Clinical Study Title	**A prospective, single-site, open-label, pharmacokinetic study of intermittent intraperitoneal vancomycin in adult subjects receiving automated peritoneal dialysis (APD)**
Clinical Study Site	Thomas Jefferson University, Philadelphia, PA
Principal Investigator	**Walter K. Kraft, M.D.** Department of Pharmacology & Experimental Therapeutics Thomas Jefferson University Hospital 132 S. 10th Street, 1170 Main Building Philadelphia, PA 19107
Co-Investigators	**Edwin Lam, Pharm.D.** **Jingjing Zhang, M.D., Ph.D.**
Protocol Date	13 December 2017
NCT	NCT03685747

Version History

Version	Date	Change History
1.0	13 December 2017	Concept Protocol
1.1	04 January 2018	Draft Protocol
2.0	03 February 2018	Protocol
3.0	14 September 2018	Protocol Revision
4.0	15 January 2019	Amendment- Clarification of post-study follow-up, addition of serum creatinine analysis, and clarification on sampling points

Abbreviations

APD	Automated Peritoneal Dialysis
AUC	Area Under Concentration-Time Curve
CAPD	Continuous Ambulatory Peritoneal Dialysis
ESRD	End Stage Renal Disease
MIC	Minimum Inhibitory Concentration
NCA	Non-Compartmental Analysis
PET	Peritoneal Equilibration Test
PK	Pharmacokinetics
PD	Peritoneal Dialysis

Table of Contents

1. INTRODUCTION 3
2. STUDY OBJECTIVES 5
2.1 Primary Objective 5
2.2 Secondary Objectives 5
3. STUDY DESIGN 5
3.1 Overview and Design 5
3.2 Schedule & Procedures 7
4. STUDY POPULATION 10
4.1 Inclusion Criteria 10
4.2 Exclusion Criteria 10
5. STUDY ENDPOINTS 10
5.1 Primary Pharmacokinetic Endpoint 10
5.2 Secondary Pharmacokinetic Endpoints 11
6. MEASUREMENTS AND EVALUATIONS 11
6.1 Study Data 11
6.2 Plasma Samples 11
7. SAMPLE SIZE AND ANALYSIS PLAN 12
8.1 Sample Size 12
8.2 Statistical and Pharmacokinetic Analysis 12
8. DATA COLLECTION AND MANAGEMENT PLAN 12
8.1 Database System Overview 12
8.2 Case Report Forms and Data Entry 12
9. SAFETY 12
10. REFERENCES 13

1. INTRODUCTION

Peritoneal dialysis (PD) is a form of renal replacement therapy indicated for those with acute kidney injury or end stage renal disease (ESRD). In 2013 PD was utilized in approximately 7% of the 660,000 prevalent patients with ESRD in the United States. Within that time, the prevalence of PD has seen an increase by over 30% between 2007 – 2014.[1] During PD, a hyperosmolar solution is introduced into the peritoneal cavity allowing solute exchange between the dialysate-contained in the cavity and blood from the perfused peritoneum. A concentration gradient is thus created allowing ultrafiltration and diffusional clearance of toxic materials. PD fluids are available as glucose-based or non-glucose based solutions. Commonly prescribed glucose-based PD solutions have been associated with peritoneal membrane injury and negative systemic effects leading to suboptimal patient and technique survival. On the other hand, newer non-glucose based solution marketed in the United States have shown to improve fluid removal during long dialysis exchanges and offer greater peritoneal membrane protection.[2]

Principles of Peritoneal Dialysis

Currently, two modalities of PD exist and is individualized based on patient and life-style specific factors. Continuous ambulatory peritoneal dialysis (CAPD) allows 4 – 5 exchanges performed manually whereas automated peritoneal dialysis (APD) involves continuous, automated, cyclical exchanges performed by a device at home during the night.[3] APD offers advantages over CAPD by allowing fluid-free or "dry" daytime dwells thereby permitting those who require PD liberty for their activities of daily living. In addition, several other advantages such as lower incidences of infection and hernias, enhanced solute clearances, and positive psychosocial impact have been reported.[3] Overall, the prevalence of APD has been increasing throughout the years as the number of patients utilizing CAPD declines.[4]

Vancomycin in Peritoneal Dialysis

Peritonitis is a common complication in PD and accounts for a large portion of hospital readmission and mortality.[1,5] In addition, severe or prolonged peritonitis can lead to membrane failure prompting the switch from PD to hemodialysis. The International Society of Peritoneal Dialysis (ISPD) recommends intraperitoneal administration as the preferred route to deliver antibiotics in the absence of systemic bacteremia.[5] Vancomycin is the most common antibiotic recommended and has notable gram-positive coverage used empirically during suspected peritonitis.

Rationale for the Proposed Study

Vancomycin is eliminated unchanged in the urine through glomerular filtration and is best characterized by a distribution and elimination phase following parenteral administration. Vancomycin's bactericidal activity is considered time-dependent with the ratio of the 24-hour area-under-the-concentration (AUC) versus time/minimal-inhibitory concentration (MIC) ratio (AUC/MIC) being the best pharmacokinetic/pharmacodynamic predictor of effectiveness. The preferred AUC/MIC ratio is $\geq$ 400. Dosing in the range of 15-30 mg/kg is recommended by several

professional societies including ISPD to maintain a serum concentration level of 15 mg/L in order to maximize efficacy and reduce toxicity, although this trough is only loosely correlated with corresponding AUC/MIC.[5,6] Furthermore, the evidence supporting this recommended trough is essentially nonexistent in PD patients on APD, where data on vancomycin bioavailability and clearance with varying degrees of peritoneal function is sparse. In addition, early pharmacokinetic studies were conducted only in patients on CAPD modalities, glucose-based prescriptions, or those on intravenous vancomycin.[7-9] Lastly, the relationship between serum concentration and site of action at the peritoneal cavity wall is not established. In totality, the goal is to close the knowledge gap in this very common use of vancomycin.

Although the ISPD advisory committee on peritonitis management recommends a 25% increase in antibiotic dose in non-anuric patients, residual kidney function may affect the exposure, clearance, distribution and serum half-life for those antibiotics administered. This however is an empiric recommendation and there is no formal quantification of how residual kidney function (RKF) may impact pharmacokinetics. The impact on RKF on vancomycin in PD is also lacking. RKF is critical for the welfare and survival of PD patients. Indeed, 2 large multicenter studies, the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD-2) (AJKD;41:1293-2302, 2003) and the Canada/USA Peritoneal Adequacy Study (CANUSA) (JASN, 12:2158-2162, 2001), both have shown statistically significant (by multivariable analyses) 12% reductions in mortality per ml/min/1.73 m^2 residual GFR increase or per 5L/week residual GFR increase, respectively. Hence, it is important to assess vancomycin pharmacokinetics in PD patients with RKF for two reasons. First, the enhanced vancomycin clearance of RKF may result in under-dosing and secondly, overdosing may result in nephrotoxicity and loss of critically important RKF. This presents a challenge when considering the bi-exponential pharmacokinetic behavior of vancomycin and produces a significant source of variability allowing controversy in the role of monitoring serum vancomycin in patients on APD.[10,11]

Interestingly, a recent retrospective analysis examining residual renal function and peritonitis outcomes show that the odds of peritonitis treatment failure for those with urinary creatinine clearances of greater than 5 mL/min were greater when compared to those who were anuric.[12] These associations further challenge the need for optimal vancomycin dosing strategies in patients on rapid-cycling modalities to maximize the efficacy, safety, and cost.

Moreover, icodextrin a non-glucose based PD fluid, is an increasingly used PD dialysate solution to complement conventional glucose-based PD fluids. Commonly prescribed glucose-based PD solutions have been associated with peritoneal membrane injury and negative systemic effects leading to suboptimal patient and technique survival. Non-glucose based solutions such as icodextrin marketed in the United States have shown to improve fluid removal during long dialysis exchanges and offer greater peritoneal membrane protection. In-vitro studies conducted with 7.5% icodextrin demonstrate physical compatibility and chemical stability, however there is a lack of information for the clearance, stability and effect on the minimum inhibitory

concentration of vancomycin in-vivo.[13] As there will be increasing use of icodextrin, characterization of vancomycin pharmacokinetics will be important.

Therefore, this current study aims to explore the pharmacokinetics and pharmacodynamics of intraperitoneal administered vancomycin in un-infected subjects on APD and explore the in-vivo behavior of vancomycin in 7.5% icodextrin PD solution.

2. STUDY OBJECTIVES

2.1 Primary Objective

- Characterize the pharmacokinetic profile of vancomycin in serum, urine, and dialysate following a single intermittent intraperitoneal dose of vancomycin in non-infected patients on automated peritoneal dialysis

2.2 Secondary Objectives

- Examine the relationship between residual kidney function and vancomycin clearance using serum, dialysate and urine
- Describe the safety, tolerability, and stability of intraperitoneal vancomycin when administered in a 7.5% icodextrin-containing dialysis solution

2.3 Exploratory Objectives

- Investigate dosing recommendations and adjustments based on population pharmacokinetic parameters generated from serum and dialysate concentrations in adult patients on APD
- Correlate the peritoneal transport function, measured using the peritoneal equilibration test (PET), to vancomycin pharmacokinetics
- Correlate dialysis adequacy, measured as a function of peritoneum urea clearance, time, and volume of dialyzer fluid (Kt/V), to vancomycin pharmacokinetics

3. STUDY DESIGN

3.1 Overview and Design

This is a prospective, single-site, open-label, pharmacokinetic study of vancomycin in infection-negative healthy adult patients on peritoneal dialysis. Prospective patients will be identified through Thomas Jefferson University Hospital nephrology practice. Subjects will be asked to consent prior to participation in the study. The majority of research activities will take place at the Thomas Jefferson University Clinical Research Unit (CRU).

Subjects will be on an APD regimen consisting of a 12-hour overnight dwell followed by a 9-hour on-cycler exchange **(figure 1)**. Vancomycin will be administered via intraperitoneal injection in 1 liter of icodextrin solution. There will be 4 exchanges during the 9-hour exchange period. A sparse sampling approach will be used in collecting blood samples. A total of 16 blood samples will be collected.

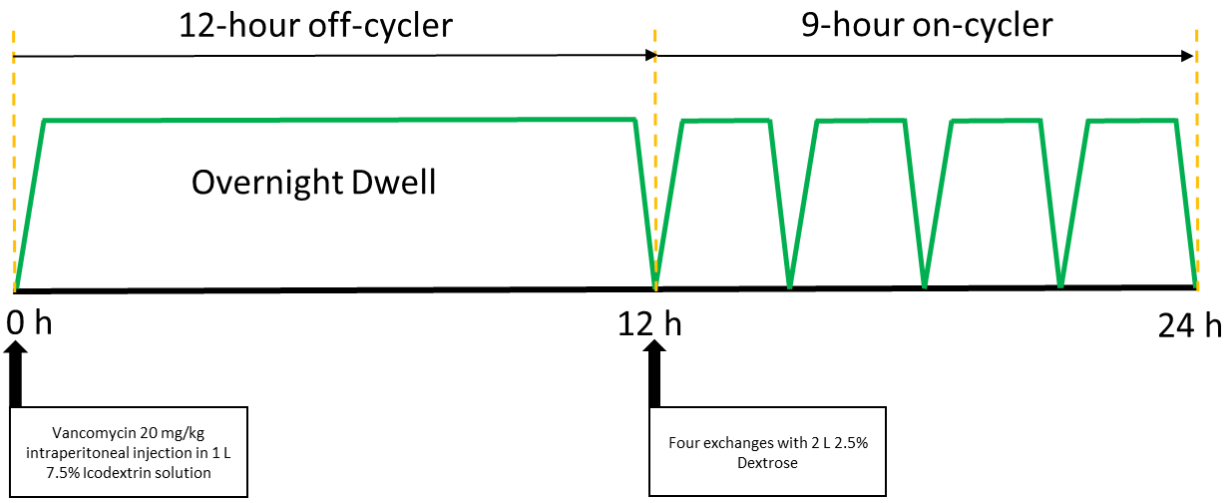

Figure 1. Schematic depiction of APD regimen.

3.2 Schedule & Procedures

A schematic is illustrated in figure 2 and study procedure detailed in table 1.

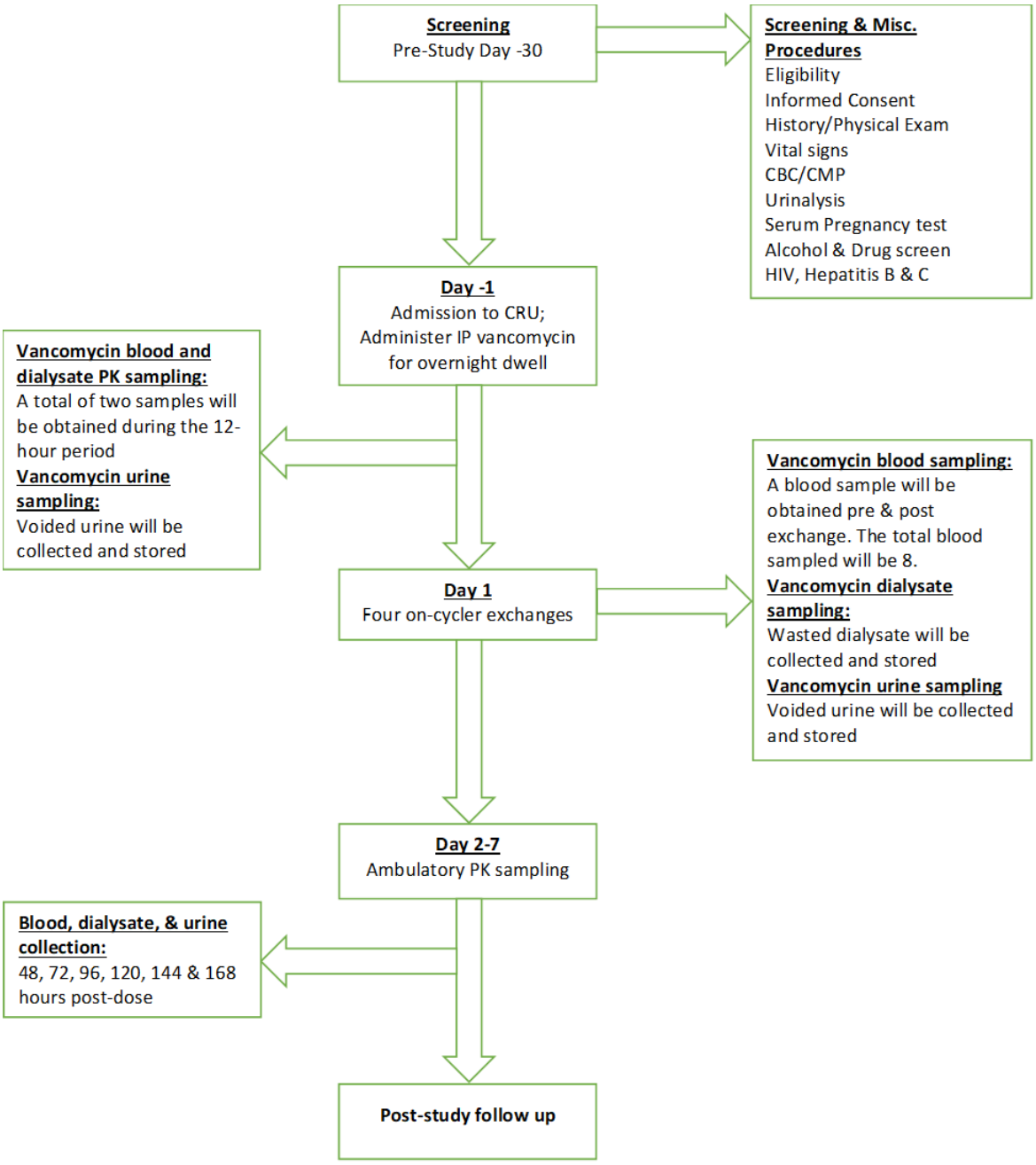

Figure 2. Study day and sampling schematic

	Procedures	Screening (Day -30)	Pre-study Day (Day -1)	Study Day 1	Study Day 2	Study Day 3	Study Day 4	Study Day 5	Study Day 6	Study Day 7	Post-study Follow-up (+7 to 10 days)
	Assessment of Eligibility	X									
	Signed Consent Form	X									
	Medical History	X									
	Concomitant Medication Review	X	X	X	X	X	X	X	X	X	
Clinical Laboratory	Pregnancy Test	X									
Clinical Laboratory	Complete Blood Count	X									X[5]
Clinical Laboratory	Comprehensive Metabolic Panel	X		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[5]
Clinical Laboratory	HIV, Hepatitis B & C	X[1]									
Clinical Laboratory	Alcohol & Drug Screen[6]	X			7						
Clinical Laboratory	Urinary Creatinine & Urea			X	X	X	X	X	X	X	
Clinical Procedures	Physical Exam	X		X	X	X	X	X	X	X	X
Clinical Procedures	Vital Signs	X		X	X	X	X	X	X	X	X
Clinical Procedures	Electrocardiogram	X									
Research Laboratory	PK Blood Sample			X	X	X	X	X	X	X	
Research Laboratory	PK Urine Sample			X	X	X	X	X	X	X	
Research Laboratory	PK Dialysate Sample			X	X	X	X	X	X	X	
Treatment	Vancomycin 20 mg/kg			X[2]							
	Assessment of Adverse Events			X	X	X	X	X	X	X	X
	CRU Evening Admission		X								
	CRU Discharge			X[3]							

[1] HIV/HBV/HCV information will be obtained from previous medical history. If the information is not available or a test was performed for ≥ 2 months, then a test will be performed during pre-screening.
[2] Vancomycin is dosed intraperitoneally in 1-liter of 7.5% icodextrin solution.
[3] Subjects are ambulatory after study day 1.
[4] Subjects will have serum creatinine analyzed within the PK sample.
[5] Laboratory assessments will be ordered at the discretion of the physician-investigator.
[6] If patient cannot produce urine, a urine drug screen will not be performed.
[7] If patient cannot produce urine, urinary creatinine and urea will not be performed.

Table 1. Summary of study procedures from pre-study to post-study follow-up.

Screening Visit for All Subjects (Day -30)

Subjects will be screened up to approximately 30 days prior to beginning the study. The screening visit will consist of:

- Previous medical history
    - HIV
    - Hepatitis B
    - Hepatitis C
    - Alcohol and drug screen
        - If the patient cannot produce urine, then a urine drug screen will not be performed and should not be considered a protocol deviation or exclusionary of participation in study
- Physical examination
- Patient consent
- Vital signs
- Electrocardiogram (ECG)
- Complete blood count
- Comprehensive metabolic panel

Study Days -1 - 1

- Physical exam and vital signs
- Urine will be immediately voided prior to dosing
- Administer vancomycin 20 mg/kg in 1 liter of 7.5% icodextrin intraperitoneally over approximately 10 to 15 minutes
- **Off-Cycler Schedule (12 hours)**
    - Blood samples will be obtained during the first 12-hour overnight dwell. A total of two samples will be taken between the time interval following dosing up until hour 12
    - Vancomycin and serum creatinine will be evaluated from blood samples collected
    - Dialysate samples will be obtained during the first 12-hour overnight dwell. A total of two samples will be taken between the time interval following dosing up until hour 12
    - Any urine voided will be collected between the time following dosing up until hour 12
        - If the patient cannot produce urine, then a urine sample will not be possible and should not be considered a protocol deviation
- **On-Cycler Schedule (9 hours)**
    - Blood will be sampled prior to and after each exchange. Since there are four exchanges, it is anticipated that a total of 8 samples will be obtained during the 9-hour on-cycler exchange period
    - Vancomycin and serum creatinine will be evaluated from blood samples collected
    - Wasted dialysate from each exchange will be collected and stored
    - Urine will be collected and pooled
        - If the patient cannot produce urine, then a urine sample will not be possible and should not be considered a protocol deviation
- Discharge from CRU

Study Days 2 – 7

- An additional 6 blood samples will be taken following study day 1, totaling 1 sample per day for the days the patient can come in. A minimum of 4 samples must be collected. If a patient cannot come in for at least 4 of the six days or blood cannot be obtained, it will be considered a protocol deviation. This will be done ideally in the morning, but at a time that takes into consideration subject availability and scheduling
- Vancomycin and serum creatinine will be evaluated from blood samples collected
- Vital signs will be taken
- Ambulatory dialysate and 24-hour urine will be collected from the subjects
    - If the patient cannot produce urine, then a urine sample will not be possible and should not be considered a protocol deviation

Post-study follow up

The post study visit will include post-study labs (at the investigator or co-investigator's discretion)*, physical exam, vital signs, and adverse event assessment obtained from the end of study. * As peritoneal dialysis patients come in to clinic regularly and have routine standard of care labs drawn, these may be used to evaluate follow- up safety as long as they are scheduled to be drawn no later than 17 days post dose.

4. STUDY POPULATION

4.1 Inclusion Criteria

- Adult male or females between 18 – 85 years old
- On a PD regimen for $\geq$ 3 months prior to study initiation

4.2 Exclusion Criteria

- Clinically significant disease unrelated to renal impairment or deemed unfit by the investigator
- Allergy or hypersensitivity to vancomycin or icodextrin-containing dialysis solution
- Active peritonitis infection
- Hospitalization within $\leq$ 3 months
- Previous intraperitoneal antibiotic treatment within 2 months
- Previous intravenous vancomycin treatment within 2 months
- Hemoglobin < 9 g/dL
- Pregnant or breast-feeding women

5. STUDY ENDPOINTS

5.1 Primary Pharmacokinetic Endpoint

Pharmacokinetic parameters such as the maximum serum concentration (C_{max}), time to maximum concentration (T_{max}), area under the concentration-time curve (AUC), half-life ($t_{1/2}$), volume of distribution (V_D), dialysate and systemic clearance, and inter-subject variability of vancomycin in subjects on APD will be estimated following a non-compartmental analysis (NCA).

Dialysate parameters will be estimated following an NCA analysis. Systemic bioavailability from the peritoneal cavity and absorption constant will be estimated.

5.2 Secondary Pharmacokinetic Endpoints

Residual kidney function as it relates to vancomycin will be assessed based on vancomycin total urinary clearance and cumulative drug excretion. The total dialysate clearance of vancomycin will be explored based on the biological fluids obtained. The safety, tolerability, and stability of vancomycin in 7.5% icodextrin solution will also be described.

5.3 Exploratory Pharmacokinetic-Pharmacodynamic Endpoints

Parameters generated from the non-compartmental analysis will be used to parameterize the population pharmacokinetic model to explore various dosing profiles. The AUC/MIC ratio will be explored to correlate exposures to the effect of vancomycin in patients on APD.

6. MEASUREMENTS AND EVALUATIONS

6.1 Study Data

Patient data will be recorded in a secured study database. Elements of interest to the study include:

- Patient demographics
  - Age
  - Sex
  - Height
  - Weight
  - Race
  - Cause of ESRD
- Laboratory parameters
  - Serum creatinine (SCr)
  - Urinary creatinine
  - Blood Urea Nitrogen (BUN)
  - Urine urea
  - Liver function

6.2 Plasma Samples

Samples will be processed per laboratory protocol in the laboratory manual.

6.3 Dialysate Samples

Samples will be processed per laboratory protocol.

6.4 Urine Samples

Samples will be processed per laboratory protocol.

7. SAMPLE SIZE AND ANALYSIS PLAN

8.1 Sample Size

Due to the exploratory nature of this pharmacokinetic study, no formal sample size calculation was performed. A total of 4 subjects will be enrolled.

8.2 Statistical and Pharmacokinetic Analysis

A non-compartmental analysis (NCA) will be utilized to estimate vancomycin pharmacokinetic parameters in patients on APD. The values generated from the NCA will be used to parameterize the population pharmacokinetic model.

Data from all patients will be analyzed simultaneously using nonlinear mixed-effects modelling software (NONMEM). A base model will be developed to characterize the data. Covariate analysis will also be evaluated in the model to explain for any intra- and inter-patient PK variability. Model qualification will be validated by using appropriate internal validation procedures based on the data and model development process.

8. DATA COLLECTION AND MANAGEMENT PLAN

8.1 Database System Overview

Data will be recorded and accessed using Research Electronic Data Capture, known as REDCap. REDCap is a secure web application designed for building and managing database information and meets compliance standards mandated by the Health Insurance Portability and Accountability Act (HIPAA) and FDA 21 CFR Part 11. Data files can be conveniently exported into various data formats (e.g. Microsoft Excel, SAS Statistical Software, R, SPSS, or STATA) for further analysis.

8.2 Case Report Forms and Data Entry

Clinical and demographic data will be collected from paper source documents. Information will be entered into an electronic case report form (eCRF). Each enrolled subject's eCRF will then be transcribed into REDCap and will serve as a central repository of all enrolled subjects in the study. A data monitor will monitor the accuracy of the study charts and data entry.

8.3 Case Report Form Storage and Backup

The eCRF will be stored in the Department of Pharmacology & Experimental Therapeutics secured server. Access will only be granted by the principal investigator or co-investigators.

9. SAFETY

Vancomycin has been previously studied in non-infected patients on peritoneal dialysis. In addition, the dose selected in this study is not devoid of the doses used in previous studies administered intravenously or through the intraperitoneal route.[7,9] The safety and tolerability of vancomycin administered through the intraperitoneal route will be assessed in this study by clinical evaluation of vital signs, physical examinations, and laboratory safety evaluations. In addition, continual serum concentration monitoring through blood sampling will be performed

as part of this research study. In addition, the likelihood for rare adverse events to vancomycin such as ototoxicity will be unlikely to occur based on the minimal dose used compared to literature.[14] Nephrotoxicity from a single IP 20 mg/kg dose of vancomycin would be extremely unlikely in stable, non-septic patients receiving no other potentially nephrotoxic medications or intravenous contrast. Major risk factors for nephrotoxicity related to vancomycin dosing include large daily doses (> 4grams/day), prolonged duration, and concurrent potentially toxic antibiotics (aminoglycosides or piperacillin-tazobactam), none of which apply to this study protocol. Other associated adverse events relating to vancomycin such as anaphylaxis and development of *Clostridium difficile* infections are considered unlikely.[15] In the event that greater than two unexpected and treatment related serious adverse events occur, the study will be halted until review from an independent study monitor is conducted. Cumulative blood draws will be restricted to less than 3 mL per sampling procedure and will be kept in strict accordance with 45 CFR 46.402(a) OHRP expedited review categories. Subjects who enrolled in the study will already have hemoglobin levels greater than 9 g/dL eliminating the concern for anemia requiring blood transfusion.

10. REFERENCES

1. Chan L, Poojary P, Saha A, et al. Reasons for admission and predictors of national 30-day readmission rates in patients with end-stage renal disease on peritoneal dialysis. *Clin Kidney J.* 2017;10(4):552-559.
2. Garcia-Lopez E, Lindholm B, Davies S. An update on peritoneal dialysis solutions. *Nat Rev Nephrol.* 2012;8(4):224-233.
3. Rabindranath KS, Adams J, Ali TZ, Daly C, Vale L, Macleod AM. Automated vs continuous ambulatory peritoneal dialysis: a systematic review of randomized controlled trials. *Nephrol Dial Transplant.* 2007;22(10):2991-2998.
4. Manley HJ, Bailie GR. Treatment of peritonitis in APD: pharmacokinetic principles. *Semin Dial.* 2002;15(6):418-421.
5. Li PK, Szeto CC, Piraino B, et al. ISPD Peritonitis Recommendations: 2016 Update on Prevention and Treatment. *Perit Dial Int.* 2016;36(5):481-508.
6. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm.* 2009;66(1):82-98.
7. Morse GD, Farolino DF, Apicella MA, Walshe JJ. Comparative study of intraperitoneal and intravenous vancomycin pharmacokinetics during continuous ambulatory peritoneal dialysis. *Antimicrob Agents Chemother.* 1987;31(2):173-177.
8. Bunke CM, Aronoff GR, Brier ME, Sloan RS, Luft FC. Vancomycin kinetics during continuous ambulatory peritoneal dialysis. *Clin Pharmacol Ther.* 1983;34(5):631-637.
9. Manley HJ, Bailie GR, Frye RF, McGoldrick MD. Intravenous vancomycin pharmacokinetics in automated peritoneal dialysis patients. *Perit Dial Int.* 2001;21(4):378-385.
10. Fish R, Nipah R, Jones C, Finney H, Fan SL. Intraperitoneal vancomycin concentrations during peritoneal dialysis-associated peritonitis: correlation with serum levels. *Perit Dial Int.* 2012;32(3):332-338.
11. Stevenson S, Tang W, Cho Y, et al. The role of monitoring vancomycin levels in patients with peritoneal dialysis-associated peritonitis. *Perit Dial Int.* 2015;35(2):222-228.

12. Whitty R, Bargman JM, Kiss A, Dresser L, Lui P. Residual Kidney Function and Peritoneal Dialysis-Associated Peritonitis Treatment Outcomes. *Clin J Am Soc Nephrol.* 2017;12(12):2016-2022.
13. Ranganathan D, Naicker S, Wallis SC, Lipman J, Ratanjee SK, Roberts JA. Stability of Antibiotics for Intraperitoneal Administration in Extraneal 7.5% Icodextrin Peritoneal Dialysis Bags (STAB Study). *Perit Dial Int.* 2016;36(4):421-426.
14. Tokgoz B, Somdas MA, Ucar C, et al. Correlation between hearing loss and peritonitis frequency and administration of ototoxic intraperitoneal antibiotics in patients with CAPD. *Ren Fail.* 2010;32(2):179-184.
15. Sun Y, Huskey RL, Tang L, et al. Adverse effects of intravenous vancomycin-based prophylaxis during therapy for pediatric acute myeloid leukemia. *Antimicrob Agents Chemother.* 2017.