Appendix L. Study Summary

Once determined eligible based on results derived from participation in the Natural History/Pathway to Prevention Study, participants will be scheduled for an initial Oral Insulin Study Visit. During the initial visit, participants will give written informed consent for the Oral Insulin Trial and complete the volunteer understanding assessment. At this time an intravenous glucose tolerance test (IVGTT) will be performed to determine the study stratum for the participant (additional samples are also collected during the initial visit. Please refer to the schedule of assessments above). However, eligibility is not dependent on the results of the IVGTT. A second IVGTT will be performed if the first phase insulin response (FPIR) of the initial test falls below a predetermined threshold. This is done to confirm below threshold results. If the FPIR is above threshold on the first test, a second test is not necessary, and the participant can be randomized when the above-threshold results are known. If the FPIR is above threshold on the second test, the participant is considered to be above threshold. Participants should be randomized after the second IVGTT (can be same day) so that randomization occurs as close to the initial treatment dose as possible.

Participants are randomized to either the oral insulin or placebo control group. Treatment assignment is double-blinded to the site and the participant. Following randomization, a subject's results will be blinded unless they indicate diabetes onset (OGTT clinical alert).

Study drug (oral insulin or placebo) is dispensed at the baseline visit and participants are scheduled for the first follow-up study visit 3 months after randomization. At the 3-month follow-up visit, study drug compliance is assessed and participants are scheduled for a 6-month follow-up study visit. Participants are then scheduled for visits every 6 months for the duration of the protocol or until the onset of T1DM.

Between each 6 month visit, participants are contacted once by phone to determine any changes in diabetes status, compliance and adverse events.