STUDY PROTOCOL

Version February 27, 2018

Vitamin D and type 2 diabetes Interim Supplement (D2di)

ClinicalTrials.gov registration number – NCT01942694
Funding: NIDDK, ODS, ADA
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PROTOCOL SIGNATURE PAGE

February 27, 2018

I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all relevant documentation (e.g. Manual of Procedures) to the study personnel that are under my supervision in relation to the D2d interim supplement study. I will discuss this material with them and ensure that they are fully informed regarding the study procedures and the conduct of the study according to 21 Code of Federal Regulations parts 50, 54, 56 and 312, to Good Clinical Practices as described in International Conference on Harmonization guideline E6, and by Institutional Review Boards.

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Investigational Institution(s)

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Site Principal Investigator Signature Date

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Site Principal Investigator Printed Name

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1. PROTOCOL SYNOPSIS

Title	Vitamin D and type 2 diabetes interim supplement (**D2di)** study.
Study Objective	The D2d interim supplement is a short-term extension of D2d to allow participants who return for the last visit of the D2d study to continue on the assigned study pills and contribute additional data while D2d results are being analyzed and the D2d Research Group and NIH explore the feasibility of a long term D2d extension study.
Study Design	After the last visit of D2d, participants will continue on their assigned study pills and will have non-visit contacts (phone or email) at 3 months and 6 months to collect (self-reported) safety and outcomes data. Procedures to be followed at the non-visit contacts are identical to D2d. Please refer to D2d protocol version 1.9. No new procedures or questionnaires are added.
Sample Size (total)	-Up to 2,325 D2d participants

2. BACKGROUND, RATIONALE AND SIGNIFICANCE

Following an extensive evaluation process, the *"Vitamin D and type 2 diabetes"* (**D2d**) study was funded by NIH in 2013 to provide definitive conclusions regarding the role of vitamin D supplementation for prevention of type 2 diabetes (t2DM) in participants with prediabetes. An extension of D2d is being considered by the D2d Research Group and the main funding agency (NIDDK).

The D2d interim supplement (D2di) study is a short-term extension of D2d to allow participants who return for the last visit of the D2d study to continue on the assigned study pills (vitamin D or placebo blinded) and contribute self-reported data while D2d results are being analyzed and the D2d Research Group and NIH explore the feasibility of a long term D2d extension study.

Because D2d is a large (=2,423), event driven trial, it will require up to 12 months to complete all the study visits, and then analyze the D2d study data, plan the D2d extension study, and obtain grant funding to conduct the extension study. D2d has excellent participant retention, and D2di provides participants an opportunity to remain engaged with the study and continue to provide self-reported data during this period.

3. HYPOTHESES AND SPECIFIC AIMS

3.1 Study Objectives

The *objectives* of the D2di study are to continue collecting self-reported data regarding the safety and efficacy of oral daily vitamin D supplementation while an extension study is being considered.

3.2 Specific Aims

1. Keep participants engaged while the long-term extension of D2d is being planned.
2. Continue collecting data in relation to the scientific aims of the primary D2d study (diabetes, cancer, cardiovascular disease and adverse events; see protocol version 1.9).

4. STUDY DESIGN, INTERVENTION AND PROCEDURES

4.1 Overview of Study Design

D2di is a short-term continuation of the currently approved version of the D2d study (version 1.9) and ***no new procedures are added.*** D2di has only non-visit encounters. The schedule and content of the encounters mimics the D2d study as described in protocol version 1.9, including the supplement about collection of cancer and cardiovascular outcomes.

5. STUDY POPULATION

5.1 Inclusion Criteria

1. Current participation in D2d regardless of adherence to study pills.
2. Informed consent to continue in D2di.

5.2 Exclusion Criteria

1. Withdrawal of consent from D2d.

6. INFORMED CONSENT PROCESS

At the last visit of D2d, participants will be asked if they are interested and willing to continue in D2di and will be presented with the informed consent form to review. A qualified member of the site research team (e.g. site PI, co-investigator, research coordinator, research assistant, or clinical research nurse) will discuss with the D2d participant the study's procedures, risks, potential benefits,

and rights as a participant and the purpose of D2di. Once all questions have been answered and concerns addressed, the D2d participant will be asked to sign the written informed consent form for D2di. The informed consent process is ongoing and interactive. Participants will be given the opportunity to ask questions throughout D2di. Participants will be told that they can cease participating at any time for any reason.

6.1 Participant Study Stipend

Participants will not receive a stipend as encounters will be by phone (or email) only.

7. STUDY INTERVENTION

Participants will continue on the treatment assignment they were randomized to during D2d. Treatment assignment will remain double masked. Unmasking for the D2d study will occur as previously planned.

8. PROCEDURES AND OUTCOME MEASURES

8.1 Study Encounters

Frequency of non-visit encounters every 3 months are similar to D2d. At each encounter, the same procedures will be followed as in D2d (questions on study pill adherence, occurrence of adverse events, changes to medical history and concomitant medication use, questions for non-diabetes outcomes).

Duration of D2di will be up to 8 months from the initiation of the D2d End-of-Study Procedures.

9. ASCERTAINMENT OF OUTCOMES

During D2di, the same outcomes data as in D2d will be collected (incident diabetes, cardiovascular disease, cancer, and adverse events). The data will be obtained via self-report only. Events will be adjudicated and safety will be assessed following similar procedures as in D2d, as described in the D2d study protocol v 1.9. There will be no laboratory testing by the study.

10. DATA AND SAFETY MONITORING

10.1 Risk-benefit analysis

The risk-benefit ratio for D2di is lower than the parent D2d study since there are no visits involved and no blood draws. Please refer to the D2d study Protocol v 1.9 and the D2d Data Safety Monitoring Plan for additional details. Participants will have the usual safety measures (serum calcium, creatinine for GFR, and urine calcium creatinine) completed at the last scheduled D2d visit if they have not had it done within the 6 months prior to that visit.

10.2 Data Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) has been established by the primary sponsor, NIDDK, to oversee the safety and other aspects of the D2d study. The DSMB will remain in place and will continue to provide independent oversight of D2di.

10.3 Ethical and Regulatory Responsibilities & Statement of Compliance

Identical to D2d. This study will be carried out in compliance with the IRB-approved protocol and related documents and in accordance with Good Clinical Practice guidelines, the applicable regulatory requirements of the Department of Health and Human Services, the International Conference on Harmonization (ICH) Guidelines and state and local legal and ethical requirements.

10.4 Confidentiality

Identical to D2d.

10.5 ClinicalTrials.gov Requirements

The parent D2d has been registered in ClinicalTrials.gov. The site will be updated to reflect the D2di extension.

11. DATA ANALYSIS

11.1 Data Analysis Plan

Overall data analysis plan will follow the D2d study.

SUPPLEMENTS AND APPENDICES

Appendix A Sample D2di Informed Consent Form