Manual of Procedures (MOP)
Section 7. Study Intervention

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7.1 STUDY PILLS MANUFACTURER AND DISTRIBUTOR

Tishcon Corporation will prepare the study pills (vitamin D_3 [cholecalciferol] and matching placebo). Tishcon produces supplements in the form of tablets, capsules and soft-gels that meet United States Pharmacopeia (USP) standards. Tishcon Corp. has facilities in Westbury, NY (soft-gel encapsulation, research and development laboratories and quality control testing) and in Salisbury, MD (encapsulation, tableting, bottling, QC laboratory and packaging and distribution). Tishcon is registered with the U.S. Food and Drug Administration and the NY State Board of Pharmacy. Tishcon is GMP-certified by the National Products Association (NPA) as well as by NSF International.

The VA Cooperative Studies Program, Clinical Research Pharmacy Coordinating Center (CRPCC) will serve as the Drug Distribution Center (DDC) for D2d. The Center supports multi-center trails by managing drug and device related activities for worldwide trials conducted for the VA and other federal organizations (e.g. NIH). The Center is located in Albuquerque, NM, in a secure 68,000 square foot facility that is registered and inspected by the Food & Drug Administration (cGMP and GCP) and Drug Enforcement Agency.

7.2 IND REQUIREMENT

The Food and Drug Administration has confirmed that an Investigational New Drug application is not required for this study.

7.3 PREPARATION OF STUDY PILLS

Tishcon Corp. will prepare the study pills (vitamin D_3 [cholecalciferol] and matching placebo) as soft-gels according to the United States Pharmacopeia standards and Good Manufacturing Practices (GMP). The raw ingredient (vitamin D_3) is manufactured by DSM Nutritional Products, LLC (Parsippany, NJ). DSM Nutritional Products operations are ISO 9001:2000 certified and follow all relevant Good Manufacturing Practices (GMP) standards. The starting material for vitamin D_3 is cholesterol, which is derived from wool grease (lanolin) from healthy sheep in Australia and New Zealand. Cholesterol is converted to 7-dehydrocholsterol, which is then irradiated with ultraviolet light to form vitamin D_3 resin. The isolated product is purified and provided to Tishcon as liquid vitamin D_3 in corn oil.

Note: The vitamin D pill contains soybean oil, gelatin, glycerin, purified water, and corn oil. Participants who are allergic to any component of the study pill (e.g., soybean) will be excluded, as described in MOP section 6.

7.4 IDENTITY, FORMULATION AND PACKAGING OF STUDY PILLS

- Tishcon Corp. will prepare the soft-gels according to the United States Pharmacopeia standards and Good Manufacturing Practices.
- Both vitamin D and placebo soft-gels are identical looking in size, shape, texture, color, odor, and taste with the same inert ingredients. Soft-gels are clear with light yellow liquid in color in #3 oval shape with an approximate size of: 0.375 by 0.260 inches.

- Tishcon Corp. will provide study pills in bulk to the DDC four times during the trial. For each lot, there will be one vitamin D batch and one placebo batch.
- The DCC provides the study pills to the clinical sites in white plastic bottles with induction seal and a plastic cap. Each bottle will contain either 240 placebo or 240 vitamin D soft gels.
- Each study pill bottle will have a 5-digit number that will be linked to the randomization code when distributed to the participant.
- All study drug labels will include information content (vitamin D_3 or matching placebo) and storage conditions (59º to 86ºF), and the following phrase: "Caution: - Limited to Investigational Use." Lot number and expiration date will not be shown on the label (see appendix for letter explaining reasoning).

7.5 QUALITY CONTROL

Based on stability studies, Tishcon Corp. has established the expiration period for both the vitamin D and placebo pills to be 24 months, at the required storage conditions. The following factors are important in defining stability: no signs of deterioration or degradation in physical appearance and potency of active ingredients continuing to fulfill product specifications.

Storage requirement for soft-gels is room temperature (range, 59º to 86ºF). Participants will be instructed not to store or leave their study medications in hot environment (e.g. inside a car in the summer) or cold environment (e.g. in refrigerators or freezers).

For each manufacturing lot, Tishcon Corp. provides the D2d Coordinating Center and DDC a Certificate of Analysis that includes the following: identification information, product name and batch number, appearance, content of active ingredient (i.e., vitamin D as cholecalciferol [D_3]), microbiology testing and heavy metal testing (see vitamin D specification in Appendix).

The DDC will conduct release testing for each Lot of study pills, which will include: appearance, identification and potency of the active ingredient. Detailed testing will be performed on the first lot as follows:

- Assaying for the potency of vitamin D in the vitamin D (active) pill at time 0, 3, 6, 12, 18 and 24 months.
- Assaying for the potency of vitamin D in the placebo pill at time 0.

Testing will be performed on each of the subsequent received lots as follows:

- Assaying for the potency of vitamin D in the vitamin D (active) pills at time 0, 12 and 24 months.
- Assaying for the potency of vitamin D in the placebo at time 0.

Reports of all testing by Tishcon Corp. and DDC will be provided to the D2d Coordinating Center for review. If the results of the DDC's initial analytic testing do not meet the product requirements, the product will be returned to Tishcon Corp. and replacement product will be provided.

The DDC will monitor the expiration date of all study pills and will notify the sites to destroy expiring medication (see letter in Appendix).

7.6 STUDY PILL SUPPLY CHAIN, SITE INVENTORY

The DDC will develop, host, manage and utilize a user-friendly intuitive Interactive Web-based Response System (the Study Pill Inventory and Randomization System [SPIRS]) for randomization, assignment of study bottles to participants (at randomization and subsequent visits), and inventory management.

Sites will receive ambient shipments of the study drug over the course of the study, approximately every 6 months. The frequency of shipments will be determined based on rates of recruitment and retention, which will be reflected in the site inventory that will be actively monitored by the DDC. Shipments will be coordinated as much as possible (e.g. all sites that are due will get a shipment at the same time). Each shipment will include both active and placebo study pills. Each shipment will contain multiple kit boxes, with each kit box containing 30 study pill bottles. The local procedures at each research pharmacy for receipt, storage and distribution of study drug will be followed. Please see appendices for examples of shipment labels.

During the study, each participant will be dispensed a new bottle every 6 months with enough pills for the next 6 months plus enough additional pills in case participants need to postpone their follow-up visit for up to 8 weeks. At each 6-month visit, the site Research Coordinator or designee will use SPIRS to request a new masked bottle for the participant by entering the participant enrollment ID in SPIRS. The system will select a bottle number from the site's inventory that will be appropriate to that participant's treatment arm using the randomization assignment for that participant. Bottles will also have a barcode with the bottle number embedded to allow the use of a scanner at the sites, if available. A pharmacist at the DDC is on-call 24/7, in the event the site study physician in consultation with the D2d Coordinating Center determines that a participant needs to be unmasked (see section 7.10).

7.7 RANDOMIZATION, DISPENSING AND ADMINISTRATION OF STUDY PILLS

7.7.1 Randomization

- Prior to the randomization visit, the site principal or co-investigator must review the inclusion and exclusion criteria and confirm the participant meets the study eligibility criteria. The investigator documents this in EDC by signing the Screening and Baseline Inclusion/Exclusion Criteria forms (see MOP section 15.6.7).
- At randomization visit, the Research Coordinator or designee will review the inclusion and exclusion criteria confirming the participant meets the study eligibility criteria prior to logging into SPIRS.
- At randomization visit, the Research Coordinator or designee will use the SPIRS to randomize the participant (enter stratification variables etc.).
- The SPIRS will assign the participant a bottle number.
- The bottle number assignment should be printed and used as source documentation.
- The assigned bottle number will be provided to the site pharmacist (or designee) and the bottle will be removed from the storage area and dispensed to the participant.
- The pharmacist will indicate in SPIRS that the bottle was removed from the storage area.

- Prior to dispensing the bottle to participant, the Research Coordinator (or designee) and a second person should each check that the number on the bottle number in hand matches what was assigned by the SPIRS system for the specific participant.

Participants will be dispensed a bottle with enough pills for 6 months plus 8 more weeks in case they need to postpone their visit.

7.7.2 Dispensing of study pills

The first study pill dose should be taken during the randomization visit.

The following instructions should be verbally reviewed with the participant each time study pills are dispensed.

- Take one study pill a day with breakfast.
- If you forget to take the pill with breakfast, take it anytime during the same day.
- If you forget to take a pill, please write it down and report it to the Research Coordinator at the next visit. Sites may provide a pill calendar, if they wish.
- Please bring your pill bottle, with all remaining pills, with you to the next visit.

Importantly, the participant should be provided with the *Information for Participant* pamphlet at each visit (see MOP section 17).

Participants should be encouraged to call the study site if they:

- Are told they have diabetes.
- Are prescribed new medications or supplements (they should call before starting the medicines).
- Experience new medical problems.
- Need to reschedule their next appointment.
- Have any questions.

After dispensing the study pill bottle to the participant it must be recorded as dispensed in the SPIRS system. Refer to the SPIRS User Guide for instructions (Appendix 5).

7.8 ASSESSMENT OF ADHERENCE

At each 6-month visit, participants will return the pill bottle with remaining pills from the prior 6 months. During the visit, the remaining pills will be counted and the number entered into the EDC system. The EDC system will calculate adherence by pill count. If adherence is less than 80%, the Research Coordinator should discuss this with the participant and try to determine the cause of the non-adherence and strategize with the participant to develop solutions.

In the event that a participant returns their study pills in a state that makes it impossible to separate and count them (e.g. if they melt together due to excessive heat or other improper storage), the bottle must still be obtained so that the number of remaining pills can be estimated based on the weight. Please contact the Coordinating Center for instructions on the specific procedures to follow.

If a new study pill bottle is dispensed to a participant between their regular 6-month visits for any reason (e.g. they lost the initial bottle), adherence is evaluated to the extent possible up to the time of replacement in the Unscheduled-Confirmatory visit form, which documents dispensing the new bottle. The following 6-month visit will document adherence from the time of replacement only and is done in the usual way.

7.9 MODIFICATION OF STUDY PILL REGIMEN

Modifications to the study pill dosage or frequency regime are *not* permitted, except in exceptional circumstances (see MOP 19, section 19.7). Study pills may be temporarily held or permanently discontinued.

7.9.1 Permanent discontinuation of study pills

❖ MOP section 7.9.1 is identical to DSMP section 5.3.1

Study participants will *permanently* discontinue the study pills without unmasking (see below) for the following reasons:

- Safety concerns, as follows:
    - Specific adverse events whose relatedness to study pills is considered to be either "probable" or "definite," as follows:
        - Hypercalcemia, as defined previously.
        - Low GFR, as defined previously.
        - High urine calcium:creatinine ratio, as defined previously.
        - Nephrolithiasis diagnosed by either the site study physician or another physician based on clinical, radiologic findings or both.
    - Other adverse event whose relatedness to study pills is considered to be either "probable" or "definite" and may put participant at risk by continuing the study pills.
    - Any other adverse event that, at the discretion of the site study physician, necessitates discontinuation of study pills.
- Participant request. If a participant requests discontinuation of study medication at any point for any other reason.

⇒ *Permanent discontinuation of study medication will be managed without unmasking (see below).*

⇒ Participants who permanently discontinue study pills will not go "off study" and will remain in the study and return for all remaining scheduled follow-up visits and procedures, consistent with the intention-to-treat principle.

⇒ Participants should be informed that their continued participation is very important.

⇒ Participants who discontinue study pills for their own reasons (i.e. NOT due to a safety concern or adverse event where discontinuation is required by the protocol) may restart study pills at a later time in the study. Prior to restarting study pills, D2d safety laboratory assessments (serum

calcium, serum creatinine for GFR, and urine calcium creatinine ratio) must be done and results within study parameters (see MOP 14).

7.9.2 Temporary discontinuation (hold) of study pills

❖ MOP section 7.9.2 is identical to DSMP section 5.3.2

Study pills may be temporarily held due to an adverse event that is unrelated to the study (e.g. vomiting associated with gastroenteritis) or a planned medical procedure or for other reasons. The reason for holding study pills, and stop and restart dates will be recorded in the participant source documents and EDC. In EDC, this is documented in the study pill distribution form at the next 6-month visit. There is no maximum amount of time that a participant can be off study pills.

During pregnancy and lactation, women will stop study pills and abstain from all study procedures, but they will not go "off study" (i.e., they will be "inactive"), as follows:

- Upon pregnancy, study pills are held, and assessments cease (other than adverse events).
- Eight weeks after pregnancy, regular assessments (e.g., glycemic and safety testing) are re-started.
- After cessation of lactation, study pills are re-started.

⇒ *Temporary holds of study medication will be managed <u>without unmasking</u> (see below).*

7.10 UNMASKING

7.10.1 Unmasking treatment assignment

❖ MOP section 7.10.1 is identical to DSMP section 5.3.3

At no time will the treatment assignment be revealed without the expressed knowledge of the site PI (or in extenuating circumstances the site co-investigator) and the Coordinating Center.

Unmasking will only occur if there is a serious adverse event (SAE) or any other adverse event (AE) whose relatedness to the study pills is "probable" or "definite," ***<u>and</u>*** the site PI (and site study physician, if site PI and physician are not the same person) determines *it is necessary for the care of the participant to be unmasked. It is expected that almost all AEs will be handled without unmasking.*

As outlined above, there are *specific adverse events when the study pills must be permanently discontinued*. Evaluation and management of these adverse events does <u>not</u> require unmasking.

If it is determined that unmasking needs to occur to appropriately care for the participant, then study pills will be held and the assignment will be disclosed only to research personnel that need to know, e.g., site PI, site study physician or both.

If after unmasking, it is subsequently determined the relatedness of the AE to study pills is "unrelated," and continuation of study pills poses no risk to the participant, then study pills can be re-started.

It is expected that unmasking will be exceedingly rare as it will be restricted to situations in which knowing the assignment will change the course of the care of the participant. When unmasking occurs, the site PI will review and report to the CC and IRB the circumstances that led to it.

7.10.2 Unmasking procedure

The following process will be implemented in the event of a request for "unmasking" of a study participant:

1. To ensure that unmasking occurs only when absolutely necessary to provide appropriate care, each case will be discussed with the D2d Principal Investigator or Project Manager. However, the site investigator will make the final decision on whether unmasking shall occur.

2. The site investigator who determines that a study participant needs to be "unmasked" will call the Coordinating Center at (617) 636-d2d2 (3232) (after hours instructions will be available on the message).

3. Prior to the unmasking of study pill assignment for safety reasons, administration of study pills must be held.

4. If after contacting the CC, it is determined that participant unmasking is necessary, the D2d study Principal Investigator or Project Manager will contact the DDC and provide the following information:

    - Study name: D2d study
    - Name of the caller and his/her role in the study
    - Name and contact information of the site PI or treating physician the DDC should contact
    - Site number
    - Participant enrollment ID number
    - Date and time the participant was instructed to hold study pills.

5. The DDC pharmacist will access the participant's treatment assignment in SPIRS and will provide the treatment assignment to the site PI or treating physician. Treatment assignment should only be disclosed to research personnel who need to know to care for the participant.

6. The site will document the following related to the unmasking in the participant's source documents:
    a. Circumstances leading up to the need to unmask, including the treatment decisions that necessitated unmasking.
    b. Date of study pills held.
    c. Contact with the CC (date, time, personnel involved, information discussed)
    d. Contact with the DDC (date, time, personnel involved, information discussed)

7. The site will document on the AE form in EDC that the unmasking occurred on the AE form by answering "Yes" to the following question, and entering the date of unmasking.
    Did the event lead to unmasking of the study pill assignment?

8. The DDC pharmacist, within 12 hours of the unmasking, will send a confirmatory e-mail to the CC Project Manager stating that an unmasking occurred, the date/time of the unmasking, and enrollment ID. The treatment assignment will not be shared with the CC.

9. The participant will remain in the study and return for all remaining follow-up visits.

10. If after unmasking, it is subsequently determined that the relatedness of the AE to study pills is "unrelated," then study pills can be re-started.

7.11 APPENDICES

Appendix 1 Study pills expiration dating

Appendix 2 Study pill specification

Appendix 3 Study pill bottle label

Appendix 4 Study pill kit box label

Appendix 5 Study pill inventory and randomization system user guide