Author’s response to reviews

Title: FimAsar-proTeinuriA Sustained reduCtion in comparison with losartan in diabetic chronic kidney disease (FANTASTIC) : study protocol for randomized controlled trial

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Version: 1 Date: 01 Nov 2017

Author’s response to reviews:

Oct, 29, 2017

Editor-in-Chief
Trials

Dear Editor-in-chief in Trials

On behalf of my coauthors, I am pleased to submit a revised version of the TRLS-D-17-00197, “The Fimasartan Proteinuria Sustained Reduction in Diabetic Chronic Kidney Disease (FANTASTIC) Study: rationale and design of fimasartan versus losartan in patients with hypertensive diabetic chronic kidney disease” that takes into account all the comments from the editor and reviewers.

We have also uploaded a detailed point-by-point response to the reviewers indicating all the changes that we have introduced in response to the reviewers.

We are very thankful again for the comments, as they have helped us improved the clarity of the paper and the presentation of the findings. I believe that this work will be of considerable interest to investigators and clinicians in hypertension and chronic kidney disease, as well as to the
general readership of your journal. I will greatly appreciate it if you consider this revised paper for publication.

The paper is not being submitted to any other journal. None of the paper’s contents have been previously published and none of the authors have any conflicts of interest associated with this paper. All authors have read and approved submission of the manuscript.

Sincerely,

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Note to Reviewers

We wanted to thank the reviewers for their constructive comments. In response to their comments, we have revised manuscript to strengthen the weak portion. We believe that this revision will be of great interest to clinicians and we thank the reviewers for pointing us in this direction. We would like to reveal that we have made changes in the manuscript, according to the reviewer’s comments. All changes in the manuscript ARE SHOWN IN RED, but not as tracked changes for your convenience.

Reviewer #1:

I reviewed the protocol of FANTASTIC study with interest. The authors have endorsed it in clear language. The study is well designed. The multi-centre participation adds strength to the study. I would like to ask the authors to consider the following comments:

Comment 1)

The authors use proteinuria and albuminuria as interchangeable terms on certain occasions which could result in confusion, e.g. in section 2.2.1 Inclusion and exclusion criteria: ‘overt proteinuria’. Adding ‘or macro-albuminuria’ helps clarify the meaning. Thus, the information in this section will mirror the inclusion criteria in the table 1. The same is seen in the title ‘Proteinuria Sustained Reduction’, while the primary outcome measure is albuminuria.

Response 1)

Thank you for your valuable comments. I totally agree with your opinion.
According to the KDIGO categories, albuminuria can be divided into the following three categories.

A1 (normal to mildly increased; <30mg/g or 3mg/mmol)
A2 (moderately increased; 30~300mg/g or 3-30 mg/mmol)
A3 (severely increased; >300mg/g, >30mg/mmol)

Among the categories, A2 is called microalbuminuria and A3 is called overt proteinuria. So, overt proteinuria is the case when the degree of albuminuria is > 300 mg/g, we described the primary outcome as “albuminuria.” Because albuminuria according to inclusion criteria in FANTASTIC study is overt proteinuria(albuminuria > 300mg/g or 30mg/mmol), we will change albuminuria to proteinuria to prevent confusion.

In response to your comment, we corrected albuminuria with proteinuria to prevent confusion.

Reference


Comment 2)

In the abstract-discussion: 'The FANTASTIC study will try to provides…..'Please revise the grammar. Also the whole paragraph better to be rephrased to render the meaning more clear.

Response 2)

Thank you for the opportunity to render the meaning more clear about the FANTASTIC study. We also think that the previous sentence is a bit vague in conveying meaning and the grammar is a little awkward.

In response, we corrected the sentence as follows and the other part of the grammar was reviewed again.

“The FANTASTIC is a clinical study to provide 1) the reno-protective effect of fimasartan and 2) the target blood pressure to reduce adverse outcomes in hypertensive diabetic CKD with overt proteinuria”.

Comment 3)
In section 2.2.2 Screening 'However, other antihypertensive drugs were administered without changing the regimens or doses' -Do they include the dihydropyridine CCB? As this might affect the level of proteinuria.

Response 3)

Thank you for your detailed comment and we have time to think again about antihypertensive medication in run-in-period.

After screening visit, during run-in-period, any treatment with ACEI/ARBs for hypertension was discontinued and other antihypertensive drugs were administered without changing the regimens or doses. If ACEI/ARB was discontinued in patients taking ACEI/ARB, the amount of proteinuria may slightly increase. However, in the case of other drugs, including dihydropyridine CCB, there is no change in regimens or doses. So, the change in the amount of proteinuria appears to be minimal and if the amount of proteinuria dose not meet the inclusion criteria at baseline visit, patients is excluded. The maintaining the dihydropyridine CCB does not seem to have a significant affect the level of proteinuria.

Comment 4)

In the same section 'subjects were instructed to visit the study site………or onset of any symptoms of suspected hypertension'. It might be more appropriate in this context to write accelerated hypertension symptoms with detailing a few of them for clarity. Meanwhile, it will be useful to detail how often they were instructed to check their blood pressure at home.

Response 4)

Thank you for your valuable comments. We think that this comment is a very important part of the safety aspect in FANTASTIC study.

In response to your comment, we described the symptoms of accelerated hypertension and numbers of frequency of check their blood pressure at home.

“…any symptoms of suspected hypertension (for example; headache, dyspnea, chest discomfort, vomiting and neurologic symptoms).”

“During the placebo run-in period, the subject was instructed to measure his/her own blood pressure with a provided oscillometric automatic device more than once a day”

Comment 5)

There is no mention of the limitations of the study.

Response 5)
Thank you for your comment. We think that the limitation part is not a necessary part of the “study protocol article”. In fact, limitation part is not often observed with most study protocol articles. The limitation part is considered to be handled in the “original article”.

Comment 6)

In section 2-6: 'The primary end point was the rate of change in albuminuria in the fimasartan group and losartan group from baseline to week 24.' I noticed that in section 2.7 other secondary endpoints '2) The change in albuminuria in the fimasartan and losartan groups from baseline to weeks, 4, 8, 12 and 24'.

It occurs to me that, if albuminuria at 24 weeks is a primary outcome then it cannot be a secondary outcome in the meantime

Response 6)

Thank you for the opportunity to proofread for our typographic error. In response, we revised it in section 2-7 as below.

“The change in proteinuria in the fimasartan and losartan groups from baseline to 4, 8 and 12 weeks”

Comment 7)

Also in section 2-7 secondary end points '4) The proportion of subjects who developed urine ACR<300 mg/g in the fimasartan and losartan groups at weeks 4, 8, 12 and 24'. This merits revision as, the inclusion criteria states ACR≥300 mg/g. It therefore becomes logical that micro-albuminuria cannot be measured as a secondary outcome.

Response 7)

At random, the patients with ACR ≥ 300 mg/g becomes enroll. The use of ARB generally reduces the amount of proteinuria. At the 4, 8, 12, and 24 weeks, patients with decreased proteinuria and reaching ACR <300mg/g may develop, and measuring the proportion of such patients does not seem to be a problem as a secondary outcome.

Comment 8)

In table 1, the inclusion criteria 'Baseline visit (visit 3) - eGFR ≥30/min/1.73m2'. It would be appropriate in the meantime to define the upper cut-off for the eGFR to fulfil the KDIGO definition of CKD.

Response 8)
Thank you for your valuable comments.

In response, CKD classification can be divided into two major categories, according to degree of GFR and albuminuria in KDIGO. It is divided into G1, G2, G3a, G3b, G4 and G5 by degree of GFR and also divided into A1, A2 and A3 by degree of albuminuria. According to the inclusion criteria (eGFR≥30/min/1.73m² and overt proteinuria) of FANTASTIC study, the enrollable groups are G1A3, G2A3, G3aA3 and G3bA3. In KDIGO, according to prognosis, G1A3 and G2A3 are high risk group and G3aA3 and G3bA3 are very high risk. So, in FANTASTIC study, upper cut-off for eGFR is not defined.

Reference


Comment 9)

In the conclusion 'It was expected to confirm the reno-protective effect of fimasartan' . This might be. It might be more appropriate to rephrase it to sound more neutral.

Response 9)

Thank you for the opportunity to clarify misunderstanding as anticipation of the results. We also think that a more neutral expression is appropriate.

In response, we corrected the sentence as follows.

“It was expected to confirm whether there is the reno-protective effect of fimasartan”

Comment 10)

In table 2 (Exclusion criteria) 'Moderate or malignant retinopathy< 6 months prior to enrolment '. Do the authors mean hypertensive or diabetic retinopathy? I find it helpful to write a few details about the criteria of retinopathy that renders them excluded.e.g moderate non proliferative diabetic retinopathy.

Response 10)

Thank you for your valuable comments. If we describe the detailed definition of retinopathy, we think that it will be more accurate when exclude the patients.
In response, we corrected the sentence as follows.

“Moderate or malignant retinopathy< 6 months prior to enrolment (e.g moderate or severe non-proliferative diabetic retinopathy, proliferative diabetic retinopathy)”

Reviewer #2

Comment 1), 2), 3) and 4)

1) Introductory paragraph needs revision to be read more easily; "Approximately" used twice in first line, consider joining sentences. "both" used in line 2 and 3, consider deleting from line 3.

2) Line 33, full stop after CKD [6-8].

3) Line 21, remove ", however"

4) Line 25, remove "Therefore"

Response 1), 2), 3) and 4)

Thank you for the opportunity to read more easily in introductory paragraph. We think that your advice has made reading more natural.

In response, we corrected the sentence as follows.

1) “Hypertension affects approximately 40% of adults worldwide and about two-thirds of patients with diabetes have concomitant hypertension.”

“Both hypertension and diabetes have a variety of vascular complications, including macrovascular and microvascular effects.”

2) “to the future progression of CKD [1-3].”

3) “There are few studies that directly compare the renal efficacy of two ARBs in hypertensive diabetes.”

4) “Most hypertension guidelines recommend that angiotensin converting enzyme inhibitors (ACEI) or ARBs be used in patients with hypertensive diabetes [4-6].”

Comment 5)

Explain why Lorsartan was chosen as comparator

Response 5)
This comment is very important comment that is as starting point for the FANTASTIC study design.

The chemical composition of fimasartan includes a bioisosteric replacement of the imidazole part of losartan with pyrimidin-4(3H)-one. Fimasartan has theoretically similar lipophilicity and half-life to those of losartan. However, fimasartan has higher potency and stronger efficacy than does losartan. Losartan has already been shown to have a reno-protective effect, characterized by reduced proteinuria and a significant delay in the progression of nephropathy in patients with diabetic nephropathy.

In summary, Fimasartan is based on losartan and has theoretically similar lipophilicity and half-life, but has higher potency and potency efficacy than losartan. Because losartan has an already proven reno-protective effect, losartan was selected as a comparator of fimasartan. These are mentioned in the discussion part.

Reference


Kellici TF, Tzakos AG, Mavromoustakos T. Rational drug design and synthesis of molecules targeting the angiotensin II type 1 and type 2 receptors. Molecules. 2015;20(3):3868-97.


Comment 6)

This study looks at two tenants, one comparing Lorsartan vs. Fimasartan, and then strict vs. standard BP control. Ideally one clear aim is preferable, I am unsure of both aims have the required statistical work-up, I cannot see any such work for the "second part" of the study comparing strict vs. standard BP control in the statistics section.

Response 6)

Thank you for your valuable comments. I totally agree with your opinion.

In the Fantastic study, the primary outcome is a reno-protective effect(rate of change in proteinuria) at 24-weeks and the major secondary outcomes are cardiovascular and renal composite endpoints at 144-weeks according with target blood pressure. The number of study population are total 468 patients according to the primary outcome, and the major secondary
outcomes are to confirm the CV outcome at 144 weeks in this calculated numbers (468) of patients (These mention is at 2.9 statistics).

In Statistic part, “The major secondary efficacy assessment was determined by the incidence of combined cardiovascular and renal composite endpoints and was assessed using Kaplan-Meier curves. The median survival time and confidence interval for the median survival time are presented. The log-rank test was used to compare the groups.” are presented. However, it is necessary to express it more clearly.

In response, we corrected the sentence as follows.

“The major secondary efficacy assessment was determined by the incidence of combined cardiovascular and renal composite endpoints and was assessed using Kaplan-Meier curves, according with target blood pressure at 144 weeks. The median survival time and confidence interval for the median survival time are presented. The log-rank test was used to compare the groups.”

Comment 7)

Please give more information on study setting, recruitment for primary care / secondary care centres / specialist centres etc. Patients identified through electronic records or at clinic visits etc.

Response 7)

Thank you for your detailed comment. It is important whether clinical research centers are primary care, secondary care centers or tertiary care centers for the quality of the study in recruitment and setting up the study. I totally agree with your detailed comment. The clinical research centers was composed of 19 nephrology, 14 cardiology and 7 endocrinology, where patient recruitment takes place are all comprised of the tertiary university hospitals in FANTASTIC study

In addition, clinical research centers was composed of 19 nephrology, 14 cardiology and 7 endocrinology not 23 nephrology and 17 cardiology. It was our typographic error. Thank you detailed comment, we were able to correct out typographic error.

In response, we corrected the sentence as follows.

“Forty clinical research centers (19 nephrology, 14 cardiology and 7 endocrinology) participated in this trial and all research centers are comprised of the tertiary university hospital”

Comment 8)

Please clarify that the reason the subjects were required to measure their own BP (which can be unreliable) as opposed to monitoring at visits, was this purely from a safety aspect?
Response 8)

Patients who have been taking ARB or ACEi will stop ARB or ACEi during the running period (4 weeks). Therefore, it is necessary to exclusion from safety aspect when the systolic blood pressure is increased more than 180mmHg, even if the blood pressure measured by their own BP can be unreliable.

Comment 9)

More information is required on the concealment mechanism and implementation.

Response 9)

Thank you for your helpful advice.

In the Fantastic Study, we used an interactive web-based randomization system (IWRS) to prevent selection bias in randomization. An independent group not involved with study implementation created a randomization schedule for study drug labelling. Randomization was stratified by study site. Eligible patients were randomized (1:1:1:1) into one of four treatment groups (fimasartan 60 mg, 120 mg, losartan 50 mg or 100 mg) using an IWRS

In response, we described more information on concealment mechanism and implementation in Section 2.3.3 Randomization.

Comment 10), 11)

10) More information on data collection methods, use of eCRF etc.

11) More information on data management and storage.

Response 10), 11)

Thank you for your advice. I think it is important to reinforce the integrity of the study by describing more information on data collection, management and storage.

The electronic CRF (eCRF) was developed by supervision of Boryung pharm’s data management team before first enrollment. Data entry will be performed by the investigators and clinical research coordinators at the participating sites using a web-based data base: Medidata Rave™ (Medidata Solutions Inc, http://www.mdsol.com). Rave™ is a commercial system designed to capture, manage, and report clinical research data. And Medidata Rave™ supports electronic record and electronic signature requirements, audit trail including US 21 CRF part 11. Through this system, each participating site is assigned a unique code, as identified by the study team. All staff is trained in using eCRF in advance and then are given each EDC’s role. The data management team also provided at each site on the data entry and data monitoring guide book.
All participating sites will use the same case report forms (CRFs). If responses to the initial inclusion and exclusion criteria provided by the individual performing the data entry fulfill study criteria, the system will dynamically generate randomization and data validation process. All data management tasks are performed by Data Management Plan (DMP). We designed eCRF and set up all DM process according the protocol and DMP documents. The DMP include all staff’s role and responsibility, each step’s definition and process, data backup and transfer etc. Auto and manual data queries are generated by CRA or DM person and will be resolved by CRCs and investigators. Through this iterative process, we will make the clean data and finally perform database lock. All database backup of eCRF will be done in real time by Medidata’s Houston data center and Boryung pharm’s database system.

In response, we described more information on data collection, management and storage in Section 2.9. Data collection and management.

Comment 12)

Is there a data safety monitoring committee, give rationale for not having one if not.

Response 12)

Fimasartan was the ninth ARB approved for the treatment of hypertension by the Korean Ministry of Food and Drug Safety in 2010; it entered the market in 2011. It has been used for several years without a special issue of adverse effect. The KDIGO guideline recommend that an ARB and ACE-I be used in adults with diabetes and CKD (non-dialysis) with urine albumin excretion >300 mg per 24 hours (Class Ib). The data safety monitoring committee was not constructed in the FANTASTIC study because all of the inclusion patients in the Fantastic study belonged to the above guideline’s recommendation and Fimasartan is used safely for many years. However, an independent centralized Event Adjudication Committee (EAC) reviews the subject's data and event-related variable data and applies a medical definition to provide professional and consistent judgment results.

Comment 13)

This is essentially a protocol publication and more detail has to be given to the different aspects from the SPIRIT checklist, this is the primary role of this publication to reinforce the integrity of the study.

Response 13)

Thank you for valuable comment. I totally agree your comment. In response, I added to this publication about more information that you comment, which was in the "not relavent" part of the SPIRIT checklist. Due to your comment, I think that the integrity of the FANTASTIC study will be reinforce.
Comment 14)

There are too many secondary end-points, can these be rationalised?

Response 14)

Thank you for your comment. We agree that the number of secondary endpoints are high compared to other studies. The major reason for this is that one of the major objective of this study is for Fimasartan to obtain KFDA approval for proteinuria and diabetic nephropathy. Although the approval would likely be obtained with the demonstration of efficacy of the primary endpoint, we wanted to demonstrate similar efficacy for various renal endpoints, both in terms of protein reduction and retardation of eGFR progression.

Reference


Comment 15)

The figure showing the flow of the study is well laid out.

Response 15)

Thank you for your compliment.

Reviewer #3: This is a nice protocol that demonstrate the reno-protective effects between ARBs and target blood pressure in hypertensive diabetic chronic kidney disease. I only have a few minor comments for the authors.

Comment 1)

Introduction (Page 4, line 26). I think reference 4 seems improper. Please change to the appropriate reference to show the annual mortality rate of CKD patients who progress to require dialysis.

Response 1)

Thank you for opportunity to fix an error that listed an improper reference.

In response, we change to the appropriate reference to show the annual mortality rate of CKD patients who progress to require dialysis as follow
Comment 2)

(Page 4, line 43-45). Please revise the sentence" Angiotensin II receptor blockers (ARB) have also been shown to reduce CKD progression of CKD." I recommend to revise that " Angiotensin II receptor blockers (ARB) have also been shown to reduce CKD progression"

Response 2)

Thank you for opportunity to proofread for our typographic error.

In response, we revised it as below

“Angiotensin II receptor blockers (ARB) have also been shown to reduce CKD progression”

Comment 3)

Methods and Discussion. Define abbreviations upon first appearance in the text and consistently use the abbreviations such as (KDIGO, ESC, JNC 8, BP, CKD, W, ESRD, eGFR, RAAS blockade)

Response 3)

Thank you for your advice.

In response, we corrected that define abbreviations upon first appearance in the text and consistently use the abbreviations

Comment 4)

(Page7, line 35) Please put the figure number: See Figure

Response 4)

Thank you for opportunity to proofread for our typographic error.

In response, we revised it that add the figure number as below

“The eligible subjects provided written consent for participation in the open-label study and clinical study (see Figure 1).”
Comment 5)

(Page 14, line 25) I think reference 21 seems improper. Please change to the appropriate and specific reference for KDIGO guideline.

Response 5)

Thank you for opportunity to fix an error that listed an improper reference.

In response, we change to the appropriate and specific reference for KDIGO guideline as follow


Comment 6)

Please use the expression as one of 12W/ 24 W or week 12/24 consistently.

Response 6)

In response, we use expression as “numbers” weeks consistently

Comment 7)

Tables (Page 19)Table 1. Please present abbreviations of ACE-I/ARB, Please modify the incomplete bracket: 300mg/g)->300mg/g (or mg/day)

Response 7)

In response, we present abbreviation of ACEI/ARB and modify the incomplete bracket in Table 1

Comment 8)

Supplementary Material Please present abbreviations in SPIRIT-figure PDF

Response 8)

In response, we present abbreviation in SPIRIT-figure