PROTOCOL NUMBER:

TITLE: Pharmacokinetics of Omadacycline in CF

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TABLE OF CONTENTS

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. Nontuberculous mycobacteria (NTM) are increasingly being isolated from the sputum of individuals with CF with estimates of prevalence increasing from 1.3 percent in 1984 to 12 percent in 2012 [1]. The prevalance of NTM increases with age from 10% in children aged 10 years, to over 30% in adults over the age of 40 years [1]. NTM can cause progressive inflammatory lung damage, a condition termed 'NTM pulmonary disease' (NTM-PD). In particular, recent epidemiological studies have demonstrated that the presence of mycobacterium abcessus complex (MABSC) in the airways of patients with CF is associated with more rapid lung function decline and a higher mortality [1]. Patients with CF are predisposed to NTM-PD due to reduced CFTR mediated reactive oxygen species generation within macrophages leading to reduced intracellular killing [2]. Management of these patients includes an intensive phase with oral azithromycin and several intravenous antibiotics (e.g. amikacin, tigecycline, imipenem) for 3-12 weeks followed by a prolonged continuation phase with oral (e.g. azithromycin, moxifloxacin, minocycline, clofazamine), and inhaled amikacin. A significant barrier to effective treatment is the limited number of safe and effective antibiotics for treatment of MABSC-PD. While macrolides have been the mainstay of treatment for many years, their efficacy is limited by reduced susceptibility. In addition, the risk for acute kidney injury and/or hearing loss is significant in patients with CF with prolonged use of amikacin. Tigecycline demonstrates good in vitro activity and is one of the primary antibiotics during the intensive phase of treatment; however, this agent is associated with significant nausea and vomiting and is only available for intravenous administration. Results of a pharmacodynamic study in a hollow fiber model determined the a dose of 100mg twice daily was needed to achieve the optimal target attainment (>90% stasis); however, this dose was estimated to cause nausea/vomiting in nearly 100% of patients [3]. Omadacycline offers a significant advancement in the management of infections involving MABSC in CF due to its excellent activity [4-6], penetration into pulmonary secretions, improved tolerability, and good oral bioavailability [7-10].

The pharmacokinetics of a number of medications have shown to be altered in patients with CF [11,12]. In general, patients with CF demonstrate an increased volume of distribution when expressed in L/Kg of body weight, and increased total body 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 omadacyline in patients with CF. The proposed study is designed to characterize the pharmacokinetics of intravenous and oral omadacycline in patients with CF and determine the optimal dosing regimen in preparation for future efficacy and safety studies in CF patients with MABSC lung infections.

The pharmacokinetics of omadacyline in healthy volunteers, special populations, and patients with complicated skin and skin structure infections has been well described [7-9]. The oral absorption is relatively rapid and the bioavailability is good. Of note is the reduced bioavailability observed with high-fat meals or in conjunction with dairy products; based on these observations omadacycline is recommended to be given under fasting conditions with no food or dairy/antacids/multivitamins for 2 and 4 hours after administration respectively [10]. Elimination of omadacycline occurs predominately through fecal excretion [10]. No dosage adjustment is necessary for renal or hepatic disease [10].

Of particular importance to the proposed study is the excellent pulmonary penetration of omadacycline noted in healthy volunteers [9]. Bronchoalveolar lavage studies performed at

steady-state following omadacycline 100mg IV daily revealed epithelial lining fluid and alveolar macrophage exposures 2-fold and 30-fold higher respectively, than free drug exposures in plasma. These exposures also exceeded that of tigecycline indicating greater pulmonary penetration with omadacycline.

Our study hypothesis is that omadacycline will exhibit good oral bioavailability in patients with CF.

2.0 OBJECTIVES AND PURPOSE

Primary Objective:

Determine the concentrations of omadacycline in plasma of patients with CF following single dose IV and PO administration.

3.0 STUDY DESIGN

This study will be conducted using a prospective single dose, single-arm design to characterize the pharmacokinetics of omadacycline intravenous/oral (IV/PO) in CF. A total of 12 adult patients with CF will participate in the study and will receive a single dose of omadacycline 100mg IV followed by a 1-week washout and receipt of 300 mg PO.

4.0 DRUG/DEVICE INFORMATION

4.1 Omadacycline (Nuzyra) is a tetracycline class antibacterial indicated for the treatment of adult patients with the following infections caused by susceptible microorganisms:

Community-acquired bacterial pneumonia (CABP)

Acute bacterial skin and skin structure infections (ABSSSI)

The recommended dosage of omadacycline is 300 mg administered once daily orally (tablet) or as an intravenous infusion (IV) of 100 mg over 0.5 hour for 7-14 days.

5.0 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Inclusion Criteria:

- Diagnosis of CF based on positive sweat chloride or known CF mutation
- Age ≥ 18 years

5.2 Exclusion Criteria

- Presence of an ongoing acute pulmonary exacerbation defined based on clinical signs & symptoms and an acute decline in relative FEV_1 of 10% or greater.
- Pregnancy or breastfeeding
- Serious past allergy to a tetracycline antibiotic

- No alcohol, nicotine, or caffeine-containing products during the study period
- Hemoglobin < 8 g/dL

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: Not applicable.

7.0 STUDY AGENT ADMINISTRATION OR INTERVENTION AND TOXICITY MANAGEMENT PLAN

7.1 You will receive omadacycline administered in doses of 100 mg intravenously over 0.5 hour followed by a 1-week washout and receipt of 300 mg PO.

AGENT	DOSE	ROUTE	DAYS	ReRx	NOTES
Omadacycline	100 mg	I.V. over 0.5 hours	1	Once	
Omadacycline	300 mg	PO	1	Once	-Fast for at least 4hours and then take omadacycline tablet with water. -After oral dosing, no food or drink (except water) is to be consumed for 2 hours and no dairy products, antacids, or multivitamins for 4 hours.

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 Omadacycline are:

The most common adverse reactions (incidence ≥2%) are nausea, vomiting, infusion site reactions, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyl transferase increased, hypertension, headache, diarrhea, insomnia, and constipation.
In the pooled ABSSSI trials, serious adverse reactions occurred in 16/691 (2.3%) of patients treated with omadacycline and 13/689 (1.9%) of patients treated with comparator. Discontinuation of treatment due to adverse events occurred in 12 (1.7%) omadacycline treated patients, and 10 (1.5%) comparator treated patients. There was 1 death (0.1%) reported in omadacycline treated patients and 3 deaths (0.4%) reported in linezolid patients in ABSSSI trials.

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

- Gastrointestinal Disorders: abdominal pain, dyspepsia
- General Disorders and Administration Site Conditions: fatigue
- Immune System Disorders: hypersensitivity
- Infections and Infestations: oral candidiasis, vulvovaginal mycotic infection
- Investigations: creatinine phosphokinase increased, bilirubin increased, lipase increased, alkaline
- phosphatase increased
- Nervous System Disorders: dysgeusia, lethargy
- Respiratory, Thoracic, and Mediastinal disorders: oropharyngeal pain
- Skin and Subcutaneous Tissue Disorders: pruritus, erythema, hyperhidrosis, urticaria

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 III: Study Calendar

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Criteria for Evaluation
The outcome status (in terms of toxicity, response, reason off study) of all eligible patients will be reported. All eligible patients who begin treatment will be included in the analysis.

10.2 Endpoint Definitions
PK parameters of omadacycline including the area under the curve, maximum concentration and time to maximum concentration in patients with CF.

11.0 SPECIAL INSTRUCTIONS:

Blood samples will be obtained predose, 0.25, 0.5, 1, 2, 3, 4, 8, 12, 24, 48, and 72 hours after the end of the IV infusion and oral dose.
Blood samples will be processed, and aliquots of plasma will be stored at -80°C until assayed for omadacycline.

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 concentration data.

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 CONTAINMENT

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 STUDY TEAM QUALIFICATIONS

Dr. Beringer has extensive experience performing pharmacokinetic studies of antibiotics and anti-inflammatory therapies in CF and other populations [13-24]. In particular, we have conducted oral bioavailability studies with doxycycline, azithromycin, linezolid, and tedizolid similar to the design of the study proposed in this application. The Center for Adult CF at USC currently provides care for 200 patients ensuring adequate numbers of patients available to conduct the study. Dr. Rao has extensive experience in conducting sponsored projects research involving new therapies for pulmonary diseases. He is Director of the Adult CF Center at USC.
Our program employs a fulltime research nurse and study coordinator who are highly skilled in conducting sponsored project research.

18.0 REFERENCES

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