INDIVIDUAL DRUG REPURPOSING CLINICAL TRIAL

RESEARCH PROTOCOL

Protocol Title: **IMPACT* Study**

***Intervention Monitoring for Pancreatitis in an Adolescent undergoing Clinical Treatment**

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Protocol Number: N1-IVAC-01

Protocol Version Date: 06MAY2025

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1. INTRODUCTION

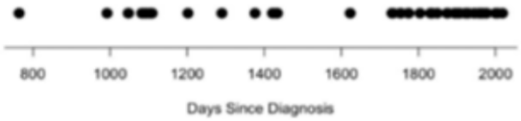


Figure 1. Participant Documented Pancreatitis Episode/Event History

We are proposing to pursue a *single case experimental design (SCED)*-based observational study of the efficacy of Ivacaftor for the treatment of chronic pancreatitis in a single participating adolescent. The study is limited to data collection and analysis and does not involve any changes in the participant's clinical care, which is determined by his team of physicians. The participant has exhausted standard treatment options and is currently taking Ivacaftor off-label without any obvious side effects for 8 weeks (as of 5/02/25).

The protocol's primary aim focuses on observing the efficacy of Ivacaftor use in delaying overt acute pancreatitis episodes in the participant over a maximum 12-month period. A secondary aim will consider patterns in changes in activity and general health consistent with potentially identifiable causes (e.g., stomach pain, compromised sleep, etc.) that may or may not be attributable to Ivacaftor's effect. We emphasize that this proposed study observes the strong mechanistic foundation and limited but suggestive preclinical data for using Ivacaftor to address acquired Cystic Fibrosis Transmembrane Conductance Regulator protein (CFTR) dysfunction in chronic pancreatitis. The careful implementation of a single case experimental design (SCED) trial, with close monitoring and validated clinical endpoints, will allow determination of whether Ivacaftor can provide tangible clinical benefits in the form of a significantly delayed interval between objectively determined acute episodes of pancreatitis requiring intervention for an adolescent who has otherwise exhausted conventional therapeutic options. The frequency of clinically documented events experienced by the participant are provided in Figure 1, where it is apparent that symptom frequencies are getting more pronounced and therefore motivate the study. We will also explore subclinical symptom profiles and potential triggers for those symptoms using wireless health monitoring devices (see section 3.5) as a secondary set of aims. Such information can provide insight into future interventions that may complement, but not detract from, any benefits of Ivacaftor (e.g., pain medications, dietary changes, etc.).

2. STUDY OBJECTIVES

The purpose of this observational study is to determine the utility of Ivacaftor treatment in an adolescent without cystic fibrosis and without a known cystic fibrosis (CFTR) variant but with chronic pancreatitis manifesting with pronounced acute pancreatitis episodes.

2.1 Primary Aim

Test the hypothesis that Ivacaftor reduces acute pancreatitis episodes that require immediate clinical attention, hospitalization, medical intervention, emergency room visits, or a need to document an acute pancreatitis episode via, e.g., Lipase measurements, in an adolescent with diagnosed pancreatitis (see Figure 1 which considers all these documented episodes and events). This hypothesis will be tested by comparing the interval or delay between acute pancreatitis episodes that require intervention while the participant is receiving Ivacaftor against legacy data on intervals while the participant was not receiving Ivacaftor. The study will also

collect and analyze any clinically-collected and clinically-validated symptoms that may be attributable to Ivacaftor side effects or inefficacy.

2.2 Secondary Aim

Determine if, during Ivacaftor treatment, the adolescent being treated exhibits patterns in changes in activity and general health consistent with identifiable triggers (e.g., stomach pain, compromised sleep, etc.) that may or may not be attributable to Ivacaftor's effect. This will be explored (see sections 4.2).

3. BACKGROUND

We describe the clinical and treatment issues associated with pancreatitis below but note that in cases of pediatric onset of pancreatitis the clinical and behavioral impacts can be unique and more pronounced and debilitating.

3.1 Pancreatitis.

Chronic pancreatitis is a progressive, long-term condition characterized by inflammation and fibrosis damaging the pancreas. Debilitating chronic pancreatitis symptoms include: repeated episodes of severe abdominal pain, often in the middle or left side of the abdomen, sometimes radiating to the back; constant mild to moderate abdominal pain between severe episodes; nausea and vomiting during painful episodes; exocrine pancreatic insufficiency leading to weight loss, malnutrition, diarrhea, and dehydration; the development of diabetes due to loss of insulin production, and in some instances, pancreatic cancer.

Although the time course and health trajectory vary from individual to individual, the progression from acute to chronic pancreatitis typically occurs within 1 to 19 years, with around one-third of patients who have recurrent acute pancreatitis eventually developing chronic disease. Over time, the cumulative burden of chronic pancreatitis symptoms—including progressive fibrosis, exocrine and/or endocrine insufficiency, and structural complications—becomes more significant. Specifically, research suggests that 16.1% of patients exhibit advanced disease features by 20 years, 38.5% by 30 years, 56.7% by 40 years, and 76.0% by 50 years. These percentages represent the proportion of patients who progress to severe manifestations of chronic pancreatitis over those time spans and underscore the need for early intervention. Notably, the median delay between onset of first symptoms and diagnosis is 6.9 years, during which fibrosis accumulates, compromising organ function and increasing the risk of pancreatic cancer.

Because of its largely idiosyncratic evolution, chronic pancreatitis presents several treatment dilemmas including:

- Pain management, for which balancing effective pain relief with the risk of medication dependence and exploring alternatives such as celiac nerve blocks, and surgical interventions are key;
- Nutritional support, where diet and enzyme replacement therapy require close monitoring to manage malnutrition and nutrient deficiencies while addressing pain and gastrointestinal symptoms
- Alcohol and smoking cessation if applicable;

- Endocrine and exocrine insufficiency, for which the timing and dosing of pancreatic enzyme supplements and insulin therapy prove complicated (especially in pediatric populations);
- Surgical interventions and the optimal timing and type of surgery to manage complications and improve quality of life are often in doubt; and
- Long-term complications, for which monitoring and managing the increased risk of other diseases, such as pancreatic cancer, require serious consideration.

Ultimately, the complex nature of chronic pancreatitis requires a multidisciplinary approach, balancing symptom management with efforts to slow disease progression and prevent complications.

3.2 Ivacaftor and pancreatitis.

Ivacaftor is a CFTR potentiator that enhances the gating function of the CFTR protein, improving chloride and bicarbonate transport across epithelial cells. This mechanism is particularly relevant for treating chronic pancreatitis associated with CFTR dysfunction, as impaired ion transport contributes to viscous secretions, ductal obstruction, and pancreatic inflammation.

Restoration of CFTR Function: Ivacaftor increases CFTR channel open probability, which increases pancreatic ductal chloride and bicarbonate ion transport and alleviates pancreatic ductal obstruction. Although it has not yet been tested through randomized controlled trials, there is preclinical and retrospective evidence that this reduces acute pancreatitis episodes in patients with CFTR variants, even in the absence of respiratory symptoms.

Improved Pancreatic Function: Studies indicate ivacaftor can partially restore pancreatic exocrine function, reducing the risk of insufficiency and improving digestive health.

Treatment for CFTR-Related Pancreatitis: In patients with CFTR variants and other contributing risk factors, Ivacaftor has effectively treated chronic pancreatitis, suggesting that CFTR-modulator therapy may have broader utility in managing pancreatitis driven by CFTR dysfunction.

3.3 Ivacaftor use in an individual with chronic pancreatitis and no CFTR gene variant.

As noted in section 3.2, Ivacaftor is a CFTR potentiator approved for specific gating defects in cystic fibrosis; however, outside of the cystic fibrosis populations, there is emerging mechanistic evidence that restoring or improving CFTR channel activity in the pancreatic ducts can support fluid and bicarbonate secretion, which is critical to preventing ductal obstruction, proteolytic enzyme activation, and consequent pancreatic injury. Although no large-scale clinical trials have tested Ivacaftor specifically in non-CF individuals without known CFTR variants, preclinical and mechanistic studies (described below) support the hypothesis that partial or acquired CFTR dysfunction contributes to the pathophysiology of CP. Therefore, we propose a single case experimental design (SCED) observation trial to assess whether Ivacaftor can reduce acute on chronic pancreatitis episodes requiring intervention (e.g., hospitalization, increased medical care, endoscopic intervention, etc.), and improve quality of life in a single individual with chronic pancreatitis lacking known *CFTR* variants.

Mechanistic Rationale: CFTR is a key ion channel in pancreatic ductal transepithelial chloride and bicarbonate secretion that creates the alkaline-rich ductal fluid secreted by the pancreas. Precise coordination of chloride and bicarbonate secretion in the pancreatic ducts establishes the optimal pH to ensure appropriate spatiotemporal enzymatic activity and preventing spurious injury to pancreatic ducts. In chronic pancreatitis, ductal epithelial cells often show reduced bicarbonate secretion even if the CFTR gene does not harbor classic disease-causing variants. Inflammatory mediators, oxidative stress, or other environmental factors can lead to functional downregulation, altered trafficking, or gating inefficiencies of the CFTR protein. Ivacaftor directly potentiates CFTR gating, helping the channel remain open longer, thereby increasing chloride and bicarbonate flux, even in appropriately folded and localized “wild-type” CFTR protein. Furthermore, if the CFTR protein is present but functionally impaired due to post-translational or acquired gating defects (e.g., inflammation-induced dysfunction), Ivacaftor may restore a higher fraction of its ductal secretory capacity.

Evidence of Acquired CFTR Dysfunction in Pancreatitis. Preclinical models of pancreatitis have shown that pharmacologically or inflammation-induced inhibition of CFTR leads to diminished pancreatic fluid secretion and more severe injury. Restoration of channel function in ex vivo preparations from normal animals has been shown to improve ductal patency, reduce intraductal enzyme activation, and mitigate some features of inflammatory damage. For example, rodent studies examining chemically induced pancreatitis (not involving CFTR variants) have demonstrated a correlation between decreased CFTR-mediated bicarbonate secretion and increased severity of pancreatic injury. When these models employed CFTR activators or potentiators in vitro, partial normalization of ductal fluid flow and pH was observed, suggesting that improvements in CFTR gating can alleviate or prevent pathologic pancreatic ductal obstruction. Additionally, experimental work on isolated human pancreatic duct cells (obtained from non-cystic fibrosis donors) indicates that pro-inflammatory cytokines (e.g., TNF-α, IL-1β), which are present in acute and chronic pancreatitis, can impair CFTR channel conductance. Pharmacological enhancement of CFTR gating has been shown to restore the channel’s ability to transport chloride/bicarbonate under these conditions.

Potential Impact on Symptoms and Hospitalization. Chronic pancreatitis is characterized by debilitating abdominal pain, largely attributed to increased ductal pressure, ongoing inflammation, and neural remodeling. By improving ductal fluid secretion, Ivacaftor could theoretically reduce ductal hypertension and, over time, lessen the local inflammation that perpetuates pain cycles. Improved pancreatic ductal drainage could also decrease the frequency of acute exacerbations and the subsequent need for hospitalization. While no published randomized trials have evaluated Ivacaftor in non-CF chronic pancreatitis, extrapolation from preclinical data and the known mechanism of improved CFTR function support the plausibility of symptomatic and clinical benefit.

Existing Preclinical and Mechanistic Studies (Non-CF, Non-CFTR Variants). There are examples of the types of evidence supporting SCED trial approach in a patient with chronic pancreatitis and putative acquired CFTR dysfunction. These studies focus on inflammatory or chemically induced pancreatitis models and cell-based assays where CFTR was inhibited or dysfunctional in the absence of a genetic CFTR variants and include the following:

- Maléth & Hegyi (2016) Demonstrated in rodent models that pharmacologic inhibitors of ductal CFTR decreased bicarbonate secretion and exacerbated pancreatitis. Subsequent in vitro rescue of CFTR gating partially reversed ductal acidification and improved enzyme drainage.

- Rakonczay et al. (2011) found that hyperstimulation-induced pancreatitis in rodents correlated with a downregulation of CFTR expression and function at the ductal level. The impairment persisted despite the absence of any CFTR variants.

- Hegyi et al (2020) pursued in vitro studies of human pancreatic duct cells exposed to inflammatory cytokines showed significant decreases in CFTR-mediated chloride/bicarbonate flux. Channel potentiators restored conductance, indicating that even wild-type CFTR can be dysregulated under inflammatory conditions and subsequently rescued by pharmacologic agents.

- Fűr et all (2021) examined CFTR expression in rodent models of cerulein induced acute pancreatitis and observed mislocalization of CFTR protein from the apical to the basolateral membrane of pancreatic ductal cells. This mislocalization correlated with impaired bicarbonate secretion and exacerbated pancreatic inflammation. The study suggests that correcting CFTR localization may alleviate disease severity in acute pancreatitis.

These examples underscore the broader principle: inflammation or environmental damage can create a functional CFTR gating defect even when the CFTR gene itself is wild-type. Ivacaftor's mechanism as a CFTR potentiator may therefore be applicable to non-mutant CFTR if the channel's gating properties are secondarily compromised. Given the mechanistic underpinnings of CFTR in pancreatic ductal fluid and bicarbonate secretion, combined with documented inflammation-induced CFTR dysfunction in chronic pancreatitis models, it is scientifically plausible that Ivacaftor may improve pancreatic ductal function, reduce pain, and decrease flare frequency in a patient with chronic pancreatitis—even in the absence of a CFTR gene variant. The strong mechanistic rationale, coupled with the severe and refractory nature of this patient's condition, justifies a carefully monitored SCED trial to observe the effect of taking Ivacaftor off-label, as already prescribed by their clinical care team.

3.4 Ivacaftor Formulation Used in the Study

Per the plan in place with the patient's clinical care team, Ivacaftor (IVADECO® 150 mg tablets) will be procured from a licensed pharmacy in Argentina, where the medication is legally manufactured and distributed for the treatment of cystic fibrosis. The formulation is commercially available and not modified or compounded in any way. It will be sourced in sealed blister packs or original manufacturer packaging, and each package will be labeled with the batch number, expiration date, and manufacturing details.

Upon receipt in the United States, the medication will be stored at controlled room temperature (15–30°C / 59–86°F) in a secure location, away from light and moisture, as indicated in the manufacturer's instructions. It will be stored in the original packaging until use to preserve integrity and prevent contamination.

The medication will be administered at home by the legal guardians of the participant, following a twice-daily oral dosing schedule (150 mg every 12 hours with fat-containing food). Guardians will be instructed not to alter the tablets (e.g., crush or split) and to report any missed doses or adverse reactions.

Any expired, damaged, or unused tablets will be returned and disposed of according to pharmaceutical waste protocols in collaboration with a licensed disposal service. Participants will be advised against discarding any drug themselves.
IVADECO® is an Ivacaftor-only formulation (monotherapy) that is equivalent to Kalydeco® (Ivacaftor 150 mg tablets) approved by the U.S. Food and Drug Administration (FDA). Both IVADECO® and Kalydeco®:

- Contain 150 mg of Ivacaftor as the active pharmaceutical ingredient.
- Are intended for oral administration in immediate-release tablet form.
- Are taken every 12 hours with fat-containing food to optimize bioavailability.
- Are metabolized through the CYP3A pathway and eliminated primarily via feces.
- Share comparable indications—targeting CF patients with gating or residual function
- CFTR mutations (e.g., G551D, R117H).

While Kalydeco® is produced by Vertex Pharmaceuticals and approved in the U.S., IVADECO® is manufactured in Argentina and approved by the national regulatory authority ANMAT (Administración Nacional de Medicamentos, Alimentos y Tecnología Médica), with bioequivalence to Kalydeco supported by overlapping pharmacokinetic data such as C_{max}, AUC, and t_{1/2} values.

The pharmacokinetics of IVADECO® in pediatric and adult populations are consistent with published clinical data from Kalydeco studies. Its use in this study does not involve off-label formulation, compounding, or chemical modification, and therefore does not pose unique safety or efficacy risks beyond those established for FDA-approved Ivacaftor (see section 4.2 for side effects and risks).

3.5 Health Monitoring Device

The wearable device to be used in this study is the Apple Watch Series 9, manufactured by Apple Inc., headquartered in Cupertino, California, USA. The specific model in use is the Apple Watch Series 9 GPS + Cellular, 45mm Aluminum Case. This device is a commercially available consumer-grade wearable health tracker cleared for general wellness use.

For this study, the Apple Watch, which the participant was already wearing prior to participation in this study, will be used to passively monitor heart rate, activity levels, and sleep duration and trends. The device does not deliver medical diagnoses or therapeutic interventions and is used solely for observational purposes. All collected data will be securely synced with the participant’s Health app on a paired Apple device, and relevant datasets (e.g., heart rate variability, resting heart rate, sleep duration) will be exported manually by the caregiver using Apple’s built-in data export features and shared with the study team in a de-identified format.

The device will be worn continuously during the study period, including overnight, and will be charged once daily. Participants will receive verbal and written instructions on safe and

appropriate usage. No alterations will be made to the firmware, software, or physical components of the device.

Data security and privacy are governed by Apple's on-device data encryption and user-controlled sharing permissions. The participant's parents will be instructed to disable automatic iCloud backup and will be given the option to opt out of any feature beyond basic passive health tracking.

The participant wore a Fitbit Sense device for a period of time and that legacy data will be reviewed as part of this study. Data security and privacy for the Fitbit are governed by Fitbit's on-device encryption and user-controlled sharing permissions. All collected data will be securely transmitted to the SCED research team for evaluation of legacy metrics.

4. STUDY DESIGN

4.1 Data collection
Data will be collected from the time period before, during, and, if the treatment is discontinued, after the subject's treatment until 12 months after the trial begins.

4.2 Data sources
Data will come from the following sources:

4.2.1
The participant's medical records

4.2.2
Records kept by the participant's parents about the patient's condition, including hospitalizations and flares

4.2.3
Wearable devices (including Apple Watch and Fitbit described in sections 3.5) that the subject has worn before or wears during the course of the study

4.3 Duration
The duration of the study will be 12 months, which is justified by the statistical analysis.

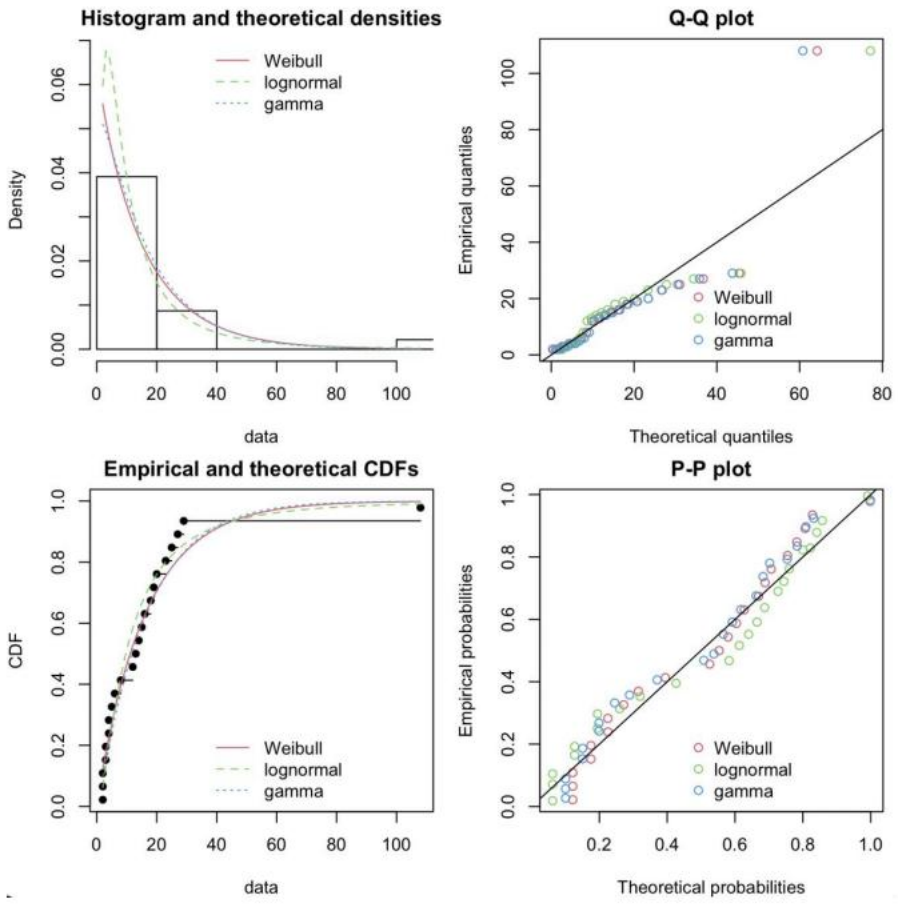
4.4 Analysis
We describe the analysis of information collected during the study's conduct, in order to make claims consistent with the primary aim of the study, which is to explore the benefits of Ivacaftor in treating the individual participant's chronic pancreatitis. In addition, we also describe the analyses of data collected to address the secondary aim, which is to identify patterns and associations involving subclinical symptoms (lingering but not acute pain after eating, disruptions in normal activity, etc.) using a wireless health monitoring device.

Table 1. Summary Participant Lipase and Event Data

Event	Days	N	Mean	SD	SE	Min	Max
Lipase Levels	2027	64	2025.53	4685.49	585.687	35	23523
Hospitalization length of stay	2027	19	2.52632	1.54087	0.3535	1	5
Hospitalization Intervals	2027	19	59.6667	105.373	27.2071	3	319
Any Event Intervals - adjacent days	2027	36	33.8889	51.5861	8.59769	2	228
Any Event - adjacent last 300 days	300	23	16.4348	21.7816	4.54178	2	108

4.41 Testing the primary hypothesis. To test the efficacy of Ivacaftor, we will *assess the probability that the participant has not experienced any clinically documented pancreatitis-related episodes or events in a significant amount of time relative to historical documented data*. Essentially, this analysis is rooted in an evaluation of the 'waiting times' between pancreatitis-related episodes and events. These documented events include the need for clinical attention, hospitalization, emergency room visits, medical intervention, or a need to document an acute pancreatitis episode via, e.g., lipase measurements (see Figure 1). Table 1 provides a summary of the Lipase measurements as well as length of hospitalizations and waiting times in different settings. Note that intervals between episodes and events do not consider the duration of hospitalizations but rather only the time (in days) between them (i.e., a 5-day hospitalization counts as one event, not 5). Given the increase in the frequency of episodes and events in the last 300 days (see Figure 1) we considered waiting times between episodes and events occurring in the last 300 days to determine waiting times that would be consistent with Ivacaftor's benefits to the participant. Figure 2 provides statistical summaries of the fit of 3 different widely used distributions to waiting time data (Weibull, lognormal, and gamma distributions). It can be seen that all 3 distributions provide a good fit to the data, although the waiting times include some outlying values suggesting an occasional dampening of symptoms whose determinants we will explore using subclinical measurements as part of a secondary aim of the proposed protocol (see section 4.4). Based on the Weibull distribution, the probability of having a 50-day interval between episodes and events would be 0.05. However, as noted the

Figure 2. Waiting Time Distribution Analysis for the



participant has experienced longer intervals in the last 300 days. For example, the participant exhibited a 108-day interval, which has a probability of 0.0017. In addition, over the course of the participant's history with pancreatitis, a 228-day interval was observed, which has a probability of 1.890049e-06. We therefore believe that the participant experienced no events and episodes over a 270-day period would be sufficient to show that Ivacaftor has provided a benefit (the probability of this occurring would be: 1.778068e-07). Despite this, we will keep the study open for 12 months (probability of no events or episodes in this interval = 8.741403e-10)

4.42 *Assessing the secondary aims*.

A health monitoring device (see section 3.5) which is already in use by the patient will be used to capture data for tracking subclinical health data and explore the relationship between health parameters and events that might correlate with these parameters. Such analyses could put the participant's natural disease history into perspective and shed light on issues that may or may not be related to Ivacaftor. The device to be used is described in section 3.5 and measures many health-related parameters, including: heart rate variability (an estimate of stress), oxygen saturation, sleep quality, and steps. All of these can be explored for their relationships with the other measures, or with the participant's symptom profile or day-to-day activities (a daily diary will be kept to document pain or notable symptoms). Since the device can be worn continuously, at least monthly analyses based on the proposed check-ins (section 5.2), will involve substantial amounts of data. The basic analysis models to be used to explore the data will be regression models. Since we will have more than 50 measures to be considered in the analyses involving the wireless health monitoring device, to determine the power of the proposed studies we will assume a conservative Bonferroni correction for multiple comparisons with nominal type I error rate of 0.05. Thus, our power calculations are based on a type I error rate of 0.05/50 = 0.001. For any given dependent variable (e.g., heart rate variability) the influence of an independent variable (e.g., mobility during the day, stress, or pain) can be assessed by the percentage of variation in the dependent variable explained by the independent variable. Using standard power calculations for regression analysis, with a total of 100, 1000, or 10,000 values of the dependent variable will can detect the effect of an independent variable that explains 18, 1.8 and 0.21 percent of the dependent variable variation, respectively, with 80% power. We note that serial correlation between the measures is likely to occur and will dampen the power to detect relationships between dependent and independent variables. We will estimate serial correlation between observations collected over time and correct for it using standard techniques (e.g., time series analysis methods such as autoregressive moving average (ARMA) models). We will this have excellent power to detect trends in health parameters that are associated with subclinical disease manifestations. The clinical significance of these trends, patterns and relationships will be discussed by the research team during the monthly check-ins with the parents and quarterly check ins with the patients clinical team as events of interest or results arise from the analyses.

4.3 Mental health and protocol-related stressors

Mental health evaluations will occur throughout the trial per routine visits with Dr. Panopoulos, which already take place. During Dr. Panopoulos's monthly meetings with the patient, she will assess any mental health concerns related to participation in the trial (i.e. data collection and observation, not the clinical treatment). If any adverse mental health effects are identified, Dr.

Panopoulos will notify the research team of anything that might compromise the continuance of the observational study.

If moderate or severe distress is identified, Dr. Panopoulos will implement therapeutic interventions (e.g., coping strategies, referral to extended mental health services). In coordination with the research team and the patient's caregivers, they will also evaluate whether continued participation in the trial is in the patient's best interest.

5. STUDY PLAN OVERVIEW

5.1 Phase One: Initiate Study and Evaluate the Health Monitoring device(s)

The initial phase of the study will involve consenting the participant, orienting the parents, the participant's physicians, and care providers to the protocol and the broader research team. We anticipate at least one meeting involving all the research team members devoted to this orientation, but if more are called for, they will be scheduled.

5.2 Phase Two: Data Collection and Analysis.

After initiation of the study, there will be monthly check-ins involving the members of the research team and the participant's parents. There will also be quarterly meetings with the patient's clinical team. These sessions will focus on issues surrounding the execution of the study, and events of interest, and ongoing data collections and physician care provider interactions.). In addition, the data collected from the wireless health device overseen by the participant's parents will be provided at least monthly by the participant's parents to the research team for analysis.

5.3 Phase Three: Closeout.

At the end of the study (12 months from its initiation), the closeout process will occur. If the participant revokes consent, the closeout process will occur. The closeout process will involve gathering all study materials, securing them at the sponsor site, and determining if there is a next step (e.g., amending the protocol for continuation and/or adding elements to it).

6. STUDY POPULATION

6.1 Number of Participants.

The proposed study is rooted in a single case experimental design (SCED) involving a particular individual so there will be only one participant.

6.2 Inclusion Criteria

The subject has been diagnosed with recurrent acute pancreatitis or chronic pancreatitis and a clinical decision has been made to treat the subject with one or more FDA-approved therapies, which may be being used off-label) to treat or prevent pancreatitis symptoms.

6.3 Recruitment.

The proposed study is rooted in a single case experimental design (SCED) involving a particular individual, so recruitment is not applicable. In addition, the participant has been using Ivacaftor off label under the supervision of their physicians and family.

7. INITIAL STUDY PROCEDURES

7.1 Pre-Enrollment Screening.

The participant and their parents will review the study protocol and consent forms with the participant's physicians. Any questions will go back to the research team for discussion and any potential revisions, which will be communicated to the IRB before signing.

7.2 Enrollment.

After the consent forms are signed, the study will commence.

8.0 FOLLOW-UP PROCEDURES

8.1 Clinical and family check-ins.

Monthly research team check-ins are scheduled that will involve the entire research team and the participant's parents. The state of the study as well as any issues will be discussed including analysis results of the wireless health monitoring device data.

8.2 Routine clinical visits.

The protocol leverages the routine care that is provided to the participant through established care streams. This involves physicians that have routine interactions with the participant as well as their parents. It is anticipated that follow-up interactions with these providers will happen spontaneously as a part of routine care already in place.

8.3 Health monitoring data aggregation.

As part of routine monthly analysis check-ins, the parents of the participant will provide collected wearable device data to Dr. Schork. This data includes metrics such as heart rate, activity levels, and sleep patterns, which are passively collected through a commercially available wearable device worn by the participant. The data will be securely transmitted to the research team. These monthly submissions are intended to monitor trends over time and support personalized insights relevant to the participant's ongoing care and the objectives of the study. The data will be securely transmitted to the research team and will be analyzed by the research team and results discussed at the monthly and quarterly check-ins if not before as interest arises.

8.4 Follow-up Clinician Visits.

The protocol leverages the routine care that is provided to the participant through established care streams. This involves physicians that have routine interactions with the participant as well as their parents. It is anticipated that follow-up interactions with these providers will happen spontaneously.

9.0 DATA COLLECTION SUMMARY

9.1 Routine monitoring by parents, caregivers, and physicians.

Data and information about the participant's health status will be gathered and assessed by the participant's physician team in conjunction with the participant's parents. Any findings that may affect the protocol and its continued execution will be shared with the research team.

9.2 Wearable health monitoring.

The use of wireless health monitoring devices will be overseen by the participant's parents in conjunction with the participant's physicians will be part of the protocol and address the protocol's secondary aim (section 2.2).

10.0 INFORMED CONSENT

10.1
The participant and their parents will have ample time to read through all of the items on the consent and contact the study coordinator with questions and concerns.

10.2
The language of the consent and the discussions will be conducted at an appropriate reading level to ensure complete understanding by participants.

10.3
The participant and their parents will sign the consent (either electronically or physically). When the signed consent form is received by the research coordinators, the database will be updated to reflect receipt of consent. One copy will be provided to the participant and their parents and one copy will become part of the electronic medical record of each participant. A third copy will be de-identified and kept in a locked file cabinet in the Principal Investigator's office, only accessible by the study personnel.

10.4
No language will be included in the consent form itself or will be used during the consenting process that will be exculpatory or imply in any way that participants waive their legal rights, or release the Principal Investigator(s) other investigators, or the sponsoring agency (Mission: Cure) from liability for negligence.

10.5
No procedures or tests will be ordered and no questionnaires or surveys will be completed until after the participant and their parents have signed the consent form and been fully enrolled.

10.6
The participant and their parents will be able to opt out of the return of results if they so choose.

11.0 LABORATORY METHODS

11.1 Clinical laboratory evaluations.

All assays of clinical tests used in the protocol will be provided by the participants' care team including their physicians. The protocol does not include any deliberate research grade assays.

11.2 Other assays.

The use of wireless health monitoring devices overseen by the participant's parents in conjunction with the participant's physicians will be part of the protocol and address the protocol's secondary aim (section 2.2).

12.0 STATISTICAL CONSIDERATIONS

The analysis methods and issues of false positive and negative results of the study for the primary aim are provided in section 4.4. They are provided for the secondary aim in section 2.2.

13.0 RETURN OF RESEARCH RESULTS OR INCIDENTAL FINDINGS

13.1 Individual Research Results.

The return of results from the data collections to the participant and their family are largely irrelevant as the participant's physicians will be actively involved in the protocol. In addition, the wireless health monitoring data will be collected by the participant's parents and provided to the research team (section 3.5).

13.2 Secondary or Incidental Findings.

During the course of data analyses, investigators and the participant's physician and care team as well as the broader research team may discover clinically meaningful information about the participant (i.e., an incidental finding). All incidental findings will be reviewed by the participant's care team and the investigators at the scheduled meetings. Additional colleagues will be consulted if needed. When deciding what to disclose, the team will take into account the health implications of the finding, if the finding is clinically actionable, or provides any potential benefits that outweigh the risks of knowing. Results will be confirmed in a CLIA-certified laboratory at no expense to the participant. If the participant and their parents opted to receive results, the report of the incidental findings will be included in the full report and returned to the participant during a meeting with Dr. Panopoulos or another study physician. If the participant and their parents consent, the report will also be sent to the participant's primary care physician. Possible disclosure of incidental findings will be discussed during the consent process. Participants will have the right not to be informed of incidental findings, and/or not have their primary care physicians informed, if they so choose.

14.0 BENEFITS AND RISKS TO PARTICIPANT

14.1 Potential Benefits.

The potential benefits of the study are very important and compelling. Currently, the participant has not exhibited long term benefits from standard interventions, so the collection of data on effects of Ivacaftor could result in clarifying if it is in fact an effective treatment for what is a debilitating and compromising condition, particularly for an adolescent. In addition, the precedents set for this study, both with respect to how it has been designed and the potential impact of showing that Ivacaftor can effectively treat chronic pancreatitis, could be far-reaching.

14.2 Potential Risks.

Because the patient is already taking Ivacaftor off-label and undergoing monthly blood draws for monitoring, there are no new additional medical risks of participation in this study. However, as in all research studies, it is possible that participants may misunderstand the purpose of the study or may feel anxious or become anxious about the thought of participating in a research study in general. There is a risk of loss of Privacy or Confidentiality associated with any study. Section 15 discusses how the study plans to maintain participant confidentiality.

14.3 Risks with Return of Research Results.

The participant and family already receive laboratory results, so no new results outside of typical standard of care will be relevant to this study.

14.4 Risks Minimized.

All blood draws are performed by a qualified phlebotomist under the auspices of the participant's current physician and health care providers. Ancillary research staff will not see any identifying participant information that could be linked to the sample. Data received by non-key personnel will be de-identified and coded information. All data will be maintained in password-protected databases with limited access. If samples are sent to a CLIA-certified laboratory for analysis, information such as the participant's name, date of birth, and the date the sample was collected may be shared with the laboratory. Samples may be stored in a CLIA-certified laboratory. Samples and data may be shared with outside researchers at the investigator's discretion for future research. Data from the study may be published in scientific journals. Publications will not include any participant identifiers.

14.5 Risks Reasonable.

This is an observational study exploring the merits of the off-label use of Ivacaftor under the supervision of the participant's physicians and research team. There are only slight risks to the study participant and the potential for benefits to future medicine could be great. Thus, the risks involved in study participation are reasonable.

14.6 Compensation.

No compensation to the participant or their family will be provided as part of the protocol.

14.7 Costs.

The costs of the study are covered by the participant's family and the sponsoring agency, Mission: Cure. There are no other financial sponsors for the study as members of the research team are part of the participant's established care team.

15.0 CONFIDENTIALITY

Every effort will be made to keep participants' medical records confidential, as well as other personal information that is gathered during this study. The medical records and information from the study tests will be treated in a confidential manner, as required by federal and state laws. Precautions will be taken to protect the privacy of the participant. The Clinical Investigator or a member of the study staff will maintain a master enrollment log containing participant name and the consent forms. All of these documents will be stored in locked cabinet(s) at the Clinical Sites or at the sponsoring agency Mission: Cure. Only the study Clinical Investigators or the study coordinator(s) will have routine access to the master enrollment log and participant identifiable information. The informed consent form discloses the limits of confidentiality and the fact that participants may be requested to disclose such information by a third party. This is a risk of participation in the study and the participants will be informed of this risk. Any biospecimens or samples obtained will remain with the ordering physician using their CLIA approved laboratory facilities. Samples will not be stored with any participant identifiers. Ancillary research team members will receive only de-identified and coded information. The samples will be banked and continued to be studied as new techniques become available. Data from the

study may be published in scientific journals and/or public data sharing databases. Publication of data will not include any participant identifiers.

16.0 HUMAN SUBJECT ISSUES

16.1 Data Sharing.

De-identified data may be published to a central data repository that allows qualified research scientists to access and look at the data. No information that can directly identify the participant will be published in the database. The consent form will discuss with the subject the risks associated with sharing of genetic de-identified information. De-identified data may be shared with collaborators. Findings from this study may be compiled into a manuscript for presentations and/or publication in a peer-reviewed journal. All published or presented data will be de-identified.

16.2 Future Use of Specimens & Data.
De-identified biospecimens and data collected under this study may be used for additional future research studies at the discretion of Mission: Cure. Data from the study may be published in scientific journals. De-identified biospecimens and/or data may be shared with external collaborators for additional future research studies at the discretion of Mission: Cure and/or the Study Investigators. IRB approval will be obtained when applicable. Other than the de-identified sample number, no PHI will remain with the stored specimen or data.

16.3 Registration into a Clinical Trials Management System.
The trial will be registered into a Clinical Trials repository and management system for this trial: clinicaltrials.gov.

16.4 Alternatives to Participation.
The individual participant can choose not to participate and this will not impact their medical care in any way.

16.5 Study Discontinuation.
Investigators and/or Mission: Cure reserve the right to discontinue the study at any time.

16.6 Records Retention.
During this study, the investigator is required to prepare and maintain adequate and accurate case histories. All study related records including consent forms, progress notes, case histories, and data collection forms will be maintained by the study team in locked file cabinets within locked offices or in password protected files.

17.0 REFERENCES

Maléth, J., and Hegyi, P. “Cellular pathways of pancreatic ductal bicarbonate secretion and their role in pancreatitis development.” Pancreas. 2016; 45(8):1171–1183.

Rakonczay, Z., et al. “The role of pancreatic ducts in the pathogenesis of acute pancreatitis.” Pancreatology. 2011; 11(5):232–241.

Hegyi, P., et al. “Pancreatic ductal bicarbonate secretion: challenge of the acinar acid load.” Frontiers in Physiology. 2020; 11:536.

Fűr, G., Pallagi, P., Venglovecz, V., Iványi, B., Oláh, A., Czakó, L., Hegyi, P., Rakonczay Jr., Z., & Kiss, L. (2021). Mislocalization of CFTR expression in acute pancreatitis and the beneficial effect of VX-661 + VX-770 treatment on disease severity. *The Journal of Physiology*, 599(21), 4955–4971.