

Document title:

Clinical Study Protocol AMENDMENT

Study Number/Cyprus National Bioethics Committee Approval Number:

EEBK/ΕΠ/2019/50

Review Bioethics Committee approving the Program:

Biomedical and Clinical Research Committee A

Study Title:

Open-Label, Single-Arm Pilot Study of the Effect of Cholecalciferol on Mucin-1 Levels in Individuals With Autosomal Dominant Tubulo-Interstitial Kidney Disease Due to MUC1 Mutations (ADTKD-MUC1)

Acronym:

CyCHOLEMUC1

Study Type:

Interventional

Date generated/Date submitted:

14 May 2019

Date of final approval:

01 July 2019

Date amendment requested:

08 July 2020

Date of last change/Date of final approval:

07 September 2020

Sponsors:

University of Cyprus

Broad Institute of MIT and Harvard

Purpose:

The document EEBK10 is the official application form to request any amendments to protocols that were previously approved. This amendment concerned the inclusion of healthy controls to the CyCHOLEMUC1 trial to investigate clinical effects of VDRA treatment.

APPLICATION FOR PROTOCOL AMENDMENT

To be completed by the Principal Investigator (s)

Programme Title
Open-Label, Single-Arm Pilot Study of the Effect of Cholecalciferol on Mucin-1 Levels in Individuals with Autosomal Dominant Tubulo-Interstitial Kidney Disease due to <i>MUC1</i> Mutations (ADTKD-<i>MUC1</i>) Πιλοτική μελέτη της επίδρασης της Χοληκαλσιφερόλης (Βιταμίνης D3) στα επίπεδα της πρωτεΐνης Mucin-1 σε άτομα με αυτοσωμική επικρατούσα διαμεσο-σωληναριακή νόσο των νεφρών λόγω μεταλλάξεων στο γονίδιο <i>MUC1</i>
Review Bioethics Committee approving the Programme
Review Bioethics Committee for Biomedical and Clinical Research A
Protocol Number given by the Cyprus National Bioethics Committee
EEBK/ΕΠ/2019/50
Date of initial approval by Review Bioethics Committee
01 July 2019
Programme duration
18 Months, starting in August 2019 – February 2021
Institution to which the Principal Investigator belong(s)
University of Cyprus
Principal Investigator's name
Prof. Constantinos Deltas

To be completed by the Cyprus National Bioethics Committee

Date of delivery of the Report to the Bioethics Committee
Date: Month: Year:
Person receiving the form on behalf of the Cyprus National Bioethics Committee

It is the responsibility of the Review Bioethics Committee to judge and decide as to whether there are reasons why this report, on the change of protocol, should be communicated to the Cyprus National Bioethics Committee.

To be completed by the Principal Investigator (s)

Give details of the changes proposed.

This open-label clinical trial involving Cypriot patients diagnosed with ADTKD-*MUC1* started in September 2019 and was concluded in January 2020. A total of 46 patients received a single high dose of Cholecalciferol and were followed as proposed in the protocol approved by your committee. The primary endpoint proposed for the trial is currently under investigation and involves the accurate measure of both mutated and wild-type MUC1 protein levels in urinary exosomes.

Preliminary results indicate that this single high dose of Cholecalciferol does not affect the biochemical and clinical presentation of participants. There were no indications of side-effects or any adverse events recorded during and after the completion of the trial. More specifically, serum creatinine values remained within the range defined by previous measurements, as well as serum urea and uric acid values. Serum PTH and Ca levels were closely monitored in all participants, and no significant responses to the administered therapy were recorded. Similarly, serum AST, ALP and ALT measurements did not reveal any effects of the administered supplement on liver metabolism nor toxicity. All other biochemical lab tests we recorded, were also stable or within a normal range. None of the participants posted any complaints regarding the study and there was not an occasion that required the activation or the use of the Clinical Coordinator's insurance contract.

Interestingly, by addressing the secondary objectives, we observed **a marked alteration of serum wild-type MUC1 protein levels**. MUC1 levels appear to respond to treatment and fluctuate during the time-points we studied. This observation will be added to the results from the primary objective to describe how patients behave when dosed with Cholecalciferol. This effect was not observed in ADTKD-*MUC1* patients treated with Ergocalciferol by our collaborators in the USA, thus suggesting a specific effect for Cholecalciferol (see previously submitted protocol for a literature review on the efficacy of the above supplements).

Nevertheless, it is imperative to describe whether the effect observed is **specifically** caused by Cholecalciferol, rather than being influenced by clinical or other factors. For this purpose, we propose an amendment to the current protocol: to prove the direct regulation of MUC1 levels in serum by Cholecalciferol, **we propose to include 25 non-carriers of a MUC1 mutation in the study as a control cohort**. Volunteers will follow the same time-course that was followed by patients, after signing the same approved consent form.

See below the recruitment criteria to be considered:

Recruitment - Inclusion criteria:

1. Participants must be already genotyped negative for the *MUC1* mutation segregating in Cyprus (we target healthy members of families that segregate the disease)
2. Ages between 18-75 years
3. Must have normal kidney function
4. Should not be suffering from any other serious conditions or chronic kidney
5. Should not be diagnosed with any form of cancer, as serum MUC1 might be found elevated due to other causes.

6. If female and of childbearing potential (premenopausal and not surgically sterile) must have a negative urine pregnancy test at the screening visit (Day -20) and be willing to use contraception from the time of the screening visit to 2 weeks following study supplement administration. Acceptable methods of birth control include abstinence, barrier methods, hormones, or an intra-uterine device.
7. Able to understand and comply with requirements of the entire study and to communicate with the study team.
8. The volunteer has not taken cholecalciferol, ergocalciferol or other Vitamin D related supplements in the month prior to study initiation.
9. Participants must agree NOT to take ergocalciferol or cholecalciferol (except for <500 IU that is contained in a daily multi-vitamin) for one month after receiving the one-time dose of cholecalciferol.
10. Written informed consent using a document that has been approved by the Cyprus National Bioethics Committee.

Recruitment - Exclusion criteria: Remain the same as in the approved protocol

Recruitment procedure: To eliminate any environmental discrepancies and expedite the outcomes of the study, we plan to include *MUC1* mutation negative individuals that live in the same geographical region as most patients do. It is desirable that candidate participants had visited the Clinical Coordinator, Dr Christoforos Stavrou, in the past to explore the possibility of being *MUC1* mutation carriers, as they belong to the large ADTKD-*MUC1* families our group is studying for more than 25 years. Therefore, we recently communicated with selected individuals to explore their interest in participating in this trial and have shortlisted 25 of them as good candidates. The final list will be prepared upon approval of this amendment.

Documents to be used: We will make use of the previously approved consent form for this project.

Study Period/Study Groups: Upon approval of this amendment, we will commence the study in the same fashion as described in the approved protocol. Participants will be divided into two or more groups for easier sample processing and logistics.

Complaints: As stated in the study protocol, complaints from participants can be submitted to the Director of the Research Support Service, Dr Marios Demetriades, at the University of Cyprus, tel. 22-894286. In case a participant suffers from a documented or an undocumented adverse effect caused by the administered supplement, Altius Insurance that provides insurance in the form of professional indemnity for Dr Christoforos Stavrou the clinical coordinator of the study, will examine and respond to claims, in full compliance with protection of privacy and personal data. Altius Insurance will examine each case as per complaints made on documented or undocumented adverse effects due to the supplement under study and will act in accordance with the firm's internal procedures. Altius Insurance is a private insurance company based in Nicosia (Corner of Kennedy Ave & Stasinou Str, tel: 22379999). With this amendment we are submitting an updated document from the insurance company Altius Insurance. See below:

Budget: This amendment will be funded by the same sponsor. A supplementary budget has been approved and will be activated upon approval by the CNBC. See below a signed approval of the budget:

Signature of Principal Investigator (s)		
Surname	Name	Signature
Deltas	Constantinos	

Have a detailed discussion on how the proposed changes can affect the rights of patients and/or volunteers.

The proposed changes will not affect any rights of the volunteers that will agree to participate. They will instead become a steppingstone towards testing a safe treatment that may help people in their communities. As described in the previous part, participants to be selected will primarily be part of our well-studied ADKTD-*MUC1* cohort. These individuals have close relatives carrying the disease and witness of how the disease can change a patient's quality of life, especially due to the complete absence of a robust and specific treatment.

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki. The project has been designed by experts with previous experience in clinical trials, aimed not to risk the health and well-being of participants under any circumstances. The therapeutic agent under study is a widely used food supplement (Cholecalciferol – Vitamin D3), thus securing the safety of this intervention. All preliminary measurements from the completion of the study protocol in Cypriot ADTKD-*MUC1* patients, enhance our confidence that the supplement administered is safe and not accountable for any adverse effects. In any case, undesired adverse events concerning this amendment will be recorded and reported.

The CY-Biobank is an established unit and handles a vast number of samples. All matters pertaining to data protection of participants will be strictly secured. In this respect, the information provided in the consent form explains adequately the aims of the project to volunteers. In fact, the encouraging first results of the approved protocol in patients with ADTKD-*MUC1*, justifies the decision of our experts' collaborators to strengthen it by extending the trial on a cohort of healthy subjects

Signature of Principal Investigator (s)		
Surname	Name	Signature
Deltas	Constantinos	