PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy and safety of ipragliflozin and metformin for visceral fat reduction in type 2 diabetes patients receiving treatment with dipeptidyl peptidase-4 inhibitors in Japan: A study protocol for a prospective, multicenter, blinded-endpoint phase IV randomized controlled trial (PRIME-V study)
AUTHORS	Koshizaka, Masaya; Ishikawa, Ko; Ishikawa, Takahiro; Kobayashi, Kazuki; Takemoto, Minoru; Horikoshi, Takuro; Shimousa, Ryouta; Takahashi, Sho; Nagashima, Kengo; Sato, Yasunori; Tatsuno, Ichiro; Terano, Takashi; Hashimoto, Naotake; Kuribayashi, Nobuichi; Uchida, Daigaku; Yokote, Koutaro

VERSION 1 - REVIEW

REVIEWER	Anders Hartmann Oslo University Hospital, Rikshospitalet, Oslo, Norway
REVIEW RETURNED	20-Jan-2017

GENERAL COMMENTS	This manuscript describes a prospective trial protocol that is already initiated. It is a prospective multicenter randomized controlled trial evaluating safety and efficacy of a SGLT-2 inhibitor (ipragliflozin) versus metformin on top of taking DPP-4 inhibitor. The primary endpoint is a reduction of visceral fat after 24 weeks of therapy. The study is novel and the end-point very intersting. Also Asian patients with type 2 diabetes have a relatively lower body mass index (BMI) and previous experience with SGLT-2 inhibitor have generally been Caucasian patients.. The protocol appears comprehensive and describes the study in detail with adequate sample-size estimations, organization, safety procedures and an endless row of secondary end-points. Minor comments: 1) The description of visceral fat CT measures of the primary end-point could have a little more detailed description in the manuscript itself being the central and novel point here. Otherwise the protocol appears very well planned albeit not completely blinded. Some points for evaluation may be: 2) Table 1. Schedule of data collection- In this table BMD (DXA scans) are not included although these measures are mentioned in the text. We have been very interested in visceral fat that can actually be measured with this method, see references below. If the authors use the data software they will have a second measure of visceral fat and may also produce a validation of the method in these diabetes patients. The method we have used: visceral fat was analyzed using the software CoreScan (enCORE version 14.10, GE Healthcare) applied on dual-energy x-ray absorptiometry (DXA)

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	scans.We did scan procedures using DXA scans with a Lunar Prodigy machine. References: von Düring ME et al. Clin Transplant 2017, 31(1). doi: 10.1111/ctr.12869. Visceral fat is strongly associated with post-transplant diabetes mellitus and glucose metabolism 1 year after kidney transplantation. von Düring ME et al Transpl Int. 2015,28:1162-71. doi: 10.1111/tri.12606. Visceral fat is better related to impaired glucose metabolism than body mass index after kidney transplantation.

REVIEWER	Konstantinos Tziomalos Medical School, Aristotle University of Thessaloniki, Greece
REVIEW RETURNED	26-Jan-2017

GENERAL COMMENTS	The present paper describes the protocol of a study aiming to compare the effects of metformin and a sodium-dependent glucose transporter-2 inhibitor on visceral fat. The topic is interesting and novel. The protocol is clear and the methods adequate. The discussion is also comprehensive and up-to-date.

VERSION 1 – AUTHOR RESPONSE

Point-by-Point Responses to Reviewer #1
The page and lines numbers mentioned in the Response refer to those of the file titled " PRIME-V_protocol_paper_20170306_Revised.docx". All modified sections are marked in red.
Reviewer #1
This manuscript describes a prospective trial protocol that is already initiated. It is a prospective multicenter randomized controlled trial evaluating safety and efficacy of a SGLT-2 inhibitor (ipragliflozin) versus metformin on top of taking DPP-4 inhibitor. The primary endpoint is a reduction of visceral fat after 24 weeks of therapy. The study is novel and the end-point very intersting. Also Asian patients with type 2 diabetes have a relatively lower body mass index (BMI) and previous experience with SGLT-2 inhibitor have generally been Caucasian patients.
The protocol appears comprehensive and describes the study in detail with adequate sample-size estimations, organization, safety procedures and an endless row of secondary end-points.
Response: Thank you for reviewing our manuscript and providing positive feedback.

Reviewer #1's Minor comments:
1) The description of visceral fat CT measures of the primary end-point could have a little more detailed description in the manuscript itself being the central and novel point here. Otherwise the protocol appears very well planned albeit not completely blinded. Some points for evaluation may be:

Response: Thank you for this suggestion. We have added a more detailed description of visceral fat CT measures of the primary end-point as follows (pages 9-10, lines 172-182):
"Visceral fat CT measurement
CT was used measure the visceral, subcutaneous, and total fat areas. The CT images are measured as the central measurement by 2 blind radiologists and the average value is calculated. The following imaging conditions will be used at all sites and for all participants: unified CT imaging; conventional method; voltage 120 kVp; dose 200 mAs; abdominal simple image reconstruction condition; field of view 500 mm; expiratory phase end position for respiratory phase; and at the fourth lumbar spine

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center level. The imaging position is the same in all the periods. To minimize exposure to radiation by positioning with scouts, the number of images obtained should be as minimal as possible. Slice width; 10 mm or 8 mm if impossible due to equipment restrictions. For facilities with multiple CT devices, unify the CT devices used for this study or, unify each patient."

λ We have also added the sentences, "Computed tomography will be used to measure visceral fat." in the Strengths section (page 4, line 35), and "Another strength of this study is the blind measurement of visceral fat by CT." in the Discussion (page 17, line 355).

Reviewer #1's Minor comments:
2) Table 1. Schedule of data collection- In this table BMD (DXA scans) are not included although these measures are mentioned in the text. We have been very interested in visceral fat that can actually be measured with this method, see references below. If the authors use the data software they will have a second measure of visceral fat and may also produce a validation of the method in these diabetes patients. The method we have used: visceral fat was analyzed using the software CoreScan (enCORE version 14.10, GE Healthcare) applied on dual-energy x-ray absorptiometry (DXA) scans. We did scan procedures using DXA scans with a Lunar Prodigy machine.

References:
von Düring ME et al. Clin Transplant 2017, 31(1). doi: 10.1111/ctr.12869.
Visceral fat is strongly associated with post-transplant diabetes mellitus and glucose metabolism 1 year after kidney transplantation.

von Düring ME et al Transpl Int. 2015,28:1162-71. doi: 10.1111/tri.12606.
Visceral fat is better related to impaired glucose metabolism than body mass index after kidney transplantation.

Response: Thank you for this suggestion. We have inserted the following sentence in the footnote of Table 1 (page 13-14, line 258-260): "*: Special examination includes whole body DXA, dietary behavior questionnaire, respiratory quotient, basal metabolism, and calorie and glucose intake for patients. CT, computed tomography; DXA, dual-energy x-ray absorption."
We have been analyzing visceral fat using the software InnerCore™ applied on dual-energy x-ray absorptiometry (DXA) scans. We did scan procedures using DXA with a Discovery™ DXA system (Hologic Inc., Marlborough, MA, USA).
We have added the following sentences (pages 11-12, lines 232-237): "Total body composition will be determined by whole body DXA using a fanbeam bone densitometer (Discovery™ DXA system; Hologic, Inc., Marlborough, MA, USA), and all the scans will be analyzed using Discovery™ software version 13.3.0.1 (Hologic, Inc., Marlborough, MA, USA), which contains the Hologic Advanced Body Composition™ assessment and InnerCore™ visceral adipose tissue assessment. Two certified technologists perform all scans."
Whole body DXA is performed for about 30% of the patients in this study, due to facility issues. However, we are planning to analyze the correlation of visceral fat area measured by CT and whole body DXA. These articles you mentioned are very interesting. We will consider citing these articles for reference when publishing our results.

Point-by-Point Responses to Reviewer #2
The page and lines numbers mentioned in the Response refer to those of the file titled " PRIME-V_protocol_paper_20170306_Revised.docx." All modified sections are marked in red.
Reviewer #2
The present paper describes the protocol of a study aiming to compare the effects of metformin and a sodium-dependent glucose transporter-2 inhibitor on visceral fat. The topic is interesting and novel.

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The protocol is clear and the methods adequate. The discussion is also comprehensive and up-to-date.

Response: Thank you for reviewing our manuscript and providing positive feedback.

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