Targeting pancreatic cancer with sodium glucose transporter 2 (SGLT2) inhibition

Washington University School of Medicine
Division of Oncology
660 South Euclid Avenue, Campus Box 8056
St. Louis, MO 63110

Protocol #: 202011019
Version Date: 07 April 2022

Principal Investigator: **Kian-Huat Lim, M.D.**
Phone: (314) 362-6157
E-mail: kian-huat.lim@wustl.edu

Sub-Investigators	**Modality**
Linda R. Peterson, M.D.	Cardiology
Joseph E. Ippolito, M.D., Ph.D.	Radiology
Janet McGill, M.D.	Endocrinology
William Hawkins, M.D.	HPB Surgery
Elena Deych, M.S.	Biostatistics

Study Drug: dapagliflozin
Study Device: N/A

IND#: 153028 EXEMPT
IND Sponsor: Linda Peterson, M.D.
NCT#: NCT04542291
Funded by: NIH Pancreas SPORE grant

Targeting pancreatic cancer with sodium glucose transporter 2 (SGLT2) inhibition

Protocol Revision History

Initial Approval Version	**06 Oct 2020**
Amendment #1 Version	**29 July 2021**
Amendment #2 Version	**07 April 2022**

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) 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 IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Table of Contents

PROTOCOL SUMMARY

Synopsis

Title:	Targeting pancreatic cancer with sodium glucose transporter 2 (SGLT2) inhibition
Study Description:	This is a first-in-human, pilot study of the feasibility and safety of dapagliflozin (in addition to standard of care treatment) for the treatment of patients with metastatic pancreatic ductal adenocarcinoma. Our primary hypothesis is that dapagliflozin is well-tolerated and safe to use in this patient population. We also hypothesize that dapagliflozin will be efficacious as an adjunct to front-line chemotherapy assessed by decreased tumor markers mediated by its pleiotropic metabolic effects.
Objectives:	Primary Objective: To assess tolerability and determine the optimal dosage of dapagliflozin added to standard of care front-line chemotherapy for metastatic pancreatic ductal adenocarcinoma. Secondary Objective: To explore the effects of dapagliflozin on metabolic and tumor response in patients with metastatic pancreatic ductal adenocarcinoma.
Endpoints:	Primary Endpoint: Toxicity by CTCAE v 5.0. Secondary Endpoints: Changes in clinical laboratory metabolic parameters (plasma glucose, ketones, HbA1c), CT-based body composition (visceral fat), and tumor markers (plasma CA19-9) and CT-quantified tumor size and tumor necrosis from pre-therapy to post-8 weeks of therapy.
Study Population:	Up to eighteen patients with metastatic pancreatic ductal adenocarcinoma undergoing treatment with nab-paclitaxel and gemcitabine in the frontline setting will be enrolled in this study. Additionally, retrospective data will be accessed for up to 16 matched controls who have received nab-paclitaxel and gemcitabine SOC chemotherapy.
Phase:	Ib
Description of Sites / Facilities Enrolling:	This study will be open to enrollment at the Siteman Cancer Center at Washington University School of Medicine.
Description of Study Intervention:	Dapaglifozin is an oral medication taken once daily.
Study Duration:	6.5 mo/subject; total time for enrollment and follow-up of all patients ~ 13 mo.
Participant Duration:	The intervention is an 8-week course of treatment.

SCHEMA

Eligible Patients
Metastatic pancreatic ductal adenocarcinoma undergoing treatment with nab-paclitaxel and gemcitabine in the frontline setting

Treatment Plan

- Dapagliflozin will be initiated PO QD at the same time as nab-paclitaxel and gemcitabine SOC chemo
- Dapagliflozin will be initiated at 5 mg PO QD, D1-D14 (2 weeks)
- Dapagliflozin will be escalated to 10 mg PO QD for 6 weeks. Dose adjustment will need to be approved by endocrinologist Dr. McGill/or another attending MD diabetologist at WUSM on the HRPO-approved study team. This dose is reflective of current clinical practice for diabetes and heart failure.
- Dapagliflozin toxicity will be assessed by criteria detailed below.
- All patients will stop taking dapagliflozin after 8 weeks of treatment.
- Nab-paclitaxel and gemcitabine chemotherapy dose adjustment will be made per oncologist's judgement.

Cohort	Days of treatment	Dapagliflozin (QD)	Gemcitabine (D1, 8, 15, q28 days)	Nab-paclitaxel (D1, 8, 15, q28 days)
Patients with metastatic PDAC, frontline setting	C1D1-C1D14	5mg	1000 mg/m^2	125 mg/m^2
	C1D15-C2D28	10 mg		

SCHEDULE OF ACTIVITIES

There is a +/- 2-day window for all assessments with the exception of C1D15, which has a -2 day window.

	Screening[1]	C1D1	C1D15	C2D1	C2D15	C2D28	EOT[8]	F/U[2]
Informed consent	X							
H&P, ECOG PS, VS	X	X	X	X	X		X	X
Meet w/Dr. McGill / endocrinologist[9]	X	X	X[11]	X[12]	X[12]		X[12]	
Weight	X	Weekly						
Pregnancy test[3]	X							
CBC	X	X	X	X	X		X	
Fasting CMP[4]	X	X	X	X	X		X	
HbA1c	X				X			
Urinalysis	X	X	X	X	X		X	
Beta-hydroxybutyrate ketone[5]		X			X			
Fasting serum c-peptide[5]		X			X			
Fasting serum glucagon[5]		X			X			
Fasting serum pancreatic polypeptide[5]		X			X			
Serum CA19-9	X	X		X			X	
Home quantitative fingerstick glucose	As clinically indicated							
Home BIOSENSE ketone breath monitoring[13]		Daily						
Urine ketone dipstick		Weekly						
CT/MRI scan	X[7]						X[6]	
Dapagliflozin[10]		PO QD C1D1 through C2D28						
SOC chemotherapy		Per SOC						
AE assessment		Continuous[14]						

1. within 14 days prior to C1D1
2. biweekly for the first month after completion of study treatment and Q4W for 3 months thereafter; the first month of f/u can be in person or by phone with local records sent to the study team, while the remainder will be chart-based
3. women of childbearing potential only
4. visits for CMP to be in morning (fasting after midnight, sips of water allowed); screening CMP may be non-fasting
5. research study (results not necessary for conduct of this study)
6. may be up to 7 days before C3D1
7. can be within 28 days before C1D1
8. end of treatment will likely align with C3D1 of SOC chemotherapy; patients may continue SOC chemotherapy at the discretion of their physician after discontinuation of study treatment with dapagliflozin
9. may occur in person or by phone
10. cycles are 28 days but dispensing will occur every 2 weeks
11. assessment by endocrinologist is required on C1D15 (-2 day window) prior to the patient taking the C1D15 dose of dapagliflozin
12. endocrinologist evaluations after C1D15 are as clinically indicated. Endocrinology evaluations at Screening, C1D1, and C1D15 are mandatory.
13. BIOSENSE monitoring to occur once daily prior to breakfast (preferably). See section 5.3 for more information.
14. Patients will be contacted weekly, either in person or by phone, while patient is taking dapagliflozin. After completion of dapagliflozin, patient contacted biweekly until 30 days after the last dose.

1.0 INTRODUCTION

1.1 Study Rationale

Dapagliflozin, a sodium glucose transporter 2 inhibitor (SGLT2i), is FDA-approved and has been used in numerous worldwide clinical trials. Much data exists regarding pharmacokinetic profiles of the drug as well as safety and dosing profiles in diabetic patients and those with heart failure.[2, 3] However, to our knowledge, this drug has not been studied in the pancreatic ductal adenocarcinoma (PDAC) patient population. PDAC patients may be deconditioned with decreased oral intake and altered nutritional profiles. Moreover, the prevalence of diabetes and impaired glucose tolerance in pancreatic cancer cases may be as high as 80%, and reports have linked molecular mediators from PDAC tumors to the development of insulin resistance in these patients.[4] Insulin deficiency is common due to local mass effects and pancreatic resection.[4] Therefore, studies need to be performed to evaluate the safety and tolerability of SGLT2i in PDAC patients who are receiving chemotherapy. This study will evaluate the effect of dapagliflozin dosing on tolerability, safety and side effects in PDAC patients. As part of an innovative component to this proposal, we will utilize quantitative ketone breathalyzers to monitor side effects remotely and with real-time result transmission to the study team that will be used alongside conventional measurement methods for ketones.

1.2 Background

1.2.1 Pancreatic Ductal Adenocarcinoma

Pancreatic ductal adenocarcinoma (PDAC) is invariably lethal. Not including COVID-19, cancer is the second leading cause of death in the United States.[5] Pancreatic cancer has the 7th highest incidence with an estimated 57,600 diagnoses this year. However, pancreatic cancer has the 4th highest mortality of all cancers.[5] PDAC is a histologic subtype of pancreatic cancer that accounts for more than 90% of all pancreatic cancers[6] and is an invariably lethal cancer with a 5 year mortality of 91%.[5] Unfortunately, mortality due to pancreatic cancer has been relatively unchanged despite advances in cancer treatments.[5] Because of the lethal progression of this disease and the inability to achieve significant increases in survival, new avenues need to be explored that delve into mechanisms that underlie disease progression, but even more importantly, mechanisms that are targeted by currently FDA-approved drugs that can be rapidly repurposed for pancreatic cancer. Metabolism is one avenue that meets all of these criteria.

1.2.2 Enhanced Glycolysis in PDAC

Glucose metabolism is a rational target for PDAC treatment. Several lines of evidence have demonstrated the prognostic potential of glucose utilization in pancreatic cancer. FDG-PET has been demonstrated as a highly sensitive modality for pancreatic cancer detection with a pooled sensitivity of 90%.[7, 8] Enhanced glycolysis is one of the most, if not the most, critical metabolic alteration in

pancreatic cancer that is driven by the *KRAS* mutation. Enhanced glycolysis has also been recognized as an important metabolic alteration in PDAC metastasis that involves the epithelial–mesenchymal transition, angiogenesis, and subsequent seeding of cancer cells in distant organs.[9, 10] One mechanism for this phenomenon involves the uptake of glucose and its conversion to lactate to recycle NAD and generate 2 ATP for the rapid energy generation required for cell viability (Warburg Effect).[11] However, tumor growth also requires anabolic metabolism, or the ability to synthesize building blocks such as DNA, RNA, proteins, and lipids. The pentose phosphate pathway (PPP) uses glucose carbons to synthesize nucleotides, aromatic amino acids and generate the reducing equivalent NADPH, pathways that other cancer nutrients, such as glutamine, cannot supply.[12] This has clinical implications, as the presence of diabetes and increased serum glucose increases the risk of PDAC.[13] To further underscore the significance of this finding, we obtained metabolic data from a cohort of over 200 early stage PDAC patients from Siteman. We identified that patients with a random serum glucose *over* 112 mg/dL at diagnosis had a significantly shorter median OS (15 months) than patients under that glucose level (29 months; p=0.004; **Figure 1**). Collectively, these data suggest that reducing PDAC tumor access to glucose may have therapeutic benefit.

1.2.3 SGLT2i in PDAC Glucose Metabolism

Sodium Glucose Transport Protein 2 (SGLT2) inhibitors impact both systemic and PDAC glucose metabolism. Metformin, an anti-diabetic drug, has been evaluated in patients with PDAC. Although metformin was initially found to increase survival in diabetic PDAC patients, recent data suggest that there is no correlation between metformin and PDAC patient survival.[9] Of note, metformin is believed to target mitochondrial oxidative phosphorylation with indirect effects on glucose uptake and metabolism. Although this works in non-cancerous cells with intact mitochondria and central carbon metabolism, metformin may not necessarily work with the same efficacy in PDAC tumor cells with dysfunctional mitochondria that may help explain the clinical results. Therefore, drugs that interfere *directly* with tumor glucose uptake or metabolism may have more efficacious results.

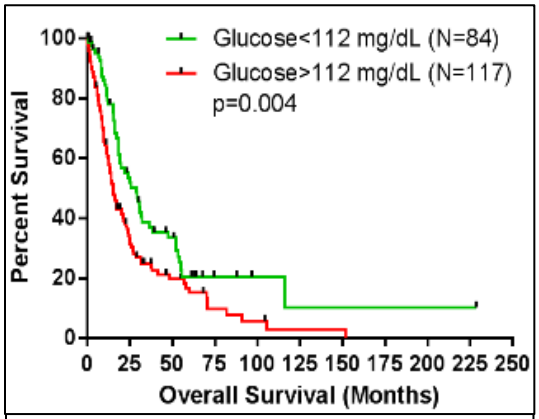


Figure 1. Higher random serum glucose at diagnosis is associated with shorter median OS (15 months vs 29 months) in Siteman PDAC patients. Threshold identified with an optimized cutoff finding algorithm.

In our search for novel metabolic therapeutics for pancreatic cancer, we have uncovered exciting new data showing mechanistic plausibility and preliminary

effectiveness of SGLT2 inhibitors (SGLT2i) for the treatment of PDAC. SGLT2i are a class of glucose-lowering drugs that inhibit renal glucose reabsorption and reduce serum glucose and increase urinary glucose as a result. They are not only FDA-approved for glycemic control in type 2 diabetes mellitus (T2DM), but they are currently showing significant potential in preventing heart failure decompensation and lowering cardiovascular risk in patients with T2DM.[14]

SGLT2i has three key benefits for PDAC therapy. First and foremost, expression of the glucose transporter SGLT2 is distinct from conventional glucose transporter (GLUT) expression in PDAC. SGLT2 immunohistochemistry successfully localizes SGLT2 expression to neoplastic duct cells, not the surrounding stroma or inflammatory cells[1] (**Figure 2A**). Second, functional expression of SGLT2 in clinical PDAC specimens has been demonstrated with the SGLT2-specific positron emission tomography (PET) tracer, [^{18}F] Me-4DG.[1] Thus, SGLT2 transporter quantification in tumors can be measured non-invasively and be used to predict response to therapy, as already has been ***done in humans*** with brain tumors.[15] Third, SGLT2i modulates systemic metabolism and therefore, tumor access to glucose is reduced, which leads to increased tumor cell death (**Figure 2B**). Lastly, SGLT2i has pleiotropic metabolic effects that decreases serum glucose, increases mild ketonemia, and reduces visceral obesity,[14, 16-22] all of which improve can survival in patients with cancer, particularly PDAC (**Figure 3**).[23-27]

1.2.4 SGLT2i in the Treatment of Other Diseases

SGLT2i therapy has been shown to be generally safe and effective for type 2 diabetes and for heart failure. Tens of thousands of patients have been studied in randomized, placebo-controlled trials including the DECLARE study[28] and EMPA-REG study.[29] In the EMPA-REG trial of 7,020 subjects with type 2 diabetes, patients receiving empagliflozin had a *lower rate of all-cause death* or a composite of major cardiovascular events. In the recent DECLARE study (N=17,160), not only was there was a lower rate of cardiovascular death or hospitalization for heart failure with dapagliflozin, but there was also a low incidence of adverse events (AEs) or serious adverse events (SAEs). In fact, there were fewer SAEs in the dapagliflozin group than in the placebo group (p<0.001). There were fewer major hypoglycemic events (p=0.02), acute kidney injury events (p=0.002), and fewer bladder cancers

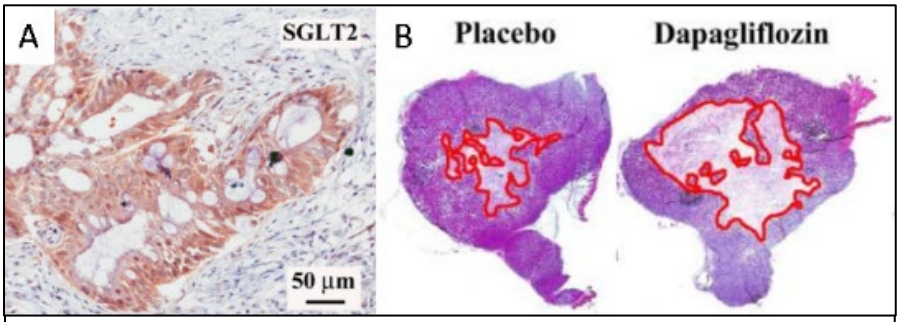


Figure 2. SGLT2 is a therapeutic target in PDAC. A. Tumor cell-specific expression of SGLT2 in PDAC. **B.** SGLT2i dapagliflozin treatment of a PDAC xenograft results in increasd tumor necrosis (red margin). Data from ref.[1]

(p=0.02). The risk of death from any cause was 7% less in the dapagliflozin group, but it did not reach statistical significance. "The rates of amputation, fracture, volume depletion, hypersensitivity, and urinary tract infections were balanced between the groups."[28] However, there were more genital infections in the dapagliflozin-treated groups (<0.001). Note that subjects in our trial will be monitored carefully for infections and will be given instructions on infection prevention. Diabetic ketoacidosis (DKA), though rare, was also higher in the SGLT2i treated group (0.3%) than in the placebo group (0.1%). Greater than 80% of these with DKA were patients with insulin-requiring diabetes.[28] For this reason, PDAC patients in this trial will not have insulin-requiring diabetes.

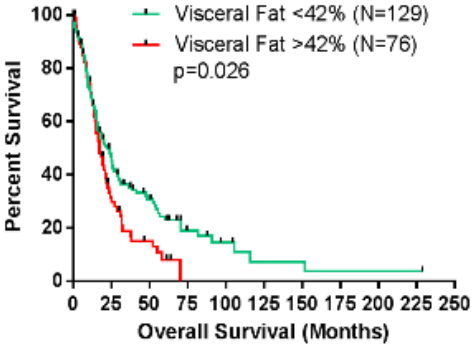


Figure 3. Increased visceral obesity measured by CT in Siteman PDAC patients has poorer outcomes. *Visceral fat % threshold identified with an optimized cutoff finding algorithm.*

The promise of SGLT2i-mediated metabolic modulation of cancer has yet to be extensively addressed in the literature and will be the focus of this proposal. As of now, only one clinical trial exists (NCT04073680) that tests the efficacy of SGLT2i in conjunction with PI-3K inhibitors in advanced solid tumors. The ability to simultaneously decrease serum glucose and inhibit tumor glucose uptake is a very appealing property of SGLT2i and not present in the vast majority of diabetic medications. Here, we will combine the SGLT2i dapagliflozin with conventional chemotherapy to assess tolerability and metabolic effects in PDAC patients. This feasibility study will set the stage for larger, more comprehensive trials in pancreatic cancer that will integrate metabolism, imaging, and therapeutics. In summary, identification of metabolic features that influence patient outcomes and are targetable with current clinical imaging and therapeutic workflows is highly innovative and represents a significant unmet need for patients with PDAC.

1.3 Study Design

This is a longitudinal, dose-finding, open label safety and tolerability phase Ib treatment study. The study hypothesis is that dapagliflozin will be well-tolerated by PDAC patients on chemotherapy as assessed by tolerability and side effect profiles. The dose escalation scheme will consist of 5 mg of dapagliflozin once per day for 2 weeks, followed by escalation to 10 mg once per day for 6 weeks if the 5 mg dose is tolerated.

1.4 Risk/Benefit Assessment

1.4.1 Known Potential Risks

The most common side effects of dapagliflozin include: (i) vaginal yeast infections and yeast infections of the penis, (2) stuffy or runny nose and sore throat, (3) changes in urination, including urgent need to urinate more often, in larger amounts, or at night.

Less likely risks include intravascular volume depletion which may manifest as symptomatic hypotension or acute transient changes in creatinine. Patients with impaired renal function (eGFR < 60 mL/min/1.73m^2), elderly patients, or patients on loop diuretics may be at increased risk for volume depletion. To mitigate against this, subjects will be educated and given handouts regarding the importance of staying hydrated and holding dapagliflozin therapy if they are not taking p.o. well. Other less likely risks are urinary tract infections, hypoglycemia (when coadministered with insulin and insulin secretagogues; to mitigate against this, subjects will be meet with an endocrinologist and be educated regarding this possibility. Patients with diabetes will be required to monitor their glucose throughout the study using home glucometers), genital mycotic infections (see Appendix C).

Rare risks include acute kidney injury requiring hospitalization and dialysis, ketoacidosis in diabetes mellitus (to mitigate against this, subjects will be educated and tested at screening. Subjects will be followed by an endocrinologist and will have home monitoring systems for ketosis. Conventional urine ketone monitoring using dipsticks will be provided to patients and will be measured weekly (see testing schedule). This will be supplemented with QD ketone breath monitoring as an investigational tool (see Appendices A and B) that will allow for frequent monitoring of abnormally high levels of ketones that will be reported to the clinical research assistant and investigators.

Note: In the DECLARE-TIMI 58 trial[28], “key safety results” are provided in Table 2 and in Table S3 in the Supplementary Material[28],. Fewer patients in the dapagliflozin group than in the placebo group discontinued the assigned regimen during the course of the trial, and fewer patients in the dapagliflozin group reported a serious adverse event or had major hypoglycemia (see the Supplementary Material[28],), acute kidney injury, or bladder cancer. The rates of amputation, fracture, volume depletion, and hypersensitivity were balanced between the groups. Diabetic ketoacidosis was more common in the dapagliflozin group than in the placebo group (0.3% vs. 0.1%; hazard ratio, 2.18; 95% CI, 1.10 to 4.30; P=0.02). More than 80% of patients with diabetic ketoacidosis were using insulin at baseline. Genital infections that led to discontinuation of the trial regimen or were considered to be serious adverse events were more common in the dapagliflozin group than in the placebo group (0.9% vs. 0.1%; hazard ratio, 8.36; 95% CI, 4.19 to 16.68; P<0.001), both in men and in women, although genital infections reported as

serious adverse events were rare (two events in each group). Six cases of Fournier's gangrene were re- ported, one in the dapagliflozin group and five in the placebo group."

In addition, "In a pool of 12 placebo-controlled studies, the most common adverse reactions (≥5%) associated with FARXIGA 5 mg, 10 mg, and placebo respectively were female genital mycotic infections (8.4% vs 6.9% vs 1.5%), nasopharyngitis (6.6% vs 6.3% vs 6.2%), and urinary tract infections (5.7% vs 4.3% vs 3.7%)." (https://www.farxiga-hcp.com/dosing.html)

1.4.2 Known Potential Benefits

- An FDA-approved indication for patients with heart failure (NYHA class II-IV) with reduced ejection fraction, to reduce the risk of CV death and hospitalization for heart failure
- An FDA-approved indication in patients with type 2 diabetes with evident cardiovascular disease (CVD) or CVD risk factors to reduce the risk of hospitalization for heart failure.
- An FDA-approved indication to improve glycemic control in patients with type 2 diabetes.
- Decrease in weight (DECLARE-TIMI 58 study)
- Decrease in systolic and diastolic blood pressure
- Significantly less likely (HR 0.53; CI 0.43-0.66) to have a 40% decrease in eGFR, ESRD, or renal death. (DECLARE-TIMI 58 study).

Additionally, known benefits of dapagliflozin in animal models include:

- Mild ketonemia (which can have anti-tumor effects)
- Increased PDAC tumor necrosis
- Decreased growth of PDAC cells
- Impairment of PDAC cells to take up glucose

1.4.3. Assessment of Potential Risks and Benefits

PDAC is a lethal disease. The overall 5-year survival rate is only 9%, and the survival rate for those with distant metastases is a dismal 3%. Clearly, there is an urgent need for new treatments that will extend survival in patients with this disease. Dapagliflozin is a generally safe, well-tolerated medication that is FDA-approved for both diabetes and heart failure with reduced ejection fraction. Dapagliflozin and other SGLT2i's are taken by tens of thousands of patients in the US and around the globe. The risk of severe adverse events (SAEs) and adverse events (AEs) is relatively low, especially when compared with placebo in trials. This low rate of potential SAEs and AEs can be made even lower by education of the subjects and following them closely in our clinical trial by our trial team **(see mitigating steps outlined above).** This low rate of potential SAEs and AEs is outweighed by the possibility of discovering and bringing to the clinic a new, oral,

once-a-day, well-tolerated, effective medication in the fight against this lethal disease – PDAC.

2.0 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints	Justification for Endpoints
Primary		
To assess tolerability and determine the optimal dosage of dapagliflozin added to standard of care front-line chemotherapy for metastatic pancreatic ductal adenocarcinoma.	Toxicity by CTCAE v 5.0.	This is a phase Ib clinical trial and as such, safety and tolerability are a primary objective.
Secondary		
To explore the effects of dapagliflozin on metabolic and tumor response in patients with metastatic pancreatic ductal adenocarcinoma.	Changes in clinical laboratory metabolic parameters (plasma glucose, ketones, HbA1c), CT-based body composition (visceral fat), and tumor markers (plasma CA19-9) and CT-quantified tumor size and tumor necrosis from pre-therapy to post-8 weeks of therapy.	The proposed beneficial effects of dapagliflozin are thought to be due to its metabolic effects on the tumor. Thus, several biomarkers of metabolism are included as secondary endpoints in addition to measures of efficacy such as tumor size changes and/or necrosis.

3.0 STUDY POPULATION

3.1 Inclusion Criteria

1. Histologically or cytologically confirmed metastatic or locally advanced pancreatic ductal adenocarcinoma, pancreatic adenosquamous carcinoma or squamous cell carcinoma

2. Patients with treated/stable brain metastases, defined as patients who have received prior therapy for their brain metastases and whose CNS disease is radiographically stable at study entry, are eligible.

3. Measurable disease defined as lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 10 mm with CT scan, as ≥ 20 mm by chest x-ray, or ≥ 10 mm with calipers by clinical exam.

4. No prior systemic therapy for pancreatic ductal adenocarcinoma in the metastatic or locally advanced setting.

5. Planning to receive treatment with nab-paclitaxel and gemcitabine.

6. At least 18 years of age.

7. ECOG performance status ≤ 1 (see Appendix D)

8. Normal bone marrow and organ function as defined below:
   a. Leukocytes ≥ 3,000/mcL
   b. Absolute neutrophil count ≥ 1,500/mcL
   c. Platelets ≥ 100,000/mcL
   d. Total bilirubin ≤ 1.5 x IULN
   e. AST(SGOT)/ALT(SGPT) ≤ 3.0 x IULN
   f. Estimated glomerular filtration rate eGFR ≥ 30 mL/min/1.73m^2

9. Because chemotherapeutic agents such as nab-paclitaxel and gemcitabine are known to be teratogenic, women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control, abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she must inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of the study, and at least one month after completion of the study

10. Agreement to adhere to Lifestyle Considerations throughout study duration (see Section 3.4).

11. Ability to understand and willingness to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable).

3.2 Exclusion Criteria

1. History of total pancreatectomy.

2. Current or previous treatment with SGLT2i or thiazolidinedione.

3. Currently receiving regularly scheduled systemic steroids in the form of prednisone or dexamethasone. Note that dexamethasone that can be prescribed for nausea on the day of chemotherapy, but in subsequent days will be replaced by a nonsteroidal anti-emetic for patients in this trial. Topical steroid ointments or creams for occasional skin rash is allowed.

4. A history of other malignancy with the exceptions of malignancies for which all treatment was completed at least 2 years before registration with no evidence of disease

and locally treated skin squamous or basal cell carcinoma.

5. History of stroke or transient ischemic attack (in the last 5 years).

6. HbA1c > 10%, unless approved by endocrinologist.

7. Currently receiving any other investigational agents.

8. A history of allergic reactions attributed to compounds of similar chemical or biologic composition to dapagliflozin, nab-paclitaxel, gemcitabine or other agents used in the study.

9. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, peripheral arterial disease, ketoacidosis, severe kidney disease (estimated glomerular filtration rate eGFR < 30 mL/min/1.73m^2), symptomatic hypotension, and chronic/frequent urinary tract infections or yeast infections.

10. Pregnant and/or breastfeeding. Women of childbearing potential must have a negative pregnancy test within 14 days of study entry.

11. Patients with HIV are eligible unless their CD4+ T-cell counts are < 350 cells/mcL or they have a history of AIDS-defining opportunistic infection within the 12 months prior to registration. Concurrent treatment with effective ART according to DHHS treatment guidelines is recommended.

3.3 Retrospective Cohort

Retrospective data will be accessed from EPIC for up to 16 matched control patients receiving nab-paclitaxel and gemcitabine SOC chemotherapy. These subjects will be enrolled under a waiver of consent.

3.4 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

3.5 Lifestyle Considerations

Patients must stay hydrated and eat a "normal" amount of carbs. Refer to Appendix E on Dietary Guidance for details, and section 5.4.1.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center OnCore database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

4.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (if applicable).

5.0 TREATMENT PLAN

5.1 Study Intervention Description

Dapagliflozin is a commercially available medication indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, to reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease or multiple cardiovascular risk factors, and to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with NYHA class

II-IV heart failure with reduced ejection fraction. By inhibiting sodium glucose cotransporter 2, dapagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, thereby increasing urinary glucose excretion. It is available as a tablet for oral administration.

In this study, dapagliflozin will be co-administered with standard of care IV chemotherapy (nab-paclitaxel and gemcitabine) for the treatment of metastatic pancreatic ductal adenocarcinoma. The chemotherapy is not being given as part of this study; it is being given as part of patients' routine care and dosing is not dictated by this protocol. Routine doses of gemcitabine and nab-paclitaxel are 1000 mg/m^2 and 125 mg/m^2, respectively, and can be modified for the patient at the oncologist's discretion.

5.2 Study Intervention Administration

Dapagliflozin is an oral drug which will be administered on an outpatient basis. Dosing will start at 5 mg QD and will increase to 10 mg QD after 2 weeks (after consultation with a study endocrinologist) if the patient is tolerating the 5 mg dose. Dapagliflozin will be given for a total of 8 weeks (2 weeks at 5 mg and 6 weeks at 10 mg). Following 8 weeks, all patients will come off of the study, regardless of treatment response. Dapagliflozin will be continued regardless of holds or modifications to standard of care chemotherapy.

Patients should take dapagliflozin at approximately the same time every day, with or without food. If a patient misses a dose (has not taken it within 6 hours of the regular time), s/he should be instructed not to take or make up that dose and to resume dosing with the next scheduled dose. Patients will be instructed to bring all unused tablets and their medication diary (Appendix F) to each study visit for assessment of compliance.

Treatment with dapagliflozin will be initiated on Cycle 1 Day 1 of standard of care chemotherapy.

During treatment and for 30 days after the last dose of dapagliflozin, AEs will be monitored weekly, either during regular office visits or phone calls, while patient is taking dapagliflozin, and after completion of therapy, follow-up will be biweekly for first month. Severe AEs that require immediate medical attention (i.e., DKA, hypoglycemia) will be reviewed promptly by an oncologist and endocrinologist. . This will be reinforced with regularly scheduled visits with the endocrinologist at screening, C1D1, C1D15, and then as clinically indicated that will be targeted to coincide the same day as the oncologist visit.

5.3 BIOSENSE Meters

BIOSENSE meters are investigational devices utilized in this trial to evaluate utility for assessing breath ketones in a non-invasive manner and therefore are being used under an IDE exemption (Appendix A). The BIOSENSE meters are provided by Readout Health. They are to be used once daily, preferably prior to breakfast, and Appendix B includes use instructions to be provided to the patient. Patients should be instructed to enter the BIOSENSE results on the diary in Appendix F.

5.4 Definitions of Evaluability

All patients who receive any study treatment are evaluable for toxicity. Patients are evaluated from first receiving study treatment until a 30-day follow up after the conclusion of treatment or death.

All patients are evaluable for disease response unless they discontinue treatment prior to completion of 8 weeks of treatment and have not had any disease assessment.

Patients who miss more than 4 doses of dapagliflozin in any one week will be considered not evaluable for treatment response and will need to be replaced.

5.5 Concomitant Therapy and Supportive Care Guidelines

See Appendix. If patients think that they have any side effect or just are feeling worse during the trial, they are to let the study team know.

There are very few drug interactions with dapagliflozin. They are detailed in the package insert. The main ones are mefenamic acid (an NSAID), rifampin, and valsartan.

5.5.1 Alcohol (Ethanol) ↔ dapagliflozin

Participants will be instructed to talk to the study doctor before using ethanol together with dapagliflozin. Alcohol may affect blood glucose levels in patients with diabetes. Both hypoglycemia (low blood sugar) and hyperglycemia (high blood sugar) may occur. Participants will be advised to avoid using alcohol if their diabetes is not well controlled or if they have high triglycerides, neuropathy (nerve damage), or pancreatitis.

5.6 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, and women who have had a tubal ligation) are required to have a negative pregnancy test within 14 days prior to the first dose of dapagliflozin.

Female and male patients (along with their female partners) are required to use two forms of acceptable contraception, including one barrier method, during participation in the study and for 1 month following the last dose of dapagliflozin.

If a patient is suspected to be pregnant, dapagliflozin should be immediately discontinued, as will be the chemotherapy. Because In addition, a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

If a female patient or female partner of a male patient becomes pregnant during therapy or within 1 month after the last dose of dapagliflozin, the investigator must be notified in order to facilitate outcome follow-up.

5.7 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, treatment may continue for 8 weeks or until one of the following criteria applies:

- Documented and confirmed disease progression
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unable to receive further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious noncompliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will still be followed as indicated in the study calendar for patient follow-up.

5.8 Duration of Follow-up

Following the end of study treatment, participants will be followed in person or by phone on a biweekly basis for the first month. Following that, chart-based follow-up Q4W will be obtained for an additional 3 months. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

5.9 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for 2 scheduled visits and is unable to be contacted by the study team.

The following actions must be taken if the participant fails to return to clinic for a required study visit:

- The study team will attempt to contact the participant and reschedule the missed visit within 2 weeks and counsel the participant on the importance of maintaining

the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

6.0 DOSE DELAYS/DOSE MODIFICATIONS

Dose modifications for nab-paclitaxel and gemcitabine will follow standard of care guidelines and will be made at the discretion of the treating oncologist. Dosing with dapagliflozin will continue even if there are interruptions or modifications to nab-paclitaxel and/or gemcitabine.

If estimated glomerular filtration ate (eGFR) falls below 30 mL/min/1.73 m^2 and/or the patient is diagnosed with end-stage renal disease or require dialysis, dapagliflozin must be discontinued.

Patients with signs and symptoms consistent with severe metabolic acidosis should be assessed for ketoacidosis regardless of presenting blood glucose levels (laboratory studies with plasma glucose of 250 mg/dL or greater and associated severe clinical symptoms such as increased urination, increased thirst and unintentional weight loss; neurologic changes such as confusion or drowsiness; metabolic acidosis with serum bicarbonate 15-18 mEq/L with elevated anion gap as well as elevated ketones. Of note, ketones may already be elevated as a result of dapagliflozin administration; thus, any of the above associated signs or symptoms suggestive of possible DKA in the setting of elevated ketones should be discussed with a study investigator immediately. If ketoacidosis is suspected, dapagliflozin should be discontinued, the patient should be evaluated, and prompt treatment should be instituted.

Because reports of necrotizing fasciitis of the perineum (Fournier's Gangrene) have been identified in patients receiving dapagliflozin, patients presenting with pain or tenderness, erythema, or swelling in the genital or perineal area, along with fever or malaise, should be assessed and discontinue dapagliflozin immediately.

Other holds and modifications to dapagliflozin may be made at the discretion of the investigator.

7.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below. Please refer to Appendix G for definitions and Appendix H for a grid of reporting timelines.

AEs that require immediate medical attention (i.e., DKA, hypoglycemia) will be reviewed promptly an oncologist and endocrinologist. All AEs (i.e. chemotherapy-related AEs and dapagliflozin-related AEs) will be recorded from time of initiation of treatment, through the 8-week treatment period, and for 30 days after discontinuation of dapagliflozin. This will allow the study team to determine if dapagliflozin impacts the frequency and/or severity of the chemotherapy-related AEs. All adverse events must be recorded on the toxicity tracking case report form (CRF) with the exception of:

- Baseline adverse events, which shall be recorded on the medical history CRF.

Refer to the data submission schedule in Section 10.0 for instructions on the collection of AEs in the EDC.

Reporting requirements for Washington University study team may be found in Section 7.1.

7.1 Sponsor-Investigator Reporting Requirements

7.1.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

7.1.2 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The Sponsor Investigator (or designee) is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to qasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

7.1.3 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** It is the responsibility of the Sponsor-Investigator to report to the FDA as follows:

- Report any unexpected fatal or life-threatening suspected adverse reaction (refer to Appendix G for definitions) no later than **7 calendar days** after initial receipt of the information.
- Report a suspected adverse reaction that is both serious and unexpected (SUSAR, refer to Appendix G) no later than **15 calendar days** after it is determined that the information qualifies for reporting. Report an adverse event (refer to Appendix G) as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:
  - A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure
  - One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug
  - An aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group
- Report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies that suggest a significant risk in humans exposed to the drug no later than **15 calendar days** after it is determined that the information qualifies for reporting.
- Report any findings from animal or in vitro testing that suggest significant risk in humans exposed to the drug no later than **15 calendar days** after it is determined that the information qualifies for reporting.
- Report any clinically important increase in the rate of a serious suspected adverse reaction of that listed in the protocol or IB within **15 calendar days** after it is determined that the information qualifies for reporting.

Submit each report as an IND safety report in a narrative format or on FDA Form 3500A or in an electronic format that FDA can process, review, and archive. Study teams must notify the Siteman Cancer Center Protocol Development team of each potentially reportable event within 1 business day after initial receipt of the information, and must bring the signed 1571 and FDA Form 3500A to the Siteman Cancer Center Protocol Development team no later than 1 business day prior to the due date for reporting to the FDA.

Each notification to FDA must bear prominent identification of its contents ("IND Safety Report") and must be transmitted to the review division in the Center for Drug Evaluation and Research (CDER) or in the Center for Biologics Evaluation and Research (CBER) that has responsibility for review of the IND. Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such ("Follow-up IND Safety Report").

7.2 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in Section 7.1 include:

- planned hospitalizations
- hospitalizations < 24 hours
- respite care
- events related to disease progression

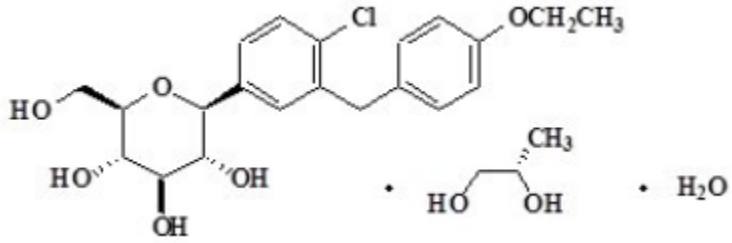
Events that do not require expedited reporting must still be captured in the EDC.

8.0 PHARMACEUTICAL INFORMATION

8.1 Dapagliflozin (Farxiga)

8.1.1 Dapagliflozin Description

Dapagliflozin is described chemically as D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4ethoxyphenyl)methyl]phenyl]-, (1*S*)-, compounded with (2*S*)-1,2-propanediol, hydrate (1:1:1). The empirical formula is $C_{21}H_{25}ClO_6 \bullet C_3H_8O_2 \bullet H_2O$ and the molecular weight is 502.98. The structural formula is:



8.1.2 Clinical Pharmacology

Sodium-glucose cotransporter 2 (SGLT2), expressed in the proximal renal tubules, is responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. Dapagliflozin is an inhibitor of SGLT2. By inhibiting SGLT2, dapagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, and thereby increases urinary glucose excretion. Dapagliflozin also reduces sodium reabsorption and increases the delivery of sodium to the distal tubule. This may influence several physiological functions including, but not restricted to, lowering both pre-and afterload of the heart and downregulation of sympathetic activity.

8.1.3 Pharmacokinetics and Drug Metabolism

Following oral administration of dapagliflozin, the maximum plasma concentration (Cmax) is usually attained within 2 hours under fasting state. The Cmax and AUC values increase dose proportionally with increase in dapagliflozin dose in the therapeutic dose range. The absolute oral bioavailability of dapagliflozin following

the administration of a 10 mg dose is 78%. Administration of dapagliflozin with a high-fat meal decreases its Cmax by up to 50% and prolongs Tmax by approximately 1 hour, but does not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful and dapagliflozin can be administered with or without food.

The metabolism of dapagliflozin is primarily mediated by UGT1A9; CYP-mediated metabolism is a minor clearance pathway in humans. Dapagliflozin is extensively metabolized, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide accounted for 61% of a 50 mg [^{14}C]-dapagliflozin dose and is the predominant drug-related component in human plasma.

Dapagliflozin and related metabolites are primarily eliminated via the renal pathway. Following a single 50 mg dose of [^{14}C]-dapagliflozin, 75% and 21% total radioactivity is excreted in urine and feces, respectively. In urine, less than 2% of the dose is excreted as parent drug. In feces, approximately 15% of the dose is excreted as parent drug. The mean plasma terminal half-life ($t_{½}$) for dapagliflozin is approximately 12.9 hours following a single oral dose of dapagliflozin 10 mg.

8.1.4 Supplier

Dapagliflozin will be provided for this trial.

8.1.5 Dosage Form and Preparation

Dapagliflozin is available as film-coated tablets at a dose of 5 mg and 10 mg.

8.1.6 Storage and Stability

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F).

8.1.7 Administration

Dapagliflozin should be taken by mouth once daily at the assigned dose.

9.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form	Prior to starting treatment

Medical History Form	
Treatment Form	Every cycle
Toxicity Form	Continuous
Treatment Summary Form	Completion of treatment
Follow Up Form	Biweekly for the first month after completion of study treatment, Month 1, 2, 3, and 4 post-EOT
Tumor Measurement Form	Baseline and 8 weeks after start of treatment
Progression Form	Time of disease progression
Death Form	Time of death
MedWatch Form	See Section 7.0 for reporting requirements

9.1 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with start of treatment (minus exceptions defined in Section 7.0) must be captured in the Toxicity Form (Appendix I). Baseline AEs should be captured on the Medical History Form.

Participant death due to disease progression should be reported on the Toxicity Form as grade 5 disease progression. If death is due to an AE (e.g. cardiac disorders: cardiac arrest), report as a grade 5 event under that AE. Participant death must also be recorded on the Death Form.

10.0 MEASUREMENT OF EFFECT

10.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients will be re-evaluated for response with standard of care computed tomography (CT/MRI) imaging, 8 weeks after the initiation of study treatment.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [30]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

10.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm by chest x-ray, as >10 mm with CT scan, or >10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice

thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

10.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based

evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [31-33]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [31].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

10.4 Response Criteria

10.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

10.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

10.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once >4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

10.4.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, an independent Data and Safety Monitoring Board (DSMB) will be specifically convened for this trial to review toxicity data. A DSMB will consist of no fewer than 3 members including 2 clinical investigators and a biostatistician. DSMB members must be employed by Washington University, Barnes-Jewish Hospital, or St. Louis Children's Hospital. Like investigators, DSMB members are subject to the Washington University School of Medicine policies regarding standards of conduct. Individuals invited to serve on the DSMB will disclose any potential conflicts of interest to the trial principal investigator and/or appropriate university officials, in accordance with institution policies. Potential conflicts that develop during a trial or a member's tenure on a DSMB must also be disclosed.

The DSM report for the DSMB will be prepared by the study team with assistance from the study statistician, will be reviewed by the DSMB, and will be submitted to the QASM Committee. The DSMB must meet at least every six months beginning six months after study activation at Washington University, no more than one month prior to the due date of the DSM report to QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study

- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

Further DSMB responsibilities are described in the DSMB charter.

The study principal investigator and coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines (please refer to Section 7.0).

Refer to the Washington University Quality Assurance and Data Safety Monitoring Committee Policies and Procedures for full details on the responsibilities of the DSMB. This is located on the QASMC website at https://siteman.wustl.edu/research/clinical-research-resources/protocol-office-prmcqasmc/.

12.0 Retrospective Review of Matched Controls

Retrospective data will be accessed from EPIC for up to 16 matched controls who have received nab-paclitaxel and gemcitabine SOC chemotherapy. This data will be obtained under a waiver of consent. All data will be deidentfied within the manuscript. Data from 2016 to present will be accessed. Only the necessary data will be pulled from EPIC and will contain lab values, demographics (date of birth, sex, race, ethnicity), imaging, tumor stage, metastatic sites, prior treatment and best results, with an emphasis on the matched treatment times for the study.

13.0 STATISTICAL CONSIDERATIONS

The study will be defined as being feasible if up to 18 patients can be recruited within the next academic year and at least 80% of patients comply with the intervention as defined as achieving 80% of the targeted level of therapeutic action assessed from laboratory measures and 80% of the planned chemotherapy doses. Data analyses will be descriptive in nature. All data will be analyzed as observed without imputation. Variables will be summarized by descriptive statistics including mean, median, standard deviation, inter-quartile range, overall and by patient characteristics of interest (e.g., male and female patients). Hematological and non-hematological toxicities will be summarized by counts and percentages, overall and by patient characteristics. Effect of SGLT2i

as assessed by urine glucose, serum and breath ketones, visceral fat, tumor enhancement/necrosis (in various format: continuous, dichotomized by median, tertiles, quartiles) or other parameters on overall and progression free survival (PFS) will be analyzed by Kaplan-Meier product limit method and log rank test or Cox regression model as appropriate.

13.1 Safety Analyses

Safety endpoints will be analyzed using summary statistics as described above acquired during treatment. AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Each AE will be counted once only for a given participant. The severity, frequency, and relationship of AEs to SGLT2i therapy will be presented by System Organ Class (SOC). AE's will be reported with the following information: start date, stop date, severity, relationship, expectedness, outcome, and duration. Adverse events leading to premature discontinuation from the study intervention and serious treatment-emergent AEs will be presented either in a table and are provided in the Data Safety Monitoring Plan.

14.0 REFERENCES

1. Scafoglio C, Hirayama BA, Kepe V, Liu J, Ghezzi C, Satyamurthy N, Moatamed NA, Huang J, Koepsell H, Barrio JR, Wright EM. Functional expression of sodium-glucose transporters in cancer. Proceedings of the National Academy of Sciences. 2015;112(30):E4111-E9. doi: 10.1073/pnas.1511698112.

2. Cada DJ, Levien TL, Baker DE. Dapagliflozin. Hosp Pharm. 2014;49(7):647-62. Epub 2014/12/06. doi: 10.1310/hpj4907-647. PubMed PMID: 25477585; PMCID: PMC4252236.

3. Kasichayanula S, Chang M, Hasegawa M, Liu X, Yamahira N, LaCreta FP, Imai Y, Boulton DW. Pharmacokinetics and pharmacodynamics of dapagliflozin, a novel selective inhibitor of sodium-glucose co-transporter type 2, in Japanese subjects without and with type 2 diabetes mellitus. Diabetes Obes Metab. 2011;13(4):357-65. Epub 2011/01/14. doi: 10.1111/j.1463-1326.2011.01359.x. PubMed PMID: 21226818.

4. Li D. Diabetes and pancreatic cancer. Molecular carcinogenesis. 2012;51(1):64-74. doi: 10.1002/mc.20771. PubMed PMID: 22162232.

5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA: a cancer journal for clinicians. 2020;70(1):7-30. doi: 10.3322/caac.21590.

6. Kleeff J, Korc M, Apte M, La Vecchia C, Johnson CD, Biankin AV, Neale RE, Tempero M, Tuveson DA, Hruban RH, Neoptolemos JP. Pancreatic cancer. Nat Rev Dis Primers. 2016;2:16022-. doi: 10.1038/nrdp.2016.22. PubMed PMID: 27158978.

7. Wang X-Y, Yang F, Jin C, Fu D-L. Utility of PET/CT in diagnosis, staging, assessment of resectability and metabolic response of pancreatic cancer. World journal of gastroenterology. 2014;20(42):15580-9. doi: 10.3748/wjg.v20.i42.15580. PubMed PMID: 25400441.

8. Jha P, Bijan B. PET/CT for Pancreatic Malignancy: Potential and Pitfalls. Journal of nuclear medicine technology. 2015;43(2):92-7. Epub 2015/04/11. doi: 10.2967/jnmt.114.145458. PubMed PMID: 25857417.

9. Yan L, Raj P, Yao W, Ying H. Glucose Metabolism in Pancreatic Cancer. Cancers. 2019;11(10). Epub 2019/10/02. doi: 10.3390/cancers11101460. PubMed PMID: 31569510; PMCID: PMC6826406.

10. Yang J, Ren B, Yang G, Wang H, Chen G, You L, Zhang T, Zhao Y. The enhancement of glycolysis regulates pancreatic cancer metastasis. Cellular and molecular life sciences : CMLS. 2020;77(2):305-21. Epub 2019/08/23. doi: 10.1007/s00018-019-03278-z. PubMed PMID: 31432232.

11. Dang CV. Links between metabolism and cancer. Genes & development. 2012;26(9):877-90. Epub 2012/05/03. doi: 10.1101/gad.189365.112. PubMed PMID: 22549953; PMCID: 3347786.

12. Payen VL, Porporato PE, Baselet B, Sonveaux P. Metabolic changes associated with tumor metastasis, part 1: tumor pH, glycolysis and the pentose phosphate pathway. Cellular and molecular life sciences : CMLS. 2016;73(7):1333-48. Epub 2015/12/03. doi: 10.1007/s00018-015-2098-5. PubMed PMID: 26626411.

13. Koo D-H, Han K-D, Park C-Y. The Incremental Risk of Pancreatic Cancer According to Fasting Glucose Levels: Nationwide Population-Based Cohort Study. The Journal of Clinical Endocrinology & Metabolism. 2019;104(10):4594-9. doi: 10.1210/jc.2019-00033.

14. Vardeny O, Vaduganathan M. Practical Guide to Prescribing Sodium-Glucose Cotransporter 2 Inhibitors for Cardiologists. JACC Heart Fail. 2019;7(2):169-72. Epub 2019/02/02. doi: 10.1016/j.jchf.2018.11.013. PubMed PMID: 30704605.

15. Kepe V, Scafoglio C, Liu J, Yong WH, Bergsneider M, Huang S-C, Barrio JR, Wright EM. Positron emission tomography of sodium glucose cotransport activity in high grade astrocytomas. Journal of neuro-oncology. 2018;138(3):557-69. Epub 2018/03/10. doi: 10.1007/s11060-018-2823-7. PubMed PMID: 29525972.

16. Blunck JR, Newman JW, Fields RK, Croom JE. Therapeutic augmentation of ketogenic diet with a sodium-glucose cotransporter 2 inhibitor in a super-refractory status epilepticus patient. Epilepsy Behav Case Rep. 2018;10:61-4. doi: 10.1016/j.ebcr.2018.05.002. PubMed PMID: 30073144.

17. Pfützner A, Klonoff D, Heinemann L, Ejskjaer N, Pickup J. Euglycemic ketosis in patients with type 2 diabetes on SGLT2-inhibitor therapy-an emerging problem and solutions offered by diabetes technology. Endocrine. 2017;56(1):212-6. Epub 2017/03/17. doi: 10.1007/s12020-017-1264-y. PubMed PMID: 28303514.

18. Pereira MJ, Eriksson JW. Emerging Role of SGLT-2 Inhibitors for the Treatment of Obesity. Drugs. 2019;79(3):219-30. doi: 10.1007/s40265-019-1057-0.

19. Tosaki T, Kamiya H, Himeno T, Kato Y, Kondo M, Toyota K, Nishida T, Shiroma M, Tsubonaka K, Asai H, Moribe M, Nakaya Y, Nakamura J. Sodium-glucose Co-transporter 2 Inhibitors Reduce the Abdominal Visceral Fat Area and May Influence the Renal Function in Patients with Type 2 Diabetes. Intern Med. 2017;56(6):597-604. Epub 2017/03/17. doi: 10.2169/internalmedicine.56.7196. PubMed PMID: 28321056.

20. Skinner R, Trujillo A, Ma X, Beierle EA. Ketone bodies inhibit the viability of human neuroblastoma cells. Journal of pediatric surgery. 2009;44(1):212-6. doi: https://doi.org/10.1016/j.jpedsurg.2008.10.042.

21. Magee BA, Potezny N, Rofe AM, Conyers RA. The inhibition of malignant cell growth by ketone bodies. Aust J Exp Biol Med Sci. 1979;57(5):529-39. PubMed PMID: 548019.

22. Fine EJ, Miller A, Quadros EV, Sequeira JM, Feinman RD. Acetoacetate reduces growth and ATP concentration in cancer cell lines which over-express uncoupling protein 2. Cancer cell international. 2009;9:14-. doi: 10.1186/1475-2867-9-14. PubMed PMID: PMC2694762.

23. Okumura S, Kaido T, Hamaguchi Y, Kobayashi A, Shirai H, Yao S, Yagi S, Kamo N, Hatano E, Okajima H, Takaori K, Uemoto S. Visceral Adiposity and Sarcopenic Visceral Obesity are Associated with Poor Prognosis After Resection of Pancreatic Cancer. Ann Surg Oncol. 2017;24(12):3732-40. Epub 2017/09/06. doi: 10.1245/s10434-017-6077-y. PubMed PMID: 28871520.

24. Sandini M, Patino M, Ferrone CR, Alvarez-Perez CA, Honselmann KC, Paiella S, Catania M, Riva L, Tedesco G, Casolino R, Auriemma A, Salandini MC, Carrara G, Cristel G, Damascelli A, Ippolito D, D'Onofrio M, Lillemoe KD, Bassi C, Braga M, Gianotti L, Sahani D, Fernandez-Del Castillo C. Association Between Changes in Body Composition and Neoadjuvant

Treatment for Pancreatic Cancer. JAMA Surg. 2018;153(9):809-15. Epub 2018/05/26. doi: 10.1001/jamasurg.2018.0979. PubMed PMID: 29801062; PMCID: PMC6583880.

25. Bian X, Dai H, Feng J, Ji H, Fang Y, Jiang N, Li W. Prognostic values of abdominal body compositions on survival in advanced pancreatic cancer. Medicine. 2018;97(22):e10988. Epub 2018/06/01. doi: 10.1097/md.0000000000010988. PubMed PMID: 29851855; PMCID: PMC6393092.

26. Sah RP, Sharma A, Nagpal S, Patlolla SH, Sharma A, Kandlakunta H, Anani V, Angom RS, Kamboj AK, Ahmed N, Mohapatra S, Vivekanandhan S, Philbrick KA, Weston A, Takahashi N, Kirkland J, Javeed N, Matveyenko A, Levy MJ, Mukhopadhyay D, Chari ST. Phases of Metabolic and Soft Tissue Changes in Months Preceding a Diagnosis of Pancreatic Ductal Adenocarcinoma. Gastroenterology. 2019;156(6):1742-52. Epub 2019/01/25. doi: 10.1053/j.gastro.2019.01.039. PubMed PMID: 30677401; PMCID: PMC6475474.

27. Cooper AB, Slack R, Fogelman D, Holmes HM, Petzel M, Parker N, Balachandran A, Garg N, Ngo-Huang A, Varadhachary G, Evans DB, Lee JE, Aloia T, Conrad C, Vauthey JN, Fleming JB, Katz MH. Characterization of Anthropometric Changes that Occur During Neoadjuvant Therapy for Potentially Resectable Pancreatic Cancer. Ann Surg Oncol. 2015;22(7):2416-23. Epub 2014/12/19. doi: 10.1245/s10434-014-4285-2. PubMed PMID: 25519927.

28. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Silverman MG, Zelniker TA, Kuder JF, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Ruff CT, Gause-Nilsson IAM, Fredriksson M, Johansson PA, Langkilde A-M, Sabatine MS. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. New England Journal of Medicine. 2018;380(4):347-57. doi: 10.1056/NEJMoa1812389. PubMed PMID: 30415602.

29. Inzucchi SE, Zinman B, McGinniss J, Schnee J, George J, Fitchett D. CONSISTENT EFFECT OF EMPAGLIFLOZIN ON COMPOSITE OUTCOMES RELATED TO HEART FAILURE: RESULTS FROM EMPA-REG OUTCOME. Journal of the American College of Cardiology. 2017;69(11 Supplement):1656. doi: 10.1016/s0735-1097(17)35045-3.

30. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47. Epub 2008/12/23. doi: 10.1016/j.ejca.2008.10.026 [doi]S0959-8049(08)00873-3 [pii]. PubMed PMID: 19097774.

31. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC, Gwyther SG. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. Journal of the National Cancer Institute. 2000;92(3):205-16. Epub 2000/02/03. doi: 10.1093/jnci/92.3.205 [doi]. PubMed PMID: 10655437.

32. Bubley GJ, Carducci M, Dahut W, Dawson N, Daliani D, Eisenberger M, Figg WD, Freidlin B, Halabi S, Hudes G, Hussain M, Kaplan R, Myers C, Oh W, Petrylak DP, Reed E, Roth B, Sartor O, Scher H, Simons J, Sinibaldi V, Small EJ, Smith MR, Trump DL, Wilding G, et al. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. Journal

of clinical oncology : official journal of the American Society of Clinical Oncology. 1999;17(11):3461-7. Epub 1999/11/05. doi: 10.1200/JCO.1999.17.11.3461 [doi]. PubMed PMID: 10550143.

33. Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, Eisenberger MA, Higano C, Bubley GJ, Dreicer R, Petrylak D, Kantoff P, Basch E, Kelly WK, Figg WD, Small EJ, Beer TM, Wilding G, Martin A, Hussain M, Prostate Cancer Clinical Trials Working G. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2008;26(7):1148-59. Epub 2008/03/04. doi: 10.1200/JCO.2007.12.4487 [doi]26/7/1148 [pii]. PubMed PMID: 18309951; PMCID: PMC4010133.

We would like to thank the Alvin J. Siteman Cancer Center at Washington University School of Medicine and Barnes-Jewish Hospital in St. Louis, Missouri, for the use of the Clinical Trials Core which provided protocol development services. The Siteman Cancer Center is supported in part by an NCI Cancer Center Support Grant #P30 CA91842.

APPENDIX A: Device IDE Exemption

READOUT
2940 Locust St.
St. Louis, MO 63103

July 28, 2020

Washington University in St. Louis Institutional Review Board

(IRB) RE: Device IDE exemption

Dear Sir or Ma'am:

Referring to the FDA Guidance document, *In Vitro Diagnostic (IVD) Device Studies-Frequently Asked Questions*, issued June 25, 2010, Readout, Inc. has determined that the BIOSENSE™ breath acetone device used in **Targeting pancreatic cancer with sodium glucose transporter 2 (SGLT2) inhibition** qualifies for an exemption from the IDE submission requirements.

Criteria	Yes	No
The in vitro diagnostic device complies with the labeling requirements in 21 CFR Part 809.10(c) and the testing:	X	
- Is noninvasive	X	
- Does not require an invasive sampling procedure that presents significant risk	X	
- Does not by design or intention introduce energy into a subject; and	X	
- Will not be used as a diagnostic procedure without confirmation by another medically established diagnostic product or procedure	X	

The study design of **Targeting pancreatic cancer with sodium glucose transporter 2 (SGLT2) inhibition** does not place the patient at any additional risk with the use of the BIOSENSE™ device. The primary tool for ketone monitoring in this study is a urinary acetoacetate test (measured weekly). The BIOSENSE™ breath ketone device is noninvasive and will be used for research purposes only. Data from the BIOSENSE™ device will not impact patient care decisions in any way.

Readout believes the strategies for use of the device during the study does not present a potential for serious risk to the health, safety, or welfare of a subject.

The device is not intended as an implant nor is it to be used in supporting or sustaining human life. The BIOSENSE™ device is not of substantial importance in diagnosing, curing, mitigating or treating disease. The device is non-invasive and not being used to determine treatment. Based on the information provided, the BIOSENSE™ device does not present a potential for serious risk to the health, safety or welfare of the subject.

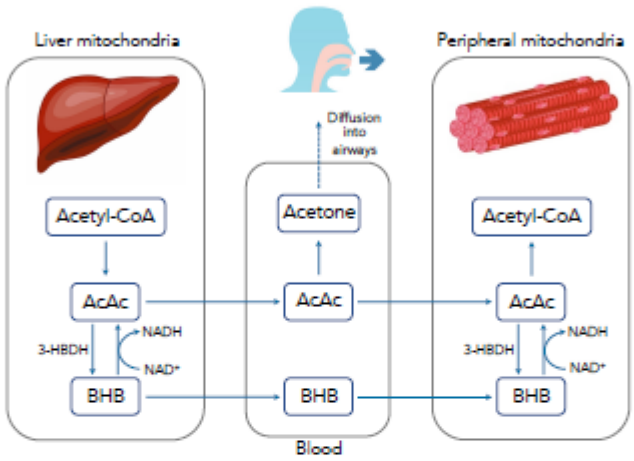
Contact:

Trey Suntrup Head of Product Readout Health
trey@readouthealth.com

APPENDIX B: BIOSENSE Information

Scientific Background

- BIOSENSE™ measures breath acetone, one of the three ketone bodies:
  - Acetoacetate (AcAc) – measured in urine
  - Beta-hydroxybutyrate (BHB) – measured in blood
  - Acetone – measured in breath



- Because acetone is derived from AcAc via spontaneously decarboxylation, breath acetone is a proxy measurement for AcAc in the blood.
- Although the three ketone bodies are related, they are not identical or interchangeable. The Research page on our website outlines the relationship between blood BHB and breath acetone as studied in our clinical trial.

The BIOSENSE™ Device

- BIOSENSE™ is the first portable breath acetone meter backed by a clinical trial.
- Its accuracy comes from the use of deep lung sampling technology:
  - The concentration of acetone is highest and most repeatable at the end of your exhale.
  - BIOSENSE™ listens to your exhale and waits until you are reaching the end. Then the device activates a small pump, which pulls your breath sample inside the device and into contact with the sensor.

How to Use BIOSENSE™

- BIOSENSE™ has two buttons: the START button and the SETTINGS button.
- To wake up the device, press and hold the START button for 3-4 seconds. Once the logo appears, you can release the button.
- The first time the device is powered on, it will ask if you want to pair to the mobile app. If yes, open the app and navigate to the pair screen on the Profile tab. Once paired, the app will set the device's clock automatically. If you do not want to use the app, press the START button and manually enter the date and time.

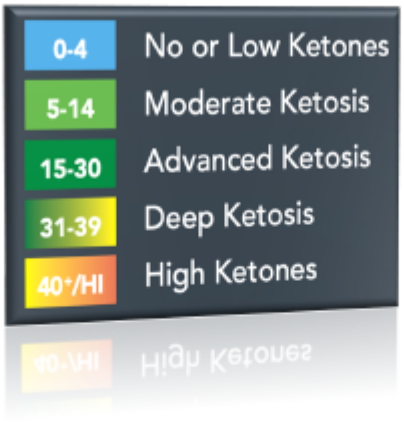
- After pairing to the app or manually setting the time, BIOSENSE™ will enter a preparing phase that lasts about 60 seconds. During this time the sensor is warming up and preparing to receive a measurement.

- When the preparing phase is complete, BIOSENSE™ will instruct the user to PRESS START. At this point you can press START to take a measurement or press the SETTINGS button to view your past measurements.

- After pressing START, there is a brief countdown before the device will tell you to BLOW. The BLOW screen will stay up for about 10 seconds, so there is no need to rush the breath.

- Technique for blowing:
  - Inhale as you normally would. There is no need for a large inhale.
  - Exhale more forcefully than normal. Pretend you are blowing large bubbles into a glass of water through a straw or blowing up a balloon vigorously. The exhale through the device should be clearly audible.
  - Near the end of your breath, you will feel a long vibration followed by two short vibrations. Continue exhaling until you feel the two short vibrations.
- After BIOSENSE™ receives your measurement, there will be a 15 second analysis period before your result is displayed.

- The device units are called ACEs, a unique unit of breath acetone. The ACEs unit is calibrated to be approximately 10x the blood BHB equivalent (e.g. 10 ACEs ~ 1.0 mmol/L BHB).
- The ACEs scale is color-coded to indicate different degrees of ketosis:



- For subjects aiming to achieve ketosis, coordinators and clinicians should use the following guidance when reviewing a subject's ACEs level:
  - 0-2 = definitively not in ketosis
  - 3 = slightly elevated ketones. The subject is moving in the right direction.
  - 4-5 = transitioning into ketosis. If this is the highest the subject can achieve, they should still be counted as compliant with the keto diet.
  - >5 = definitely in ketosis
- The device should be charged overnight once every few days. With a frequency of 3 measurements/day, the device battery should last 4-5 days. The device can be charged using the included micro USB cable.

otential Confounders

- The quick start guide contains guidance about confounders to the breath acetone measurement.
- The primary confounder is ethanol and minty flavorings from menthol. Subjects should be instructed to wait 60 minutes after eating or using:
  - Toothpaste
  - Mouthwash
  - Cough drops
  - Chewing gum or breath mints

    - Lip balm
    - Artificial sweeteners
- After consuming alcohol, subjects should wait until the next morning to test. If a subject knows they will be drinking alcohol at night, they should plan to complete all of their measurements for that day before drinking.
- Occasionally the sensor will fail to warm up completely during the preparation cycle. If this happens, the user may see an error message:

- After this message appears, the device will perform additional sensor prep and then allow the user to Press Start.

APPENDIX C. Handout for patients for prevention of yeast infections

If you think you may have an infection, call your oncology clinic team.

Prevention of yeast infections in Women (from Mayo clinics)
https://www.mayoclinic.org/diseases-conditions/yeast-infection/symptoms-causes/syc-20378999)

To reduce your risk of vaginal yeast infections, wear underwear that has a cotton crotch and doesn't fit too tightly.

It might also help to avoid:

- Tight-fitting pantyhose
- Douching, which removes some of the normal bacteria in the vagina that protect you from infection
- Scented feminine products, including bubble bath, pads and tampons
- Hot tubs and very hot baths
- Unnecessary antibiotic use, such as for colds or other viral infections
- Staying in wet clothes, such as swimsuits and workout attire, for long periods of time

Prevention of yeast infections in Men (from Medical News Today)
https://www.medicalnewstoday.com/articles/184715#prevention

To prevent infections, the head of the penis and the foreskin should be kept clean and dry. Daily washing, with particular attention to cleaning the penis, is essential.

Here are some hygiene tips:

- The foreskin should be pulled back so that the glans is exposed.
- The area should be washed thoroughly and gently with warm water. Soap may irritate, so it should be avoided.
- An aqueous cream or some other neutral nonsoap cleanser may be used, but it should be completely rinsed off.
- Before replacing the foreskin, the glans should be completely dry.
    - Men who tend to develop balanitis after sex should wash their penis after engaging in sexual activity.

Avoiding irritants

If symptoms appear to be linked to substances present in condoms or lubricants, there are condoms available for sensitive skin.

It is best to use non-biological washing powder for underwear and to make sure all the detergent is rinsed out. People who work with chemicals or have traces of potential irritants on their hands should wash them before using the bathroom.

APPENDIX D: ECOG Performance Status Scale

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX E. Dietary guidance

- **You will need to stay hydrated** while on the study drug, dapagliflozin.
    - If you cannot stay hydrated for any reason, please call your oncology clinic team.

- **You will need to take in a 'normal' amount of carbohydrates** when you are taking an SGLT2 inhibitor, such as dapagliflozin, in order to avoid the rare possibility of excessive 'ketone' levels in the blood.
    - If you cannot eat adequate carbohydrates (e.g. bread, crackers, sweets, milk, fruit) for any reason, please call your oncology clinic team.
- **Alcohol may affect blood sugars while taking dapagliflozin. Please contact your oncology clinic team with questions.**

To help guide you on an adequate amount of carbohydrates/day (~250g/day) please see the attached information sheets. Please call your oncology clinic team with any questions.

250 grams of carbohydrate/day is actually about 17 carb servings (255 g) with each carbohydrate serving equaling approximately 15 grams

A serving of 15 gm is:
A small piece of fruit or a cup of berries or melon
1 slice bread
4-6 crackers
1/2 cup cooked cereal, potatoes, corn or peas
3/4 cup dry unsweetened cereal
1 cup soup
1 cup of milk
1 oz potato chips or 3 cups popcorn
6 oz flavored Greek yogurt
1/2 cup Ice cream
2 small cookies

30 gm carb equals:
Large Apple, pear or banana
1 cup of Chili with beans

45 gm carb equals:
1 cup rice or pasta

60 gm carb equals:
1 large baked potato

APPENDIX F: PATIENT'S MEDICATION DIARY

Today's Date: _____ Agent: dapagliflozin Cycle: _____

Patient Name: _____ Study ID#: _____

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each 28 day cycle.
    a. Cycle 1 instructions: Take _____mg (___capsules) of dapagliflozin at approximately the same time each day, with or without food for days 1 through 14.Your dose may change starting day 15. Your dose starting at day 15 will be _____mg (___capsules) of dapagliflozin at approximately the same time each day, with or without food.
    b. Cycle 2 instructions: Take _____mg (___capsules) of dapagliflozin at approximately the same time each day, with or without food
2. Record the date, the number of capsules taken, and when you took them.
3. If you forgot to take your dapagliflozin dose within 6 hours of your regular time, then do not take a dose that day. Restart taking it the next day.
4. If you have any questions or notice any side effects, please record them in the comments section. Record the time if you should vomit.
5. Please return the forms to your physician or your study coordinator when you go to your next appointment. Please bring your unused study medications and/or empty bottles with you to each clinic visit so that a pill count can be done.

Day	Date	What time was dose taken?	# of tablets taken	BIOSENSE value	Comments
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					

24				
25				
26				
27				
28				

APPENDIX G: Definitions for Adverse Event Reporting

A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

Definition: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

Definition: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

C. Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

D. Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: an adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
- A life-threatening adverse event

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

E. Protocol Exceptions

Definition: A planned change in the conduct of the research for one participant.

F. Deviation

Definition: Any alteration or modification to the IRB-approved research without prospective IRB approval. The term "research" encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

APPENDIX H: Reporting Timelines

Expedited Reporting Timelines			
Event	**HRPO**	**QASMC**	**FDA**
Serious AND unexpected suspected adverse reaction			Report no later than 15 calendar days after it is determined that the information qualifies for reporting
Unexpected fatal or life-threatening suspected adverse reaction			Report no later than 7 calendar days after initial receipt of the information
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	Report via email after IRB acknowledgment	
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.		
A series of minor deviations that are being reported as a continuing noncompliance	Report within 10 working days.		
Protocol exception	Approval must be obtained prior to implementing the change		
Clinically important increase in the rate of a serious suspected adverse reaction of that list in the protocol or IB			Report no later than 15 calendar days after it is determined that the information qualifies for reporting
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.		
Breach of confidentiality	Within 10 working days.		
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days.		

Expedited Reporting Timelines			
Event	**HRPO**	**QASMC**	**FDA**
	If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.		

Routine Reporting Timelines			
Event	**HRPO**	**QASMC**	**FDA**
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review	Adverse events will be reported in the toxicity table in the DSM report which is typically due every 6 months.	The most current toxicity table from the DSM report is provided to the FDA with the IND's annual report.
Minor deviation	Report summary information at the time of continuing review.		
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.		
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.		