1 TITLE PAGE

MEDICAL UNIVERSITY OF SOUTH CAROLINA

Study Protocol

An Efficacy and Safety Study of Ivacaftor in Patients With Cystic Fibrosis and Two Splicing Mutations
IND Number: 131831

Date and Version of Protocol: 22 June 2015 (Version 1.0)

2 PROTOCOL SYNOPSIS

Title	An Efficacy and Safety Study of Ivacaftor in Patients With Cystic Fibrosis and Splicing Mutations
Clinical Phase	N of 2 Study
Objective	To evaluate the efficacy and safety of ivacaftor in two patients (sisters) who have a splicing mutation and pancreatic sufficiency
Endpoints	Primary • Absolute change in percent predicted forced expiratory volume in 1 second (FEV_1) from baseline through Week 24 Key Secondary • Relative change in percent predicted FEV1 from baseline through Week 24 • Achievement of mycobacterial culture conversion (negative culture) by Week 24 Secondary • Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values (i.e., liver function tests) • Absolute change in sweat chloride from baseline through Week 24 • Absolute change in respiratory symptom scores from baseline at Week 24
Study Population	Sisters with specific mutations
Number of Subjects	2
Study Duration	Subjects will be treated for 6 months and followed for 7 months
Study Design	This postmarketing N of 2 study is designed to evaluate the efficacy and safety of open-label ivacaftor treatment in two sisters with cystic fibrosis and pancreatic sufficiency. They have a splicing mutation that is predicted to respond favorably to ivacaftor therapy. In addition to measurement of usual clinical outcomes (i.e. lung function, nutritional status), there is great interest on the impact on nontuberculous mycobacteria (NTM) airways infection. Subjects will undergo sputum cultures at baseline and monthly during treatment, initially in the absence of anti-NTM therapy but with the intent to treat with antibiotics if there is persistence of the infection in cultures. Other clinical outcomes will include changes in sweat chloride, lung function and weight. Safety measures will include periodic assessment of liver enzymes. All serious and non-serious adverse events will be collected
Assessments	Efficacy: spirometry, sweat chloride testing, CRISS, sputum cultures (bacteria and mycobacteria), height, and weight Safety: AEs, clinical laboratory assessments (liver function tests), vital signs, physical examinations, and pulse oximetry
Statistical Analyses	Statistical analysis details will be provided in the Statistical Analysis Plan (SAP), which will be finalized before the clinical data lock for the study.

3 SCHEDULE OF ASSESSMENTS

The Schedule of Assessments is shown in Table 3-1

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Event/Assessment	**Day 1**	**Day 30**	**Day 60**	**Day 90**	**Day 120**	**Day 150**	**Day 180**	**Day 210**
Informed consent	x							
Medical history	x							
Demographics[a]	x							
Physical examination	x	x	x	x	x	x	x	x
Height and weight	x	x	x	x	x	x	x	x
Sweat test	x	x		x			x	x
Spirometry	x	x	x	x	x	x	x	x
Genetic testing[b]	x							
Liver function tests[c]	x			x			x	
Sputum cultures[d]	x	x	x	x	x	x	x	x
CRISS	x	x	x	x	x	x	X	x
Adverse events		x	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x
Study drug dispensed	x	x	x	x	x	x		

[a] Demographics include sex, race, and age. Baseline characteristics include age at CF diagnosis, *CFTR* genotype

[b] Genetic testing will get confirm that the two mutations are not on the same allele (with a cryptic additional mild mutation on the other allele)._

[c] Safety labs include liver enzymes (ALT, AST, GGT)_

[d] Sputum will be tested for bacteria and mycobacteria (including AFB smear and culture). Susceptibility testing will not be performed

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5 LIST OF ABBREVIATIONS

Abbreviation	Definition
ALT	Alanine transaminase
AST	Aspartate transaminase
BMI	body mass index
CF	cystic fibrosis
CFF	Cystic Fibrosis Foundation
CFTR	CF transmembrane conductance regulator gene
CFTR	CF transmembrane conductance regulator protein
CRF	case report form
EDC	electronic data capture
EU	European Union
FEV_1	Forced expiratory volume in one second
G551D	*CFTR* missense gene mutation that results in the replacement of a glycine residue at position 551 of CFTR with an aspartic acid residue
G551D	CFTR protein with a replacement of a glycine residue at position 551 with an aspartic acid residue
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transaminase
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
IEC	independent ethics committee
IRB	institutional review board
MAC	Mycobacteria avium complex
MedDRA	Medical Dictionary for Regulatory Activities
NTM	Non-tuberculous mycobacteria
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
US	United States
WHO-DD	World Health Organization Drug Dictionary

6 INTRODUCTION

Overview of Cystic Fibrosis

Cystic fibrosis (CF) is a chronically debilitating autosomal recessive disease with high morbidity and premature mortality that affects approximately 30,000 individuals in the United States (US)[1] and 36,000 individuals in the European Union (EU).[2] The disease is caused by mutations in the CF transmembrane conductance regulator gene (*CFTR*), which results in absent or deficient function of the CF transmembrane conductance regulator protein (CFTR) at the cell surface.[4] CFTR is an epithelial chloride channel responsible for helping to regulate salt and water absorption and secretion in various tissues. The failure to regulate chloride transport in these organs results in the multisystem pathology associated with CF.[5] In the lungs, obstruction of airways with thick mucus, establishment of a chronic bacterial infection in the airways, and damaging inflammatory responses are all thought to play a role in causing irreversible structural changes in the lungs and, ultimately, respiratory failure. Progressive loss of lung function is the leading cause of mortality.[1,3] Currently there is no cure for CF, and, despite adjunctive treatments with nutritional supplements, antibiotics, and mucolytics[6], the median predicted age of survival of individuals born today with CF is approximately 40 years of age.[1,7]

More than 1800 mutations in the *CFTR* gene have been identified.[8] Mutations in the *CFTR* gene have been classified based on the molecular and functional consequence of the mutation on the CFTR protein[9,10,11] and can be generally considered to reduce the quantity of functional CFTR protein that reaches the epithelial cell surface or reduce the function of CFTR protein located at the cell surface. *CFTR* gene mutations that affect the quantity of functional cell surface CFTR protein include defects that reduce CFTR protein synthesis and defects that impede the cellular processing and delivery of CFTR proteins to the cell surface.

CFTR gene mutations associated with minimal CFTR function include

- mutations associated with severe defects in the ability of the CFTR channel to open and close, known as defective channel gating or “gating mutations”;
- defects in the cellular processing and delivery to the cell surface;
- no (or minimal) CFTR synthesis; and
- severe defects in channel conductance.

One approach to increasing the level of chloride transport through the CFTR channels is to treat with a potentiator, a compound that increases the channel gating activity of CFTR protein located at the cell surface, resulting in increased chloride transport.[10,12] Potentiators represent a therapeutic strategy to treat CF. A modest restoration of chloride secretion through the action of a potentiator could prevent the hyperabsorption of water across the apical surface of epithelial cells, allowing for proper maintenance of airway hydration. Adequate airway hydration could alleviate the cycle of mucus plugging, infection, and inflammation that leads to irreversible structural changes in the lungs, and eventually respiratory failure for patients with CF. There is a supposition that potentiators can facilitate chloride secretion in patients with CF who express at least some amount of residual CFTR protein at the cell surface.[13]

Overview of Ivacaftor and Rationale for Study

Ivacaftor, a compound developed by Vertex Pharmaceuticals Incorporated, is classified as a CFTR potentiator. Commercially-available ivacaftor (Kalydeco^{TM}; 150-mg tablets) was approved in the US and the EU in 2012 for the treatment of CF in patients 6 years of age and older who have the *G551D* mutation in the *CFTR* gene. The indication for ivacaftor has since been expanded to include additional mutations (*G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R,* and *R117H*) based on the demonstration of clinical efficacy. Ivacaftor is an orally bioavailable small molecule CFTR potentiator that targets the underlying defect in CF. As such, ivacaftor is a member of a new class of drugs, known in the literature as CFTR modulators, that provides a new therapeutic approach to the treatment of CF.

Since ivacaftor has been made available there are a growing number of reports of its successful use outside of the labeled indications. These include demonstration of pulmonary efficacy in patients with the indicated mutations but whose lung function is more severe than treated in the clinical trials, but also for patients with mutations that are predicted to respond to CFTR potentiation but are not in the label as an indicated mutations. For example, there is a report of successful treatment of sinus disease in a patient with the mutations F508del and 2585delT and the highly publicized account of a patient with F508del and 3849+10kb, C—T in which United Healthcare initially declined coverage of the medication but eventually reversed the decision. He was seen to complete a marathon not long after.

In addition, since ivacaftor is delivered systemically there is an expectation there could be clinical benefits outside of its primary indication (i.e. improvement in pulmonary function). There are growing reports of non-pulmonary benefits of CFTR potentiation including the sinus disease noted above. The GOAL study, an observational study of a treated cohort of patients with the G551D mutation, demonstrated increased nutritional parameters (i.e. weight and BMI) likely because of normalization of the intestinal pH resulting in improved digestion and absorption of calories (REF). There are reports of pregnancy in female patients who had previously been unable to conceive, presumed because of changes to the cervical mucus thought to cause a mechanical barrier to fertility (REF). Finally, the GOAL study has also shown a reduction in the prevalence of *Pseudomonas* infection in treated patients (REF). This could be because of improved mucociliary clearance and a mechanical reduction in the bacterial load but an additional hypothesis is that enhanced mucociliary clearance causes an increase of local production of nitric oxide, known to have an antimicrobial effect and to be a key part of host defense against infection (REF).

This study is intended to assess the effects of ivacaftor in two related patients with a CFTR splicing mutation (3120 G>A). A splicing mutation results in a reduction in functional CFTR present at the cell surface because of inefficient splicing of the final mRNA product, but the protein product is presumed to be normal. Ivacaftor is known to potentiate normal CFTR and would then be expected to potentiate the product of a splicing mutation. The question is whether there is sufficient protein present in the apical membrane in a patient with a splicing mutation such that treatment with ivacaftor could result in a clinical benefit. The patients of interest for this study have a splicing mutation and have a reasonable probability of response given a milder manifestation of initial clinical presentation and evidence of residual CFTR function (i.e. pancreatic sufficiency). The first patient is a 36 year old female with CF, who

was first diagnosed at the age of 18 years with hemoptysis. Her genotype is 3120 G>A and 3659delC. The first mutation is a splicing mutation so there should be some protein at the cell surface; the other is a premature stop codon so little CFTR should be present. She has a sweat chloride of 85 mmol/L (1997) and a fecal elastase >500 (12-2-13). She has moderately severe lung disease with a history of lobar resection prior to her diagnosis of CF. She has chronic sinus disease. Her sputum cultures had previously grown *Pseudomonas* but this has not been present since 2010. Currently she has *Mycobacterium abscessus* in her sputum cultures with positive smears despite antibiotic therapy. It is hypothesized there could be better response to antibiotic therapy if there was adequate CFTR potentiation. The purpose of six months of treatment is to measure a change in the microbiology in the presence of antibiotics. The second patient is her older sister, who was diagnosed only after the first patient had been diagnosed. Her symptoms have predominantly been sinusitis, but she has mild obstructive airways disease, chronic infection with *Pseudomonas*, pancreatic sufficiency, and suffered a bout of acute pancreatitis due to a pancreatic stone (not from the gallbladder). She also had a mycobacterial infection (MAC) that appears to have been eradicated with antibiotic therapy. However, this is based on culture conversion (persistently negative cultures) while on therapy and she is being monitored now off antibiotic therapy.

7 STUDY OBJECTIVE

To evaluate the efficacy and safety of ivacaftor in two sisters known to have a splicing mutation of CFTR.

8 STUDY ENDPOINTS

- The primary measures of efficacy will include spirometry and sweat chloride compared to baseline.
- Secondary measures of efficacy will include change in weight (BMI), respiratory symptoms (CRISS), and sputum microbiology with particular interest in mycobacterial cultures, including semi-quantitative smear and culture results.

9 STUDY DESIGN

9.1 Overview of Study Design

This postmarketing N of 2 study is designed to evaluate the efficacy and safety of open-label ivacaftor treatment in two sisters with cystic fibrosis and pancreatic sufficiency. They have a splicing mutation that is predicted to respond favorably to ivacaftor therapy. In addition to measurement of usual clinical outcomes (i.e. lung function, nutritional status), there is great interest on the impact on nontuberculous mycobacteria (NTM) airways infection.

Subjects will undergo sputum cultures at baseline and monthly during treatment, initially in the absence of anti-NTM therapy but with the intent to treat with antibiotics if there is persistence of the infection in cultures. Other clinical outcomes will include changes in sweat chloride, lung function, respiratory symptoms (CRISS), and weight. Safety measures will include periodic assessment of liver enzymes. All serious and non-serious adverse events will be collected

9.1.1 Day 1

The investigator will obtain informed consent from the subjects (Note: they have already expressed interest in participation prior to protocol development but are aware of planned study procedures). Subjects will have blood drawn for genetic testing and undergo a physical examination, including height and weight, and measurement of baseline measures for efficacy and safety (i.e. sweat test, spirometry, respiratory symptoms (CRISS), sputum cultures for bacteria and mycobacteria, and liver enzyme testing). The subjects will commence dosing of ivacaftor on this day.

9.1.2 Months 1, 2, 3, 4, 5, and 6

Patients will be evaluated for any changes in health or medications. They will undergo physical examination, including height and weight. They will undergo measurement of efficacy outcomes (sweat test, spirometry, CRISS, sputum cultures) and safety (liver enzyme tests) as per the Study Assessment Schedule (Table 3-1).

9.2 Rationale for Study Design

The primary efficacy measures (changes in sweat chloride, respiratory symptoms, and spirometry) are expected to change in the short term (i.e. 2-4 weeks) as shown in clinical trials, but measurement through the duration of the study will demonstrate persistence of effect with chronic therapy. The other key assessment will be the change in sputum culture results, especially related to mycobacteria. It is expected that these changes will take more time to be realized, accounting for the planned 6 months of therapy and monitoring.

As this is an n-of-2 study, there is no value to a blinded aspect for the study. Treatment will be open-label and clinical outcomes will be assessed by the individuals.

10 SELECTION OF STUDY POPULATION

10.1 Inclusion Criteria

Subjects include two identified sisters with CF gene mutations expected to respond to ivacaftor. They fulfill the following criteria:

- Subjects are >18 years of age and able to provide informed consent.
- Subjects reside in the US and are willing to be treated with ivacaftor.
- Subjects have the splicing mutation of interest.
- Subjects are willing and able to perform requirements of the study.

10.2 Exclusion Criteria

There are no relevant exclusion criteria for this n-of-2 study.

11 ASSESSMENTS

11.1 Timing of Assessments

The timing of assessments is shown in Table 3-1.

11.2 Subject and Disease Characteristics

Subject and disease characteristics include the following: *CFTR* genotype, sex, race, age, weight, height, body mass index (BMI), age at CF diagnosis, and relevant medical history. Supplemental medical history may be collected from the Cystic Fibrosis Foundation (CFF) Patient Registry.

11.3 Ivacaftor Exposure

The start and stop dates of all ivacaftor treatment will be recorded; all unique dosing intervals will be recorded during the study.

11.4 Prior and Concomitant Medications

Information regarding all medications administered before study enrollment and through the last study visit will be recorded.

11.5 Safety

11.5.1 Adverse Events

All serious and non-serious adverse events will be assessed and documented.

12 STATISTICAL AND ANALYTICAL PLANS

Data analysis will be performed by the investigator.

12.1 Sample Size and Power

This study is based upon the call for n-of-1 trials in clinical medicine; that is, single subject clinical trials that consider an individual patient as the sole unit of observation in a study investigating eth efficacy of an intervention (Lillie et al 2011), which is the heart of individualized medicine. As the patients of interest are sisters with the same mutation and similar clinical issues, this will be an n-of-2 trial. No power analysis is necessary.

12.2 Analysis Sets

There is only one set of data to be analyzed, consisting of the 2 subjects enrolled in this study. They will comprise both the **Enrolled Set** and the **Safety Set**.

12.3 Statistical Analyses

This section presents a summary of the planned statistical analyses of safety. Analysis details will be provided in the Statistical Analysis Plan (SAP) for this study, which will be finalized before study database lock.

12.3.1 General Considerations

Continuous data variables (e.g., FEV_1) will be summarized using descriptive summary statistics. Categorical data (e.g., sex) will be summarized. All subject data, including those derived, will be presented in the subject data listings.

12.3.2 Background Characteristics

12.3.2.1 Subject Disposition

The number of subjects in each disposition category (e.g., enrolled; prematurely discontinued from the study; and completed the study) will be summarized.

12.3.2.2 Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be captured: *CFTR* genotype, sex, race, age, weight, height, BMI, sweat chloride, spirometry, CRISS, and sputum culture results.

12.3.2.3 Prior and Concomitant Medications

Only prior and concomitant corticosteroids and ivacaftor will be collected. Medications taken during the collection period specified in Section 11.4 will be summarized by preferred term using the World Health Organization Drug Dictionary (WHO-DD) for the Safety Set as frequency tables in 2 parts:

- Prior medication: medication that started before the first dose of ivacaftor, regardless of when dosing of the medication ended.
- Concomitant medication: medication received at or after the first dose of ivacaftor, medication that was received before initial dosing of ivacaftor and continued after initial dosing, or medication with missing stop date.

Medications that started before the first dose of ivacaftor and continued after the first dose of ivacaftor will be summarized separately as prior medications and concomitant medications, respectively. Medications with a missing start date will be considered to have a start date before the first dose of ivacaftor.

12.3.2.4 Ivacaftor Exposure

Exposure to ivacaftor (i.e., duration of treatment) will be summarized for the Safety Set in terms of duration of treatment a subject received (in days). Duration of treatment will be summarized by descriptive summary statistics.

12.3.3 Efficacy Analysis

Change (absolute change) from baseline will be calculated as post-baseline value - baseline value. Relative change from baseline will be calculated as (post-baseline value - baseline value)/baseline value.

12.3.4 Safety Analysis

Safety analyses will be based on the Safety Set. All safety data will be presented in individual subject data listings.

12.3.4.1 Adverse Events

All adverse events with start date on or after enrollment date through the last study visit will be summarized. Adverse events are defined in Section 13.1.1. Adverse event summary tables will include the following:

- all adverse events;
- related (identified as related to ivacaftor by the investigator) adverse events;
- adverse events leading to treatment discontinuation;
- serious adverse events (SAEs); and
- adverse events by relationship.

Summaries will be presented by MedDRA system organ class and preferred term using frequency counts and percentages. A subject with multiple occurrences of the same adverse event or a continuing adverse event will be counted only once, by relationship.

12.4 Interim Analyses

No interim analyses will be performed but safety will be monitored throughout.

13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

13.1 Adverse Event and Serious Adverse Event Documentation and Reporting

13.1.1 Definition of an Adverse Event

For this study, an adverse event is defined as any untoward medical occurrence in a subject during the study, including any newly-occurring event or previous condition that has increased in severity or frequency after the informed consent form is signed.

A subset of adverse events may meet serious criteria. The definition of an SAE and reporting procedures for SAEs are detailed in Section 13.1.2. The definitions below apply to both adverse events and SAEs.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the subject was enrolled in the study are not to be considered adverse events unless the condition deteriorated in an unanticipated manner during the study (e.g., surgery was performed earlier than planned).

13.1.2 Definition of a Serious Adverse Event

An SAE is any adverse event that meets any of the following criteria:

- Fatal (death, regardless of cause, that occurs during participation in the study, or occurs after participation in the study and is suspected of being possibly related to ivacaftor).
- Life-threatening, such that the subject was at immediate risk of death from the reaction as it occurred.

- Inpatient hospitalization or prolongation of hospitalization, with the exception of planned or elective hospitalization.
- Persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Congenital anomaly or birth defect.
- Important medical event that, based upon appropriate medical judgment, may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above (e.g., an allergic bronchospasm requiring intensive treatment in an emergency room or at home).

13.1.3 Documentation of Adverse Events

From the time informed consent is signed through the last study visit all adverse events will be collected. The following data should be documented for each adverse event:

- Description of the event
- Classification of "serious" or "not serious"
- Date of first occurrence and date of resolution (if applicable)
- Causal relationship to ivacaftor exposure
- Action taken
- Outcome
- Concomitant medication or other treatment given

For all other adverse events considered related to ivacaftor, see Section 13.1.7.2.

13.1.4 Adverse Event Causality

Every effort should be made by the investigator to assess the relationship of the adverse event, if any, to ivacaftor exposure. Causality should be classified using the categories presented in Table 13-1.

Table 13-1 Classification for Adverse Event Causality

Classification	Definition
Related	There is a suspected association between the event and the administration of ivacaftor, a plausible mechanism for the event to be related to ivacaftor and causes other than the ivacaftor have been ruled out, and/or the event re-appeared on re-exposure to ivacaftor
Not related	The event is believed related to an etiology other than the ivacaftor. (The alternative etiology should be documented in the study subject's medical record)

13.1.5 Action Taken with Ivacaftor

The investigator will classify the action taken with regard to ivacaftor due to the adverse event. The action taken should be classified according to the categories shown in Table 13-2.

Table 13-2 Classification for Ivacaftor Action Taken With Regard to an Adverse Event

Classification	Definition
Dose Not Changed	Ivacaftor treatment not changed in response to an adverse event
Drug Interrupted	Ivacaftor administration interrupted in response to an adverse event
Drug Withdrawn	Ivacaftor administration permanently discontinued in response to an adverse event
Not Applicable	Action taken regarding ivacaftor administration does not apply. "Not applicable" should be used in circumstances such as when the ivacaftor

	treatment had been completed before the adverse event began and no opportunity to decide whether to continue, interrupt, or withdraw treatment is possible

13.1.6 Adverse Event Outcome

An adverse event should be followed until the investigator has determined and provided the final outcome. The outcome should be classified according to the categories shown in Table 13-3.

Table 13-3 Classifications for Outcome of an Adverse Event

Classification	Definition
Recovered/Resolved	Resolution of an adverse event with no residual signs or symptoms
Recovered/Resolved with Sequelae	Resolution of an adverse event with residual signs or symptoms
Not Recovered/Not resolved (Continuing)	Either incomplete improvement or no improvement of an adverse event, such that it remains ongoing
Fatal	Outcome of an adverse event is death. "Fatal" should be used when death is at least possibly related to the adverse event
Unknown	Outcome of an adverse event is not known (e.g., a subject lost to follow-up).

13.1.7 Reporting Procedure for Adverse Events and Pregnancy

All serious and non-serious vision-related events (as defined in Section 13.1.1) that occur after obtaining informed consent and assent (where applicable) through the last study visit, regardless of causality, must be reported to the MUSC IRB **within 24 hours** of their awareness.

13.1.7.1 Additional Adverse Event Reporting Procedures

Investigators are encouraged to report any adverse reactions suspected due to ivacaftor to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Investigators should also report any suspected adverse reactions related to ivacaftor, other than those being collected as part of the study, as well any pregnancies, to Vertex Pharmaceuticals Incorporated at 1-877-752-5933.

13.2 Administrative Requirements

13.2.1 Ethical Considerations

The study will be conducted in accordance with the ethical principles founded in the Declaration of Helsinki, and according to local applicable laws and regulations. The institutional review board (IRB) will review all appropriate study documentation to safeguard the rights, safety, and well-being of the subjects. The study will only be conducted at MUSC.

13.2.2 Subject Information and Informed Consent

Subjects must also be informed that participation is voluntary and that they may withdraw

from the study at any time, without prejudice to their current or future care. Documentation of the discussion and the date of informed consent must be recorded in the subject's medical record or a study/clinic chart. Once all of their questions have been answered and they have voluntarily agreed to participate in the study, each subject will be asked to sign and date the ICF. Informed consent must be obtained from each subject before the performance of any study-related activity.

13.2.3 Investigator Compliance

No modifications to the protocol should be made without the approval of the IRB, except where the modification is necessary to eliminate an apparent immediate hazard to human subjects. Any departures from protocol must be fully documented in the source documentation and in a protocol deviation log.

13.2.4 Access to Records

The records must also be available for direct inspection, verification, and copying, as required by applicable laws and regulations, by officials of the regulatory health authorities (FDA and others). The investigator must comply with applicable privacy and security laws for use and disclosure of information related to the research set forth in this protocol.

13.2.5 Subject Privacy

To maintain subject confidentiality, all case report forms (CRFs), study reports, and communications relating to the study will identify subjects by assigned subject numbers. The FDA (or other regulatory authority) may also request access to all study records, including source documentation, for inspection.

As applicable, in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and associated privacy regulations, a subject authorization to use personally identifiable health information may be required from each subject before research activities begin. This authorization document must clearly specify which parties will have access to a subject's personal health information, for what purpose, and for how long.

13.2.6 Record Retention

The investigator will maintain all study records according to ICH GCP guidelines and/or applicable local regulatory requirement(s), whichever is longest

13.3 Data Quality Assurance

The investigator will prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. Study data for each enrolled subject will be entered into a CRF by site personnel using a secure, electronic data capture (EDC) application. Any changes to study data will be made to the CRF and documented in an audit trail, which will be maintained within the study database.

13.4 Data Capture

It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the subject's CRF. Source documentation supporting the CRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, adverse events, other observations, and subject status.

The investigator will retain the CRF data and corresponding audit trails that show all updates to data, with user identification, date, and time.

13.5 Publications and Clinical Study Report

13.5.1 Publication of Study Results

Any and all scientific, commercial, and technical information in this protocol or elsewhere should be considered the confidential and proprietary property of the investigator. The investigator shall not disclose private information to any third party except to such of the investigator's employees and staff as have been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The investigator shall not use such information for any purpose other than determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.

The investigator understands that the information developed from this postmarketing treatment study will be considered the property of the investigator but may be disclosed as required to other clinical investigators, the FDA, and other government agencies.

The investigator will be responsible for publication and/or disclosure of study results but will review the data under the terms and conditions of a separate written agreement between Vertex and the investigator and/or the investigator's institution.

13.5.2 Study Report

A clinical study report will be written by the investigator. Vertex will review the report and submit the study report to the FDA.

14 REFERENCES

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