on so making this strategy not as appealing.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

ESPS manuscript NO: 25600

Title: Telbivudine vs tenofovir in hepatitis B e antigen-negative chronic hepatitis B patients: Optima roadmap study

Reviewer's code: 01562153

Reviewer's country: Taiwan

Science editor: Shui Qiu

Date sent for review: 2016-03-18 10:58

Date reviewed: 2016-03-31 18:36

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" type="checkbox"/> [Y] Accept
<input checked="" type="checkbox"/> [Y] Grade B: Very good	<input checked="" type="checkbox"/> [Y] Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> [] High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> [] Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> [Y] No	<input type="checkbox"/> [] Minor revision
<input type="checkbox"/> Grade E: Poor		BPG Search:	<input type="checkbox"/> [] Major revision
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> [Y] No	

COMMENTS TO AUTHORS

In this manuscript, the authors evaluated the efficacy and safety comparison of telbivudine-roadmap and tenofovir-roadmap in hepatitis B e antigen (HBeAg)-negative chronic hepatitis B (CHB) patients. They found that over 92% of patients in each treatment arm achieved HBV DNA level <300 copies/mL at Week 52, that both arms were similar in key secondary efficacy variables, e.g. the percentage of patients achieving HBV DNA <300 copies/mL, ALT normalization, and the safety profile, and that telbivudine arm showed an eGFR improvement. This was a prospective, randomized clinical trial. The data were appropriately presented and interpreted. The manuscript was well prepared. Although the originality of this manuscript is not high enough, the article may provide useful information to the clinicians in managing patients with chronic hepatitis B.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

ESPS manuscript NO: 25600

Title: Telbivudine vs tenofovir in hepatitis B e antigen-negative chronic hepatitis B patients: Optima roadmap study

Reviewer's code: 02444986

Reviewer's country: Turkey

Science editor: Shui Qiu

Date sent for review: 2016-03-18 10:58

Date reviewed: 2016-04-04 17:29

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input checked="" type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

Comments: ? If this is a "non-inferiority study", why there is a combination treatment group. Otherwise, statistical analysis should be done on 3 groups (telbivudin monotherapy, tenofovir monotherapy and combination treatment) ? 24 weeks is too early to add on another NA in HBe antigen negative patients. ? There is No data on previous antiviral treatment of patients, except that they ewre not treated within 6 mounts previous to randomization. ? There is no data on fibrosis scores of patients, although it is stated that all patients had liver biyopsy with in 12 months. ? There is too much dropout from the study, although both NA have very well established safety profile. ? There is no approval or participation of the pharmaceutical company for telbivudine (Novartis).

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

ESPS manuscript NO: 25600

Title: Telbivudine vs tenofovir in hepatitis B e antigen-negative chronic hepatitis B patients: Optima roadmap study

Reviewer's code: 02444960

Reviewer's country: Spain

Science editor: Shui Qiu

Date sent for review: 2016-03-18 10:58

Date reviewed: 2016-04-14 08:06

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

This manuscript describes the roadmap concept utilizing add-on therapy comparing efficacy and safety of telbivudine with tenofovir, which could be useful in clinical practice, as a predictable tool for achieving optimal efficacy with a low emergence of drug resistance. The methodology is appropriate and the results are consistent with discussion and conclusions. This manuscript is of interest to be published on World Journal of Hepatology.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Hepatology

ESPS manuscript NO: 25600

Title: Telbivudine vs tenofovir in hepatitis B e antigen-negative chronic hepatitis B patients: Optima roadmap study

Reviewer's code: 00069297

Reviewer's country: China

Science editor: Shui Qiu

Date sent for review: 2016-03-18 10:58

Date reviewed: 2016-04-13 09:51

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

The authors provided some important information to manage the HBV infected patients. The manuscript was well prepared and written.