DIAgnosing GDM usiNg Oral Sugar InStead (DIAGNOSIS)

Randomized crossover study comparing the standard glucose beverage and Dex4® tablets for 2 hour oral glucose tolerance testing in pregnant women with a positive screen on the 50g glucose tolerance challenge for gestational diabetes

Protocol Number: *REB 418-2018*

Principal Investigator: *Dr. Baiju Shah*

Regulatory Sponsor: Sunnybrook Research Institute
Funding Agency: Sunnybrook AFP Innovation Fund
Investigational Product: *Dextrose monohydrate tablets (Dex4®)*

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SPONSOR STATEMENT OF COMPLIANCE

This study will comply with the International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Participants, as well as applicable regulatory and institutional requirements.

Personnel listed below are authorized to sign the protocol and any subsequent protocol amendments on behalf of the sponsor:

Name:
(Print) _____

Title:
(Print) _____

Signature: _____

Date of Approval:
(yyyy-mmm-dd) _____

PROTOCOL SIGNATURE PAGE

I have read this protocol in its entirety l and its appendices. I agree to comply with the requirements of the study protocol and procedures for data recording/reporting and acknowledge my responsibility for the well-being of each research participant, and to ensure that all persons involved in study activities are adequately informed about the protocol, the investigational product, and their trial-related duties. The signature below constitutes the agreement to conduct this study in accordance with the REB approved protocol, GCP and applicable regulatory requirements, including confidentiality, ethical guidelines and regulations regarding the conduct of research in humans.

Qualified Investigator:

Name:
(Print) _____

Title & Institution:
(Print) _____

Signature: _____

Date of signature:
(yyyy-mmm-dd) _____

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LIST OF ABBREVIATIONS

The following abbreviations describe terms, documents and study personnel used in the conduct of this study protocol.

AE	Adverse Event/Adverse Experience
CC	Coordinating Centre
CIOMS	Council for international Organizations of Medical Sciences
CRF	Case Report Form
CCTS	Centre for Clinical Trial Support
EC	Ethics Committee
ICH	International Conference on Harmonisation
IP	Investigational Product
pCRF	Paper Case Report Form
GCP	Good Clinical Practice
ICF	Informed Consent Form
PHI	Personal Health Information
PI	Principal Investigator
PM	Product Monograph
QI	Qualified Investigator
REB	Research Ethics Board
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
SRI	Sunnybrook Research Institute
SUADR	Serious and Unexpected Adverse Drug Reaction
TMF	Trial Master File

PROTOCOL SUMMARY

Protocol Title (Short Title)	DIAgnosing GDM usiNg Oral Sugar InStead (DIAGNOSIS) Randomized crossover study comparing the standard glucose beverage and Dex4® tablets for 2 hour oral glucose tolerance testing in pregnant women with a positive screen on the 50g glucose tolerance challenge for gestational diabetes
Protocol Number	Assigned REB number 418-2018.
Phase	II
Study Design	Phase II randomized controlled crossover study
Study Duration	6 months
Setting	Single-centre
Sample Size	28 required by power calculation, aiming to recruit 42 (accounting for 33% loss)
Main Inclusion Criteria	• Positive 50g GCT result between 7.8-11.0 mmol/L • singleton pregnancy
Primary Outcome(s):	2 hour serum glucose value after the carbohydrate challenge. The study is powered to assess equivalence between Dex4® tablets and 75g of glucose beverage.
Secondary Outcome(s):	Side effects associated with Dex4® tablets and participant preference of using Dex4® tablets or the standard glucose beverage for OGTT testing.
Investigational Product (IP) and Planned Use	The investigational product to be used is (Dex4®) dextrose monohydrate tablets, containing 4g of dextrose monohydrate per tablet equivalent to 3.64g of dextrose anhydrous. After a minimum 8 hour fast, 21 Dex4® tablets will be ingested over the span of 5 minutes. Venous blood sampling for serum glucose will be taken prior to ingestion , and 1 and 2 hours (+/- 15 minutes) after ingesting the Dex4® tablets.
Statistical Analysis:	To evaluate equivalence, the mean of the differences at each time point (fasting, 1 hr and 2 hrs after glucose beverage/Dex4® tablets) will be calculated and a two-sample equivalence-test will be used to compare the means. Based on previous reports of intra-individual variation in 2 hour OGTT of 16.7% for serum glucose measurement (21), Dex4® tablets will be considered equivalent to glucose beverage if the equivalence margin is less than or equal to 20%.

1 KEY ROLES AND CONTACT INFORMATION

Regulatory Sponsor:	Sunnybrook Research Institute (SRI) 2075 Bayview Avenue, Room H1 45 Toronto, ON Canada M4N 3M5
Principal Investigator:	Dr. Baiju Shah
Academic Research Organization:	Centre for Clinical Trial Support, SRI 2075 Bayview Avenue Toronto, ON Canada M4N 3M5
Qualified Investigators/Institutions:	Dr. Baiju Shah Sunnybrook Health Sciences Centre 2075 Bayview Avenue, Room H1 45 Toronto, ON Canada M4N 3M5
Clinical laboratory/Departments	*Sunnybrook Biochemistry Lab* *2075 Bayview Ave., Rm CG-68A*

2 INTRODUCTION

This study document is the protocol for research involving human participants. This study is to be conducted according to Canadian and international standards, and in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice E6 (ICH-GCP), World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Participants, as well as applicable regulatory and institutional requirements and research policies.

2.1 Background

Gestational diabetes mellitus (GDM) is defined as any degree of hyperglycemia with onset or first recognition during pregnancy (5-6). Up to 70% of women with GDM will develop type 2 diabetes mellitus (T2DM) during their lifetime (3). Diabetes Canada and the Society of Obstetricians and Gynecologists of Canada recommend that pregnant women be screened for GDM between 24-28 weeks of pregnancy (7,8). The current 2-step approach for GDM detection involves a screening test and a diagnostic test, both of which use a liquid glucose challenge. In Canada, most pregnant women routinely undergo screening for GDM by consuming 50g of a liquid glucose solution and having a blood test for serum glucose after 1 hr, this test is commonly known as the 50g glucose challenge test (50g GCT). Women with a positive screening test (serum glucose 7.9 to 11.0 mmol/L) take a second test to confirm the diagnosis. For the second test, called a 2 hour oral glucose tolerance test (OGTT), women fast for 8 hours and then consume 75g of glucose beverage, and serum glucose levels are taken at fasting, 1 and 2 hours after drinking the glucose beverage. The 75g OGTT is the gold standard and is performed for GDM diagnosis.

Unfortunately, up to 30% of women do not tolerate glucose beverage (9-11). Side effects include: nausea, vomiting, bloating, abdominal pain, diarrhea, sweating and headache which may prevent them from completing testing for GDM (9-11). If women cannot complete screening, the diagnosis of GDM may be missed, increasing the risk of complications for mothers and their babies, such as a larger baby and trauma during delivery. Women who have had a history of GDM are at higher risk of developing cardiometabolic complications such as lipid abnormalities, hypertension and hyperinsulinemia (5, 15). GDM also carries a risk for later development of T2DM to the mother and fetus (2, 3). Unfortunately, GDM prevalence has doubled in the past 10 years in all ethnic populations and reaches 25-32% in some (16-19), with an estimated 19% of cases proceeding on to become T2DM within the first 9 years after pregnancy (2). Because of T2DM's long asymptomatic phase, many women will have already developed health complications by the time they are diagnosed. A missed diagnosis of GDM is a missed opportunity to intervene and offer prevention for T2DM.

Other alternatives to the standard glucose beverage such as jelly beans and candy twists (Twizzlers) have been suggested in the literature but are limited by their diagnostic accuracy and portion size, respectively (13). However, Dex4® tablets may not have this issue. As Dex4® tablets are normally used to correct hypoglycemia in people living with diabetes, portion sizes

are manufactured to be more precise compared to most candies, and lots are regularly analyzed to confirm tablet size, hardness, and dextrose monohydrate content.

The purpose of this study is to compare the positive and negative effects of Dex4® tablets, as an alternative form of fast acting carbohydrate, compared to the current standard diagnostic test, glucose beverage. We hypothesis that because of their availability in solid, chewable form, variety of flavours and lack of carbonation, Dex4® tablets may result in fewer side effects than glucose beverage and provide an equivalent carbohydrate challenge for diagnosis gestational diabetes.

2.2 Clinical Data to Date

There have been previous studies using glucose beverage alternatives including jelly beans and candy twists, with improved tolerance (fewer side effects of nausea, vomiting, bloating, diarrhea, sweating, headache) as reported by the patients. In a study using jelly beans for 50g 1-hr glucose challenge testing, side effects were reported in 38% of participants and 20% with jelly beans (P <.001), and were preferred by 76% of participants (P <.001).

However, previously used candy alternatives are limited by the varying portion size of conventional candy and have poor diagnostic accuracy.

Recently the makers of the standard glucose beverage used at our institution Jamp pharmaceuticals, issued a recall on a large number of their glucose beverage lots as they were not in compliance with the Health Canada standard that the actual glucose content of the drink is within 10% of the labeled glucose content (16). The supplier of glucose beverages for our institution has changed to Teva Pharmaceuticals as of June 1 2019. Dex4® regularly tests their lots and individual tablets to confirm consistency and accuracy of tablet size, hardness, and dextrose monohydrate content, and has agreed to provide a certificate of analysis for each lot of Dex4® tablets used in the trial (15).

2.3 Potential Risks/Benefits and Rationale

The participant population consists of 28 pregnant women between 24-32 weeks' gestation who have screened positive for gestational diabetes on the 50g glucose challenge test. The main drawback to participation is that women will have to undergo two fasting, 1 hour and 2 hour glucose values within one week. Risks involved with participating in the study include: possibility of pain, bruising, swelling or infection related to drawing blood, allergic reaction symptoms such as itching, facial swelling and anaphylaxis upon consumption if the participant has an allergy to corn based products such as dextrose. These risks will be minimized by screening patients for dextrose allergy before having them sign the informed consent form.

The benefit may not be directly to the patient as they will still need to complete the standard 75g glucose beverage test but they will be contributing to new knowledge on alternatives to the standard test that may benefit other pregnant women, including themselves, in the future.

The ultimate goal of this project is to improve women's health by 1) allowing more women to be screened for GDM and 2) providing an equivalent glucose beverage alternative with fewer side effects, making the screening process more comfortable for patients who cannot tolerate

glucose beverage. Improving the tolerability of the test is important because there is growing evidence that GDM significantly increases the risk of short and long term adverse consequences for both the fetus and the mother (10,11). Accurate diagnosis may allow women to implement preventative measures such as healthy lifestyle, which has shown to be effective in preventing T2DM in women with previous GDM (19,20). There have been recent quality control issues with the commercially available glucose beverage product (16), so this alternative test could become the standard test if the dose calibration is found to be more reliable.

3 STUDY OBJECTIVES

3.1 Primary Objective

Primary objective 1 (PO-1): to determine if Dex4® tablets is equivalent to glucose beverage for use in the 2-hr 75g OGTT in pregnant women between 24-32 weeks gestation who have screened positive for GDM.

3.2 Secondary Objective(s)

Secondary objective (SO-1): to determine if women have fewer side effects and prefer the standard (glucose beverage) OGTT test or the alternative (Dex4® tablets) OGTT test

4 STUDY DESIGN

4.1 General Design

Our project is a population-based, prospective randomized crossover study. Women who fall into the screen positive group of the 50g GCT (1 hour serum glucose of 7.8-11 mmol/L) will be offered participation in the study. 28 Participants will be recruited and will be randomly assigned using a pre-populated allocation table to take either the standard OGTT test (75g of glucose beverage) first or the alternative OGTT test (21 Dex4® tablets) first. The first test will be referred to as OGTT-1 and the second test will be referred to as OGTT-2. After completing OGTT-1 at the first test appointment, a questionnaire about pregnancy, health, diet and exercise habits, and side effects from the first test will be completed by the participant (Questionnaire A). After completing OGTT-2 at their second test appointment, a questionnaire about side effects from the second test and test preference will be completed by the participant (Questionnaire B). Each woman will complete both tests within one week and each subject will serve as their own control. Results will be kept blinded in the case report forms until both OGTT tests are done. Serum glucose will be measured using the same internationally standardised glucose-oxidase method (RocheDiagnosis) in the Sunnybrook Biochemistry lab. After serum glucose measurement, all results will be sent to the research team but only the standard of care glucose beverage test data will appear in electronic (or classical) medical records and be used for GDM diagnosis.

The following data will be collected by questionnaire at the first OGTT appointment:

- Estimated date of delivery
- # of previous pregnancies
- Previous diagnosis of GDM
- Pre-pregnancy weight (kg);
- Height (cm);
- Ethnic group (Caucasian, Indigenous, Hispanic, South Asian, East Asian, African, Middle Eastern, Other)
- History of macrosomic infant - ≥ 4000 g
- Polycystic ovary syndrome (yes-no);
- Medication (for corticosteroid use);
- First degree family history of T2DM
- Length of fast (hrs)
- Side effects (nausea, vomiting, headache, dizziness, sweating, other)

The following data will be collected by questionnaire at the second OGTT appointment:

- Side effects
- Preference for Dex4® or glucose beverage

4.2 Primary Outcomes/Endpoint(s)

The primary outcome measures are fasting 1hr and 2hr PG levels from the Dex4® and glucose beverage OGTTs. Serum glucose values after a carbohydrate load have significant intra-individual variation, if done on the same person but at a different time the results can vary up to 16.7% (21) The two tests will be considered equivalent if the difference between them is less than or equal to 20%.

4.3 Secondary Outcomes/Endpoint(s)

The secondary outcome measures are side effects associated with Dex4® tablets and participant preference of using Dex4® tablets or the standard glucose beverage for OGTT testing.

5 PARTICIPANT SELECTION AND WITHDRAWAL

This is a study of diagnostic test validity in pregnant women, so this vulnerable population is the only population that can be studied. Women will be offered enrollment if they fall into the screen positive group after a 50g GCT. Only singleton pregnancies will be included as twin gestations can have higher glucose values and this may impact the generalizability of the results. Women can withdraw from the study at any time, but will be encouraged to complete the standard glucose beverage test as this is the only validated test to provide a diagnosis of GDM at this time. A sample of 28 will provide 80% power at alpha of 0.05 for a test of equivalence with Dex4® tablets assuming a 20% margin of equivalence. The sample size calculation was carried out using PASS Version 12 (Hintze, J. (2014). NCSS, LLC. Kaysville, Utah.) Accounting for loss to follow up of 33%, 42 women will need to be recruited, respectively. Based on data from Alberta, 20% of women screen positive on a 50g GCT (22). Approximately 230 women deliver at Sunnybrook every month, of those 45 will screen positive on the GCT. Assuming a 20% successful recruitment rate we should be able to complete recruitment in 4-6 months. Eligibility criteria must be met by 32 weeks' gestation to allow enrollment in the study.

5.1 Inclusion Criteria

Each participant must meet all of the following inclusion criteria to participate in this study:

1. Positive 50g GCT result between 7.8-11.0 mmol/L
2. Female
3. Singleton pregnancy
4. Informed consent obtained and signed

5.2 Exclusion Criteria

All participants meeting any of the following exclusion criteria at baseline will be excluded from participation in this study:

1. Use of steroids, terbutaline, or metformin within the last 4 weeks.
2. previous diagnosis of diabetes type 1 or 2 outside of pregnancy or diagnosis with any form of diabetes prior to 20 weeks of pregnancy
3. allergy to any ingredients (including the non-medicinal ingredients) in Dex4® tablets or Glucodex solution.

5.3 Participant Recruitment

After women receive a positive 50g GCT result, they are contacted by their obstetrical provider and advised to complete a 75g OGTT. At this point they will be informed of the study and offered for the study staff to contact the patient to discuss the trial in more detail. Obstetrical offices will also have recruitment posters and brochures offering women to contact the trial team directly. If the woman agrees to participate, informed consent will be obtained prior to participation. Women will be considered enrolled in the study upon signing of the informed consent form

5.3.1 Randomization Procedures (if applicable)

Participants in this study will be randomly assigned using a pre-populated allocation table produced by the study's biostatistician to take either the standard OGTT test (75g of glucose beverage) first or the alternative OGTT test (21 Dex4® tablets) first.

5.3.2 Blinding and Unblinding Procedures (if applicable)

The study treatment is not blinded.

The results of the Dex4® OGTT will not be considered clinically relevant and will not be disclosed to the participant and the obstetrical care team. The results of the standard OGTT will be released to the obstetrical care team upon completion so that patients' standard clinical care is not delayed.

5.4 Participant Withdrawal and Discontinuation of IP

5.4.1 Reasons for Withdrawal/Discontinuation of IP

At their own discretion, participants may withdraw from the study at any time and for any reason. Study participants may also be withdrawn from the study at the discretion of the investigator for any of the following reasons:

- The investigator(s) decide(s) that continuing in this study would be harmful to the participant.
- The participant is unable or unwilling to follow the study procedures
- The pregnancy is terminated/lost

5.4.2 Data Collection and Follow-up for Withdrawn Participants

Participants withdrawing from the study will be contacted by the study research team requesting a final visit and to follow up with any unresolved adverse events. Once withdrawn from the study, no further study procedures or evaluations should be performed, or additional study data collected. However, every effort should be made to obtain permission to document the reason for withdrawal and to collect participant outcomes where possible. Any data collected prior to the withdrawal of consent may be retained and used by the sponsor.

6 INTERVENTIONS

6.1 Investigational Product

The investigational product is 4g dextrose monohydrate tablets from Dex4®. They will be used as an alternative carbohydrate source to glucose beverage in 2-hr OGTT testing in this trial.

6.1.1 Acquisition, Formulation and Packaging

6.1.1.1 Acquisition and Formulation

The investigational product will be provided free of charge from the manufacturer. Dex4® conducts testing of each lot and will provide the certificate of analysis for the lots used in the study.

6.1.1.2 Packaging

The investigational product is packaged in bottles of 50 tablets each. Participants will be provided with 21 tablets.

6.1.2 Treatment Assignment Procedures

All participants will complete both arms of the study (2-hr OGTT with glucose beverage and with Dex4® tablets).

6.1.3 Dosage, Preparation and Administration

OGTT testing with both glucose beverage and Dex4® tablets will occur once patients are enrolled. The glucose beverage is the standard of care test and may be performed in the hospital lab by trained phlebotomists. The comparator test with the Dex4® tablets will be performed by a research coordinator with phlebotomy experience or in the hospital lab, depending on availability. Both tests will occur after at least 8 hours fasting, and will require three 2 mL blood samples each, drawn via venipuncture. Results of the glucose beverage test will be recorded in Sunnycare and results of OGTT with Dex4® will faxed to the study coordinator with the associated study ID number. Serum glucose results will not be disclosed to the obstetrical care team until both OGTT tests are done. Serum glucose will be measured using the same internationally standardized glucose-oxidase method (Roche Diagnosis) in the Sunnybrook Biochemistry lab. After serum glucose measurement, all results will be sent to the research team but only the glucose beverage OGTT test data will appear in electronic (or classical) medical records.

6.1.4 Receiving, Storage, Dispensing and Return

6.1.4.1 Receipt of Investigational Product

Dex4® will ship the investigational product to the research offices in the Women and Babies department at Sunnybrook Health Sciences Centre and the Dex4® tablets will be stored at room temperature. The Dex4® tablets do not require any special handling.

Upon receipt of the investigational product and/or study supplies, an inventory will be performed and a receipt log filled out and signed by the research team member accepting the shipment. The designated study staff will count and verify that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable product in a given shipment will be documented in the study files. The study sponsor will be notified of any damaged or unusable product that was supplied to the site.

6.1.4.2 Storage and Stability

The Dex4® tablets will be stored in the bottles that they were shipped in at room temperature as per the product monograph. The investigational product will be reconciled by the research team at regular intervals, in addition to reconciliations performed during monitoring. Reconciliation will include verification of investigational product kit/device assignment, inventory and dispensing documentation.

6.1.4.3 Dispensing of Investigational Product

21 tablets will be dispensed to each participant; After the fasting blood glucose is drawn they will be instructed to consume the tablets and no more than 300ml of water within 5 min.

6.1.4.4 Return and/or Destruction of Investigational Product

At the completion of the study, there will be a final reconciliation of investigational product shipped, used, and remaining. This reconciliation will be documented. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused investigational product. Documentation of investigational product destroyed on site will be retained in the study files.

6.1.5 Participant Compliance Monitoring and Assessment

The participants will be observed taking the IP by the research staff and will not need to take the IP home or administer it on an ongoing basis. Participants who do not/are not able to take all 21 tablets or who vomit the tablets within 120 minutes will not be included in the primary outcome assessment. However, data regarding side effects will be retained for the secondary outcomes.

6.1.6 Prior and Concomitant Medications/Treatments

Participants may be on concomitant medications as appropriate to their pregnancy but these are not expected to interfere with the investigational product or standard glucose beverage.

Medications that will result in an exclusion from the study include: glucocorticoids (including betamethasone), terbutaline and metformin.

6.2 Behavioral Intervention(s) Description (if applicable)

During the time between the two OGTT tests, participants will be asked to refrain from drinking alcohol, and performing nonroutine exercise.

6.2.1 Administration of Intervention

Participants will be asked to ingest 21 Dex4® tablets and no more than 300ml of water within 5 minutes. Blood draws will be performed at fasting (before ingesting the dextrose monohydrate tablets), as well as 1 hour after (+/- 15 minutes) and 2 hours (+/- 15 minutes) after ingesting the dextrose monohydrate tablets.

7 STUDY SCHEDULE AND PROCEDURES

7.1 Screening

Women will have had to test positive on the 50g glucose challenge test, which would have already been part of their routine care.

7.2 Study visits/Follow up

Screening Appointment: Eligibility will be confirmed and participants will sign the information and consent form.

Test Visit 1: OGTT-1 will be performed. Study staff will administer Questionnaire A for visit 1

Test Visit 2: OGTT-2 will be performed within 1 week of OGTT-1 study staff will administer Questionnaire B for visit 2

7.3 Early Termination Visit

If the participant discontinues their participation in the study, the information about the participant and blood samples that were collected before they left the study may still be used. No new information will be collected (and no further testing of the blood sample will be done) without the participant's approval.

The Principal Investigator will keep any personal information about the participants in a secure and confidential location for 25 years and then destroy it according to Sunnybrook policy.

7.4 Protocol Deviations

It is the responsibility of the investigator to ensure that only investigative procedures, as outlined in this protocol are performed on study participants; the occurrence of deviations from the protocol or SOPs are limited; and compliance with the regulations is maintained. Planned deviations from the protocol must not be implemented without prior agreement from the sponsor and approval from the local REB/ethics committee (EC), as required, unless to eliminate an immediate hazard to a participant.

Planned or unplanned deviations may occur on the part of the participant, the investigator, or study research team. In resolution to a deviation, corrective/preventative actions are to be developed and implemented in a timely manner. Protocol deviations will be documented and reported as required and assessed where necessary during analysis.

8 ASSESSMENT OF SAFETY

The safety of research participants is foremost and should always be considered throughout the conduct of research.

8.1 Definitions

8.1.1 Adverse Events

An adverse event (AE) means any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment, and includes an adverse drug reaction (ADR).

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

8.1.2 Serious Adverse Events

A serious adverse event (SAE) or reaction is any untoward occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or in significant disability/incapacity,
- Is a congenital abnormality or a birth defect.

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

8.1.3 Unexpected Adverse Event

An unexpected adverse event is any AE that is not identified in nature, severity or frequency in the current Investigator’s Brochure or Product Monograph.

8.1.4 Unexpected Adverse Drug Reaction (ADR)

An ADR is an adverse reaction, the severity of which is not consistent with the applicable Investigator’s Brochure or Product Monograph. All noxious and unintended responses to a medicinal product related to any dose should be considered an ADR.

The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

The expression “causal relationship” is meant to convey that in general there are facts, evidence or arguments to suggest a reasonable causal relationship. All serious and unexpected ADRs

will have expedited reporting to regulatory agencies following ICH-GCP and local regulatory requirements.

8.2 Assessment of an Adverse Event

8.2.1 Relationship (Causality/Relatedness)

The causality assessment is the determination, according to the investigator's clinical judgment, of the existence of a reasonable possibility that the study drug (IP) caused or contributed to an adverse event.

If the investigator or delegated sub-investigator is unsure about whether or not the study drug caused or is related to the event, then the event will be handled as "related" to the study drug for reporting purposes of the trial. If the causality assessment is "unknown but not related" to the study drug, this should be clearly documented in the source documents.

8.2.2 Expectedness

Events are classified as unforeseen or unexpected if the nature, severity or frequency is not consistent with the risk information set out in the Product Monograph (PM) or label.

8.2.3 Seriousness

Events are classified as serious if associated with effects threatening the life or physiological functions of a participant. Refer to the definition for "Serious Adverse Events" in section 8.1.2.

8.2.4 Severity

The term "severe" is often used to describe the intensity (severity) of a specific event (e.g. mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on participant/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. The terms "serious" and "severe" are not synonymous. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.3 Adverse Event Recording

Investigations into potential adverse events should be done during each contact with a participant. Investigations may be done through specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded promptly in the source document, and assessed by an investigator in a timely manner allowing sufficient time to meet required reporting timelines for SAEs and SUADRs if needed. Adverse event CRFs should be completed using source documents by a delegated research team member in a timely manner/within 15 days of site awareness. All clearly related signs, symptoms, and abnormal diagnostic procedures should be recorded in the source document, though should be grouped under one diagnosis.

The following are not considered AEs and therefore do not require recording:

- Pre-existing diseases or conditions identified and recorded at screening/baseline unless, at the discretion of the investigator, the disease or condition worsens in severity or frequency

- At the discretion of the investigator, events considered likely manifestations of the underlying disease or that commonly occur in the study population independent of IP exposure

- Elective medical or surgical procedures.

8.4 Reporting of SAEs and Unanticipated Events

8.4.1 Investigator reporting: Notifying the REB

Serious adverse events and unanticipated events should be recorded and reported to the REB in accordance with local reporting requirements and timelines.

8.4.2 Investigator reporting: Notifying the Sponsor

The investigator is responsible for reporting serious adverse events and serious and unexpected adverse drug reactions (SUADRs) to the sponsor in accordance with applicable regulations and reporting requirements and timelines.

Events that are assessed to be **serious and unexpected and related or cannot be ruled out as related** to the investigational product are considered SUADRs. Reporting for SUADRs should include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. The minimum information required includes at least one identifiable participant, one identifiable reporter, one serious reaction, and one suspect product.

Additionally, a Suspect Adverse Reaction Report – CIOMS I Form must be completed by the investigator and forwarded to the Sponsor within 24 hours of site awareness. Information on other possible causes of the event, such as concomitant medications and illnesses should also be provided as soon as is made available.

8.4.3 Sponsor Reporting of SUADRs: Notifying Health Canada

The regulatory sponsor is responsible for reporting serious adverse events and SUADRs to regulatory authorities in accordance with local expedited reporting requirements and timelines. In addition, the Sponsor will complete the ADR Expedited Reporting Summary Form and submit this form in conjunction with the completed CIOMS Form to the appropriate Health Canada directorate.

8.5 Type and Duration of Follow-up for Adverse Events

AEs occurring as of the first administered dose of the investigational product and for a follow up period of 120 minutes after the last administered dose, will be collected. AEs recorded during

this period will be followed through to resolution, or until the event is assessed as chronic or stable.

8.6 Reporting and Entry Timelines

Study investigators will report SAEs to the sponsor within the following timelines:

- All deaths and immediately life-threatening events, whether related or unrelated, will be recorded and reported to the sponsor within 24 hours of site awareness.
- Serious adverse events other than death and immediately life-threatening events, regardless of relationship, will be reported to the sponsor within 72 hours of site awareness.

Adverse event information will be entered into the CRF in a timely manner and **no later than 15 days** from the time the investigator becomes aware of the event.

9 SITE MONITORING, AUDITING AND INSPECTING

9.1 Site Monitoring Plan

Site monitoring is conducted to ensure the safety of human study participants and the protection of their rights and well-being. Monitoring also verifies that collected study data is accurate, complete and verifiable by source documentation and that the study is conducted in accordance with the protocol and operating procedures.

Monitoring for this study is the responsibility of the sponsor. The delegated monitor will evaluate study processes and documentation based on the approved protocol/amendment(s), Part C, Division 5 of the Food and Drug Regulations, the International Conference on Harmonisation (ICH), E6: Good Clinical Practice guidelines (GCP) and institutional policies.

The extent and nature of monitoring is outlined in the Monitoring Plan. The monitoring plan specifies the frequency of monitoring, monitoring procedures, the level of site monitoring activities (e.g., the percentage of participant data to be reviewed), and the distribution of monitoring reports. Monitoring activities will be performed both in person and remotely. Reports of findings identified during monitoring activities will be provided to sites detailing any required actions. Documentation of monitoring activities and findings will be provided to the site study team and the study QI. The institution and/or local REB reserve the right to conduct independent audits as necessary.

The Investigator is responsible for ensuring monitors and/or quality assurance reviewers are given access to all study-related documents noted above and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and have adequate space to conduct the monitoring visit or audit.

9.2 Auditing and Inspecting

The investigator will provide direct access to source data/documents for the purposes of study-related monitoring, audits, and inspections by the REB, the sponsor, and applicable regulatory bodies. The investigator will permit the review of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.) and will ensure access to applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

10 STATISTICAL CONSIDERATIONS

10.1 Study Hypotheses

We hypothesis that Dex4® tablets will provide an equivalent carbohydrate challenge for diagnosis gestational diabetes and result in fewer side effects than glucose beverage.

10.2 Sample Size Considerations

Serum glucose values after a carbohydrate load have significant intra-individual variation, if done on the same person but at a different time the results can vary up to 16.7% (21) The two tests will be considered equivalent if the difference between them is less than or equal to 20%. For a mean one hour (+/- 15 minutes) post 75g carbohydrate load serum blood glucose of 10.6 mmol/L (standard deviation of 1.78 mmol/L) a sample of 28 will provide 80% power at alpha of 0.05 for a test of equivalence with Dex4® tablets assuming a 20% margin of equivalence. The sample size calculation was carried out using PASS Version 12 (Hintze, J. (2014). NCSS, LLC. Kaysville, Utah.) Accounting for loss to follow up of 33%, 42 women will need to be recruited, respectively. Based on data from Alberta, 20% of women screen positive on an 50g GCT (22). Approximately 230 women deliver at Sunnybrook every month, of those 45 will screen positive on the GCT. Assuming a 20% successful recruitment rate we should be able to complete recruitment in 4-6 months.

10.3 Stopping Rules

This study will be stopped prior to its completion if: (1) the intervention is associated with adverse events that call into question the safety of the intervention; (2) difficulty in study recruitment or retention will significantly impact the ability to evaluate the study endpoints; (3) any new information becomes available during the trial that necessitates stopping the trial; or (4) other situations occur that might warrant stopping the trial.

10.4 Final Analysis Plan

Serum glucose values after a carbohydrate load have significant intra-individual variation, if done on the same person but at a different time the results can vary up to 16.7% (21) The two tests will be considered equivalent if the difference between them is less than or equal to 20%. For a mean one hour post 75g carbohydrate load serum blood glucose of 10.6 mmol/L (standard deviation of 1.78 mmol/L) a sample of 28 will provide 80% power at alpha of 0.05 for a test of equivalence with Dex4® tablets assuming a 20% margin of equivalence. The sample size calculation was carried out using PASS Version 12 (Hintze, J. (2014). NCSS, LLC. Kaysville, Utah.) Accounting for loss to follow up of 33%, 42 women will need to be recruited, respectively.

To evaluate equivalence, the mean of the differences at each time point (fasting, 1 hr and 2 hrs after glucose beverage/Dex4® tablets) will be calculated and a two-sample equivalence-test will be used to compare the means. Based on previous reports of intra-individual variation in 2 hour OGTT of 16.7% for blood glucose measurement (21), Dex4® tablets will be considered equivalent to glucose beverage if the equivalence margin is less than or equal to 20%.

11 DATA HANDLING AND RECORD KEEPING

11.1 Confidentiality

Information about study participants will be kept confidential and managed according to the requirements of the Personal Health Information Protection Act of 2004 (PHIPA) and the Research Ethics Board. PHIPA outlines the rules for the collection, use and disclosure of personal health information. The Act requires each participant to consent to the collection, use and access of personal health information (PHI), unless consent is waived by the REB. Where consent is required, each participant must be informed of the following:

- What PHI will be collected during this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research participant to revoke their authorization for use of their PHI.

In the event that a participant revokes authorization to collect or use PHI, the investigator may use all information collected prior to the revocation of participant authorization. For participants that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the participant is alive) at the end of their scheduled study period.

11.2 Source Documents

Source data/documents are original documents, data and records in a clinical study that are necessary for the reconstruction and evaluation of the study. Examples of these original documents and data records include, but are not limited to:

- Worksheets
- hospital records
- medical records
- memorandum
- participants' diaries or evaluation checklists
- pharmacy dispensing records
- recorded data from automated instruments (i.e. ECGs)
- copies or transcriptions certified after verification as being accurate and complete
- participant files and records kept at the pharmacy
- entries entered directly into the printed CRF

The following data points will be recorded directly on the CRFs, and will be considered source data as no prior written or electronic record of data may be available:
The following data will be collected by questionnaire at the first OGTT appointment:

- Previous diagnosis of GDM
- Pre-pregnancy weight (kg);
- Height (cm);
- Ethnic group (Caucasian, Indigenous, Hispanic, South Asian, East Asian, African, Middle Eastern, Other)
- History of macrosomic infant - ≥ 4000 g
- Polycystic ovary syndrome (yes-no);
- First degree family history of T2DM
- Length of fast (hrs)
- Side effects (nausea, vomiting, headache, dizziness, sweating, other)

The following data will be collected by questionnaire at the second OGTT appointment:

- Side effects(nausea, vomiting, headache, dizziness, sweating, other)
- Preference for Dex4® or glucose beverage

Each participating site will maintain appropriate medical and research records for this study, in addition to regulatory and institutional requirements for the protection of confidentiality of participants. If electronic source data is printed it should be signed and dated by the investigator to confirm content and filed with other source documents.

11.3 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study personnel under the supervision of the investigator. All source documents and applicable laboratory reports should be reviewed as needed and used to ensure that data collected for the purposes of the study are accurate and complete. Contemporaneous review of laboratory results and the assessment of clinical significance for those results considered out of range should be documented by means of dated signature by the reviewing investigator. Study personnel, including data entry team members, should use source documents to complete case report forms (CRFs).

As part of the safety plan for this study, the investigator will review individual study participant records to ensure that appropriate mechanisms to protect the safety of study participants are being followed, that protocol requirements are being adhered to, and that data is accurate, complete, and secure. Participant records include, but are not limited to: consent forms, case report forms, data forms, laboratory specimen records, inclusion/exclusion forms, and medical charts. All study data will be collected by a member of the study research team and recorded in accordance with applicable procedures.

11.4 Data Capture

11.4.1 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. Paper case report forms (pCRFs) will be used to collect data for this study. CRFs are to be completed by data capture personnel and signed off by the investigator in a timely manner. Good documentation practices should be implemented according to standard operating procedures. All data requested on the CRF must be recorded and verifiable by source document.

11.5 Records Retention

The Principal Investigator will keep any personal information about the participants in a secure and confidential location for 10 years and then destroy it according to Sunnybrook policy. It is the responsibility of the REB, investigator and regulatory sponsor to retain study essential documents as per local regulatory requirements and GCP Guidelines.

Study essential documents must be maintained in a secure and confidential manner for participating Canadian sites for a period of 25 years. For the purposes of this study, the start date of the retention period is the date of the final report of the trial. Exceptions may be made for sites which close prematurely, wherein the start date for the retention period will be the date of notification to Health Canada of the sites closure. Sites conducting this study outside of Canada must maintain study records for the required retention period as stipulated by local regulatory authorities. All study records are then to be destroyed according to local and national policy and requirements. It is the investigator's responsibility to request authorization for destruction at the completion of the retention period and/or for the sponsor to inform the investigator/institution when these documents may be destroyed.

11.6 Clinical Trial Registration

In accordance with Health Canada's Notice "Registration and Disclosure of Clinical Trial Information, November 30, 2007", the sponsor will be responsible for registering the study on Clinicaltrials.gov (*www.clinicaltrials.gov*) , a publicly available registry that conforms to international standards for registries.

12 QUALITY CONTROL AND QUALITY ASSURANCE

As per ICH-GCP and local regulations, the sponsor is responsible for ensuring the implementation and maintenance of systems that support quality assurance and quality control.

The study must be conducted in compliance with the study protocol and all data collected must be accurate and verifiable by source document(s). For the purpose of monitoring and auditing by the Sponsor, and inspection by regulatory authorities, the site will provide direct access to all study related source data/documents. The sponsor will verify that the study is conducted and data has been collected, documented (recorded), and reported in compliance with the protocol, GCP, and applicable regulatory requirements.

Data for the study will be centrally stored and managed by the study sponsor). Quality assurance and control measures will be implemented to ensure training for specific trial–related tasks beyond the usual scope of practice. The only procedure or intervention requiring additional training and considered study specific is the Dex4 OGTT and will be reviewed for documentation of training and/or qualification.

13 ETHICS CONSIDERATIONS

13.1 Ethical Standard

The investigator will ensure that this study is conducted in accordance with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Participants of Research, and codified in the Tri-Council Policy Statement and/or the ICH E6.

13.2 Research Ethics Board (REB)

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the REB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the REB before the changes are implemented in the study, unless to eliminate an immediate hazard.

13.3 Consent

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. A consent form describing in detail the study procedures and risks will be reviewed with and given to each participant. Consent forms will be REB-approved, and the participant is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the participant and answer any questions that may arise. The participant will sign the informed consent document prior to any study-related assessments or procedures. Participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to participants for their records.

Prior to involvement in any study-related activities, consent must be obtained in writing for each participant using the current REB approved informed consent from. It is the responsibility of the investigator to ensure that all advertisements and written information, including the informed consent form, disseminated to participants has been approved by the local REB prior to use. The ethics approved Informed Consent Form (ICF) and any other written information, must be provided to each participant, allowing ample time to ask and have answered any questions prior to making a decision regarding participation. Neither the investigator nor study staff should unduly influence or coerce a participant to participate in the study.

The ICF will be signed and dated by the participant and individual obtaining consent. The consent process will be documented in the clinical or research record.

The original ICF, in its entirety, will be maintained by the site, and a complete copy of the signed ICF provided to the participant. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The provision of consent is an ongoing process and should be maintained throughout the duration of the study. Participants may withdraw consent at any time throughout the course of the study.

14 PUBLICATION/DATA SHARING POLICY

Authorship on study publications will adhere to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals of the International Committee of Medical Journal Editors. These requirements state “Authorship credit should be based on:

1) Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;

2) Drafting the article or revising it critically for important intellectual content; and

3) Final approval of the version to be published.

Authors should meet conditions 1, 2, and 3.” Where journal policies permit, all study site investigators who played a contributing role in the trial, including to its accrual, will be included in an Acknowledgement section.

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APPENDICES

APPENDIX A: SCHEDULE OF EVENTS

Study Plan: