Author’s response to reviews

Title: Uro-Vaxom® versus placebo for the prevention of recurrent symptomatic urinary tract infections in participants with chronic neurogenic bladder dysfunction: a randomised control feasibility study

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Version: 1  Date: 14 Feb 2019

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Reviewer #1: A well written and thoroughly planned feasibility study looking into an area of importance in this patient population. The methodology is sound and the study design appropriate for the research question. The proposed significant effect size of 0.5 seems reasonable and the outcome measures are both pragmatic and appropriate. My only comment would be that I think the presence/absence of an indwelling catheter (suprapubic or urethral) should be documented in the baseline information and a sub-analysis performed in this group as the incidence of UTI could be significantly different. If the incidence is not found to be different then this would also be useful information.

We collect this information at baseline and ask at 6 month visit if their method of bladder management had changed during the course of the study.

We will report the rate of infection in the two subgroups, but would not undertake any statistical comparison.

Reviewer #2: This is a very interesting study protocol on prevention of recurrent UTI in patients with chronic neurogenic bladder dysfunction with Uro-Vaxom vs placebo.

The study protocol is well-structured and well presented. It is a feasibility study and therefore will only include a relatively small number of patients (n=48).

I only have a few questions and comments:
1) I agree that in NBD-patients the definition of symptomatic UTI is not well defined. It is therefore justified that the authors use as surrogate parameter the “need” for antibiotic therapy indicated either by the treating physician or the patient who is used to manage their UTI episodes. There is no other pragmatic way, which is justified because the study is blinded and placebo-controlled.

No comment needed

2) It is appreciated that during the study the different symptoms observed by the patients for each UTI episode will be carefully registered and analysed.

No comment needed

3) Since this is not a study on antibiotic therapy of acute UTI episodes, I agree that urine cultures are not an essential part of the study, although I assume that they will be registered when performed.

No comment needed (we will not know about all cultures undertaken)

4) At 3 and 6 months urine culture is, however, part of the protocol. Therefore at this time points not only the amount of bacteriuria, but also the cultured bacteria including routine susceptibility testing should be recorded.

We will report results available from standard local cultures.

5) Of course, I agree that asymptomatic bacteriuria at 3 and 6 months should be registered, but I do not agree that their presence or absence can be taken as an efficacy parameter. The studies of the University of Lund have even shown, that presence of ABU could be correlated with positive outcome (reduction of recurrences).

Thank you for pointing this out. We have added a sentence in the discussion and referenced the work at University of Lund.

6) The authors have cited one study with Urovaxom in NBD patients (Hachen et al 1990). In the meantime another study, although retrospective, was published and could be cited: Jörg Krebs, Stefanie Fleischli, Jivko Stoyanov, Jürgen Pannek. Effects of oral immunomodulation therapy on urinary tract infections in individuals with chronic spinal cord injury—A retrospective cohort study. Neurourology and Urodynamics. 2018;1-7. DOI: 10.1002/nau.23859

Thank you, have added to our references, but feel it’s a weak study design.
7) I also have problems that patients taking (long-term) antibiotic prophylaxis (not antibiotic treatment) can be included into the study. It would be ok, if only the feasibility of such a study is the main aim. But of course I assume that these patients will be clearly indicated in the outcome analysis.

Yes.

Overall this will be a very important and needed study, whether immunomodulation with oral Uro-Vaxom could be an effective prevention of rec UTI in these patients.

Further changes

I have made the changes (tracked) in the attached document. I have also made minor changes to the affiliations and to the acknowledgment sections.