

PROTOCOL NUMBER:

TITLE: Steady-State Pharmacokinetics of Tedizolid in CF

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TABLE OF CONTENTS

SCHEMA, SYNOPSIS, OR STUDY SUMMARY

	PAGE
1.0 <u>BACKGROUND AND HYPOTHESES</u>	_ 1 _
2.0 <u>OBJECTIVES AND PURPOSE</u>	_ 1 _
3.0 <u>STUDY DESIGN</u>	_ 1 _
4.0 <u>DRUG/DEVICE INFORMATION</u>	_ 1 _
5.0 <u>SELECTION AND WITHDRAWAL OF SUBJECTS</u>	_ 2 _
6.0 <u>DESCRIPTIVE FACTORS/STRATIFICATION/RANDOMIZATION SCHEME</u>	_ 2 _
7.0 <u>STUDY AGENT ADMINISTRATION OR INTERVENTION AND TOXICITY MANAGEMENT PLAN</u>	_ 2 _
8.0 <u>ASSESSMENT OF EFFICACY AND SAFETY</u>	_ 2 _
9.0 <u>CLINICAL AND LABORATORY EVALUATIONS</u>	_ 3 _
10.0 <u>CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS</u>	_ 3 _
11.0 <u>SPECIAL INSTRUCTIONS</u>	_ 3 _
12.0 <u>DATA COLLECTION AND MONITORING</u>	_ 3 _
13.0 <u>STATISTICAL CONSIDERATIONS</u>	_ 4 _
14.0 <u>REGISTRATION GUIDELINES</u>	_ 4 _
15.0 <u>BIOHAZARD CONTAINMENT</u>	_ 4 _
16.0 <u>ETHICAL AND REGULATORY CONSIDERATIONS</u>	_ 4 _
17.0 <u>REFERENCES</u>	_ 4 _

APPENDICES

- I: Informed Consent
- II: Study Calendar

1.0 BACKGROUND AND HYPOTHESES

Cystic fibrosis (CF) is a genetic disorder characterized by a chronic cycle of airway infection, obstruction, and inflammation leading to progressive loss of lung function and eventual respiratory failure. Over the past decade the prevalence of infections involving *Methicillin Resistant Staphyococcus Auerus* (MRSA) in CF has increased dramatically.[1] Importantly, recent epidemiological studies have demonstrated that the presence of MRSA in the airways of patients with CF is associated with more rapid lung function decline [2] and a higher mortality [3]. Management of these patients includes prompt initiation of antibiotics at the onset of acute pulmonary exacerbations. A significant barrier to effective treatment is the limited number of safe and effective antibiotics for treatment of MRSA pulmonary infections. While vancomycin has been the mainstay of treatment for many years, its efficacy is limited by reduced susceptibility. In addition, the risk for acute kidney injury is significant in patients with CF due to the concomitant use of tobramycin for treatment of coinfection with *Pseudomonas aeruginosa*. While linezolid has demonstrated to be efficacious in the treatment of acute pulmonary exacerbations in CF, its use is significantly limited due to the high prevalence of depression (29-46%), which is often treated with selective serotonin reuptake inhibitors/serotonin non-epinephrine reuptake inhibitors(SSRIs/SNRIs) [4]. Tedizolid offers a significant advancement in the management of infections involving MRSA in CF due to its excellent activity, penetration into pulmonary secretions, proven safety, and reduced potential for drug interactions with antidepressants.

The pharmacokinetics of a number of medications has shown to be altered in patients with CF. [5,6] In general, patients with CF demonstrate an increased volume of distribution when expressed in liter/kilogram (L/Kg) of body weight, and increased renal clearance. In addition, the oral bioavailability of lipophilic medications is reduced due to pancreatic insufficiency. To our knowledge no study has evaluated the pharmacokinetics of tedizolid in patients with CF. The proposed study is designed to characterize the pharmacokinetics of intravenous and oral tedizolid in patients with CF and determine the optimal dosing regimen in preparation for future efficacy and safety studies in CF patients experiencing acute pulmonary exacerbations.

RATIONALE FOR SPUTUM TEDIZOLID CONCENTRATIONS:

Determination of the pulmonary penetration of antibiotics is vital to predicting the optimal dosing regimen for treatment of lung infections. Several different sampling methods are reported in the literature including bronchoalveolar lavage and induced or expectorated sputum. The choice of sampling technique is dependent upon multiple factors such as the site of infection, convenience, and need for serial samples. Cystic fibrosis is characterized by chronic respiratory infection/inflammation that leads to airway remodeling and progressive loss of lung function. The site of the infection/inflammation is predominately endobronchial rather than alveolar. This is consistent with the location of Cystic Fibrosis Transmembrane conductance regulator (CFTR) within the submucosal glands and acinar serous cells of the airways. Therefore, the ideal sample for drug concentrations would be from the endobronchial space which is best obtained by induced or expectorated sputum. Fiberoptic bronchoscopy, being invasive and costly, is poorly suited for serial sampling of airway secretions. In addition, bronchoscopy with lavage is thought primarily to sample the alveolar space rather than the airways alone. Numerous publications including those from our group have utilized expectorated sputum to successfully characterize the disposition of various antibiotics within the airways and determine optimal dosing regimens for treatment of airway infections in CF.²³⁻²⁸

Our study hypothesis is that tedizolid will exhibit excellent oral bioavailability and sputum penetration in patients with cystic fibrosis.

2.0 OBJECTIVES AND PURPOSE

Primary Objective:

Determine the steady-state concentrations of tedizolid in plasma and sputum of patients with CF.

Secondary Objective:

Determine the target attainment for the pharmacodynamic endpoint.

3.0 STUDY DESIGN

This study will be conducted using a prospective multiple dose, crossover design to characterize the steady-state pharmacokinetics of tedizolid intravenous/oral (IV/PO) in CF. A total of 12 adult patients with CF will participate in the study and will receive tedizolid 200mg IV or PO once daily for 3 doses followed by a minimum 2 day washout and receipt of the remaining dosage form.

4.0 DRUG/DEVICE INFORMATION

4.1 Tedizolid (Sivextro)

Tedizolid is an oxazolidinone antibiotic with potent activity against methicillin resistant *S. aureus* (MRSA). Tedizolid is approved for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible bacteria.

The recommended dosage of tedizolid is 200 mg administered once daily orally (tablet) or as an intravenous infusion (IV) over 1 hour for six days.

The most common adverse reactions (incidence of > 2%) are nausea, headache, diarrhea, vomiting, and dizziness.

5.0 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Inclusion Criteria:

CF patients admitted to the hospital for pulmonary exacerbation as defined by CF Pulmonary Guidelines and Fuchs et al (1994) (e.g. increased cough/sputum production, shortness of breath, chest pain, loss of appetite/weight, and lung function decline)

Diagnosis of CF based on positive sweat chloride or known CF mutation

Age > 18 years

Patients able to spontaneously expectorate sputum

CF patients with or without MRSA positive sputum will be included

5.2 Exclusion Criteria

AST/ALT > 3 x ULN

Thrombocytopenia (Platelets < 150,000)

Anemia (hematocrit < 30)
Any clinically significant abnormality noted on physical exam thought to interfere with the conduct of the study.
Pregnancy
No alcohol, nicotine, or caffeine-containing products during the study period
Patients taking monoamine oxidase inhibitors and/or serotonergic agents.

5.3 Withdrawal Criteria

Subject can be discontinued from the study for any of the following reasons:
Subject's personal reasons
Allergic reaction to the medication
Other significant study related adverse events

6.0 STRATIFICATION/DESCRIPTIVE FACTORS/RANDOMIZATION SCHEME

6.1 Stratification factors: Not applicable.

6.2 Descriptive factors: Not applicable.

6.3 Randomization:

Randomization sequence will be created using Excel 2007 (Microsoft, Redmond, WA, USA) with a 1:1 allocation using random block sizes of 2.

Subjects will be randomized to receive one of the two treatment sequences:

Oral Tedizolid for days 1 to 3 then Intravenous Tedizolid for days 10 to 12.

Intravenous Tedizolid for days 1 to 3 then Oral Tedizolid for days 10 to 12.

7.0 STUDY AGENT ADMINISTRATION OR INTERVENTION AND TOXICITY MANAGEMENT PLAN

7.1 Depending on the treatment arm of the study, you will receive Tedizolid administered in doses of 200 mg intravenously over 1 hour or 200 mg PO once daily for 3 doses.

AGENT	DOSE	ROUTE	DAYS	ReRx	NOTES
Tedizolid	200 mg	I.V. over 1 hours	1-3 or 10-12	Once daily	Total of 3 doses of IV and
Tedizolid	200 mg	PO	1-3 or 10-12	Once daily	Total of 3 doses of PO and

7.2 Criteria for removal from the study

7.21 A patient may always be removed from study whenever he/she wishes.

7.22 A patient may be removed from the study if they experience an allergic reaction to the medication.

7.3 Ancillary treatments.

Patients may continue to take their medications for treatment of CF

8.0 ASSESSMENT OF EFFICACY AND SAFETY

8.1 Side effects/Toxicities to be monitored.

Possible side effects of Tedizolid are:

The most common adverse reactions in patients treated with tedizolid were nausea (8%), headache (6%), diarrhea (4%), vomiting (3%), and dizziness (2%). The median time of onset of adverse reactions was 5 days for both Tedizolid with 12% occurring on the second day of treatment in both treatment groups.

Serious adverse reactions occurred in 12/662 (1.8%) of patients treated with Tedizolid and in 13/662 (2.0%) of patients treated with the comparator. Tedizolid was discontinued due to an adverse reaction in 3/662 (0.5%) of patients and the comparator was discontinued due to an adverse reaction in 6/662 (0.9%) of patients

The following selected adverse reactions were reported in Tediazolid treated patients at a rate of less than 2% in these clinical trials:

Blood and Lymphatic System Disorders: anemia

Cardiovascular: palpitations, tachycardia

Eye Disorders: asthenopia, vision blurred, visual impairment, vitreous floaters

General Disorders and Administration Site Conditions: infusion-related reactions

Immune System Disorders: drug hypersensitivity

Infections and Infestations: Clostridium difficile colitis, oral candidiasis, vulvovaginal mycotic infection

Investigations: hepatic transaminases increased, white blood cell count decreased

Nervous System Disorders: hypoesthesia, paresthesia, VIIth nerve paralysis

Psychiatric Disorders: insomnia

Skin and Subcutaneous Tissue Disorders: pruritus, urticaria, dermatitis

Vascular Disorders: flushing, hypertension

8.11 Patients will be asked about the presence of nausea, vomiting, diarrhea, or headache.

8.12 CBC and CMP will be monitored at baseline

8.2 Adverse Event Reporting:

8.21 Any significant adverse events that occurs during the course of the study will be documented and reported.

8.22 Reports will be submitted to: IRB, FDA (MedWatch)

8.3 Data Monitoring Committee (if applicable)
Not applicable

9.0 CLINICAL AND LABORATORY EVALUATIONS AND STUDY CALENDAR

See Appendix A

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

The outcome status (in terms of toxicity, response, reason off study, progression, and survival) of all eligible patients will be reported. All eligible patients who begin treatment will be included in the analysis of survival and time-to-failure.

Endpoint Definitions

11.0 SPECIAL INSTRUCTIONS:

Blood samples will be obtained at the following time points after the third dose of each dosage form: 0 (predose), 0.5, 1, 2, 3, 4, 8, 24, and 48 hours postdose.

In the case where the patient is discharged home early, we will offer subjects the option of having a trained healthcare professional come to the subject's home to perform the 24 hour and 48 hour blood and sputum sampling. A phleobomist not affiliated with USC will come to the subject's home to collect the 24 hour and/or 48 hour blood and sputum sample.

In order for the study visit to be conducted in the subject's home, the subject's name, address and contact telephone number will be provided to the home provider vendor. The home provider vendor will provide the information to a courier, who will pick up the blood and sputum from the subject's home. If you do not want your information provided to the home provider vendor or courier, the subject cannot participate in the home visit.

It is possible that the home provider vendor may not be available in the subject's area or in time for the study visit. In this rare event, the subject will be required to complete the study visit at the study doctor's office.

Expectorated sputum samples will be obtained from individual patients after the third dose of each dosage form as follows:

Patients	Time of sputum collection
1-12	Predose
1-3	0.5-1h
4-6	2h
7-9	3h
10-12	4h

1-4	8h
5-8	24h
9-12	48h

Blood and sputum samples will be processed and stored at -80°C until assayed for tedizolid.

12.0 DATA COLLECTION AND MONITORING

Data will be collected on case report forms, which will be retained for the duration of the study. Data will include subject demographics, clinical characteristics, laboratory data, and results of pharmacokinetic analyses. Data will be coded and stored on a password protected electronic database.

13.0 DATA/STATISTICAL CONSIDERATIONS

13.1 Pharmacokinetic analysis

Pharmacokinetics will be performed using standard noncompartmental methods. The maximum concentration and time to maximum concentration will be from the observed data. The area under the curve will be calculated using the trapezoidal rule. Absolute bioavailability will be determined by a ratio of the AUC_{po}/AUC_{iv}.

In addition, population pharmacokinetic analysis will be performed using the maximum likelihood estimation via the EM algorithm with sampling (MLEM) as implemented in ADAPT 5 (Biomedical Simulations Resource, University of Southern California). Multiple candidate models will be evaluated to identify the model that best describes the observed plasma and sputum concentration data.

Monte Carlo simulations will be performed to determine the target attainment for the lung exposures (sputum AUC_{24h}/MIC > 20) with different dosing regimens using the SIM module in ADAPT 5. MIC distributions used in the simulations will be based on recently published susceptibility data [29].

13.2 Statistical Analysis

Twelve patients with CF will participate in this study. The endpoints for this study are descriptive in nature and the sample size is similar to other studies with these endpoints. Patient demographics, clinical characteristics, and pharmacokinetic parameters will be summarized using descriptive statistics.

14.0 REGISTRATION GUIDELINE

14.1 Subjects will be registered into the study through submission of the research order form, informed consent, and patient bill of rights to the Clinical Trials Office (CTO) at USC..

15.0 BIOHAZARD COMTAINMENT

Not applicable

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

All institutional and Federal regulations concerning the Informed Consent form will be fulfilled. The study will be conducted in adherence to ICH Good Clinical Practice.

17.0 REFERENCES

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Appendix I: Informed Consent
Appendix II: Study Calendar

	Screening	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6-10	Day 7-11	Day 8-12	Day 9-13	Day 10-14
Informed Consent	X										
Medical History	X										
Medication History	X										
Height, weight	X										
Vital signs ^A	X	X	X	X	X	X	X	X	X	X	X
Safety labs ^B	X										
IV drug administration ^Q		X ^C	X ^C	X ^C			X ^F	X ^F	X ^F		
PO drug administration		X ^E	X ^E	X ^E			X ^D	X ^D	X ^D		
Blood Pharmacokinetics (PK) ^G				X					X		
Sputum Pharmacokinetics (PK): pre dose ^H				X							
Sputum PK: 0.5 to 1 hour post dose				X ^I					X ^I		
SputumPK: 2 hours post dose				X ^J					X ^J		
SputumPK: 3 hours post dose				X ^K					X ^K		
SputumPK: 4 hours post dose				X ^L					X ^L		
SputumPK: 8 hours post dose				X ^M					X ^M		

SputumPK:Q 24 hours post dose					X ^O					X ^O	
SputumPK:Q 48 hours post dose						X ^P					X ^P

- A. Vital signs to include blood pressure, heart rate, temperature, respiratory rate.
- B. Safety labs to include complete blood count with differential, complete metabolic panel
- C. For the treatment arm A: IV Tedizolid will be done on days 1 to 3.
- D. For the treatment arm A: PO Tedizolid will be done on days 10 to 12. Days 10 and 11 the dose of oral Tedizolid will be done at home for the subject. A telephone call will be done to remind the subject to take the PO Tedizolid.
- E. For the treatment arm B: PO Tedizolid will be done on days 1 to 3. Days 1 and 2 can be done at home. A telephone call will be done to remind the subject to take the PO Tedizolid.
- F. For the treatment arm B: IV Tedizolid will be done on days 10 to 12.
- G. All subjects will have a pre dose blood PK levels, 0.5 hour, 1, 2, 3, 4, 8, 24 and 48 hours post dose of Tedizolid (IV or PO). A 5mL EDTA tube will be used to collect the blood PK sample.
- H. All subjects will have a pre dose sputum sample (IV or PO).
- I. Subject number 1-3 will need to produce a sputum sample at this time period (IV or PO).
- J. Subject number 4-6 will need to produce a sputum sample at this time period (IV or PO).
- K. Subject number 7-9 will need to produce a sputum sample at this time period (IV or PO).
- L. Subject number 10-12 will need to produce a sputum sample at this time period (IV or PO).
- M. Subject number 1-4 will need to produce a sputum sample at this time period (IV or PO).
- N. Subject number 5-8 will need to produce a sputum sample at this time period (IV or PO).
- O. Subject number 9-12 will need to produce a sputum sample at this time period (IV or PO).
- P. IV Tedizolid is be infused over 60 minutes.
- Q. The option of home health vendor to collect the 24 and 48 hour blood and sputum sampling.