Protocol Cover Page

Official Title of the Study:

Title: TRANSITION: An observational study of the effects on sweat chloride and clinical outcomes of transition from lumacaftor/ivacaftor to tezacaftor/ivacaftor

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Background

While CF therapeutic development previously targeted the signs and symptoms of the disease, in the last 5 years, two drugs that treat the basic defect in CF have been approved, ivacaftor (iva) and lumacaftor/ivacaftor (lum/iva). This class of drugs, deemed cystic fibrosis transmembrance conductance regulator (CFTR) modulators, variably improve CFTR function as measured by pilocarpine iontophoresis and sweat collection, and clinical outcomes including lung function, body mass index (BMI), rate of exacerbations and patient reported quality of life.

In patients with the G551D mutation who received ivacaftor, there was a marked decrease in sweat chloride (absolute change from baseline, -48.7 mmol/L) and a robust improvement in lung function measured as measure by absolute change from baseline of percent predicted forced expiratory volume in 1 sec ($ppFEV_1$) of 10.6%.[1] Changes in sweat chloride and lung function were much more modest in the phase II study of lum/iva for patients homozygous for the F508del mutation: for patients who received 400 mg of lumacaftor plus 250 mg every 12 hours, absolute change in sweat chloride from baseline was -10.3mmol/L at day 56; the change in absolute ppFEV1 was not statistically signficant.[2] (Table) Change in sweat chloride was not assessed in the pivotal phase III studies of lum/iva[3], however, subsequent studies have shown a larger improvement in sweat chloride following lum/iva treatment than was observed in the phase III and phase IV studies: [4-7]

In the phase III study of tez/iva[8], the improvement in sweat chloride at week 24 was approximately half that observed in the open label and phase II studies of lum/iva. (Table) While the correlation between improvement in sweat chloride and lung function is poor[9], and a minimum threshold for change in sweat chloride that correlates with clinical outcomes has yet to be defined,[10] it has also not been determined if an increase in sweat chloride caused by a transition from one drug to another would adversely impact clinical outcomes. From the N of 1 study (NCT01685801), during which patients cycled on and off kalydeco in a blinded fashion, we do know that patients' sweat chlorides did increase to baseline and clinical outcomes declined to baseline when CFTR modulator exposure was removed.

The clinical outcomes assessed in the phase III studies of lumacaftor/ivacaftor and tez/iva were similar, and included lung function, rate of pulmonary exacerbations, BMI, and CFQ-R scores.[3,11] Although there was a slightly higher improvement in lung function improvement between the phase III studies for the different drug combinations, the rate of decline in pulmonary exacerbations was similar between the two drug combinations. In contrast, the improvement in BMI that was observed in the lum/iva study was not seen in the tez/iva study. (Table) Whether the lack of improvement in BMI is related to differential effects of lumacaftor versus tezacaftor on the gut, or the sensitivity of the gut to changes in sweat chloride is unknown.

While the clinical outcomes between the phase III studies of lum/iva and tez/iva were similar, tez/iva has three advantages that are likely to make it more appealing to patients and providers than lum/iva. First, because lumacaftor is a major CYP3A4 inducer, there are numerous drug-drug interactions (DDIs) for patients and physicians to consider with its use including with hormonal contraception and commonly used anti-fungal and nontuberculous mycobacteria medications.[12] Tezacaftor is neither a major inducer nor inhibitor, and therefore has fewer DDIs.

Second, in addition to its improved DDI profile, the phase II and phase III studies of tezacaftor showed no increased respiratory events with drug initiation as occurred in phase III studies of lum/iva. Finally, tez/iva will be the form the basis of triple drug combination therapy for which incredibly promising data has been demonstrated in phase II trials. Thus, with positive clinical efficacy data, fewer DDIs, an improved tolerance profile, and we expect FDA approval of tez/iva in the first quarter of 2018.[13]

Table. Outcome differences between modulator studies for patients homozygous for F508del CFTR

	Week 24 Δ Sweat mmol/L	Week 24 Δ Lung Function ppFEV1	Week 24 Δ BMI kg/m^2	% Reduction in PEx
Phase II orkambi[2]	10.3*	NS*	NA	NA
TRAFFIC/TRANSPORT[3]	NA	2.8≠	0.24	39%
Open label 6-11yo[5]	-24.8	NS	0.65	NA
Randomized 6-11[6]	-20.8	2.4	NS	NA
Prospect[4]	-17.7	1.6	0.6	NA
Expanded access[7]	−20.2 (−24.3, −16.1)	NS	NS	59%#
EVOLVE[8]	−10.1 (−11.4 to −8.8).	4.0	NS	35%

Outcomes at week 24 unless otherwise noted. *D56; ≠For patients who received approved lum/iva dose; #compared with 24 weeks prior to study
NS= not statistically significant

Hypothesis:
Following tez/iva approval, there will be rapid uptake of tez/iva for patients homozygous for F508del CFTR; as a result of the transition from lum/iva to tez/iva, sweat chloride will increase leading to an adverse impact on clinical outcomes.

Specific Aims:

1. Determine the rationale for patient transition from lum/iva to tez/iva
    a. Patient/MD questionnaire
2. Evaluate the impact of transition on CFTR function
    a. Pilocarpine electrophoresis and sweat chloride measurement
3. Evaluate the impact of transition on pulmonary health
    a. Spirometry
    b. Change in use of short-acting bronchodilator (SABA) or long-acting bronchodilator (LABA)
    c. Pulmonary exacerbations
    d. CFQ-R respiratory score
4. Evaluate the impact of transition on gastrointestinal health
    a. Weight/BMI
    b. Fecal elastase
    c. Liver function tests
    d. HgbA1C

   e. OGTT
   f. CFQ-R gastrointestinal (GI) score
5. Evaluate the impact on general health
   a. CFQ-R total score
   b. Change in use of contraception methods for women of child bearing potential

Primary Endpoint

Change in sweat chloride concentration by pilocarpine iontophoresis following transition of therapy

Secondary Endpoints

Rationale for transition
Pulmonary function by spirometry
Occurrence of pulmonary exacerbations
CFQ-R respiratory domain score
CFQ-R GI score
Change in weight and BMI
Change in fecal elastase
Change in liver function tests (ast, alt, alk phos, bili, ggt)
Change in use of short-acting bronchodilator (SABA) or long-acting bronchodilator (LABA)
Change in use of insulin

Significance: While it is possible that there will be no change in sweat chloride or small changes that are without clinical significance, systematic collection of data as patients transition from lum/iva to tez/iva would permit rapid identification of any safety issues. Because the U.S. always leads the way with approval and reimbursement of new therapeutics, our experience with this transition will help guide its conduct for physicians and patients in the rest of the world.

Experimental Design and Methods

Study population: All patients from the Colorado CF program at National Jewish Health with CF who are ≥ 12 years of age at the time of visit 1 who transition from use of lum/iva to tez/iva based on the clinical decision of their physician.

Inclusion criteria:

1) Confirmed diagnosis of CF based on the following criteria: Positive sweat chloride ≥60mEq/liter (by pilocarpine iontophoresis) and genotype with two F508del CFTR mutations, and accompanied by one or more clinical features consistent with the CF phenotype
2) Male or female subjects ≥ 12 years of age
3) Ability to reproducibly perform spirometry (according to ATS criteria)
4) Physician decision to treat with tezacaftor/ivacaftor
6) Ability to understand and sign a written informed consent or assent and comply with the requirements of the study
9) Continuous use of orkambi for at least 1 month prior to visit 1

Exclusion criteria:

1) History of hypersensitivity to tezacaftor and/or ivacaftor
2) Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data.
3) Any acute lower respiratory symptoms treated with oral, inhaled or IV antibiotics or systemic corticosteroids within the 2 weeks prior to Visit 1.
4) Major or traumatic surgery within 12 weeks prior to Visit 1.
5) For women of child-bearing potential: a positive pregnancy test at Visit 1.
6) For those participants undergoing OGTT (i.e. non-diabetics), unable or unwilling to fast (including enteric tube feedings) for at least 6 hours prior to each OGTT visit.
7) Initiation of any new chronic therapy (e.g., ibuprofen, Pulmozyme®, hypertonic saline, azithromycin, TOBI®, Cayston®) within 4 weeks prior to Visit 1.
8) Use of an investigational agent within 28 days prior to Visit 1.
9) History of lung or liver transplantation, or listing for organ transplantation.

Screen Fail Criteria

Any consented patient who is excluded from the study enrollment is considered a screen failure. All screen failures must be documented with the reason for the screen failure adequately stated. Screen failures may be able to re-screen, at the discretion of the investigator.

Study Design:

This study is a single center study of clinical and laboratory outcomes in patients ≥ 12 who transition from use of lum/iva to tez/iva. Clinical and laboratory measurements will be measured at baseline, 1 month, 3 months, and 6 months after initiation of tez/iva. The length of study participation will be approximately 6 months.

Baseline visit (visit 1; Day 0):

The baseline visit can be performed in the 1-30 ± 7 days prior to transition from lum/iva to tez/iva.

Prior to conducting any study-related activities, written informed consent/assent will be obtained, signed and dated by the subject and/or parent/guardian.

The CFQ-R and Transition Patient Questionnaire will be administered.

A medical history including diagnosis of CF, current medications and other relevant past medical history will be obtained. Concomitant medications will be reviewed. Vital signs will be collected including height, weight, temperature, blood pressure, respirations and baseline pulse oximetry. Clinical laboratory tests will be performed including CBC with differential, chemistry profile, and HgbA1C. Subjects (nondiabetics only) who have not undergone oral glucose tolerance test (OGTT) in the year prior to visit will undergo OGTT (funded by the study) and will need to fast 6 hours prior to the OGTT. Participants may choose to have an IV placed for the blood draws needed for the OGTT. For women of child bearing potential, urine pregnancy test will be obtained. Stool will be collected at the visit (or collected prior to the visit and brought frozen). Subjects will undergo spirometry according to ATS criteria.[14] Subject will do spirometry after their normal morning regimen of treatments, and should repeat this same regimen prior to

spirometry with each study visit. Subjects will undergo pilocarpine iontophoresis with sweat collection.

Post-transition (visit 2; Day 1-30 ± 7, or 2 weeks after treatment for exacerbation)

Note: If subject comes in with symptoms of a pulmonary exacerbation requiring treatment, is currently being or has recently been treated for a pulmonary exacerbation reschedule the subject to return for the study visit two weeks after completion of the acute systemic therapies.

The CFQ-R will be administered.

Concomitant medications will be reviewed. Vital signs will be collected including height, weight, temperature, blood pressure, respirations and baseline pulse oximetry will be recorded. Clinical laboratory tests will be performed including CBC with differential, chemistry profile, and HgbA1C. A urine pregnancy test (for females of child-bearing potential) will be performed. Stool will be collected at the visit (or collected prior to the visit and brought frozen). Subjects will undergo spirometry according to ATS criteria.[14] Subjects will undergo pilocarpine iontophoresis with sweat collection.

Post-transition (visit 3; Day 90 ± 7 or 2 weeks after treatment for exacerbation):

Note: If subject comes in with symptoms of a pulmonary exacerbation requiring treatment, is currently being or has recently been treated for a pulmonary exacerbation reschedule the subject to return for the study visit two weeks after completion of the acute systemic therapies.

The CFQ-R will be administered.

Concomitant medications will be reviewed. Vital signs will be collected including height, weight, temperature, blood pressure, respirations and baseline pulse oximetry will be recorded. Clinical laboratory tests will be performed including CBC with differential, chemistry profile, and HgbA1C. A urine pregnancy test (for females of child-bearing potential) will be performed. Stool will be collected at the visit (or collected prior to the visit and brought frozen). Subjects will undergo spirometry according to ATS criteria.[14] Subjects will undergo pilocarpine iontophoresis with sweat collection.

Post-transition (visit 4; Day 180 ± 7 or 2 weeks after treatment for exacerbation):

Note: If subject comes in with symptoms of a pulmonary exacerbation requiring treatment, is currently being or has recently been treated for a pulmonary exacerbation reschedule the subject to return for the study visit two weeks after completion of the acute systemic therapies.

The CFQ-R will be administered.

Labs will be drawn and fecal elastase will be collected. Each subject will undergo pilocarpine iontophoresis with sweat collection. Clinical laboratory tests will be performed including CBC with differential, chemistry profile, HgbA1C. A urine pregnancy test (for females of child-bearing potential) will be performed. Subjects will undergo OGTT. Concomitant medications will be

reviewed, and changes will be recorded. Fecal elastase will be collected. Subjects will undergo spirometry according to ATS criteria.

Outcome measurements and Procedures

Assessment of lung function: Spirometry will be performed at the visits according to ATS standards.

Assessment of pancreatic function: In order to determine if there is a change in pancreatic function as a result of transition from lum/iva to tez/iva, subjects will collect and freeze a stool sample at home to bring to the study visit, or a sample will be collected at each research visit. At the first and final visits, subjects will undergo standard clinical OGTT (recommended by the CF Foundation to be performed annually) to evaluate whether the subject has CF-related diabetes. Blood will be collected at each visit for HgbA1C to assess changes in glucose metabolism.

Clinical laboratory tests will be performed including complete blood count with differential, comprehensive chemistry profile [including sodium, potassium, bicarbonate, blood urea nitrogen, creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, and total bilirubin), and GGT will be performed at each visit. A urine pregnancy test (for females of child-bearing potential) will be performed to determine subject eligibility to participate.

Sweat test: Pilocarpine iontophoresis will be performed and sweat collected according to CFF standards. Sweat volume will be recorded and sweat rate collected. Sweat will be collected using the Macroduct ® collection system. Samples will be shipped to the TDN Core laboratory in Aurora, CO for sodium and chloride concentration measurement.

Assessment of health related quality of life: The CFQ-R is designed to measure CF-specific patient-reported health-related quality of life. The 48 questions encompass five domains including physical symptoms, role functioning (e.g. school/work), psychological and emotional functioning, energy/fatigue, and social functioning. The four domains specific to CF that are measured are: eating disturbances, body image, embarrassment caused by symptoms, and treatment burden. This questionnaire has been validated in CF patients.[15] The questionnaire will be administered at the initial and end of treatment visits for each treatment period prior to any procedures.

Assessment of number of pulmonary exacerbations: The number of pulmonary exacerbations requiring oral or IV antibiotics will be recorded for one year prior to study entry and during study participation. A pulmonary exacerbation will be defined as follows:

A clinical event of new or worsening pulmonary or systemic symptoms beyond normal day-to-day variation that causes the physician to treat with systemic (oral or intravenous) antibiotic(s).
- This definition does not require that a certain set or number of signs and symptoms is present
- This definition excludes prophylactic antibiotics given at regularly scheduled times

☐ If the antibiotics are prescribed by another treating physician, the site physician must confirm that the antibiotics were given for a PEx, based on his/her evaluation of the clinical event.

Patient reimbursement

In accordance with TDN guidelines, patients will be reimbursed according to the following schedule:

Visit	Visit 1	Visit 2	Visit 3	Visit 4	Total
Payment	$ 120*	$ 75	$ 75	$ 150*	$ 420

*Subjects who must undergo OGTT will receive an additional $50 for each visit as a result of the extra time for OGTT

Pregnancy

If a female subject becomes pregnant during the study, the subject will be discontinued from the study.

Data Analysis

Based on sweat chloride changes observed from Phase III/IV studies of lumacaftor/ivacaftor[4-7] compared to that of tezacaftor/ivacaftor in patients homozygous for F508del[8], there was an approximatelyy 10 mmol/L improvement in sweat chloride for patients treated with lum/iva versus tez/iva. A sample size of 23 achieves 91% power to detect a mean of paired differences in sweat chloride of 10.0 mmol/L with an estimated standard deviation of differences of 14.0 (based on sample sizes and CIs) and with a significance level (alpha) of 0.05 using a two-sided paired t-test. To account for a 10% screen failure and 10% attrition rate, we will enroll 28 patients.

Of the 528 patients with CF who are active in our center's registry, there are currently 195 patients who are homozygous for F508del. Additionally, approximately 60 new patients per year are seen in the NJH CF program, and approximately 38% are F508del homozygous. Based on our 2016 Therapeutics Development Network metrics, 20% of our total CF population enrolled into observational studies. Thus, we expect to be able to enroll an adequate number of subjects.

The data analysis for this study will be performed by the principal investigator with assistance from biostatistician, Douglas Everett, PhD. This protocol is a pilot study designed to evaluate physiologic changes after a change in the commercially available CFTR modulator for patients homozygous for the F508del mutation. Primary and secondary outcome measures will be reported as means +/- standard deviations. Patient data will be assumed to comprise a normal distribution. Paired t tests will be used to compare primary and secondary outcome measures pre- and post- CFTR modulator transition. Values of $P < 0.05$ will be considered significant. Repeated measures analysis using a mixed effect model to compare results between the different time points.

.Adverse Events (AE)

An adverse event (AE) is any untoward medical occurrence in a subject that is participating in this clinical investigation and *is a result of the research study procedures.*

The Investigator will monitor for the occurrence of study procedure-related AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the subject CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study procedure.

During this observational study, the combination therapy tez/iva is expected to be a marketed product prescribed in accordance with its approved usage. Any adverse event that an investigator believes is related to tezacaftor/ivacaftor and that is clinically significant should be reported directly to the FDA via a MedWatch form. This definition will include the following:

- AEs not previously observed in the subject that emerge during the study period, including signs or symptoms associated with CF that were not present prior to the study period
- Complications that occur as a result of protocol-mandate interventions (e.g. sputum induction)
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period

Subjects will be questioned and/or examined by the Investigator or her designee for evidence of adverse events related to study procedures..

Subjects having adverse events will be monitored with relevant clinical assessments and laboratory tests as determined by the investigator. All adverse events will be followed to satisfactory resolution or stabilization of the event(s.) Any actions taken and follow-up results will be recorded on the appropriate page of the CRF, as well as in the subject's source documentation. Follow-up laboratory results will be filed with the subject's source documentation.

For all adverse events related to study procedures that require the subject to be discontinued from the study, relevant clinical assessments and laboratory tests will be repeated until satisfactory resolution or stabilization of the event(s.)

A serious event will be determined as follows:

- It results in death
- It is life threatening
- It requires or prolongs inpatient hospitalization (with the exception of pulmonary exacerbation unrelated to study drug)
- It results in persistent or significant disability/incapacity

- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product
- It is considered a significant medical event by the investigator based on medical judgment

Grading of AEs will be as follows:

•Mild: Transient or mild discomfort (<48 hours); no interference with the subject's daily activities; no medical intervention/therapy required

•Moderate: Mild to moderate interference with the subject's daily activities; no or minimal medical intervention/therapy required

•Severe: Considerable interference with the subject's daily activities; medical intervention/therapy required; hospitalization possible

To determine the causality of AE and SAE the follow guidelines will be assessed:

• Definitely: There is a plausible temporal relationship between the onset of the AE a study procedure, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE abates or resolves upon discontinuation of the procedure.

•Probably: There is a plausible temporal relationship between the onset of the AE and the change in modulator therapy, and the AE follows a typical response to tez/iva but a potential alternative cause may be present.

•Unlikely: There is a reasonable possibility that the onset of the AE is related to the study procedure, but an alternative cause seems more likely.

•Unrelated: Evidence exists that the AE has an etiology other than the transition from lum/iva to tez/iva (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to the transition from lum/iva to tez/iva e.g., cancer diagnosed 2 days after first dose of study drug.)

Subject and Study Stopping Criteria

Criteria for Study Termination

The study may be terminated if the FDA issues unexpected black box warnings about tez/iva use based on post-marketing data.

Subjects who discontinue treatment with tez/iva for clinical reasons will be asked to complete all study visits.

Subjects may be rescreened at a later date if it is anticipated that they will meet eligibility criteria.

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STUDY FLOWCHART

	Baseline	Post-transition	Post-transition	Post-transition
Visit	**1**	**2**	**3**	**4**
Day(s)	0	30 ± 7	90 ± 7	180 ± 7
Informed consent	x			
Demographics	x			
Medical history	x			
Concomitant medications and airway clearance	x	x	x	x
Bacterial colonization	x			
Vital signs	x	x	x	x
Spirometry	x	x	x	x
Height	x			
Weight	x	x	x	x
CFQ-R	x	x	x	x
Clinical labs - CBC with differential, HbA1c, and Chemistry profile	x	x	x	x
Pregnancy test#	x	x	x	x
Sweat testing	x	x	x	x
OGTT (only for nondiabetics)	x*			x
Stool collection	x	x	x	x
Adverse events	x	x	x	x

* If not done within 1 year of baseline visit

for women of child-bearing age