Talking Points about the Use of Diabetes Medications (e.g., metformin) in D2d

General information

Currently, the FDA approved indication for Metformin is for treatment of type 2 diabetes. Metformin is the first option for treatment of type 2 diabetes. There are data (DPP study) that metformin delays the progression of diabetes in people at high risk for diabetes (pre-diabetes). Use of metformin for prevention of diabetes is uncommon (less than 5% of people with pre-diabetes are prescribed metformin) because there is considerable disagreement among clinicians as to whether medications should be used to prevent diabetes. However, with increased awareness of pre-diabetes, use of metformin is becoming more common.

Why should diabetes medications (e.g., metformin) not be used in D2d participants prior to the diagnosis of diabetes?

The primary outcome of D2d is development of diabetes; therefore, it is critical that medications that interfere with development of diabetes (e.g., metformin) are not used for prevention of diabetes (pre-diabetes).

Physicians would most likely prescribe metformin for their patients whose glycemia numbers are rising and are at the highest risk of developing diabetes. If these participants are placed on metformin, their glucose numbers improve and it would be exceedingly unlikely to meet diabetes criteria per D2d.

Importantly, if vitamin D works as hypothesized, then more participants on placebo will be put on metformin (since their glycemic results are worsening faster), reducing their diabetes risk during follow-up, thereby preventing detection of a risk difference between D and placebo. The net result is that D2d will not realize the necessary number of outcomes to test the primary hypothesis.

What should the site do if a participant reports that her doctor wants to prescribe metformin (for pre-diabetes or diabetes) and has not started taking metformin yet?

1. Congratulate the participant for following the protocol and for calling you to inform you.
2. Ask participant to stay off metformin and inform her that the study physician will get in touch with her PCP to have a discussion about metformin.
3. As soon as possible, the study physician will contact the PCP to discuss the case (including review of laboratory tests) and assess the intent of the PCP in relation to metformin use. This is very important and is included in the approved version 1.8 of the protocol.
    a. If the PCP agrees to withhold use of metformin and not initiate pharmacotherapy for pre-diabetes or other diagnoses (e.g., metabolic syndrome, diabetes) and allow follow-up for diabetes progression within D2d (i.e., by glycemic testing analyzed by the Central Lab), Unscheduled Confirmatory (UNCO) testing will be done. The participant will also need to be in agreement with this plan.
    b. If the PCP (or participant) is determined to start metformin regardless of the results of D2d-specific glycemic testing, UNCO is not done and the diagnosis of diabetes or indication for starting a medication will be adjudicated.
4. Regardless of 3a or 3b, the participant will continue on the assigned D2d treatment and be followed for incident diabetes.

When should I speak to participants about the use of diabetes medications, e.g., Metformin?

Investing early pays off. The conversation should start during the consent process. Avoiding the use of metformin (and other diabetes medications) for pre-diabetes and immediately notifying the site if a diabetes medication is prescribed are critical aspects of the consent discussion. The person conducting the consent

process should ask questions to garner the participants understanding of the study, their expectations, their willingness to comply with study procedures, and their willingness to permit the study staff to share information with their doctors. It is also absolutely essential to confirm that the participant understands the importance of contacting the study site prior to starting any diabetes medication (for diabetes, pre-diabetes or other indication). The participant brochure (MOP 17, appendix 1), which includes a list of diabetes medications, should be provided and reviewed.

Ideally, prior to randomization, PCPs will be informed that the participant is eligible for D2d and the study discourages use of metformin unless diabetes is diagnosed by D2d (see MOP 17, appendix 3a). If time does not allow notification prior to randomization, the PCP should be notified as soon as possible after randomization that the participant has enrolled in the D2d study (MOP 17, appendix 3b) with an explanation of the main purpose of the D2d study and why starting diabetes medications prior to the in-study diagnosis of diabetes jeopardizes the study.

At every visit, including the scheduled contact (M09, M15 etc.) between visits, these concepts should be reinforced with the participant. A new copy of the participant brochure (MOP 17, appendix 1) should be provided and reviewed at every visit.

After each visit, a letter should be sent to the participant and the PCP informing them of study results (diabetes or no diabetes), including information about use of metformin. See MOP 17 for templates.

The CC has updated the letter and communication tools to emphasize the importance of this issue.

Is there a proposed way to discuss this issue during the consent and at every visit?

There are 3 scenarios in relation to starting a diabetes medication during D2d.

1. You are diagnosed with diabetes through study testing. In this case, we provide the actual test results to you and your doctor. It is up to you and your doctor to decide whether treatment with a diabetes medication is needed. Depending on the severity of diabetes, treatment with medication may not be needed.
2. Your doctor makes the diagnosis of diabetes between scheduled D2d visits. In this case, **you need to let us know right away (call or email) before you start taking a diabetes medication**. The study doctor will talk to your doctor to find out whether your doctor plans to start a diabetes medication. Depending on what your doctor has decided, **we may ask you to come to clinic to do testing for diabetes according to study procedures before you start any medication.**
3. You have not been diagnosed with diabetes but your doctor prescribes a diabetes medication for prevention of diabetes or for weight loss. Use of a medication for prevention of diabetes is uncommon (less than 5% of people with pre-diabetes are prescribed medications) because there is a lot of disagreement among doctors as to whether medications should be used to prevent diabetes. In relation to D2d, starting a medication for pre-diabetes interferes with the study because it prevents us from finding out whether taking vitamin D can prevent diabetes. It essentially 'muddies' the waters – does that make sense? So essentially we are asking if you feel comfortable holding off on taking any diabetes medications until you are diagnosed with diabetes during the study, which uses the American Diabetes Association criteria for diabetes?