Author's response to reviews

Title: International Active Surveillance Study of Women Taking Oral Contraceptives (INAS-OC Study)

Authors:

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Author's response to reviews: see over
Dear Ms. Hoffman,

MS: 1220621916238169
International Active Surveillance Study of Women Taking Oral Contraceptives (INAS-OC Study)
Juergen C Dinger, Kristina Voigt and Anita Assmann

Thank you for considering our revised manuscript for publication in BMC Medical Research Methodology. We also thank the reviewer for her comments.

The manuscript has been revised a second time, and we hope you will now find it acceptable for publication.

Please find attached our revised manuscript along with a detailed response to the reviewer’s comments below.

Major Compulsory Revisions

Comment 1: Why did you choose to look at this particular regimen? Why not look at other pills, such as other so called 3rd generation progestins compared with 2nd generation? Or look at continuous or other extended regimens. The fact that you have chosen this particular pill does make it seem like this is a marketing study, despite the claims of independence.

Author’s response: This is a post-authorization safety study (PASS) which was requested by the FDA. The FDA wanted more data on the safety - and in particular on the incidence of VTE - of this recently approved pill regimen. The study is a phase IV commitment to FDA and the study protocol was discussed at length and approved by FDA. As such its content is not a “marketing” study.

In the revised version of the protocol we have mentioned the fact that this PASS is a phase IV commitment to FDA.
Comment 2: Page 4. You present a detailed account of adjudication for DVT. But what about for the other primary outcomes?

Author’s response: The submitted manuscript provided a detailed description for VTE (DVT and pulmonary embolism). From a statistical point the primary variable is VTE. For the sake of brevity we describe only the procedure for VTE. In the revised manuscript we have added a sentence that the same procedure applies for ATE (myocardial infarction and cerebrovascular accidents) and that the Safety Monitoring and Advisory Board – based on interim results - may decide to use the same adjudication procedure for other outcomes of interest too.

Comment 3: Page 6. Will the participants provide written informed consent?

Author’s response: Please refer to the previous versions of the manuscript. The answer to this question is given in the section ‘Study Participants’: “… This information will be provided on an informed consent and data privacy form which must be signed by all study participants prior to study entry.”

Comment 4: Page 7. Will the participating physicians be given incentives to recruit a certain number of DRSP/EE 24d users?

Author’s response: The participating physicians do not receive an incentive for prescribing DRSP/EE 24d. The study is designed to reflect the typical prescribing behavior of physicians and is contructed to interfere as little as possible in the prescribing decision. The protocol states: “The whole process of patient information of this study should not start before the discussion and prescription of the new OC has taken place.”

Comment 5: Page 8. How will contraceptive information be collected and how often? Will it be validated by prescription databases or clinic records?

Author’s response: The participating physicians check the entries in the baseline questionnaires for correctness and completeness, including the initial prescription information. Each woman then receives a follow-up questionnaire every six months, where she is requested to fill in information on all current medication use, including whether she is still using an OC. Exact brand names and dates for stopping or switching are documented. Studies have demonstrated that healthy young user reported OC intake (i.e., no “passive” patients but healthy women who actively take responsibility for contraception) data are at least as reliable as prescription databases or clinic records as a mere prescription does not necessarily establish exposure. We have seen hundreds of cases were women had an OC prescriptions for long time intervals but did not use these OCs because of a change in their partnership or because of a short-term decision for a planned pregnancy.

In the section on follow-up we have added a sentence stating that OC exposure will be recorded.
Comment 6: Page 8. Again what about other outcomes - how will they be confirmed?

Author’s response: In the section “Validation of Self-reported Events” it is clearly stated: “This procedure is mandatory for all serious clinical outcomes (incl. VTE and ATE). In the revised manuscript we have added a definition of “serious adverse event”.

Comment 7: Page 9. Will there be any monitoring of the sites? To verify informed consent enrollment procedures, look at source docs, etc.?

Author’s response: The study concept is based on direct contacts between the study team and the patients. Each informed consent form has to be checked by our study team. The contact between our study team and the participating women is independent of the recruiting physician. Therefore, it is easy for us to ensure the existence of the patient. In addition, the validation of self-reported outcomes is based on original medical records of the attending physician (the physician who diagnosed or treated the reported outcome). Please note that the attending physician is in almost all cases not identical with the recruiting physician, because the participating gynecologists do not treat VTE or ATE. An ATE or VTE is often a reason to stop use OC use. The majority of women with these events have no longer a reason to consult their gynecologist. Therefore the gynecologists are usually not aware of these events.

Comment 8: Page 10. You need to define what will be included as an ATE.

Author’s response: A definition was added in the “Background” section.

Comment 9: Page 10. What is the difference in incidence of VTE and other outcomes that you are trying to rule out? I.e., the degree of inferiority of the new treatment compared with the standard treatment that your study attempts to exclude?

Author’s response: From a statistical point of view the primary variable is the VTE hazard ratio between DRSP/EE 24d and Other OCs. Therefore, the power calculation is based on VTE. As stated in the section ‘Size of the Study’, the incidence of VTE is ~9/10,000 WY and the null hypothesis to be tested is: $HR_{VTE} \geq 2$ (i.e., the VTE hazard ratio for DRSP/EE 24d vs. Other OCs is higher or equal to 2). I.e., in case that the actual VTE incidence for standard treatment is 9/10,000 WY the statistical power of this study is sufficient to rule out a difference of 9/10,000 WY. It is obvious that the statistical power to exclude an increased incidence of other outcomes is dependent on their incidence.

Comment 10: Page 11. What is the primary analysis population?

Author’s response: The submitted manuscripts states in section ‘Data Analysis’: “The final analyses will include both an “as treated” (AT) and where necessary also an intention-to-treat (ITT) analysis. The safety conclusions of the study, however, will
be based on the AT analyses because the ITT approach potentially dilutes differences between treatments.” Therefore, it is clear that the AT population is the primary analysis population for this study.

Comment 11: What about GCP? This is not a randomized trial but many principles still apply. Will you follow GCP?

Author’s response: The answer is given in EMEA Guidelines on Pharmacovigilance for Medicinal Products for Human Use (Volume 9A). In this document it is clearly stated (p. 91): “The guidance on Good Clinical Practice does not apply to non-interventional post-authorisation studies”. Instead the guideline refers to Good Pharmacoepidemiological Practices (cf. pages 46, 91 and 101 of Volume 9A). In the section ‘study management’ of our manuscript it is stated that the study will be conducted in accordance with the ‘Guidelines for Good Pharmacoepidemiology Practices (GPP)’ issued by the International Society for Pharmacoepidemiology in 2004, as well as ‘Good Epidemiological Practice (GEP) – Proper Conduct in Epidemiologic Research’ issued by the European Epidemiology Federation in 2004, and the ethical principles that have their origin in the Declaration of Helsinki.

Comment 12: Page 12. What is the four-eye principle?

Author’s response: The “four-eye principle” in very simple words means that a person should not control her or his own work. I.e., that each work process that is relevant for the overall quality of the study has to be quality controlled by an independent second person. A Google search suggests that the ‘four-eye’ principle is an established term. Nevertheless, we have included an explanation in the revised manuscript.


Author’s response: The INAS study is an all comers study. There is no form of penalization or advantage for the participating physician to prescribe a specific OC. The EURAS study has shown that the used study design ensures representative recruitment of OC users. Therefore, selection bias will not play a major role in the INAS study. It is important to differentiate between selection bias and preferential prescribing. It is well known that new OCs are potentially prescribed to high risk patients (e.g., obese women). This, however, does not establish selection bias, but confounding. It is actually our goal to identify preferential prescribing by documenting confounders as complete as possible in non-interventional studies.

Comment 14: Page 13. How can you state that “All known confounders will be accounted for”? How? For example you would not have information on factor V Leiden a known confounder.

Author’s response: The text of the manuscript actually reads: “Although all known confounders are documented in detail at baseline adjustment or stratification cannot be done for unknown confounders.” The study questionnaires ask explicitly for hypercoagulability disorders. In many cases information on genetic disorders will not be available. In contrast, information on a family history as well as a personal history will be available. However, the statement that known confounders are documented in
detail is correct. Nevertheless, in the revised protocol we have reworded the sentence as follows: “Although all confounders known for the individual women are documented in detail at baseline adjustment or stratification cannot be done for unknown confounders.”

Comment 15: Page 13. How does the chosen design minimize the impact of referral and misclassification bias?

Author’s response: This is a prospective cohort study and the outcomes of interest are not identified or reported by a specific group of physicians (hospital and/or emergency room based physicians, GPs, radiologists, internists, etc.). In contrast, the outcomes of interest are self-reported by study participants and validated via the attending physicians. In this way all diagnosed VTEs are captured. E.g., it does not matter if an US women with high socioeconomic status (and probably a user of an expensive OC) is treated as an out-patient by a private specialist and an US women of lower socioeconomic and without sufficient health insurance status is treated in an emergency room of a public hospital.

In general, misclassification bias is reduced by the blinded adjudication of 3 independent specialists at the end of the study (for details please refer to the ‘Methods’ and the ‘Validation’ section of the manuscript). The fact that this adjudication is done in a blinded manner minimizes in particular the potential for differential misclassification.

Comment 16: Page 13. How does the chosen design minimize the impact of the healthy user effect?

Author’s response: Long-term users are excluded in this study. Therefore, the impact of the healthy user effect is minimized.

Minor Essential Revisions

Comment 17. Page 2. Do you mean 24 in the following statement “it can be assumed that a 21-day regimen of DRSP/EE 24d would not be associated with a higher risk of venous thromboembolism (VTE) than DRSP/EE 21d.”?

Author’s response: The sentence is correct. Nevertheless, we have reworded the sentence as follows: “Based on the lower estrogen dose of DRSP/EE 24d, it can be assumed that a 21-day regimen of this pharmaceutical formulation would not be associated with a higher risk of venous thromboembolism (VTE) than DRSP/EE 21d.”

Please do not hesitate to contact me if you have any further queries.
I look forward to hearing from you.

Yours sincerely,

Jürgen C. Dinger, MD, PhD