PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Medroxyprogesterone acetate plus metformin for fertility-sparing treatment of atypical endometrial hyperplasia and endometrial carcinoma: trial protocol for a prospective, randomized, open, blinded-endpoint design, dose response trial (FELICIA Trial)
AUTHORS	Mitsuhashi, Akira; Kawasaki, Yohei; Hori, Makoto; Fujiwara, Tadami; Hanaoka, Hideki; Shozu, Makio

VERSION 1 – REVIEW

REVIEWER	Robert Fruscio University of Milan-Bicocca Milan, Italy
REVIEW RETURNED	22-Nov-2019

GENERAL COMMENTS	Very interesting protocol on an uncommon disease as athypical endometrial iperplasia and endometrial cancer in young women with childbearing desire. The management of these patients is usually challenging, requiring thoughtful evaluation and careful follow up. The protocol is written in a good english, is clear and exhaustive; the only remark is that it is not specified how the response to therapy and the endometrial evaluation durin mainteinance will be performed; will a biopsy be taken at each visit? Finally, at least the flowchart of the study should be provided in english and not only in japanese.

REVIEWER	ATTILIO DI SPIEZIO SARDO UNIVERSITY FEDERICO II OF NAPLES
REVIEW RETURNED	30-Nov-2019

GENERAL COMMENTS	This is a well written and well designed protocol. The trial aims to identify the appropriate dose of metformin to be combined with medroxyprogesterone acetate therapy for fertility -sparing treatment of patients with AEH and EC. My suggestions: 1) Please define how many women with AEH and how many with EC the authors aim to enroll. 2) I would add subgroup analyses in AEH vs EC 3) Add subgroup analyses according to BMI (e.g. obese or overweight only) 4) I would add Immunochemistry for ER and PR receptors at the time of biopsy and subgroup analyses accordingly

	5) Authors should add more details about randomization sequence generation: computer based? any block? 6) Add more details on allocation concealment 7) why not placebo?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Very interesting protocol on an uncommon disease as athypical endometrial iperplasia and endometrial cancer in young women with childbearing desire. The management of these patients is usually challenging, requiring thoughtful evaluation and careful follow up.
The protocol is written in a good english, is clear and exhaustive; the only remark is that it is not specified how the response to therapy and the endometrial evaluation durin mainteinance will be performed; will a biopsy be taken at each visit?
Finally, at least the flowchart of the study should be provided in english and not only in japanese.

Response: According to the reviewer's suggestion, we have added the flowchart of the trial during the treatment period in the supplementary file.

After remission, we have been managing the patients carefully to detect early recurrence. Patients are examined every three months until three years after the initial treatment (at the time of evaluation for the primary endpoint). After that, patients are examined every six months.
Follow up was performed by using endometrial sampling with a pipelle biopsy or other appropriate equipment (Methods and analysis section, Maintenance period subsection, page 14, lines 2-3).

Reviewer: 2

This is a well written and well designed protocol. The trial aims to identify the appropriate dose of metformin to be combined with medroxyprogesterone acetate therapy for fertility -sparing treatment of patients with AEH and EC.
My suggestions:

1) Please define how many women with AEH and how many with EC the authors aim to enroll.

Response: The number of patients with the target disease is small. Furthermore, the population ratio between AEH and EC was 1:1.5 in several previous studies. However, because we would like to recruit a larger number of patients, the number of patient allocation between AEH and EC has not been decided.

2) I would add subgroup analyses in AEH vs EC
3) Add subgroup analyses according to BMI (e.g. obese or overweight only)
4) I would add Immunochemistry for ER and PR receptors at the time of biopsy and subgroup analyses accordingly

Response: Answers to the above comments 2), 3), and 4)
As pointed out by the reviewer, subgroup analyses are interesting and important. However, there are only 40 patients in each group, we are thinking that the subgroup analysis might have insufficient power to detect a significant difference between groups. We have already started this trial, so we could not change the protocol regarding the study's primary and secondary endpoints. The main objective is to evaluate the efficacy of metformin; we will retrospectively analyze the points raised by the reviewer additionally.

5) Authors should add more details about randomization sequence generation: computer based? any block?

6) Add more details on allocation concealment

Response: Answers to the above comments 5), and 6)
According to editorial request, we revised the "Randomization" section, pages 12 as follows:
"Randomizaion
After confirming the fulfillment of the eligibility criteria, patients are randomly assigned to arm A (MPA alone group), arm B (MPA + metformin 750 mg / day group), and arm C (MPA + metformin 1500 mg / day group) in a 1:1:1 allocation via a dynamic and centralized randomization procedure implemented with the DATATRAK Electronic Data Capture system (DATATRAK ONE V.14.1.0; https://secure.datatrak.net). Minimization imbalance Method with a probability of 0.9 is used for randomization[19]. The stratification factors to be balanced across treatment arms are BMI, histology, and marital status. "

7) why not placebo?
Response: First, we conducted a placebo controlled trial. However, we could not obtain any support from metformin pharmaceutical manufacturers besides getting adverse event reports. As metformin is cheap and an old drug, manufacturing a placebo is very expensive because the production line has to be stopped temporarily. Therefore, we gave up on the idea of using placebo and decided to conduct this trial using the Prospective randomized open blinded end-point (PROBE) method.
Finally, our protocol was approved by PMDA to be performed under the PROBE method.

VERSION 2 – REVIEW

REVIEWER	attilio di spiezio sardo university of naples, federico II, naples, Italy
REVIEW RETURNED	19-Dec-2019

GENERAL COMMENTS	very important RCT. I suggest to use placebo or at least a single blind with blind of outcome assessor

VERSION 2 – AUTHOR RESPONSE

very important RCT.
I suggest to use placebo or at least a single blind with blind of outcome assessor

Response:

We fully agree that double and single blind studies using placebo controls among others are superior. First, we conducted a placebo controlled trial. However, we could not obtain any support from metformin pharmaceutical manufacturers besides getting adverse event reports. As metformin is cheap and an old drug, manufacturing a placebo is very expensive because the production line has to be stopped temporarily. Therefore, we gave up on the idea of using placebo and decided to conduct this trial using the Prospective randomized open blinded end-point (PROBE) method.
Finally, our protocol was approved by PMDA to be performed under the PROBE method.
We could not change the protocol as the trial had already been initiated.
We added the following sentence in discussion section on page 21 line 18 “Finally, the PMDA approved our protocol for conducting this study based on the PROBE design. ”