Investigational New Drug

Minocin® (minocycline) for Injection
A PHASE I, OPEN-LABEL, SINGLE-DOSE TRIAL TO DETERMINE THE SAFETY AND PHARMACOKINETICS OF MINOCIN® (MINOCYCLINE) FOR INJECTION IN SUBJECTS WITH RENAL INSUFFICIENCY

Protocol No.: MDCO-MIN-16-03

Minocin 702
U.S. NDA No.: 50-444/S-047
EuDRACT No.: 2016-002247-41
PROTOCOL VERSION: 3.0

Development Phase	Phase I	
Sponsor	The Medicines Company 8 Sylvan Way Parsippany, NJ 07054, USA	
Sponsor Representative in the European Union	The Medicines Company – UK Medical.Information@THEMEDCO.com +44 1235 448 500	
Principal Investigator	Volker Burst, MD University Hospital Cologne Department II for Internal Medicine Kerpener Str. 62 50937 Koeln, Germany	
Sponsor Representatives		
Medical Director	Name:	Jeffery Loutit, MBChB
Project Lead	Name:	David Sylvester
Global Safety Officer	Name:	Isabelle Degeyter, MD
IMI/Combacte NET		
Medical Lead	Name:	Oliver Cornely, MD
Project Lead	Name:	Vassiliki Dimitriou
Issue Date	Date:	28 July 2017

CONFIDENTIAL

Property of The Medicines Company

May not be used, divulged, published or otherwise disclosed without the consent of The Medicines Company

This study will be conducted in compliance with Good Clinical Practice (GCP) and protection of the subject as required by the regulations and directives in operation at this time.

IN CASE OF EMERGENCY

Emergency Contact Information

Role in Study	Name	Telephone Number
Medical Director	Jeffery Loutit, MBChB	+1-650-888-5007
Global Safety Officer	Isabelle Degeyter, MD	+1-973-290-6120

KEY CONTACTS

Role in Study	Name	Contact Information
Academic Lead/ Medical Monitor	Oliver Cornely, MD	University Hospital of Cologne (UKK) Clinical Trials Center Cologne (CTCC) Department I for Internal Medicine Kerpener Str. 62 50937 Koeln Germany tel +49 172 2442726 +49 221 478-88120 oliver.cornely@uk-koeln.de
Sponsor Medical Lead	Jeffery Loutit, MBChB	The Medicines Company Health Science Infectious Disease Care 3033 Science Park Road San Diego, CA 92121 USA tel +1 650 888-5007 +1 858 875-6665 jeff.loutit@themedco.com
Trial Statistician	Stefanie Hamacher	University Hospital of Cologne (UKK) Institute of Medical Statistics, Informatics and Epidemiology (IMSIE) Kerpener Str. 62 50937 Koeln Germany tel +49 221 478-6517 stefanie.hamacher@uni-koeln.de
Sponsor Project Lead	David Sylvester	The Medicines Company 3033 Science Park Road San Diego, CA 92121 USA tel +61-488-100-096 david.sylvester@themedco.com

Role in Study	Name	Contact Information
UKK Project Lead	Vassiliki Dimitriou	University Hospital of Cologne (UKK) Department I for Internal Medicine Kerpener Str. 62 50937 Koeln Germany tel +49 221 478-98302 vassiliki.dimitriou@uk-koeln.de

INSTITUTIONS INVOLVED

Responsibility	Address
Bioanalytical Laboratory and Pharmacokinetic Analysis	North Bristol NHS Trust Southmead Hospital Bristol Department of Medical Microbiology Westbury on Trym Bristol, BS10 5NB United Kingdom
Clinical Laboratory	University Hospital of Cologne (UKK) Institute of Clinical Chemistry Kerpener Str. 62 50937 Koeln Germany
Data Management	University Hospital of Cologne (UKK) Clinical Trials Center Cologne (CTCC) Kerpener Str. 62 50937 Koeln Germany

Protocol Signatories

Sponsor Representative

Jeffery Loutit, MBChB
The Medicines Company

Elizabeth Morgan for J. Loutit
Signature Date 07 Sept 2017

Principal Investigator and Clinical Site

Priv. Doz. Dr. Volker Burst
University Hospital Cologne
Department II for Internal Medicine

Signature Date 08. Sept. 2017

IMI / Combacte NET Academic Work Package Lead Medical Monitor

Prof. Dr. Oliver A. Cornely
University Hospital Cologne
Clinical Trials Centre Cologne

Signature Date 11. Sept. 2017

IMI / Combacte NET Trial Statistician

Stefanie Hamacher
University Hospital of Cologne
IMSIE

i.V. S. Steiner 12. 9. 2017
Signature Date

1. PROTOCOL SYNOPSIS

Name of Sponsor/Company: The Medicines Company
Name of Finished Drug: Minocin® (minocycline) for Injection, referred to as Minocin IV in this protocol
Name of Active Ingredient: Minocycline
Title of Study: A Phase I, Open-Label, Single-Dose Trial To Determine The Safety And Pharmacokinetics Of Minocin® (Minocycline) For Injection In Subjects With Renal Insufficiency
Phase of Development: Phase I
Study Centers: A single German study site is planned
Number of Subjects: The study is designed to enroll approximately 40 subjects. There will be approximately 24 subjects with varying degrees of renal insufficiency, approximately 8 subjects with normal renal function, and 8 subjects receiving hemodialysis (HD) therapy.
Principal Investigator: Volker Burst, MD
Study Period: The study is planned to take place over approximately 24 weeks depending on rate of enrollment.
Objectives: • To evaluate the safety and tolerability of Minocin IV in subjects with renal insufficiency and in subjects receiving HD therapy • To assess the pharmacokinetics (PK) of Minocin IV in subjects with renal insufficiency and in subjects receiving HD therapy
Methodology: This is a Phase I, open-label, single-dose study to assess the safety, tolerability, and PK of Minocin IV in adults with varying degrees of renal insufficiency and in adult subjects receiving HD therapy as compared to subjects with normal renal function. There will be at least 8 subjects assigned to each of the following groups based on estimated glomerular filtration rate [eGFR] calculated at screening, using CKD-EPI 2009 for Groups 1-3, and using Cockroft-Gault for Group 4 (normal renal function). Group 5 is instead assigned by the requirement for HD therapy. • Group 1: Mild renal insufficiency (eGFR 60-89 mL/min/1.73m^2) • Group 2: Moderate renal insufficiency (eGFR 30 to < 60 mL/min/1.73m^2) • Group 3: Severe renal insufficiency (eGFR < 30 mL/min/1.73m^2) not receiving HD therapy • Group 4: Healthy subjects with normal renal function (eGFR ≥ 90 mL/min/1.73m^2) • Group 5: Subjects with end stage renal disease (ESRD) receiving HD therapy 3 times a week for at least 3 months prior to Day 1

Analysis of data will be based on Creatinine Clearance measurement by 24 h urine collection on Day 1.

Subjects with mild, moderate, and severe renal insufficiency (Groups 1, 2, and 3, respectively) will be enrolled in the study concurrently.

Once the mild, moderate, and severe renal insufficiency groups are fully enrolled, healthy subjects (Group 4) will be matched to the pooled mean values of age (± 10 years), body mass index (BMI; ± 20%), and gender.

Group 5 will be enrolled after completion of Groups 1-4. It will include subjects who require HD therapy 3 times a week for at least 3 months prior to Day 1. Subjects in Group 5 will receive Minocin IV twice over the course of the study, once before HD therapy (Period 1) and once after (Period 2). Periods 1 and 2 do not have to occur in sequence for any given subject. A Washout Period will occur between the 2 Periods regardless of the sequence of the Periods. The Washout Period will be scheduled to ensure that study drug administration is at least 6 days apart and no more than 14 days apart.

Inclusion Criteria:

Subjects will be included in the study if they meet all of the following criteria:

1. A signed informed consent form, the ability to understand the study conduct and tasks that are required for study participation, and a willingness to cooperate with all tasks, tests, and examinations as required by the protocol, whether in the hospital or after discharge, for the duration of the study;
2. Adult male or female between 18 and 85 years of age (inclusive) at the time of screening;
3. Subject has a BMI $\geq$ 18.5 kg/m^2 and $\leq$ 45 kg/m^2;
4. Pulse measured at screening/baseline must be within the ranges $\geq$ 45 to $\leq$ 115 beats per minute (bpm, taken after resting in a semi-recumbent position for at least 5 minutes);
5. Have sufficient peripheral vascular access, based on the Investigator's assessment, for all PK blood sample collections to take place (Central venous access may be possible for HD subjects, please refer to Section 9.3.2 and Section 9.5.2);
6. Female subject is surgically sterile (bilateral tubal occlusion), postmenopausal, or if of childbearing potential, agrees to abstinence or to use a highly efficient method of birth control (i.e., intrauterine device [IUD] or intrauterine hormone-releasing system [IUS] or vasectomized male partner, or hormonal contraceptives [estrogen and progestogen combined or progestogen only] with inhibition of ovulation, oral hormonal contraceptives must be supplemented with the use of condoms), between inclusion and for 7 days after the completion of the study;
7. Subject agrees to limit exposure or use protective measures (e.g., to wear sunglasses, protective clothing, sunscreen with high light protection factor, etc.) when in sunlight or ultraviolet light throughout the study;

Subjects with Renal Insufficiency:

8. Assessment of renal insufficiency for assignment to study groups will be based on measurements of eGFR calculated by CKD-EPI 2009 equation at the screening visit to determine eligibility;

Subjects with Normal Renal Function:

9. Normal volunteers matched by age (± 10 years), BMI (± 20%), and gender to the pooled mean values of the mild, moderate, and severe renal insufficiency groups;
10. Have a eGFR ≥ 90 mL/min calculated by Cockcroft-Gault equation at the screening visit to determine eligibility;

Hemodialysis Subjects:

11. Receiving stable HD (Kt/V > 1.2, determined within 6 months before inclusion) at least 3 times a week for at least 3 months;
12. Otherwise considered to be clinically stable with respect to underlying renal impairment, as determined by the Investigator, and based upon a medical evaluation that includes a medical history, physical examination, laboratory tests, and electrocardiogram (ECG);
13. Have clinical laboratory test results that are considered clinically stable in the opinion of the Investigator, especially if the clinical abnormality or laboratory parameter is deemed associated with the subject's underlying renal impairment;
14. A stable medication regimen is required, defined as not starting new drug(s) or significant changes in dosage(s) within 3 weeks prior to Day -1, or during the conduct of the study. Changes of medications in HD subjects are subject to dialysis site protocols such that erythropoiesis-stimulating agents (ESAs), iron, and vitamin D can be changed based on the then current subject status and dialysis unit standard practice and subject safety prior to screening.

Exclusion Criteria:

Subjects will be excluded from the study if there is evidence of any of the following at screening or check-in, as appropriate:

1. Subject with normal renal function has any condition, including findings in the medical history or in pre-study assessments, that are capable of altering the distribution, metabolism, or elimination of drugs or that constitute a risk or a contraindication for the participation in the study or completing the study;
2. Current evidence or history of malignancy, excluding basal cell carcinoma, requiring active treatment or management;
3. Positive breath test for alcohol and/or positive urine or saliva test for drugs of abuse at screening or baseline;
4. Has a history or presence of alcohol/drug abuse within the 30 days prior to enrollment. Alcohol abuse is defined as regularly consuming >3 units/day (21 units per week for men), >2 units/day (14 units/week) for women. A unit is defined as a can of 4% beer (330 mL), approximately 190 mL of 6-7% beer (malt liquor), a glass of 40% spirits (30 mL), a glass of wine (100 mL);
5. Blood or plasma donation within past 2 months;
6. Vigorous exercise from 48 hours prior to Day -1 until the day of discharge from the study;
7. Surgery within 48 hours prior to inclusion or surgery planned during the study period;

8. Liver function abnormalities at screening (or Day -1) (defined by an elevation in bilirubin, aspartate aminotransferase [AST], or alanine aminotransferase [ALT] 1.5 x upper limit of normal [ULN] of the normal range for subjects based on age and sex);
9. Raised magnesium levels at screening or Day -1 (defined by an elevation in magnesium above the ULN);
10. Females who are pregnant or nursing or who have a positive pregnancy test result at the Screening Visit or Day -1;
11. Males who are unwilling to practice abstinence or use an acceptable method of birth control during the entire study period (i.e., condom with spermicide, where locally available);
12. Presence of known raised intracranial pressure;
13. Use of isotretinoin;
14. History of significant hypersensitivity or allergic reaction to tetracycline antibiotics;
15. History of seizures (e.g., epilepsy), head injury, or meningitis requiring ongoing anti-seizure medications;
16. Receipt of any investigational medication or investigational device during the last 30 days prior to inclusion;
17. QTc >500 msec or history of prolonged QT syndrome;
18. Use of products containing alcohol within 48 hours before dosing;
19. Unable or unwilling, in the judgment of the Investigator, to comply with the protocol;
20. Subjects that have known active hepatitis B (HBV) or C (HCV), or human immunodeficiency virus (HIV) infection or have known immune deficiency disease at screening;
21. Concurrent use of medications known to affect the elimination of serum creatinine (e.g., trimethoprim/sulfamethoxazole [Bactrim®] or cimetidine [Tagamet®]. See Section 8.2.2 for full list) within 30 days prior to the first dose of study drug, or anticipated need for these therapies through the last PK sample;
22. An employee of the Investigator or study center or Sponsor, with direct involvement in the proposed study or other studies under the direction of that Investigator or study center or the Sponsor, or a family member of the employee or the Investigator;

Subjects with Renal Insufficiency:

23. Have a sitting systolic blood pressure (BP) > 180 mm Hg or < 90 mm Hg or have a sitting diastolic BP > 110 mm Hg or < 50 mm Hg at the Screening Visit; for HD subjects with BP outside these limits before HD, measurement can be repeated;
24. Use of any other prescription or nonprescription drugs, grapefruit/grapefruit juice, or dietary or herbal supplements within 14 days prior to Day -1 other than those listed below:
    a. Medications required to treat underlying renal disease or medical conditions related to renal disease are permitted;

b. Medications required to treat other pre-existing comorbidities and medical conditions (not related to renal disease) are permitted, provided that dosing is stable for 3 weeks prior to Day -1;

c. Oral contraceptives are permitted for birth control;

d. Doses of concomitant medications (except hormonal contraceptives, hormone replacement therapy for females, and insulin) must be stable for 3 weeks prior to Day -1. Minor dose changes consistent with treatment practices may be permitted at the discretion of the Sponsor's Medical Monitor;

e. Acetaminophen/paracetamol (≤ 1 g/day) and low-dose acetylsalicylic acid (ASA; i.e., ≤ 325 mg per day) are permitted;

Subjects with Normal Renal Function:

25. Abnormal and clinically significant findings on physical examination, medical history, serum chemistry, hematology, or urinalysis per Investigator discretion;

26. Have a sitting systolic BP > 150 mm Hg or < 90 mm Hg or have a sitting diastolic BP > 90 mm Hg or < 50 mm Hg at the Screening Visit;

27. Use of any prescription or nonprescription drugs, grapefruit/grapefruit juice, or dietary or herbal supplements within 14 days prior to Day -1 other than those listed below:

a. Oral contraceptives are permitted for birth control;

b. Acetaminophen/paracetamol (≤ 1 g/day), ibuprofen, and low-dose ASA (i.e., ≤ 325 mg per day) are permitted.

Test Drug/Device, Dose, and Mode of Administration:

Minocin IV doses should be prepared by a pharmacist (or qualified designee). Minocin IV 200 mg will be administered intravenously into a peripheral vein over 60 minutes in 100 ml 0.9% Sodium Chloride Injection (referred to as Normal Saline for the remainder of the document). Central venous access may be possible for HD subjects; please refer to Section 9.3.2 and Section 9.5.2.

Duration of Treatment:

The planned length of participation in the study for each subject with mild, moderate, or severe renal insufficiency and normal renal function (excluding screening) is approximately 5 days from check-in on Day -1 (Day -1 procedures can also be completed pre-dose on Day 1 at the site's discretion) through completion of the Day 4 post-dose procedures. Subjects will remain within the clinic for the duration of the single-dose period until completion of the post-dose procedures on Day 4. Subjects will receive a follow-up phone call on Day 6 (with a window of + ≤2 days). The total duration of participation, excluding screening period and including follow-up call, for each subject will be approximately 7-9 days.

Subjects with HD will participate in two 5 day periods; Periods 1 and 2, each from check-in on Day -1 (Day -1 procedures can also be completed pre-dose on Day 1 at the site's discretion) through completion of the Day 4 post-dose procedures. During each period, subjects will be confined to the clinic during Day -1 through Day 4. To separate Periods 1 and 2, a Washout Period will be scheduled to ensure that study drug administration is at least 6 days apart and no more than 14 days apart. Subjects will receive a follow-up phone call on Day 6 (with a window of + ≤ 2 days) after their second

dosing. The total duration of participation, excluding screening period, for each subject will be approximately 12-23 days.
Reference Therapy, Dose, and Mode of Administration: This is an open-label study with no reference treatment or placebo.
Criteria for Evaluation: **Endpoints:** • To evaluate the safety and tolerability of Minocin IV in subjects with renal insufficiency and in subjects receiving HD therapy (see below section **Safety**) • To assess the PK of Minocin IV in subjects with renal insufficiency and in subjects receiving HD therapy (see below section **Pharmacology**)
Efficacy: Efficacy will not be assessed in this study.
Safety: Assessment of Adverse Events (AEs) will be performed from the first administration of Investigational Medicinal Product (IMP) on Day 1 through end-of-study. Changes from baseline in physical examination findings, safety laboratory test results, ECGs, and vital signs will be evaluated. A Data Monitoring Committee (DMC) will review safety data as described in the DMC Charter.
Pharmacology: Serial plasma samples will be collected to determine concentrations of minocycline (see Section 1.1 Schedule of Events Flowchart). Plasma concentrations and PK parameters for Minocin IV will be summarized by time point using descriptive statistics (n, mean, standard deviation, coefficient of variation, median, minimum, and maximum). Plasma minocycline concentration versus time data will be analyzed to estimate the following PK parameters: area under concentration-time curve (AUC) from time zero to the time of the last measurable concentration ($AUC_{0\text{-last}}$), AUC from time zero to infinity ($AUC_{0\text{-inf}}$), maximum measured plasma concentration (C_{max}), minimum plasma concentration (C_{min}), time to C_{max} (T_{max}), elimination half-life ($t_{1/2}$), total body clearance (CL), and volume of distribution (V_{SS}) for each subject.
Methods: This sample size was selected based on previous experience attempting to minimize the number of subjects on study drug while obtaining sufficient PK data from different subjects to produce a good estimate of exposure. Descriptive statistics will be performed for demographic and medical baseline characteristics, medications, laboratory values, vital signs and ECG results. Additional shift tables will be provided for laboratory values and ECG results. AEs will be listed, and number (percentage) of subjects reporting AEs and number (percentage) of AEs will be tabulated. Other safety data will be summarized as appropriate. An analysis of the PK and AEs will be performed based on gender.

1.1. SCHEDULE OF EVENTS/ASSESSMENTS

Schedule of Events for Subjects with Mild, Moderate, and Severe Renal Insufficiency and Healthy Volunteers - Groups 1-4

STUDY DAY►	SCREEN (<28)	-1[1]	1	1	1	1	1	1	1	2	2	3	4 Final Visit	6 (+≤2) Follow-Up Call
STUDY HOUR ►			**0**	**1**	**2**	**4**	**8**	**12**	**18**	**24**	**36**	**48**	**72**	
EVENT▼														
Informed Consent	X													
Med. History / Demographics	X	X												
Conmed Review	X	X----------												
BMI	X	X												
PE / Charlson Comorbidity Index	X	X											X	
RR/BP/HR/Temperature	X	X	X	X		X				X		X	X	
ECG (12-lead)[2]	X	X	X			X				X			X	
Hem/Coag/Chem/UA[3]	X	X											X	
Urine Drug/Alcohol Screen	X	X												
Pregnancy Test[4]	X	X	X										X	
Adverse Events			X----------											
CrCl / 24 h urine collection			X----------											
PK Blood Collection			X	X	X	X	X	X	X	X	X	X	X	
Inclusion/Exclusion Criteria	X	X												
Dose (1 h infusion)			X											

Abbreviations: Conmed=concurrent medications; BMI=Body Mass Index; RR=respiratory rate; BP=blood pressure; HR=heart rate; ECG=electrocardiogram; Hem=hematology; Coag=coagulation; Chem=chemistry; UA=urinalysis; CrCl=creatinine clearance; PE=physical examination; PK=pharmacokinetics; h=hour

[1] Day -1 procedures, with the exception of triplicate ECG and assessment of Adverse Events, only need to be repeated if screening was >3 days prior to Day 1. Day -1 procedures can also be completed pre-dose on Day 1 at the site's discretion.

[2] On Day -1, ECGs should be performed in triplicate and may be repeated if necessary at the Investigator or Sponsor's discretion.

[3] Serum Creatinine from Screening Chemistry will be used for calculation of CrCl for renal function determination. Cockcroft-Gault will be used for Group 4 (normal renal function) and CKD-EPI 2009 for Groups 1-3 (renal insufficiency).

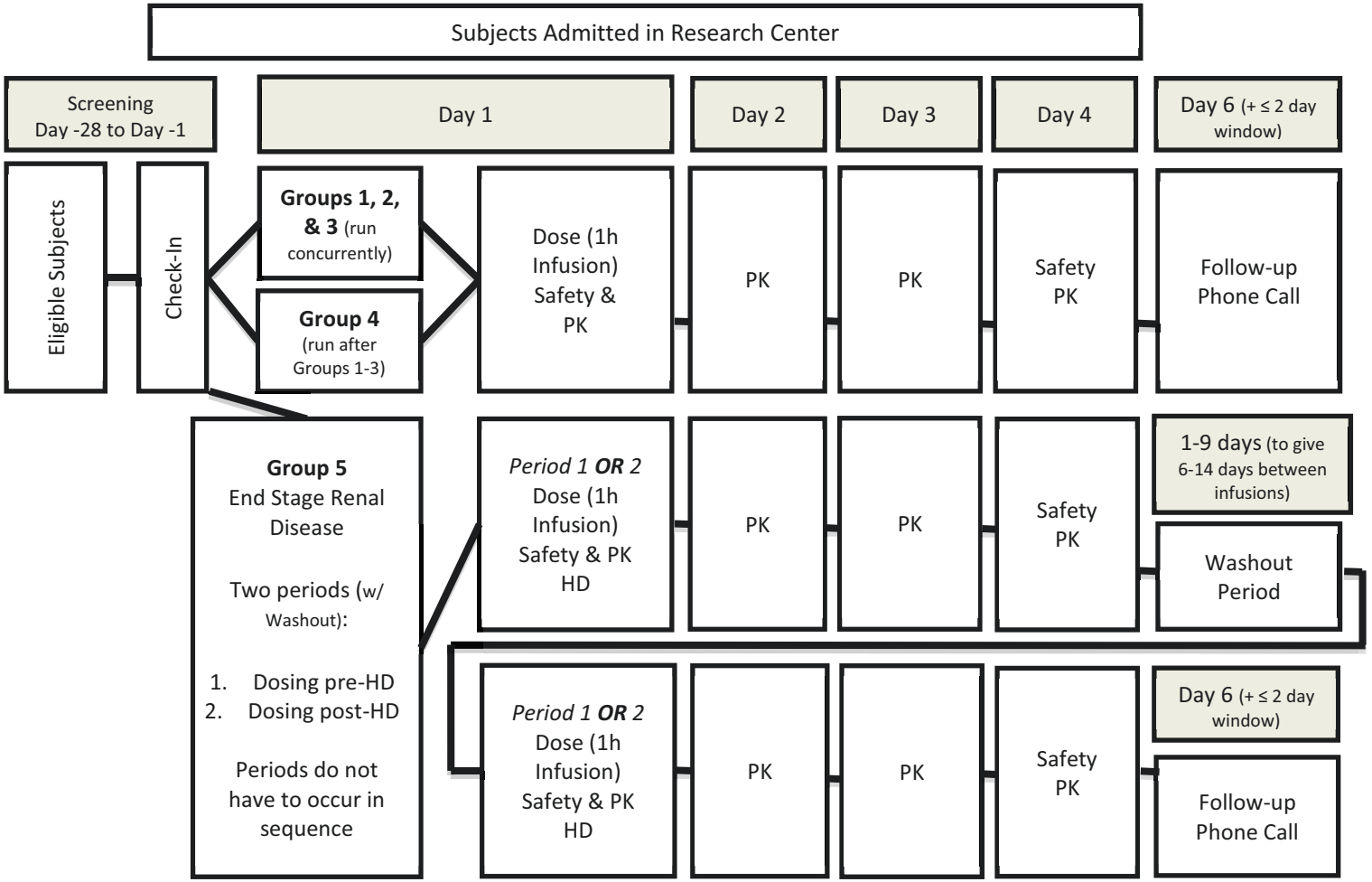
[4] Serum pregnancy should be performed during screening and Day -1. Urine pregnancy test should be performed before dosing on Day 1.

Schedule of Events for Subjects with End Stage Renal Disease - Group 5

		Period 1[1]					Washout Period[2]	Period 2 [1]					
STUDY DAY►	**Screening Period (<28)**	**-1**	**1**	**2**	**3 (48 h)**	**4 (72 h)**	**(Duration 1-9 days)**	**-1**	**1**	**2**	**3 (48 h)**	**4 (72 h)**	**6 (+≤2) Follow-up Call**
Informed Consent	X												
Medical History / Demographics	X	X						X					
Conmed Review	X	X----------						X----------					X
BMI	X	X						X					
PE / Charlson Comorbidity Index	X	X				X		X				X	
RR/BP/HR/Temperature[3]	X	X	X	X	X	X		X	X	X	X	X	
ECG (12-lead)[4]	X	X	X	X		X[10]		X	X	X		X[10]	
Hem/Coag/Chem	X	X				X[10]		X				X[10]	
Drug Screen	X	X						X					
Alcohol Screen	X	X						X					
Pregnancy Test[5]	X	(X)				X[10]		(X)				X[10]	
Adverse Events[6]		(X)	X----------					(X)	X----------				X
Hemodialysis[7]			X		(X)	(X)			X		(X)	(X)	
Hourly dialysate aliquots[7]			X						X				
PK Blood Collection[8]			X	X	X	X			X	X	X	X	
Inclusion/Exclusion Criteria	X	X[9]						X[9]					
Dose (1h infusion) – prior to dialysis (Period 1)			X										
Dose (1h infusion) – after dialysis (Period 2)									X				

[1] Periods 1 and 2 do not have to occur in sequence, but Washout Period is required regardless of order. Procedures denoted by brackets "(X)" vary by period order / subject (see footnotes for each).
[2] The Washout Period will occur between the Periods 1 and 2, and will be scheduled to ensure that study drug administration is 6-14 days apart. Any AEs will be reviewed at the time of 2nd check-in.
[3] Vital signs, including RR/BP/HR/Temperature, will be taken at: pre-dose, 1, 4, 24, 48, and 72 hours after the start of dosing for both Periods 1 and 2.
[4] ECG (12-lead) will be taken at: Day -1 (in triplicate at Day -1 of the 1st period conducted), then at pre-dose, 4, 24, and 72* hours after the start of dosing for both Periods 1 and 2. (*See footnote 10)
[5] Serum pregnancy test should be performed during screening, the first Day -1 (whichever period is conducted first), and at the final Day 4 visit (whichever period is completed last).
[6] AEs will be reviewed from Day 1 time of dosing through to the Day 6 [+ ≤2] Follow-Up Call. AEs during the Washout should be recorded at the second Day -1, upon subject's return to site.
[7] HD will be done Day 1 pre- or post-dosing, depending on Period (1 or 2), then at Day 3 OR 4, then as per subject's usual schedule throughout the Washout Period; In Period 1, Day 1, a pre-spent dialysate sample is collected prior to initiating HD, then hourly dialysate samples (with aliquots) through the end of HD; In Period 2, Day 1, only a pre-spent dialysate sample is required.
[8] Plasma samples will be collected for PK assessments at: 0, 1, 2, 4, 8, 12, 18, 24, 36, 48, 72 hours after the start of dosing for both Periods 1 and 2.
[9] Inclusion/Exclusion Criteria should be checked at Day -1 of whichever period is conducted first (Day -1 before the subject's first day of dosing).
[10] Complete these assessments only if Day 4 is the final, end-of-study visit for a subject. Because Periods 1 and 2 do not have to occur in sequence, the Day 4 of either period may be a subject's final in-patient visit. For the first period (prior to Washout), do not complete these procedures. For an early termination complete all of these procedures.

2. SCHEMATIC DIAGRAM OF TRIAL DESIGN



Plasma PK samples at the following time points:
Groups 1-4: pre-dose, 1, 2, 4, 8, 12, 18, 24, 36, 48, 72 hours after the start of dosing
Group 5: pre-dose, 1, 2, 4, 8, 12, 18, 24, 36, 48, 72 hours after the start of dosing for both Periods 1 and 2

Group 5 Dialysate samples at the following time points:
Period 1, Day 1: pre-spent dialysate sample prior to initiating HD, then hourly dialysate samples through the end of HD
Period 2, Day 1: pre-spent dialysate sample prior to initiating HD

TABLE OF CONTENTS

1. PROTOCOL SYNOPSIS 7
1.1. SCHEDULE OF EVENTS/ASSESSMENTS 13
2. SCHEMATIC DIAGRAM OF TRIAL DESIGN 15
3. LIST OF ABBREVIATIONS 20
4. INTRODUCTION 23
4.1. Background 23
4.2. Minocin IV (Minocycline for Injection) 24
4.2.1. Nonclinical Studies 24
4.2.2. Clinical Studies 24
4.2.3. Known and Potential Risks and Benefits 24
4.3. Study Rationale 26
4.4. Study Population 26
5. TRIAL OBJECTIVES AND PURPOSE 27
5.1. Objectives 27
6. TRIAL DESIGN 28
6.1. Type/Design of Trial 28
6.2. Study Endpoints 29
7. SUBJECT POPULATION 30
7.1. Number of Subjects 30
7.2. Inclusion Criteria 30
7.3. Exclusion Criteria 31
7.4. Withdrawal Criteria 33
8. TREATMENT OF SUBJECTS 35
8.1. Study Medications 35
8.1.1. Minocin IV 35
8.1.2. Packaging and Labeling 35
8.1.3. Storage 35
8.1.4. Accountability 35
8.2. Concomitant Medications 36
8.2.1. Permitted Concomitant Medications 36
8.2.2. Prohibited Concomitant Medications 36

8.3. Restrictions 37
8.4. Blinding 37
9. SCHEDULE AND SEQUENCE OF PROCEDURES 38
9.1. Screening Period (Day -28 to Day -1) 38
9.1.1. Screening 38
9.1.2. Informed Consent 38
9.1.3. Subject Confinement 39
9.2. Study Conduct for Groups 1-4 39
9.2.1. Check-in Procedures (Day -1) 39
9.2.2. Single-dose Administration of Minocin IV (Day 1) 40
9.2.3. Ongoing Clinical Assessment (Day 2) 40
9.2.4. Ongoing Clinical Assessment (Day 3) 40
9.2.5. Final In-patient Clinical Assessment (Day 4) 41
9.2.6. Follow-Up Telephone Call (Day 6 + ≤ 2 days) 41
9.3. Study Conduct for Group 5 HD Subjects – Period 1: Dose Administration Prior to Dialysis 41
9.3.1. Check-in Procedures for HD Subjects (Period 1, Day -1) 42
9.3.2. Single-dose Administration of Minocin IV (Period 1, Day 1) 42
9.3.3. Ongoing Clinical Assessment (Period 1, Day 2) 43
9.3.4. Ongoing Clinical Assessment (Period 1, Day 3) 44
9.3.5. Ongoing Clinical Assessment (Period 1, Day 4) 44
9.4. Washout Period 45
9.5. Study Conduct for Group 5 HD Subjects – Period 2: Dialysis Prior to Dose Administration 45
9.5.1. Check-in Procedures (Period 2, Day -1) 45
9.5.2. Single-dose Administration of Minocin IV (Period 2, Day 1) 46
9.5.3. Ongoing Clinical Assessment (Period 2, Day 2) 46
9.5.4. Ongoing Clinical Assessment (Period 2, Day 3) 47
9.5.5. Ongoing Clinical Assessment (Period 2, Day 4) 47
9.6. Study Conduct for Group 5 HD Subjects – Follow-Up Telephone Call (last Period Day 6 + ≤ 2 days) 47
9.7. Early Termination 48
10. PROTOCOL ASSESSMENTS 49

10.1. Assessment of Safety 49
10.1.1. Adverse Events 49
10.1.2. Body Mass Index (BMI) 49
10.1.3. Vital Signs 49
10.1.4. Physical Exam and Charlson Comorbidity Index 49
10.1.5. ECG 49
10.1.6. Clinical Laboratory Tests 50
10.1.6.1. Hematology 50
10.1.6.2. Coagulation 50
10.1.6.3. Chemistry 50
10.1.6.4. Urinalysis 50
10.1.6.5. Human Chorionic Gonadotropin (Pregnancy Test) 50
10.1.6.6. Testing for Drugs of Abuse 51
10.1.6.7. Breath Alcohol Testing 51
10.1.6.8. Creatinine Clearance 51
10.1.7. Birth Control Measures 51
10.2. Assessment of Efficacy 52
10.3. Assessment of Pharmacokinetics 52
10.3.1. Sampling and Processing 52
11. ADVERSE EVENTS 53
11.1. Definitions 53
11.1.1. Adverse Event 53
11.1.1.1. AE Severity 53
11.1.1.2. Study Drug Causality 54
11.1.2. Serious Adverse Event 54
11.1.3. Medication Errors 55
11.1.4. Adverse Event of Special Interest (AESIs) 56
11.1.5. Special Situations 56
11.2. Procedure for Non-Serious Adverse Event Recording 56
11.3. Procedure for Serious Adverse Event Reporting 56
11.4. Procedure for Medication error reporting for Study Drugs 57
11.5. Procedure For Reporting Adverse Events Of Special Interest 57
11.6. Procedure For Reporting Pregnancies/Lactation Exposure 57

11.7. Procedure For Reporting Special Situations 57
12. DATA COLLECTION 58
13. STATISTICAL PLAN 59
13.1. Sample Size 59
13.2. Randomization 59
13.3. General Statistical Considerations and Definitions 59
13.3.1. General Statistical Methods 59
13.3.2. Analysis Population 59
13.3.2.1. Intent-to-Treat (ITT) Population 59
13.3.2.2. Modified Intent-to-Treat (mITT) Population 59
13.3.2.3. PK Population 60
13.3.2.4. Per-Protocol (PP) Population 60
13.3.2.5. Safety Population 60
13.3.3. Missing Data Handling 60
13.4. Statistical Analyses 60
13.4.1. Demographic and Background Characteristics 60
13.4.2. Study Drug and Concomitant Medications 60
13.4.2.1. Adverse Events 60
13.4.2.2. Laboratory Tests 60
13.4.2.3. Vital Signs 61
13.4.2.4. ECGs 61
13.4.2.5. Pharmacokinetic Parameters 61
14. RECORDS RETENTION 62
15. QUALITY CONTROL AND QUALITY ASSURANCE 63
15.1. Monitoring 63
15.2. Auditing 63
15.3. Protocol Deviations 63
16. ETHICS AND RESPONSIBILITY 64
16.1. Informed Consent 64
16.2. Ethics Committee 64
17. CONFIDENTIALITY 65
18. INVESTIGATOR AGREEMENT 66
19. REFERENCES 67

3. LIST OF ABBREVIATIONS

A. baumannii	*Acinetobacter baumannii*
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-inf}}$	AUC from time 0 to infinity
$AUC_{0\text{-last}}$	AUC from time 0 to time of the last quantifiable concentration
BMI	Body mass index
BP	Blood Pressure
bpm	Beats per minute
BUN	Blood urea nitrogen
CDAD	*Clostridium difficile*-associated diarrhea
CDC	Centers for Disease Control and Prevention
C. difficile	*Clostridium difficile*
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	Clearance
C_{max}	Maximum observed drug concentration
C_{min}	Minimum observed drug concentration
CrCl	Creatinine clearance
CS	Clinically Significant
CTCAE	Common Terminology Criteria for Adverse Events
CTCC	Clinical Trials Center Cologne
CTFG	Clinical Trial Facilitation Group
d	Day(s)
DMC	Data Monitoring Committee
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
ESA	Erythropoiesis-stimulating agent
ESRD	End-stage renal disease
EU	European Union
FDA	Food and Drug Administration
GAIN	Generating Antibiotic Incentives Now
GCP	Good Clinical Practice

GPV	Global Pharmacovigilance Department
h	hour
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HD	Hemodialysis
HIV	Human Immunodeficiency Virus
HR	Heart rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals
IH	Intracranial hypertension
IMP	Investigational medicinal product
IMSIE	Institute of Medical Statistics, computer Science and Epidemiology
INR	International Normalized Ratio
ITT	Intent-to-treat
IUD	Intra-uterine device
IUS	Intra-uterine system
IV	Intravenous
kg	Kilogram(s)
max	Maximum
MDCO	The Medicines Company
MDR	Multi-drug resistant
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
MI	Myocardial infarction
min	Minute(s), Minimum
mITT	Modified intent-to-treat
mL	Milliliter(s)
msec	Milisecond
n	Number
NCS	Not clinically significant
NDA	New drug application
PE	Physical exam
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per-protocol
PT	Prothrombin time
Q1	1st Quarter (of the year)
Q3	3rd Quarter (of the year)
QTc	Corrected QT interval
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical analysis plan

SD	Standard deviation
SOP	Standard Operating Procedure
$t_{1/2}$	Half-life
T_{max}	Time of the maximum drug concentration
UA	Urinalysis
UKK	University Hospital of Cologne
ULN	Upper limit of normal
US, USA	United States of America
USP	United States Pharmacopeia
WHO	World Health Organization
VSS	Volume of distribution

4. INTRODUCTION

This study will evaluate the safety, tolerability, and pharmacokinetics (PK) of Minocin IV (Minocycline for Injection).

Minocycline was first approved in the United States (US) as both oral and intravenous (IV) formulations in the 1970s. Only oral dosage formulations of minocycline have been approved for use in countries in the European Union (EU). A new formulation of Minocin IV has been approved in the US that enables administration of minocycline in a smaller volume of fluid. The Medicines Company plans to conduct a development program in the EU for Minocin IV for the treatment of infections due to *Acinetobacter baumannii*, and this new formulation supports the planned study of higher doses of minocycline.

This study will be conducted in compliance with Good Clinical Practices (GCP) including the Declaration of Helsinki and all applicable regulatory requirements.

Additional details regarding Minocin IV can be found in the Investigator's Brochure.

4.1. Background

Minocycline is a tetracycline derivative. The approved indication for Minocin IV includes the treatment of infections due to susceptible strains of several important gram-positive and gram-negative pathogens, including *Acinetobacter* species.

Acinetobacter infections are associated with high morbidity and mortality [Munoz-Price and Weinstein, 2008]. Antibacterial agents frequently used to treat *Acinetobacter* infections include aminoglycosides, cephalosporins, and carbapenems; however, resistance to these first-line agents is increasing, leaving only unproven agents available for treatment [Shlaes et al, 2013; Munoz-Price and Weinstein, 2008]. In view of this increasing resistance, both EU and US governments have identified multi-drug resistant (MDR) *Acinetobacter* infections as a public health risk [EU MEMO/08/788; US Generating Antibiotic Incentives Now (GAIN) Act; and Centers for Disease Control (CDC) Antibiotic Resistance Threats Report].

It is noteworthy that while minocycline has been approved since the 1970s, recent studies indicate that minocycline remains highly active in vitro against *Acinetobacter* species. Importantly, minocycline has been found to be active against strains that are resistant to doxycycline or tigecycline [Munoz-Price and Weinstein, 2008].

The original IV formulation of minocycline, Minocin (minocycline) for Injection, was approved in the US on 26 October 1972. Only oral dosage formulations of minocycline and Minocin have been approved for use in countries in the EU since the 1970s [Minocycline tablets SmPC, 2011; Minocin MR Capsules SmPC, 2014]. The new formulation of Minocin IV was approved in the US on 17 April 2015 (NDA 50,444). The new formulation is comprised of minocycline hydrochloride with magnesium sulfate to improve the stability of minocycline solutions at a more physiological pH, which enables administration of minocycline in a smaller volume of fluid.

The Medicines Company plans to conduct three Phase I safety and pharmacology studies (including this study) and one Phase III study to support the overall development strategy for Minocin IV in the EU.

4.2. Minocin IV (Minocycline for Injection)

Minocin® (minocycline) for Injection, also known as RPX-602 and referred to as Minocin IV in this protocol, is an IV formulation of minocycline, a derivative of tetracycline.

Minocin IV is supplied as a sterile lyophilized cake in a single-use 10 mL glass vial with a rubber stopper and an aluminum over-seal. Each vial contains 108 mg of minocycline hydrochloride equivalent to 100 mg minocycline, 269 mg of magnesium sulfate heptahydrate equivalent to 27 mg of magnesium (an inactive ingredient), and sodium hydroxide (to adjust pH).

4.2.1. Nonclinical Studies

The non-clinical development program for Minocin IV consists of in vitro antibacterial potency studies against clinical isolates and in vivo in mouse and rat infection models; in vitro and in vivo pharmacokinetic and metabolism studies; and a battery of non-clinical toxicity, safety, and local tolerance studies, including 14 day IV repeat-dose studies in rats and dogs, safety pharmacology studies in rats and dogs, and local tolerance studies in mice and rabbits.

Additional details regarding the nonclinical development program for Minocin IV can be found in the Investigator's Brochure.

4.2.2. Clinical Studies

Clinical pharmacokinetic and safety information are available from the US Prescribing Information for Minocin IV [Minocin for Injection PI, 2015], and while no randomized controlled trials of IV minocycline in patients with *A. baumannii* infection exist, clinical efficacy data are available from published case report series that indicated successful treatment.

IV minocycline has been in use for over four decades and has a well-established safety profile. Recent clinical safety data have been generated from studies of potential non-antimicrobial effects of minocycline [Casha et al, 2011; Fagan et al, 2010], and these studies utilized multiple doses, at a higher dose level than that being studied here.

Additional details regarding the clinical studies conducted for Minocin IV can be found in the Investigator's Brochure.

4.2.3. Known and Potential Risks and Benefits

In general, the risk of significant adverse events (SAEs) related to Minocin IV is minimal and consistent with taking intravenous doses of a tetracycline antibiotic. The following adverse reactions have been observed in patients receiving tetracyclines and are included in the Minocin® (minocycline) Investigator's Brochure.

Drug rash with eosinophilia and systemic symptoms, including fatal cases, have been reported with minocycline use. If this syndrome is recognized, the drug should be discontinued immediately.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. This has been reported with minocycline. As this is a single-dose study, phototoxic reactions are not expected; however, as a precaution, subjects will be instructed to limit their exposure to sunlight and ultraviolet light, to wear sunglasses and protective clothing, and to use sun protection products (such as sunscreen) with a high light protection factor throughout the course of the study.

Central nervous system side effects including light-headedness, dizziness, or vertigo have been reported with minocycline. These symptoms may disappear during therapy and usually disappear rapidly when the drug is discontinued.

Clostridium difficile (*C. difficile*) associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Minocin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

Intracranial hypertension (IH; pseudotumor cerebri) has been associated with the use of tetracyclines, including Minocin. Clinical manifestations of IH include headache, blurred vision, diplopia, and vision loss; papilledema can be found on fundoscopy. Women of childbearing age who are overweight or have a history of IH are at greater risk for developing tetracycline-associated IH. Concomitant use of isotretinoin and Minocin should be avoided because isotretinoin is also known to cause pseudotumor cerebri. Although IH typically resolves after discontinuation of treatment, the possibility for permanent visual loss exists.

The anti-anabolic action of the tetracyclines may cause an increase in blood urea nitrogen (BUN). While this is not a problem in those with normal renal function, in patients with significantly impaired function, higher serum levels of tetracycline may lead to azotemia, hyperphosphatemia, and acidosis.

Minocin IV, like other tetracycline-class antibacterials, can cause fetal harm when administered to a pregnant woman. The use of drugs of the tetracycline class during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). Enamel hypoplasia has also been reported.

All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth rate has been observed in premature human infants given oral tetracycline in doses of 25 mg/kg every 6 hours.

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity has been noted in animals treated early in pregnancy.

As with other antibacterial preparations, use of Minocin may result in overgrowth of nonsusceptible organisms, including fungi.

Because Minocin IV contains magnesium, close monitoring is recommended; it should be used with caution in patients with heart block or myocardial damage.

Minocin IV is contraindicated in individuals who have shown hypersensitivity to any of the tetracyclines or to any components of the product formulation.

The safety monitoring practices employed by this protocol (i.e., physical examination, vital signs, 12-lead electrocardiogram [ECG], hematology, coagulation, serum chemistry, urinalysis, and adverse event [AE] collection) are adequate to protect the subjects' safety and should detect AEs.

The approximate volume of blood planned for collection from each subject over the course of the study presents no undue risk to the subjects.

There will be no direct health benefit for trial participants from receipt of study drug. An indirect health benefit to the healthy subjects enrolled in this trial is the free medical tests received at screening and during the study.

A complete description of relevant risks of Minocin IV, including reported adverse reactions that have been observed in patients receiving tetracyclines, can be found in the Investigator's Brochure [see references].

4.3. Study Rationale

The purpose of this study is to collect safety, tolerability, and PK data from a single IV infusion of Minocin IV administered to subjects with renal insufficiency and subjects receiving hemodialysis (HD) therapy as compared to subjects with normal renal function. The safety, tolerability, and PK data will support the compound as a potential clinical candidate in Europe and allow recommendations of Minocin IV dose levels to be administered to renal insufficiency patients.

4.4. Study Population

The study is designed to enroll approximately 40 subjects. There will be approximately 24 subjects with varying degrees of renal insufficiency, approximately 8 subjects with normal renal function, and 8 subjects receiving HD therapy.

5. TRIAL OBJECTIVES AND PURPOSE

5.1. Objectives

- To evaluate the safety and tolerability of Minocin IV in subjects with renal insufficiency and in subjects receiving HD therapy
- To assess the PK of Minocin IV in subjects with renal insufficiency and in subjects receiving HD therapy

6. TRIAL DESIGN

6.1. Type/Design of Trial

This is a Phase I, open-label, single-dose study to assess the safety, tolerability, and PK of Minocin IV in adults with varying degrees of renal insufficiency and in adult subjects receiving HD therapy as compared to subjects with normal renal function.

There will be at least 8 subjects assigned to each of the following groups based on estimated glomerular filtration rate [eGFR] calculated at screening, using CKD-EPI 2009 [Levey, A. S. et al, 2009] for Groups 1-3, and using Cockroft-Gault for Group 4 (normal renal function). Group 5 is instead assigned by the requirement for HD therapy.

- Group 1: Mild renal insufficiency (eGFR 60-89 mL/min/1.73m^2)
- Group 2: Moderate renal insufficiency (eGFR 30 to < 60 mL/min/1.73m^2)
- Group 3: Severe renal insufficiency (eGFR < 30 mL/min/1.73m^2) not receiving HD therapy
- Group 4: Healthy subjects with normal renal function (eGFR ≥ 90 mL/min/1.73m^2)
- Group 5: Subjects with end stage renal disease (ESRD) receiving HD therapy 3 times a week for at least 3 months prior to Day 1

Subjects with mild, moderate, and severe renal insufficiency (Groups 1, 2, and 3, respectively) will be enrolled in the study concurrently.

Once the mild, moderate, and severe renal insufficiency groups are fully enrolled, healthy subjects (Group 4) will be matched to the pooled mean values of age (± 10 years), body mass index (BMI; ± 20%), and gender.

Within Groups 1-4, subjects will receive a single dose on Day 1. Subjects are required to remain admitted in the research unit from Day -1 until discharge on Day 4. A follow-up phone call will occur on Day 6 (with a window of + ≤ 2 days).

Group 5 will be enrolled after completion of Groups 1-4. It will include subjects who require HD therapy 3 times a week for at least 3 months prior to Day 1. Subjects in Group 5 will receive Minocin IV twice over the course of the study, once prior to HD therapy (Period 1) and once after (Period 2). Periods 1 and 2 do not have to occur in sequence for any given subject. A Washout Period will occur between the 2 Periods regardless of the sequence of Periods. The Washout Period will be scheduled to ensure that study drug administration is at least 6 days apart and no more than 14 days apart.

Group 5 subjects will be required to remain admitted in the research unit from Day -1 until Day 4 of each period. A follow-up phone call will occur on Day 6 (with a window of + ≤ 2 days) of the subject's second period.
Subjects that discontinue the study early are required to complete Early Termination procedures.

Safety will be assessed throughout the study, and serial blood samples will be collected for the safety and PK assessment of Minocin IV.

A Data Monitoring Committee (DMC) will be compiled for the work package of the IMI COMBACTE-Net project. The DMC will review safety data after inclusion of 12 subjects within Groups 1, 2, and 3, and after completion of Group 4, before dosing of Group 5. Details of the DMC's roles and responsibilities can be found in the DMC Charter.

6.2. Study Endpoints

The endpoints of this trial are:

- To evaluate the safety and tolerability of Minocin IV in subjects with renal insufficiency and in subjects receiving HD therapy;
- To assess the PK of Minocin IV in subjects with renal insufficiency and in subjects receiving HD therapy.

7. SUBJECT POPULATION

7.1. Number of Subjects

The study is designed to enroll approximately 40 subjects. There will be approximately 24 subjects with varying degrees of renal insufficiency, approximately 8 subjects with normal renal function, and 8 subjects receiving HD therapy.

7.2. Inclusion Criteria

Subjects will be included in the study if they meet all of the following criteria:

1. A signed informed consent form, the ability to understand the study conduct and tasks that are required for study participation, and a willingness to cooperate with all tasks, tests, and examinations as required by the protocol, whether in the hospital or after discharge, for the duration of the study;
2. Adult male or female between 18 and 85 years of age (inclusive) at the time of screening;
3. Subject has a BMI $\geq$ 18.5 kg/m^2 and $\leq$ 45 kg/m^2;
4. Pulse measured at screening/baseline must be within the ranges $\geq$ 45 to $\leq$115 beats per minute (bpm, taken after resting in a semi-recumbent position for at least 5 minutes);
5. Have sufficient peripheral vascular access, based on the Investigator's assessment, for all PK blood sample collections to take place;
6. Female subject is surgically sterile (bilateral tubal occlusion), postmenopausal, or if of childbearing potential, agrees to abstinence or to use a highly efficient method of birth control (i.e., intrauterine device [IUD] or intrauterine hormone-releasing system [IUS] or vasectomized male partner, or hormonal contraceptives [estrogen and progestogen combined or progestogen only] with inhibition of ovulation, oral hormonal contraceptives must be supplemented with the use of condoms), between inclusion and for 7 days after the completion of the study;
7. Subject agrees to limit exposure or use protective measures (e.g., to wear sunglasses, protective clothing, sunscreen with high light protection factor, etc.) when in sunlight or ultraviolet light throughout the study;

Subjects with Renal Insufficiency:

8. Assessment of renal insufficiency for assignment to study groups will be based on measurements of eGFR calculated by CKD-EPI 2009 equation at the screening visit to determine eligibility [Levey, A. S. et al, 2009];

Subjects with Normal Renal Function:

9. Normal volunteers matched by age (± 10 years), BMI (± 20%), and gender to the pooled mean values of the mild, moderate, and severe renal insufficiency groups;

10. Have a eGFR ≥ 90 mL/min calculated by Cockroft-Gault equation at the screening visit to determine eligibility;

Hemodialysis Subjects:

11. Receiving stable HD (Kt/V > 1.2, determined within 6 months before inclusion) at least 3 times a week for at least 3 months;
12. Otherwise considered to be clinically stable with respect to underlying renal impairment, as determined by the Investigator, and based upon a medical evaluation that includes a medical history, physical examination, laboratory tests, and ECG;
13. Have clinical laboratory test results that are considered clinically stable in the opinion of the Investigator, especially if the clinical abnormality or laboratory parameter is deemed associated with the subject's underlying renal impairment;
14. A stable medication regimen is required, defined as not starting new drug(s) or significant changes in dosage(s) within 3 weeks prior to Day -1, or during the conduct of the study. Changes of medications in HD subjects are subject to dialysis site protocols such that erythropoiesis-stimulating agents (ESAs), iron, and vitamin D can be changed based on the then current subject status and dialysis unit standard practice and subject safety prior to screening.

7.3. Exclusion Criteria

Subjects will be excluded from the study if there is evidence of any of the following at screening or check-in, as appropriate:

1. Subject with normal renal function has any condition, including findings in the medical history or in pre-study assessments, that are capable of altering the distribution, metabolism, or elimination of drugs or that constitute a risk or a contraindication for the participation in the study or completing the study;
2. Current evidence or history of malignancy, excluding basal cell carcinoma, requiring active treatment or management;
3. Positive breath test for alcohol and/or positive urine test for drugs of abuse at screening;
4. Has a history or presence of alcohol/drug abuse within the 30 days prior to enrollment. Alcohol abuse is defined as regularly consuming >3 units/day (21 units per week for men), >2 units/day (14 units/week) for women. A unit is defined as a can of 4% beer (330 mL), approximately 190 mL of 6-7% beer (malt liquor), a glass of 40% spirits (30 mL), a glass of wine (100 mL);
5. Blood or plasma donation within past 2 months;
6. Vigorous exercise from 48 hours prior to Day -1 until the day of discharge from the study;

7. Surgery within 48 hours prior to randomization or surgery planned during the study period;
8. Liver function abnormalities at screening (or Day -1) (defined by an elevation in bilirubin, aspartate aminotransferase [AST] or alanine aminotransferase [ALT] 1.5 x upper limit of normal [ULN] of the normal range for subjects based on age and sex);
9. Raised magnesium levels at screening or Day -1 (defined by an elevation in magnesium above the ULN);
10. Females who are pregnant or nursing or who have a positive pregnancy test result at the Screening Visit or Day -1;
11. Males who are unwilling to practice abstinence or use an acceptable method of birth control during the entire study period (i.e., condom with spermicide, where locally available);
12. Presence of known raised intracranial pressure;
13. Use of isotretinoin;
14. History of significant hypersensitivity or allergic reaction to tetracycline antibiotics;
15. History of seizures (e.g., epilepsy), head injury, or meningitis requiring ongoing anti-seizure medications;
16. Receipt of any investigational medication or investigational device during the last 30 days prior to randomization;
17. QTc > 500 msec or history of prolonged QT syndrome;
18. Use of products containing alcohol within 48 hours before dosing;
19. Unable or unwilling, in the judgment of the Investigator, to comply with the protocol;
20. Subjects that have known active hepatitis B (HBV) or C (HCV), or human immunodeficiency virus (HIV) infection or have known immune deficiency disease at screening;
21. Concurrent use of medications known to affect the elimination of serum creatinine (e.g., trimethoprim/sulfamethoxazole [Bactrim®] or cimetidine [Tagamet®]. See Section 8.2.2 for full list) within 30 days prior to the first dose of study drug or anticipated need for these therapies through the last PK sample;
22. An employee of the Investigator or study center or Sponsor, with direct involvement in the proposed study or other studies under the direction of that Investigator or study center or the Sponsor, or a family member of the employee or the Investigator;

Subjects with Renal Insufficiency:

23. Have a sitting systolic blood pressure (BP) > 180 mm Hg or < 90 mm Hg or have a sitting diastolic BP > 110 mm Hg or < 50 mm Hg at the Screening Visit;
24. Use of any other prescription or nonprescription drugs, grapefruit/grapefruit juice, or dietary or herbal supplements within 14 days prior to Day -1;
    a. Concomitant medications required to treat underlying renal disease or medical conditions related to renal disease are permitted;
    b. Medications required to treat other pre-existing comorbidities and medical conditions (not related to renal disease) are permitted, provided that dosing is stable for 3 weeks prior to Day -1;
    c. Oral contraceptives are permitted for birth control;
    d. Doses of concomitant medications (except hormonal contraceptives, hormone replacement therapy for females, and insulin) must be stable for 3 weeks prior to Day -1. Minor dose changes consistent with treatment practices may be permitted at the discretion of the Sponsor's Medical Monitor;
    e. Acetaminophen/paracetamol (≤ 1 g/day) and low-dose acetylsalicylic acid (ASA; i.e., ≤ 325 mg per day) are permitted;

Subjects with Normal Renal Function:

25. Abnormal and clinically significant findings on physical examination, medical history, serum chemistry, hematology, or urinalysis per Investigator discretion;
26. Have a sitting systolic BP > 150 mm Hg or < 90 mm Hg or have a sitting diastolic BP > 90 mm Hg or < 50 mm Hg at the Screening Visit;
27. Use of any other prescription or nonprescription drugs, grapefruit/grapefruit juice, or dietary or herbal supplements within 14 days prior to Day -1;
    a. Oral contraceptives are permitted for birth control;
    b. Acetaminophen/paracetamol (≤ 1 g/day), ibuprofen and low-dose ASA (i.e., ≤ 325 mg per day) are permitted.

7.4. Withdrawal Criteria

All subjects have the right to withdraw at any point during treatment without prejudice. The Investigator can discontinue any subject at any time if medically necessary. It will be documented whether or not each subject completed the clinical study. If for any subject, study treatment or observations were discontinued, the reason will be recorded, and the Sponsor should be notified promptly. Reasons that a subject may discontinue participation in a clinical study are the following:

1. Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition or circumstance that indicates to the Principal Investigator (PI) that continued participation is not in the best interest of the subject and/or does not allow them to adhere to the requirements of the protocol;
2. Subject's decision to withdraw;
3. Requirement of prohibited concomitant medication;
4. Physician's decision;
5. Subject's failure to comply with protocol requirements or study-related procedures;
6. Lost to follow-up;
7. Termination of the study by the Sponsor, or designee, or regulatory authorities.

It is imperative to obtain complete follow-up data for all subjects whether or not they receive their assigned treatment or have discontinued study drug. All data collected up until the time of subject withdrawal is to be entered into the electronic case report form (eCRF). In addition, every attempt should be made to collect follow-up information except for those subjects who specifically withdraw consent for release of such information. All procedures and laboratory specimens or tests requested for evaluation following administration of the study drug should be carried out when possible whether or not a subject continues to receive treatment according the protocol.

The clinical report will include reason(s) for subject withdrawals as well as details relevant to the subject withdrawal. If a subject is withdrawn from the trial prior to study completion, the subject will undergo all procedures scheduled for study completion (Day 4 - final in-patient clinical assessment) as appropriate (see Section 9.2.5 for subjects in Groups 1-4, and Section 9.3.5 / Section 9.5.5 for HD subjects in Group 5). Any subject withdrawn due to an AE (whether serious or non-serious) or clinically significant abnormal laboratory test values will be evaluated by the PI or a monitoring physician and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels, as judged by the PI.

Subjects withdrawn for reasons other than drug-related AEs with fewer than 4 PK samples within 24 hours of dosing will be replaced. Subjects who drop-out/are withdrawn before taking any study drug will be replaced.

8. TREATMENT OF SUBJECTS

8.1. Study Medications

Each subject in Groups 1-4 will receive a single 200 mg dose of Minocin IV over 60 minutes. Subjects in Group 5 will receive a single dose of Minocin IV in Period 1 and another single dose in Period 2.

8.1.1. Minocin IV

Minocin IV will be supplied as a sterile lyophilized powder in single-use 10 mL glass vials. Each vial contains 108 mg of minocycline hydrochloride equivalent to 100 mg of minocycline. Two vials will be prepared for each dose to give 200 mg of minocycline.

Each dose will be reconstituted and further diluted in 100 mL of 0.9% Sodium Chloride Injection and administered as a constant rate IV infusion over 1 hour via a single dedicated peripheral venous line. If a peripheral line is not an option and a central line is in place then this can be used, provided that an appropriate flush is used. Details of Minocin IV preparation and administration are included in the study Pharmacy Manual.

8.1.2. Packaging and Labeling

Minocin IV will be provided by the Sponsor. Infusion bags of normal saline will be provided by the study site pharmacy.

Medication labels will comply with regulatory requirements.

8.1.3. Storage

Minocin IV will be stored in a secure area at room temperature (20 to 25°C). Once reconstituted and diluted into an IV bag, Minocin IV may be stored at either room temperature for up to 4 hours or refrigerated at 2 to 8°C (36 to 46°F) for up to 24 hours. Access should be strictly limited to the study pharmacists or designees.

Further details of Minocin IV storage can be found in the Pharmacy Manual.

8.1.4. Accountability

The Investigator or designee must maintain an inventory record of Minocin IV received and all doses administered to assure the regulatory authorities and the Sponsor that the study drug will not be dispensed to any person who is not a subject under the terms and conditions set forth in this protocol. Study drug accountability forms and specific instructions can be found in the Pharmacy Manual.

The Minocin IV supplied for use in this study is to be prescribed only by the PI or designated sub-investigators and may not be used for any purpose other than that outlined in this protocol.

Used (empty) study drug vials may be destroyed on site following recording of dosing on the master and individual subject accountability logs by the pharmacist or designee.

All unused Minocin IV will be destroyed on site once it has been inventoried and the monitor has reviewed the accountability records. In the event that Minocin IV needs to be

returned for any other reason, the site will receive a written request listing the lot number(s) to be returned and the reason for the return request.

8.2. Concomitant Medications

All medications taken during the 14 days prior to dosing will be recorded and reviewed by the PI or their designee.

8.2.1. Permitted Concomitant Medications

During the study, 1 gram per day or less of acetaminophen/paracetamol and low dose ASA (i.e., ≤ 325 mg per day) are permitted.

Acetaminophen/paracetamol may be administered orally at the discretion of the PI or their designee for intercurrent illness or AEs. If needed on dosing day, acetaminophen/paracetamol should not be taken until at least 2 hours after dosing.

For subjects with renal insufficiency, concomitant medications required to treat underlying renal disease or medical conditions related to renal disease are permitted.

Medications required to treat other pre-existing comorbidities and medical conditions (not related to renal disease) are permitted, provided that dosing is stable for 3 weeks prior to Day -1 and the medications are not specified in Section 8.2.2, Prohibited Concomitant Medications.

Oral contraceptives are permitted for birth control.

Doses of concomitant medications (except hormonal contraceptives, hormone replacement therapy for females, and insulin) must be stable for 3 weeks prior to Day -1. Minor dose changes consistent with treatment practices may be permitted at the discretion of the Sponsor's Medical Monitor.

8.2.2. Prohibited Concomitant Medications

With the exception of those medications listed in Section 8.2.1 Permitted Concomitant Medications, the use of any other prescription or nonprescription drugs, grapefruit/grapefruit juice, or dietary or herbal supplements will be prohibited for 14 days prior to Day -1 until discharge.

Several drugs, such as cimetidine, trimethoprim, corticosteroids, pyrimethamine, phenacemide, salicylates, and active vitamin D metabolites, have been reported to increase plasma creatinine without influencing its glomerular filtration [Andreev E. et al, 1999]. These medications are prohibited for 30 days prior to the first dose of study drug through the last PK sample.

If drug therapy other than that specified by the protocol is taken, a joint decision will be made by the PI and Sponsor to continue or discontinue the subject.

8.3. Restrictions

Consumption of foods and beverages containing the following substances will be prohibited as indicated:

- **Alcohol**: Beverages containing alcohol should not be consumed 48 hours or less prior to Day -1 until the end of the study.

8.4. Blinding

This is an open-label study.

9. SCHEDULE AND SEQUENCE OF PROCEDURES

The Study Schedule of Events Tables are outlined in Section 1.1, which summarize the study assessments by time point. A schematic diagram of the trial design is provided in Section 2.

The sample times for assessments/procedures are in relation to the start of drug infusion.

9.1. Screening Period (Day -28 to Day -1)

9.1.1. Screening

Screening will begin within 28 days prior to first dosing. The subject informed consent will be obtained prior to any study procedures being performed. Screening Visit can be combined with Day -1 visit. Subjects will have to meet all eligibility criteria before being enrolled in the study.

The following assessments/procedures will be performed at the Screening Visit:

- Informed consent
- Inclusion/exclusion criteria
- Medical history and demographics
- Review of concomitant medications
- BMI calculation (using recorded height and weight)
- Physical examination
- Vital signs assessment (systolic and diastolic blood pressure, pulse, respiratory rate, and temperature)
- 12-lead ECG administration
- Hematology, coagulation, serum chemistry, and urinalysis (for HD subjects, urinalysis is not required)
- Urine drug/alcohol screen (for HD subjects, serum or saliva drug screen is acceptable)
- Serum pregnancy test (women of childbearing potential only)
- Renal function determination using CrCl (calculated by CKD-EPI 2009); however, for HD subjects, study admission will be based on receiving HD therapy 3 times a week for at least 3 months prior to Day 1.

9.1.2. Informed Consent

Prior to any study-related activities, an informed consent form (ICF), approved by a regional ethics committee (EC), must be personally signed and dated by the subject. The format and content of the ICF must be agreed upon by the Investigator(s), appropriate regional EC, and Sponsor or designee. The subject's original signed and dated ICF (together with any subsequent amended versions approved by the regional EC must be

retained by the Investigator in the subject's file. A copy of the original signed and dated ICF must be given to the subject.

9.1.3. Subject Confinement

If a subject meets all of the inclusion and exclusion criteria and provides consent, he/she may be enrolled in the study and will be admitted to the research unit the day before the first dose of study medication. Subjects will remain within the clinic for the duration of the single-dose period until completion of the post-dose procedures on Day 4.

Subjects with HD will participate in two 4-day periods (Periods 1 and 2), and during each period, subjects will be confined to the clinic through Day 4. To separate the periods, a Washout Period will be scheduled to ensure that study drug administration is at least 6 days apart and no more than 14 days apart. Subjects are not required to be in the clinic during the
Washout Period.

9.2. Study Conduct for Groups 1-4

9.2.1. Check-in Procedures (Day -1)

Day -1 procedures, with the exception of triplicate ECG, only need to be repeated if screening was > 3 days prior to Day 1.

Day -1 procedures may be performed on Day 1, pre-dose, at the site's discretion.

Subject eligibility will be reviewed for each subject to ensure that subjects remain eligible for the study since screening.

The following assessments/procedures will be performed:

- Review of inclusion/exclusion criteria
- Review of concomitant medications and changes to medical history
- Review of medical history and update with any new information since screening
- Weight recorded and BMI calculated (using height from screening)
- Physical examination including components needed to calculate the Charlson Comorbidity Index
- Vital signs: systolic and diastolic blood pressure, pulse, temperature, and respirations
- 12-lead ECG (performed in triplicate)
- Hematology, coagulation, serum chemistry, and urinalysis
- Urine drug screen
- Alcohol breath test (only if subject is suspected of being under the influence of alcohol

- Serum pregnancy test

9.2.2. Single-dose Administration of Minocin IV (Day 1)

The following assessments/procedures will be performed pre-dose on Day 1 (only required if Day -1 procedures are completed outside noted time windows):

- Review of concomitant medications and changes to medical history
- Review of AEs;
- Vital signs: systolic and diastolic blood pressure, pulse, respiration rate, and temperature before dosing, and at the following times post-dose: 1 and 4 hours
- 12-lead ECG before dosing and at 4 hours post-dose
- Urine or serum pregnancy test

Once all pre-dose assessments are completed, the Minocin IV infusion can begin. All subjects will receive 200 mg Minocin IV infused over 1 hour

- Plasma samples will be collected for PK assessments at the following time points: pre-dose (0), 1 (end-of-infusion), 2, 4, 8, 12, and 18 hours after dosing
- Review of AEs
- 24 hour urine collection for creatinine clearance

9.2.3. Ongoing Clinical Assessment (Day 2)

The following assessments/procedures will be performed on Day 2:

- Vital signs: systolic and diastolic blood pressure, pulse, respiration rate, and temperature at 24 hours post-dose
- 12-lead ECG at 24 hours post-dose
- Review of concomitant medications
- Review of AEs
- Plasma samples will be collected for PK assessments at 24 and 36 hours after dosing

9.2.4. Ongoing Clinical Assessment (Day 3)

The following assessments/procedures will be performed on Day 3:

- Vital signs: systolic and diastolic blood pressure, pulse, respiration rate, and temperature at 48 hours post-dose
- Review of concomitant medications
- Review of AEs
- Plasma samples will be collected for PK assessments at 48 hours after dosing

9.2.5. Final In-patient Clinical Assessment (Day 4)

Subjects will remain confined until all assessments have been completed on Day 4, or at early termination. Should any subject withdraw or be withdrawn from the study, all the end-of-study evaluations scheduled for Day 4 (plus plasma PK sample collection) should be performed at the time of discontinuation, if possible (see Section 9.7).

- Review of concomitant medications
- Physical examination
- Vital signs: systolic and diastolic blood pressure, pulse, respiration rate, and temperature
- 12-lead ECG
- Hematology, coagulation, serum chemistry, and urinalysis
- Serum pregnancy test
- Review of AEs
- Plasma samples will be collected for PK assessments at 72 hours post dosing

9.2.6. Follow-Up Telephone Call (Day 6 + ≤ 2 days)

On Day 6 (plus a ≤ 2 day window), subjects will be contacted once by telephone to determine the status of ongoing AEs and concomitant medications. Subject-reported data will be documented in the subject's study-specific files and included in the clinical database, as appropriate.

9.3. Study Conduct for Group 5 HD Subjects – Period 1: Dose Administration Prior to Dialysis

In order to determine the impact of HD on the PK of Minocin IV, PK blood samples will be collected in the same subjects (Group 5) at a time when Minocin IV is administered immediately prior to HD and again at a time when Minocin IV is administered immediately following HD. The two administrations will be separated by a Washout Period.

For Group 5 during Period 1, study drug administration will occur prior to dialysis on Day 1, and subjects will remain in the clinical center until completion of all study assessments on Day 4. Subsequent dialysis will be done at either Day 3 or Day 4, following as close as possible to the subject's usual HD therapy schedule (when applicable).

For Group 5 during Period 2, dialysis will occur prior to study drug administration on Day 1, and subjects will remain in the clinical center until completion of all study assessments on Day 4. Subsequent dialysis will be done at either Day 3 or Day 4, following as close as possible to the subject's usual HD therapy schedule (when applicable).

Periods 1 and 2 do not have to occur in sequence for any given subject. Therefore, the final in-patient evaluations will be on Day 4 of Period 1 or 2, whichever period occurs second.

Dialysis will be done following subject's usual HD therapy schedule throughout the Washout Period and follow-up period.

Should any subject withdraw or be withdrawn from the study, all the end-of-study evaluations scheduled for Day 4 (plus plasma PK sample collection) should be performed at the time of discontinuation, if possible (see Section 9.7).

9.3.1. Check-in Procedures for HD Subjects (Period 1, Day -1)

The Day -1 procedures may be performed on Day 1, pre-dose at the site's discretion.

- Inclusion/Exclusion Criteria should be reviewed at Day -1 of whichever period is conducted first (Day -1 before the subject's first day of dosing)
- AEs that occurred during the Washout Period should be reviewed at Day -1 of whichever period is conducted second (Day -1 before the subject's second day of dosing).
- Review of concomitant medications
- Review of medical history and update with any new information since screening (only for Day -1 of whichever period is conducted first)
- Weight recorded and BMI calculated (using height from screening)
- Physical examination including components needed to calculate the Charlson Comorbidity Index
- Vital signs: systolic and diastolic blood pressure, pulse, temperature, and respirations
- 12-lead ECG (to be performed in triplicate at Day -1 of whichever period is conducted first [Day -1 before the subject's first day of dosing])
- Hematology, coagulation, and serum chemistry
- Saliva drug screen
- Alcohol breath test (only if subject is suspected of being under the influence of alcohol)
- Serum pregnancy test (only for Day -1 of whichever period is conducted first)

9.3.2. Single-dose Administration of Minocin IV (Period 1, Day 1)

The following assessments/procedures will be performed on Pre-Dose on Day 1 (only required if Day -1 procedures are completed outside noted time windows):

- Review of concomitant medications

- Vital signs: systolic and diastolic blood pressure, pulse, respiration rate, and temperature before dosing, and at the following hours post-dose: 1, and 4 hours
- 12-lead ECG before dosing and at 4 hours post-dose
- The study drug IV infusion lock and PK sampling lock should be placed in the arm opposite of the HD access. The PK sampling lock should be placed distal to the IV infusion lock to prevent contamination of the PK samples. If a peripheral line is not an option and a central line is in place then this can be used, provided that an appropriate flush is used. Instances where the infusion and/or PK lock cannot be placed in this manner should be discussed with the Sponsor to ensure the infusion and sample collection is not compromised.
- Once all pre-dose assessments/procedures are completed, the Minocin IV infusion can begin. All subjects will receive 200 mg Minocin IV infused over 1 hour.
- The infusion should be scheduled so that infusion ends approximately 2 hours **BEFORE** dialysis is started
- Plasma samples will be collected for PK assessments at the following time points: pre-dose (0), 1 (end-of-infusion), 2, 4, 8, 12, and 18 hours after dosing
- Transport subject from the clinical center to the dialysis center (if required)
- Complete HD therapy session using a non-reuse dialyzer
- Collect a pre-spent dialysate sample prior to initiating HD and then hourly dialysate samples (with aliquots) during dialysis and through the end of dialysis
- Upon completion of dialysis, return the subject to the clinical center
- Review of AEs

9.3.3. Ongoing Clinical Assessment (Period 1, Day 2)

The following assessments/procedures will be performed on Day 2, period 1:

- Review of concomitant medications
- Vital signs: systolic and diastolic blood pressure, pulse, respiration rate, and temperature at 24 hours post-dose
- 12-lead ECG at 24 hours post-dose
- Review of AEs
- Plasma samples will be collected for PK assessments at 24 and 36 hours after dosing

9.3.4. Ongoing Clinical Assessment (Period 1, Day 3)

The following assessments/procedures will be performed on Day 3, period 1:

- Review of concomitant medications
- Vital signs: systolic and diastolic blood pressure, pulse, respiration rate, and temperature at 48 hours post-dose
- Review of AEs
- Plasma samples will be collected for PK assessments at 48 hours after dosing
- HD therapy can be completed on Day 3 or at Day 4, before or after other procedures, per the subject's usual frequency of HD therapy.
  - Complete HD therapy session using a non-reuse dialyzer

9.3.5. Ongoing Clinical Assessment (Period 1, Day 4)

Subjects will remain confined until all assessments have been completed on Day 4 of period 1.

The following assessments/procedures will be performed on Day 4:

- Review of concomitant medications
- Physical examination
- Vital signs: systolic and diastolic blood pressure, pulse, respiration rate, and temperature at 72 hours
- Review of AEs
- Plasma samples will be collected for PK assessments at 72 hours after dosing
- HD therapy can be completed on Day 3 or at Day 4, before or after other procedures, per the subject's usual frequency of HD therapy.
  - Complete HD therapy session using a non-reuse dialyzer
- Release from clinical center

Because Periods 1 and 2 do not have to occur in sequence, this visit may be a subject's final in-patient clinical assessment visit. If this visit is the final in-patient clinical assessment visit for a subject, the following additional assessments should be conducted:

- 12-lead ECG at 72 hours post-dose
- Hematology, coagulation, and serum chemistry
- Serum pregnancy test

9.4. Washout Period

The Washout Period will occur between the 2 periods regardless of the sequence of periods. Therefore, subjects will be released from the clinical center after completion of all study assessments on Day 4 of Period 1 or 2, whichever period is first. The Washout Period will be scheduled to ensure that study drug administration is at least 6 days apart and no more than 14 days apart, so it will be between 1 and 9 days in duration.

Subjects will be encouraged to contact the site and provide details of any AEs that occur during the Washout Period. Adverse events that occurred during the Washout Period will be reviewed at the time of check-in for whichever period is second.

9.5. Study Conduct for Group 5 HD Subjects – Period 2: Dialysis Prior to Dose Administration

9.5.1. Check-in Procedures (Period 2, Day -1)

The following assessments/procedures will be performed:

- Inclusion/Exclusion Criteria should be reviewed at Day -1 of whichever period is conducted first (Day -1 before the subject's first day of dosing)
- AEs that occurred during the Washout Period should be reviewed at Day -1 of whichever period is conducted second (Day -1 before the subject's second day of dosing).
- Review of adverse events (only AEs related to the study should be captured on Day -1 of whichever period is conducted first for a subject, and unrelated events should be captured as medical history)
- Review of concomitant medications
- Review of medical history and update with any new information since screening (only for Day -1 of whichever period is conducted first)
- Weight recorded and BMI calculated (using height from screening)
- Physical examination including components needed to calculate the Charlson Comorbidity Index
- Vital signs: systolic and diastolic blood pressure, pulse, temperature, and respirations
- 12-lead ECG (to be performed in triplicate at Day -1 of whichever period is conducted first [Day -1 before the subject's first day of dosing])
- Hematology, coagulation, and serum chemistry
- Saliva drug screen
- Alcohol breath test (only if subject is suspected of being under the influence of alcohol)
- Serum pregnancy test (only for Day -1 of whichever period is conducted first)

9.5.2. Single-dose Administration of Minocin IV (Period 2, Day 1)

The following assessments/procedures will be performed Pre-Dose on Day 1 (only required if Day-1 procedures are completed outside noted time windows):

- Review of concomitant medications
- Review of AEs
- Vital signs: systolic and diastolic blood pressure, pulse, respiration rate, and temperature before dosing, and at the following hours post-dose: 1, and 4 hours
- 12-lead ECG before dosing and at 4 hours post-dose
- A pre-spent dialysate sample is collected prior to initiating HD
- Complete HD therapy session using a non-reuse dialyzer
- Transport subject from the clinical center to the dialysis center and back once HD is complete (if transportation to another unit is required)
- The study drug IV infusion lock and PK sampling lock will be placed in the arm opposite of the HD access. The PK sampling lock will be placed distal to the IV infusion lock to prevent contamination of the PK samples. If a peripheral line is not an option and a central line is in place then this can be used, provided that an appropriate flush is used. Instances where the infusion and/or PK lock cannot be placed in this manner should be discussed with the Sponsor to ensure the infusion and sample collection is not compromised.
- Once all pre-dose assessments/procedures and dialysis are completed the Minocin IV infusion can begin. All subjects will receive 200 mg Minocin IV infused over 1 hour.
- The infusion should be scheduled so that infusion begins approximately 2 hours **AFTER** dialysis is completed
- Plasma samples will be collected for PK assessments at the following time points: pre-dose (0), 1 (end-of-infusion), 2, 4, 8, 12, and 18 hours after dosing

9.5.3. Ongoing Clinical Assessment (Period 2, Day 2)

The following assessments/procedures will be performed on Day 2, period 2:

- Review of concomitant medications
- Vital signs: systolic and diastolic blood pressure, pulse, respiration rate, and temperature at 24 hours post-dose
- 12-lead ECG at 24 hours post-dose
- Plasma samples will be collected for PK assessments at 24 and 36 hours after dosing
- Review of AEs

9.5.4. Ongoing Clinical Assessment (Period 2, Day 3)

The following assessments/procedures will be performed on Day 3, period 2:

- Review of concomitant medications
- Vital signs: systolic and diastolic blood pressure, pulse, respiration rate, and temperature at 48 hours post-dose
- Review of AEs
- Plasma samples will be collected for PK assessments at 48 hours after dosing
- HD therapy can be completed on Day 3 or at Day 4, before or after other procedures, per the subject's usual frequency of HD therapy.
    - Complete HD therapy session using a non-reuse dialyzer

9.5.5. Ongoing Clinical Assessment (Period 2, Day 4)

Subjects will remain confined until all assessments have been completed on Day 4, period 2.

The following assessments/procedures will be performed on Day 4:

- Review of concomitant medications
- Physical examination
- Vital signs: systolic and diastolic blood pressure, pulse, respiration rate, and temperature at 72 hours
- Review of AEs
- Plasma samples will be collected for PK assessments at 72 hours after dosing
- HD therapy can be completed on Day 3 or at Day 4, before or after other procedures, per the subject's usual frequency of HD therapy.
    - Complete HD therapy session using a non-reuse dialyzer
- Release from clinical center

Because Periods 1 and 2 do not have to occur in sequence, this visit may be a subject's final in-patient clinical assessment visit. If this visit is the final in-patient clinical assessment visit for a subject, the following additional assessments should be conducted:

- 12-lead ECG at 72 hours post-dose
- Hematology, coagulation, and serum chemistry
- Serum pregnancy test

9.6. Study Conduct for Group 5 HD Subjects – Follow-Up Telephone Call (last Period Day 6 + ≤ 2 days)

Following the final in-patient clinical assessment visit (Day 4 of Period 1 or 2, whichever period occurs second), subjects will be contacted by telephone for study follow-up. On

Day 6 (plus a ≤ 2 day window), subjects will be contacted once by telephone to determine status of ongoing AEs and concomitant medications. Subject-reported data will be documented in the subject's study-specific files and included in the clinical database, as appropriate.

9.7. Early Termination

An Early Termination Visit is required for any subject that discontinues the study prior to Day 4 (or the final period Day 4, for Group 5 HD subjects). All Day 4 visit procedures should occur during the Early Termination Visit, as well as the collection of any PK samples (if applicable). A follow-up phone call should occur approximately 3 days from the Early Termination Visit.

10. PROTOCOL ASSESSMENTS

10.1. Assessment of Safety

10.1.1. Adverse Events

Subjects will be carefully monitored for AEs by the Investigator during the designated study period (see Section 11 for details).

10.1.2. Body Mass Index (BMI)

BMI will be calculated using the following equation:

BMI= Weight (kg)/Height (m^2)

10.1.3. Vital Signs

Vital signs assessments will include systolic and diastolic blood pressure, pulse, body temperature, and respirations.

Subjects should be resting in a semi-recumbent position for at least 5 minutes prior to and during vital signs measurements.

10.1.4. Physical Exam and Charlson Comorbidity Index

Physical examinations include, at a minimum, assessment of the following systems: skin, head, ears, eyes, nose and throat, respiratory system, cardiovascular system, gastrointestinal system, neurological condition, blood and lymphatic systems, and the musculoskeletal system. A licensed physician will conduct the examinations.

Presence or history of the components of the Charlson Comorbidity Index will also be collected at screening and Day -1. The Charlson Comorbidity Index involves recording specific medical conditions, (e.g., myocardial infarction, dementia, chronic obstructive pulmonary disease, etc.) against the index to provide an overall score and to estimate prognosis [Charlson, Mary E. et al., 1987].

Physical examination may be performed at various unscheduled time points if deemed necessary by the Investigator.

10.1.5. ECG

12-lead ECGs will be assessed.

Triplicate 12-lead ECGs, each separated by at least 1 minute, will be taken at Day -1 (For Group 5: Day -1 of the first period conducted). ECGs will be taken following resting in the semi-recumbent position for 5 minutes. The average value for the triplicate will be utilized for assessing QTc exclusion criteria.

All subsequent post-dose ECGs will be single readings. However, if one of the following occurs, then the ECG will be repeated in triplicate (separated by at least 1 minute):

- QTc increase from baseline triplicate average > 30 msec
- QRS duration > 130 msec

- PR interval > 240 msec

If the "recheck" triplicate's average is still above these parameters, then the Investigator shall be notified for decision on further action.

The same model of ECG machine should be used for check-in and post-dose readings for all subjects.

A +/- 10 minute time window is permitted.

ECGs will be interpreted and signed and dated by the PI or qualified designee. The ECGs will be classified as normal, having a clinically insignificant abnormality (NCS), or having a clinically significant abnormality (CS). In addition, ECG parameters of ventricular rate, PQ or PR interval, QRS duration, and QT interval (corrected and uncorrected) will be noted on the eCRF.

All CS findings will be recorded as AEs.

10.1.6. Clinical Laboratory Tests

Clinical laboratory tests will be conducted at the site's local lab. Lab results and lab reports will be kept as source documents. Abnormal lab ranges must be documented as CS or NCS by a study Investigator and filed with the source documents.

At a minimum, the following lab tests should be performed during the designated time points:

10.1.6.1. Hematology

Hemoglobin, Hematocrit, White blood cell count (with automated differential), Red blood cell count, Platelet count

10.1.6.2. Coagulation

Activated partial thromboplastin time (aPTT), international normalized ratio (INR)

10.1.6.3. Chemistry

Urea, Serum creatinine, Total bilirubin, Direct bilirubin, Alkaline phosphatase, Aspartate aminotransferase, Alanine aminotransferase, Albumin, Total protein, Glucose, Calcium, Chloride, Sodium, Magnesium, Potassium, Uric acid, Lactate dehydrogenase, Phosphorus

10.1.6.4. Urinalysis

Midstream urine sample analyzed by dipstick (Note: microscopic examination of sediment will only occur if a strong positive result is observed).

10.1.6.5. Human Chorionic Gonadotropin (Pregnancy Test)

Pregnancy tests are required for women of childbearing potential only.

10.1.6.6. Testing for Drugs of Abuse

Amphetamines, barbiturates (not in saliva test screen), benzodiazepines, cannabinoids, cocaine, methadone, and opiates will be tested in urine for Groups 1-4, in saliva for Group 5.

10.1.6.7. Breath Alcohol Testing

Breath alcohol test is only required for subjects suspected of being under the influence of alcohol.

10.1.6.8. Creatinine Clearance

Estimated glomerular filtration rate will be calculated at screening by CKD-EPI 2009 equation (subjects with renal insufficiency) or Cockroft-Gault (subjects with normal renal function) equation, to assign subjects to group [Levey, A. S. et al, 2009].

For subjects in Groups 1, 2, 3, and 4, a 24 hour urine collection will be done on Day 1 to determine creatinine clearance for further analysis of data.

10.1.7. Birth Control Measures

Female subjects that are not postmenopausal are expected to use highly effective birth control measures as defined by the European Heads of Medicines Agencies Clinical Trial Facilitation Group (CTFG) between randomization and for 7 days after the completion of the study. Highly effective methods of birth control are [UK MHRA, 2014]:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
    - oral (in combination with male condom)
    - intravaginal
    - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation
    - oral (in combination with male condom)
    - injectable
    - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomized partner
- sexual abstinence

There is no evidence of a drug-drug interaction between tetracyclines and hormonal contraceptives [RCOG, 2012]. There is some possibility that antibiotics in general can

change the gut flora and potentially inhibit absorption of hormonal contraceptives, but there is no recommendation to practice additional barrier contraception with these agents. In consideration of CTFG guidance [UK MHRA, 2014] and in the absence of data from a clinical PK interaction study, subjects in this trial must only use oral hormonal contraceptives when in combination with male condom.

10.2. Assessment of Efficacy

Efficacy will not be assessed in this study.

10.3. Assessment of Pharmacokinetics

The PK sample collection times are all from the start of the study drug infusion.

10.3.1. Sampling and Processing

For the PK blood samples, the following deviation windows from the actual sampling times are permitted:

Nominal Time Reporting Standard

- > 0-4 h - 2 minutes
- > 4 h +/- 5 minutes

After collection of the PK samples, blood will be centrifuged and plasma collected and frozen. For specific collection and storage procedures, please refer to the Study PK Manual.

11. ADVERSE EVENTS

11.1. Definitions

11.1.1. Adverse Event

Adverse Event (AE): Any untoward medical occurrence in a subject or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Planned hospital admissions and/or surgical operations for an illness or disease that existed before the study drug was given or the subject was randomized in a clinical study are not to be considered AEs.

Adverse events or abnormal test findings will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the Sponsor/Investigator.

The date and time of onset, duration, and outcome (resolved, improved, unchanged, worse, fatal, or unknown/lost to follow-up) of each event will be noted. All AEs will be reported in detail as indicated on the eCRF.

11.1.1.1. AE Severity

The severity of an AE will be assessed by the Investigator. The Investigator should ensure that any subject experiencing an AE receives appropriate medical support until the event resolves.

The Investigator and/or sub-investigator will classify the severity of AEs according to Common Terminology Criteria for Adverse Events (CTCAE) as follows:

Grade 1 = mild

Grade 2 = moderate

Grade 3 = severe

Grade 4 = life-threatening or disabling

Grade 5 = death related to AE

If a condition cannot be identified in the CTCAE, the following definitions will be used:

Mild: asymptomatic or mild symptoms OR clinical or diagnostic observations only OR intervention not indicated.

Moderate: minimal, local or noninvasive intervention indicated OR limiting age appropriate instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).

Severe or medically significant but not immediately life-threatening:

hospitalization or prolongation of hospitalization indicated OR disabling OR limiting selfcare activities of daily living (e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications, not being bedridden).

Life-threatening: urgent intervention indicated.

11.1.1.2. Study Drug Causality

The relationship of an AE to study drug will be assessed with consideration to the following criteria:

- Temporal relationship to the initiation of study medication
- Response of the event to withdrawal of study medication
- AE profile of concomitant therapies
- Clinical circumstances during which the AE occurred
- Subject's clinical condition and medical history

Categorization of causality will be designated by the Investigator as stated below:

Reasonable possibility - There are facts (evidence) or arguments to suggest a causal relationship between the event and the investigational medicinal product (IMP).

No Reasonable possibility - There are few to no facts (evidence) or arguments to suggest a causal relationship between the event and the IMP.

11.1.2. Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening, i.e., the subject was, in the opinion of the Investigator, at immediate risk of death from the event as it occurred (it does not include an event that, had it occurred in a more severe form, might have caused death),
- Results in a significant, persistent or permanent change, impairment, damage or disruption in the subject's body function/structure, physical activities and/or quality of life,
- Requires in-subject hospitalization or prolongs hospitalization,
- Is a congenital anomaly/birth defect, or
- Is another medically significant event where medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that

might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

- A distinction should be drawn between serious and severe AEs. Severity is an estimate or measure of the intensity of an AE, while the criteria for serious AEs are indications of adverse subject outcomes for regulatory reporting purposes. A severe AE need not necessarily be considered serious and a serious AE need not be considered severe. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a myocardial infarction (MI) that may be considered minor could also be an SAE if it prolonged hospitalization.

11.1.3. Medication Errors

Medication error refers to any unintended error in the dosing and/or administration of the study drug as per instructions in the protocol. Medication errors generally fall into 4 categories as follows:

- wrong study drug;
- wrong dose (including dosing regimen, strength, form, concentration, amount);
- wrong route of administration;
- wrong subject (i.e., not administered to the intended subject)

Medication Errors include occurrences of overdose and underdose of the study drug, and abuse and misuse.

Overdose: Unintentional administration of a quantity of the study drug given per administration or per day that is above the maximum recommended dose according to the reference safety information or protocol for the study drug. This also takes into account cumulative effects due to overdose.

Underdose: Unintentional administration of a quantity of the study drug given per administration or per day that is under the minimum recommended dose according to the reference safety information or protocol.

Abuse of a medicinal product: Persistent or sporadic, intentional excessive use of medicinal products that is accompanied by harmful physical or psychological effects.

Misuse: Intentional and inappropriate use of a study drug not in accordance with the prescribed or authorized dose, route of administration, or not within the legal status of its supply.

11.1.4. Adverse Event of Special Interest (AESIs)

An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the Sponsor's study drug or program, which warrants ongoing monitoring and rapid communication by the Investigator to the Sponsor. Such an event might warrant further investigation in order to characterize and understand it.

There are no AESIs identified for the study drug Minocin IV in this protocol.

11.1.5. Special Situations

Special Situations is a comprehensive term that encompasses safety information related to products for which global regulations require collection, evaluation, and/or reporting to regulatory authorities.

Additional special situations not previously defined include the following:

- Pregnancy/lactation exposures with or without any AEs related to the parent or child
- Suspected transmission via a medicinal product of an infectious agent
- Drug interactions
- Occupational exposure
- Unexpected benefit

11.2. Procedure for Non-Serious Adverse Event Recording

All non-serious AEs that occur from the first administration of IMP through the Follow-Up Call (Day 6 [+ ≤ 2]), must be assessed and recorded on the source documents and eCRF regardless of causal relationship to the study drug.

All AEs, occurring throughout the study or at the Final Visit, considered possibly or probably related to the study drug, will be followed until the subject is stable or the AE is resolved.

11.3. Procedure for Serious Adverse Event Reporting

Note: This procedure may need to be followed for reporting Special Situations.

All SAEs that occur from the first administration of IMP through the Follow-Up Call (Day 6 [+ ≤ 2]), must be reported to the Sponsor's Global Pharmacovigilance (GPV) Department or its designated representative within 24 hours of awareness of the event using the provided study specific SAE Report Form. In addition to completing the SAE Report Form, each SAE must be entered on the appropriate page of the eCRF.

When death occurs with an SAE, the cause of death must be reported as an SAE. "Fatal" will be reported as the outcome for these events.

The Investigator must assess the causality for each SAE/AESI.

The Sponsor or its designated representative will contact the Investigator, if necessary, to clarify any of the event information. The Investigator should provide any follow-up information for the event to the Sponsor or its designated representative on an updated SAE/AESI Report Form as soon as it becomes available.

If the Investigator is notified of a SAE/AESI that occurs post-study period, that he or she wishes to report to the Sponsor or its designated representative (e.g., an event suspected to be causally related to study drug), the event should be reported through the process described above.

Where appropriate, if required by local regulations or procedures, the Investigator should report these events to the EC and/or national regulatory authority in addition to the Sponsor.

11.4. Procedure for Medication error reporting for Study Drugs

Medication errors with or without an associated AE as described in Section 11.1.3 need to be recorded as medication errors in the eCRF.

Medication errors with an associated SAE need to be recorded as medication errors in the eCRF and reported to the Sponsor's GPV Department or its designated representative as described in Section 11.1.2.

A mis-dosing protocol deviation (refer to Section 15.3) would need to be reported as a medication error if it was an "unintended error" as defined in Section 11.1.3.

11.5. Procedure For Reporting Adverse Events Of Special Interest

There are no AESIs identified for the study drug, Minocin IV, in this protocol.

11.6. Procedure For Reporting Pregnancies/Lactation Exposure

Occurrences of pregnancy/lactation exposure in a study subject or study subject's partner should be reported within 24 hours using the Pregnancy/Lactation Exposure Reporting form. In cases where a pregnancy/lactation exposure occurs with a SAE, the Serious Adverse Event Report form should be used to report the SAE and the Pregnancy Reporting Form should be used to report the pregnancy. When a pregnancy occurs without any concurrent SAE, the Pregnancy Reporting Form may be submitted alone. The pregnancy must be followed through to outcome of pregnancy. Any pregnancy that occurs from the first administration until 30 days after last dose needs to be reported.

11.7. Procedure For Reporting Special Situations

If there is an occurrence of a Special Situation event, defined in Section 11.1.4, report this occurrence to the Sponsor as per Section 11.3, Procedure for Serious Adverse Event Reporting. Note: The Special Situations event does not need to be serious to be reported on the SAE/AESI Report form.

12. DATA COLLECTION

An electronic data capture (EDC) system will be used for this trial. The IT infrastructure and data management staff will be supplied by Clinical Trials Center Cologne. All users will be trained on the technical features of the EDC as well as the content of the eCRF via an e-learning course prior to gaining access to the EDC. A UserID/Password will be granted after training. This ID is not to be shared amongst the study staff. All users must have a unique account to enter or review data. The eCRF should be filled out by the site 5 days after the Day 4 visit (of each period for Group 5) and 3 days after the Day 5-7 follow-up. It is not expected that the eCRF will serve as source for any data collected in this trial. If there is a reason for a site to do so, it must be approved by Sponsor and documented in the site files.

Prior to the database being locked, the Investigator or designee will review, approve and sign/date each completed eCRF. This signature serves as attestation of the Investigator's responsibility for ensuring that all data entered into the eCRF are complete, accurate and authentic. After the end of the trial, a copy of the data will be provided to the site. This copy will contain the final data, an audit trail of activity on the data, and any queries and answers that were posted for data clarification.

13. STATISTICAL PLAN

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP). The SAP will be prepared by the Institute of Medical Statistics, Informatics and Epidemiology and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate and included in the plan.

13.1. Sample Size

This sample size was selected based on previous experience attempting to minimize the number of subjects on study drug while obtaining sufficient PK data from different subjects to produce a good estimate of exposure. It has been determined adequate to meet the study objectives. Eight subjects per group are planned, hence n = 40 subjects in total.

13.2. Randomization

This is an open-label, single-dose study, with only one active arm and no randomization.

13.3. General Statistical Considerations and Definitions

13.3.1. General Statistical Methods

Descriptive statistical analyses will be performed. Number of subjects (n), arithmetic mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum (min), and maximum (max) will be given for quantitative variables. Absolute and relative frequencies are given for qualitative variables. If variables are measured over time, each time point will be summarized. Summaries of the number and frequency and/or raw data listings of AEs will be presented. 95% confidence intervals will be given where reasonable. An analysis of the PK and AEs will be performed based on gender. No interim analysis is planned.

13.3.2. Analysis Population

The following populations will be used for data analyses and/or presentation.

13.3.2.1. Intent-to-Treat (ITT) Population

All subjects enrolled into the trial. Classification will be based on the subject's group (degree of renal function).

13.3.2.2. Modified Intent-to-Treat (mITT) Population

All ITT subjects who receive at least one dose of study drug.

13.3.2.3. PK Population

All subjects who have any valid samples measured for study drug levels. This will be used for PK analysis.

13.3.2.4. Per-Protocol (PP) Population

All mITT subjects who received their assigned study drug without major protocol violations. The PP population will be finalized during a data review before database lock. This will be the supportive population for the analyses.

13.3.2.5. Safety Population

The safety set will be the mITT population (for definition see Section 13.3.2.2).

13.3.3. Missing Data Handling

Unless otherwise specified, missing data will not be imputed and will be excluded from the associated analysis.

13.4. Statistical Analyses

13.4.1. Demographic and Background Characteristics

Subject demographics and baseline characteristics will be summarized descriptively by subject's group (degree of renal function) using the ITT, mITT, PK, and PP.

13.4.2. Study Drug and Concomitant Medications

Listings and frequency counts of each prior (pre-baseline) medication and concomitant (baseline or later) medication will be provided by subject's group (degree of renal function). Medications will be coded using the most updated version of the World Health Organization (WHO) Drug Dictionary available (e.g., version WHODDE 01 DEC 2015 or later).

13.4.2.1. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) dictionary will be used for coding AEs. The current version will be used when coding is started. All AEs are listed by subject with severity, relationship to study drug, and subject's group.

The number (percentage) of subjects reporting AEs and the total number (percentage) of AEs will be tabulated by each preferred term, system-organ class, severity, relationship to study drug, and subject's group. AE analysis is done for Safety Population.

13.4.2.2. Laboratory Tests

Laboratory values will be summarized descriptively by group, including changes and percent changes from baseline at each time point.

Numerical values of laboratory parameters from different (if any) local laboratories with different units and normal ranges (if any) will be converted to the conventional units and normalized to a standard set of reference/normal ranges. The normalization process will

be performed and separated by each of the laboratory parameters. A shift analysis by normal range will be done, which counts the number of subjects with a low, normal, or high value at baseline and a low, normal, or high value post-baseline.

13.4.2.3. Vital Signs

Change and percent change from baseline in vital signs will be summarized descriptively at each scheduled time point by treatment group.

13.4.2.4. ECGs

PR, QRS, QT, and QTc intervals will be summarized descriptively. A normal-abnormal shift table will be presented for ECGs. ECG results will be classified using frequency counts for normal, abnormality that is NCS, and CS abnormality by group and time point of collection.

13.4.2.5. Pharmacokinetic Parameters

The plasma concentration-time data for minocycline will be analyzed by non-compartmental methods. Groups are compared regarding plasma $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, C_{max}, and T_{max}. Individual as well as mean time-concentration profiles will be graphed. Statistical analysis of dose proportionality of exposure parameters will be performed.

Detailed methods used and the results obtained will be included in a separate PK report.

14. RECORDS RETENTION

Current EU Directives / Regulations and International Conference on Harmonization (ICH) guidelines collectively require that essential clinical trial documents (including case report forms) other than subject's medical files must be retained for the following time period:

- for at least 15 years after completion or discontinuation of the trial,
- or for at least two years after the granting of the last marketing authorization in the European Community and when there are no pending or contemplated marketing applications in the European Community,
- or for at least two years after formal discontinuation of clinical development of the study drug.

Subject's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution, or private practice. The documents can be retained for a longer period, however, if required by the applicable regulatory requirements or by agreement with the Sponsor.

To comply with these requirements, the Investigator will not dispose of any records relevant to this study without either (1) written permission from the Sponsor or (2) providing an opportunity for the Sponsor to collect such records. The Investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study, including the hard copy or discs received from the Sponsor of the final data. Such documentation is subject to inspection by the Sponsor or its agents, the CA, United States Food and Drug Administration (FDA), and/or other regulatory agencies.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1. Monitoring

The Sponsor has ethical, legal, and scientific obligations to carefully follow this study in accordance with established research principles and applicable regulations. The Investigator, as part of his/her responsibilities, is expected to cooperate with the Sponsor in ensuring that the study adheres to the protocol and ICH GCP requirements.

As part of a concerted effort to fulfill these obligations, the Sponsor's (or Sponsor designees') monitor will visit the center(s) during the study in accordance with the Monitoring Plan set forth for this trial. The Investigator will permit the Sponsor (and designees) to monitor the study as frequently as is deemed necessary and provide access to medical records/source documents to ensure that data are being recorded adequately, that data are verifiable, and that protocol adherence is satisfactory.

15.2. Auditing

The Sponsor (and designees) may conduct audits at the study center(s). Audits will include, but not be limited to, study drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. The Investigator agrees to permit audits conducted at a reasonable time in a reasonable manner.

Regulatory authorities worldwide may also inspect the Investigator during or after the study. The Investigator should contact the Sponsor (and designees) immediately if this occurs, and must permit regulatory authority inspections.

15.3. Protocol Deviations

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of the subject requires immediate intervention, based on the judgment of the Investigator (or a responsible, appropriately trained professional designated by the Investigator). In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the Investigator or designee must contact the Sponsor, or their agent, at the earliest possible time by telephone. This will allow an early joint decision regarding the subject's continuation in the study. The Investigator and the Sponsor will document this decision. The EC will be informed of all protocol changes by the Investigator in accordance with the EC established procedure. No deviations from the protocol of any type will be made without complying with all the EC-established procedures.

The following Protocol Deviations will require additional information in the eCRF explaining why the deviation occurred and what will be done to prevent it from re-occurring:

- Inclusion criteria violation
- Exclusion criteria violation
- Dosing errors

16. ETHICS AND RESPONSIBILITY

This study will be conducted in compliance with the protocol, the Sponsor's standard operating procedures (SOPs) and/or guidelines, the FDA regulations, the ICH GCP guidelines, the Declaration of Helsinki, and other local regulations, as applicable.

16.1. Informed Consent

Written informed consent will be obtained from all subjects before any study-related procedures (including any pre-treatment procedures) are performed. The Investigator(s) has both ethical and legal responsibility to ensure that each subject (and their guardian or legally authorized representative) being considered for inclusion in this study is given a full explanation of the protocol. This shall be documented on a written informed consent form, which shall be approved by the same EC responsible for approval of this protocol. Each informed consent form shall include the elements required by ICH, Part E6, Section 4.8 and any applicable local regulations. The Investigator agrees to obtain approval from the Sponsor of any written informed consent form used in the study, preferably prior to submission to the EC.

Once the appropriate essential information has been provided to the subject and fully explained by the Investigators (or a qualified designee) and it is felt that the subject understands the implications of participating, the subject and the Investigator (or designee) shall sign the EC-approved written informed consent form. The subject shall be given a copy of the signed informed consent form, and the original shall be filed appropriately, according to the institution. A second copy may be filed in the subject's medical record, if allowed by the institution.

16.2. Ethics Committee

This protocol, the written informed consent form, and any materials presented to subjects shall be submitted to the EC identified with this responsibility. Notification in writing of approval must come from the EC chairman or secretary, to the Investigator, either as a letter or as a copy of the appropriate section of the EC meeting minutes where this protocol and associated informed consent form were discussed. The Investigator will not participate in the decision. If the Investigator is an EC member, the written approval must indicate such non-participation in the voting session. The Investigator will submit status reports to the EC as required by the governing body. The EC must be notified by the Investigator in writing of the interruption and/or completion of the study; the Investigator must promptly report to the EC all changes in research (protocol amendments) and will not make such changes without EC approval, except where necessary to eliminate apparent immediate hazards to human subjects. In cases where it is necessary to eliminate immediate hazards to subjects, the EC must then be notified of the change as per local requirements. The Investigator is required to maintain an accurate and complete record of all written correspondence to and received from the EC and must agree to share all such documents and reports with the Sponsor.

17. CONFIDENTIALITY

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without written prior permission from the Sponsor. However, authorized regulatory officials and Sponsor personnel will be allowed full access to the records. All medications provided and subject bodily fluids and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor.

Only unique subject numbers in eCRFs will identify subjects. Their full names may, however, be made known to a product regulatory agency or other authorized official if necessary.

Sponsor commits to comply with all applicable data protection laws and regulations and take all appropriate measures to ensure that subjects' data is processed securely and appropriately. Sponsor adheres to the privacy principles of notice, choice, accountability for onward transfer, security, data integrity, purpose limitation, access, and enforcement regarding the collection, use, and retention of personal information from European Economic Area countries and Switzerland. In addition, Sponsor's Global Commercial General Liability with Umbrella Liability and Global Products / Clinical Trial Liability policy includes coverage for the processing of subjects' data.

18. INVESTIGATOR AGREEMENT

I have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal, and scientific information necessary to conduct this study. I will personally conduct the study as described.

I will provide copies of the protocol to all physicians, nurses, and other professional personnel responsible to me who will participate in the study. I will discuss the protocol with them to assure myself that they are sufficiently informed regarding Minocin IV, safety parameters, and the conduct of the study in general. I am aware that this protocol must be approved by the Ethics Committee (EC) responsible for such matters in the Clinical Study Facility where Minocin IV will be tested prior to commencement of this study. I agree to adhere strictly to the attached protocol. I understand that this EC-approved protocol will be submitted to relevant regulatory authorities by the Sponsor, as appropriate. I agree that clinical data entered on case report forms by me and my staff will be utilized by the Sponsor in various ways such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow Sponsor monitors and auditors full access to all medical records/source documents at the research facility for subjects screened or randomized in the study.

I agree to provide all subjects with informed consent forms, as required by government and International Conference on Harmonization (ICH) regulations. I further agree to report to the Sponsor any adverse experiences in accordance with the terms of this protocol, ICH guideline, Part E6, Section 4.11 and applicable local regulations.

Principal Investigator (Signature)	Date
Principal Investigator (Printed Name)	Protocol Version: Original Version
Institution Name	

19. REFERENCES

Andreev, E. et al. A rise in plasma creatinine that is not a sign of renal failure: which drugs can be responsible? J Intern Med. 246(3):247-52 (1999)

Antibiotic Resistance Threats in the United States. Centers for Disease Control and Prevention (CDC). 2013.

Casha, S. et al. Results of a Phase II placebo-controlled randomized trial of minocycline in acute spinal cord injury. Brain 135, 1224-1236 (2012).

Charlson, Mary E. et al. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. Journal of Chronic Diseases. 40 (5): 373–83 (1987)

Fagan, S. C. et al. Minocycline to improve neurologic outcome in stroke (MINOS): a dose-finding study. Stroke 41, 2283-2287 (2010).

Generating Antibiotic Incentives Now (GAIN) Act, United States, 2012.

Levey, A. S. et al. A New Equation to Estimate Glomerular Filtration Rate. Ann Intern Med. 150(9): 604–612 (2009)

Memo/08/788, European Commission Press Release Database, 15 Dec 2008.

MINOCIN® (minocycline) for Injection 100 mg/vial [US Prescribing Information]. The Medicines Company; Parsippany, NJ. April 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/050444s049lbl.pdf. Accessed 1 February 2016.

Minocin IV [package insert] Parsippany, NJ: The Medicines Company; April 2015.

Minocin IV Investigator's Brochure, Edition 1, August 2015.

MINOCIN® MR 100 mg Modified Release Capsules [Summary of Product Characteristics]. Meda Pharmaceuticals; Bishop's Stortford, UK. March 2014. Available at: http://www.medicines.org.uk/emc/medicine/21139. Accessed 1 February 2016.

Minocycline Tablets 100 mg [Summary of Product Characteristics]. Actavis UK Ltd; Devon UK. August 2011. Available at: http://www.medicines.org.uk/emc/medicine/24177. Accessed 1 February 2016.

Munoz-Price LS, Weinstein RA. Acinetobacter Infection. New Engl J Med. 2008;358:12.

RCOG Faculty of Sexual & Reproductive Healthcare. Clinical Guidance - Drug Interactions with Hormonal Contraception, Clinical Effectiveness Unit. 2012:1755-103X

Shlaes DM, Sahm D, Opiela C et al. The FDA reboot of antibiotic development. Antimicrobial Agents and Chemotherapy. 2013;57:4605-07.

UK MHRA. Recommendations related to contraception and pregnancy testing in clinical trials. Advisory non-binding guidance supported by national competent authorities represented at the CTFG-meeting in Rome 2014-09-15. 2014

This is a representation of an electronic record that was signed electronically.
This page is a manifestation of the electronic signature(s).

Approval	David Sylvester Clinical 30-Aug-2017 15:27:34 GMT+0000

Approval	Jeff Loutit Medical 31-Aug-2017 01:33:52 GMT+0000

Approval	Liz Morgan Clinical 06-Sep-2017 00:10:09 GMT+0000

Signature Page for MDCO-CLIN-002575 v1.0