ANCILLARY REVIEWS

DO NOT DELETE. Submit the completed checklist below with your protocol.

Which ancillary reviews do I need and when do I need them? Refer to HRP-309 for more information about these ancillary reviews.			
Select yes or no	**Does your study…**	*If yes…*	***Impact on IRB Review***
☐ **Yes** ☒ **No**	Include Gillette resources, staff or locations	*Gillette Scientific review and Gillette Research Administration approval is required. Contact: research@gillettechildrens.com*	**Required prior to IRB submission**
☒ **Yes** ☐ **No**	Involve Epic, or Fairview patients, staff, locations, or resources?	*The Fairview ancillary review will be assigned to your study by IRB staff Contact:* ancillaryreview@Fairview.org	**Approval must be received prior to IRB committee / designated review.** **Consider seeking approval prior to IRB submission.**
☒ **Yes** ☐ **No**	Include evaluation of drugs, devices, biologics, tobacco, or dietary supplements or data subject to FDA inspection?	*The regulatory ancillary review will be assigned to your study by IRB staff Contact: medreq@umn.edu* *See: https://policy.umn.edu/research/indide*	
☐ **Yes** ☒ **No**	Require Scientific Review? Not sure? See guidance in the Investigator Manual (HRP-103).	*Documentation of scientific merit must be provided. Contact: hrpp@umn.edu*	
☐ **Yes** ☒ **No**	Relate to cancer patients, cancer treatments, cancer screening/prevention, or tobacco?	*Complete the CPRC application process. Contact: ccprc@umn.edu*	
☐ **Yes** ☒ **No**	Include the use of radiation? (x-ray imaging, radiopharmaceuticals, external beam or brachytherapy)	*Complete the AURPC Human Use Application and follow instructions on the form for submission to the AURPC committee. Contact: barmstro@umn.edu*	**Approval from these committees must be received prior to IRB approval;** **These groups**
☐ **Yes** ☒ **No**	Use the Center for Magnetic Resonance Research (CMRR) or MR from Masonic Institute for the Developing Brain (MIDB) as a study location?	*Complete the CMRR pre-IRB ancillary review Contact: ande2445@umn.edu*	

☐ **Yes** ☒ **No**	Include the use of recombinant or synthetic nucleic acids, toxins, or infectious agents?	*Complete the IBC application via eprotocol.umn.edu*	**each have their own application process.**
☐ **Yes** ☒ **No**	Include the use of human fetal tissue, human embryos, or embryonic stem cells?	*Contact OBAO for submission instructions and guidance*	
☒ **Yes** ☐ **No**	Include PHI or are you requesting a HIPAA waiver?	*If yes, HIPCO will conduct a review of this protocol.* *Contact: privacy@umn.edu*	
☒ **Yes** ☐ **No**	Plan to use CTSI Monitoring services, and/or have an IND, IDE, or designated NSR-IDE by the UMN IRB?	*The CTSI monitoring ancillary review will be assigned to your study by IRB staff.* *Please note eligibility criteria here.* *Contact: fencl003@umn.edu*	**Approval must be received prior to IRB approval.** **These groups do not have a separate application process but additional information from the study team may be required.**
☐ **Yes** ☒ **No**	Use data from CTSI Best Practices Integrated Informatics Core? Formerly the AHC Information Exchange (IE)?	*The Information Exchange ancillary review will be assigned to your study by IRB staff* *Contact: bpic@umn.edu*	
☐ **Yes** ☒ **No**	Use the Biorepository and Laboratory Services to collect tissue for research?	*The BLS ancillary review will be assigned to your study by IRB staff.* *Contact: Jenny Pham* *Pham0435@umn.edu*	
☐ **Yes** ☒ **No**	Have a PI or study team member with a conflict of interest?	*The CoI ancillary review will be assigned to your study by IRB staff* *Contact: becca002@umn.edu*	
☒ **Yes** ☐ **No**	Need to be registered on clinicaltrials.gov?	*If you select "No" in ETHOS, the clinicaltrials.gov ancillary review will be assigned to your study by IRB staff* *Contact: fencl003@umn.edu*	
☒ **Yes** ☐ **No**	Require registration in OnCore?	*If you select "No" or "I Don't Know" in ETHOS, the OnCore ancillary review will be assigned to your study by IRB staff* *Contact: oncore@umn.edu*	**Does not affect IRB approval.**

PROTOCOL COVER PAGE

Protocol Title	Efficacy and safety of GLP-1 agonist therapy in overweight and obese subjects with cystic fibrosis-related diabetes: a pilot study
Principal Investigator/Faculty Advisor	Name: Amir Moheet
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IND/IDE # (if applicable)	IND 165316
IND/IDE Holder	Amir Moheet, MBBS
Investigational Drug Services # (if applicable)	6127
Version Number/Date:	Version 5.1, 09 Aug 2024

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1.1	19 APR 2023	Changes made in response to 4/7/23 IRB letter	Y
1.2	22Sep2023	Changes made per DSMB recommendations, added IDS #, updated participant reimbursement to include mileage – added federal mileage reimbursement rate	Y
1.3	09Oct2023	OGTT protocol language and schedule of events table clarified	Y
1.4	17Nov2023	Use of MacCAT-CR specifically indicated per IRB stip when appropriate, instead of shorter UBACC tool per Courtney Jarboe upon review 12/20/23 of this MOD and original IRB analyst's Modifications Required Letter dated 13Nov2023	N
2.0	30Nov2023	PHQ-9 language, CGM start changed from Week 10 to week 8, and schedule of events updated	Y
3.0	21Dec2023	MacCAT-CR language clarified to match intended meaning of IRB stip for Revision 1.4	N
4.0	31Jan2024	Updated inclusion criteria – insulin therapy removed	Y
5.0	28Mar2024	Updates per CR stips letter dated 22Mar2024	Y
5.1	09Aug2024	Updated monitoring language added per HRPP audit report 7/31/2024.	Y

Table of Contents

ABBREVIATIONS/DEFINITIONS

- CF-cystic fibrosis
- GLP-1RA-Glucagon like peptide 1 receptor agonist
- CFRD -Cystic fibrosis related diabetes
- CFTR-cystic fibrosis transmembrane conductance regulator
- ETI- Elexacaftor/Tezacaftor/Ivacaftor
- OGTT-oral glucose tolerance test and on glycemic outcomes as measured by
- CGM-continuous glucose monitoring
- SC-subcutaneous
- SMBG-self-measured blood glucose
- AE -adverse effects
- AUC-Area under the curve
- BMI-body mass index
- CFQ-R- Cystic Fibrosis Questionnaire-Revised
- CRF-case report forms
- CVD-cardiovascular disease
- DHQ- Diet History Questionnaire
- DPP-4- dipeptidyl peptidase-4
- DSMB-Data safety and monitoring board
- FEV1-Forced expiratory volume
- GI-gastroenterology
- GIP- glucose-dependent insulinotropic polypeptide
- PHQ-9-Patient Health Questionnaire-9
- MacCAT-CR - MacArthur Competence Assessment Tool for Clinical Research
- UBACC - Revised University of California, San Diego Brief Assessment of Capacity to Consent

1.0 Objectives

1.1 Purpose:

The overall goal of this proposal is to collect pilot data for safety and feasibility metrics to support a future larger randomized controlled trial. In this study, we will examine the safety and tolerability of GLP-1RA semaglutide for overweight/obese adult patients with CFRD. We hypothesize that weekly administration of the long-acting GLP-1RA semaglutide to overweight/obese CFRD patients will be safe and well tolerated.

Specific Aim 1: Collect pilot data on the safety and feasibility of weekly semaglutide therapy in overweight and obese patients with CFRD to support a future larger randomized controlled trial.

Hypothesis 1: Weekly therapy with GLP-1RA semaglutide will be safe and well tolerated in overweight/obese adults with CFRD.

Specific Aim 2: Collect preliminary data to examine the impact of semaglutide therapy on insulin secretion, glucagon and glucose levels as measured by oral glucose tolerance test (OGTT), and on glycemic outcomes as measured by continuous glucose monitoring (CGM) and HbA1c.

Hypothesis 2a: Treatment with semaglutide will lower glucose levels, and increase insulin and C-peptide area under the curve (AUC) during the OGTT as compared to baseline.

Hypothesis 2b: Treatment with semaglutide will improve glycemic control as indicated by time in range on CGM and HbA1c

2.0 Background

2.1 Significance of Research Question/Purpose:

Increasing prevalence of overweight/obesity in CF: CF has classically been associated with malnutrition and being underweight [1]. A high calorie diet has been the standard of care for several decades, to offset the negative energy expenditure created by malabsorption, increased work of breathing, chronic inflammation, and pulmonary exacerbations [2]. Intense emphasis on nutritional augmentation and advancement in medical therapies including recent introduction of CFTR modulators have significantly reduced the prevalence of malnutrition in CF. However, this success has been accompanied by a significant rise in overweight/obesity in CF, which is beginning to resemble the global trend of obesity in the general population. In 2005, Kastner-Cole et al [3] reported the prevalence of overweight and obesity in patients with CF (homozygous ΔF508) in the United Kingdom to be 9.1% and 1.1%, respectively. In this study, there was a positive association between BMI and FEV1 in adults up to BMI of 23 kg/m^2. Stephenson et al.[4] evaluated longitudinal changes in nutrition at the Toronto CF Center, comparing the adult nutritional status from before 1990 to after 2000.

Underweight decreased from 20.6% to 11.1% while overweight/obese increased from 7% to 18.4%. According to the 2019 US CF Foundation registry report 23.1% of adults with are overweight and 8.3% are obese and the prevalence of adult overweight/obesity has more than doubled since 1999[5]. In a recent cross-sectional analysis of 484 adults with CF seen at the U of MN CF Center between 2015-2017, we reported that 25.6% of patients were overweight and 6.6% were obese [6]. It was particularly striking that 25% of patients with severe CF mutations had BMI in the overweight/obese category. Overweight and obese patients in our CF cohort were more likely to have hypertension and higher levels of total cholesterol, LDL-cholesterol and triglyceride.

CFTR modulator therapies target the underlying defect causing CF, so may reduce the factors that historically drove under-nutrition in CF. In fact, many studies have demonstrated weight gain in modulator-treated patients. A recent systematic review examined 13 CFTR modulator trials between 2012-2017 found strong evidence for weight gain in Ivacaftor-treated patients with a G511D mutation, but weaker evidence for weight gain with Lumacaftor/Ivacaftor or Tezacaftor/Ivacaftor treatment [7]. Elexacaftor/Tezacaftor/Ivacaftor (ETI), approved in late 2019, was not included in the systematic review. ETI is a "highly effective" CFTR modulator for individuals with eligible CFTR variants, providing similar level of CFTR function as Ivacaftor. While longitudinal data for ETI is not available, in single-center study of 94 adults, we reported an average of 2.4% increase in weight after 3 months of ETI therapy [8].

Is obesity harmful in CF? Traditionally, because of concern about the known deleterious impact of undernutrition, because it was difficult for CF patients to gain and maintain weight, and because there was no evidence of cardiovascular disease in this population, CF patients were encouraged to eat extra calories and gain weight, without a weight "ceiling". In the past we showed that there was no additional pulmonary advantage for BMI greater than 28-29 [6]. Recently, evidence is emerging that overweight/obesity may have a negative impact on patients with CF. In the general population, there is a well-known association between obesity and CVD. We have recently shown that overweight and obese patients at the UMN CF Center are more likely to have hypertension and higher levels of total cholesterol, LDL-cholesterol and triglyceride, and have found a handful of patients who have had a myocardial infarction, which has not previously been reported in CF. There are not enough data to say whether other problems known to be associated with obesity in the general population might also emerge in CF, but it is certainly plausible to assume that problems like decreased lung function, joint problems, liver steatosis/cirrhosis, and cancer might aggravate conditions already associated with CF. Thus, there is rationale to explore the safety and efficacy of treatments that promote weight loss in CF.

Role of incretin therapy for obesity: Besides type 2 diabetes, GLP-1 RA are also approved for treatment of obesity. Incretin hormones have been shown to play a role in regulation of appetite and food intake [9]. The mechanism whereby peripherally administered GLP-1 inhibits food intake is not clear. GLP-1 receptors are expressed in many regions of the brain and in particular in the arcuate nucleus and other hypothalamic regions involved in them regulation of food intake [9]. It has been postulated that GLP-1 effect on appetite could be through interaction with sensory neurons in the gastrointestinal tract or central effect on the brain. In clinical trials, GLP-1RA were shown to lower body weight by reducing appetite and hunger, increasing satiety and reducing food cravings [10]. Childhood eating habits strongly influence adult eating behaviors in general population studies, which suggests that overweight/obese people with CF may have difficulty transitioning to a lower-calorie diet after a lifetime of consuming high-calorie, high-fat foods. Therefore, GLP-1RA therapy would be an attractive therapeutic option in obese and overweight patients with CF.

Role of incretin hormones in the pathogenesis of dysglycemia in CF: The pathophysiology underlying the development of glucose intolerance and CFRD in subjects with CF is multifactorial and not fully understood. The earliest insulin defect seen in CF is loss of first-phase insulin response with post prandial hyperglycemia. This pattern suggests dysregulation in the incretin hormone axis. GLP-1 and GIP are incretin hormones released by intestinal cells in response to ingestion to meal. The primary actions of incretin hormones are to stimulate insulin secretion and to inhibit glucagon secretion, thereby lowering post-prandial glucose excursions [9]. Previous studies have examined the role of incretin hormones in CF related glucose intolerance. In one study, GLP-1 was found to be significantly lower in patients with CF and CFRD compared to in healthy controls [11]. In another study, Perano et al [12] showed that pancreatic enzyme replacement therapy improved GLP-1 and GIP secretion and postprandial glycemia. In a small study of subjects with CF and pancreatic insufficiency and impaired glucose tolerance, treatment with GLP-1 RA showed improvement in post-prandial glucose excursion, primarily due to slower gastric emptying [13]. Both GIP and GLP-1 are rapidly degraded by the aminopeptidase protease dipeptidyl peptidase-4 (DPP-4). In a recent study Kelly et al examined the effect of sitagliptin (a DPP-4 inhibitor) on various measures of β-cell function and glycemia in CF with abnormal glucose tolerance [14]. Sitagliptin intervention in this study augmented meal-related incretin responses with improved early insulin secretion and glucagon suppression without affecting post-prandial glycemia. These studies provide data to support the role of incretin hormones in CF related dysglycemia and provide strong rationale to further investigate these drugs in the treatment of CFRD.

Novel pharmacological strategies are needed CFRD management in setting of overweight/obesity: CFRD is the most common extra pulmonary complication of CF and was identified by the CF community as one of the top priorities for CF research. Insulin

is the treatment of choice for CFRD and is associated with improvement in glycemic control, nutritional status and lung function[15]. However, in the current era of highly effective CFTR modulator therapies and increasing prevalence of overweight/obesity in CF, there is urgent need to develop novel pharmacological strategies for management of CFRD. Many patients with CFRD are now also developing a phenotype of type 2 diabetes with obesity, insulin resistance and high insulin requirement. In clinical practice, medications approved for type 2 diabetesare increasingly being used for treatment of CFRD . However, there is limited clinical trial data to recommend the use of these medications. We found that 61% of the patients with CFRD followed at U of MN have BMI >25. Semaglutide, a GLP-1RA administered weekly through subcutaneous (SC) injection has been FDA approved for management of type 2 diabetes and obesity. It is highly effective in improving glycemic control and inducing weight loss. It has been widely studied in trials of type 2 diabetes and obesity and found to be safe and well tolerated. GLP1 –RA therapy can provide an effective treatment option for this emerging and important clinical problem of CFRD complicated by obesity.

2.2 Preliminary Data:

There are no clinical trial data on chronic use of GLP-1RA in CFRD. In a small study of 6 patients (average age 17 yrs) with CF and impaired glucose tolerance, a single dose of exenatide (GLP-1RA) was shown to acutely improve post prandial glycemia compared to placebo [13]. CF patients with pancreatic insufficiency have been shown to have impaired secretion of GLP-1 and higher postprandial glucose excursions compared to healthy controls [11,16]. Pancreatic enzyme replacement therapy has been shown to improve GLP-1 secretion and improve postprandial hyperglycemia in CF patients compared to control [11]. In a published single case report, the GLP-1RA semaglutide in combination with basal insulin for 3 months improved glycemic control and induced weight loss without significant GI side effects. In this patient with pancreatic insufficiency, serial pancreatic enzyme measurements did not change and there was improvement in fasting c-peptide level post treatment with semaglutide[17]. These small studies suggest a possible role of incretin-based therapies in CFRD.

Existing Literature:

See section 2.1

3.0 Study Endpoints/Events/Outcomes

3.1 Primary Endpoint/Event/Outcome:

The primary outcomes are related to feasibility, including safety and treatment tolerability. Safety will be evaluated as the proportion (in %) of participants who experience a serious adverse event during the study. Tolerability will be evaluated as the proportion (in %) of participants who discontinue their assigned treatment due to side effects.

3.2 Secondary Endpoint(s)/Event(s)/Outcome(s):

Secondary outcomes will be change in glucose and insulin area under the curve during the OGTT and the time to peak insulin level. Additional secondary outcome measures include time in range, glycemic variability and time below range based on CGM, HbA1c, moderate/mild adverse events and insulin dose (IU/day for both bolus and basal).

4.0 Study Intervention(s)/Investigational Agent(s)

4.1 Description:

Semaglutide (Ozempic®) is a GLP-1RA, which is given as a self-administered weekly SC injection. Semaglutide is FDA approved for treatment of type 2 diabetes and obesity. Semaglutide will be initially started at 0.25 mg weekly dose. The weekly dose will be increased to 0.5 mg at the 4 week time point and to 1 mg at 8 weeks (as per manufacturer prescribing information). Semaglutide doses will be titrated up to and kept on the target 1 mg weekly dose until the end of the study. Subjects who cannot tolerate the 1 mg dose will be maintained at the maximum tolerated dose. Participants will receive treatment for a total of 12 weeks. Study drug will be discontinued at the end of the study. Participants will not permitted to start any other new diabetes medication (besides insulin) during the study period.

Safety will be assessed as the proportion of enrolled participants who experience severe adverse events (AE). Tolerability will be evaluated as the proportion (in %) of participants who discontinue their assigned treatment due to side effects. We will collect data on consent rate (proportion of all participants who were contacted and eligible who consented), and completion rate (proportion of subjects who complete all study visits).

4.2 Drug/Device Handling:

• IND to be shipped to, stored, logs maintained, and dispensed per Fairview Health Services Investigational Drug Policy.

• IDS# 6127

4.3 Biosafety:

Not applicable

4.4 Stem Cells:

Not applicable

4.5 Fetal Tissue:

Not applicable

5.0 Procedures Involved

5.1 Study Design:

This open label, single arm pilot study, will examine the safety and tolerability of GLP-1RA semaglutide for overweight/obese adult patients with CFRD.

5.2 Study Procedures:

Study protocol: Participants will be recruited from UMN CF center. The screening and recruitment process is reviewed later in sections 8 and 11 respectively. After completing baseline labs, CGM monitoring and OGTT (table 1), subjects will be started on semaglutide 0.25 mg given as self-administered weekly SC injections. Standard checklist will be developed to titrate semaglutide dose using the manufacturer prescribing information and adverse effects criteria as reviewed in the DSMB plan. Subjects will be initially started on semaglutide 0.25 mg weekly. The weekly dose will be increased to 0.5 mg at the 4 week time point and to 1 mg at 8 weeks (as per manufacturer prescribing information). Dose will be titrated down to the next lower dose if subject experiences moderate adverse effects (AE) and medication will be discontinued if severe AE are experienced. AE criteria are reviewed in DSMB plan (See Section 15.2). Semaglutide dose will be titrated up to and kept on the target 1 mg weekly dose till the end of the study. Subjects who cannot tolerate the 1 mg dose will be maintained at the maximum tolerated dose. To reduce the risk of hypoglycemia in subjects on insulin therapy, doses of bolus and basal insulin will be reduced by 20% at the time of initiation of semaglutide treatment. Patients will not be allowed to change the type of insulin delivery (daily insulin injections vs insulin pump) during the study period. Patients will continue with their usual method of glucose monitoring including self-measured blood glucose (SMBG) using finger sticks or personal CGM. Participants will not permitted to start any other new diabetes medication (besides insulin) during the study period. If applicable,the insulin dose will be adjusted in accordance with SMBG and personal CGM readings. In accordance with the current guidelines [15], the treatment targets are fasting or premeal glucose between 70 and 130 mg/dl, and 2–3 h post-prandial glucose <180 mg/dl. For patient utilizing personal CGM, the treatment targets will be a glucose time-in-range (70-180 mg/dl) greater than 70% of the time, hypoglycemia (glucose <70mg/dl) <4% of the time, and major hypoglycemia (glucose <54 mg/dl) <1% of the time [18]. Glycemic data will be reviewed at all study visits and telephone contacts (figure 1) after the initial of therapy and if applicable insulin doses will be adjusted as needed. As a general guideline basal insulin would be reduced by 10% for fasting hypoglycemia on finger stick glucose reading < 70 mg /dL or glucose < 70 mg/dl for > 15 minutes on CGM. Basal insulin would be reduced by 15% for fasting hypoglycemia on finger stick glucose reading < 54 mg /dL or glucose < 54 mg/dl for ≥15 minutes on CGM. For Post meal hyperglycemia preceding insulin bolus dose would be increased by 10% if there

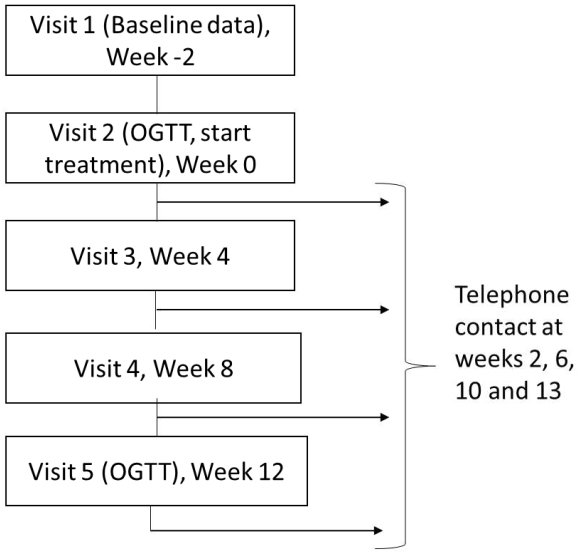

Figure 1. Flow chart of the study

is pattern of 2 hour post meal glucose readings between 181 and 250 mg/dl on finger stick or in the 181-250 range for ≥ 15 minute on CGM. If there is pattern of 2 hour post meal readings > 250 mg/dl on finger stick or > 250 mg/dl for ≥ 15 minutes preceding insulin bolus dose would be increased by 15 %. If applicable, insulin dose adjustment would be at the discretion of the study investigator to maintain the glucose readings in the target range. Investigator will also take into account other factors such as any missed insulin dose or timing of meal bolus. Participants will receive treatment for a total of 12 weeks. Study drug will be discontinued at the end of the study. If applicable, insulin will be adjusted at week 12 at the end of the study and during telephone visit at week 13 to return to baseline.

Five visits (figure 1) to the study center will be scheduled (weeks -2, 0, 4, 8 and 12) at which information will be collected about concomitant medications, if applicable basal and bolus insulin doses , any GI side effects, body weight, blood pressure, and heart rate. Number of hypoglycemic events will be monitored and captured based on the American Diabetes Association definitions of hypoglycemia. Study visit 1 could occur at CSC, DCRU or CRU. Visits 2, 3, 4 and 5 will occur at CRU. OGTT will performed at visit 2 before starting semaglutide and repeated at the end of the study. Blood samples (around 20-40mL) will be collected at Visit 2 and 5 for lipase, electrolytes, HbA1c, liver function and renal function; and at Visit 3 and 4 for electrolytes and renal function. Serum pregnancy test will be done at visit 1 prior to treatment initiation for all subjects who could become pregnant. Urine pregnancy testing will be done at visits 2, 3, and 4. These participants must agree to take precautions that are effective in preventing pregnancy throughout this study, which could include complete abstinence from sexual intercourse; oral, injectable, or implanted hormonal contraceptives; intrauterine device; or tubal ligation

Semaglutide will be started at visit 2 (week 0) and the patient will self-administer the first dose in the clinical research unit. Following data would be collected at the enrollment: age, sex, date of birth, diagnosis of CF (genotype and sweat test results), date of diagnosis of diabetes mellitus, FEV1, date of last hospitalization for pulmonary exacerbation and initiation of any systemic steroid therapy. We will collect a list of the subject's current and active medications. Start date and history of CFTR modulator therapies. We would also collect data regarding trajectory of weight change since the start of highly effective CFTR modulator therapy. Details of clinical and safety outcomes collected at each study visit are listed in table 1. A CGM Dexcom G6 will be started for up to 10 days at study visit 1 and the week 8 time point. Patients using their own clinical CGM would be allowed to continue using personal CGM. All study procedures including CGM, OGTT and labs are being done for research only and not as part of clinical care. Participants will be encouraged to schedule follow up with their usual diabetes provider within 4-6 weeks after the study conclusion.

Two-hour OGTT Protocol:

1. Subject will arrive fasting for at least 8 hours except for water. If subject has not been fasting, the study visit must be rescheduled.

2. Subjects are admitted to the clinical research unit. Finger stick glucose would be checked. Study will be rescheduled if the morning fasting blood glucose is >200 mg/dl when a participant arrives for the OGTT.
3. An IV is placed for sequential laboratory draws.
4. The oral glucose solution (Glucola) at the dose of 1.75 g/kg (max 75 gm) is administered at time zero.
5. Blood will be drawn prior to and at 10, 30, 60, 90, and 120 minutes post glucose ingestion for glucose, insulin, c-peptide and glucagon,GLP-1 (active and total) and GIP. Samples will be processed, batched and frozen.
6. Sample for Glucagon, GLP-1 (active and total) and GIP would send to the Cytokine Reference Lab at the University of Minnesota for analysis using ELISA. Insulin, C-peptide and glucose samples will be sent to the University of Minnesota Advanced Research and Diagnostic Laboratory for analysis.
7. Obtain fingerstick BG on glucometer at 90 and 120 minute time points to identify any hypoglycemia.
    - If blood sugar < 70 mg/dl but > 50 mg/dl and not symptomatic, continue research protocol.
    - If Blood sugar < 70 mg/dl but > 50 mg/dl and symptomatic (feeling shaky, hungry, faint, pale) call provider
    - If Blood sugar < 50 mg/dl, repeat glucometer STAT and if still <50 mg/dl, call provider and give 4 oz juice.
8. If the OGTT is stopped early due to hypoglycemia, the next time point of labs should be drawn and the patient should be given at least 15 grams of carbohydrates until BG is at least 70 mg/dl.
9. If applicable, patients will be instructed to take the last dose of their usual basal insulin dose 24 hours before the OGTT but withhold all rapid-acting insulin boluses for at least 8 hours prior to the OGTT.
10. The second OGTT will be scheduled 2-4 days after the last dose of semaglutide.

	Visit 0 Telephone Pre-Screening	**Screening/Visit 1 baseline**	**Visit 2 OGTT, start therapy**	**Telephone contact**	**Visit 3**	**Telephone contact**	**Visit 4**	**Telephone contact**	**Visit 5 End of study**	**Post study Telephone contact**
Time (weeks)		-2 ± 1	0	2 ± 1	4 ± 1	6 ± 1	8 ± 1	10 ± 1	12 ± 1	13 ± 1
Estimated time for study visit	30-60 min	60-90 min	4-5 hours	30 min	60 min	30 min	60 min	30 min	4-5 hours	30 min
Assessment of inclusion/ exclusion criteria	X	X[AN]								
Demography Medical history	X	X[AN]								
Concomitant medication	X	X[AN]	X		X		X		X	
Consent		X								
Monitoring of AE				X	X	X	X	X	X	X
Blood test (renal function, electrolytes etc.)			X		X		X		X	
Review FSBG				X	X	X	X	X	X	X
Patient centered outcome questionnaires		X			X		X		X	X
PHQ-9		X			X		X		X	
Vital signs, weight			X		X		X		X	
OGTT			X						X	
CGM		X					X			
HbA1c			X						X	
Serum Pregnancy test		X								
Urine Pregnancy test			X		X		X			
Insulin dose titration			X	X	X	X	X	X	X	X
Drug accountability					X		X		X	
Study drug dose titration					X		X			

Table 1. Study visits.
min, minutes; AE, adverse effects; FSBG, finger stick blood glucose, AN (as needed: medications and medical history may be reviewed at Pre-Screening phone call or at Screening/Visit 1)

Feasibility outcomes: In this pilot study, we will collect data on important parameters that are needed to design a future larger clinical trial to test the hypothesis that weekly administration of the long-acting GLP-1RA semaglutide to overweight/obese CFRD patients will be safe and well tolerated. Safety will be assessed as the proportion of enrolled participants who experience severe adverse events (AE). Tolerability will be evaluated as the proportion (in %) of participants who discontinue their assigned treatment due to side effects. We will collect data on consent rate (proportion of all

participants who were contacted and eligible who consented), and completion rate (proportion of subjects who complete all study visits). If the pilot study demonstrates feasibility, then a larger and fully powered trial would be needed to test the hypothesis. We will also collect data on adherence to treatment intervention, and on the time needed to collect, clean and analyze data. Reasons for not consenting will be collected from subjects who decline participation in the study. To monitor for compliance, patients will be asked to bring used semaglutide pens at each study visit. Used semaglutide pen will be checked for any remaining doses. Participants will be assessed for depression and suicidal ideation with the Patient Health Questionnaire-9 (PHQ-9) at the baseline visit and visits 3 ,4 and 5. A participant will be referred to a mental health provider or primary care provider if the participant has a PHQ-9 score of ≥10 , any suicidal behavior, or any suicidal ideation.

Patient centered outcomes will also be collected as part of feasibility metrics including the Gastroparesis Cardinal Symptom Index (GCSI; 9 items) for capturing gastroparesis symptoms [21]. We will also utilize the Patient Assessment of Gastrointestinal Disorders Symptom Severity Index (PAGI-SYM; 20 items) questionnaire that members of the CF community have identified as a patient-reported outcome measure that captures the CF experience with GI disease [22]. We expect to screen 50 participants to recruit 10 participants. We will consider a consent rate of 20%, a completion rate of 80% as the criteria for assessing feasibility.

5.3 Study Duration:

This study will be conducted over 24 months. Duration of anticipated participation for an individual participant's would be around 15 weeks (Figure 1). Duration anticipated to enroll all study subjects is around 12 months. Duration anticipated to complete all study procedures, including any long-term follow-up, and data analysis is 24 months.

5.4 Use of radiation*:*

Not applicable

5.5 Use of Center for Magnetic Resonance Research*:*

Not applicable

6.0 Data and Specimen Banking

6.1 Storage and Access:

Deidentified data will be stored in REDCap or UMN Box for future research use. Only the research team will have access to stored data.

6.2 Data:

Deidentified data banked for future analyses may include clinical and demographic information, lab results, patient-centered outcomes survey responses and treatment data.

6.3 Release/Sharing:

Data will be shared with other researchers who request it, under the following conditions:

- Requester provides protocol and IRB approval or Determination of Non-Human Participants Research.
- Requester completes Data Use Agreement form as developed by the Health Information Privacy and Compliance Office at the University of Minnesota.
- Any data or specimen can be shared but all identifiers will be removed. Requester will not be provided with link between identity and study code.

7.0 Sharing of Results with Participants

7.1 If requested results of HbA1C and OGTT will be shared with the participants and their CF pulmonary provider. These labs will be shared in-person, via a letter or email to the participants and by a letter faxed to CF pulmonary providers. If requested, CGM glucose data will be shared with the participants.

7.2 Sharing of genetic testing:

N/A

8.0 Study Population

8.1 Inclusion Criteria:

- Adult subjects 18 years or older with CFRD
- BMI >26 kg/m2
- Diagnosis of pancreatic insufficiency (based on treatment with pancreatic enzyme replacement therapy)
- A participant who is capable of becoming pregnant must agree to take precautions that are effective in preventing pregnancy throughout this study. These methods could include one of the following 1. Complete abstinence from sexual intercourse; 2. Oral, injectable, or implanted hormonal contraceptives 3. Intrauterine device 4. Tubal ligation

8.2 Exclusion Criteria:

- personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2 (MEN2)
- acute pulmonary exacerbation requiring IV antibiotics or systemic glucocorticoids within 4 weeks prior to baseline study procedures
- gastrointestinal(GI) symptom exacerbation defined by current nausea/vomiting or diarrhea at the baseline assessment
- history of chronic GI problems requiring hospitalization in the 1 year prior to baseline
- history of clinically symptomatic pancreatitis
- history of clinically significant gastroparesis
- history of eating disorders

- less than 24 weeks since start of a new CFTR corrector/modulator therapy
- pregnancy or lactation
- severe CF liver disease
- chronic kidney disease
- Non-English speakers and those unable to read in English
- Uncontrolled major depressive disorder (defined as PHQ-9 score of ≥10)
- Diagnosis of other severe psychiatric disorders (e.g., schizophrenia, bipolar disorder)
- A Patient Health Questionnaire-9 (PHQ-9) score of ≥10 at screening visit
- A lifetime history of suicidal attempt
- Suicidal ideation within the past 1 year before screening visit

8.3 Pre-Screening and Screening:

Using a combination of participant self-report and medical record review, research staff will confirm each inclusion and exclusion criteria to determine eligibility of potential participants who are identified by their treating provider or those who respond to recruitment materials.

Potential participants who respond to recruitment solicitation will be contacted by phone. Study staff will provide an overview of the study by following the IRB-approved phone script. This script includes all required and appropriate additional elements of consent disclosure related to the pre-screening process. Participants will be asked to provide verbal consent prior to conducting the initial phone screen. Participants who consent to proceed with the pre-screening process will be documented by study staff. If participants are found to be potentially eligible during phone screening, they will be invited to the study for a full written consent process in person at their scheduled Screening /Visit 1 that covers the remainder of the study, as described in this protocol. If it is determined that the patient is not eligible or not interested during the pre-screening process, any documentation obtained will be securely shredded. During the pre-screening process, if the patient reports current suicidal ideation, we will offer support and let them know that we will communicate this to their primary or CF care team or a mental health provider to provide further evaluation and resources.

As this is a greater than minimal risk study, if there is a question or concern of a participant's capacity to consent, study staff will utilize the MacCAT-CR tool solely (instead of the shorter UBACC tool) to exclude patients with diminished capacity to consent.

If there is no concern of a participant's capacity to consent, we will not utilize the MacCAT-CR tool.

9.0 Vulnerable Populations

9.1 Vulnerable Populations:

Population / Group	Identify whether any of the following populations will be focus of the research (targeted), included, but not necessarily the focus or excluded from participation in the study.
Children	Excluded
Pregnant women/fetuses/neonates	Excluded
Prisoners	Excluded
Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders	Excluded
Non-English speakers	Excluded
Those unable to read (illiterate)	Excluded
Employees of the researcher	Excluded
Students of the researcher	Excluded
Undervalued or disenfranchised social group	Included but not the focus
Active members of the military (service members), DoD personnel (including civilian employees)	Included but not the focus
Individual or group that is approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.	Excluded
Individual or group that is disadvantaged in the distribution of social goods and services such as income, housing, or healthcare.	Included but not the focus

Individual or group with a serious health condition for which there are no satisfactory standard treatments.	Primary focus of the research
Individual or group with a fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior).	Excluded
Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research.	Excluded

9.2 Additional Safeguards, if any, to ensure inclusion is appropriate:

Undervalued/disenfranchised social groups, Active members of the military, and Individuals or groups that are disadvantaged in the distribution of social goods and services may be included but are not the focus of this study. We will not be screening for this so a participant's inclusion in these groups may not be known. However, as an additional safeguard, we plan to provide assurance of confidentiality, freedom to decline to participate, and the right to withdraw at any time without penalty.

Individuals or groups with a serious health condition for which there are no satisfactory standard treatments are the primary focus of this study. As an additional safeguard, participants will be fully informed of the potential risks and benefits of the research study. They will also be reminded that their relationship with their provider or the UMN will not be affected by their decision whether or not to participate in this study.

If there is a concern or question of a participant's capacity to consent, study staff will utilize MacCAT-CR tool solely (instead of the shorter UBACC tool) to exclude patients with diminished capacity to consent.

If there is no concern of a participant's capacity to consent, we will not utilize the MacCAT-CR tool.

9.3 If research includes potential for direct benefit to participants, provide rationale for any exclusions indicated in the table above:

Safety and efficacy of OZEMPIC® have not been established in pediatric patients (younger than 18 years). It is currently approved only in adults with type 2 diabetes.

There are limited data with semaglutide use in pregnant women to inform a drug-associated risk for adverse developmental outcomes. Based on animal reproduction studies, there may be potential risks to the fetus from exposure to semaglutide during pregnancy.

10.0 Local Number of Participants

10.1 Local Number of Participants to be Consented:

Up to 15 participants will be consented to account for replacement of drop-outs

11.0 Local Recruitment Methods

11.1 Recruitment Process:

Participants will be recruited from UMN CF center. Recruitment related text will be send to UMN Cystic Fibrosis Center email listserv to assist with recruiting subjects with cystic fibrosis. Only CF Center patients who opt in to the listserv will receive these communications. They may unsubscribe at any time. Patients who opt in to the listserv sign a form when providing their email address. They are opting in to receive any news sent out through the listserv, which may include research study opportunities.

Potential participants will be identified using clinic records and letters will be sent to potential participants by their provider, including study investigators. Clinics include the CF clinics, Endocrine clinics, or Pulmonary clinics; all located at the Clinics and Surgery Center.

The IRB-approved Minnesota CF Center database/CFF Patient Registry (IRB# 7405M00054) will be queried for subjects who meet study inclusion and exclusion criteria. Patients who are followed at the Center sign consent for the use of their clinical data for research and are aware of the possibility of being contacted for research participation. The potential subjects are followed at our CF Center. Subjects identified through database query will be contacted by the research coordinators or the investigators. Contact will be made either at the time of a routine clinic visit, email or by phone. Those who have opted out of research will not be contacted.

In addition, study information including contact information will be posted within ClincalTrials.gov and Study Finder.

11.2 Identification of Potential Participants:

Participants could self-identify in response to UMN Cystic Fibrosis Center email listserv and contact the research staff; at that point, research staff will verbally confirm basic eligibility.

Research staff will review Fairview medical record for opt-out status for patients identified using medical records who are then sent recruitment letters. The recipients of the recruitment letter will be the PI's patients.

Research staff will also supplement as needed self-identifier recruitment by reviewing medical records of affiliated study clinicians. Providers who have a treating relationship with the patient may discuss research opportunities during a clinical encounter regardless of research opt-out status.

11.3 Recruitment Materials:

- CF listserv email text
- Recruitment Letter

11.4 Payment:

Participants will be compensated at the completion of study visits 2, 3, 4, 5 at the following rates for a total of $600:

- Visit 2: $100
- Visit 3: $100
- Visit 4: $100
- Visit 5: $100
- Study Completion: $200

Compensation will be issued using the ClinCard debit card program or by check issued by the University of Minnesota and sent to the participant's home address.

Participants will be reimbursed for travel expenses for onsite study visits including mileage, as per standard federal rates for reimbursement.

12.0 Withdrawal of Participants

12.1 Withdrawal Circumstances:

Participants will be withdrawn without their consent if at any point following enrollment they develop any of the exclusion criteria.

Participants will be withdrawn and stopped from study drug, if they experience serious adverse events related to study drug or procedure, recurrent severe hypoglycemia, suicidal ideation or development of depression PHQ $\geq$ 10, pregnancy or at the discretion of the DSMB.

Participants are free to withdraw from participation in the study at any time.

12.2 Withdrawal Procedures:

No additional data will be collected from a participant who withdraws from the study.

If a participant wishes to withdraw or we determine that the participant should withdraw, we will terminate data collection and discuss with the participant the

reasons for withdrawal. All data collected up to that point will be used in analysis unless the participant wishes for their data not to be used.

12.3 Termination Procedures:

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator, funding agency, IND/IDE sponsor, and regulatory authorities, as appropriate. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension. The study team will notify the participants of the study termination.

13.0 Risks to Participants

13.1 Foreseeable Risks:

Hypoglycemia related to OGTT: The OGTT is a routine clinical procedure which patients with CF undergo on an annual basis for CFRD screening. Reactive hypoglycemia can occur during OGTT. Fingerstick BG will be obtained on glucometer at 90 and 120 minute time points to identify any hypoglycemia. OGTT will be stopped if BG goes < 50 mg/dl

IV Risks: There may be pain involved with the IV placement. There is a small risk of bleeding under the skin that will produce a bruise. An infection is extremely rare with the placement of the IV for frequent sampling.

CGM Skin Reactions: The CGM sensor may produce pain when it is inserted into the skin. There is a low risk for developing a local skin infection at the site of the sensor needle placement. Itchiness, redness, bleeding and bruising at the insertion site may occur as well as local tape allergies.

Risk of fasting: Since the study participants will present fasting to one of the study sessions, some participants may experience hunger, irritability, fidgetiness, and/or lack of cooperation or attention. Furthermore, mild headaches, shakiness and/or dizziness may be experienced secondary to the fasting requirement.

Risks of questionnaires: The questionnaires will assess personal details such as information about treatment satisfaction, health status and symptoms, and diet history. These questions may bring to mind uncomfortable thoughts, emotions or memories. Some participants may face fatigue, embarrassment, frustration, or other challenges while completing these questionnaires. To mitigate this risk, participants will be reminded that participation in the study is voluntary and as such, they may skip individual questions or the questionnaire entirely.

Side effects related to Semaglutide: The most common adverse reactions, reported with Ozempic® (semaglutide) are nausea, vomiting, diarrhea, abdominal pain, and constipation.

Common AE table taken from Ozempic® (semaglutide) prescribing information is copied below (https://www.ozempic.com/prescribing-information.html,

Common Adverse Reactions

Table 1 shows common adverse reactions, excluding hypoglycemia, associated with the use o OZEMPIC® in the pool of placebo-controlled trials. These adverse reactions occurred mor commonly on OZEMPIC® than on placebo and occurred in at least 5% of patients treated wit OZEMPIC®.

Table 1. Adverse Reactions in Placebo-Controlled Trials Reported in ≥5% of OZEMPIC®-Treated Patients with Type 2 Diabetes Mellitus

Adverse Reaction	Placebo (N=262) %	OZEMPIC® 0.5 mg (N=260) %	OZEMPIC® 1 mg (N=261) %
Nausea	6.1	15.8	20.3
Vomiting	2.3	5.0	9.2
Diarrhea	1.9	8.5	8.8
Abdominal pain	4.6	7.3	5.7
Constipation	1.5	5.0	3.1

We will use a checklist of AE reported in the Ozempic® prescribing information to monitor for side effects at all study visits. Hypoglycemic events will be captured using the American Diabetes Association definitions.

Other Adverse Reactions per Ozempic® (semaglutide) prescribing information are listed below.

i. Hypoglycemia: Insulin induced hypoglycemia--- semaglutide may reduce insulin requirements, which would become evident as subjects would experience more hypoglycemia.

   Insulin dose will be titrated to avoid hypoglycemia.

   Participants will be educated on the signs and symptoms of hypoglycemia. They will also be provided with an information sheet containing instructions for how and when to seek medical care and notify the study staff in the event of any hypoglycemia or other adverse events.

ii. Injection Site Reactions: In placebo-controlled trials, injection site reactions (e.g., injection-site discomfort, erythema) were reported in 0.2% of OZEMPIC®-treated patients.

iii. Increases in Amylase and Lipase: In placebo-controlled trials, patients exposed to OZEMPIC® had a mean increase from baseline in amylase of 13% and lipase of 22%. These changes were not observed in placebo-treated patients.

We are recruiting patients with CF who are pancreatic insufficient and are likely not at risk of acute pancreatitis because of very little remaining exocrine tissue. We will monitor lipase level at baseline and week 12.

iv. Pancreatitis: In glycemic control trials, acute pancreatitis was confirmed by adjudication in 7 OZEMPIC®-treated patients (0.3 cases per 100 patient years) versus 3 in comparator-treated patients (0.2 cases per 100 patient years). One case of chronic pancreatitis was confirmed in an OZEMPIC®-treated patient. In a 2-year trial, acute pancreatitis was confirmed by adjudication in 8 OZEMPIC®-treated patients (0.27 cases per 100 patient years) and 10 placebo-treated patients (0.33 cases per 100 patient years), both on a background of standard of care.

We are recruiting patients with CF who are pancreatic insufficient and are likely not at risk of acute pancreatitis because of very little remaining exocrine tissue. We will monitor lipase level at baseline and week 12.

v. Cholelithiasis: In placebo-controlled trials, cholelithiasis was reported in 1.5% and 0.4% of patients-treated with OZEMPIC® 0.5 mg and 1 mg, respectively. Cholelithiasis was not reported in placebo-treated patients.

vi. Increases in Heart Rate In placebo-controlled trials, OZEMPIC® 0.5 mg and 1 mg resulted in a mean increase in heart rate of 2 to 3 beats per minute. There was a mean decrease in heart rate of 0.3 beats per minute in placebo-treated patients.

Heart rate and blood pressure will be monitored at each study visit.

vii. Fatigue, Dysgeusia and Dizziness Other adverse reactions with a frequency of >0.4% were associated with OZEMPIC® include fatigue, dysgeusia and dizziness.

viii. Hypersensitivity Reactions: Serious hypersensitivity reactions (e.g., anaphylaxis and angioedema) have been reported.

ix. Risk of Thyroid C-cell Tumors: In mice and rats, semaglutide caused a dose-dependent and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure at clinically relevant plasma exposures [see Nonclinical Toxicology. It is unknown whether OZEMPIC® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined.

x. Diabetic Retinopathy Complications: In a 2-year trial involving patients with type 2 diabetes and high cardiovascular risk, more events of diabetic retinopathy complications occurred in patients treated with OZEMPIC® (3.0%) compared to placebo (1.8%). The absolute risk

increase for diabetic retinopathy complications was larger among patients with a history of diabetic retinopathy at baseline (OZEMPIC® 8.2%, placebo 5.2%) than among patients without a known history of diabetic retinopathy (OZEMPIC® 0.7%, placebo 0.4%).

xi. Acute Kidney Injury: There have been postmarketing reports of acute kidney injury and worsening of chronic renal failure, which may sometimes require hemodialysis, in patients treated with GLP-1 receptor agonists. Some of these events have been reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. Excessive weight loss: Excessive weight loss leading to BMI going below the minimum goal threshold of 22 in women and 23 in men with cystic fibrosis, could be a potential concern.

We are recruiting subjects > BMI of 26 and so risk of BMI going below this threshold over 3 months therapy is unlikely. Should this occur the semaglutide dose will be reduced or discontinued.

Suicidal behavior and ideation have been reported in clinical trials with other weight management products. Semaglutide under the brand name WEGOVY® is approved for chronic weight management. WEGOVY® prescribing information recommends avoiding WEGOVY® (semaglutide) in patients with a history of suicidal attempts or active suicidal ideation. WEGOVY® will not be used in the current study.

General participation risks: There is always the risk of a loss of confidentiality in any study. Participant identifiable information will be stored securely to minimize this risk.

13.2 Reproduction Risks:

Pregnant women will not be eligible for participation.

13.3 Risks to Others:

Not applicable. No risk to others.

14.0 Potential Benefits to Participants

14.1 Potential Benefits:

Treatment with Semaglutide may result in improvement glucose control and weight loss, however these benefits cannot be guaranteed.

15.0 Statistical Considerations

15.1 Data Analysis Plan:

The primary outcomes are related to feasibility, including safety and treatment tolerability. Safety will be evaluated as the proportion (in %) of participants who experience a serious adverse event during the study. Tolerability will be evaluated as the proportion (in %) of participants who discontinue their assigned treatment due to side effects. A 95% exact confidence interval will also be calculated for the primary outcomes. Secondary outcomes will be change in glucose and insulin area under the curve during the OGTT and the time to peak insulin level. Additional secondary outcome measures include time in range, glycemic variability and time below range based on CGM, HbA1c, moderate/mild adverse events and if applicable insulin dose (IU/day for both bolus and basal). An exploratory analysis will be done to examine any potential impact of baseline β cell function as measured by OGTT based outcomes on the response and side effects to the study drug.

Safety will be assessed as the proportion of enrolled participants who experience severe adverse events (AE). Tolerability will be evaluated as the proportion (in %) of participants who discontinue their assigned treatment due to side effects. We will collect data on consent rate (proportion of all participants who were contacted and eligible who consented), and completion rate (proportion of subjects who complete all study visits).

We will also collect data on adherence to treatment intervention, and on the time needed to collect, clean and analyze data. Reasons for not consenting will be collected from subjects who decline participation in the study.

We will consider a consent rate of 20%, a completion rate of 80% as the criteria for assessing feasibility.

Study data will be collected using REDCap (https://www.ctsi.umn.edu/researcher-resources/tools-and-software/redcap). Data analysis will be carried out using SAS software version 9.4 (SAS Institute Inc., Cary, NC).

15.2 Power Analysis:

10 adult subjects with CF will be recruited. This sample size was chosen based on feasibility considerations. This is a pilot study and is not fully powered to demonstrate efficacy. This study will provide preliminary data (estimates of serious AE rate, tolerance, and effect sizes as well as of its variance) for a future larger placebo-controlled clinical trial.

15.3 Statistical Analysis:

Demographics and baseline characteristics of enrolled participants will be summarized using descriptive statistics. Mean, median, standard deviation, inter-quartile range, and range will be calculated for continuous outcomes at each time points as well as their changes compared to the baseline. Boxplots and trajectory curves will be plotted to display the distributions and longitudinal changes of the

variables. Paired t test or Wilcoxon signed-rank test (a nonparametric test) will be used to compare baseline with the final time point measures. Missing data will be excluded from analysis (when evaluating change from pre to post, participants with missing data at either pre or post will be excluded). The analyses will be done on an intention-to-treat basis, which will consist of all patients who receive at least one dose of study drug (once a patient is enrolled, he/she will be included in analysis, unless there is missing data for pre-post change); regardless of whether he/she completed the treatment).

15.4 Data Integrity:

The PI will periodically review data for completeness and to ensure that all procedures are being followed as detailed in the protocol. The assigned Regulatory Specialist will also perform periodic quality assurance monitoring at any point requested by the PI.

16.0 Health Information and Privacy Compliance

16.1 Select which of the following is applicable to your research:

☐ My research does not require access to individual health information and therefore assert HIPAA does not apply.

x I am requesting that all research participants sign a HIPCO approved HIPAA Disclosure Authorization to participate in the research (either the standalone form or the combined consent and HIPAA Authorization).

☐ I am requesting the IRB to approve a Waiver or an alteration of research participant authorization to participate in the research.

Appropriate Use for Research:

☐ An external IRB (e.g. Advarra) is reviewing and we are requesting use of the authorization language embedded in the template consent form in lieu of the U of M stand-alone HIPAA Authorization. Note: External IRB must be serving as the privacy board for this option.

16.2 Identify the source of Private Health Information you will be using for your research (Check all that apply)

☐ I will use the Informatics Consulting Services (ICS) available through CTSI (also referred to as the University's Information Exchange (IE) or data shelter) to pull records for me

x I will collect information directly from research participants.

☐ I will use University services to access and retrieve records from the Bone Marrow Transplant (BMPT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) database.

x I will pull records directly from EPIC.

☐ I will retrieve record directly from axiUm / MiPACS

☐ I will receive data from the Center for Medicare/Medicaid Services

☐ I will receive a limited data set from another institution

☐ Other. Describe:

16.3 Explain how you will ensure that only records of patients who have agreed to have their information used for research will be reviewed.

During the pre-screening process, only those patients who have not opted out of having their records used for research will be screened. However, providers who have a treating relationship with the patient may discuss research opportunities during a clinical encounter regardless of research opt-out status and opt-out status will not matter if a participant contacts us first.

16.4 Approximate number of records required for review:

We anticipate reviewing 50 records in order to meet our required sample size.

16.5 Please describe how you will communicate with research participants during the course of this research. Check all applicable boxes

☐ This research involves record review only. There will be no communication with research participants.

☐ Communication with research participants will take place in the course of treatment, through MyChart, or other similar forms of communication used with patients receiving treatment.

x Communication with research participants will take place outside of treatment settings. If this box is selected, please describe the type of communication and how it will be received by participants.

We may communicate with participants via:

- Telephone (using a study-specific phone number);

- Text message if participants agree that we may communicate with them by text message by signing the Unsecured Email Authorization Form and/or UMN Text Guidelines and Consent for Text Message Correspondence For Research Participants Form, if they have not signed previously.;

- Unsecure email if the participants agree that we may communicate with them through unsecured emails by signing the Unsecured Email Authorization Form, if they have not signed previously.

16.6 Explain how the research team has legitimate access to patients/potential participants:

Patients come from the Study Investigator's patient population and/or are followed at the MN CF Center.

The research team will be permitted to access sources of private information once enrolled because all participants will be required to sign a HIPAA waiver at the time of informed consent.

16.7 Location(s) of storage, sharing and analysis of research data, including any links to research data (check all that apply).

☐ In the data shelter of the Information Exchange (IE)

☐ Store ☐ Analyze ☐ Share

☐ In the Bone Marrow Transplant (BMT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) Database

☐ Store ☐ Analyze ☐ Share

x In REDCap (recap.ahc.umn.edu)

x Store x Analyze x Share

☐ In Qualtrics (qualtrics.umn.edu)

☐ Store ☐ Analyze ☐ Share

x In OnCore (oncore.umn.edu)

x Store ☐ Analyze ☐ Share

x In the University's Box Secure Storage (box.umn.edu)

x Store xAnalyze x Share

x In an AHC-IS supported server. Provide folder path, location of server and IT Support Contact:

MedDerm (\\med.ahc.umn.edu\med) (N:)

x Store ☐ Analyze ☐ Share

☐ In an AHC-IS supported desktop or laptop.

Provide UMN device numbers of all devices:

☐ Store ☐ Analyze ☐ Share

☐ Other. Describe:

Indicate if data will be collected, downloaded, accessed, shared or stored using a server, desktop, laptop, external drive or mobile device (including a tablet

computer such as an iPad or a smartform (iPhone or Android devices) that you have not already identified in the preceding questions

☐I will use a server not previously listed to collect/download research data

☐I will use a desktop or laptop not previously listed

☐I will use an external hard drive or USB drive ("flash" or "thumb" drives) not previously listed

☐I will use a mobile device such as an tablet or smartphone not previously listed

16.8 Consultants. Vendors. Third Parties.

N/A

16.9 Links to identifiable data:

All data will be labeled with an identification code unique to the participant. Study staff will keep the mapping of this identification code to the identity of the participant separately from the data in REDCap, UMN Box, or an HST-IS supported server. Any internal data reports will use only these codes and will not use any identifiable information. Any external data reports, abstracts, publications, presentations, etc. will present de-identified, grouped, and/or aggregate data. Any reports to the University of Minnesota IRB (such as Adverse Event reporting and annual renewal reports) will be kept confidential; they will not include participant- identifiable information; only the participant's identification code will be used.

16.10 Sharing of Data with Research Team Members.

Only IRB-approved members of the study team will have access to the data. Data will be shared through the medical record, OnCore, REDCap, HST-IS secure server, or UMN Box.

16.11 Storage of Documents:

Paper documents will be stored in a locked cabinet in a locked research office only accessible to research staff. Electronic documents will be stored in REDCap, UMN Box, and an HST-IS supported server.

16.12 Disposal of Documents:

We will retain research documents for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified. HIPAA forms will be retained for 6 years.

If the records are moved offsite during or after this time period, they will be housed in the Academic Health Center Storage Facility at the following address:

Reuse/AHC Warehouse 883 29th Ave SE Minneapolis, MN 55414. Records are retrievable at any time once they are moved to this storage facility.

We will then dispose of paper documents in a secure UMN shredding/document destruction box. All electronic documents will be archived in the HST-IS supported server.

17.0 Confidentiality

17.1 Data Security:

All standard confidentiality procedures will be observed for this study and all research staff will be trained before they will be allowed contact with participants or data.

All University of Minnesota confidentiality and privacy policies and procedures will be followed by all research staff.

CRF data for this study will be entered into a REDCap database, which uses a MySQL database via a secure web interface with data checks used during data entry to ensure data quality. REDCap includes a complete suite of features to support HIPAA compliance, including a full audit trail, user-based privileges, and integration with the institutional LDAP server. The MySQL database and the web server are housed on secure servers operated by the University of Minnesota Academic Health Center's Information Systems group (AHC-IS). The servers are in a physically secure location on campus and are backed up nightly, with the backups stored in accordance with the AHC-IS retention schedule of daily, weekly, and monthly tapes retained for 1 month, 3 months, and 6 months, respectively. Weekly backup tapes are stored offsite. The AHC-IS servers provide a stable, secure, well-maintained, and high-capacity data storage environment, and both REDCap and MySQL are widely used, powerful, reliable, well-supported systems. Access to the study's data in REDCap will be restricted to the members of the study team by username and password.

REDCap™ files will be exported to shared drives housed under HIPAA-compliant AHCIS servers on the MedDerm (\\med.ahc.umn.edu\med)(N:) shared drive or UMN Box. Any other identifiable electronic data, including logs, will also be password-protected and stored on this HIPAA-compliant server and UMN Box. Only study members will have access to the MedDerm folder/server and UMN Box. All paper data, source or CRF or otherwise, will be kept in locked cabinets in locked research offices.

In order to certify study data entered into REDCap, completed REDCap data collection forms will be printed, reviewed and verified (by signing and dating) as final by the PI or a designated member of the study team. Upon review and verification, the data on these forms will serve as the final study data.

Consent documents will not be placed in the participant's medical record.

Vitals, height/weight and CGM will not be entered in the participants' medical records.

17.2 Data Sharing:

Prior to sharing any study data, all personal identifiers will be removed from the dataset and replaced with participants' unique study identifier. The link associating participants with their study identifier will not be shared with outside researchers. Data will only be shared with other researchers after they have provided the study protocol and IRB approval (or Determination of Non-Human Participants Research), and completed a Data Use Agreement form with the Health Information Privacy and Compliance Office at the University of Minnesota.

18.0 Provisions to Monitor the Data to Ensure the Safety of Participants

18.1 Data Integrity Monitoring.

While there will be no planned interim data analysis, the PI will periodically review data for completeness and to ensure that all procedures are being followed as detailed in the protocol.

The study will be monitored twice yearly in accordance with CTSI monitoring policies.

The study will permit trial-related monitoring, audit, IRB review, and regulatory inspection, providing direct access to source data/documents.

18.2 Data Safety Monitoring.

It will be the responsibility of the Principal Investigator to oversee the safety of the study. The PI will review cumulative raw data, trends in AEs, SAEs and UPIRTSO on an ongoing basis. Safety data will be captured in the CRFs for each visit. Any safety event meeting the IRB's urgent reporting criteria will be reported to the IRB within its published timelines.

In addition to the PI's responsibility for oversight, a data and safety monitoring board (DSMB) will be established, which will include at least one obesity medicine specialist or endocrinologist, and one biostatistician. DSMB members will not be affiliated with the study. The DSMB will meet regularly (frequency to be determined by DSMB members but no less than every six months) during the study to review data and evaluate participant safety.

A charter for the DSMB will be developed and approved by its members along with a plan for frequency of data review prior to the commencement of the study. Review materials for the DSMB will be prepared and presented by the study biostatistician. A report from each meeting will be sent to the PI and co-investigators advising on the continuation of the study and any suggestions for trial improvement. This report will also be sent to the IRB. Important charges of the DSMB will be to closely monitor progress and timelines related to recruitment

goals, fidelity to the protocol (e.g. regularly review the number and types of protocol deviations), and to closely monitor the quality and integrity of the data. The DSMB will communicate any concerns relevant to these issues of study conduct to the PI and note specific recommendations for improvement in meeting reports.

Adverse Event (AE) vs. Serious Adverse Event (SAE): An adverse event is any undesirable experience associated with the use of a medical product in a participant. A serious adverse event (SAE) will immediately be reported to the FDA when the participant outcome is:

- **Death:** Report if you suspect that the death was an outcome of the adverse event, and include the date if known.
- **Life-threatening:** Report if suspected that the patient was at substantial risk of dying at the time of the adverse event, or use or continued use of the device or other medical product might have resulted in the death of the patient.
- **Hospitalization (initial or prolonged):** Report if admission to the hospital or prolongation of hospitalization was a result of the adverse event. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).
- **Disability or Permanent Damage:** Report if the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant, persistent or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities and/or quality of life.
- **Congenital Anomaly/Birth Defect:** Report if you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.
- **Required Intervention to Prevent Permanent Impairment or Damage (Devices):** Report if you believe that medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.
- **Other Serious (Important Medical Events):** Report when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

Severity of an adverse event: The following guidelines will be used to describe severity of an adverse event.

- **Mild:** Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate:** Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe:** Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

Relationship to study intervention: The following guidelines will be used to describe the "relatedness" of an adverse event.

- **Related:** The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related:** There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

Expectedness: The Investigator will be responsible for determining whether an adverse event is expected or unexpected. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

Reporting of adverse events: Information on all adverse events will be collected including the:

- Event description
- Time of onset
- Assessment of severity
- Relationship to study intervention
- expectedness
- Time of resolution/stabilization of the event

All adverse events occurring while on study will be documented appropriately regardless of relationship. All adverse events will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an adverse event. However, if

the participant's condition deteriorates at any time during the study, it will be recorded as an adverse event.

The investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious adverse events) or 30 days (for serious adverse events) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of the adverse event since the last visit.

19.0 Provisions to Protect the Privacy Interests of Participants

19.1 Protecting Privacy:

Participants will sign a consent form and a HIPAA Authorization which will detail what data and under what circumstances will be shared with research staff and non-research staff.

It is not anticipated that any survey will ask intrusive or difficult questions. However, surveys will be explained in full detail in the consent so that participants can make informed decisions before they enroll.

The consent will also detail under which conditions any information may be shared with those outside of the internal research staff.

Confidentiality of the research participants will be maintained. All data will be stored in locked offices and will not be released without consent of participants. Data to be used in scientific presentations or publications will not contain participant identifiers.

All material will be used exclusively for research. Pre-existing chart (electronic medical record) information may also be used. Data obtained will be stored in a confidential database. The principal investigator and designated study staff will have access to the linkages, which will be stored in a separate, secured location. Hard copies of data, including source documents with identifiers, will be kept in locked file cabinets in a locked office until the completion and publication of the study, at which time any identifiers will be removed and data will be stored at a secure storage facility for 7 years. Access to the locked file cabinet will be given to the study coordinators and principal investigator only.

19.2 Access to Participants*:*

Participants will sign a consent and HIPAA authorization.

Some of the participants, but not all, will be patients of the Fairview system and some will be patients of the PI. Accessing their medical records with their permission will make it easier for them to participate in the study so that we can verify their diagnoses without asking them to find and share copies of their medical records in order to qualify for the study. If they do not wish for the study to access their medical records directly, they may also share the components of their medical records that support their diagnosis.

20.0 Compensation for Research-Related Injury

20.1 Compensation for Research-Related Injury:

In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to the subject or their insurance company

20.2 Contract Language:

Not applicable. No contract.

21.0 Consent Process

21.1 Consent Process (when consent will be obtained):

At the start of the study, informed consent will be obtained by the research coordinator or PI in person. All consent procedures will take place remotely or at the CSC or clinical research unit (CRU) in a private room. The entire consent document will be verbally explained to eligible participants, including all study procedures and expectations, risks, benefits, and what volunteering means. Candidates will be given time to read the consent before their scheduled Screening/Visit 1, ask questions, and have as much time needed to review. The study team will ask the participant questions about the informed consent form to assess comprehension. If the study team feels the participant understands what's being asked of them, the participant and study team will sign the informed consent form. This will be done prior to any procedures being conducted. The participants may withdraw consent at any time throughout the course of the study. Photocopy of signed ICF/HIPAA will be provided to the participant. Throughout the study, specific risks and procedures will be reviewed to ensure continued voluntary and informed consent.

21.2 Waiver or Alteration of Consent Process (when consent will not be obtained):

Not applicable. No waiver or alteration of consent will be requested or used.

21.3 Waiver of Written/Signed Documentation of Consent (when written/signed consent will not be obtained):

We are requesting a waiver of written/signed documentation of consent for the pre-screening portion of this study. A short phone script will be read to the participant before any pre-screening questions are asked. The participant will need to provide verbal consent to answering these pre-screening questions before proceeding. This waiver will not adversely affect the rights and welfare of the participants. Their clinical care with the CF care team and with M Health Fairview will not be affected adversely by their pre-screening responses. Furthermore, we will obtain written consent at the Screening/Visit 1 in person.

21.4 Non-English Speaking Participants:

Not applicable. No non-English speaking participants will be enrolled.

21.5 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age):

Not applicable. No individual under the age of 18 will be enrolled.

21.6 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent:

Not applicable. No adult with cognitive impairment or with fluctuating or diminished capacity will be enrolled. The PI and study staff with consent delegation have completed necessary Capacity to Consent trainings and will be available for assessments as necessary and appropriate using the MacCAT-CR process solely (not the shorter UBACC tool).

21.7 Adults Unable to Consent:

Not applicable. All individuals will be able to consent for themselves.

22.0 Setting

22.1 Research Sites:

All participant-facing procedures including consent will take place remotely, at CSC, or clinical research unit (CRU). Non-participant involved activities will take place in coordinator and staff offices.

22.2 International Research:

Not applicable

23.0 Multi-Site Research

Not applicable. Single site only.

24.0 Coordinating Center Research

Not applicable

25.0 Resources Available

25.1 Resources Available:

The CF center at the University of Minnesota cares for about 540 patients including 400 adults and 140 children (excluding transplant patients). These data indicate that we have the eligible patient to recruit successfully for this pilot study.

We have an established research team at the MN CF Center. Our research team has adequate space and equipment to perform the research procedures.

Participants will be referred to an endocrinologist or their personal physician for any medical or psychological evaluation that may be required as a result of the research. We have a dedicated CF Center clinical team. The care and well-being of our patients is priority over research. If the patient needs medical care due to a consequence of the research study, it will be provided to them.

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